SYNTHESIS AND OXIDATIVE REACTIVITY OF ORGANOPOLYSULFIDES

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT

Using a new set of conditions, the synthesis of various symmetrical and unsymmetrical polysulfides has been achieved in high yield and purity by the *in situ* reaction of polysulfide chlorides and mercaptans. The oxidative reactivity of this class of compounds has also been investigated using electrophilic oxidizing agents. The influences of the sulfur-chain length effect and the alkyl substituent effect have been quantified. A comparative study revealed the predominance of each effect depending on the polysulfide concerned.

A wide variety of symmetrical and unsymmetrical polysulfide-polyoxides have been isolated by direct oxidation of various substrates using nucleophilic and electrophilic oxidizing agents and by non-oxidative procedures. Various intermediates have also been detected using low temperature oxidation experiments. The characterization of this class of compound was essentially achieved by NMR spectroscopy. The structures of the key derivatives have been confirmed by X-ray crystallography.

The electrophilic oxidation of many different polysulfide-polyoxides allowed a better understanding of this type of reaction which was found to be regiospecific in most cases. Although the sulfenyl sulfur atoms are generally more reactive than sulfinyl sulfurs, the internal sulfenyl sulfur was surprisingly non-reactive towards electrophilic oxidizing agents and on specific occasions, the oxidation has been shown to take place preferentially at the sulfinyl sulfur rather than the internal sulfenyl sulfur. Clear evidence of the stereospecificity of some of these reactions has also been reported.

The decomposition of most of these symmetrical and unsymmetrical polysulfide-polyoxides has also been investigated. Although the decomposition mixture was very complex in most cases, a detailed decomposition study as well as a careful analysis of the products allowed a proposal of a general mechanism. Although this mechanism is far from being straight-forward, it has been found to be consistent with all the decomposition experiments reported here.

RÉSUMÉ

La réaction *in situ* de mercaptans et de chlorure de disulfures a permis l'isolation en bon rendement de plusieurs polysulfures (symétriques et non symétriques). La sélectivité de l'oxydation de cette classe de composées a également été étudiée en fonction de différents paramètres. Utilisant des oxydants électrophiliques, il a été possible de quantifier l'influence de la longueur de la chaîne d'atome de soufre ainsi que du degré de substitution du dialkyl polysulfure considéré. La prépondérance de chacun de ces deux effets a aussi clairement été identifiée par le biais d' expériences comparatives.

Une grande variété de polysulfures-polyoxydes (symétriques et non symétriques) ont également été synthétisées par oxydation directe de différents substrats et par réaction de condensation. Plusieurs intermediaires ont été détectés lors d'oxydations à basse température. La charactérisation de cette classe de composés a essentiellement été réalisée par spectroscopie RMN. Les structures des analogues les plus importants ont été confirmées par analyse crystallographique.

L'oxydation de nombreux polysulfures-polyoxydes a permis une meilleure compréhension de ce type de réaction qui s'avère être régiospécifique dans la plupart des cas. Bien que le soufre d'un groupe sulfényl soit généralement plus réactif que celui d'un groupe sulfinyl, les soufres internes de plusieurs dérivés de trisulfures ne sont curieusement pas réactif envers les oxydants électrophiliques. Ainsi pour un bon nombre d'analogues, l'oxydation se fait sur le soufre externe (sulfinyl) plutôt que sur le soufre interne (sulfényl). La stéréospécificité de certaines de ces réactions a clairement été démontrée.

La décomposition de la plupart des dérivés de cette classe de composés a été étudiée en détail. Bien que les mélanges de produits de décomposition soient très complexes dans la plupart des cas, l'étude approfondie des produits de reaction a permis de proposer un mécanisme général pour la décomposition de cette classe de composés. Ce mécanisme s'est révélé être très satisfaisant dans tous les cas étudiés, bien qu'il soit relativement complexe.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Dr. D. N. Harpp without whom the accomplishment of this work would not have been possible. His dedication, optimism, patience, trust and scientific expertise have been essential for the success of this experience. I deeply respect him for his outstanding human, social and professional qualities.

I also wish to thank all the people from Lab. 240, from the chemistry department, from Montreal and from France that took part to some extent and at different levels to the completion of this work.

Finally, Elf Aquitaine and Elf Atochem are gratefully acknowledged for financial support and technical assistance.

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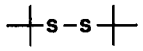
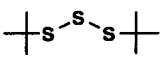
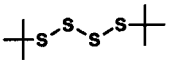
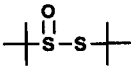
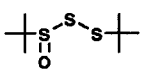
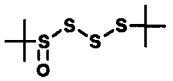
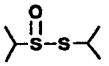
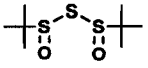
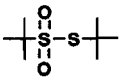
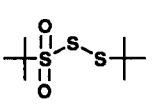
INDEX OF ABBREVIATIONS

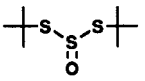
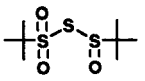
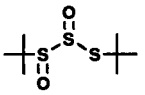
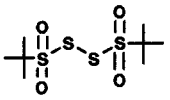
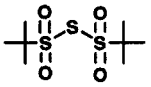
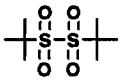
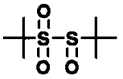
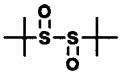
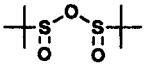
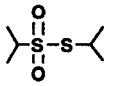
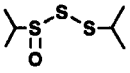
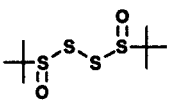
[ ]	concentration
σ	standard deviation
Å	Ångstrom
Bp.	boiling point
^{o}C	degrees Celsius
ca.	circa
cm	centimeter
d	deuterium
DMD	dimethyldioxirane
m-CPBA	*meta*-chloroperbenzoic acid
m-CBA	*meta*-chlorobenzoic acid
EI	electron impact
eq.	equivalent
g	gram
gc	gas chromatography
hr	hour
kcal	kilocalories
L	litre
lit.	literature
m	*meta*
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
M	molar
mm	millimeter
mmol	millimole
mol	mole
Mp.	melting point
MS	mass spectrometry
N	normality
nm	nanometer
NMR	nuclear magnetic resonance

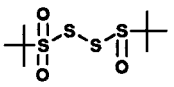
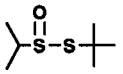
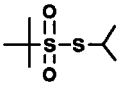
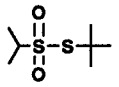
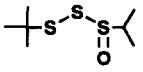
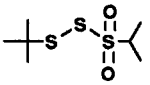
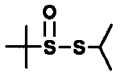
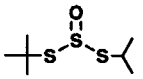
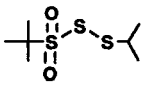
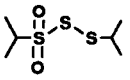
ppm	parts per million
R_f	relative mobility
s	second
p	*para*
t	tertiary
n	normal
t-Bu	tertiary butyl
Bz	benzyl
i-Pr	isopropyl
Adm	Adamantyl
n-Bu	normal butyl
tlc	thin layer chromatography

INDEX OF STRUCTURES

In order to help the reader, the following table presents a list of the main compounds used throughout this work. Due to the variety of the compounds synthesized and the complexity of the decomposition mixtures, this list might be very helpful for a better understanding of Chapter 3 and 4 in particular. The compounds are listed in increasing order of entry as they appear in the text. For each structure, the first name correspond to the nomenclature proposed in the introduction of Chapter 3 and the second one is the name usually found in the literature.

Entry	Compound	Proposed name	Literature name
118b		di-*t*-butyl disulfide	di-*t*-butyl disulfide
118c		di-*t*-butyl trisulfide	di-*t*-butyl trisulfide
118d		di-*t*-butyl tetrasulfide	di-*t*-butyl tetrasulfide
120b		di-*t*-butyl disulfide-1-oxide	di-*t*-butyl thiosulfinate
120c		di-*t*-butyl trisulfide-1-oxide	*t*-butylsulfinyl *t*-butylsulfenyl thioanhydride
120d		di-*t*-butyl tetrasulfide-1-oxide	*t*-butylsulfinyl *t*-butylsulfenyl dithioanhydride
123b		diisopropyl disulfide-1-oxide	diisopropyl thiosulfinate
130a **130b**		meso and d,l di-*t*-butyl trisulfide-1,3-dioxide	RR/RS di-*t*-butylsulfinyl thioanhydride
144		di-*t*-butyl disulfide-1,1-dioxide	di-*t*-butyl thiosulfonate
145		di-*t*-butyl trisulfide-1,1-dioxide	*t*-butylsulfonyl *t*-butylsulfenyl thioanhydride
149			*t*-butylsulfinyl chloride

Entry	Compound	Proposed name	Literature name
156		di-*t*-butyl trisulfide-2-oxide	di-*t*-butyl dithiosulfite
157		di-*t*-butyl trisulfide-1,1,3-trioxide	*t*-butylsulfonyl *t*-butylsulfinyl thioanhydride
158[d]		di-*t*-butyl trisulfide-1,2-dioxide	*t*-butylsulfinyl *t*-butyl thiosulfite
159		di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide	di-*t*-butylsulfonyl dithioanhydride
161		di-*t*-butyl trisulfide-1,1,3,3-tetraoxide	di-*t*-butylsulfonyl thioanhydride
163			*t*-butylsulfinic acid
164			*t*-butylsulfonic acid
165		di-*t*-butyl disulfide-1,1,2,2-tetraoxide	*t*-butyl *vic*-disulfone
166[d]		di-*t*-butyl disulfide-1,1,2-trioxide	*t*-butylsulfinyl *t*-butylsulfone
167[d]		di-*t*-butyl disulfide-1,2-dioxide	*t*-butyl *vic*-disulfoxide
168a 168b			*t*-butylsulfinic anhydride
169		diisopropyl disulfide-1,1-dioxide	diisopropyl thiosulfonate
172		diisopropyl trisulfide-1-oxide	isopropylsulfinyl isopropylsulfenyl thioanhydride
174a 174b		di-*t*-butyl tetrasulfide-1,4-dioxide	di-*t*-butylsulfinyl dithioanhydride

Entry	Compound	Proposed name	Literature name
175		di-*t*-butyl tetrasulfide-1,1,4-trioxide	*t*-butylsulfonyl *t*-butylsulfinyl dithioanhydride
179		*t*-butyl isopropyl disulfide-2-oxide	*t*-butylisopropyl thiosulfinate
180			isopropylsulfinyl chloride
185a		*t*-butyl isopropyl disulfide-1,1-dioxide	isopropyl *t*-butyl thiosulfonate
185b		*t*-butyl isopropyl disulfide-2,2-dioxide	*t*-butyl isopropyl thiosulfonate
190		*t*-butyl isopropyl trisulfide-3-oxide	isopropylsulfinyl *t*-butylsulfenyl thioanhydride
191		*t*-butyl isopropyl trisulfide-3,3-dioxide	isopropylsulfonyl *t*-butylsulfenyl thioanhydride
193		*t*-butyl isopropyl disulfide-1-oxide	isopropyl *t*-butyl thiosulfinate
196		*t*-butyl isopropyl trisulfide-2-oxide	isopropyl *t*-butyl dithiosulfite
199a		*t*-butyl isopropyl trisulfide-1,1-dioxide	*t*-butylsulfonyl isopropylsulfenyl thioanhydride
199b		diisopropyl trisulfide-1,1-dioxide	isopropylsulfonyl isopropylsulfenyl thioanhydride

CHAPTER 1. INTRODUCTION

Sulfur has been known for more than four thousand years and has been detected in almost every part of the universe.[1] Its high natural abundance and unique physical characteristics have always created great interest. Over the centuries, the influence of sulfur can be found in literature, alchemy and in the names of cities and landmarks.[1]

Low molecular weight organosulfur compounds have a less glorious past because of their obnoxious odor and since the first discovery of diethyl sulfide, diethyl disulfide and ethanethiol by Zeise,[2] sulfur chemists have had a bad reputation and were known as "bearers of ill-wind". However, within the last century, the discovery of a vast number of organosulfur compounds in nature shows that most of them do not have this disagreeable odor. Moreover, the Allium family[3] is well known for having remarkable flavorants and odorants all having in common one element: sulfur.

Nowadays, the chemistry of organic sulfur compounds is a developing branch in organic chemistry, both in new synthetic reactions and in theoretical investigations.[4] In addition, the use of organosulfur compounds is growing in industry, agriculture, and medicine.

One of the main classes in organic sulfur compounds are those characterized by structure **1**, in which chains of sulfurs are terminated by two groups which can be the same, different or connected to form cyclic polysulfides.

R-S-Sx-R' **(x = 1, 2, 3...)**

1

The literature is abundant with studies on polysulfides. In the present investigation, a brief overview of the natural occurrence and synthesis of di- and trisulfides is presented as well as a thorough survey on the oxidation of disulfides.

---

1 F. Raulin and G. Toupance, *J. Mol. Evol.*, **9**, 329 (1977).

2 a) W. C. Zeise, *Jutus Liebig's Ann. Chem.*, **8**, 215 (1833); b) W. C. Zeise, *ibid.*, **11**, 1 (1834).

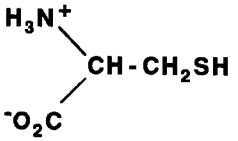
3 E. Block, *Angew. Chem. Int. Ed. Engl.*, **31**, 1135 (1992).

4 For a general overview of organosulfur chemistry, see E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York (1978).

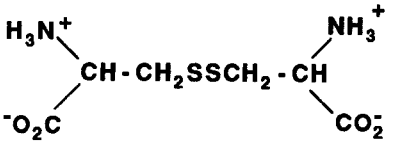
1.1. Natural Occurrence of Di- and Trisulfides

1.1.1. Monera, Protoctista, Animalia and Fungi

Disulfides are widespread in living organisms and they are often essential with biochemical processes. The most important of this class of compounds are probably the polypeptides containing the amino acid cysteine (**2**). In natural peptides, cysteine is not common with its free thiol function, but in most cases two cysteine residues are linked by a bridged disulfide to form disulfide cystine (**3**) derivatives. These S-S bonds are essential for the bioactivity of the peptides. In the natural molecules containing many cystine residues, the bridged disulfides have specific positions in the sequence of amino acids; changing them would modify their properties.

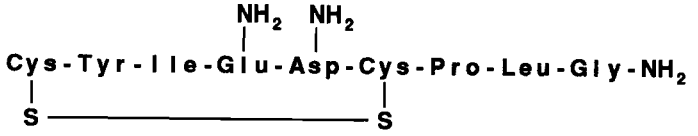


2



3

An example of a cystine-containing polypeptide is the pituitary hormone oxytocin[5] (**4**) characterized by a single bridged disulfide in positions 1 and 6; this molecule causes uterine contraction in childbirth. For the first identification and synthesis of a hormone, du Vigneaud was awarded a Nobel prize in 1955.



4

Another pituitary hormone is vassopressin[6] (**5**) characterized by a slightly different sequence of amino acids; it has an anti-diuretic activity and occurs in most mammals.

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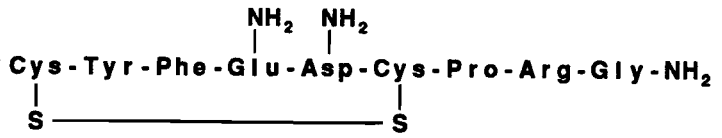
5 a) V. du Vigneaud, C. Ressler and S. Tripett, *J. Biol. Chem.*, **205**, 949 (1953); b) C. Ressler, *Science*, **128**, 1281 (1958).

6 a) V. du Vigneaud, H. C. Lawler and E. A. Popenoe, *J. Am. Chem. Soc.*, **75**, 4880 (1953); b) A. V. Schally, R. Guillemin, *J. Biol. Chem.*, **239**, 1038 (1961).



5

Other polypeptides contain more than one disulfide linkage. The most familiar one is the pancreatic hormone insulin which is of prime importance in the regulation of glucose metabolism. Conotoxine,[7] enterotoxine,[8] and pancreatic ribonuclease[9] may also be mentioned. In the past few years, most of the research in this area has been focussed on the synthesis of polypeptides with site-specific disulfide cross links.[10]

Among the non-peptide disulfides, α-lipoic acid (**6**) is one of the most important cyclic polysulfides. Isolated from the liver, it acts as co-factor[11] in metabolism and growth and is involved in oxidative decarboxylation[12] and photosynthesis.[13] There are

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7 a) Y. Nishiuchi, K. Y. Kumagaye, Y. Noda, T. X. Watanabe, S. Sakakibara, *Pept. Chem.*, 77 (1985); b) Y. Nishiuchi, K. Y. Kumagaye, Y. Noda, T. X. Watanabe, S. Sakakibara, *Biopolymers*, **25**, 61 (1986).

8 Y. Shimonishi, Y. Hidaka, M. Koizumi, M. Hane, S. Aimoto, T. Takeda, T. Miwatani, Y. Takeda, *FEBS Letters*, **215**,165 (1987).

9 a) E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, **3**, Chemical Publishing Co., New York, p. 263 (1960); b) D. M. Rothwarf and H. A. Scheraga, *J. Am. Chem. Soc.*, **113**, 6293 (1991).

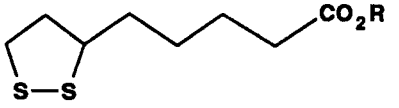
10 a) F. Cavelier, J. Daunis, R. Jacquier, *Bull. Soc. Chim. Fra.*, **6**, 789 (1989); b) A. E. Ferentz, J. Wiorkievicz-Kuczera, M. Karplus, and G. L. Verdine, *J. Am. Chem. Soc.*, **115**, 7569 (1993); c) J. T. Goodwin and G. D. Glick, *Tetrahedron Lett.*, **34**, 5549 (1993); d) A. E. Ferentz, T. A. Keating, and G. L. Verdine, *J. Am. Chem. Soc.*, **115**, 9006 (1993).

11 a) L. J. Reed, B. G. Bebusk, I. C. Gunsalus and C. S. Hornberger, *Science*, **114**, 93 (1951); b) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce and E. L. R. Stokstad, *J. Am. Chem. Soc.*, **74**, 3455 (1952); c) I. C. Gunsalus, L. Struglia and D. J. O'Kane, *J. Biol. Chem.*, **194**, 859 (1952); d) L. J. Reed, I. C. Gunsalus, G. H. F. Schakenberg, Q. F. Soper, H. E. Boaz, S. F. Kern and T. V. Parke, *J. Am. Chem. Soc.*, **75**, 1267 (1953).

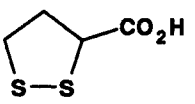
12 a) D. E. Griffiths, *Genet. Biog. Chloroplasts Mitochondria, Interdiscip. Conf.*, Th. Buecher, W. Neupert and W. Sebald, Eds., Amsterdam: North-Holland, 175 (1976); *Chem. Abstr.*, **87**, 97500 (1976); b) D. E. Griffiths, *Biochem. J.*, **160**, 809 (1976); c) M. D. Partis, R. L. Hyams and D. E. Griffiths, *FEBS Lett.*, **75**, 47 (1977); d) D. E. Griffiths, R. L. Hyams and M. D. Partis, *Biochem. Soc. Trans.*, **5**, 1283 (1977); e) R. Johnston, S. Sharf and R. S. Criddle, *Biochem. Biophys. Res. Commun.*, **77**, 1361 (1977); f) D. E. Griffiths, *Mol. Biol. Memb., (Proc. Symp.), 1977*, S. Fleisher, Y. Hatefi and D. H. Maclennan, Eds., New York: Plenum Press, 275 (1978); *Chem. Abstr.*, **90**, 67803 (1978).

13 a) M. Calvin and J. A. Barltrop, *J. Am. Chem. Soc.*, **74**, 6153 (1952); b) M. Calvin and P. Massini, *Experimentia*, **8**, 445 (1952); c) D. F. Bradley and M. Calvin, *Arch. Biochem.*

many other biological applications of α-lipoic acid and most of them were recently reviewed by Teuber.[14] 1,2-Dithiolane-3-carboxylic acid (**7**)[15] occurs naturally as a metabolite of α-lipoic acid and esterification of this carboxylic acid with tropine leads to the formation of brugine (**8**),[16] which was also isolated from different species of mangrove trees.



6



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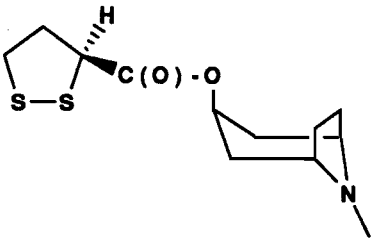


8

In the animalia family, 1,2-dithiolanes have been isolated from the anal secretion of animals belonging to the genus *Mustela*.[17] They include 3,3-dimethyl-(**9**), 3-ethyl-(**10**), 3-propyl-(**11**) and 3,4-dimethyl-(**12**) 1,2-dithiolanes.[18] These compounds are used for chemical communication and area repellents. Dimethyl trisulfide has also been found to be a communicative secretion of the mandibular gland of the ponerine ant *paltothyreus*

Biophys., **53**, 99 (1954); d) D. F. Bradley and M. Calvin, *Proc. Natl. Acad. Sci.*, **41**, 563 (1955); e) M. Calvin, *J. Chem. Soc.*, 1895 (1956); g) M. Calvin, *Angew. Chem.*, **68**, 253 (1956).

14 a) L. Teuber, *Sulfur Reports*, **9**, 257 (1990); b) T. Von Zglinicki, I. Viswedel, L. Truemper, W. Augustin, *Mech. Ageing Dev.*, **57**, 233 (1991); *Chem. Abstr.*, **114**, 179939 (1991); c) L. I. Reed, I. C. Gunzalus, B. G. Debusk and C. S. Hornberger, *Science*, **114**, 93 (1993).

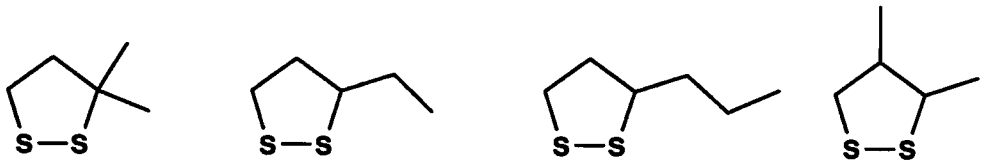
15 H. C. Furr, H.-H. Chang and D. B. McCormick, *Arch. Biochem. Biophys.*, **185**, 576 (1978).

16 a) J. W. Loder and G. B. Russell, *Tetrahedron Lett.*, 6327 (1966); b) J. W. Loder and G. B. Russell, *Aust. J. Chem.*, **22**, 1271 (1969); c) A. Kato, *Phytochemistry*, **14**, 1458 (1975).

17 a) H. Schildknecht, I. Wilz, F. Enzmann, N. Grund and M. Ziegler, *Angew. Chem. Int. Ed. Engl.*, **15**, 242 (1976); b) E. Albone, *Chem. Brit.*, **13**, 92 (1977); c) C. Brinck, R. Gerell and G. Odham, *Oikos*, **30**, 68 (1978); d) D. R. Crump, *J. Chem. Ecol.*, **6**, 341 (1980); e) D. R. Crump, *J. Chem. Ecol.*, **6**, 837 (1980); f) V. E. Sokolov, E. S. Albone, P. F. Flood, P. F. Heap, M. Z. Kagan, V. S. Vasilieva, V. V. Roznov and E. P. Zinkevich., *J. Chem. Ecol.*, **6**, 805 (1980); g) H. Schildknecht, C. Birkner and D. Krausz, *Chem.-Ztg.*, **105**, 273 (1981); h) H. Schildknecht, C. Birkner, *Chem.-Ztg.*, **107**, 267 (1983).

18 a) E. Vernet-Maury, E. H. Polak and A. Damael, *J. Chem. Ecol.*, **10**, 1007 (1984); b) T. P. Sullivan and D. R. Crump, *J. Chem. Ecol.*, **10**, 1809 (1984); c) T. P. Sullivan, D. R. Crump and D. S. Sullivan, *J. Chem. Ecol.*, **14**, 379 (1988); d) T. P. Sullivan, D. R. Crump and D. S. Sullivan, *J. Chem. Ecol.*, **14**, 363 (1988); e) B. K. Clapperton, E. O. Minot and D. R. Crump, *Anim. Behav.*, **36**, 541 (1988).

tarsatus.[19] This trisulfide has been identified as a volatile compound produced by the bacteria *Pseudomonas putrefaciens*[20] in sterile fish muscle and as a trace component with dimethyl tetrasulfide in the volatiles from swine manure.[21]



9 **10** **11** **12**

The composition of the putrid odor of the striped skunk's (*Mephitis mephitis*) defensive musk has always been subject to controversy. It was first thought that the obnoxious odor was due to 1-butanethiol[22] but Andersen and Bernstein[23] have shown that the presence of 1-butanethiol had been misinterpreted by trans-2-butene-1-thiol. In their study they also mentioned the presence of *trans*-2-butenyl methyl disulfide. Recently Emsley[24] claimed that there was no disulfide but instead, thioacetate derivatives.

Finally, some polysulfides were detected in the analysis of meat and milk. Head space gas chromatography of volatile compounds revealed the presence of dimethyl disulfide in milk[25] and in cooked meat.[26] Sulfur-containing compounds such as 3,5-dimethyl-1,2,4-trithiolane (**13**), 3,6-dimethyl-1,2,4,5-tetrathiane (**14**), and 1,2,3,5,6-

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19 G. Casnati, A. Ricca and M. Pavan, *Chem. Ind. (Milan)*, **49**, 57 (1967).

20 A. Miller, R. A. Scalan, J. S. Lee and L. M. Libbey, *Appl. Microbiol.*, **26**, 18 (1973).

21 A. Yasuhara and K. Fuwa, *Bull. Chem. Soc. Jpn.*, **50**, 3029 (1977).

22 a) T. B. Aldrich, *J. Exp. Med.*, **1**, 323 (1893); b) E. Beckmann, *Pharm. Zentralhalle Dsch.*, **37**, 557 (1896).

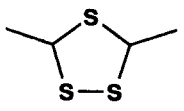
23 a) K. K. Andersen and D. T. Bernstein, *J. Chem. Ecol.*, **1**, 493 (1975); b) K. K. Andersen and D. T. Bernstein, *J. Chem. Ed.*, **55**, 159 (1978).

24 J. Emsley, *Science*, **249**, 31 (1990).

25 a) E. Sterken and A. G. Kempton, *dev. Ind. Microbiol.*, **15**, 226 (1974); b) R. M. Pierami and K. E. Stevenson, *J. Dairy Sci.*, **59**, 1010 (1975); c) G. Urback, *J. Chromatogr.*, **404**, 163 (1987).

26 a) T. E. Kinlin, R. Muralidhara, A. O. Pittet, S. Sanderson, and J. P. Walradt, *J. Agr. Food Chem.*, **20**, 1021 (1972); b) H. W. Brinkman, H. Copier, J. J. M. Deleuw, and S. Boen Tjjan, *J. Agr. Food Chem.*, **20**, 177 (1972); c) S. J. Wratten and D. J. Faulkner, *J. Org. Chem.*, **41**, 2465 (1976); d) P. Dubs and M. Johno, *Helv. Chim. Acta*, **61**, 1404 (1978); e) G. Ohloff and I. Flament, *Prog. Chem. Org. Nat. Prod.*, **36**, 231 (1979).

pentathiepane (**15**) were detected. Synthetic derivatives of such compounds are used to create meat-like aroma.[27] Very recently, a novel access to bis(2-methylfur-3-yl) disulfide (**16**) as well as other disulfide derivatives was reported.[28] Compound **16** was discovered to be one of the most active meat-flavor chemicals.



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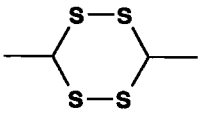
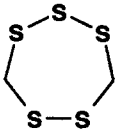


14



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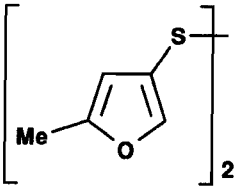

16

During the last decade, the enediyne class of compounds has received great attention[29] because of its powerful anti-cancer activity. These compounds were derived from bacterial sources and are known as antibiotics; they act by cleaving DNA by a rather interesting mechanism. Among this class, two molecules are unusual trisulfides which are calicheamicin γ^{I}_{1}[30] (**17**) and esperamicin A_1[31] (**18**) whose structures were elucidated in 1987. These molecules have been subjected to extensive chemical, biological, and biomedical researches and inspired the synthesis of a number of enediyne derivatives to probe, mimic or even enhance their chemical and biological action. This family of compounds, their bacterial sources, biological mode of action and synthesis

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27 a) P. Werkoff, W. Bretschneider, M. Guentert, R. Hopp, M. Koepsel, H. Surburg, *Chem. Mikrobiol. Technol. Lebensm.*, **13**, 111 (1991); *Chem. Abstr.*, **115**, 254485 (1991); b) Z. Yuangang, H. C. Tang, *J. Agr. Food Chem.*, **39**, 1145 (1991); c) T. A. Misharina, R. V. Golovnya, M. P. Artamonova, N. K. Zhuravskaya, *Chem. Mikrobiol. Technol. Lebensm.*, **14**, 27 (1992); *Chem Abstr.*, **117**, 107116 (1992).

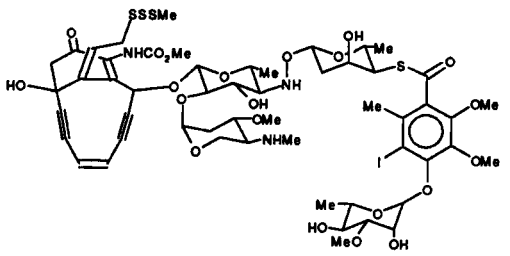
28 U. A. Huber and D. Bergamin, *Helv. Chem. Acta*, **76**, 2528 (1993).

29 For a complete review see: K. C. Nicolaou and W.-M. Dai, *Angew. Chem. Int. Ed. Engl.*, **30**, 1387 (1991)

30 a) M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, D. B. Borders, *J. Am. Chem. Soc.*, **109**, 3464 (1987); b) M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton,W. J. Mcgahren, D. B. Borders, *J. Am. Chem. Soc.*, **109**, 3464 (1987).

31 a) J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawagushi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.*, **109**, 3461 (1987); b) J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawagushi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.*, **109**, 3462 (1987).

have been well reviewed by Nicolaou[29] and very recently the total synthesis of calicheamicin γ^{I}_{1} was published.[32]



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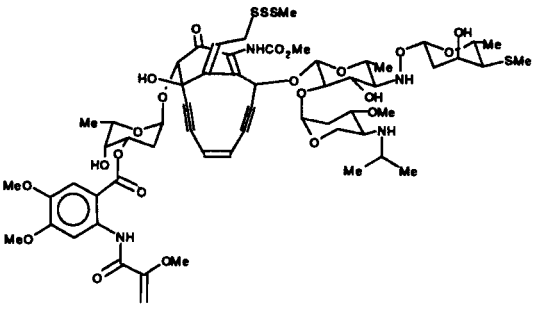

18

The family of fungal toxins is a very important class of bioactive compounds. Among them, bridged di- and trisulfides are characterized by epidithiadioxopiperazine (**19**) and epitrithiadioxopiperazine (**20**) systems respectively. This class of compounds has been extensively reviewed[33] in the past, thus only some of the highlights and recent developments will be covered here. Some representative examples include gliotoxin (**21**), sirodesmin (**22**) and sporidesmin (**23**) for the bridged disulfides and the corresponding thiodehydrogliotoxin (**24**), sirodesmin C (**25**), and sporidesmin C (**26**) and E (**27**) for the bridged trisulfides. Epidi- and trithiadioxopiperazine compounds possess anti-viral, -bacterial and -fungal activity; however their extreme toxicity to mammalian cells has prevented therapeutic applications.

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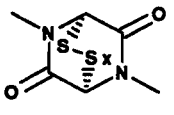
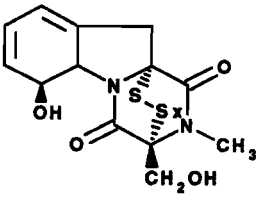
32 a) R. D. Groneberg, T. Miyasaki, N. A. Stylianides, T. J. Schulze, W. Stahl, E. P. Screiner, T. Suzuki, Y. Iawabushi, A. L. Smith, and K. C. Nicolaou, *J. Am. Chem. Soc.*, **115**, 7593 (1993); b) A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizumo, H. Saimoto, G. R. Scarlato, T. Suzuki, and , *J. Am. Chem. Soc.*, **115**, 7612 (1993); c) K. C. Nicolaou, C. W. Hummel, M. Nakada, K. Shibayama, E. N. Pitsinos, H. Saimoto, Y. Mizumo, K. U. Baldenius, and A. L. Smith, *J. Am. Chem. Soc.*, **115**, 7625 (1993).

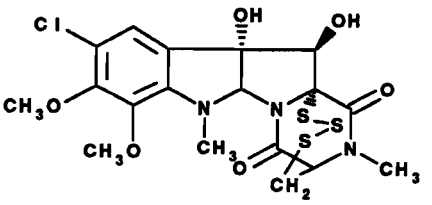
33 a) D. Brewer, D. E. Hannah and A. Taylor, *Can. J. Microbiol.*, 12, 1187 (1966); b) R. Hodges and J. S. shannon, *Aust. J. Chem.*, **19**, 1059 (1966); c) A. Taylor, *Biochemistry of Some Foodborne Microbial Toxins*, R. I. Mateles and G. N. Wogan, Eds., Cambridge, Mass.: M.I.T. Press, 69 (1967); d) D. Brewer, R. Rahman, S. Safe, and A. Taylor, *Chem. Commun.*, 1571 (1968); e) R. Rahman, S. Safe, and A. Taylor, *J. Chem. Soc. (c)*, 1665 (1969); f) S. Safe, and A. Taylor, *J. Chem. Soc. (c)*, 432 (1970); g) A. Taylor, *Microbial Toxins Vol. VII*, A. Ciegler and S. J. Ajl, Eds., New York: Academic Press, 337 (1971); h) T. Sato and T. Hino, *Tetrahedron*, **32**, 507 (1976); i) J. D. M. Herscheid, M. W. Tjhuis, J. H. Noordik, and H. Ç. J. Ottenheijm, *J. Am. Chem. Soc.*, **101**, 1159 (1979); j) P. J. Curtis, D. Greatbanks, B. Hesp, A. F. Cameron, and A. A. Freer, *J. Chem. Soc., Perkin I*, 180 (1979); k) G. W. Kirby and D. J. Robins, *The Biosynthesis of Mycotoxins*, P. S. Stein, Ed., New York: Academic Press, 301 (1980); l) W. B. Turner and D. C. Aldridge, *Fungal Metabolites II*, New York: Academic Press, 417 (1983).



19: x=1
20: x=2



21: x=1
24: x=2



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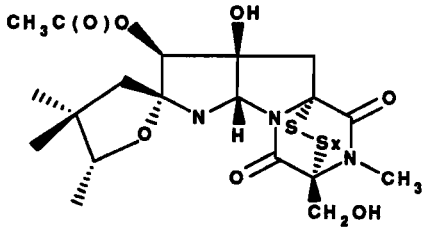
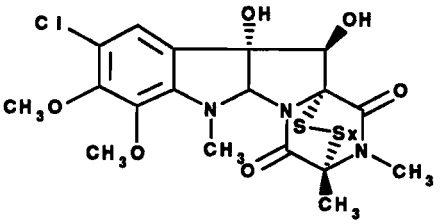


22: x=1
25: x=2



23: x=1
27: x=2

Many recent studies report new bioactivity,[34] toxicity causes[35] and mode of action[36] of this class of epidi- and trithiadioxopiperazine compounds. New members of the class are also reported[37] as well as studies of their biological action. Some examples

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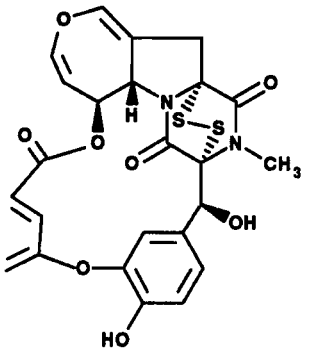
34 a) J. Pepys, *Immunologic Diseases*, M. Santer, Ed., Boston: Little Brown, 692 (1978); b) M. Turner-Warwick, *Postgrad. Med. J.*, **55**, 642, (1979); c) P. B. Marsh, P. D. Miller and J. M. Kla, *Mycopathologia*, **69**, 67 (1979); d) R. D. Eichner and A. Müllbacher, *Aust. J. Exp. Biol. Med. Sci.*, **62**, 479 (1984); e) A. Müllbacher and R. D. Eichner, *Proc. Natl. Acad. Sci. USA*, **81**, 3835 (1984); f) A. Müllbacher, D. Hume, A. W. Braithwaite, P. Waring and R. D, Eichner, *Proc. Natl. Acad. Sci. USA*, **84**, 3822 (1987); g) M. Sakai and M. Watanuki, *Agric. Biol. Chem.*, **51**, 2167 (1987); h) M. Sakai, M. Watanuki and M. Mutai, **Jpn. Kokai, Tokkyo Koho JP 61,277,617** (1985); *Chem. Abstr.*, **106**, 162584 (1987); i) B. E. Tuch, J. R. Lissing and M. G. Suranyi, *Immunol. Cell. Biol.*, **66**, 307 (1988).

35 R. W. Jones and J. G. Hancock, *J. Gen. Microbiol.*, **134**, 2067 (1988).

36 a) A. W. Braithwaite, R. D. Eichner, P. Waring and A. Müllbacher, *Mol. Immunol.*, **24**, 47 (1987); b) R. Munday, *J. Appl. Toxicol.*, **7**, 17 (1987); c) R. D. Eichner, P. Waring, A. Geue, A. W. Braithwaite and A. Müllbacher, *J. Biol. Chem.*, **41**, 361 (1988); d) P. Waring, R. D. Eichner, A. Müllbacher and A. Sjaarda, *J. Biol. Chem.*, **263**, 18493 (1988).

37 a) H. Minato, M. Matzumoto, and T. Katayama, *J. Chem. Soc., Perkin I*, 1819 (1973); b) G. M. Strunz, M. Kakushima, and M. A. Stillwell, *Can. J. Chem.*, **53**, 295 (1974); c) K. Norizuki, H. Seya, S. Nakajima, K. Kawai, K. Norizuki, S. Udagawa and M. Yamazaki, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **28**, 41 (1986); *Chem. Abstr.*, **106**, 134811 (1987); d) N. Kawahara, K. Nozawa, S. Nakajima and K. Kawai, *J. Chem. Soc., Perkin Trans. I*, 2099 (1987); e) M. Soledade, C. Padras, S. R. Abrams, G. Séguin-Swartz, J. W. Quail and Z. Jia, *J. Am. Chem. Soc.*, **111**, 1904 (1989).

are emestrin (**28**), phomalirazine (**29**), dithiosilvatin (**30**), emethallicin A (**31**), hialodendrin (**32**) and verticillin C (**33**).



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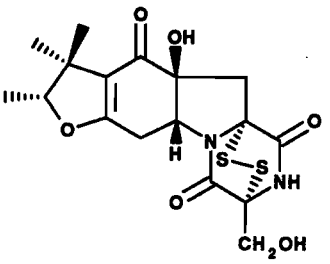

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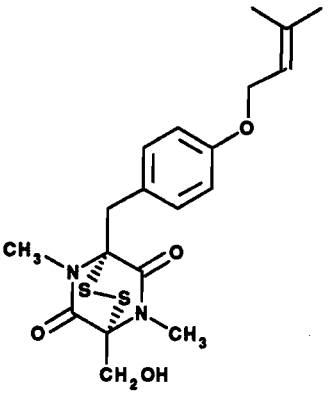

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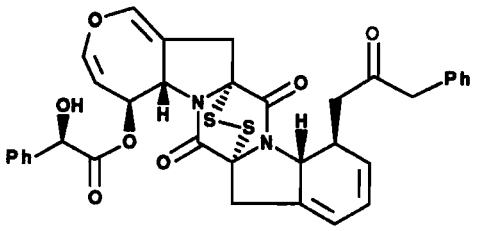

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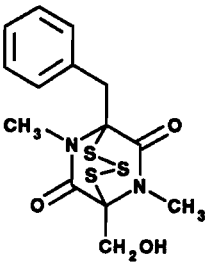

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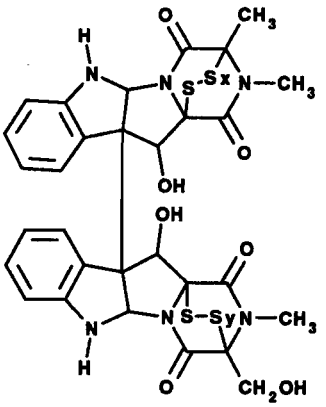

33: x=2 and y=3 or x=3 and y=2

1.1.2. Plantae and Algae

The Allium species[38] include garlic (*Allium sativum L.*), onion (*Allium cepa L.*), leek (*Allium ampeloprasum L. var. porrum*), scallion (*Allium fistulosum*), shallot (*Allium ascalonicum auct.*), great-headed ("elephant") garlic (*Allium ampeloprasum L. var. holmense*), wild garlic (*Allium ursinum*), chive (*Allium schoenoprasum L.*), Chinese chive (*Allium tuberosum L.*) and caucas (*Allium victorialis L.*) and are used as spices and foods. They have also been reported[39] to possess some medicinal value, especially garlic

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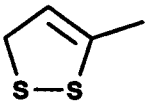
38 A. I. Virtanen, *Angew. Chem. Int. Ed. Engl.*, **1**, 299 (1962).

39 Y. Morimitsu and S. Kawakishi, *Phytochemistry*, **29**, 3435 (1990)

and onion. All these plants contain some organosulfur compounds and their flavors are often due to allylic sulfur compounds. The Allium species have been widely investigated[40] for their beneficial effects in preventing coronary thrombosis, arteriosclerosis, hyperlipidemia and rheumatic arthritis, as well as for their therapeutic effect on many vascular diseases. Furthermore, essential oils of garlic and onion have been found to be very good anti-platelet compounds.[41] The main compounds of these plants are allyl disulfide, allyl trisulfide, unsymmetric methyl allyl polysulfides as well as methyl propyl, dipropyl and 1-propenyl propyl polysulfides.[42] In addition, two new five-member ring disulfide compounds,[43] **34** and **35**, were isolated from garlic oil. Very recently, the Allium family was very well reviewed by Block,[3] in which the natural occurrence the bioactivity and the mode of action of most of the compounds isolated from these Allium species are reported.



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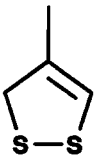

35

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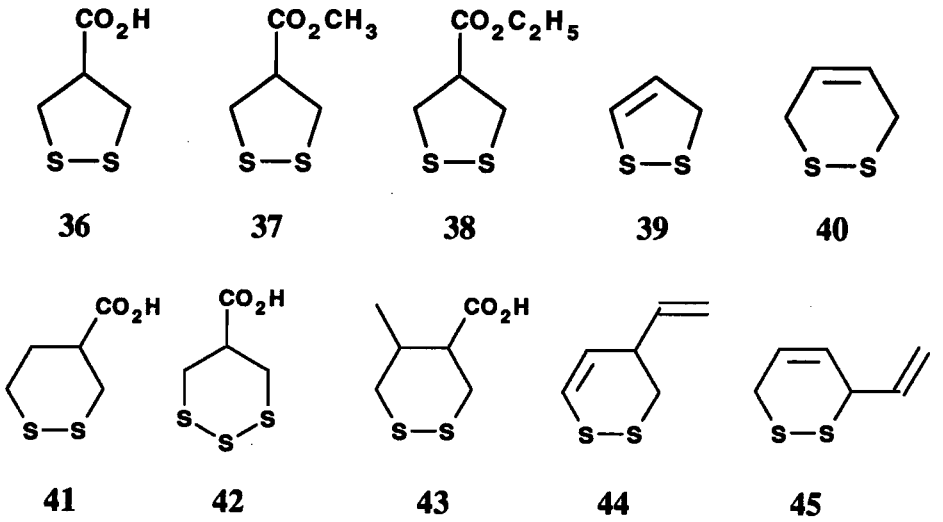
40 a) A. Bordia, H. C. Bansal, S. K. Arora, and S. V. Singh, *Atherosclerosis*, **21**, 15 (1975); b) R. K. Argawal, H. A. Dewar, D. J. Newell, and D. Das, *Atherosclerosis*, **27**, 347 (1977).

41 a) H. Weisenberger, H. Grube, E. Koening, H. Pelzer, *FEBS Lett.*, **26**, 105 (1972); b) T. Augusti, M. E. Benaim, H. A. Dewar, And R. Virden, *Atherosclerosis*, **21**, 409 (1975); c) K. I. Baghurst, M. J. Raj, and A. S. Truswell, *Lancet*, **1**, 101 (1977); d) C. Phillips and N.L. Poiser, *Lancet*, 1, 1051 (1978); e) A. N. Marheja, J. Y vanderhoek, and J. M. Bailey, *Lancet*, **1**, 781 (1979); f) A. N. Marheja, J. Y Vanderhoek, and J. M. Bailey, *Prostaglandins Med.*, **2**, 413 (1979); g) T. Ariga, S. Oshiba, and T. Tamada, *Lancet*, **1**, 150 (1981); h) R. Apitz-Castro, S. Cabrera, M. R. Curz, E. Ledezma, and M. K. Jain, *Thrombosis Res.*, **32**, 155 (1983); i) M. Liakopoulou-Kyriakides, Z. Sinakos, and D. A. Kyriakidis, *Phytochemistry*, **24**, 600 (1985); j) E. Block, S. Ahmad, M. K. Jain, R. W. Crecely, R. Apitz-Castro, and M. R. Cruz, *J. Am. Chem. Soc.*, **106**, 8295 (1986); k) K. C. Srivastava, *Prostaglandins Leukotrienes Med.*, **24**, 43 (1986); l) S. Kawakishi and Y. Morimitsu, *Lancet*, **1**, 330 (1988).

42 a) W. G. Galetto and A. A. Bednarczyk, *J. Food Sci.*, **40**, 1165 (1975); b) L. Schreyen, P. Dirinck, F. Van Wassenhove, and N. Schamp, *J. Agric. Food Chem.*, **24**, 336 and 1147 (1976); c) H. Nishimura, C. H. Wijaya, J. Mitzutani, *J. Agric. Food Chem.*, **36**, 353 (1988); d) C. H. Wijaya, H. Nishimura, T. Tanaka, J. Mizutani, *J. Food Sci.*, **56**, 72 (1991).

43 Z. Ding, J. Ding, C. Yang, and Y. Saruwatari, *Yunan Zhiwu Yanjiu*, **10**, 223 (1988); *Chem. Abstr.*, **110**, 22443 (1989).

Asparagusic acid (**36**) is probably the most common compound isolated from the asparagus family and is used as a plant growth regulator.[44] Asparagus also contains the methyl (**37**) and ethyl (**38**) esters of **36**. 1,2-Dithiole (**39**) and 3,6-dihydro-1,2-dithiin (**40**) contribute to the characteristic odor of cooked asparagus while other six member ring derivatives such as 1,2-dithiane-4-carboxylic acid (**41**), 1,2,3-trithiane-5-carboxylic acid (**42**), 5-methyl-1,2-dithiane-4-carboxylic acid (**43**), 3-vinyl-3,4-dihydro-1,2-dithiin (**44**) and 3-vinyl-3,6-dihydro-1,2-dithiin (**45**) were also isolated from this family.[44e]



36 **37** **38** **39** **40**

41 **42** **43** **44** **45**

Naturally occurring 1,2-dithiolanes have also been found in different species of mangrove trees. Brugine (**8**)[16] was the major alkaloid isolated from members of the family Rhyzophoraceae; 4-hydroxy-1,2-dithiolane (**46**) was found in the stem and bark of *Bruguiera cylindrica*,[45] and gerrardine (**47**), a structural analog, was isolated from *C. Guianensis*.[46] Finally, the alkaloid cassipourine (**48**) was found in *Cassipourea gummiflua*.[47]

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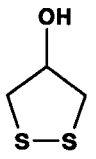
44 a) Y. Kitahara, H. Yanagawa, T. Kato and N. Takahashi, *Plant and Cell Physiol.*, **13**, 923 (1972); b) H. Yanagawa, T. Kato, Y. Kitahara and Y. Kato, *Tetrahedron Lett.*, 2549 (1972); c) Y. Kitahara, T. Kato, H. Yanagawa, H. Aizawa and T. Watanabe, **Jpn. Pat. 74,117,616** (1974); *Chem. Abstr.*, **82**, 134039 (1974); d) H. Yanagawa, *Plant and Cell Physiol.*, **17**, 931 (1976); e) R. Tressl, M. Holzer, M. Apetz, *J. Agric. Food Chem.*, **25**, 455 (1977).

45 a) G. Claeson, *Acta. Chem. Scand.*, **13**, 1709 (1959); b) A. Kato and J. Takahashi, *Phytochemistry*, **15**, 220 (1976).

46 A. Kato, M. Okada and Y. Hashimoto, *J. Nat. Prod.*, **47**, 706 (1984).

47 M. G. Etlinger, A. Kjaer, *Recent Advances in Phytochemistry*, **1**, 59 (1968).



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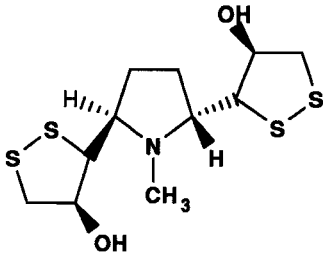

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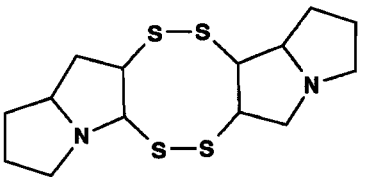
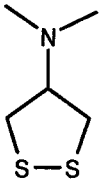


48

Many different organosulfur compounds have been isolated from algae.[48] In 1934, nereistoxin (**49**)[49] (4-(*N*,*N*-dimethyl amino)-1,2-dithiolane) was isolated from marine annelids of the genera *Lumbriconereis* and *Lumbrenereis*[50] and used as an insecticide.[51] Charatoxin (**50**) and its corresponding trisulfide, were found in different Chary species.[52] These algae have a strong inhibitory effect on photosynthesis, suppressing the growth of phytoplankton in their area. Compound **50** has also been used as an insecticide.[53]



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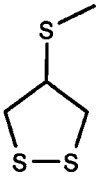

50

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48 C. Christophersen and U. Anthoni, *Sulfur Reports*, **4**, 365 (1986).

49 S. Nitta, *J. Pharm. Soc. Jpn.*, **54**, 648 (1934).

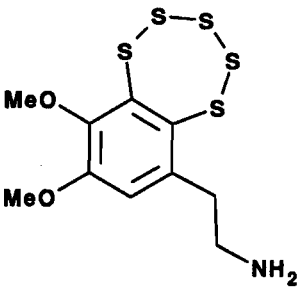
50 a) Y. Hashimoto and T. Okaichi, *Ann. N. Y. Acad. Sci.*, **90**, 607 (1960); b) T. Okaichi and Y. Hashimoto, *Agric. Biol. Chem.*, **26**, 224 (1962).

51 a) K. Konishi, *Agr. Biol. Chem. (Tokyo)*, **32**, 1199 (1968); b) R. M. Pinder, K. Brewster, D. W. Swanston, *Chim. Ther.*, **5**, 261 (1970); *Chem. Abstr.*, **74**, 42297; c) M. Injac and K. Dulic, *Proc. Br. Crop Prot. Conf. Pests Dis.*, **3**, 1117 (1984); d) G. C. Scott, J. A. Pickett, M. C. Smith, C. M. Woodstock, P. G. W. Harris, R. P. Harman and H. D. Koetecha, *Proc. Br. Crop Prot. Conf. Pests Dis.*, **1**, 133 (1984).

52 a) U. Anthoni, C. Christophersen, J. O. Madsen, S. Wium-Anderson and N. Jacobson, *Phytochemistry*, **19**, 1228 (1980); b) S. Wium-Anderson, U. Anthoni, C. Christophersen and G. Houen, *Oikos*, **39**, 187 (1982).

53 a) N. Jacobson and L.-E. K. Pederson, *Pestic. Sci.*, **14**, 90 (1983); b) L.-E. Nielsen and L.-E. K. Pederson, *Experimentia*, **40**, 186 (1984).

Recently, varacin **(51)**,[54] the first naturally occurring compound determined to contain this ring system of 5 sulfur atoms, was isolated from a marine ascidian from the genus *Lissoclinum*. Varacin exhibited significant anti-fungal and cytotoxic activities and is one of the most potent human colon anti-cancer agents.[55] Lissoclonitoxin A **(52)**[56] is a closely related tunicate metabolite and contains a trithiane ring system. The total synthesis of varacin derivatives has already been reported.[57]



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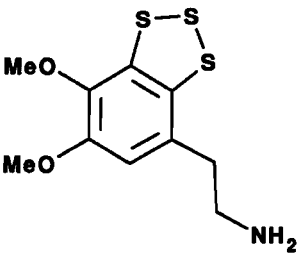
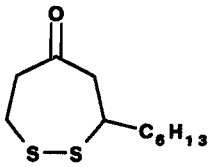


52

3-Methyl-1,2-dithiepane-5-one **(53)**, a seven member ring disulfide, trisulfide **(54)** as well as its tetrasulfide derivative, have been detected in the Hawaiian brown algae *Dictyopteris plagiogramma*.[58] The red algae *Chondria californica*[26a] contains a wide variety of organosulfur compounds. Characteristic examples are the 1,2,4-trithiolane **(55)**, its sulfoxide derivative **(56)**, 1,2,4,5-tetrathiane **(57)**, lenthionine **(15)**, 1,2,4,6-tetrathiepane **(58)** and the corresponding sulfone **(59)** as well as 1,2,4,5,7,8,10,11-octathiacyclododecane **(60)**.



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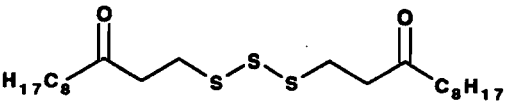

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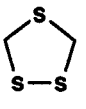

55

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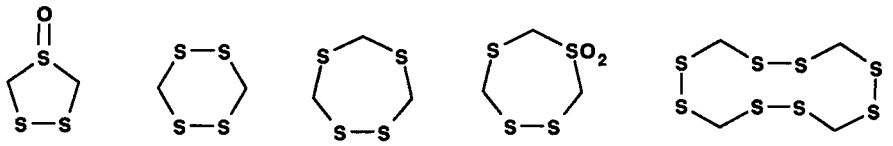
54 B. S. Davidson, T. F. Molinski, L. R. Barrows, C. M. Ireland, *J. Am. Chem. Soc.*, **113**, 4709 (1991).

55 P. W. Ford and B. S. Davidson, *J. Org. Chem.*, **58**, 4523 (1993).

56 M. Litaudon and M. Guyot, *Tetrahedron Lett.*, **32**, 911 (1991).

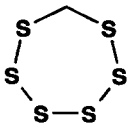
57 V. Behar and S. J. Danishefsky, *J. Am. Chem. Soc.*, **115**, 7017 (1993).

58 a) P. Roller, K. Au, R. E. Moore, *J. Chem. Soc., Chem. Commun.*, 503 (1971); b) R. E. Moore, *J. Chem. Soc., Chem. Commun.*, 1168 (1971).



56 **57** **58** **59** **60**

Shiitake (*Lentinus edodes* Sing.) is an edible mushroom highly prized in China and Japan. The fresh mushroom is not highly odorous but upon drying or crushing, the characteristic aroma of lenthionine (**15**) gradually develops.[59] Compounds **55**, **58**, and 1,2,3,4,5,6-hexathiepane (**61**) were three other cyclic sulfur compounds also reported[60] in the dry mushroom. A recent study[61] of the volatiles of the shiitake mushroom identified the presence of additional compounds such as dimethyl disulfide and dimethyl trisulfide. These and 13 new sulfur compounds were reported by Chen and Ho.[62] Compound **55** was also detected in other varieties of mushrooms but only cyclic sulfur compounds were reported.[63] Another mushroom, *Boletus edulis*[64,26c] has yielded 3,5-dimethyl-1,2,4-trithiolane (**13**).



61

Plants from the family *Compositae*, one of the most thoroughly investigated[65] of all plant families, are the only known source of naturally occurring 1,2-dithiins. A review

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59 a) K. Morita, S. Kobayashi, *Tetrahedron Lett.*, **6**, 573 (1966); b) S. Wada, H. Nakatani, K. Morita, *J. Food Sci.*, **32**, 559 (1967); c) K. Yasumoto, K. Iwami, H. Mitsuda, *Mushroom Sci.*, **9**, 371 (1976).

60 K. Morita, S. Kobayashi, *Chem. Pharm. Bull.*, **15**, 988 (1967).

61 a) B. A. Charpentier, M. R. Savenants, R. A. Sanders, *The Shelf Life of Foods and Beverages*, G. Charalambous, Ed., Elsevier Science, Amsterdam, pp. 413-433 (1986); b) E. Block, *J. Org. Chem.*, **59**, 2273 (1994).

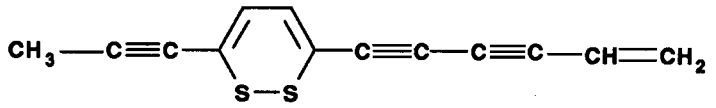
62 C. C. Chen, C. T. Ho, *J. Agric. Food Chem.*, **34**, 830 (1986).

63 C. C. Chen, S.-D. Chen, J.-J Chen, C.-M. Wu, *J. Agric. Food Chem.*, **32**, 999 (1984).

64 A. F. Thomas, *J. Agric. Food Chem.*, **4**, 955 (1973).

65 F. Bohlmann, T. Burkhardt and C. Zdero, *Naturally Occurring Acetylenes*, New York: Academic Press (1973).

by Freeman and coworkers[66] presents an extensive list of such compounds and their origins. Some characteristic examples are the dithiacyclohexadiene polyines such as **62-65** where **62** and **63** are better known as thiarubrines A and B.



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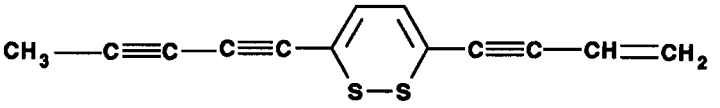

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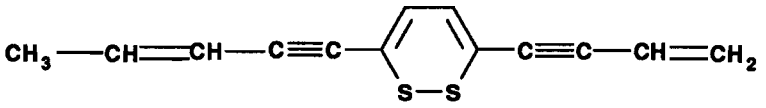

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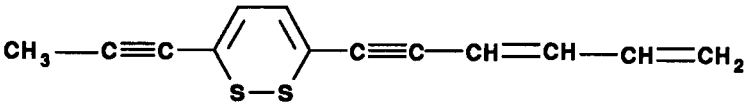

65

Recent studies[67] have shown the natural occurrence of thiarubrine derivatives **66-69** from the roots of *Ambrosia chamissonis*. The bioactivity of thiorubrine A and other dithiapolyacetylenes has been investigated[68] especially for the anti-viral and nematicidal applications.

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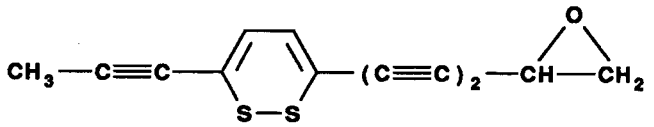
66 F. Freeman, D. S. H. L. Kim, E. Rodriguez, *Sulfur Reports*, **9**, 207 (1989).

67 a) F. Balza, I. Lopaz, E. Rodriguez and G. H. N. Towers, *Phytochemistry*, **28**, 3523 (1989); b) F. Balza and G. H. N. Towers, *Phytochemistry*, **29**, 2901 (1990).

68 a) J. B. Hudson and G. H. N. Towers, *Bioact. Mol.*, **7**, 315 (1988); b) E. Rodriguez, *ACS Symp. Ser.*, **380**, 432 (1988).



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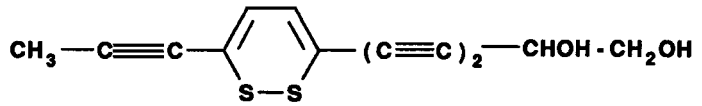

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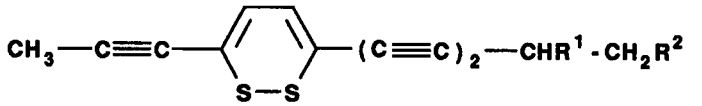

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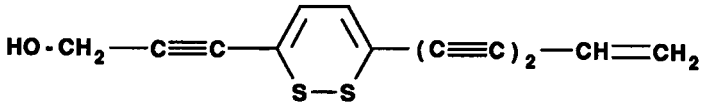
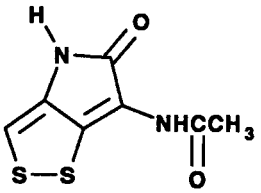


69

Other cyclic disulfides such as homolycin (**70**), thiolutin (**71**) and aureothricin (**72**) were all isolated from *Streptomyces* and exhibit a strong antibiotic activity. Unfortunately, it was impossible to use their bioactivity because of their high toxicity.[69]



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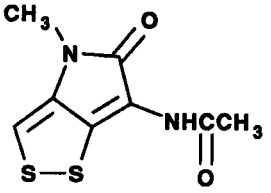

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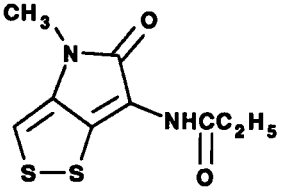

72

Cabbage (*Brassica oleracea var capitata*) and other cruciferous vegetables produce many volatile sulfur compounds such as 1,2-dithiole-3-thione (**73**)[69] upon tissue disruption. Recent studies[70] of the volatiles of these plants revealed the presence of dimethyl di- and trisulfides which are generally responsible for the objectionable sulfurous aromas and overcooked off-flavors. Similar sulfur compounds have been detected in the investigation of the volatile profile of the caper (*Capparis spinosa L.*).[71]

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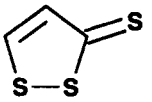
69 L. Field, *Organic Chemistry of Sulfur*, S. Oae, Ed., Plenum Press: New York/London, 1977, pp. 309-316.

70 H.-W Chin, R. C. Lindsay, *J. Food Sci.*, **58**, 835 (1993).

71 H. Brevard, M. Brambilla, A. Chaintreau, J.-P Marion, H. Diserens, *Flavour Fragrance J.*, **7**, 313 (1992); *Chem. Abstr.*, **119**, 47888 (1993).

Finally, dimethyl disulfide and diisopropyl disulfide were found in eucalyptus[9a] of the family *Myrtaceae*.



73

1.1.3. Petroleum Oils

The total geological resources of petroleum in the Earth are approximately 9.5 10^{10} tons and the average sulfur content of petroleum is about 1%. This means that the petroleum in the Earth's interior contains approximately 10^9 tons of sulfur or 4-7x10^{10} tons of various organic compounds, such as mercaptans, sulfides, disulfides, thiophenes and other more complicated species.[72] A review article by Boberg[73] and Czogalla presents an impressive list of sulfur compound in fossil fuels. They reported more than 70 different types of organosulfur compounds, from mercaptans to anellated thiophenes, as well as many derivatives.

In petroleum fractions, certain sulfur compounds are dominant with respect to boiling range. The distribution of sulfur compounds is as follows.

Fraction boiling below 150°C: Alkane- and cycloalkanethiols, dialkyl, alkyl cycloalkyl sulfides, disulfides, monocyclic sulfides, thiophenes with one or two short side chains are found.

Fractions with the boiling range 150°C to 250°C: Alkane-, arene- and cycloalkanethiols, dialkyl, alkyl cycloalkyl, and alkyl aryl sulfides, polysulfides, mono-, bi-, and tricyclic sulfides, thiaindanes, thiophenes with up to four short side chains and thiophenes with one anellated ring are present here.

Fraction boiling above 250°C: Thiophenes, isothiaindanes, dithienyls, thiochinolones, thiazoles, allenated thiophenes with higher molecular weight have been reported.

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72 a) D. N. Harpp, J. Roberstson, K. Laycock and D. Butler, *Sulfur Reports*, **4**, 1995 (1985); b) G. F. Bolshakov, *Sulfur Reports*, **5**, 103 (1986).

73 C.-D. Czogalla and F. Boberg, *Sulfur Reports*, **3**, 121 (1983).

Although organosulfur components in petroleum oils can be deleterious in a number of ways[74] (catalyst poisoning, metal corrosion, undesirable color, deposit formation in engines), these materials have been found to be extremely useful in various applications in industry.[75,72]

Rubber is cured with vulcanization initiators among which disulfides play an important role. For example, 2,2'-di(benzothiazolyl)disulfide is able to undergo decomposition by a radical mechanism and vulcanizes rubber even in the absence of sulfur.[72] Phenol disulfides are used as vulcanizing agents in the rubber and adhesive industries. These products are highly effective in imparting heat and aging resistance properties to rubber. The major uses of these products include the manufacture of chlorobutyl rubber and inner-liner for tires, as well as white sidewall construction and off-road tires.[76]

Disulfides are also used for the extraction of metals such as gold and palladium. They are very active floatation agents of copper-nickel and copper-molibdenic sulfide ores.[72] SULFA-HITECH is a dimethyl disulfide-based sulfur solvent used to dissolve sulfur deposited in the production strings of sour gas wells. Other proposed uses include the dissolution of sulfur in sour-gas pipelines and in refineries and chemical plant flowlines.[76]

Additives play an important role in industrial oils, transmission fluids and turbine lubricants. They are added to refined base oils -generally petroleum oil, but sometimes synthetic fluids- to enhance detergency, dispersancy, wear protection, acid neutralization, and frictional properties. In this way, additive-treated lubricants contribute to longer equipment life, lower maintenance and improve field performance.[77] The antiwear agents that form a protective film on engine parts and then reduce wear are usually alkyl

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74 a) J. C. Morrell, W. L. Benedict, and J. Egloff, *Ind. Eng. Chem.*, **28**, 122 (1936); b) L. R. sheppard, *World Oil*, **129**, 193 (1949); c) W. K. Meerbott, A. H. Cherry, B. Chernoff, J. Crocoll, J. D. Heldman, and C. J. Kaemmerlen, *Ind. Eng. Chem.*, **46**, 2026 (1954).

75 a) G. H. Denison and P. C. Condit, *Ind. Eng. Chem.*, **37**, 1102 (1945); b) E. B. Greenhill, *J. Inst. Petrol.*, **34**, 659 (1948); c) R. B. Thompson, R. G. Druge, and J. A. Chemicek, *Ind. Eng. Chem.*, **41**, 2715 (1949).

76 Elf Atochem NA, Inc., King of Prussia, Pennsylvania, private communication.

77 R. W. Bruce, *Fundamentals of Lubrication*, **Societey of Tribologists and Lubrication Engineers**, Lubrication Education course (1989).

polysulfides[78] (a mixture of di-, tri-, and tetrasulfide). The same alkyl polysulfides are used to decrease copper corrosion.[79] Finally, organic polysulfides (mainly disulfides) have been investigated[77, 80] as antioxidant additives to prevent or control the oxidation of oil. Disulfide oxidation has been widely studied[81] and is discussed in the next section. A number of intermediate oxidation products, as well as products from side reactions have been identified by isolation under carefully controlled oxidation conditions, the ultimate product being the corresponding sulfonic acid.

1.2. Oxidized Derivatives of Disulfides

1.2.1. Monoxide Derivative of Disulfides (Thiosulfinates)

Cavallito and coworkers[82] were pioneers in the field of thiosulfinate ester chemistry. They first isolated and characterized allicin **(74)** (allyl 2-propene-1-thiosulfinate) from common garlic (*Allium sativuum*) and also prepared other alkyl thiosulfinates. Since then, many groups of researchers have been interested by the biological,[83] antitumor,[84] anti viral[82b,85] and anti fungal[82c,86] activities of this class of

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78 E. F. Arretz, G. T. Carroll, R. T. Clark, **Eur. Pat. Appl. EP 529,388** (1993).

79 E. F. Perozzi, A. G. Papay, **U.S. Patent 5,174,922** (1992).

80 a) M. S. Kharasch, A. Fono, and W. Nudenburg, *J. Org. Chem.*, **15**, 748 (1950); b) A. J. Bridgewater and M. D. Sexton, *J. Chem. Soc., Perkin II*, 530 (1978).

81 a) F. Freeman, *Chem. Rev.*, **64**, 117 (1984); b) H. J. Coleman, R. L. Hopkins, and C. J. Thompson, *Int. J. Sulfur Chem., B (Quart. Rept.)*, **6**, 42 (1971).

82 a) C. J. Cavallito and J. H. Bailey, *J. Am. Chem. Soc.*, **66**, 1950 (1944); b) C. J. Cavallito, J. S. Buck and C. M. Suter, *J. Am. Chem. Soc.*, **66**, 1952 (1944); c) L. D. Small, J. H. Bailey and C. J. Cavallito, *J. Am. Chem. Soc.*, **69**, 1710 (1947).

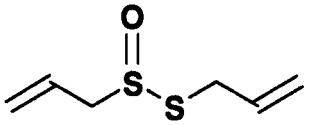
83 a) A. Kato and M. Numata, *Tetrahedron Lett.*, 203 (1972); b) H. Yanagawa, T. Kato and Y. Kitahara, *Tetrahedron Lett.*, 1173 (1973).

84 a) A. S. Weisberger and J. Pensky, *Science*, **126**, 1112 (1957); b) A. S. Weisberger and J. Pensky, *Cancer Res.*, **18**, 1801 (1958); c) A. F. Hirsch, C. Piantadori and J. L. Irvin, *J. Med. Chem.*, **8**, 10 (1965).

85 E. D. Wills, *Biochem. J.*, **63**, 514 (1956).

86 R. M. Dodson, V. Srinivasan, K. S. Sharma and R. F. Sauers, *J. Org. Chem.*, **37**, 2367 (1972).

compounds. Murray and coworkers[87] have studied the possibility of in *vivo* photo oxidation of the disulfide bond of key peptides such as insulin and α-lipoic acid (**6**), to their corresponding thiosulfinates. The low stability of such molecules may have an important role in various metabolites. Thiosulfinates have also been used in chemical industry as antioxidants and stabilizers[88] as mentioned in the previous section.



74

Since the discovery of allicin, a few other naturally occurring thiosulfinates have been reported,[26a,83,89] most of them bearing the 1,2-dithiolane 1-oxide moiety such as β-lipoic acid[90] which is the 1-oxide derivative of **6**. Very recently, (+)-leinamycin (**75**) was isolated from a culture of broth of *Streptomyces sp.*. Its total synthesis as well as its antitumor activity have been reported.[91]

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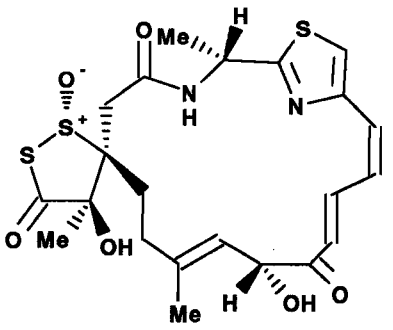
87 a) R. W. Murray, R. D. Smetana and E. Block, *Tetrahedron Lett.*, 299 (1971); b) R. W. Murray, and S. L. Jindal, *Photochem. Photobiol.*, **16**, 147 (1972); c) R. W. Murray, and S. L. Jindal, *J. Org. Chem.*, **37**, 3516 (1972).

88 a) D. Barnard, L. Bateman, E. R. Cole and J. I. Cunneen, *Chem. Ind. (London)*, 918 (1958); b) D. Barnard, L. Bateman, M. E. Cain, J. Colclough and J. I. Cunneen, *J. Chem. Soc.*, 5339 (1961); c) L. Bateman, M. E. Cain, J. Colclough and J. I. Cunneen, *J. Chem. Soc.*, 3570 (1962); d) J. I. Cunneen and D. F. Lee, *J. Appl. Polym. Sci.*, **8**, 699 (1964); e) A. Rahman and A. Williams, *J. Chem. Soc., B*, 1391 (1970).

89 a) A. Kato and T. Okutani, *Tetrahedron Lett.*, 2959 (1972); b) G. Pattenden and A. J. Shuker, *Synlett.*, 717 (1991).

90 a) E. L. Patterson, J. A. Brockman, Jr., F. P. Day, J. V. Pierce, M. E. Macchi, C. E. Hoffman, C. T. O. Fong, E. L. R. Stokstad and T. H. Jukes, *J. Am. Chem. Soc.*, **73**, 5919 (1951); b) J. A. Brockman, Jr., E. L. R. Stokstad, E. L. Patterson, J. V. Pierce and M. E. Macchi, *J. Am. Chem. Soc.*, **76**, 1827 (1954).

91 Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, **115**, 8451 (1993); and references cited therein.



75

The main characteristic of this class of compounds is their unusual reactivity that often leads to complex product mixtures as well as their low stability that has always been a problem in the study of their chemistry. Recently, a few detailed reviews[92] have been devoted to the chemistry of thiosulfinates. Thus, only the highlights and the recent advances will be described in this section.

1.2.2. Formation of Thiosulfinates

Sulfenic acids are generally quite reactive and only a few are stable at room temperature. Extensive studies[93] on this class of compound have shown that unlike common acids, the anhydride form of sulfenic acids (which has the thiosulfinate structure)[94] is thermodynamically favored (**equation 1**). As a result, most of the reactions that involve the formation of sulfenic acids lead to the isolation of the corresponding thiosulfinate.[95]

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92 a) E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3921 (1974); b) N. Isenberg and M. Grdinic, *Int. J. Sulfur. Chem.*, **8**, 307 (1973); c) J. L. Kice and J. P. Cleveland, *J. Am. Chem. Soc.*, **95**, 109 (1973); d) P. L. Folkins, Ph.D. Thesis, McGill University, 1991; e) J. J. Hoyle, *The Chemistry of Sulfinic Esters and their Derivatives*, S. Patai, Ed., New York: John Wiley and Sons Ltd., Chapt. 4 (1990).

93 a) F. A. Davis, S. Q. A. Rizvi, R. Ardecky, D. J. Gosciniak, A. J. Friedman, S. G. Yocklovich, *J. Org. Chem.*, **45**, 1650 (1980); b) W. S. Allison, *Acc. Chem. Res.*, **9**, 293 (1976); and references cited therein.

94 E. Vinkler and F. Klivenyl, *Acta. Chim. Acad. Sci. Hung.*, **11**, 15 (1957); *Chem Abstr.*, **52**, 6242 (1958).

95 a) N. Kharasch, S. J. Petempa, and H. L. Wehrweister, *Chem. Rev.*, **39**, 269 (1946); b) H. J. Backer, *Recl. Trav. Chim. Pays-bas.*, **70**, 95, 99 (1951); c) H. J. Backer, *Recl. Trav. Chim. Pays-bas.*, **71**, 418 (1952); e) T. C. Bruice and A. B. Sayigh, *J. Am. Chem. Soc.*, **81**, 3416 (1959); d) T. Zinke and K. Eismayer, *Chem. Ber.*, **51**, 751 (1981).

$$2\ RSOH \longrightarrow RS(=O)\text{-}SR + H_2O \qquad \text{(eq. 1)}$$

Peracid oxidation of disulfides[96] is the best method for the preparation of symmetric thiosulfinates. Kinetic studies[97] have shown that a lone pair of electrons on the disulfide attacks the electrophilic peroxy acid oxygen. Comparative studies[97,98] using a variety of disulfides have concluded that electronic effects are more important than steric effects. However, the peroxidation of unsymmetric disulfides results generally in a mixture of the two thiosulfinates by a lack of regioselectivity.[92,99] This synthetic procedure is very efficient for alkyl and cyclic disulfides[82c,99,100] but gives relatively low yields in case of diaryl disulfides. Very recently, the synthesis and X-ray of the first isolable dithiiranes, 3-(1,1,3,3-tetramethyl-4-oxo-4-phenylbutyl)-3-phenyldithiirane-1-oxide[101] **(76)**, was reported. Oxidation of the sulfoxide of bicyclic 1,3-dithiethane **77** using a large excess of Oxone[102] afforded **76** in 57% yield.

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96 W. E. Savigne and J. A. Maclaren, *The Chemistry of Organic Sulfur Compounds*, vol. 2, Eds., N. Kharasch and C. Y. Meyers, Chap. 15, Pergamon Press, London, p. 367.

97 G. Leandri and A. Tundo, *Ann. Chim. (Rome)*, **44**, 74 (1954).

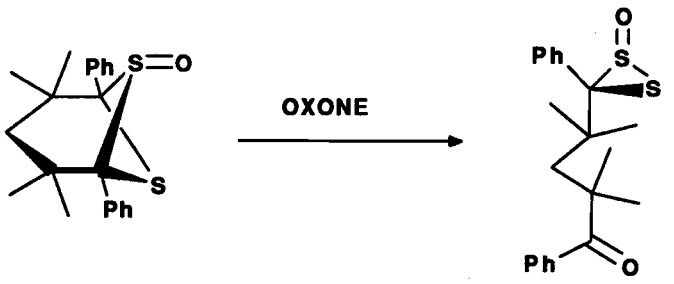
98 W. Walter and P. M. Hell, *Justus Liebigs Ann. Chem.*, **727**, 35, 50 (1969).

99 a) S. Oae, T. Kataka and Y. H. Kim, *Bull. Chem. Soc. Jpn.*, **55**, 2484 (1982); b) A. K. Bhattacharya and A. G. Hortman, *J. Org. Chem.*, **43**, 2728 (1978).

100 a) A. Schöberl, H. Thausent and H. Graefje, *Angew. Chem.*, **68**, 213 (1956); b) W. E. Savigne, J. Eager, J. A. Maclaren and C. M. Roxburgh, *Tetrahedron Lett.*, 3289 (1964); c) P. Allen, Jr. and J. W. Brook, *J. Org. Chem.*, **27**, 1019 (1962); d) N. Isenberg and H. F. Herbrandson, *Int. J. Sulfur Chem.*, A, **1**, 179 (1971); e) D. N. Harpp and A. Granata, *Synthesis*, 782 (1978); f) S. Oae and T. Takata, *Tetrahedron lett.*, **21**, 3213 (1980).

101 A. Ishii, T. Akazawa, M.-Z. Ding, *J. Am. Chem. Soc.*, **115**, 4914 (1993).

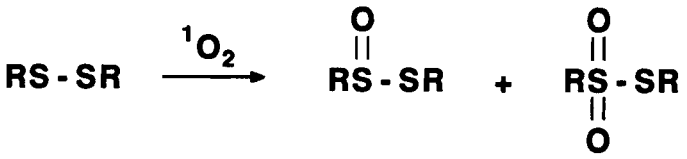
102 a) W. Adam, R. H. Curci, J. O. Edwards, *Acc. Chem. Res.*, **22**, 205 (1989); b) R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989).



77 **76**

Different inorganic oxidizing agents such as periodate,[103] permanganate,[103b,c] persulfate[104] and dinitrogen tetroxide[105] have been reported to be efficient in the conversion of disulfides to thiosulfinates. However, this procedure requires the use of cyclic disulfides, otherwise cleavage of the S-S bond takes place leading to a mixture of thiosulfonates.[100]

The generation of singlet oxygen ($^1O_2$) by the photosensitization of molecular oxygen or use of triphenylphosphite ozonide, allows the conversion of symmetrical disulfides to the corresponding thiosulfinates and a small amount of thiosulfonates[87,106] **(equation 2).**



(eq. 2)

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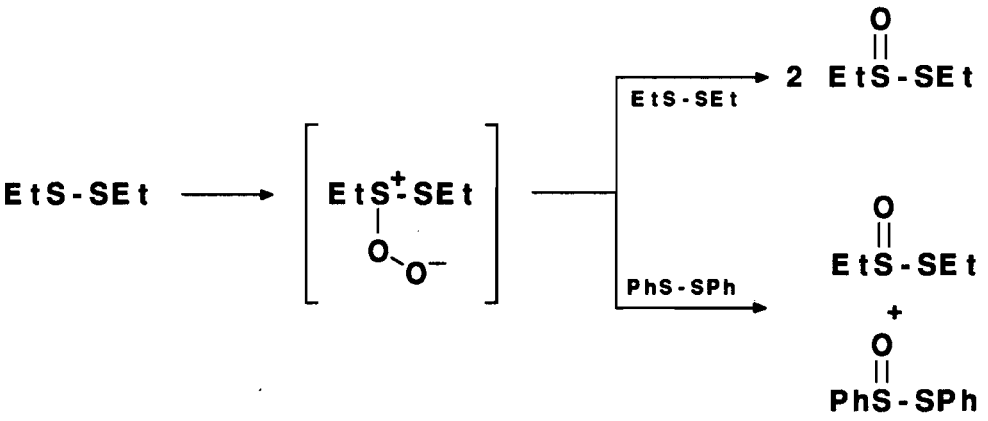
103 a) L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1970); b) S. Tamagaki, H. Hirota and S. Oae, *Bull. Chem. Soc. Jpn.*, **46**, 1247 (1973); c) S. Oae, T. Nabeshima and T. Takada, *Heterocycles*, **18**, 41 (1982); d) B. J. Evans, D. J. Takahashi, W. K. Musher, *Phosphorus, Sulfur Silicon Relat. Elem.*, **73**, 5 (1992).

104 a) M. Calvin, H. Grizaback and R. C. Fuller, *J. Am. Chem. Soc.*, **77**, 2659 (1955); b) G. Bergson, *Acta Chem. Scand.*, **15**, 1611 (1961).

105 S. Oae, Y. H. Kim, T. Takata, and D. Fukushima, *Tetrahedron Lett.*, 1195 (1977).

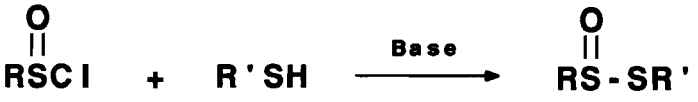
106 a) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954); b) M. Calvin, H. Grizaback, and R. C. Fuller, *J. Am. Chem. Soc.*, **77**, 2659 (1955); c) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969); d) F. E. Stary, S. L. Jindal, and R. W. Murray, *J. Org. Chem.*, **40**, 58 (1975).

Mechanistic studies[107] using an equimolar mixture of two symmetric disulfides reveal that 0.5 equivalents of oxidizing agent convert the initial mixture into the corresponding thiosulfinate mixture (**Scheme 1**). The fact that no S-S bond cleavage was observed, confirmed the possibility of a peroxy intermediate as reported in the photo oxidation of sulfides.[108] A parallel study[92a] revealed that the regioselectivity of photo oxidation was controlled by steric effects. This oxidation technique was applied to alkyl and aryl disulfides,[92a,87c] cystine and its derivatives[109] as well as α-lipoic acid.[106d]



SCHEME 1

The main problems of the direct oxidation of disulfides are the lack of regiospecificity when unsymmetric disulfides are used and the formation of by-products such as thiosulfonates which are not always easy to separate. The most general method of preparing thiosulfinate esters[110] is to react a sulfinyl chloride with thiols in the presence of base such as a tertiary amine (**equation 3**).



(eq. 3)

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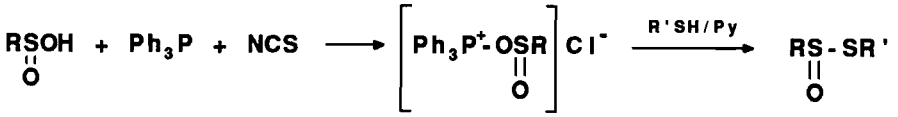
107 a) J.-J. Liang, C.-L. Gu, M. L. Kasher, C. S. Foote, *J. Am. Chem. Soc.*, **105**, 4717 (1983); b) W. Ando and T. Takata, *Singlet O_2*, Vol. III, Ed., A. A. Frimer, Chap. 1, CRC Press, Florida, (1985).

108 a) Y. Watanabe, N. Kuriki, K. Ishiguro and Y. Sawaki, *J. Am. Chem. Soc.*, **113**, 2677 (1991); b) K. Nahm, Y. Li, J. D. Evanseck, K. N. Houk and C. S. Foote, *J. Am. Chem. Soc.*, **115**, 4879 (1993); c) C. Schöneich, A. Aced and K.-D. Asmus, *J. Am. Chem. Soc.*, **115**, 4879 (1993).

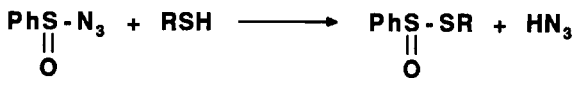
109 W. E. Savigne, J. A. Maclaren, *Org. Sulfur Compd.*, **2**, 367 (1966).

110 H. J. Backer and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas.*, **73**, 129 (1954).

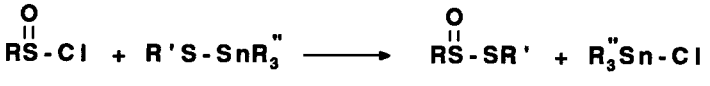
Similar procedures have been reported using sulfinic acid and triphenylphosphine in the presence of *N*-chlorosuccinimide[111] **(equation 4)**, benzenesulfinyl azide and thiols[112] **(equation 5).** Treatment of sulfinyl chlorides with organotin mercaptides gives thiosulfonates in excellent isolated yield[113] **(equation 6).**



(eq. 4)



(eq. 5)



(eq. 6)

The regiospecificity of these different techniques is very high and there is no limitation of the R and R' group. Finally, there is almost no formation of by-products which can be crucial in the synthesis of some thiosulfinates.

1.2.3. Stability and Reactivity of Thiosulfinates

As mentioned previously, most of the thiosulfinates studied are rather unstable. However, cyclic thiosulfinates do not decompose as easily as illustrated by compound **78**[114] which is stable up to 166°C. The determination of the sulfur-sulfur bond energy of two thiosulfinates (36 kcal mol^{-1} for diphenyl derivative[115] and 46 kcal mol^{-1} for the dimethyl derivative[116]) has shown that the introduction of an oxygen atom on one of the

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111 a) M. Furukawa, T. Ohkawara, Y. Yagushi, M. Isoda and T. Hitoshi, *Synthesis*, 937 (1980); b) Y. Nogushi, M. Isoda, K. Kuroki, and M. Furukawa, *Chem. Pharm. Bull.*, **30**, 1646 (1982).

112 T. J. Maricichi and C. N. Angeletakis, *J. Org. Chem.*, **49**, 1931 (1984).

113 D. N. Harpp, T. Aida and T. H. Chan, *Tetrahedron Lett.*, 24, 5173 (1983).

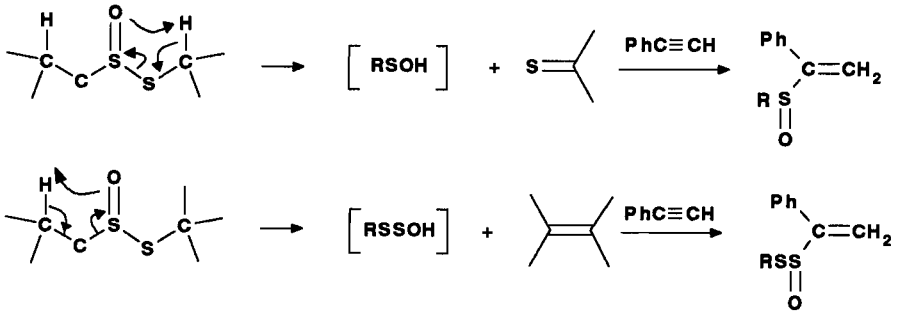
114 F. Wudl, R. Gruber, and A. Padwa, *Tetrahedron Lett.*, 2133 (1969).

115 P. Koch, E. Ciuffarin and A. Fava, *J. Am. Chem. Soc.*, **92**, 5971 (1970).

116 E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3929 (1974).

sulfur atoms of the disulfide bond leads to a bond energy decrease by 20 to 30 kcal mol^{-1}. Kice[117] suggested this was due to the high stability of the thiosulfinic radical ($RS(=O)^{\cdot} \leftrightarrow RS^{\cdot}(=O)$). These results were confirmed by parallel investigations[118] of differently oxidized derivatives of several disulfides. In all cases, it appears that the thiosulfinate has the longest S-S bond of the series. Block and O'Connor[116] also found a direct correlation between the bulkiness of alkyl thiosulfinates and their stability.

As stated already, the decomposition of thiosulfinates was first thought to be a simple disproportionation. However, detailed studies have shown that the mechanism is much more complicated. Block and O'Connor[116] have shown that when hydrogen atoms are present on the carbon α to the sulfenyl sulfur or the carbon β to the sulfinyl sulfur cyclo-elimination reactions can take place **(Scheme 2)**. Using acetylenes as trapping agents, they showed that the formation of alkanesulfenic acid intermediates were favored and gave α,β unsaturated sulfoxides **(equation 7)**. However, when no hydrogen atom was available on the carbon α to the sulfenic sulfur, the reaction proceeded through the alkanethiosulfoxilic acid intermediate **(equation 8)**.



SCHEME 2

For thiosulfinate esters that can not undergo cyclo-elimination such as aryl thiosulfinates, a disproportionation was postulated to proceed *via* a homolytic chain

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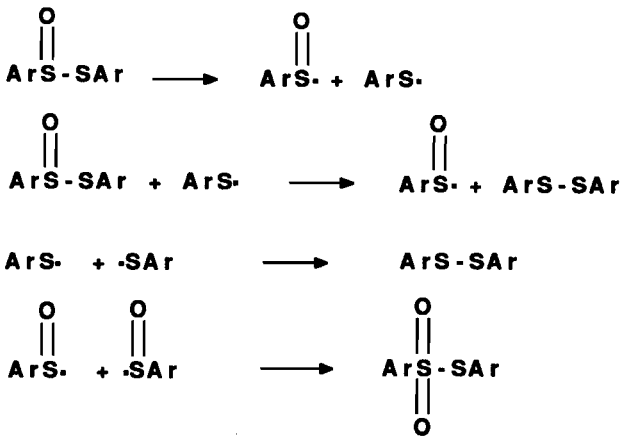
117 J. L. Kice, *Sulfur in Organic and Inorganic Chemistry*, A. Senning, Ed., New York: Marcel Dekker, Vol. 1, Chap. 6 (1971).

118 a) J. H. Noordik and A. Vos, *Recl. Trav. Chim. Pays-Bas*, **86**, 156 (1967); b) C. Th. Kiers and A. Vos, *Recl. Trav. Chim. Pays-Bas*, **91**, 126 (1972); c) G. H. Wahl, Jr., J. Bordner, D. N. Harpp and J. G. Gleason, *J. Chem. Soc., Chem. Commun.*, 985 (1972); d) G. H. Wahl, Jr., J. Bordner, D. N. Harpp and J. G. Gleason, *Acta Cryst., Sect. B*, **28**, 2272 (1973); e) C. Th. Kiers and A. Vos, *Recl. Trav. Chim. Pays-Bas*, **97**, 166 (1978).

mechanism starting by S-S bond cleavage (**Scheme 3**).[116,119] Detailed kinetic studies using optically active and oxygen-18 labelled phenyl benzenethiosulfinate confirmed this homolytic mechanism.[92c,120]



SCHEME 3

The hydrolysis of thiosulfinates under alkaline conditions has been investigated in detail. The main controversy consists over whether the hydroxide ion attacks the sulfinyl or the sulfenic sulfur.[121] A careful study of the rearrangement products of the hydrolysis of unsymmetric thiosulfinates as well as ^{18}O tracer experiments carried out by Oae and coworkers,[122] favor an attack at the sulfinyl sulfur in agreement with the hard and soft acids and bases ("HSAB") theory.[123]

Further studies[122b] of the reactivity of thiosulfinates have shown that these compounds can be alcoholized to the corresponding sulfinate in the presence of various catalysts such as iodine, bromine or hydrogen chloride (**equation 9**).

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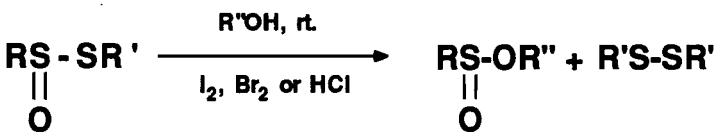
119 a) L. Senatore, E. Ciuffarin and A. Fava, *J. Am. Chem. Soc.*, **92**, 3035 (1970); b) P. Koch, E. Ciuffarin and A. Fava, *Int. J. Sulfur Chem., C*, **6**, 167 (1971).

120 a) J. L. Kice and G. B. Large, *Tetrahedron Lett.*, 3537 (1965); b) W. E. Savigne and A. Fava, *J. Chem. Soc., Chem. Commun.*, 417 (1965); c) J. L. Kice and G. B. Large, *J. Am. Chem. Soc.*, **90**, 4069 (1968).

121 a) S. Oae, Y. Yoshikawa and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **42**, 2899 (1969); b) S. Oae, K. Nomura, Y. Yoshikawa and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **42**, 2903 (1969); c) J. L. Kice and T. E. Rogers, *J. Am. Chem. Soc.*, **96**, 8009, 8015 (1974).

122 a) S. Oae, T. Takata, Y. H. Kim, *Tetrahedron Lett.*, 4219 (1977); b) T. Takata and S. Oae, *Bull. Chem. Soc. Jpn.*, **55**, 3937 (1982).

123 R. G. Pearson and S. Søngstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).



(eq. 9)

Similar investigations using several nucleophiles have shown that thiosulfinates can be converted to a variety of sulfoxides by Grignard reactions.[124] Using superoxide anion radicals,[125] the reaction afforded potassium sulfinate and sulfonate along with the symmetrical disulfide. Finally, thiosulfinates react with secondary amines, enamines and cyanide ion.[126]

1.3. Oxidation of Thiosulfinate Esters

The oxidation of disulfides and thiosulfinates affords the following oxidized derivatives of disulfides; namely thiosulfinates (**79**), *vic*-disulfoxides (**80**), thiosulfonates (**81**), sulfinyl sulfones (**82**) and *vic*-disulfones (**83**). Although alkyl, aryl and some cyclic derivatives of compounds **79** and **81-83** have been isolated, characterized and studied in terms of chemical properties,[94,110,115,127] there has always been a considerable controversy about the existence of *vic*-disulfoxides.

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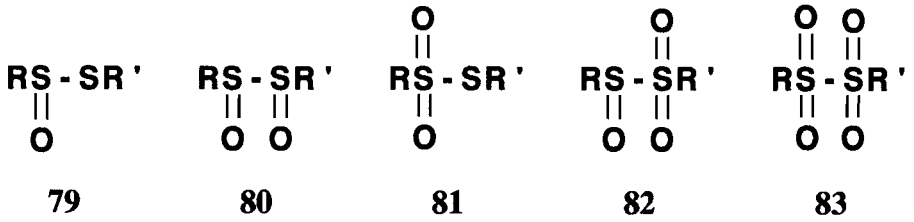
124 L. Sagramora, P. Koch, A. Garbesi and A. Fava, *J. Chem. Soc., Chem. Commun.*, 985 (1967).

125 S. Oae and T. Takata, *Bull. Chem. Soc. Jpn.*, **54**, 2712 (1981); and references therein.

126 M. Furukawa, S. Tsuji, Y. Kojima, S. Hayashi, *Chem. Pharm. Bull.*, **21**, 2391 (1973); and references cited therein.

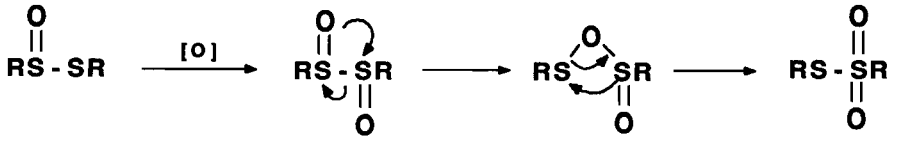
127 a) S. Smiles, D. T. Gibson, *J. Chem. Soc.*, **125**, 176 (1924); b) J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1331 (1951); c) H. Bredereck, A. Wagner, H. Beck, and R. G. Klein, *Ber. Dtsch. Chem. Ges.*, **93**, 2736 (1951); d) P. Allen, Jr., and J. W. Brook, *J. Org. Chem.*, **27**, 1019 (1962); e) J. L. Kice and N. E. Pawlowski, *J. Am. Chem. Soc.*, **86**, 4898 (1964); f) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **88**, 5236 (1966); g) G. C. Denzer, Jr. P. Allen, Jr. P. Conway, and J. M. Van Der Veen, *J. Org. Chem.*, **31**, 3418 (1966); h) J. L. Kice and K. Ikura, *J. Am. Chem. Soc.*, **90**, 7378 (1968); i) J. L. Kice, C. G. Venier, G. B. Large, and L. Heasley, *J. Am. Chem. Soc.*, **91**, 2028 (1969); j) J. L. Kice and N. Favstritsky, *J. Org. Chem.*, **35**, 114 (1970); k) L.-P. O. Farng and J. L. Kice, *J. Am. Chem. Soc.*, **103**, 1137 (1981); l) F. Freeman and C. N. Angeletakis, *J. Org. Chem.*, **47**, 4194 (1982).



79 **80** **81** **82** **83**

As described previously, nucleophilic attack of thiosulfinates should take place at the sulfinyl sulfur, and the more electron rich sulfenyl sulfur should be the preferred site of peroxy acid oxidation according to the "HSAB" theory.[123] Thus, since the beginning of the century,[128] it has been believed that the result of the electrophilic oxidation of thiosulfinates should be the corresponding *vic*-disulfoxides.[128-137] However, the only compound isolated from such reactions has always been the corresponding thiosulfonates although evidence of the elusive *vic*-disulfoxides were recently reported by low temperature spectroscopy using alkyl, aryl and cyclic thiosulfinates.[92d,81]

Although the *vic*-disulfoxide intermediate had been proposed to explain various biological reactions in the late 30's,[128] Barnard[129] was actually the first to try to isolate *vic*-disulfoxides. Reacting benzenesulfinyl chloride with zinc, he isolated phenyl benzylthiosulfonate rather than the expected *vic*-disulfoxide. The electrophilic oxidation of differently substituted thiosulfinates was studied by kinetics[130] and a direct concerted isomerization of *vic*-disulfoxides to thiosulfonates was suggested by Modena and coworkers **(equation 10)**.



(eq. 10)

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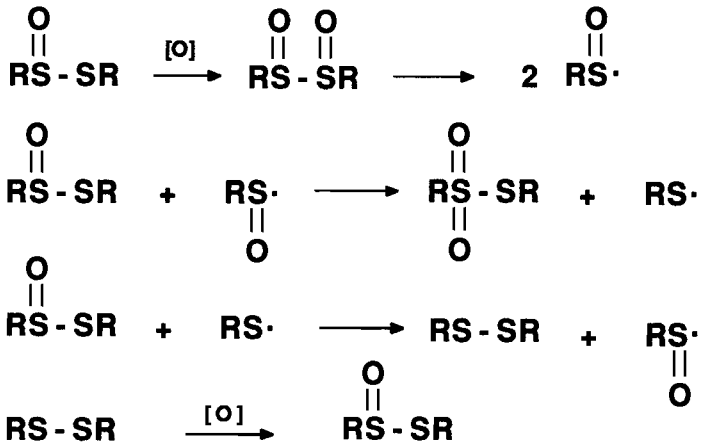
128 a) T. F. Lavigne, G. Toennies, and E. D. Wagner, *J. Am. Chem. Soc.*, **56**, 242 (1934); b) T. F. Lavigne, *J. Biol. Chem.*, **113**, 583 (1936); c) G. Toennies, T. F. Lavigne, *J. Biol. Chem.*, **113**, 571 (1936); d) G. Medes and N. Floyd, *Biochem. J.*, **31**, 1330 (1939); e) R. Emilozzi and L. Pichat, *Bull. Soc. Chim. Fr.*, 1887 (1959).

129 D. Barnard, *J. Chem. Soc.*, 4673 (1957).

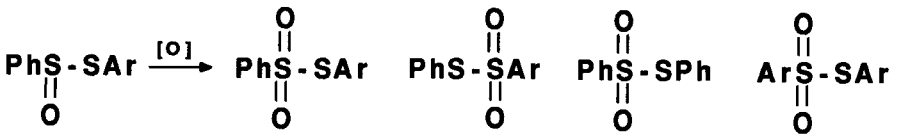
130 a) U. Marangeli, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.*, **90**, 681 (1960); *Chem. Abstr.*, **55**, 16510i (1961); b) G. Modena and P. E. Todesco, *Ric. Sci.*, **30**, 1788 (1960); *Chem. Abstr.*, **55**, 16510f (1961).

Barnard and Percy[131] proposed that *vic*-disulfoxides were formed but collapsed immediately through a homolytic cleavage of the S-S bond giving the corresponding thiosulfonates and disulfides (**Scheme 4**). Product analysis, kinetic studies, use of unsymmetrical thiosulfinates as well as ^{35}S labelled experiments and radical detection, ruled out the mechanism previously reported but did not produce clear evidence of *vic*-disulfoxides.



SCHEME 4

Chau and Kice[132] studied the electrophilic oxidation of some fluoro-arylthiosulfinates at -20°C using low temperature ^{19}F NMR spectroscopy. Although they were unable to identify any trace of *vic*-disulfoxide and disulfide (which disagree with the Barnard proposal), the product analysis suggested that at least 25% of the oxidation was taking place at the sulfinyl sulfur. The other 75% were following the expected formation of the *vic*-disulfoxide which could immediately give sulfinyl radicals leading finally to a mixture of two symmetric and two unsymmetric thiosulfonates (**equation 11**).

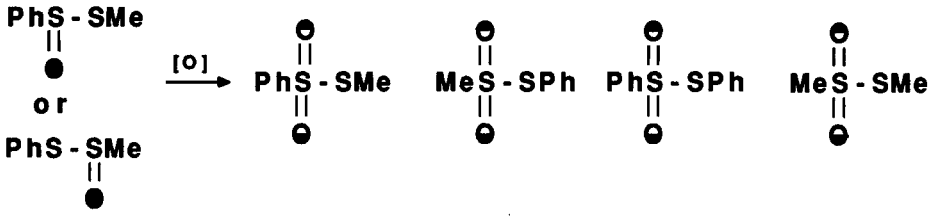


(eq. 11)

131 D. Barnard and E. J. Percy, *Chem. Ind. (London)*, 1332 (1960).

132 M. M. Chau and J. L. Kice, *J. Am. Chem. Soc.*, **98**, 7711 (1976).

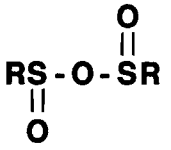
More concrete evidence of the formation of *vic*-disulfoxides during the oxidation of unsymmetric disulfides and thiosulfinates was given by Oae and coworkers.[105,133] A very interesting study based on product analysis, ^{18}O tracer experiments and a ^{1}H NMR study, confirmed the mechanism proposed by Chau and Kice. Although they did not observe any *vic*-disulfoxide, they suggested a homolytic cleavage of the S-S bond, followed by a head-to-tail recombination of the different sulfinyl radicals to give the four stable thiosulfonates **(equation 12)**.



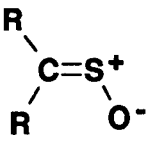
(eq. 12)

^{18}O = ●

The major breakthrough in this field of sulfur chemistry was undoubtedly the investigation of the peroxy acid oxidation of symmetric alkyl thiosulfinates at low temperature carried out by Freeman and coworkers.[134] Using ^{13}C and ^{1}H NMR, they were able to identify the diastereomeric signals of various alkyl *vic*-disulfoxides at -40°C. Upon warming to room temperature, they also detected sulfinic anhydride **84** and sulfine **85** derivatives. In this case, no thiosulfonate was observed at -40°C, which proved that the oxidation of alkyl thiosulfinates takes place exclusively at the sulfenyl sulfur. The fact that part of the oxidation of the aryl thiosulfinates occurred at the sulfinyl sulfur can be explained by the conjugation of the aryl moiety with a lone pair of electrons of the sulfenyl sulfur, thus decreasing its electron density.[134b]



84

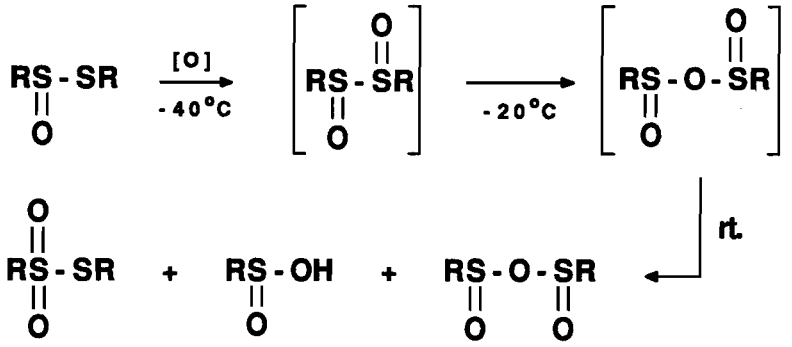


85

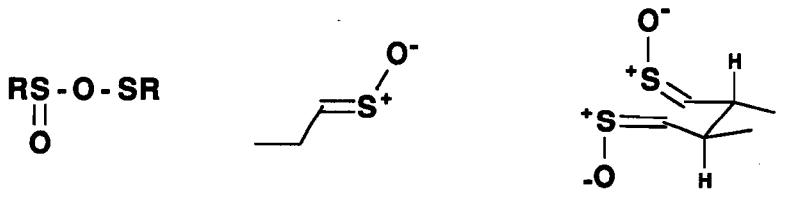
133 S. Oae, T. Takata, Y. H. Kim, *Bull. Chem. Soc. Jpn.*, **55**, 2484 (1982).

134 a) F. Freeman, C. N. Angeletakis, and T. J. Maricichi, *Tetrahedron Lett.*, **22**, 1867 (1981); b) F. Freeman, C. N. Angeletakis, *J. Org. Chem.*, **46**, 3981 (1981); c) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc.*, **103**, 6232 (1981); d) F. Freeman, C. N. Angeletakis, W. J. Pietro, and W. J. Hehre, *J. Am. Chem. Soc.*, **104**, 1161 (1982); e) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc.*, **104**, 5766 (1982); f) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc.*, **105**, 4039 (1983).

Freeman and Angeletakis[134f] proposed various heterolytic mechanisms to explain the thermal decomposition of alkyl *vic*-disulfoxides. In all cases, cyclo-elimination and hydrolysis of the *vic*-disulfoxides and sulfinic anhydrides were suggested to explain the formation of the decomposition products (**Scheme 5**). *O,S*-Sulfenyl sulfinates (**86**) were proposed as intermediates in most of these decomposition mechanisms. Recently, Block and Bayer[135] carefully reinvestigated the first naturally occurring sulfine (**87**) from the onion as well as the first bis(thial *S*-oxide) (**88**). The formation of compound **88** involves the rearrangement of a *vic*-disulfoxide and confirms the mechanism proposed by Freeman which was also supported by theoretical calculations.[134a] The difference in the decomposition mechanisms of aryl *vic*-disulfoxides and alkyl *vic*-disulfoxides was explained as described previously for the decomposition of thiosulfinates.



SCHEME 5



86 **87** **88**

The oxidation of cyclic thiosulfinates has also been reported. Using low temperature NMR, Folkins and Harpp[136] reported clear evidence for the formation of *vic*-disulfoxides (**89**) from the peroxy acid oxidation of bridged bicyclic thiosulfinates (**90**).

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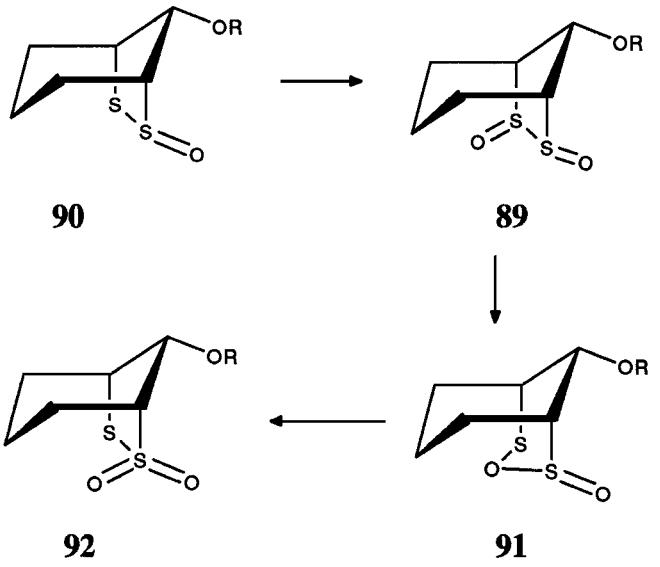
135 E. Block and T. Bayer, *J. Am. Chem. Soc.*, **112**, 4584 (1990); and references cited therein.

136 a) P. L. Folkins, D. N. Harpp, *J. Am. Chem. Soc.*, **113**, 8998 (1991); b) P. L. Folkins, D. N. Harpp, *J. Am. Chem. Soc.*, **115**, 3066 (1993).

A thermal decomposition study of **89** from -30°C to room temperature as well as careful analysis of the decomposition products allowed the detection of intermediates such as *O,S*-sulfenyl sulfinates (**91**) up to room temperature. The mechanism proposed involves the exclusive formation of *vic*-disulfoxides such as **89**, homolytic cleavage of the S-S bond, *O,S*-sulfenyl sulfinates (**91**) formation by head-to-tail sulfinyl radical rearrangement and final recombination giving the expected thiosulfonates (**92**) (**Scheme 6**).

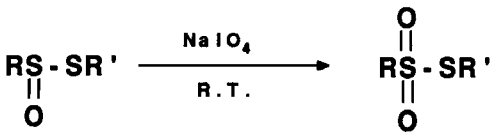


90 **89**

92 **91**

SCHEME 6

Selective oxidation of unsymmetric thiosulfinates to their corresponding thiosulfonates were obtained using various inorganic oxidizing agents such as $NaIO_4$, $NaIO_3$, SeO_2, $KMnO_4$, $NaCl_3$ and N_2O_4, the best results being obtained with periodate.[100f,137] Product analysis as well as comparison with electrophilic oxidizing agents clearly revealed a nucleophilic oxidation without any S-S bond fission, under mild acid catalytic conditions and in quantitative yield (**equation 13**). Oxidation of a mixture of symmetric disulfides gave an unexpected mixture of the four symmetric and unsymmetric thiosulfonates for unknown reasons.[137a]



(eq. 13)

137 a) Y. H. Kim, T. Takata, and S. Oae, *Tetrahedron Lett.*, 2305 (1978); b) S. Oae, D. Fukushima, and Y. H. Kim, *Chem. Lett.*, 297 (1978); c) T. Takata, Y. H. Kim, and S. Oae, *Bull. Chem. Soc. Jpn.*, **54**, 1443 (1981).

CHAPTER 2. SYNTHESIS AND OXIDATIVE REACTIVITY OF POLYSULFIDES

2.1. Synthesis of Polysulfides

The previous chapter illustrated the crucial role of polysulfides in industry, agriculture, and medicine. The increasing need of obtaining higher synthetic efficiency and enhanced bioactivity has led to the synthesis of a wide variety of polysulfides in order to mimic, enhance and understand their natural properties.

Nowadays, many different synthetic methods[138] have been developed for the preparation of symmetric and unsymmetric polysulfides. However, due to the variety of the cases studied, none of these procedures has been found to be universal for various reasons such as availability and preparation of the reagents, relatively long reaction times, difficulty of the work-up of the reaction mixtures, toxicity problems, lack of selectivity and low yields. Therefore, new techniques are still under study to minimize such disadvantages.

2.1.1. Synthesis of Symmetric and Unsymmetric Disulfides

The preparation of symmetric alkyl and aryl disulfides is commonly achieved in good yield by oxidation of the corresponding thiols[139] using a variety of oxidizing agents and conditions depending on the applications.

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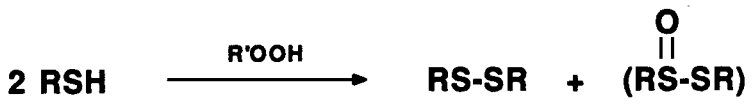
138 a) H. A. Reid, *Organic Chemistry of Bivalent Sulfur*, 3, Chemical Publishing Co., New York, p. 362 (1960); b) D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem.*, 1, 211 (1971); c) K. D. Gundermann and K. Humke, *Houben-Weyl. Methoden Der Organischen Chemie*, Ed., G. Thieme Verlag, p. 129 (1985).

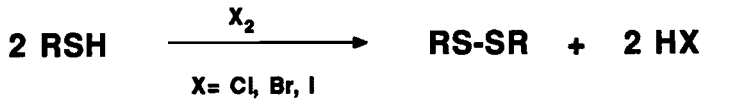
139 G. Capozzi and G. Modena, *The Chemistry of the Thiol Group*, Pt. 2, S. Patai, Ed., New York: John Wiley and Sons Ltd., p. 785 (1974).

The use of chemical oxidizing agents has been extensively studied and there is an endless list of various procedures. Peroxidic oxidizing agents[139,140] such as hydrogen peroxide, hydroperoxide and peroxy acids allow the transformation of mercaptans to their corresponding disulfides but further oxidation occurs when using excess oxidant **(equation 14)**.



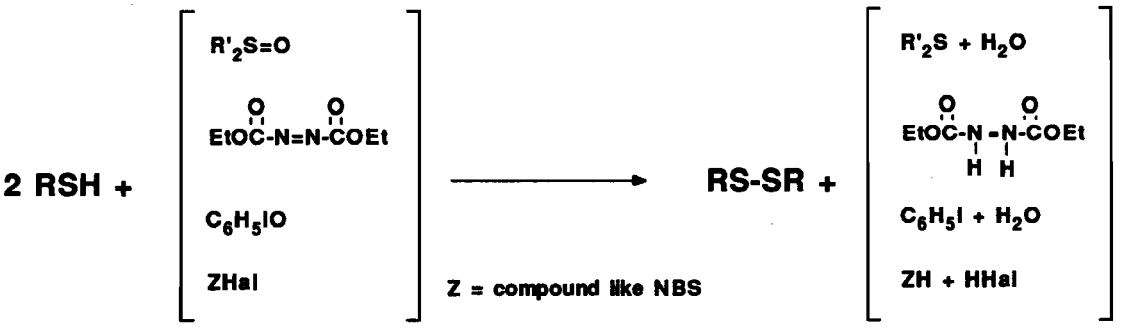
(eq. 14)

Oxidation of thiol by halogens[141] such as chlorine, bromine and iodine has been extensively used and excess of halogen leads to the formation of the trihalide ($R\text{-}S\text{-}Hal_3$) derivative **(equation 15)**.



(eq. 15)

A large number of other organic chemical oxidizing agents have been used for the transformation of mercaptans to the corresponding symmetric disulfides. The most common ones are listed in **Scheme 7**.



SCHEME 7

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140 D. S. Tarbell, *Organic Sulfur Compounds*, N. Kharash, Ed., Pergamon Press, New York, **1**, Chapt. 10, p. 97 (1961).

141 a) S. R. Sandler and W. Karo, *Organic Functional Group Preparation*, Academic Press, New York, **III**, p. 142 (1972); b) J. P. Danehy, B. T. Doherty and C. P. Hegan, *J. Org. Chem.*, **36**, 2525 (1971).

The thiol oxidation can also be achieved using metal ions and metal oxides. One of the most common metal ions employed is ferric largely used in the rubber industry.[142] Other metal ions[143] such as cesium, cobalt and vanadium are also employed and such an oxidation probably arose from a chain reaction **(equation 16)**.

$$2\ RSH + 2\ M^{2+} \longrightarrow RS\text{-}SR + 2\ M^{+} + 2\ H^{+} \qquad \textbf{(eq. 16)}$$

Recently, the use of ceric ammonium nitrate was reported to be a mild and efficient method of preparing disulfides.[144] Similarly, oxidation of thiols to disulfides with bis(2,2'-bipyridyl)-copper(II) permanganate produces alkyl and aryl disulfides in almost quantitative yields.[145]

Metal oxides like MnO_2, PbO_2, CrO_3, Fe_2O_3, Co_2O_3, and CuO are also very efficient for the oxidation of thiols to disulfides.[146] Very recently, sodium tellurite was reported[147] as an efficient oxidizing agent for thiols under mild phase-transfer conditions **(equation 17)**.

$$2\ RSH \xrightarrow[r.\ t,\ 1\ h]{Na_2TeO_3,\ Bu_4NaOH/H_2O,\ C_6H_6} RS\text{-}SR \qquad \textbf{(eq. 17)}$$

Thiols can be converted to disulfides on exposure to air or molecular oxygen and this transformation is very sensitive to various catalysts. Kinetic studies using different

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142 B. S. Thyagarajan, *Chem. Rev.*, **58**, 439 (1958).

143 a) J. Hill and A. McAuley, *J. Chem. Soc.*, 2405 (1968); b) J. Hill and A. McAuley, *J. Chem. Soc.*, 156 (1968); c) W. F. Pickering and A. McAuley, *J. Chem. Soc.*, 1173 (1968).

144 D. N. Dhar and A. K. Bag, *Indian J. Chem.*, **23B**, 974 (1984).

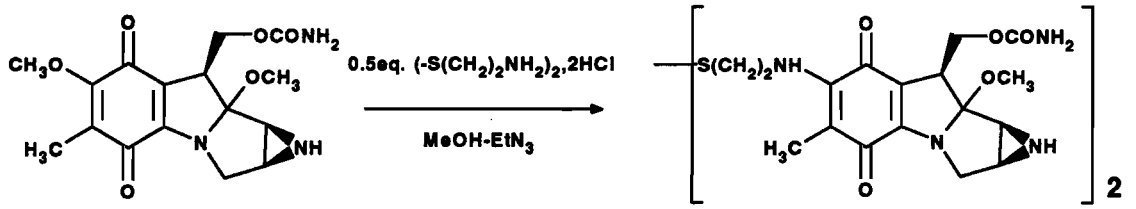
145 H. Firouzabadi, M. Naderi, A. Sardarian and B. Vessal, *Synth. Commun.*, **13**, 611 (1983).

146 a) E. P. Papadopoulos, A. Jarrar and C. H. Issidorides, *J. Org. Chem.*, **31**, 615 (1966); b) T. J. Wallace, *J. Org. Chem.*, **31**, 1217 (1966); c) T. Mukaiyama and T. Endo, *Bull. Chem. Soc. Japan*, **40**, 2388 (1967).

147 H. Suzuki, S.-I. Kawato and A. Nasu, *Bull. Chem. Soc. Japan*, **65**, 626 (1992).

strong bases as catalysts have been thoroughly studied[148] in order to optimize such processes. Aliphatic amines[149] have also been used for the transformation of arylthiols. In basic, aqueous solution, the addition of metal ions greatly enhances the rate of the reaction probably because of co-ordination between the metal ion and molecular oxygen.[139] Finally, organic redox systems such as hydroquinone and p-phenylenediamine in basic medium also catalyze the auto oxidation of thiols to disulfides.[150]

Very recently, the synthesis of disulfide derivatives of mitomycin[151] **(93)** using hydroquinone, gave some compounds that showed remarkable antitumor activity **(Scheme 8).**



93

SCHEME 8

Electrochemical and photochemical oxidation affords another mode of oxidation of thiols to their corresponding disulfides. These two oxidation techniques were very well reviewed in the past[152] **(equation 18 and 19).**

$$2\ RSH \rightleftharpoons RS\text{-}SR + 2\ H^+ + 2\ e^- \qquad \textbf{(eq. 18)}$$

$$2\ RSH \xrightarrow{h\nu} RS\text{-}SR + H_2 \qquad \textbf{(eq. 19)}$$

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148 C. F. Cullis, J. D. Hopton and D. L. Trimm, *J. Appl. Chem.*, **18**, 330 (1968); and references cited therein.

149 A. A. Oswald, F. Noel and A. J. Stephenson, *J. Org. Chem.*, **26**, 3969 (1961).

150 a) G. H. Meguerian, *J. Am. Chem. Soc.*, **77**, 5019 (1955); b) R. H. Rosenwald, *Petrol. Processing*, **11**, 91 (1956).

151 M. Kono, Y. Saitoh, M. Kasai K. Shirahata, M. Morimoto, *J. Antibiotics*, **9**, 1428 (1993).

152 A. R. Knight, *The Chemistry of the Thiol Group*, S. Patai, Ed., New York: John Wiley and Sons Ltd., Chapt. 10, p. 455 (1974).

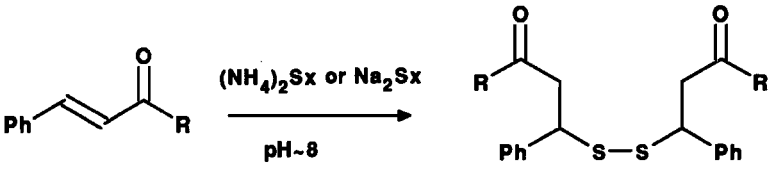
Symmetric disulfides have also been synthesized using different kinds of polysulfide anions.[138] The most common method is the reaction of an alkyl halide with sodium disulfide.[153] Alkyl disulfides are obtained by this reaction in fair yields **(equation 20)**.

$$2\ RBr + Na_2S_2 \longrightarrow RS\text{-}SR + 2\ NaBr \qquad \textbf{(eq. 20)}$$

A novel alkylation with tetrathiotungstates and tetrathiomolybdates afforded a facile route to disulfides from alkyl halides[154] **(equation 21)**.

$$2\ RX + [MS_4] \xrightarrow[M=W \text{ or } M=Mo]{\text{piperidine}} RS\text{-}SR \qquad \textbf{(eq. 21)}$$

Recently, the synthesis of symmetric disulfides from various polysulfide anions and α,β-unsaturated carbonyl compounds was also reported[155] **(equation 22)**.



(eq. 22)

Concerning the preparation of unsymmetric disulfides, the oxidation procedures described previously lack the ability to differentiate thiols. As a result, a 1:2:1 mixture of the three possible disulfides is obtained except in rare cases.[156] However, these oxidation

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153 a) B. Holmberg, *Ann.*, 359 (1908); b) B. Holmberg, *Chem. Ber.*, **43**, 220 (1910).

154 P. Dhar and S. Chandrasekaran, *J. Org. Chem.*, **54**, 2998 (1989).

155 E. B. Krein and Z Aizenshtat, *J. Org. Chem.*, **58**, 6103 (1993).

156 D. T. Mcallan, T. V. Cullum, R. A. Dean and F. A. Fiedler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

reactions are successful for the preparation of cyclic disulfides from dithiols.[157] This is the method of choice for the synthesis of cross-linked disulfide polypeptides.[10,158]

Because of the lack of selectivity in the oxidation of thiols as well as the difficulty of separating a mixture of disulfides, the synthesis of unsymmetric disulfides has mostly been achieved by the reaction of a thiol or a sulfide with sulfenyl derivatives containing a suitable leaving group.[141]

A wide variety of leaving groups have been used since the beginning of the century. Mixed disulfides were first obtained by the reaction of thiols with Bunte salts[159] (**94**). Reactions of sulfenyl halides (**95**) with mercaptides have been reported[160] to be successful in some specific cases. The thiocyanate leaving group (**96**) has been used with or without pyridine.[161] Thiosulfinates (**79**) and thiosulfonates (**81**) give fair yields of disulfides when treated with thiols.[82c,162] More complex leaving groups have been used and higher product purity has been obtained. The reactions of sulfenyl hydrazides (**97**), sulfenyl thioureas (**98**) and sulfenyl thiocarbonates (**99**) with thiols afford the corresponding unsymmetric disulfides.[163] Thiolysis of thiophthalimides (**100**) and thiosuccinimides (**101**) give high yields and high purity of a large series of disulfides.[164]

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157 D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3259 (1970).

158 V. duVigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953).

159 H. B. Footner and S. Smiles, *J. Chem. Soc.*, 2887 (1925).

160 a) I. B. Douglass, F. T. Martin and R. Adder, *J. Org. Chem.*, **16**, 1297 (1951); b) H. Brintzinger and M. Laangheck, *Chem. Ber.*, **86**, 557 (1953); c) H. Brintzinger and H. Schmahl, *Chem. Ber.*, **87**, 314 (1954).

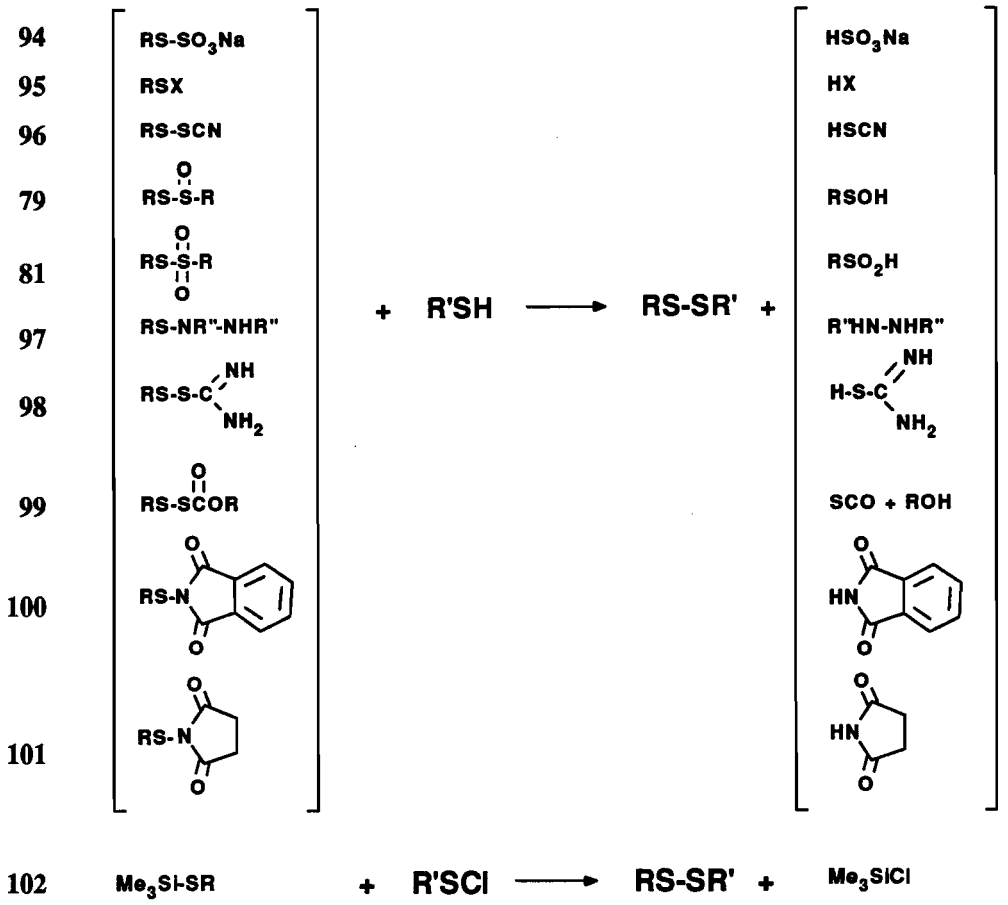
161 a) H. Lechner and M. Wittner, *Chem. Ber.*, **55**, 1474 (1922); b) M. Nakasaki, *J. Inst. Polytech. Osaka City Uni.*, **1**, 1922 (1951).

162 a) A. Schöberl, H. Taussent and H. Grafje, *Ann. Chem.*, **68**, 216 (1956); b) L. Field, T. C. Owen, R. R. Crenshaw and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961); c) L. Field, H. Harle, T. C. Owen and A. Ferretti, *J. Org. Chem.*, **29**, 1632 (1964).

163 a) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968); b) K. Sirakawa, O. Aki, T. Tsujikawa and T. Tsuda, *Chem. Pharm. Bull.*, **18**, 235 (1970); c) S. J. Brois, J. F. Pilot and H. W. Barnum, *J. Am. Chem. Soc.*, **92**, 7629 (1970).

164 a) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. Van Horn and J. P Snyder, *Tetrahedron Lett.*, 3551 (1970); b) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970).

Sulfenyl chlorides **(95)** and thiotrimethylsilanes **(102)** also lead to unsymmetric disulfides.[165] These results are illustrated in **Scheme 9**.



SCHEME 9

More recently, Capozzi and coworkers[166] were able to synthesize aryl and alkyl unsymmetric disulfides by reacting thiosulfinates **(79)** with thiotrimethylsilane **(102)** **(equation 23)**.

(eq. 23)

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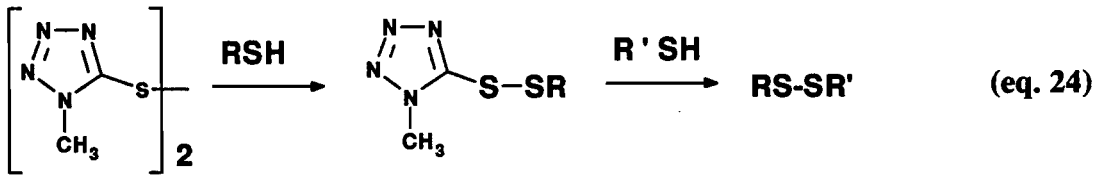
165 D. N. Harpp, B. T. Friedlander, C. Larsen, K. Steliou and A. Stockton, *J. Org. Chem.*, **43**, 3482 (1978).

166 G. Capozzi, A. Capperucci, A. Degl'Innocenti, R. Del Duce and S. Menichetti, *Tetrahedron Lett.*, **30**, 2995 (1989).

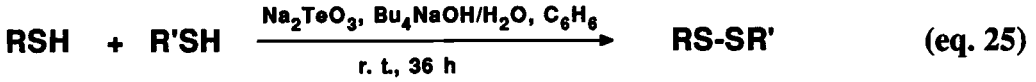
The synthesis of symmetric and unsymmetric disulfides was also reported[167] using bis(1-methyl-1H-tetrazol-5yl) disulfide **(103) (equation 24)**.



(eq. 24)

103

Finally, Suzuki and coworkers[147] used sodium tellurite as a mild and selective oxidizing agent that allows the conversion of aryl and primary alkyl thiols to unsymmetric disulfides **(equation 25)**.



(eq. 25)

As stated earlier, all of these procedures suffer from some disadvantages which range from the availability of the starting materials, the yield and reaction time, to the stability of the final product in the reaction conditions. Hence, the development of new procedures for the synthesis of symmetric and unsymmetric disulfides is still under investigation.

2.1.2. Results and Discussion

In order to study the oxidation of trisulfides (Chapter 3, 4), several symmetric and unsymmetric trisulfides were needed. Facing some problems with the conventional procedures of trisulfide syntheses, a new set of conditions that allowed the facile synthesis of symmetric and unsymmetric trisulfides was developed (see next section). This novel technique was extended to the synthesis of symmetric and unsymmetric disulfides.

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167 M. Ohtani and M. Narisada, *J. Org. Chem.*, **56**, 5475 (1991).

The preparation method that was developed is a modification of the procedures that involve the reaction of sulfenyl halides with mercaptans.[141,160] The general principle is the formation of the sulfenyl chloride (**95**) and the subsequent reaction with a thiol in the presence of pyridine. In all the cases reported,[141,160] **95** was prepared using chlorine gas, purified and then reacted with thiol. The main problems encountered were preparation and stability of compound **95** as well as reactivity of thiols with certain sulfenyl chlorides, not to mention the inconvenience of working with chlorine gas.

The first step of this modified procedure for the preparation of disulfides is the formation of sulfenyl chloride (**95**) which is achieved by a dropwise addition of the first thiol (**R-SH**) to sulfuryl chloride at low temperature (-78°C). The sulfenyl chloride formed is subsequently reacted *in situ* at -78°C by addition of a mixture of the second thiol (**R'-SH**) and two equivalents of pyridine (**equation 26**).

$$\mathrm{RSH} \xrightarrow[-78\,^\circ\mathrm{C}]{\mathrm{SO_2Cl_2}} \underset{\mathbf{95}}{[\mathrm{RSCl}]} \xrightarrow[-78\,^\circ\mathrm{C}\ \textit{in situ}]{\mathrm{R'SH\ pyridine}} \mathrm{RS\text{-}SR'} \qquad \textbf{(eq. 26)}$$

For the preparation of symmetric disulfides, a solution of two equivalents of thiol and pyridine is added to one equivalent of sulfuryl chloride at low temperature and reduced pressure (~300 mm Hg) (**equation 27**).

$$2\ \mathrm{RSH} \xrightarrow[-78\,^\circ\mathrm{C},\ 1\ \mathrm{hour}]{\mathrm{SO_2Cl_2}\ ,\ \mathrm{pyridine}} \mathrm{RS\text{-}SR} \qquad \textbf{(eq. 27)}$$

Sulfuryl chloride is a stronger chlorinating agent than chlorine[168] and reacts almost quantitatively with most thiols. The reaction is carried out at low temperature to avoid the decomposition of the sulfenyl chloride[141] formed and under reduced pressure to remove the sulfur dioxide that evolved. Pyridine is used to enhance the nucleophilicity of the thiol and to trap the acid chloride formed.[169]

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168 W. A. Thaler, W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2069 (1961).

169 W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **97**, 2075 (1968).

The list of the symmetric disulfides **(104)** and the unsymmetric disulfides **(105)** prepared, their NMR characteristics as well as the yields of the reactions is reported in **Table 1**.

Table 1[a]: Disulfides Prepared and Their Characterization Data.

Entry	R-SS-R'	^{1}H NMR ($CDCl_3$) δ ppm	^{13}C NMR ($CDCl_3$) δ ppm	% Yield
118b	***t*-Bu-SS-*t*-Bu**	1.28 (s, 18H)	30.56, 45.97	100
104b	**Trityl-SS-Trityl**	7.29 (m, 30H)	73.51, 126.96, 127.46, 130.57, 143.82	98
104c	**Adm-SS-Adm**	1.68 (m, 6H), 1.85 (m, 6H) 1.91-2.06 (m, 3H)	30.01, 36.11, 43.04, 47.28	94
104d	**Bz-SS-Bz**	3.59 (s, 4H), 7.31 (m, 10H)	43.07 (CH_2), 127.26, 128.32, 129.26, 137.18	100
105a	***t*-Bu-SS-*i*-Pr**	1.25 (d, 6H), 1.29 (s, 9H), 2.86 (sept., 1H)	22.47, 29.92, 41.61, 47.22	92
105b	***i*-Pr-SS-*t*-Bu**	1.24 (d, 6H), 1.28 (s, 9H), 2.85 (sept., 1H)	22.47, 29.92, 41.61, 47.22	83
105c	**Bz-SS-*t*-Bu**	1.38 (s, 9H), 3.97 (s, 2H), 7.32 (m, 5H)	29.65, 45.62 (CH_2), 47.95, 127.31, 128.44, 129.13, 137.26	91

[a] All products are isolated and show single spot tlc and single peak gc.

This one pot synthesis of disulfides is carried out in less than 2 hours. The symmetric disulfides studied were obtained in almost quantitative yield under these conditions. For the preparation of dityrityl disulfide **(104b)** that caused considerable difficulty in the past[170], the use of DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) was necessary. Using pyridine, an equimolar mixture of trityl mercaptan and trityl sulfenyl chloride was obtained probably because of the remarkable stability of the latter.

Unsymmetric disulfides were obtained in fair isolated yields when tertiary and secondary alkyl sulfenyl chlorides were employed. However, when benzylthiol was used as the first thiol, an equimolar mixture of the two symmetrical disulfides was obtained.

170 C. R. Williams, J. Robertson, D. N. Harpp, unpublished results.

This is explained by the fact that under these conditions benzylthiol reacts faster with benzyl sulfenyl chloride than it does with sulfuryl chloride. To solve this problem, benzyl sulfenyl chloride was obtained quantitatively by the reaction of benzyl disulfide and sulfuryl chloride[169] and it was then reacted *in situ* with the second thiol to give **105c (equation 28)**.

$$\text{BzS-SBz} \xrightarrow[\text{r. t.}]{SO_2Cl_2} [\text{BzSCl}] \xrightarrow[\text{r. t.}\quad \textit{in situ}]{\textit{t}\text{-BuSH, pyridine}} \text{BzS-S}\,\textit{t}\text{-Bu} \qquad \text{(eq. 29)}$$

This new set of conditions provides a facile, mild and selective preparation method of disulfides. The main advantages are use of commercial reagents, short reaction times, high yields as a one-pot procedure.

2.1.3. Synthesis of Symmetric and Unsymmetric Trisulfides

Contrary to the synthesis of disulfides, little attention has been devoted to the preparation of trisulfides, although they have numerous applications as shown in Chapter 1.

The synthesis of symmetric trisulfides is relatively facile but the main limitation is the formation of other polysulfides which are often difficult to separate from the product mixture. The usual method of preparation of symmetric trisulfides involves the reaction of two equivalents of thiol with purified sulfur dichloride[171] **(equation 29)**.

$$2\ \text{RSH} + SCl_2 \longrightarrow \text{RS-S-SR} \qquad \text{(eq. 29)}$$

A similar reaction using diimidazolylsulfide instead of sulfur dichloride gives symmetrical trisulfides in good yield and high purity.[172]

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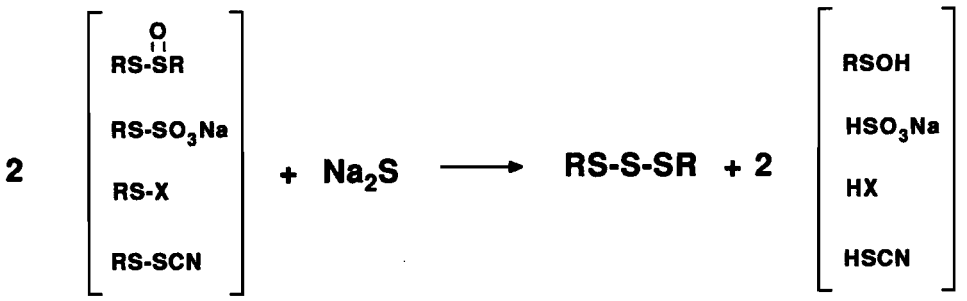
171 A. Schöberl and A. Wagner, *Methoden der Organischen Chemie*, E. Muller, Ed., Stuttgart, **9**, Chapt. 4 (1955).

172 A. Banerji and G. P. Kalena, *Tetrahedron Lett.*, 3003 (1980).

Sodium sulfide has been extensively used. It has been reacted with thiosulfinates[173] (**79**), Bunte salts [174] (**94**) and sulfenyl halides[175] (**95**). Other heavy metal sulfides (PbS, HgS, Ag_2S and Tl_2S) as well as hydrogen sulfide have been employed to convert aryl sulfenyl chlorides, sulfenyl thiocyanates (**96**) and sulfenyl bromides to the desired trisulfides.[176] In all cases, the trisulfide was obtained in relatively pure form (**Scheme 10**).



SCHEME 10

Almost quantitative yields of symmetric trisulfides were reported[78,177] when thiols were oxidized by elemental sulfur using various amines as catalyst (**equation 30**).

(eq. 30)

Recently, a novel method of synthesis of symmetrical trisulfides was developed by Capozzi and coworkers[178] by reacting thiosulfinates (**79**) or thiosulfonates (**81**) with

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173 J. D. Buckman and L. Field, *J. Org. Chem.*, **32**, 454 (1967).

174 a) B. Milligan, B. Saville and J. M. Swan, *J. Chem. Soc.*, 4850 (1961); b) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 2901 (1965).

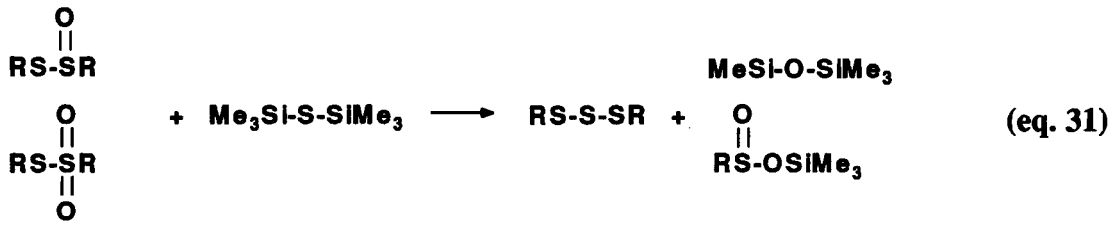
175 a) L. R. M. Pitombo, *Chem. Ber.*, **95**, 2960 (1962); b) H. Brintzinger and M. Laangheck, *Chem. Ber.*, **87**, 325 (1954).

176 H. Lecher, *Chem. Ber.*, **58**, 417 (1925).

177 B. D. Veineyard, *J. Org. Chem.*, **31**, 601 (1966).

178 G. Capozzi, A. Capperucci, A. Degl'Innocenti, R. Del Duce and S. Menichetti, *Tetrahedron Lett.*, **22**, 2991 (1989).

bis(trimethylsilyl)sulfide (**106**). This procedure affords alkyl and aryl trisulfides in yields ranging from 75 to 95% (**equation 31**).



(eq. 31)

106

The formation of symmetric trisulfides has also been reported as a major product in the decomposition study of various organosulfur compounds.[179]

Contrary to the synthesis of symmetrical trisulfides, the unsymmetric variety requires one or more extra steps. Thus, the preparation of cyclic trisulfides generally implies the synthesis of an intermediate which is then converted to the desired cyclic trisulfide. The direct conversion of dithiols to the corresponding trisulfides by straightforward methods leads to a mixture of di- and trisulfides.[180] The first intermediate reported was bis(sulfenyl)thiocarbonate (**107**) which was then decomposed by alkoxide to the cyclic trisulfide[181] (**equation 32**). Other intermediates such as silyl and tin sulfides afford the desired cyclic trisulfides[182] (**equation 33**). Trithiolanes and pentathiepanes have also been prepared by the reaction of an alkene with elemental sulfur.[183] This technique was used in the total synthesis of varacin.[57]

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179 a) L. Field and W. B. Lacefield, *J. Org. Chem.*, **31,** 3555 (1966); b) D. A. Armitage and M. J. Clark, *J. Chem Soc., C*, 2840 (1971); c) D. N. Harpp and A. Granata, *Tetrahedron Lett.*, **35,** 3001 (1976).

180 G. Goor and M. Anteunis, *Synthesis*, 329 (1975).

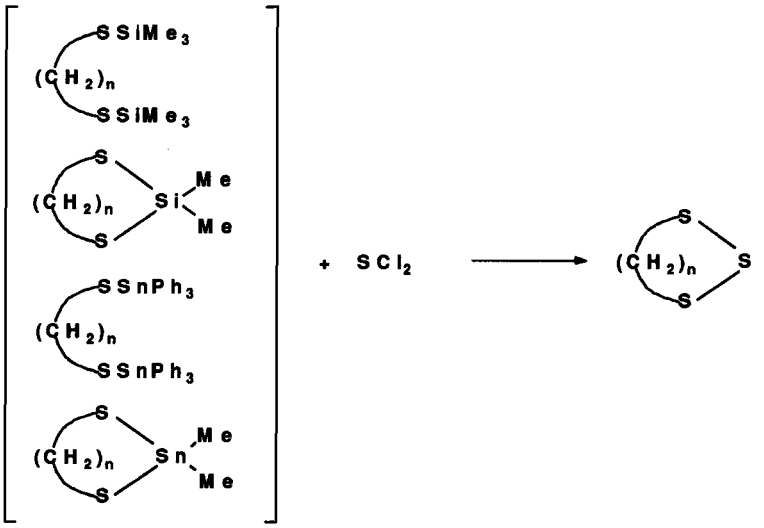
181 D. N. Harpp and A. Granata, *J. Org. Chem.*, **44**, 4144 (1979).

182 N. Yamazaki, S. Nakahama, K. Yamaguchi and T. Yamaguchi, *Chem. Lett.*, 1355 (1980).

183 P. D. Bartlett and T. Ghosh, *J. Org. Chem.*, **52**, 4937 (1987); and references cited therein.

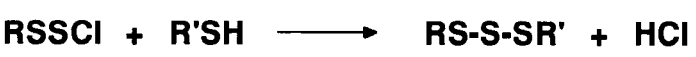
(eq. 32)

107



(eq. 33)

Because of the instability and the difficulties to separate mixed trisulfides,[138a,184] marginal methodologies have been developed for the synthesis of unsymmetric trisulfides. The most common one is the reaction of thiosulfenyl chloride **(108)** with mercaptans[185] **(equation 34)**. However, this procedure is seriously limited because of instability and unavailability of thiosulfenyl chlorides.



(eq. 34)

108

184 T. L. Pickering, K. J. Saunders and A. V. Tobolsky, *J. Am. Chem. Soc.*, **89**, 2364 (1967).

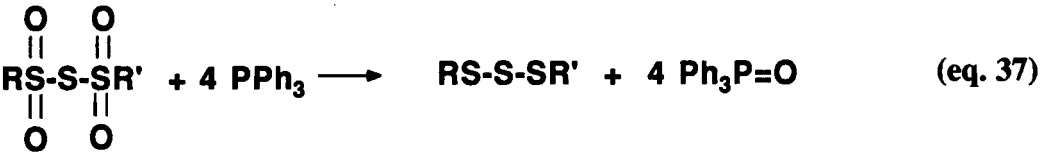
185 a) H. Böhme and G. van Am, *Justus Liebigs Ann. Chem.*, **62**, 617 (1958); b) Z. S. Ariyan and L. A. Wiles, *J. Chem. Soc.*, 1725 (1962); c) C. von Szczepanaski, J. Heindl, E. Schroeder, H. J. Kessler and U. Redmann, *German Patent*, 2114653, (1972); *Chem. Abstr.* **78**, 3942 (1973).

A similar procedure involves the nucleophilic attack of thiols to *N*-arylamidothiosulfite (**109**). Unfortunately, both di- and trisulfides are formed[186] **(equation 35)**.

109

The use of rare hydrodisulfides (**110**) with sulfenyl chloride (**95**) or thiocyanate (**96**) has also been reported[187] **(equation 36)** as well as an awkward desulfurization reaction using dialkyl sulfonic thioanhydrides (**111**) in the presence of triphenylphosphine[188] **(equation 37)**.

110



111

Some years ago, two very useful and general methods for unsymmetrical trisulfide preparation were reported. The first one requires the preparation of stable alkyl or aryl phthalimido disulfides (**112**) which are then converted to the desired trisulfides by the nucleophilic attack of thiols[138b,189] **(equation 38)**. This procedure has been successfully used in the preparation of calicheamicin γ^{I}_{1},[32] although long reaction times (*ca.* 100 h) are usually required for complete conversion when aliphatic thiols are

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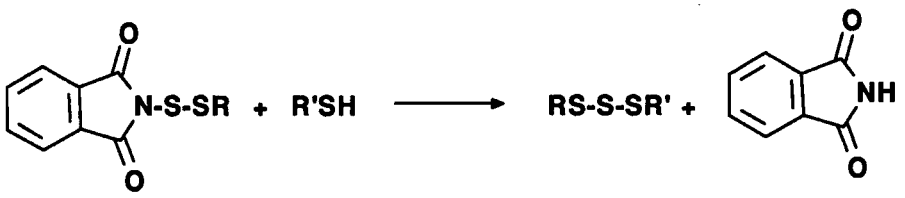
186 G. Kresze and H. P. Patzschke, *Chem. Ber.*, **93**, 380 (1960).

187 T. Nakabayashi and J. Tsurugi, *J. Org. Chem.*, **26**, 2482 (1961).

188 S. Hayashi, M. Furukawa, J. Yamomoto and K. Hamamura, *Chem. Pharm. Bull.*, **15**, 1310 (1967).

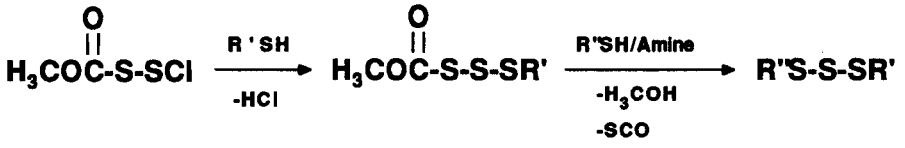
189 A. B. Sullivan and K. Boustany, *Int. J. Sulfur Chem. A*, **1**, 207 (1971).

employed. An effective method was reported in 1984 by Barany[190] which requires the preparation of methoxycarbonyldisulfenyl chlorides (**113**) which are then treated with the requisite mercaptan to afford methoxycarbonyl trisulfides (**114**). While the precursors can generally be prepared in yields of *ca.* 80%, the yields of the next step to give the unsymmetrical trisulfides average about 60% (**equation 39**).



(eq. 38)

112



(eq. 39)

113 **114**

2.1.4. Results and Discussion

As stated earlier for the synthesis of disulfides, a simple method has been developed and it delivers a variety of symmetric (**115**) and unsymmetric (**116**) trisulfides in good overall yield and purity (**Table 2**). The procedure that was used is actually a modification of the previously described[185] nucleophilic attack of thiols to thiosulfenyl chloride (**108**). However, attempts to isolate unsymmetric trisulfides by this technique were reported[138b] to be unsuccessful.

The conditions developed for the synthesis of unsymmetric trisulfides involves the preparation of thiosulfenyl chloride by addition of an equimolar solution of the first thiol (**R-SH**) to a freshly distilled solution of sulfur dichloride at low temperature (-78°C). The reaction mixture is kept at -78°C and a solution of the second thiol (**R'-SH**) and pyridine is added dropwise *in situ*. General work-up affords the desired trisulfide (**Scheme 11**). In most cases studied, no purification is necessary except when the first

190 A. W. Mott and G. Barany, *Synthesis*, 657 (1984).

thiol used is primary. In these cases, chromatography, recrystallization or distillation are used for purification.

SCHEME 11

Apparently, under these specific reaction conditions, the first thiol reacts quantitatively with sulfur dichloride to give a thiosulfenyl chloride which is stable at low temperature. This then reacts with the second thiol to give the unsymmetrical trisulfide. Pyridine is used to trap the hydrogen chloride evolved and to enhance the nucleophilicity of the thiols. *t*-Butyl thiosulfenyl chloride was stable enough to be isolated and characterized at room temperature.[191] This illustrates the quantitative formation of thiosulfenyl chloride in the first part of the synthesis. When the first thiol was primary, some symmetrical trisulfides were formed (up to 20% for *n*-butyl mercaptan **(116d)**). The fact that the only by-products identified were trisulfides suggest that in some cases the thiol reacts faster with the thiosulfenyl chloride formed than it does with the sulfur dichloride.

The same set of conditions was applied to the synthesis of symmetric trisulfides. In this case the procedure is even simpler. Two equivalents of thiol were added dropwise to one equivalent of purified sulfur dichloride in the presence of pyridine and at low temperature (-78°C) **(equation 40)**. General work-up afforded quantitative yields of the various trisulfides **(Table 2)**.

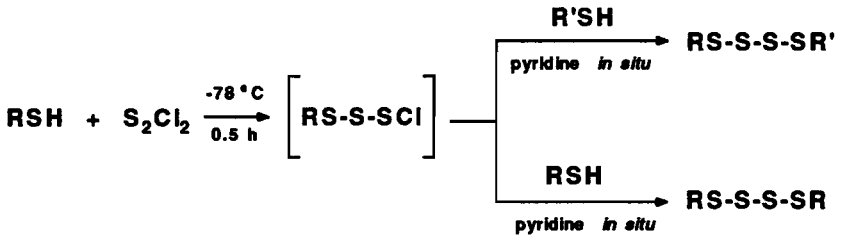
191 E. K. Moltzen and A. Senning, *Sulfur Lett.*, **4**, 169 (1986).

Table 2[a]: Trisulfides Prepared and Their Characterization Data.

Entry	R-SSS-R'	^{1}H NMR ($CDCl_3$) δ ppm	^{13}C NMR ($CDCl_3$) δ ppm	% Yield
115a	***i*-Pr-SSS-*i*-Pr**	1.34 (d, 6H) 3.19 (sept., 1H)	22.44, 41.72	98
115b	***n*-Bu-SSS-*n*-Bu**	0.90 (t, 3H), 1.41 (m, 2H); 1.68 (m, 2H), 2.82 (t, 2H)	13.56, 21.55, 30.75, 38.36	94
115c	***p*-*t*-BuPh-SSS-*p*-*t*-BuPh**	1.33 (s, 18H), 7.42 (AB, 4H)	31.23, 34.63, 126.12, 130.65, 133.11, 151.74	98
115d	**Bz-SSS-Bz**	4.06 (s, 4H), 7.35 (m, 10H)	43.19 (CH_2), 127.64, 128.68, 129.34, 135.58	100
115e	***p*-Cl-Bz-SSS-*p*-Cl-Bz**	3.98, (s, 4H), 7.68 (m, 8H)	42.10 (CH_2), 128.68, 130.66, 133.39, 134.90	100
118c	***t*-Bu-SSS-*t*-Bu**	1.36 (s, 18H)	29.88, 48.91	100
116a	***t*-Bu-SSS-*i*-Pr**	1.35 (d, 6H), 1.36 (s, 9H) 3.19 (sept., 1H)	22.48, 29.85, 41.93, 48.74	96
116b	***t*-Bu-SSS-Bz**	1.39 (s, 9H), 4.11 (s, 2H), 7.35 (m, 5H)	29.82, 43.07 (CH_2), 49.11, 127.33, 128.40, 129.34, 136.43	75[b]
116c	***t*-Bu-SSS-*p*-Cl-Bz**	1.38 (s, 9H), 4.01 (s, 2H), 7.27 (m, 4H)	29.81, 42.12 (CH_2), 49.08, 128.63, 130.62, 133.35, 134.91	57[b]
116d	***n*-Bu-SSS-*p*-Cl-Bz**	0.93 (t, 3H), 1.41 (m, 2H) 1.71 (m, 2H), 2.88 (t, 2H) 3.97 (s, 2H), 7.26 (m, 4H)	13.56, 21.55, 30.76, 38.39, 42.05 (CH_2), 128.61, 130.61, 133.35, 134.90	34[c]
116e	***n*-Bu-SSS-Bz**	0.91 (t, 3H), 1.43 (m, 2H) 1.70 (m, 2H), 2.88 (t, 2H) 4.09 (s, 2H), 7.35 (m, 5H)	13.59, 21.54, 30.76, 39.39, 42.91 (CH_2), 127.38, 128.44, 129.31, 134.69	25[b]
116f	***p*-Cl-Bz-SSS-Bz**	3.90 (s, 2H), 4.04 (s, 2H), 7.30 (m, 9H)	42.07 (CH_2), 43.02 (CH_2), 127.52, 128.53, 128.66, 129.34, 130.65, 133.38, 134.89, 135.60	40[c]

[a].All products are isolated and show single spot tlc and single peak gc; [b].Silica gel chromatography using 5% chloroform/hexanes; [c].Recrystallization from hexanes; [d].Attempted distillation.

This procedure was extrapolated to the synthesis of tetrasulfides **(117)** **(Table 3)**. The only change was the use of freshly distilled sulfur monochloride instead of sulfur dichloride **(equation 41)**. Quantitative yields of di-*t*-butyl tetrasulfide **(117a)** were obtained. However, the synthesis of unsymmetric tetrasulfides led to a mixture of the three possible tetrasulfides. The purification of *t*-butyl-isopropyl tetrasulfide **(117b)** was unsuccessful and the yield was determined by gc analysis.



(eq. 41)

Table 3[a]: Tetrasulfides Prepared and Their Characterization Data.

Entry	R-SSSS-R'	^{1}H NMR ($CDCl_3$) δ ppm	^{13}C NMR ($CDCl_3$) δ ppm	% Yield
118d	***t*-Bu-SSSS-*t*-Bu**	1.38 (s, 9H)	30.16, 49.01	98
117b	***t*-Bu-SSSS-*i*-Pr**	1.37 (d, 6H), 1.38 (s, 9H) 3.24 (sept., 1H)	22.63, 30.12, 41.97, 49.00	30[d]
117c	***p*-Cl-Bz-SSSS-*n*-Bu**	0.93 (t, 3H), 1.42 (m, 2H) 1.72 (m, 2H), 2.92 (t, 2H) 4.08 (s, 2H), 7.30 (m, 4H)	13.60, 21.52, 31.01, 39.03, 42.61 (CH_2), 128.75, 130.71, 133.57, 134.69	43[c]

[a].All products are isolated and show single spot tlc and single peak gc; [b].Silica gel chromatography using 5% chloroform/hexanes; [c].Recrystallization from hexanes; [d].Attempted distillation.

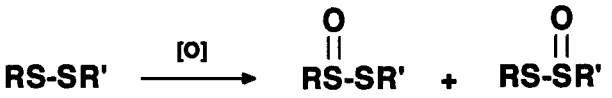
The previous uses of sulfur dichloride to form unsymmetric trisulfides failed in most cases.[138b] The reason of the success of this new set of conditions may be assigned to the *in situ* reaction at low temperature of the thiosulfenyl chloride that avoids its decomposition, to the use of pyridine for reasons stated earlier or possibly to a better quality of the commercially available starting materials.

A major advantage of this procedure[192] is that it is extremely rapid (*ca.* 2 h), does not require the isolation of intermediates and permits the reaction to take place in one vessel in yields comparable or even better than the one reported[138b] using previously described methods.

2.2. Oxidative Reactivity of Alkyl Polysulfides

2.2.1. Introduction

In order to study the decomposition of oxidized derivatives of trisulfides (Chapter 4), some samples of oxidized unsymmetric trisulfides were needed. Facing some problems of regiospecificity in the peracid oxidation of unsymmetric trisulfides, the oxidative reactivity of alkyl polysulfides was further investigated by trying to quantify the influence of the electronic and steric effects on the oxidation of alkyl polysulfides **(equation 42)**.



(eq. 42)

To our knowledge, few similar studies have been reported. Block and O'Connor[92a] oxidized a mixture of two unsymmetric alkyl disulfides. Using peroxy acid as the oxidizing agent, they found that the more electron rich sulfur was predominantly oxidized. Photo-oxidation of the same mixture revealed that the less hindered sulfur was predominantly oxidized. The comparison of these two modes of oxidation showed that the peroxy acid oxidation was controlled by electronic effects while the photo-oxidation appeared to be mainly influenced by steric effects. Careful analysis of the ratio of the two regioisomeric thiosulfinates permitted the quantification of the electronic effect in the case of peroxy acid oxidation and the steric effect for the photo-oxidation. These results

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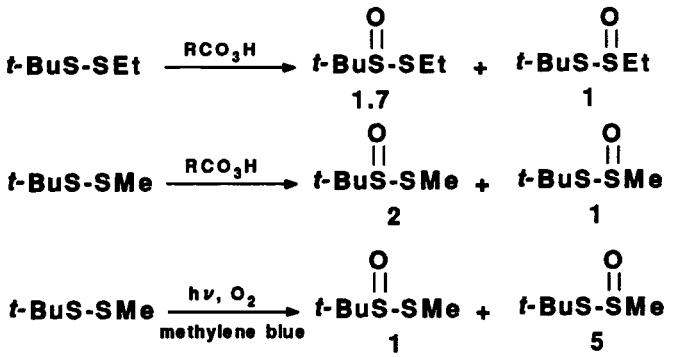
192 The work described on p. 41-52 has been accepted for publication: G. Derbesy and D. N. Harpp, *Tetrahedron Lett.*, **35**, 0000 (1994), in press.

are summarized in **Scheme 12**. Similar experiments have been also reported using unsymmetric deuterated methyl disulfides.

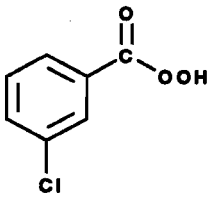


SCHEME 12

The present study focuses on the peroxy acid oxidation of equimolar mixtures of symmetrical alkyl polysulfides. As reported by Block and coworkers,[92a] the steric effect does not significantly influence the regioselectivity of the oxidation. The electronic effect can be assigned to either the number of sulfurs of the polysulfides studied (mono-, di-, tri- or tetrasulfides) or the electron donating ability of the alkyl group chosen. These two factors have first been studied separately and then compared in various cases.

2.2.2. Sulfur Chain-Length Effect

The first part of the study concerns the influence of the number of sulfur atoms on the rate of oxidation of the alkyl polysulfide which will be called "sulfur chain-length effect". To avoid the interference due to the electronic and the steric effects of the alkyl groups attached to the sulfur-chain, all the examples chosen are di-*t*-butyl polysulfides **118**. The oxidizing agent used is *m*-chloroperbenzoic acid (*m*-CPBA) (**119**).



119

To measure this sulfur chain-length effect, an equimolar mixture of di-*t*-butyl sulfide, di-*t*-butyl disulfide, di-*t*-butyl trisulfide and di-*t*-butyl tetrasulfide was oxidized using 1/4 equivalent of *m*-CPBA. Under these conditions, only one of the di-*t*-butyl polysulfides could be 100% oxidized to its corresponding 1-oxide derivative. ^{1}H NMR and ^{13}C NMR spectroscopy of the reaction mixture allowed the identification of the final products and the determination of the ratios of 1-oxide derivatives **120** formed. The percentages of the compound found in the reaction mixture are listed in **Table 4**.

Table 4: di-*t*-Butyl Polysulfides Oxidation with 1/4 Equivalent of *m*-CPBA

Entry	Compounds	Before Oxidation (%)[a]	After Oxidation (%)[a]	% 1-Oxide Formed[b]
118a	*t*-Bu-S-*t*-Bu	25	3	
118b	*t*-Bu-SS-*t*-Bu	23	22	
118c	*t*-Bu-SSS-*t*-Bu	26	26	
118d	*t*-Bu-SSSS-*t*-Bu	26	26	
120a	*t*-Bu-S(O)-*t*-Bu	0	22	88
120b	*t*-Bu-S(O)S-*t*-Bu	0	1	4.3
120c	*t*-Bu-S(O)SS-*t*-Bu	0	<1	<4
120d	*t*-Bu-S(O)SSS-*t*-Bu	0	<1	<4

[a] Percentages were calculated from ^{1}H NMR integration; [b] The percentage of 1-oxide formed is the relative ratio of **120** after oxidation to the corresponding **118** before oxidation.

A sample calculation is as follows. The relative percentage of each polysulfide before oxidation was derived from the quantities mixed (eg.: 100 x Number of moles of **118a** / Total number of moles of **118a+118b+118c+118d**). After oxidation, the percentages of unreacted polysulfides and 1-oxide formed were calculated from the relative integration of each one on ^{1}H NMR (100 x Integral of **118a** / Total integration). The percentage of 1-oxide formed is the relative ratio of **120** after oxidation to the corresponding **118** before oxidation (e.g.: % of **120a** formed = 100 x 22 / 25 = 88). These values were then reported in the corresponding Graph.

Table **4** shows that di-*t*-butyl sulfide reacts much faster than the other polysulfides under peroxy acid oxidation conditions (it was estimated to be at least 20 times faster than di-*t*-butyl disulfide). However, it is impossible from these data to determine the difference in reactivity between the other polysulfides. For these reasons, the same equimolar mixture of di-*t*-butyl polysulfides was oxidized with 1 equivalent of *m*-CPBA. This experiment should have given complete transformation of all the

polysulfides to their 1-oxide derivatives. However, the formation of di-*t*-butyl sulfone (**121**) was observed and a clear difference in the reactivity of di-, tri- and tetrasulfide was measured (**Table 5**).

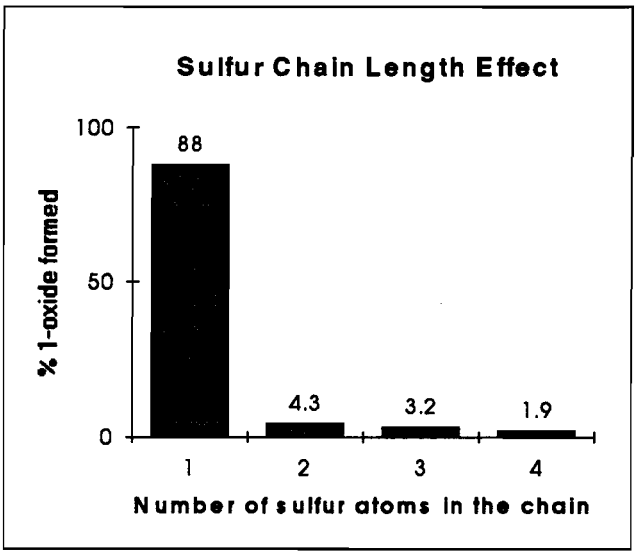
Table 5: di-*t*-Butyl Polysulfides Oxidation with 1 Equivalent of *m*-CPBA

Entry	Compounds	Before Oxidation (%)[a]	After Oxidation (%)[a]	% 1-Oxide Formed[b]
118a	*t*-Bu-S-*t*-Bu	26	0	
118b	*t*-Bu-SS-*t*-Bu	25	1	
118c	*t*-Bu-SSS-*t*-Bu	25	7	
118d	*t*-Bu-SSSS-*t*-Bu	24	14	
120a	*t*-Bu-S(O)-*t*-Bu	0	16	-
120b	*t*-Bu-S(O)S-*t*-Bu	0	24	96
120c	*t*-Bu-S(O)SS-*t*-Bu	0	18	72
120d	*t*-Bu-S(O)SSS-*t*-Bu	0	10	42
121	*t*-Bu-$S(O)_2$-*t*-Bu	0	10	-

[a]. Percentages were calculated from ^{1}H NMR integration; [b].The percentage of 1-oxide formed is the relative ratio of **120** after oxidation to the corresponding **118** before oxidation.

From these two sets of data it is obvious that the reaction is controlled by the electronic effects rather than steric effects because the very hindered di-*t*-butyl sulfide is oxidized much faster than the other di-*t*-butyl polysulfides. Increasing the number of sulfur atoms decreases the reactivity of the external sulfur. In addition, 10% of di-*t*-butyl sulfone (**121**) is formed which shows that di-*t*-butyl sulfoxide (**120a**) reacts as fast as di-*t*-butyl tetrasulfide (**118d**) under peroxy acid oxidation conditions.

Graph 1 summarizes the preceding data on the oxidative reactivity of di-*t*-butyl polysulfides by the consideration of the data in Tables **4** and **5**. Table **4** gives the estimated 20 fold factor between the oxidative reactivity of di-*t*-butyl sulfide and di-*t*-butyl disulfide. The results presented in Table **5** permit the quantification of the difference in reactivity of di-*t*-butyl di-, tri- and tetrasulfide. These data are then processed to be consistent with those of Table **4**.



GRAPH 1: % 1-oxide formed vs # of sulfurs

From this graph it is clear that di-*t*-butyl sulfide reacts much faster than any other di-*t*-butyl polysulfide. The difference between the di-, tri- and tetrasulfide is much smaller and diminishes as the number of sulfur atoms increases. These results were somewhat expected[92c] and qualitatively agree with those reported by Field and Foster[193] in their study of the metaperiodate oxidative reactivity of cyclic sulfides and disulfides. However, although they have shown that the cyclic sulfide was the only compound oxidized, no data were available on the peroxy acid oxidative reactivity of a series of dialkyl polysulfides.

2.2.3. Alkyl Substitution Effect

The second part of this study concerns the electron donating ability of the alkyl group of the polysulfides that will be called "alkyl substitution effect". The main objective is to measure the influence of the substitution of the alkyl group (primary, secondary or tertiary) on the peroxy acid oxidative reactivity of various symmetric dialkyl disulfides (**118b, 122, 104d**). Alkyl disulfides are chosen because they present an average reactivity (previous section) and the oxidizing agent is *m*-CPBA (**119**).

In the present study, an equimolar mixture of di-*t*-butyl disulfide, diisopropyl disulfide and benzyl disulfide is oxidized by 1/3 equivalents of pure *m*-CPBA. Under these conditions, only one of the disulfides could be 100% oxidized to its corresponding 1-oxide derivative. ^{1}H NMR and ^{13}C NMR spectroscopy of the reaction mixture allowed

193 L. Field and C. H. Foster, *J. Org. Chem.*, **35**, 749 (1970).

the identification of the final products and the determination of the ratios of 1-oxide derivatives (**120b, 123b-c**) formed. The percentages of all the compounds found in the reaction mixture are listed in **Table 6**.

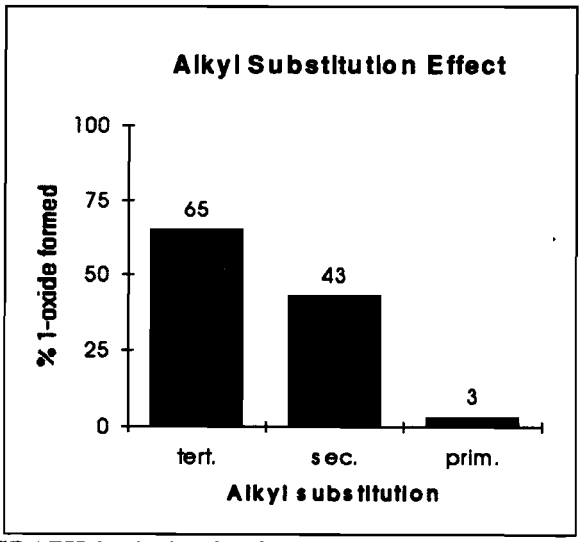
Table 6: Alkyl Disulfides Oxidation with 1/3 Equivalent of *m*-CPBA

Entry	Compounds	Before Oxidation (%)[a]	After Oxidation (%)[a]	% 1-Oxide Formed[b]
118b	*t*-Bu-SS-*t*-Bu	34	12	
122	*i*-Pr-SS-*i*-Pr	30	17	
104d	Bz-SS-Bz	36	35	
120b	*t*-Bu-S(O)S-*t*-Bu	0	22	65
123b	*i*-Pr-S(O)S-*i*-Pr	0	13	43
123c	Bz-S(O)S-Bz	0	1	3

[a] Percentages were calculated from ^{1}H NMR integration; [b] The percentage of 1-oxide formed is the relative ratio of thiosulfinate **123** after oxidation to the corresponding disulfide before oxidation.

The analysis of these results shows that steric hindrance is not a major factor because the oxidation takes place predominantly at the sulfur adjacent to the more hindered alkyl group. It is also clear that the electron-donating ability of the alkyl groups controls the oxidative reactivity of the disulfides because under these conditions, benzyl disulfide (**104d**) is barely oxidized.

Graph 2 summarizes the preceding data on the oxidative reactivity of dialkyl disulfides. Correction factors for deviation from a perfect 1:1:1 ratio of disulfides (**118b, 122, 104d**) were applied by using the percentage of 1-oxide formed as data for the y axis.

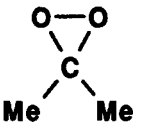


GRAPH 2: % 1-oxide formed vs alkyl substitution

Graph 2 clearly shows that di-*t*-butyl disulfide (**118b**) is oxidized around 1.5 times faster than isopropyl disulfide (**122**) which reacts at least 10 times faster than benzyl disulfide (**104d**). These results were not expected and indicate the importance of the electron donating ability of the alkyl group which greatly influences the nucleophilicity of the adjacent sulfur. This study might be very useful for the synthesis of unsymmetric 1-oxide dialkyl polysulfides by peroxy acid oxidation of the corresponding polysulfides (**equation 42**).

2.2.4. Comparison of the two Effects

The third part of this study is the comparison of the sulfur chain-length effect and the alkyl substitution effect. It is of interest to know which is more important and under which circumstance. This can be achieved by comparing the oxidative reactivity of the opposite extreme compounds of two separate categories; for example a tertiary disulfide *vs* a primary sulfide. The oxidizing agents used are *m*-CPBA (**119**) and dimethyl dioxirane (**124**).



124

In the present study, an equimolar mixture of di-*t*-butyl disulfide (**118b**) and benzyl sulfide (**125**) is oxidized with 1/2 equivalent of *m*-CPBA so that only one of these two compounds could be 100% oxidized. The same reaction was repeated using an equimolar mixture of di-*t*-butyl trisulfide (**118c**) and benzyl disulfide (**104d**). The two previously described reactions were repeated using dimethyl dioxirane instead of *m*-CPBA as oxidizing agent to confirm that the peroxy acid used[92c] did not significantly influence the ratios of final products.

In all four experiments, ^{1}H NMR and ^{13}C NMR spectroscopy of the reaction mixtures allowed the identification of the final products and the determination of the ratios of 1-oxide derivatives (as previously detailed). The percentage of each compound found in the reaction mixtures are listed in **Table 7**.

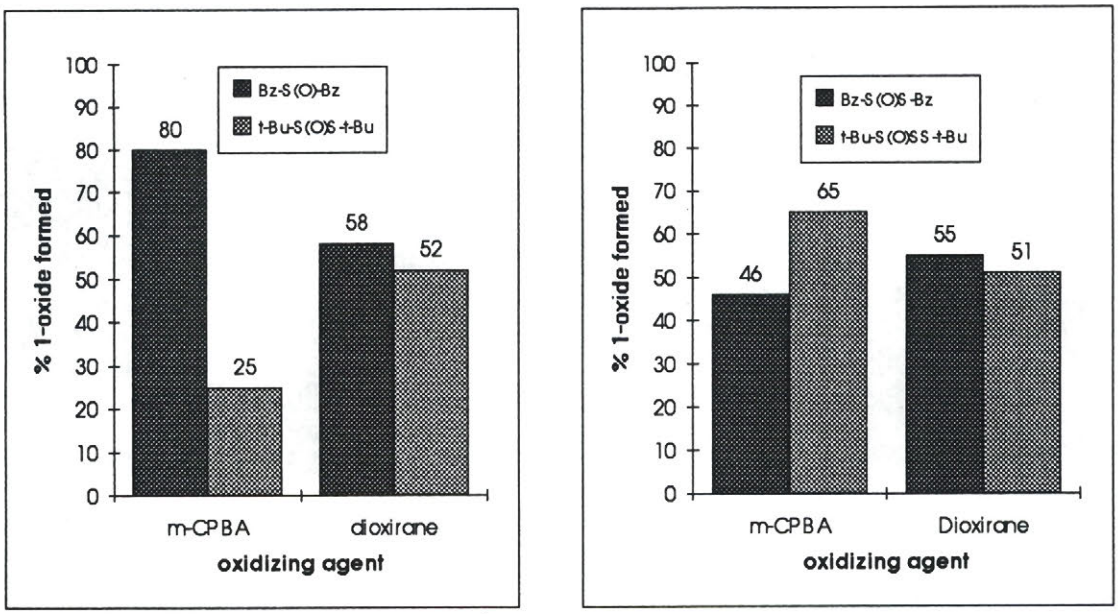
Table 7: Comparison of Sulfur-Chain Length Effect and Alkyl Substitution Effect.

Entry	Compounds	*m*-CPBA Oxidation (%)[a]			Dioxirane Oxidation (%)[a]		
		Before	After	% 1-Oxide Formed[b]	Before	After	% 1-Oxide Formed[b]
118b	*t*-Bu-SS-*t*-Bu	51	38		50	24	
125	Bz-S-Bz	49	10		50	21	
120b	*t*-Bu-S(O)S-*t*-Bu	0	13	25	0	26	52
126	Bz-S(O)-Bz	0	39	80	0	29	58
118c	*t*-Bu-SSS-*t*-Bu	48	17		53	26	
104d	Bz-SS-Bz	52	28		47	21	
120c	*t*-Bu-S(O)SS-*t*-Bu	0	31	65	0	27	51
123c	Bz-S(O)S-Bz	0	24	46	0	26	55

[a] Percentages were calculated from ^{1}H NMR integration; [b] The percentage of 1-oxide formed is the relative ratio of 1-oxide alkyl polysulfide after oxidation to the corresponding alkyl polysulfide before oxidation.

The analysis of the results presented in Table **7** shows that benzyl sulfide **(125)** reacts faster than di-*t*-butyl disulfide **(118b)** which implies that the sulfur chain-length effect is more important than the alkyl substitution effect. However, under the same conditions, di-*t*-butyl trisulfide **(118c)** reacts as fast or even faster than benzyl disulfide **(104d)**. It can be concluded that when the number of sulfur atoms is greater than 2 the alkyl substitution effect becomes predominant.

Graph 3 summarizes the data of Table **7**. Correction factors for deviation from a perfect 1:1 ratio of the considered polysulfides were applied by using the percentages of 1-oxide formed as data for the y axis.



GRAPH 3: Sulfur Chain Length Effect *Vs* Alkyl Substitution Effect

Graph **3** shows that benzyl sulfide **(125)** reacts almost 3.2 times faster than di-*t*-butyl disulfide **(118b)** when *m*-CPBA is used but only 1.2 times faster with dioxirane. In contrast, di-*t*-butyl trisulfide **(118c)** reacts 1.3 times faster than benzyl disulfide **(104d)** when *m*-CPBA is used and slightly slower with dioxirane.

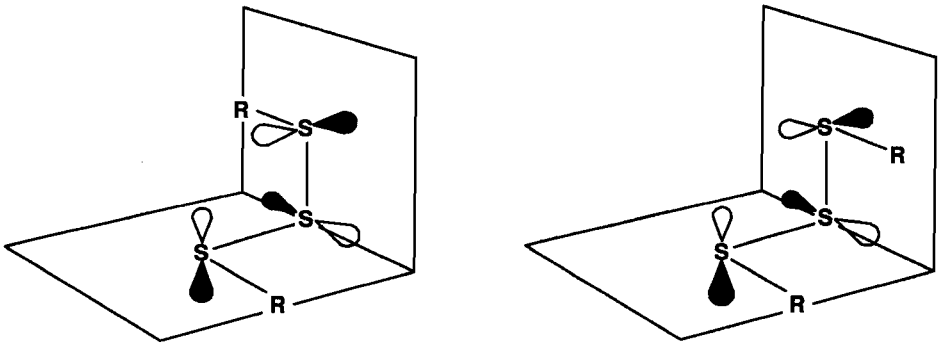
The conclusions are that if the number of sulfur atoms of the polysulfides studied is equal to or less than 2, the reaction is controlled by the sulfur chain-length effect. However, when the number of sulfur atoms is higher than 2, the oxidation reaction is more influenced by the alkyl substitution effect. The difference in the oxidative reactivity of dialkyl polysulfides using *m*-CPBA and dioxirane could be explained by the fact that there is less steric hindrance using dioxirane rather than *m*-CPBA. It should also be mentioned that dioxirane is more reactive than *m*-CPBA and thus, it is less selective as shown in Graph **3**.

CHAPTER 3. OXIDATION OF POLYSULFIDES

3.1. Introduction

In the early days of the chemistry of polysulfides, the main controversy was centered on the arrangement of the sulfur atoms, whether they were linear or branch-bonded. Although the branch-bonded hypothesis had been supported by the facile desulfurization of polysulfides and the explanation of certain decomposition mechanisms,[194] the linear hypothesis was confirmed by a wide variety of physical techniques and especially by crystallography.[187,195]

Nowadays, there is no doubt about the straight-chain structure of trisulfides. However, the chemical behavior of trisulfides is linked to the dihedral angle (θ) about the S-S bonds. By a simple analogy with disulfide bonding,[92e] the theoretical valency angle of sulfur atoms in a trisulfide would be predicted to be about 90° in order to minimize the interaction between adjacent lone pairs of electrons located in the 3p orbitals. Thus, the three sulfurs form a plane and two forms of a trisulfide can exist which are the *cis* and *trans* rotational isomers (**Figure 1**).



Trans *Cis*

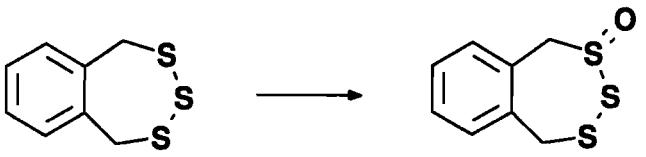
Figure 1

194 a) D. Barnard, T. H. Houseman, M. Porter, B. K. Tidd, *Chem. Commun.*, 371 (1969); b) C. R. Williams and D. N. Harpp, *Sulfur Reports*, **10**, 103 (1990); c) M. C. Demarcq, *J. Chem. Research (S)*, 450 (1993).

195 J. Donohu, *J. Am. Chem. Soc.*, **72**, 2701 (1950).

Other crystallographic studies[196] have shown that the S-S bond lengths of organic trisulfides ranges from 2.04Å to 2.065Å and that the central sulfur valency angle varies between 103° and 107°.

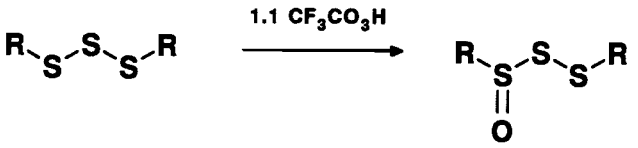
Although the oxidation of disulfides has been extensively studied (see Chapter 1), very little has been done on the oxidation of trisulfides. They are known to undergo this reaction and one of the first examples involves the oxidation of 2,3,4-benzotrithiepin (**127**) by monoperphthalic acid giving the corresponding 1-oxide (**equation 43**).[174b]



(eq. 43)

127

A detailed study of the oxidation of tri- and tetrasulfides was reported by Steudel and coworkers[197] in 1977. Using one equivalent of trifluoroperacetic acid with di-*t*-butyl trisulfide (**118c**) and 2-naphthyl trisulfide (**128**), they reported the isolation of the corresponding trisulfide-1-oxides (**120c** and **129**) in poor yields due to decomposition problems (**equation 44**).



(eq. 44)

118c: R = *t*-Bu
128: R = 2-$C_{10}H_7$

120c: R = *t*-Bu
129: R = 2-$C_{10}H_7$

Using 2 equivalents of the same oxidant on **118c**, they reported the synthesis of the related trisulfide-1,3-dioxide (**130**). Compound **130** was found to be stable for less

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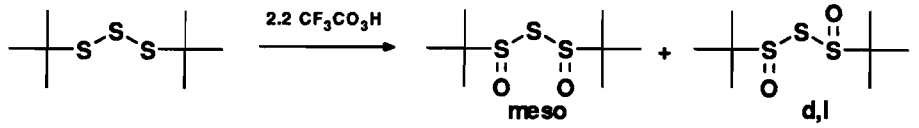
196 a) O. Foss, *Organic Sulfur Compounds*, N. Kharasch, Ed., Pergammon Press Inc., New York, Vol. 1, pp. 75-96 (1961); b) W. A. Pryor, *Mechanisms of Sulfur Reactions*, McGraw-Hill Book Company Inc., New York, p. 16 (1962); c) I. A. Abu-Yousef, R. C. Hynes, D. N. Harpp, unpublished results.

197 a) R. Steudel and J. Latte, *Chem. Ber.*, **110**, 423 (1977); b) R. Steudel, *Phosphorus and Sulfur*, **23**, 33 (1985).

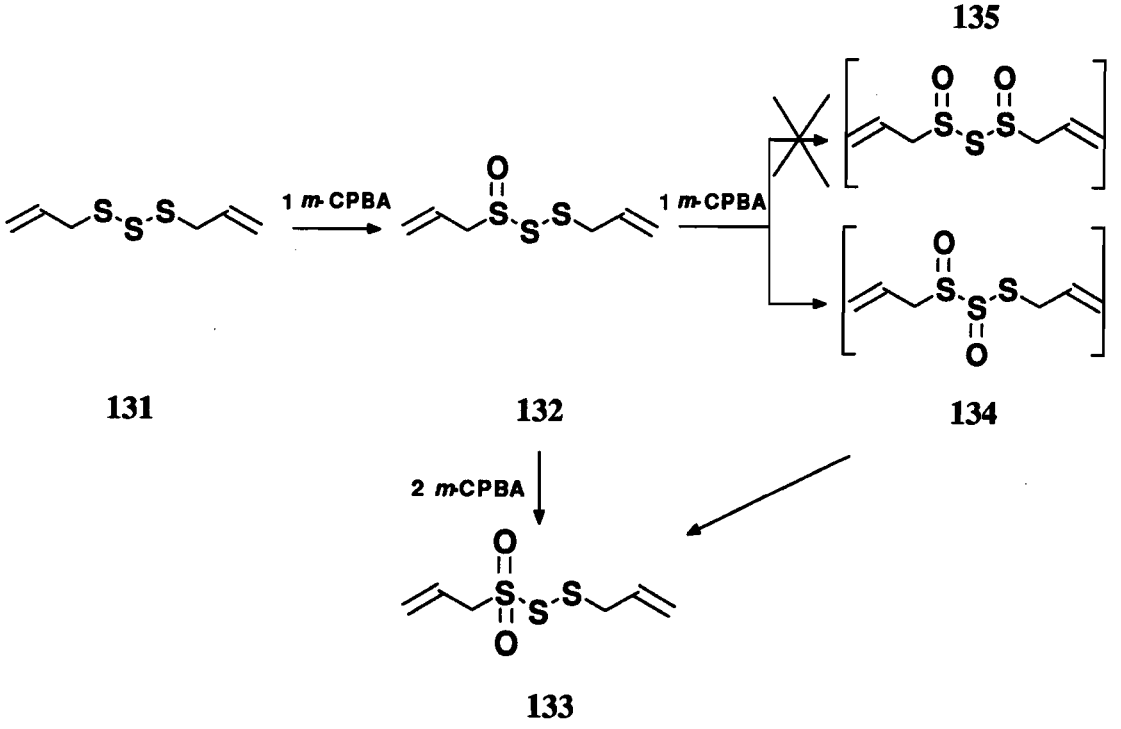
than 2 hours at room temperature and no comments were made on the possible existence of diastereoisomers (meso, d,l) **(equation 45)**.



(eq. 45)

118c **130**

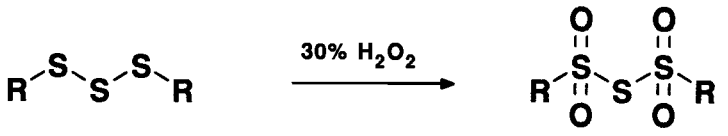
Very recently, Freeman and coworkers[198] reported the oxidation of bis(2-propenyl) trisulfide **(131)** and its monoxide derivative. The one equivalent *m*-CPBA oxidation of **131** gave the corresponding trisulfide-1-oxide **(132)**. Subsequent 1 and 2 equivalent *m*-CPBA oxidation of **132** afforded bis(2-propenyl) trisulfide-1,1-dioxide **(133)** in moderate yields. By analogy with what was observed with the corresponding bis(2-propenyl) disulfide, they suggested that the oxidation of **132** occurs at the 2 position giving trisulfide-1,2-dioxide **(134)** that can rearrange to **133**, rather than at the 3 position that would give the trisulfide-1,3-dioxide **(135)** as reported by Steudel[197] **(Scheme 13)**.



SCHEME 13

198 F. Freeman, X.-B. Ma and R. I.-S. Lin, *Sulfur Lett.*, **15**, 253 (1993).

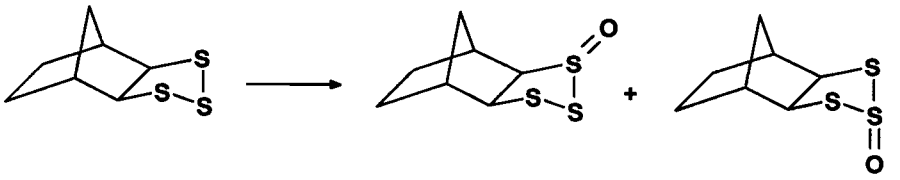
The oxidation of alkyl trisulfides **136** with excess 30% hydrogen peroxide in glacial acetic acid affords the corresponding trisulfide-1,1,3,3-tetraoxides **137**. From these results, it was suggested that the sulfur-chain may not be broken during oxidation and that the central sulfur was not affected by electrophilic oxidizing agents[199] **(equation 46)**.



(eq. 46)

136 **137**

In contrast, Bartlett and Ghosh[200] have found that the *m*-CPBA oxidation of norbornentrithiolane (*exo*-3,4,5-trithiatricyclo[5.2.1.0]decane[201]) **(138)** gives a mixture of the corresponding *exo*- and *endo*-trithiolane-1-oxide **139** as well as the *endo*-trithiolane-2-oxide (*exo*-3,4,5-trithia-*endo*-4-oxotricyclo[5.2.1.0]decane **(140))** **(equation 47)**.



(eq. 47)

138 **139** **140**

Very recently, a similar study had been reported by Sato and coworkers.[202] *m*-CPBA oxidation of two benzotrithiole analogues **141** afforded a mixture of both benzobistrithiole-1- and 2-oxides (**142** and **143**) in reasonable yields. Using *N*-bromosuccinimide instead of *m*-CPBA, they observed the formation of **142** and only

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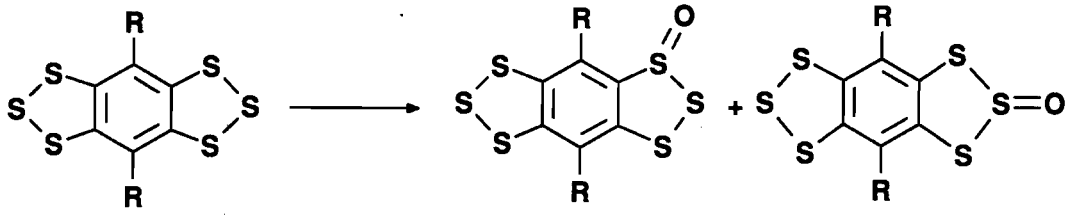
199 F. Fehér, K. H. Shaefer, W. Z. Becher, *Naturforsch., B. Anorg. Chem. Org. Chem.*, **17B**, 847 (1962).

200 F. Ghosh and P. D. Bartlett, *J. Am. Chem. Soc.*, **110**, 7499 (1988).

201 W. Watson, P. C. Jain, P. D. Bartlett and T. Ghosh, *Acta Crystallogr., C: Cryst. Struct. Commun.*, **42**, 332 (1986).

202 N. Yomoji, S. Takahashi, S.-I Chida, S. Ogawa and R. Sato, *J. Chem. Soc., Perkin Trans. I*, 1995 (1993).

traces of **143**. Finally, replacing *m*-CPBA by *N*-iodosuccinimide the only compound isolated was benzobistrithiole-2-oxide **143 (Scheme 14)**.

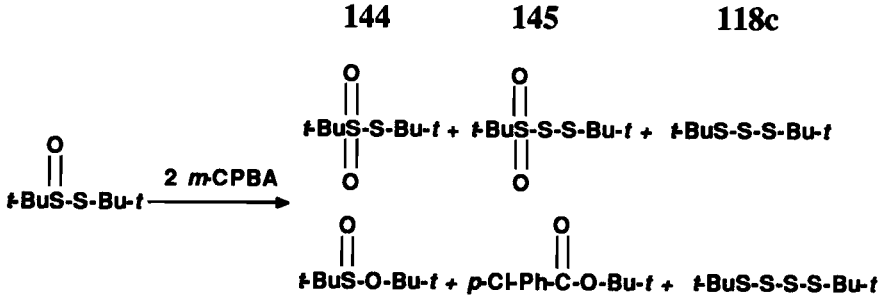


141
R = Me, Et

142 **143**

SCHEME 14

Other studies[116,203] on the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) using 2 equivalents of *m*-CPBA revealed the formation of di-*t*-butyl disulfide-1,1-dioxide (**144**), di-*t*-butyl trisulfide-1,1-dioxide (**145**), *t*-butyl-3-chlorobenzoate (**146**) and *t*-butyl *t*-butylsulfinate (**147**) as well as small amounts of di-*t*-butyl tri- (**118c**) and tetrasulfides (**118d**) **(equation 48)**.



120b **147** **146** **118d**

(eq. 48)

Di-*t*-butyl trisulfide-1-oxide (**120c**) was independently synthesized by the addition of *t*-butyl hydrodisulfide (**148**) to *t*-butyl sulfinyl chloride (**149**) in the presence of pyridine[204] **(equation 49)**. However, **120c** could not be completely purified by silica gel chromatography. The analysis of the decomposition mixtures obtained after attempted purification by silica gel chromatography or high vacuum distillation

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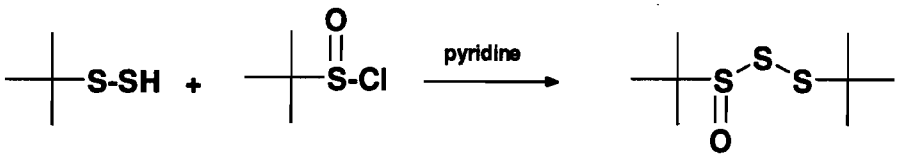
203 a) F. W. Bass and S. A. Evans Jr., *J. Org. Chem.*, **45**, 710 (1980); b) F. Freeman and C. Lee, *J. Org. Chem.*, **53**, 1263 (1988).

204 I. P. Bleeker and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas*, **100**, 459 (1981).

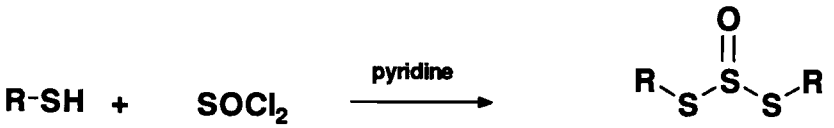
suggested that compound **120c** disproportionated to an equimolar mixture of di-*t*-butyl tetrasulfide (**118d**) and di-*t*-butyl disulfide-1,1-dioxide (**144**). These results partially disagree with what was reported by Steudel and Latte.[197]



(eq. 49)

148 **149** **120c**

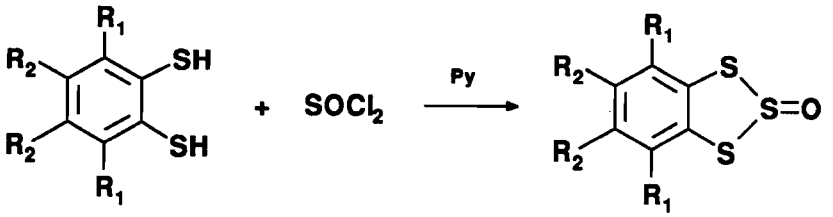
Another synthetic approach for the preparation of oxidized derivatives of trisulfides was reported by Field and Lacefield.[179a] They synthesized various symmetric and unsymmetric trisulfide-2-oxides (**150**) by reacting mercaptans with thionyl chloride in the presence of pyridine (**equation 50**). The study of the decomposition of compounds **150** at 100°C gave an equimolar mixture of the corresponding disulfide and trisulfide as well as sulfur dioxide.



(eq. 50)

150

This procedure was extended[202,205] to the synthesis of trithiolane-2-oxide (**151**) analogs of benzotrithiole in fair yield (**equation 51**).

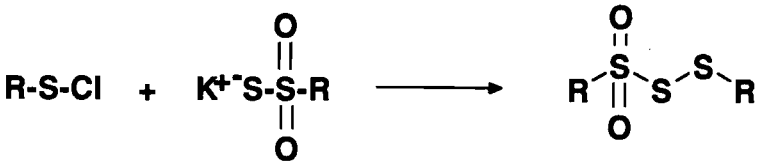


(eq. 51)

151

205 N. Yomoji, S.-I Satoh, S. Ogawa and R. Sato, *Tetrahedron Lett.*, **34**, 673 (1993).

Finally, trisulfide-1,1-dioxides (**152**) were also isolated by a non-oxidative approach.[206] Reaction of a sulfenyl chloride (**95**) and a potassium thiosulfonate (**153**) salt gave the corresponding trisulfide-1,1-dioxide (**152**) (**equation 52**).



(eq. 52)

95 **153** **152**

In the early days of the oxidation of trisulfides, the analytical techniques used were IR, MS, and elemental analysis. However, these techniques were not really reliable in revealing the nature of the compounds formed. The use of NMR spectroscopy greatly favors a better understanding of this class of compounds. The ^{1}H NMR and ^{13}C NMR spectra of some oxide derivatives of polysulfides as well as the deshielding and shielding effects due to the addition of oxygen atoms have been well reviewed.[207]

The oxidation of trisulfides has created controversy about the regiochemistry of the oxidation as well as the identity of the oxidized derivatives formed. These compounds are reported to be quite unstable and very odorous which tends to limit their characterization. Finally, to our knowledge, only peroxy acid oxidizing agents have been used in the oxidation of linear trisulfides. For these reasons, we decided to further investigate this class of compounds. The present study was centered on the oxidation of di-*t*-butyl trisulfide and it was then extended to other polysulfides.

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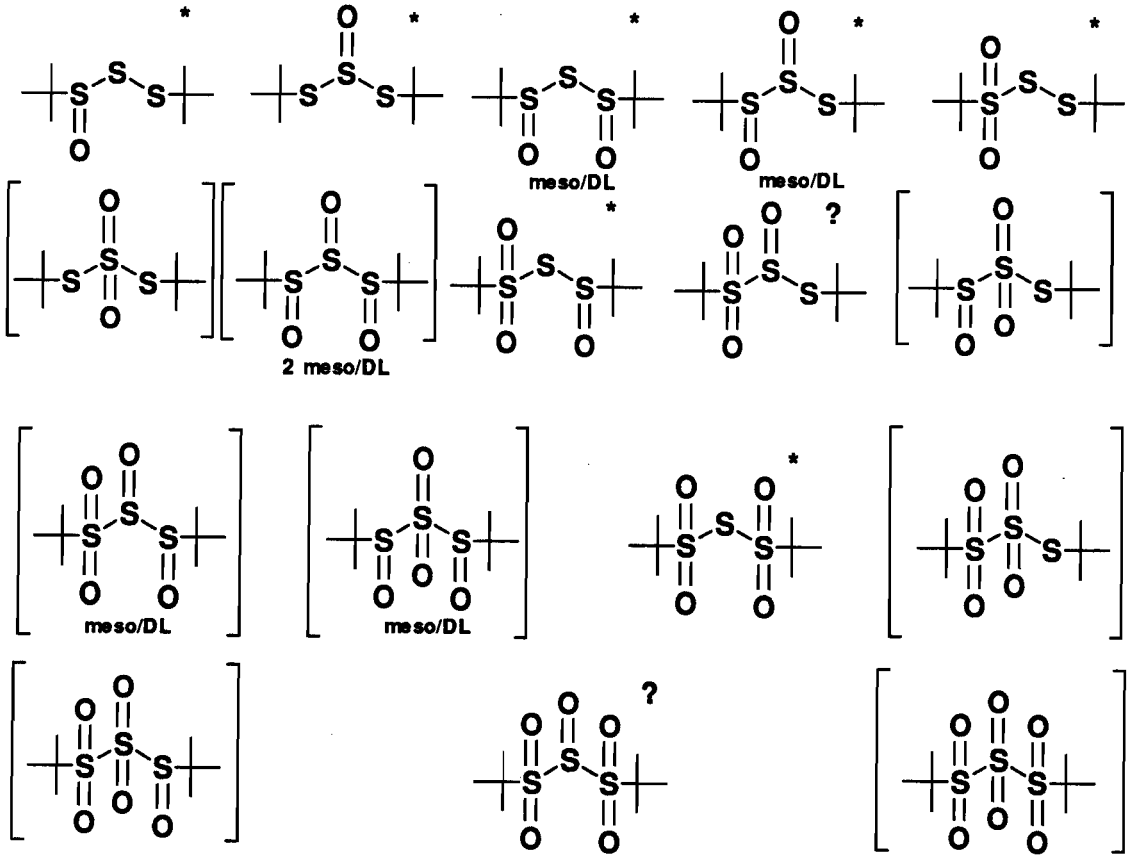
206 C. R. Williams, Ph.D. Thesis, McGill University, 1991.

207 F. Freeman and C. Lee, *Mag. Res. Chem.*, **26**, 813 (1988); and references cited therein.

3.2. Oxidation of di-*t*-Butyl Trisulfide

Di-*t*-butyl trisulfide was chosen because it has a preferred *trans* conformation due to the presence of the bulky *t*-butyl groups that should induce some stability to the corresponding oxidized derivatives. This trisulfide is also manufactured by the Elf Atochem corporation and used as an oil additive for anti wear properties.[78] There are 17 possible positional isomers of oxide analogs of di-*t*-butyl trisulfide; the total number of isomers due to diastereoisomers because of the chirality of the sulfinyl group in some arrangements is 24 (**Scheme 15**). Although some of them are unlikely to be isolated or even detected ([]), it would be interesting to isolate and fully characterize a significant number of them (*) in order to have a general understanding of this class of compounds.

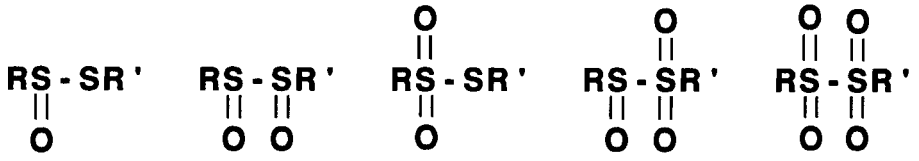


SCHEME 15

The nomenclature of organosulfur compounds has always been complex and confusing.[4,208] Looking at Scheme **15**, it appears that the naming of this class of

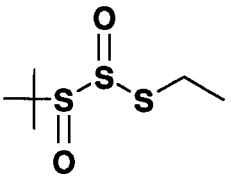
208 S. J. Bodzay, Ph.D. Thesis, McGill University, 1986.

compounds is not going to be straight-forward using the traditional rules of nomenclature. The molecules of this work create unusual problems, thus we propose a consistent scheme which we hope will aid the reader. The disulfide analogs of the compounds represented in Scheme **15**, are usually named according to the "e-i-o" rule that corresponds to the oxidation number at the sulfur. In the literature, there is a general agreement on the nomenclature of thiosulfinates (**79**), *vic*-disulfoxides (**80**), thiosulfonates (**81**), sulfinyl sulfones (**82**) and *vic*-disulfones (**83**).

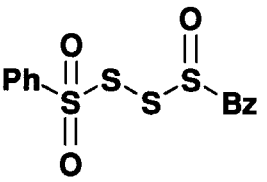


79 **80** **81** **82** **83**

To dramatize the difficulty, the simplest organic disulfide (CH_3SSCH_3) is commonly called dimethyl disulfide. However, recent trends are proposing to use the sulfane nomenclature (dimethyl disulfane). Older systems propose 2,3-dithiabutane and to be consistent with the "e-i-o" rule, it would be dimethyl thiosulfenate. The nomenclature of the trisulfide analogs is even more complex and to date, these compounds are known in the literature as sulfenic sulfinic thioanhydride (RS(O)SSR), dithiosulfite (RSS(O)SR), disulfinic thioanhydride (RS(O)SS(O)R), sulfenic sulfonic thioanhydride ($RS(O)_2SSR$), sulfinic sulfonic thioanhydride ($RS(O)_2SS(O)R$) and disulfonic thioanhydride ($RS(O)_2SS(O)_2R$). Such nomenclature is quite perplexing particularly for those not familiar with organosulfur chemistry and becomes almost impossible to visually perceive[200] by name alone when unsymmetric di-, tri- and tetrasulfide analogs are used as reported in this thesis. For these reasons, a consistent, customized nomenclature was adopted here. The names are based on the skeleton of the molecule whether it is a di-, tri- or tetrasulfide. The number of oxygen atoms is represented by the suffix mono-, di-, tri- and tetraoxides. The position of these oxygen atoms is defined by numbers (1, 2, 3 or 4) that represents a specific sulfur atom in the sulfur-chain. For unsymmetric analogs, the first substituent named is the one attached to the sulfur number 1 and is defined by its degree of substitution (aryl>tertiary alkyl>secondary alkyl>primary alkyl) and higher molecular weight in the rare cases of equal substitution. Typical examples are *t*-butyl-ethyl trisulfide-1,2-dioxide (**154**) and phenyl-benzyl tetrasulfide-1,1,4-trioxide (**155**) (see Index of structures).



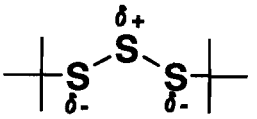
154



155

According to the nomenclature used in the literature, these two compounds could have been named *t*-butyl sulfinyl ethyl thiosulfite (**154**) and phenyl sulfonic benzyl sulfinic dithioanhydride (**155**).

The preparation of such compounds can be achieved by either a condensation approach or direct oxidation as stated earlier. Considering that the three sulfur atoms of a symmetric trisulfide are not equivalent, the external sulfurs adjacent to *t*-butyl groups being electron rich (δ-) and the internal one relatively electron poor (δ+), the oxidation of di-*t*-butyl trisulfide using nucleophilic and electrophilic oxidizing agents[209] should allow the synthesis of a wide variety of di-*t*-butyl trisulfide-polyoxides (**Scheme 16**).



SCHEME 16

3.2.1. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-1-Oxide (120c)

As previously mentioned, the synthesis of di-*t*-butyl trisulfide-1-oxide (**120c**) has already been reported by a direct oxidation of di-*t*-butyl trisulfide (**118c**) using trifluoroperacetic acid; in addition, a condensation procedure was used.[197,204] In both cases, the impossibility of completely purifying the final product did not allow the full characterization of **120c**.

In the present study, the oxidation of di-*t*-butyl trisulfide is reported using various electrophilic oxidizing agents and the nature of the compound formed is confirmed by a parallel synthesis of **120c** by a modification of Engberts's procedure.[204]

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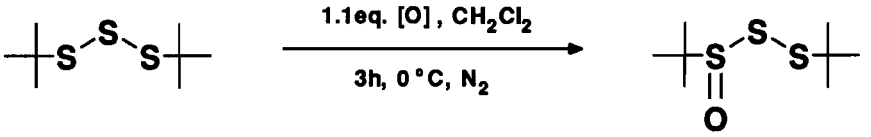
209 W. Adam, W. Haas and B. B. Lohray, *J. Am. Chem. Soc.*, **113**, 6202 (1991).

The oxidation of di-*t*-butyl trisulfide (**118c**) has first been achieved using 1 equivalent of *m*-CPBA at low temperature under an inert atmosphere. The reaction mixture was stirred for 3 h in methylene chloride because the *meta*-chlorobenzoic acid (*m*-CBA) formed is not soluble in this solvent (**equation 53**). The same experiment was repeated using a 40% solution of peracetic acid as oxidizing agent and no major difference was noticed.

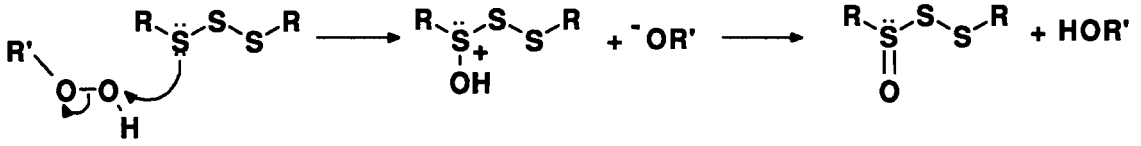


(eq. 53)

118c **120c**

[O] = *m*-CPBA 92%
[O] = CH_3CO_3H 88%

By analogy with the *m*-CPBA oxidation of sulfides,[100f,210] the external sulfur atoms of a symmetric trisulfide which are electron rich are believed to react by attack of one of their two lone pairs of electrons on the electrophilic oxygen of the peracid. Rapid proton transfer leads to the trisulfide-1-oxide and the corresponding acid (**Scheme 17**).



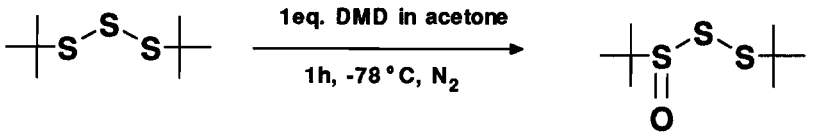
SCHEME 17

Following the reaction by tlc, it was found that the usual work-up that consists of washing the reaction mixture with water and 1 N solution of base (NaOH or Na_2CO_3) led to a partial decomposition of **120c** (up to 20%). However, concentrating the reaction mixture by roto-evaporation of methylene chloride and cooling it to -78°C gave an almost complete precipitation of *m*-CBA and allowed the isolation of the trisulfide-1-oxide in a high yield (the by-product being unreacted starting material).

The preparation of **120c** was also attempted using dimethyldioxirane (DMD). The dropwise addition of 1 equivalent of an acetone solution of DMD to a cooled (-78°C)

210 C. Srinivasan, A. Chellamani and P. Kuthalingam, *J. Org. Chem.*, **47**, 428 (1982).

solution of di-*t*-butyl trisulfide in acetone gave an almost quantitative yield of the trisulfide-1-oxide desired in less than 1 h **(equation 54)**.

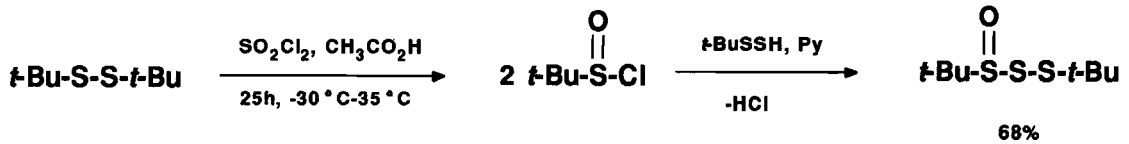


(eq. 54)

118c **120c (98%)**

DMD is generally considered to be a stronger oxidizing agent[209] than *m*-CPBA and it seems to be also true for the oxidation of trisulfides. The mechanism suggested earlier for the oxidation of trisulfides applies to DMD oxidation except that acetone is formed instead of the acid.[211] Although the preparation of DMD is somewhat delicate, it is a very efficient and simple procedure (no work-up is necessary).

The synthesis of di-*t*-butyl trisulfide-1-oxide **(120c)** was also achieved by a modified procedure of Bleecker's[204] method in order to confirm its isolation. The addition of sulfuryl chloride to di-*t*-butyl disulfide **(118b)** in acetic acid gave an almost quantitative yield of *t*-butyl sulfinyl chloride[212] **(149)** after more than 20 h of reaction (the by-product being traces of *t*-butyl sulfenyl chloride). Compound **149** was directly reacted with *t*-butyl hydrodisulfide[213] **(148)** in the presence of pyridine (mainly used to trap the hydrochloric acid formed). General work-up of the reaction mixture afforded a reasonable yield of the desired **120c** which had identical properties of the one isolated by oxidation of **118c (Scheme 18)**.



118b **149** **120c**

SCHEME 18

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211 A. L. Baumstark and D. B. Harden, Jr., *J. Org. Chem.*, **58**, 7615 (1993).

212 J. H. Youn and R. Hermann, *Tetrahedron Lett.*, **27**, 1493 (1986).

213 G. Derbesy and D. N. Harpp, *Sulfur Lett.*, **14**, 199 (1992).

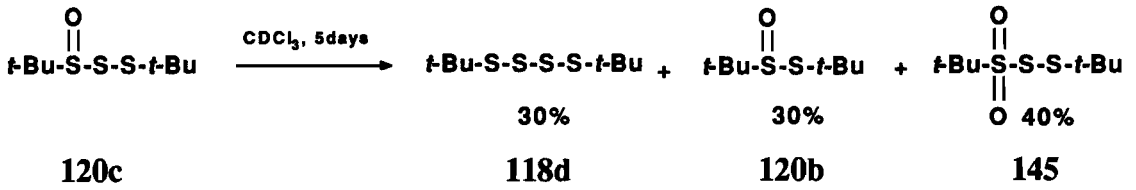
The purification of di-*t*-butyl trisulfide-1-oxide (**120c**) was achieved by using silica gel chromatography or activated alumina chromatography. As reported by Engberts, some decomposition problems were encountered when using silica gel chromatography. However, using alumina chromatography, a pure product is easily obtained. Either of the three oxidizing agents gives good results although DMD might be the one of choice. In all cases, the use of excess oxidizing agent or carrying out the reaction at higher temperature than 0°C gives decomposition products that seriously complicate the purification procedure.

Di-*t*-butyl trisulfide-1-oxide (**120c**) was characterized by ^{1}H and ^{13}C NMR (see Table **12** at the end of this section) as well as by mass spectrometry. The ^{1}H NMR spectrum of **120c** should give 2 distinct signals for the 2 non-equivalent *t*-butyl groups, one being adjacent to a sulfinyl sulfur and the other to a sulfenyl sulfur. However, in deuterated chloroform these two peaks partially overlap (difference in chemical shift is 0.05 ppm) because of the slow relaxation times of the *t*-butyl groups. The relaxation time of **120c** was calculated by applying a pulse angle of 180° after the normal 90° pulse angle at various intervals of time. Processing of the data gives the relaxation time (1.5 s) which is illustrated by a straight line spectrum. By reducing the sweep width from 400 to 50 Hz, multiplying the number of points by 2 and entering a relaxation time for **120c** of 1.5 s it was possible to observe 2 sharp singlets that have the correct integration. Using benzene-d_6 as solvent, the two peaks were very well separated. The ^{13}C NMR spectrum showed 4 peaks corresponding to the two non equivalent tertiary carbons (lower field) and the 2 sets of methyl groups (higher field).

Attempts to obtain suitable crystals for X-ray analysis were unsuccessful. Because of decomposition problems, the recrystallization had to be carried out at low temperature (below 0°C). Using non-polar solvents (petroleum ether, hexane and *n*-pentane), only very thin crystals could be obtained (the recrystallization of the tetrasulfide analog gave similar results). On two occasions, the low temperature X-ray analysis of slightly thicker crystals has been attempted. Unfortunately, the first crystal was too thin and did not diffract properly and in the second case the crystal decomposed due to condensation problems. In polar solvents (isopropanol, methanol, water/methanol) no crystallization took place.

The decomposition products of di-*t*-butyl trisulfide-1-oxide were also determined (a detailed decomposition study of **120c** is reported in Chapter 4). The percentages of

decomposition products presented below are the average values of a large number of experiments. The decomposition of **120c** in deuterated chloroform is complete after 5 days at room temperature. The products formed are di-*t*-butyl tetrasulfide (**118d**), di-*t*-butyl trisulfide-1,1-dioxide (**145**) and di-*t*-butyl disulfide-1-oxide (**120b**) (**Scheme 19**). No sulfur dioxide could be detected by pH paper when a sample of **120c** was heated at 50°C (complete decomposition of the sample took place, 12 h).



120c **118d** **120b** **145**

SCHEME 19

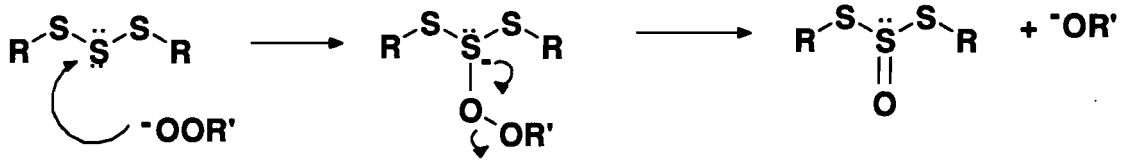
Although di-*t*-butyl trisulfide-1-oxide (**120c**) is relatively unstable and quite odorous, it can be isolated in fair yield and is easily characterized. No trace of di-*t*-butyl trisulfide-2-oxide (**156**) has ever been detected in any of the experiments previously described. This result suggests that the oxidation of **118c** is regiospecific and only delivers **120c**. Thus, it implies that the external sulfur is much more nucleophilic than the internal one. In addition, the reaction seems to be controlled by electronic effects since the steric effects would favor the formation of **156**. These results contrast with those obtained during the oxidation of trithiolane derivatives where a mixture of the 1- and 2-oxide analogs was isolated.[200,202]

3.2.2. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-2-Oxide (156)

Although di-*t*-butyl trisulfide-2-oxide (**156**) has already been synthesized by the previously described method, the nucleophilic oxidation of di-*t*-butyl trisulfide to the corresponding **156** has never been attempted to our knowledge.

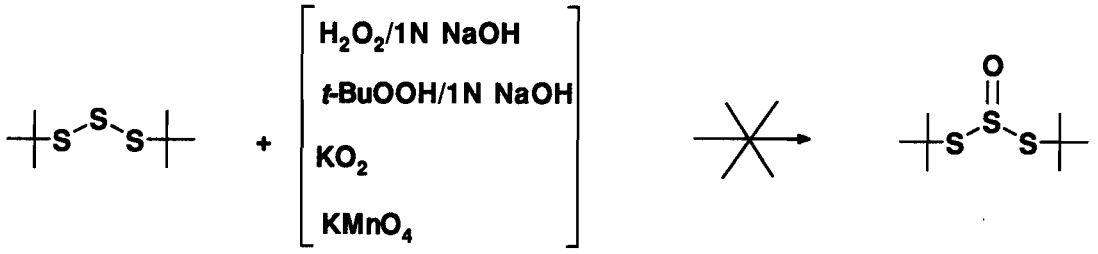
By analogy with the nucleophilic oxidation of sulfides and disulfides,[100f,103] the oxidizing agent would attack the central sulfur of the trisulfide which is relatively electron poor due to the two adjacent sulfurs. Normal rearrangement of the ionic

intermediate formed should give the trisulfide-2-oxide as major reaction product **(Scheme 20)**.



SCHEME 20

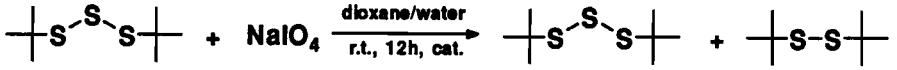
In the present study, the oxidation of di-*t*-butyl trisulfide **(118c)** was attempted using strong nucleophilic oxidizing agents.[209] In our hands, the reactions of oxidation of **118c** using H_2O_2/1N NaOH, *t*-BuOOH/1N NaOH, KO_2 or $KMnO_4$ were unsuccessful even at high temperatures and for long periods of time. When the conditions were too drastic, the normal decomposition of di-*t*-butyl trisulfide was eventually observed **(Scheme 21)**.[214]



118c **156**

SCHEME 21

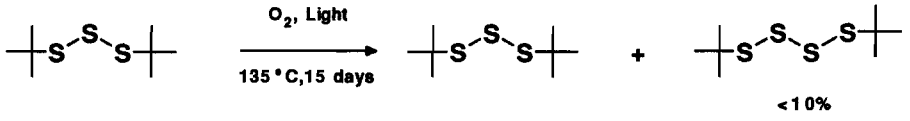
Using $NaIO_4$ under the conditions described by Oae and coworkers,[137a] the reaction products were a mixture of di-*t*-butyl di- and trisulfides **(equation 55)**. However, the ratio of di- and trisulfide varied considerably from one reaction to another. The reaction was repeated several times using 1, 1.5 and 2 equivalents of $NaIO_4$ but it was impossible to rationalize these results.



118c **118c** **118b** **(eq. 69)**

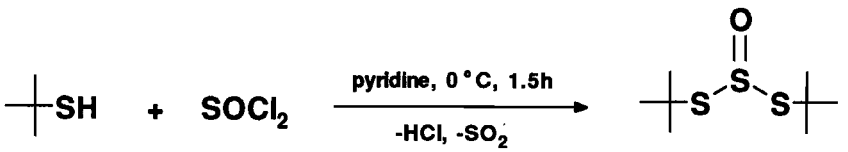
214 Elf Atochem N. A., Inc., King of Prussia, Pennsylvania, private communication.

Considering that the photochemical oxidation of disulfides is controlled by steric effects,[92a] it was thought that the photo-oxidation of di-*t*-butyl trisulfide (**118c**) should give the corresponding trisulfide-2-oxide as major product because the internal sulfur is the less hindered of the three and thus its attack should be favored. A solution of **118c** in dodecane was heated to 135°C under light and pure oxygen was bubbled through it. After 2 weeks under these conditions, the analysis of the reaction mixture did not show any trace of di-*t*-butyl trisulfide-2-oxide (**156**) and only normal thermal decomposition of the trisulfide had occurred (**equation 56**).[214]



118c **118c** **118d** (eq. 56)

The preparation of di-*t*-butyl trisulfide-2-oxide (**156**) has been achieved according to Field's procedure.[179a] The addition of 2 equivalents of *t*-butyl mercaptan to thionyl chloride affords compound **156** in a very good yield. Recrystallization from *n*-pentane gives the desired material in high purity (**equation 57**).



156 (90%) (eq. 57)

The characterization of di-*t*-butyl trisulfide-2-oxide (**156**) was achieved by NMR (see Table **12** at the end of this section) and mass spectrometry. Clear, colorless prisms were obtained by recrystallization from a 20/80 hexanes/*n*-pentane mixture and were submitted for X-ray analysis. The ORTEP drawing of **156** is represented on Figure **2** and the selected bond lengths, bond angles and dihedral angles are gathered on Table **8**. From these data it is clear that the molecule is asymmetric (different S-S lengths), contrary to what is observed by NMR. The length of the S-S bonds are not too much affected by the presence of the oxygen and they still lie in the range of 2.04-2.06Å. The angle made by the three sulfurs is, as expected, around 90°, but the one about the S-S bonds are about 101° due to the repulsion of the oxygen atom. For the same reasons, the valency angle of one of the methyls of the *t*-butyl groups is 6-8° smaller than the others which have

normal tetrahedral values (~110°). The torsion angles observed confirm the *trans* position of the *t*-butyl groups towards the three sulfur atom plane.

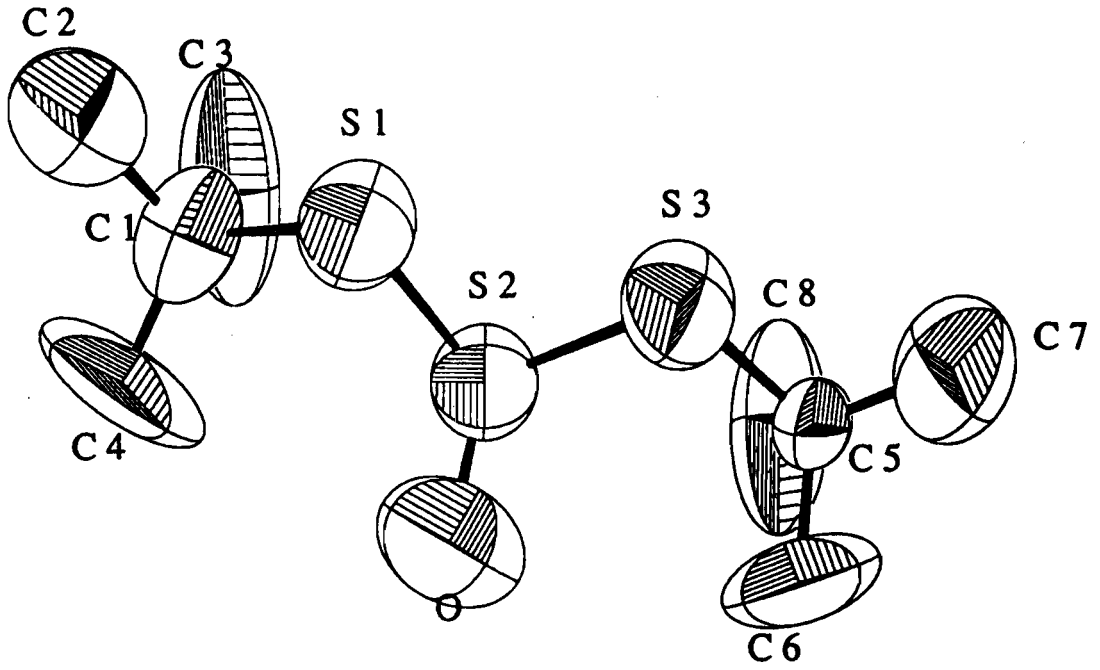


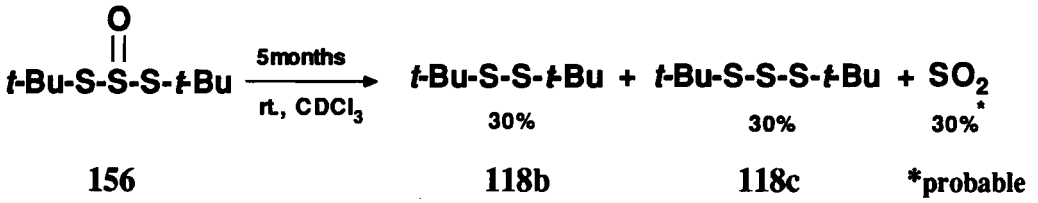
Figure 2: ORTEP Drawing of di-*t*-Butyl Trisulfide-2-Oxide (156)

Table 8: Bond lengths, valency angles and torsion angles for 156

Bond Lengths (Å)			
S(2)-S(1)	2.066(9)[a]	S(2)-S(3)	2.045(10)
S(2)-O	1.54(22)		
S(1)-C(1)	1.87(3)	S(3)-C(5)	1.88(3)
Valency Angles (°)			
S(1)-S(2)-S(3)	89.8(4)		
S(1)-S(2)-O	110.1(9)	S(3)-S(2)-O	109.5(9)
S(2)-S(1)-C(1)	101.1(10)	S(2)-S(3)-(C5)	101.6(8)
S(1)-C(1)-C(2)	100.9(19)	S(3)-C(5)-C(6)	112.7(22)
S(1)-C(1)-C(3)	108.1(22)	S(3)-C(5)-C(7)	106.6(19)
S(1)-C(1)-C(4)	112.8(25)	S(3)-C(5)-C(8)	112.7(21)
Torsion Angles (°)			
S(3)-S(2)-S(1)-C(1)	164.5(11)	S(1)-S(2)-S(3)-C(5)	-178.8(10)
O-S(2)-S(1)-C(1)	-84.9(13)	O-S(2)-S(3)-C(5)	70.0(12)

[a]. Estimated σ's refer to the last digit.

The decomposition products of di-*t*-butyl trisulfide-2-oxide (**156**) were also determined (a detailed decomposition study of **156** is reported in Chapter 4). After 5 months in deuterated chloroform at room temperature, compound **156** gave an equimolar mixture of di-*t*-butyl tetrasulfide (**118d**) and di-*t*-butyl trisulfide (**118c**) as reported by Field[179a] (**Scheme 22**). Strong evidence of SO_2 evolution were given by the change of color (yellow to red) of the pH paper when a sample of **156** was heated at 80°C until complete decomposition (12 h).



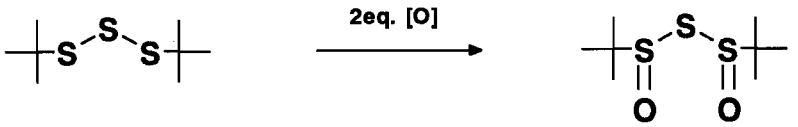
SCHEME 22

Di-*t*-butyl trisulfide-2-oxide (**156**) was synthesized in high yield and purity and was fully characterized. Nucleophilic oxidation of di-*t*-butyl trisulfide (**118c**) that should have afforded **156** was unsuccessful. These results suggest that the internal sulfur which was not nucleophilic enough to attack the electrophilic oxidizing agents (see previous section) is not electrophilic enough to react with nucleophilic oxidizing agents. No migration of the oxygen on position 2 to the external sulfur has been detected contrary to what is observed using oxide derivatives of some trithiolanes.[200,202]

3.2.3. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-1,3-Dioxide (130)

The synthesis of di-*t*-butyl trisulfide-1,3-dioxide (**130**) has been reported by Steudel.[197] However, compound **130** was only partially characterized and its existence has recently been subjected to controversy by Freeman[198] as described earlier.

In the present study, the preparation of **130** has been achieved using electrophilic oxidizing agents. The oxidation of di-*t*-butyl trisulfide (**118c**) was carried out at low temperature and under inert atmosphere by the addition of 2 equivalents of either *m*-CPBA, DMD or CH_3CO_3H. In all cases, di-*t*-butyl trisulfide-1,3-dioxide (**130**) crystallized from cooled *n*-pentane (**equation 58**).

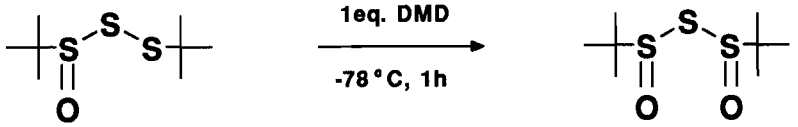


(eq. 58)

118c **130**

[O] = *m*-CPBA 96%
[O] = CH_3CO_3H 60%
[O] = DMD 99%

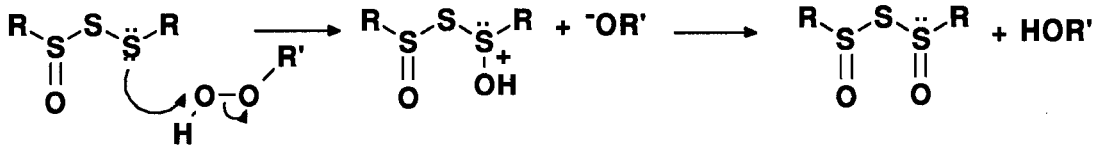
A parallel study consisted of oxidizing di-*t*-butyl trisulfide-1-oxide (**120c**). Under the same conditions, compound **120c** was reacted with 1 equivalent of DMD and afforded the desired trisulfide-1,3-dioxide (**130**) (**equation 59**).



(eq. 59)

120c **130** (94%)

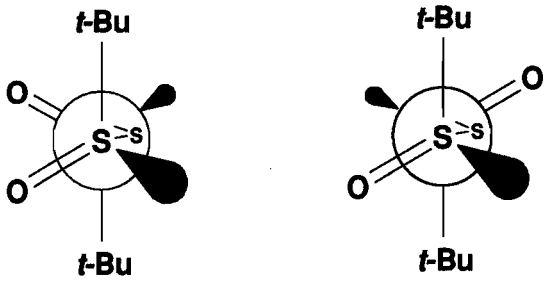
These results suppose that the trisulfide is first converted to its 1-oxide derivative by nucleophilic attack of the external sulfur as described earlier. The remaining electrophilic oxidizing agent is believed to react with the second bivalent terminal sulfur which is the more electron rich of the three sulfurs. Rapid proton transfer releases the desired trisulfide-1,3-dioxide (**Scheme 23**) which present two asymmetric sulfoxide functions that should give two diastereomeric signals by NMR analysis.



SCHEME 23

The characterization of di-*t*-butyl trisulfide-1,3-dioxide (**130**) was achieved by NMR (see Table **12** at the end of this section) and mass spectrometry. The ^{13}C NMR signals of a sample of **130** that was kept at low temperature showed a single peak for the tertiary carbon. After 3 h at room temperature, the ^{13}C NMR presented two close peaks of equal intensity in the tertiary carbon region; the new signal was 0.4 ppm upfield. After

6 hours at room temperature, only the higher field signal was detectable (see spectra in Chapter 4). These results suggest that the first compound formed is the kinetically favored diastereoisomer **130a** and over time it converts to the thermodynamically favored diastereoisomer **130b**. Molecular modeling *via* MMX calculations using the PCMODEL program[215] predicts the meso isomer **(130b)** to be the thermodynamic compound by 15.5 kcal/mol. The isomerisation implies a cleavage of the molecule that can be homolytic or heterolytic. The mechanism of conversion of **130a** to **130b** as well as the decomposition pathway are discussed in detail in Chapter 4.



130a **130b**

The recrystallization of compound **130** gave suitable crystals for X-ray analysis. Unfortunately, they have a very low stability even when stored in the freezer (< 1 week). The low temperature X-ray analysis has been attempted but was unsuccessful because of decomposition problems.

Di-*t*-butyl trisulfide-1,3-dioxide **(130)** is readily decomposed after 12 hours at room temperature. Analysis of the decomposition mixture by NMR allowed the determination of the main final products; di-*t*-butyl disulfide-1-oxide **(120b)**, di-*t*-butyl trisulfide-1,1-dioxide **(145)** and di-*t*-butyl trisulfide-1,1,3-trioxide **(157)** **(Scheme 24)**. A full discussion on the decomposition of **130** is presented in Chapter 4.

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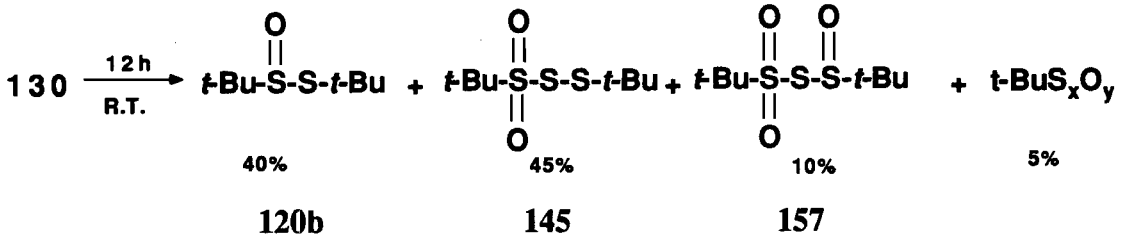
215 This program was obtained from Serena Software, Bloomington, Indiana and used with helpful consultation with Dr. K. Steliou, Boston University, Boston, Massachussetts.



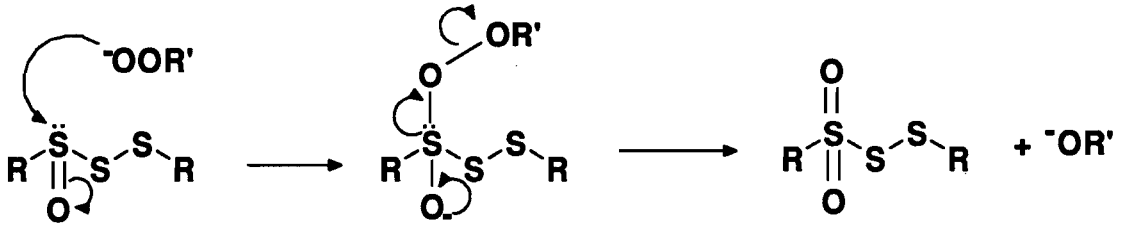
SCHEME 24

The only product isolated from the oxidation of di-*t*-butyl trisulfide or di-*t*-butyl trisulfide-1-oxide was **130** when the temperature was kept below -20°C. Once again, this oxidation reaction appears to be regiospecific.

3.2.4. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-1,1-Dioxide (145)

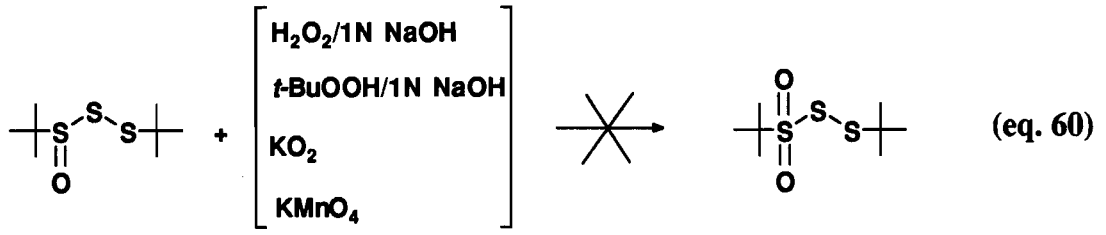
To our knowledge, the synthesis of di-*t*-butyl trisulfide-1,1-dioxide **(145)** by direct oxidation has never been reported. However, compound **145** has already been isolated as a by-product of the synthesis of **120b**[203] and from the decomposition of **120c**. In the present study, the preparation of **145** has been attempted using nucleophilic and electrophilic oxidizing agents.[209] It has also been isolated from the decomposition of **120c** and **130**.

By analogy with what is reported on the synthesis of disulfide-1,1-dioxides,[137a] the nucleophilic oxidation of trisulfide-1-oxides **(120c)** should proceed by a preferential attack of the oxygen to the electron poor sulfur (the sulfinyl sulfur)[100f,103] **(Scheme 25)**.



SCHEME 25

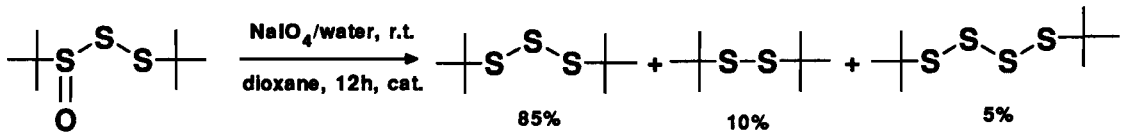
However, using various nucleophilic oxidizing agents[209] such as H_2O_2/1N NaOH, *t*-BuOOH/1N NaOH, KO_2 and $KMnO_4$, no reaction was observed when the reaction mixture was kept below 0°C and di-*t*-butyl trisulfide-1-oxide (**120c**) remained unchanged after several days. At higher temperature, the normal decomposition of **120c** (described earlier) occurred (**equation 60**).



(eq. 60)

120c **145**

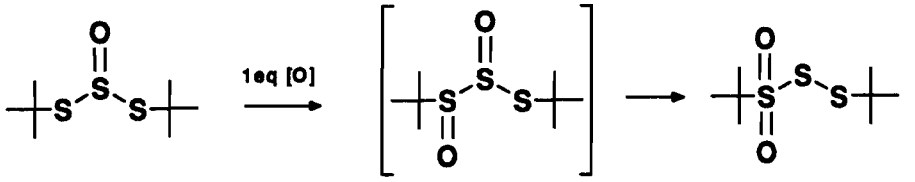
Using 1 equivalent of $NaIO_4$ under the conditions described by Oae and coworkers,[137a] the main reaction product was di-*t*-butyl trisulfide (the remaining products were 10% of disulfide **118b** and 5% of tetrasulfide **118d**) (**Scheme 26**).



120c **118c** **118b** **118d**

SCHEME 26

The preparation of di-*t*-butyl trisulfide-1,1-dioxide (**145**) was actually achieved in a very good yield by DMD oxidation of di-*t*-butyl trisulfide-2-oxide (**156**). Using other oxidizing agents such as *m*-CPBA and CH_3CO_3H, the yields observed were much lower (**equation 61**). The *m*-CPBA oxidation of **156** was repeated using different solvents, at different temperatures and under various conditions. The results of these experiments are reported in Chapter 4.



156 158 145

[O] = *m*-CPBA	48%
[O] = CH_3CO_3H	36%
[O] = DMD	85%

Di-*t*-butyl trisulfide-1,1-dioxide (**145**) was fully characterized by NMR and mass spectrometry (see Table **12** at the end of this section). Recrystallization from hexanes gave colorless crystals that were suitable for X-ray analysis. The ORTEP drawing is represented on Figure **3** and the selected bond lengths, valency angles and torsion angles in Table **9**. It is interesting to note that the presence of the 2 oxygen atoms has a great effect on the S-S bonds and there is a difference of 0.11Å between the length of the $S(O)_2$-S bond and the S-S bond. The angle made by the three sulfur atoms is also affected and it is 15° higher than the minimal interaction value of 90°. The asymmetry of the molecule is also reflected by most of the other measurements.

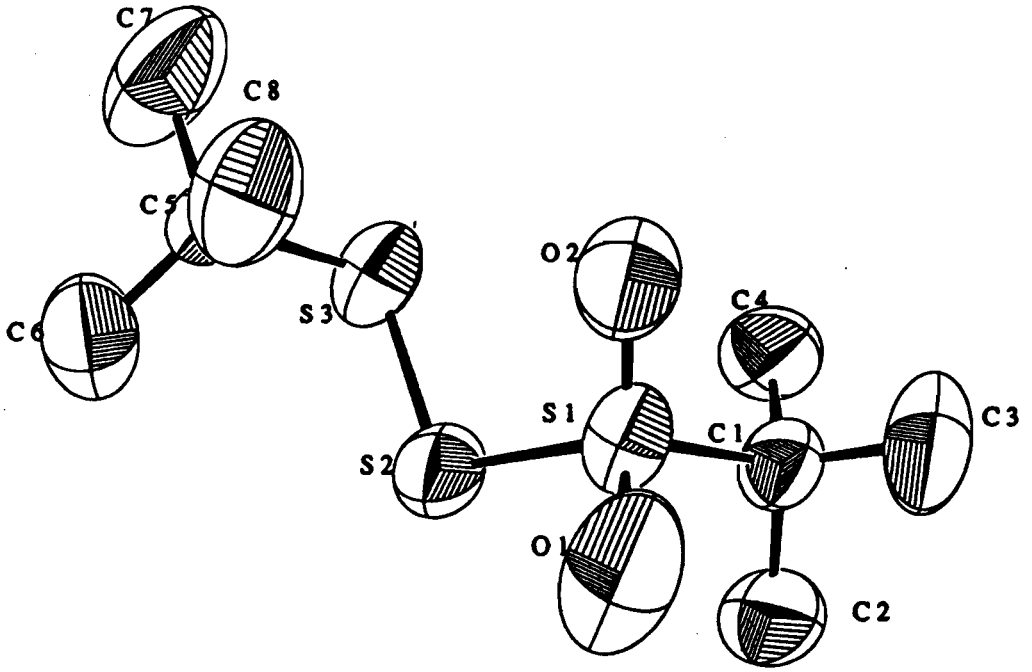


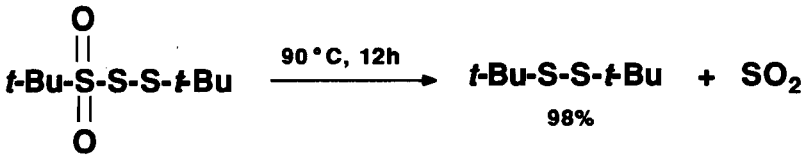
Figure 3: ORTEP Drawing of di-*t*-Butyl Trisulfide-1,1-Dioxide (145)

Table 9: Bond lengths, valency angles and torsion angles for 145[a]

Bond Lengths (Å)			
S(2)-S(1)	2.1159(24)	S(2)-S(3)	2.0093(24)
S(1)-O(1)	1.421(5)	S(1)-O(2)	1.442(5)
S(1)-C(1)	1.825(6)	S(3)-C(5)	1.845(6)
Valency Angles (°)			
S(1)-S(2)-S(3)	105.31(10)	O(1)-S(1)-O(2)	119.7(3)
S(2)-S(1)-O(1)	104.0(3)	S(2)-S(1)-O(2)	108.57(20)
S(2)-S(1)-C(1)	106.20(23)	S(2)-S(3)-(C5)	105.56(20)
S(1)-C(1)-C(2)	108.5(4)	S(3)-C(5)-C(6)	112.0(5)
S(1)-C(1)-C(3)	104.5(5)	S(3)-C(5)-C(7)	104.0(5)
S(1)-C(1)-C(4)	109.0(4)	S(3)-C(5)-C(8)	110.0(4)
Torsion Angles (°)			
S(3)-S(2)-S(1)-C(1)	99.5(2)	S(1)-S(2)-S(3)-C(5)	-97.4(2)
O(1)-S(1)-S(2)-S(3)	145.6(3)	O(2)-S(1)-S(2)-S(3)	17.1(2)

[a]. Estimated σ's refer to the last digit.

A decomposition study of di-*t*-butyl trisulfide-1,1-dioxide (**145**) at room and elevated temperature revealed that it is very stable at 25°C. However, compound **145** readily decomposed to di-*t*-butyl disulfide (**118b**) after 12 hours at reflux in carbon tetrachloride (**equation 62**). Strong evidence of sulfur dioxide evolving was given by the change of color (yellow to red) of the pH paper that was placed over the reaction mixture. These results are in favor of a sulfur dioxide extrusion mechanism.

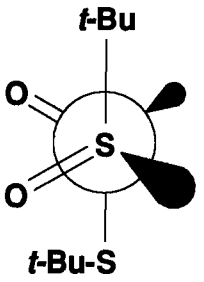


(eq. 62)

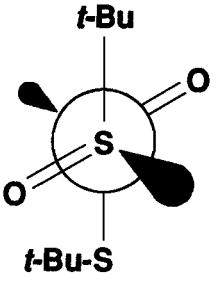
145 **118b**

It is surprising that di-*t*-butyl trisulfide-1-oxide (**120c**) does not react with nucleophilic oxidizing agents while sulfoxides[100f,210] and thiosulfinates[137] are reported to be easily converted to their corresponding sulfones and thiosulfonates by this type of nucleophilic oxidation. A possible reason is that the reaction has to be carried out at low temperature to avoid the decomposition of **120c**.

The synthetic approach that leads to the isolation of di-*t*-butyl trisulfide-1,1-dioxide (**145**) is believed to proceed by rearrangement of the corresponding trisulfide-1,2-dioxide (**158**). The fact that oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) gives **145** brings another unambiguous proof of attack of the sulfenyl sulfur rather than the sulfinyl sulfur and formation of a 1,2-dioxide intermediate as discussed in Chapter 1. In a separate experiment, the NMR signals of di-*t*-butyl trisulfide-1,2-dioxide (**158**) were clearly detected by low temperature NMR (see Table **12** at the end of this section) from -60°C up to -40°C. However, only one of the 2 diastereoisomers could be detected with certainty. These results are consistent with those reported by Freeman in the study of the di-*t*-butyl *vic*-disulfoxide (disulfide-1,2-dioxide) (see Chapter 4).[134c] Molecular modeling *via* MMX calculations using the PCMODEL program[215] could not be carried out (missing parameters). However, by analogy with what has previously been described for di-*t*-butyl trisulfide-1,3-dioxide (**130**), the meso isomer (**158b**) should be thermodynamically favored. To our knowledge, this is the first time that a trisulfide-1,2-dioxide has been detected and a full discussion on this detection and the rearrangement of **158** to **145** is presented in Chapter 4.



158a



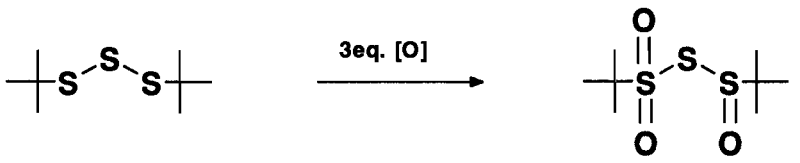
158b

3.2.5. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-1,1,3-Trioxide (157)

To our knowledge, the synthesis of trisulfide-1,1,3-trioxide of the type of **157** has never been reported and very few of the disulfide analogs are known.[127e,f,l]

In the present study, the preparation of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has been achieved using various oxidizing agents on different substrates. Compound **157** was first isolated from the 3 equivalent oxidation of di-*t*-butyl trisulfide (**118c**) with *m*-

CPBA, DMD and CH_3CO_3H at low temperature and under an inert atmosphere **(equation 63)**.

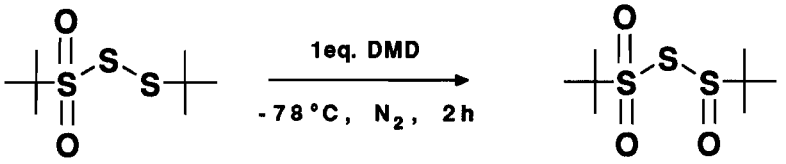


(eq. 63)

118c **157**

[O] = *m*-CPBA 79%
[O] = CH_3CO_3H 36%
[O] = DMD 90%

A similar preparation of **157** was carried out by reacting di-*t*-butyl trisulfide-1,1-dioxide (**145**) with 1 equivalent of DMD at low temperature and in an inert atmosphere. Evaporation of the solvent gave a high yield of **157** as a white powder **(equation 64)**.



(eq. 64)

145 **157 (93%)**

The characterization of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) was carried out by the use of NMR (Table **12** at the end of this section) and mass spectrometry. Recrystallization of **157** from *n*-pentane afforded colorless prisms that were suitable for X-ray analysis. Figure **4** represents the ORTEP drawing of **157** and Table **10** the selected bond lengths and angles. The S-S bond lengths of **157** are longer than the ones of a regular trisulfides. As discussed later, the S-S bond bearing the dioxide is 0.04Å shorter than the S-S bond bearing only 1 oxygen. The relative large difference in there S=O bond lengths has also been noted in by Harpp and coworkers.[118d] The valency angle of the internal sulfur is 10° higher than the minimum interaction value of 90°. The other data reflect again the asymmetry of the molecule considered.

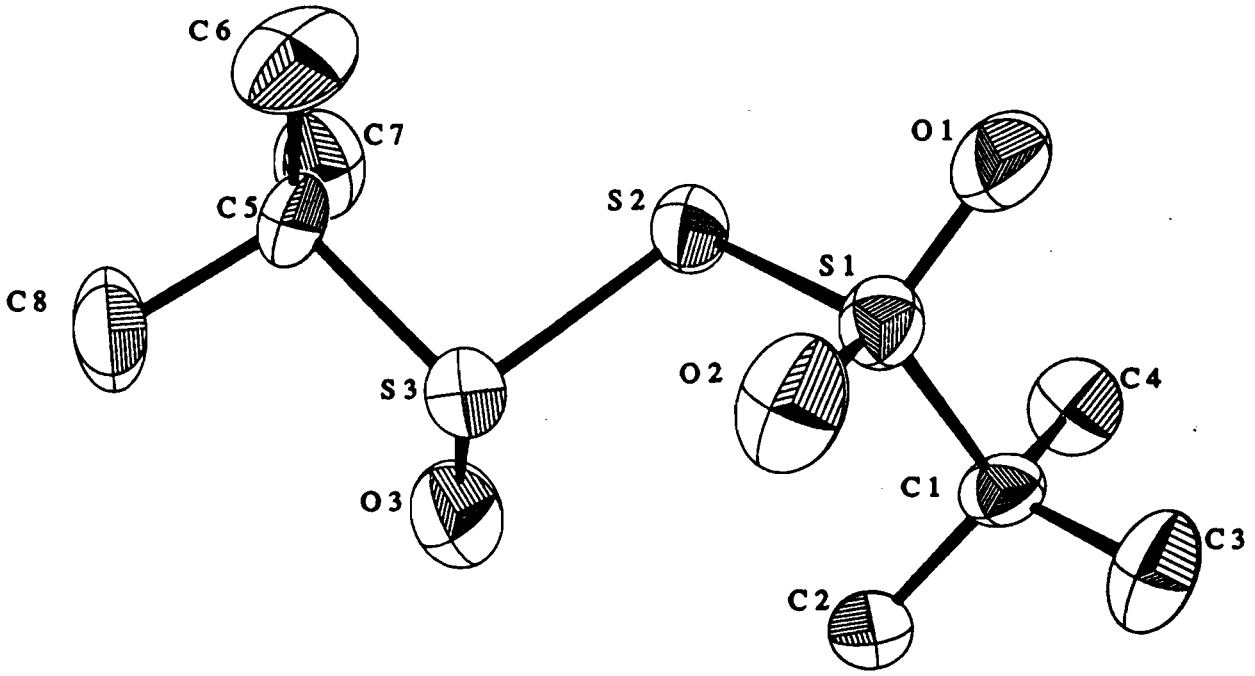


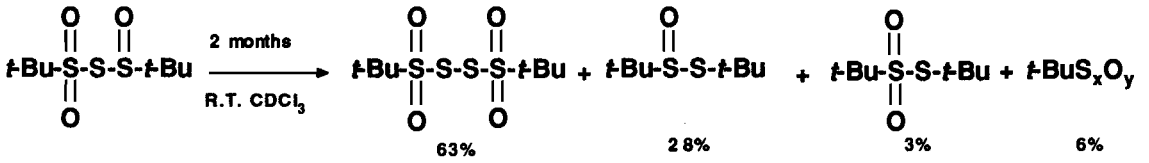
Figure 4: ORTEP Drawing of di-*t*-Butyl Trisulfide-1,1,3-Trioxide (157)

Table 10: Bond lengths, valency angles and torsion angles for 157[a]

Bond Lengths (Å)					
S(2)-S(1)	2.095(3)	S(2)-S(3)	2.136(4)		
S(1)-O(1)	1.427(7)	S(1)-O(2)	1.393(9)	S(3)-O(3)	1.490(10)
S(1)-C(1)	1.834(10)	S(3)-C(5)	1.860(11)		
Valency Angles (°)					
S(1)-S(2)-S(3)	100.23(14)	O(1)-S(1)-O(2)	120.9(6)		
S(2)-S(1)-O(1)	102.7(3)	S(2)-S(1)-O(2)	108.5(3)	S(2)-S(3)-O(3)	108.2(4)
S(2)-S(1)-C(1)	107.0(3)	S(2)-S(3)-(C5)	96.9(3)		
S(1)-C(1)-C(2)	109.5(7)	S(3)-C(5)-C(6)	110.4(9)		
S(1)-C(1)-C(3)	107.4(6)	S(3)-C(5)-C(7)	101.7(7)		
S(1)-C(1)-C(4)	104.8(8)	S(3)-C(5)-C(8)	107.9(7)		
Torsion Angles (°)					
S(3)-S(2)-S(1)-C(1)	-92.8(3)		S(1)-S(2)-S(3)-C(5)	142.6(4)	
O(1)-S(1)-S(2)-S(3)	-153.7(4)		O(2)-S(1)-S(2)-S(3)	-24.5(4)	

[a] Estimated σ's refer to the last digit.

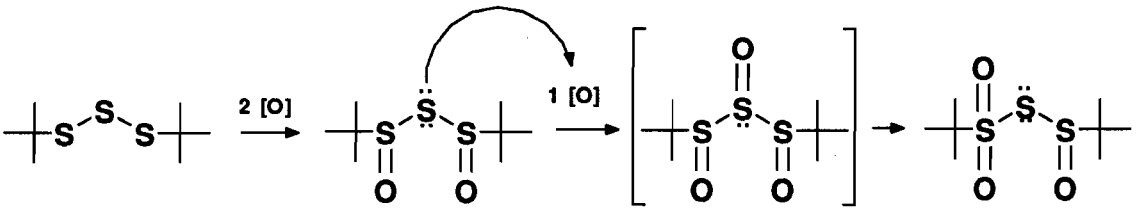
The decomposition of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has been studied at room temperature in deuterated chloroform. It was found to be rather stable and gave after 15 days, di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) and **120b** as major compounds as well as small amounts of **144** and other alkyl polysulfide-polyoxides (**Scheme 27**). A discussion on the decomposition mechanism of **157** is presented in Chapter 4.



157 **159** **120b** **144**

SCHEME 27

The synthesis of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has been achieved by oxidation of **118c** and **145**. In both cases, the desired product was isolated. Using 3 equivalents of oxidizing agent, di-*t*-butyl trisulfide-1,3-dioxide (**130**) was formed and then it reacted with the remaining electrophilic oxidizing agent to give **157** (see Chapter 4). By analogy with the oxidation of thiosulfinate esters (see Chapter 1), it would be thus extrapolated that the internal sulfenyl sulfur of **130** is more electron rich than the external sulfinyl sulfur. Thus, the reaction should proceed through the formation of a very reactive di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) that should rapidly rearrange to **157** (**Scheme 28**).

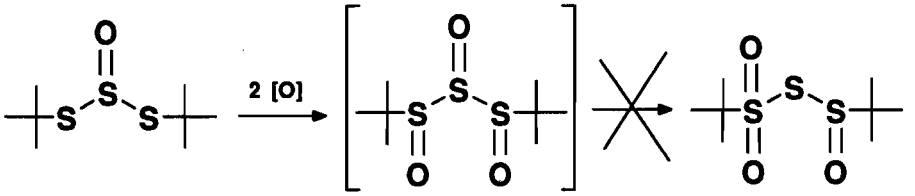


118c **130** **160** **157**

SCHEME 28

In a separate experiment, the detection of di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) was attempted by low temperature NMR. The 2 equivalent *m*-CPBA oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) was carried out at -60°C (the melting point of $CDCl_3$ is -64°C). Compound **160** could not be clearly identified which is not really surprising

knowing that the trisulfide-1,2-dioxide **158** is barely stable at -60°C as seen earlier. However, according to equations **58** and **61** that describe the preparations of trisulfide-1,3-dioxide **130** and trisulfide-1,2-dioxide **158** respectively, it is thought that the very reactive **160** is formed and immediately rearranges to the trisulfide-1,1,3-trioxide **157** as proposed in the last step of Scheme **28**. However, no trace of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) could be detected in any of the many attempted oxidations of the trisulfide-2-oxide (**156**) even when the reaction was carried out below -80°C using DMD as oxidizing agent (**equation 65**).

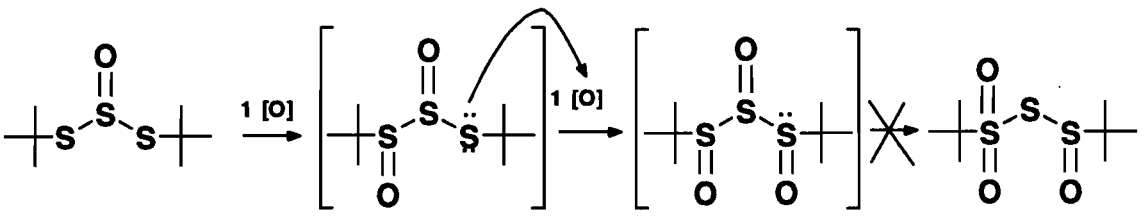


(eq. 65)

156 **157**

[O] = *m*-CPBA ($CDCl_3$, -60°C, 6 h)
[O] = DMD (Acetone, <-80°C, 5 h)

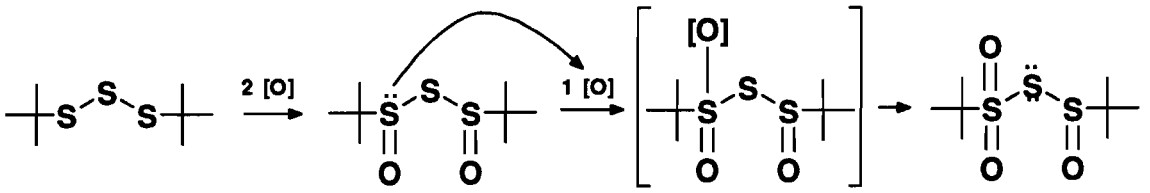
These detection experiments likely rule out the mechanism proposed in Scheme **28** for the 3 equivalent oxidation of di-*t*-butyl trisulfide (**118c**) to **157** because if **160** existed it would not give **157** as demonstrated by equation **65** where the **160** intermediate is more likely to be formed than in Scheme **28** (**Scheme 29**).



156 **158** **160** **157**

SCHEME 29

In addition, in contrast with any reaction that implies the rearrangement of di-*t*-butyl polysulfide-1,2-dioxide,[203] the formation of **157** and its tetrasulfide analog (presented at the end of this chapter) is very clean and can be achieved in fair, overall yield. According to these results, the only possible mechanism for the formation of **157** is the attack of the electrophilic oxidizing agent by the sulfinyl sulfur rather than the central sulfur (**Scheme 30**). Another proof of this electrophilic oxidative non-reactivity of the internal sulfur is given by equation **70** where no attack takes place at the central sulfenyl sulfur as reported in the literature.[174b,199]

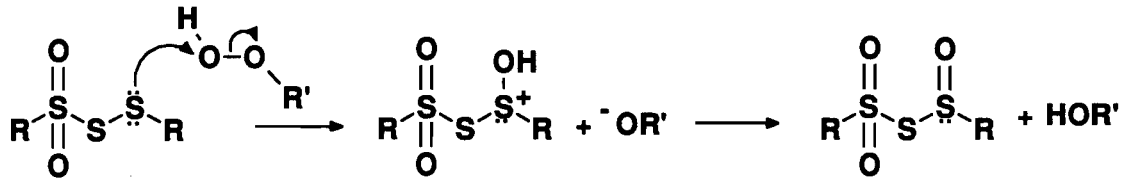


118c **130** **157**

SCHEME 30

To our knowledge, this is the first clear evidence of a preferred attack at a sulfinyl sulfur rather than the internal sulfenyl sulfur. A detailed discussion on the possible formation and the decomposition of di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) is presented in Chapter 4.

Finally, the oxidation of **145** affords **157** by attack of the external sulfenyl sulfur which is more electron rich than the internal one (**Scheme 31**). In this case, the yield is slightly higher (94%) and the reaction is much faster than the reaction in Scheme **30** because the sulfur atom that reacts is much more nucleophilic than the sulfinyl sulfur of **130**.



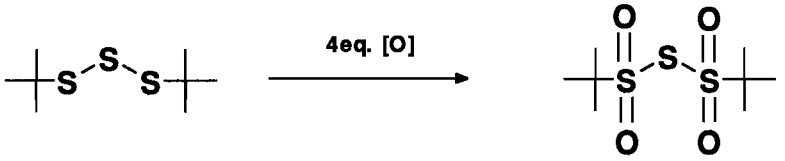
145 **157**

SCHEME 31

3.2.6. Synthesis, Characterization and Reactivity of di-*t*-Butyl Trisulfide-1,1,3,3-Tetraoxide (161)

The synthesis of alkane trisulfide-1,1,3,3-tetraoxide (ethyl, propyl, isopropyl and *n*-butyl) has been reported using excess hydrogen peroxide.[199] In the present study, the oxidation of di-*t*-butyl trisulfide (**118c**) and di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) was carried out using various electrophilic oxidizing agents.[209]

Di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) was first prepared by oxidation at low temperature of the corresponding trisulfide using 4 equivalents of either *m*-CPBA, DMD or CH_3CO_3H. In all cases compound **161** was isolated as a white solid (**equation 66**).

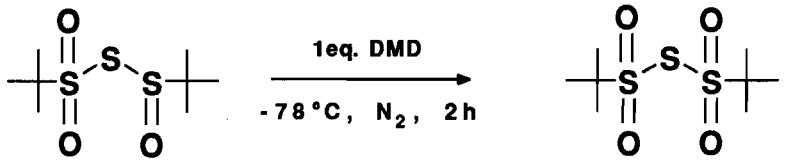


(eq. 66)

118c **161**

[O] = *m*-CPBA 53%
[O] = CH_3CO_3H 25%
[O] = DMD 64%

A parallel study showed that the 1 equivalent DMD oxidation of **157** at low temperature afforded compound **161** in a good yield (**equation 67**).



(eq. 67)

157 **161 (78%)**

The characterization of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) was accomplished using NMR (Table **12** at the end of this section) and mass spectrometry. Recrystallization of **161** from *n*-pentane afforded colorless crystals suitable for X-ray analysis. The ORTEP drawing of **161** is shown in Figure **5** and Table **11** gives the corresponding selected bond lengths and angles. Compound **161** is symmetrical and has a mirror of symmetry. The S-S bond lengths of **161** are equal but stretched by 0.03Å compared to the known trisulfides.[196] The valency angle of the internal sulfur is 19° higher than the minimum interaction value of 90° because of the repulsion induced by the presence of the four oxygen atoms.

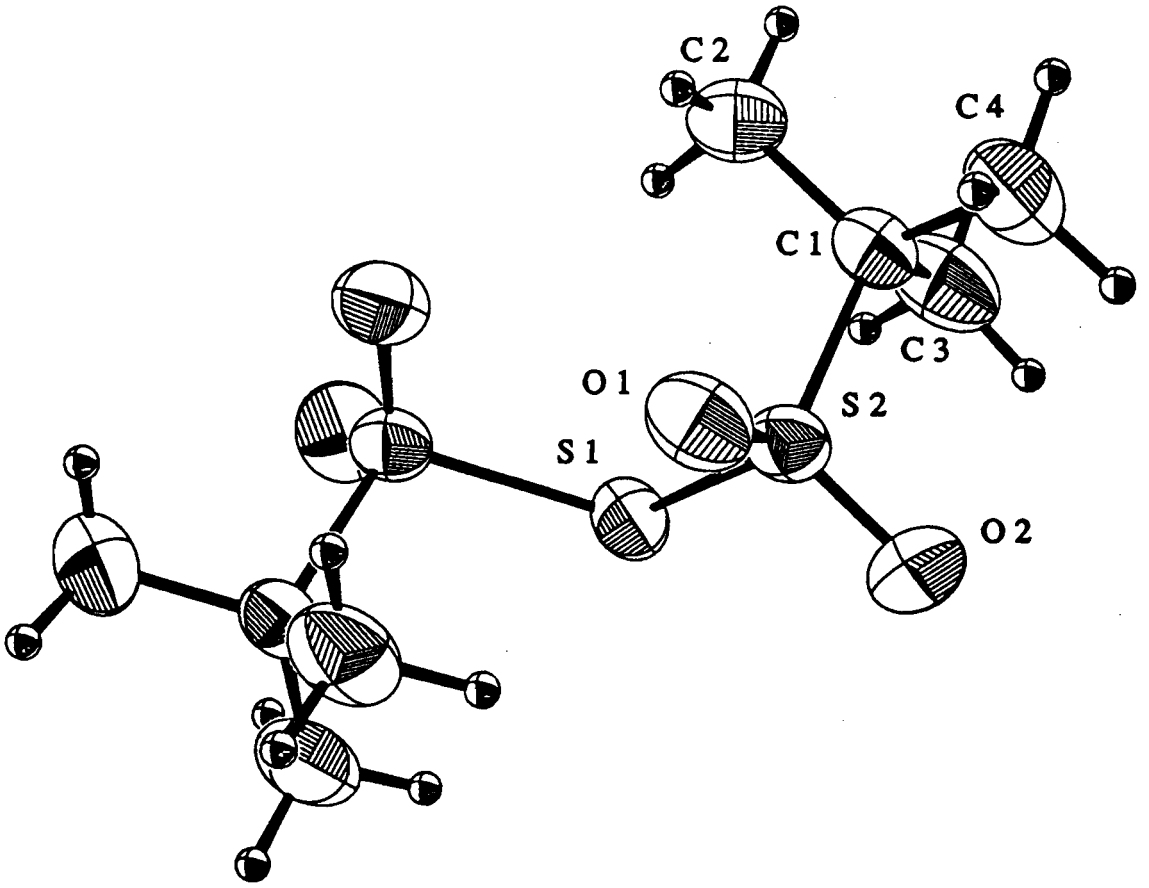


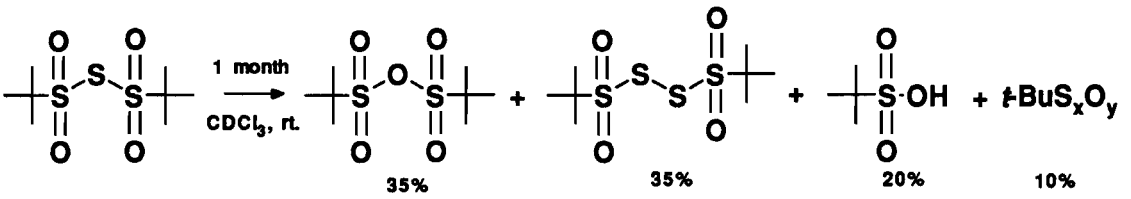
Figure 5: ORTEP Drawing of di-*t*-Butyl Trisulfide-1,1,3,3-Tetraoxide (161)

Table 11: Bond lengths, valency angles and torsion angles for 161[a]

Bond Lengths (Å)			
S(2)-S(1)	2.1175(12)	S(2)-S(3)	2.1175(12)
S(1)-O(1)	1.410(3)	S(1)-O(2)	1.440(3)
S(1)-C(1)	1.823(4)		
Valency Angles (°)			
S(1)-S(2)-S(3)	109.52(7)	O(1)-S(1)-O(2)	118.67(17)
S(2)-S(1)-O(1)	111.00(12)	S(2)-S(1)-O(2)	101.29(13)
S(2)-S(1)-C(1)	106.20(23)		
S(1)-C(1)-C(2)	107.7(3)		
S(1)-C(1)-C(3)	109.1(3)		
S(1)-C(1)-C(4)	104.4(3)		
Torsion Angles (°)			
S(3)-S(2)-S(1)-C(1)	95.0(1)	S(1)-S(2)-S(3)-C(5)	95.0(1)
O(1)-S(1)-S(2)-S(3)	25.5(1)	O(2)-S(1)-S(2)-S(3)	152.4(1)

[a]. Estimated σ's refer to the last digit.

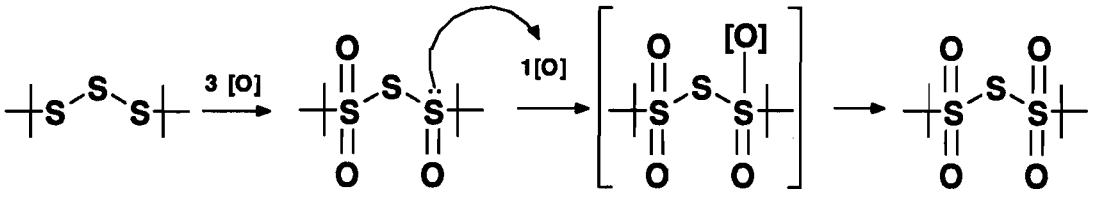
The decomposition of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) in deuterated chloroform at room temperature was followed by NMR spectrometry. After 1 month, the analysis of the spectrum showed the formation of various products. The main decomposition products were an equimolar mixture of the di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) and the postulated *t*-butyl sulfonic anhydride (**206** *vide infra*) as well as significant amounts of *t*-butyl sulfonic acid **164**. Small quantities of sulfinic acid **163**, di-*t*-butyl disulfide-1,1-dioxide **144** and other derivatives were also detected (**Scheme 32**).



161 **206** **159** **164**

SCHEME 32

The desired di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) was obtained by oxidation of either **118c** and **157**. In the first case, oxidation to compound **157** takes place as previously described. By analogy with what is described for the preparation of **157**, the formation of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide is explained by nucleophilic attack of the sulfinyl sulfur which was previously shown to be more electron rich than the internal sulfur. The 1 equivalent oxidation of **157** to **161** is rationalized by the same mechanism (**Scheme 33**). As noticed for the preparation of **157**, this reaction is very clean and much slower than the one involving the attack of a sulfenyl sulfur. However, using a large excess of electrophilic oxidizing agent (described in the next section), a very high yield of **161** can be obtained and no addition takes place at the central sulfur.

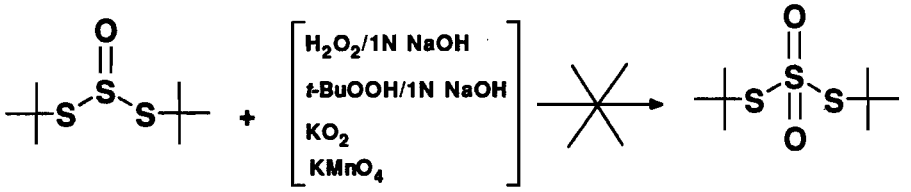


118c **157** **161**

SCHEME 33

3.2.7. Attempts Toward the Synthesis of Other Oxide Derivatives of di-*t*-Butyl Trisulfide

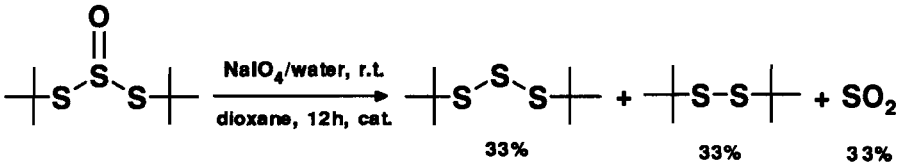
The synthesis of di-*t*-butyl trisulfide-2,2-dioxide (**162**) was attempted by nucleophilic oxidation as well as a non-oxidative approach. Oxidation of **156** at room temperature using strong nucleophilic oxidizing agents[209] such as H_2O_2/1N NaOH, *t*-BuOOH/1N NaOH, KO_2 and $KMnO_4$ were unsuccessful. Under mild conditions, no conversion of the starting material was observed after several days. Under more drastic conditions, the analysis of the reaction mixture showed a mixture of polysulfides that was impossible to rationalize as reported by Field[179a] (**equation 68**).



(eq. 68)

156 **162**

Using 1 equivalent of $NaIO_4$ under the conditions described by Oae and coworkers,[137a] some reaction takes place (change in color) and gives an equimolar mixture of di- and trisulfides which are the usual decomposition products of **156** (**equation 69**).

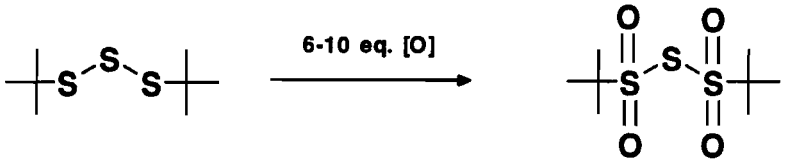


(eq. 69)

156 **118c** **118b**

By analogy with the synthesis of **156**, the preparation of **162** was attempted by adding *t*-butyl mercaptan to 0.5 equivalents of sulfuryl chloride in the presence of pyridine at low temperature. Under these conditions, a quantitative yield of di-*t*-butyl disulfide was isolated. The mechanism of this reaction has been explained (Chapter 2) by the formation of the sulfenyl chloride which then reacts with the remaining *t*-butyl mercaptan.

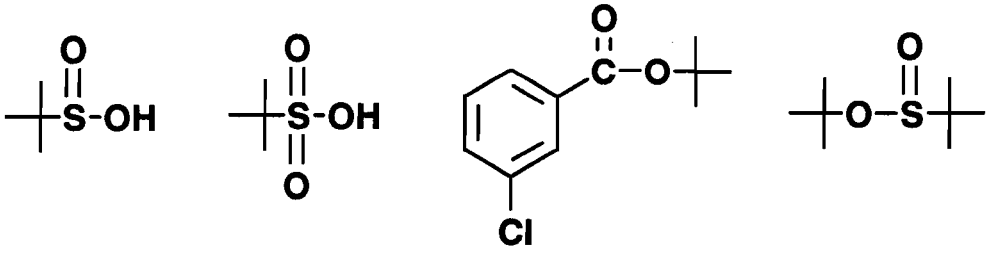
The preparation of pent- and hexoxide derivatives of di-*t*-butyl trisulfide (**118c**) were attempted by using 6-10 equivalents of *m*-CPBA and DMD at low and room temperatures. In all cases, the only compound formed was di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (**equation 70**). These results clearly show that no oxidation is taking place at the central sulfur under these conditions because if any pent- or hexoxide derivative was formed, its decomposition products should be easily detected.



(eq. 70)

118c **161**

The synthesis of di-*t*-butyl trisulfide-1,2,3-trioxide (**160**), di-*t*-butyl trisulfide-1,1,2,3-tetraoxide and the pentoxide analog were also attempted. Di-*t*-butyl trisulfide-2-oxide (**156**) was oxidized with 2, 3 and 4 equivalents of *m*-CPBA or DMD according to the normal oxidation procedures. The analysis of the reaction mixtures resulted in undefined and not separable mixtures. The main products identified were *t*-butyl sulfinic acid (**163**), *t*-butyl sulfonic acid (**164**), *t*-butyl-3-chlorobenzoate (**146**) and *t*-butyl *t*-butylsulfinate (**147**)[134c] as well as the trisulfide-1,1-dioxide **145** and the disulfide-1-oxide **120b**. The ratios of these compounds depend on the number of equivalents of electrophilic oxidizing agent employed.



163 **164** **146** **147**

3.3. Conclusions

The present study allowed the isolation of different di-*t*-butyl trisulfide-polyoxides which are illustrated on Figure **6**. The low temperature detection of two intermediates was also attempted.

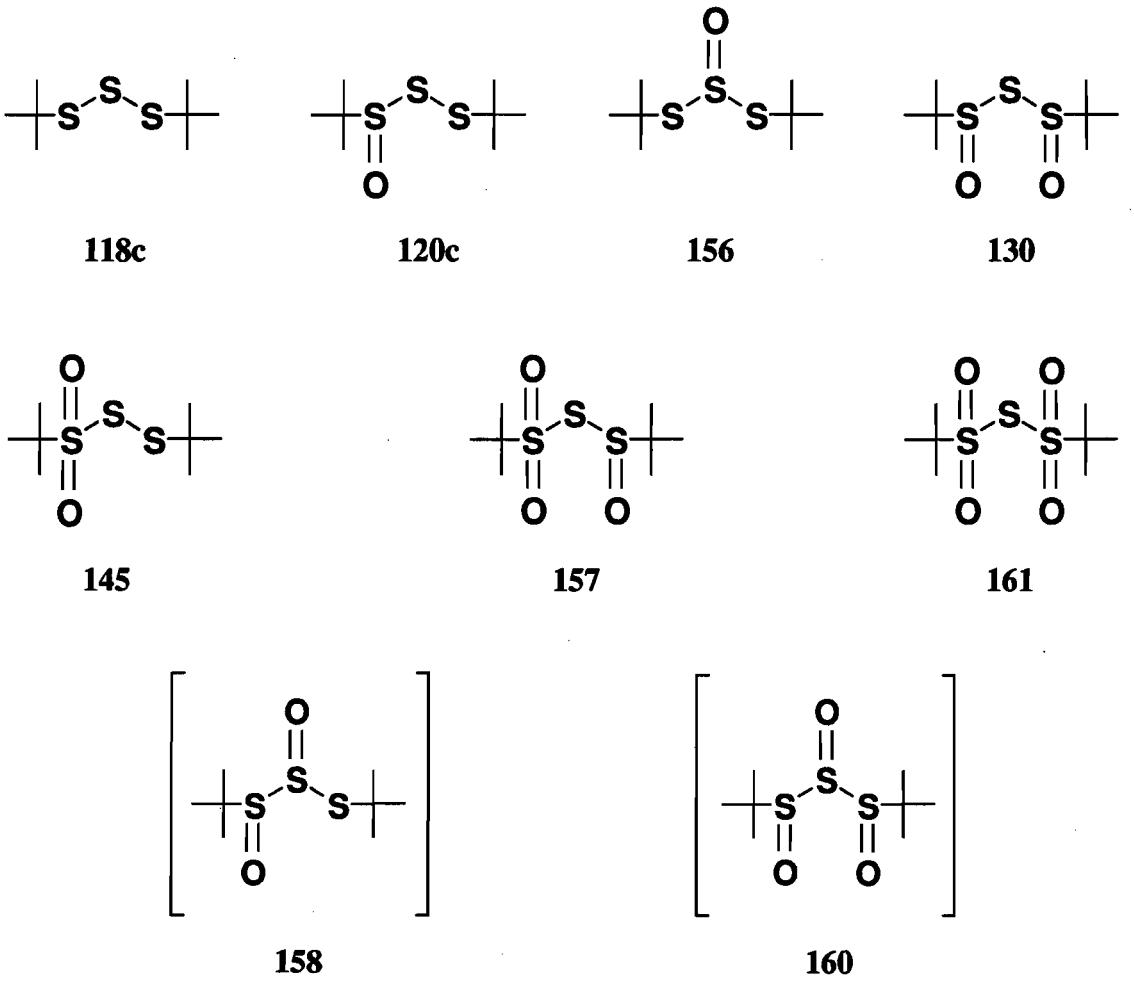
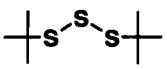
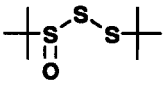
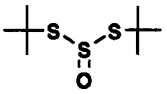
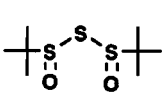
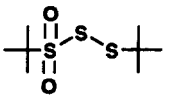
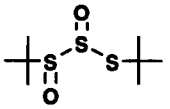
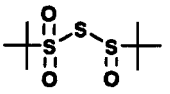
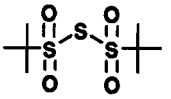


Figure 6: di-*t*-Butyl Trisulfide-Polyoxides

3.3.1. NMR and Mass Spectrometry Study

The oxide derivatives of di-*t*-butyl trisulfide presented in Figure **6** were characterized by ^{1}H NMR and ^{13}C NMR and their respective chemical shifts are reported in Table **12**.

Table 12: ^{1}H and ^{13}C NMR Chemical Shifts (δ ppm) of *t*-Butyl Trisulfide-Polyoxides[a,b]

Entry	$R\text{-}S_3O_n\text{-}R'$	C	CH_3	H	C'	CH'_3	H'
118c		48.91	29.88	1.347			
120c		60.67	23.79	1.385	48.73	29.80	1.390
156		52.10	31.80	1.545			
130a		62.39	24.17	1.410			
130b		62.02	24.18	1.422			
145		70.06	24.18	1.465	49.95	29.86	1.395
158[d]		59.34	23.06	1.393	52.77	31.91	1.293
157		71.38	23.99	1.551	63.08	24.51	1.463
161		73.45	24.15	1.545			

[a] Recorded using deuterated chloroform ($CDCl_3$) as NMR solvent; [b] Relaxation time (t_1) used: t_1= 2s; [c] **130a** and **130b** represent the two diastereoisomers of **130**; [d] The spectra were obtained at -60°C and do not represent a specific diastereoisomer.

For unsymmetric molecules (**120c**, **145**, **157**, **158**), the more deshielded tertiary carbon (C in Table **12**) is bonded to the sulfur of higher oxidation in ^{13}C NMR and the related methyl groups (H and CH_3 in Table **12**) are the more shielded in both ^{1}H and ^{13}C NMR.

The analysis of the ^{13}C NMR data shows that the addition of 1 oxygen on a sulfur α to a *t*-butyl group has a great deshielding effect (11-13 ppm when a sulfinyl group is formed and 9-10 ppm when a sulfonyl group is formed) on the tertiary carbon and a moderate to small shielding effect (5-6 ppm when a sulfinyl group is formed and 0-1 ppm when a sulfonyl group is formed) on the corresponding methyl group. When the added oxygen is on the sulfur in the β position to the *t*-butyl group, it has a weak (<3 ppm) deshielding effect on the tertiary carbon and a small (<2 ppm) shielding effect on the methyl group. When the oxygen atom is added on the sulfur in the γ position to the *t*-butyl group, it has a weak shielding or deshielding (-1 to +1 ppm) effect on the tertiary carbon and methyl groups depending on the molecule. These shielding and deshielding effects are also observed in proton NMR but they are more difficult to see as the scale is much smaller.

It can been seen that the α effect is by far the most important. The quantification of these effects can be a very good predicting tool. For example, di-*t*-butyl trisulfide-1,3-dioxide (**130**) should show a tertiary carbon signal between 61 and 63 ppm and a corresponding methyl signal between 24 and 25 ppm. The actual values (62.02, 62.39/24.17, 24.18) lie exactly in the range predicted and this confirm the existence of **130** which was subject to controversy (**Figure 7**).

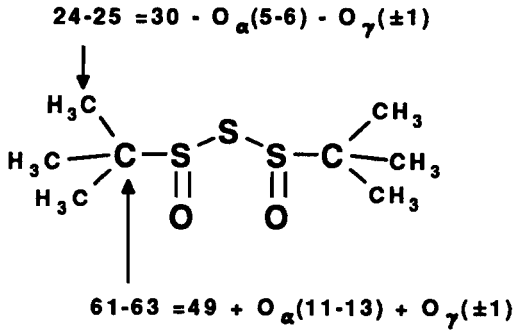


Figure 7

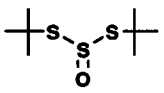
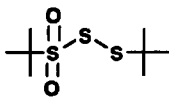
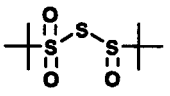
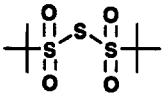
The mass spectra of the different di-*t*-butyl trisulfide-polyoxides were recorded. The relative intensities of the typical fragmentation are gathered in the experimental section of Chapter 3. The different samples have been carried out by direct inlet using EI

or CI ion source depending on their respective sensitivity and at different temperatures according to their respective vaporization properties. The typical fragmentation is *t*-Bu$^{+\cdot}$, *t*-BuS(O)$^{+\cdot}$, *t*-BuS(O)$_2^{+\cdot}$ and *t*-BuS$^{+\cdot}$ which have various intensities (0%-100%) depending on the compound. In most cases, the M$^{+\cdot}$ peak is very small, and the loss of 1 oxygen atom seems relatively facile.

3.3.2. Crystallography Study

The X-ray analysis of some of the di-*t*-butyl trisulfide-polyoxides allowed the unambiguous characterization of these materials. Although nothing has been reported on the structures of trisulfide-polyoxides, there are a few reports on trisulfides,[196] disulfides,[92d,216] and disulfide polyoxides[118] that could give some likely values as to their S-S bond lengths and valency angles. The S-S bond lengths of different disulfides, trisulfides, thiosulfinates and thiosulfonates vary from 2.02Å to 2.098Å, the longest one being that of the thiosulfinates. The corresponding S-S-S bond angles lie between 90° and 107°. The S-S bond lengths and angles observed in the present study are gathered in Table **13**.

Table 13: S-S Bond Lengths and Angles of di-*t*-Butyl Trisulfide-Polyoxides[a]

Entry	S(1)-S(2)-S(3)	S(1)-S(2) (Å)	S(2)-S(3) (Å)	S(1)-S(2)-S(3) (°)
156		2.066(9)	2.045(10)	89.8(4)
145		2.1159(24)	2.0093(24)	105.31(10)
157		2.095(3)	2.136(4)	100.23(14)
161		2.1175(12)	2.1175(12)	109.52(7)

[a] Estimated σ's refer to the last digit.

216 I. A. Abu-Yousef, R. C. Hynes and D. N. Harpp, *Tetrahedron Lett.*, **34**, 4289 (1993).

The S-S bond lengths of this class of compounds vary by more than 0.12Å depending on the molecule. This amplitude is more than twice the variation observed for the disulfide, thiosulfinate and thiosulfonate derivatives of *5H,8H*-dibenzo[*d,f*][1,2]-dithiocin.[92d] However, the length of the S-S(O) bond is the longest as reported for the disulfide analogs.

When the oxygen is on S(2) the difference in the S-S bond lengths is 0.021Å which is representative of the asymmetry of the molecule due to the chiral sulfinyl sulfur. However, these two bond lengths lie in the range of regular trisulfides. Meanwhile, the valency angle of the sulfinyl sulfur is much smaller than the one reported for trisulfides, but it is very close to the one of disulfides (90°). Consequently, the addition of an oxygen atom on the internal sulfur of a trisulfide does not affect much the S-S bond lengths but it considerably decreases its valency angle. The addition of an oxygen atom on the external sulfurs has a strong increasing effect (0.12Å) on the sulfinyl sulfenyl bond and a small decreasing effect (0.02Å) on the other S-S bond. It also decreases the internal sulfur valency angle by about 5° to 8°. Finally, the addition of 2 oxygen atoms on the same external sulfur has a moderate increasing affect (0.07Å) on the S-S bond bearing the sulfur dioxide group and a moderate decreasing effect (0.05Å) on the other S-S bond; it has virtually no effect on the bond angles.

By analogy with what has been discussed earlier about the shielding and deshielding effect of oxygen in the ^{1}H and ^{13}C NMR, this X-ray analysis could be used to determine the bond lengths and angles of other di-*t*-butyl trisulfide-polyoxides which could also be compared to molecular modeling calculations. For instance, the addition of 2 oxygen atoms on the internal sulfur should even more decrease its valency angle and therefore facilitate the extrusion of sulfur dioxide as suggested in Chapter 4. The fact that the sulfinyl sulfenyl (S(O)-S) bond length is the longest, confirms the preferred breaking of that bond as proposed in Chapter 4. It could also explain why the trisulfide-polyoxide analogs that bear a sulfinyl sulfur are less stable than the others. As a result, the sulfonyl sulfenyl ($S-S(O)_2$) bond is shorter than the sulfinyl sulfenyl (S-S(O)) bond for di- and trisulfide derivatives. Considering that the valency angle of the sulfonyl moiety is about 130° (O=S=O), these results suggest that the dipole-dipole interaction of the 2 oxygen atoms reduces their individual influence on the corresponding S-S bond **(Figure 8)**.

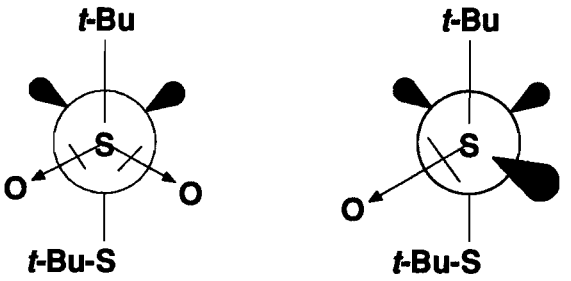
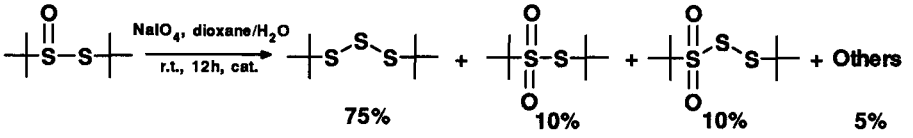


Figure 8: Dipole-Dipole Interaction

3.3.3. Nucleophilic Oxidation

The nucleophilic oxidation of di-*t*-butyl trisulfide as well as the 1- and 2-oxide analogs was examined in some detail. In each case, the major products observed are the corresponding di-, tri- and tetrasulfides. Using H_2O_2/1N NaOH, *t*-BuOOH/1N NaOH, KO_2 or $KMnO_4$, the oxidation of various substrates was unsuccessful. However, using $NaIO_4$, a reaction takes place (change in color) but does not deliver the expected products although the nucleophilic oxidation of supposedly less reactive aryl and primary alkyl thiosulfinates as well as disulfides is reported[135a] to be very effective (quantitative yield). A separate experiment revealed that the $NaIO_4$ oxidation of di-*t*-butyl disulfide-1-oxide (di-*t*-butyl thiosulfinate) **(120b)** only afforded 10% of the expected disulfide-1,1-dioxide (thiosulfonate) **144 (equation 71)**.

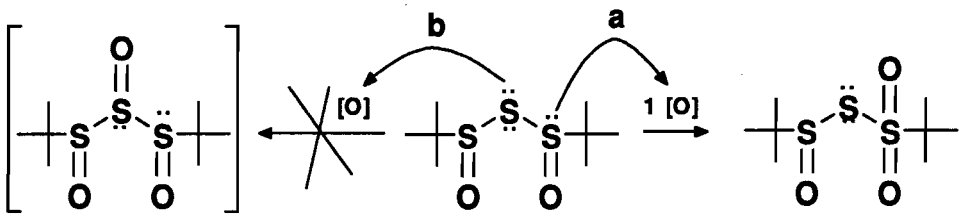


120b **118c** **144** **145** **(eq. 71)**

These results tend to confirm the hypothesis[135] that the nucleophilic oxidation is controlled by steric effects and thus, in the case of di-*t*-butyl polysulfides, steric hindrance is such that none of the expected product is formed. All of these oxidations are solvent and oxidant concentration dependent. No consistent oxidation behaviour is evident in this case. More limited studies by Field[179a] and Bartlett[200] concluded similarly.

3.3.4. Electrophilic Oxidation

The oxidation of di-*t*-butyl trisulfide and its oxide analogs afford a wide variety of products in a regiospecific manner. The more electron rich of the three sulfurs attacks the electrophilic oxidizing agent. The internal sulfur is surprisingly non-reactive to electrophilic oxidizing agents and in all the reactions and mechanisms presented here, the reaction at the central sulfur can be ruled out. In contrast with some current thinking that the sulfenyl sulfur is more electron rich that the sulfinic sulfur, the preparation of the trisulfide-1,1,3-trioxide **157** and the trisulfide-1,1,3,3-tetraoxide **161** are the first clear examples,[198] to our knowledge, of preferred attack at the sulfinic sulfur (path a) rather than at the available internal sulfenyl sulfur (path b).



157

Freeman and coworkers proposed that the oxidation of bis(2-propenyl) trisulfide-1-oxide takes place at the lower electron density sulfur atom adjacent to the sulfinyl sulfur but this was not proved and is contrary to the preparation and isolation of di-*t*-butyl trisulfide-1,3-dioxide (**130**).

Although common electrophilic oxidizing agents give satisfying results, dimethyl dioxirane is the oxidizing agent of choice considering its high reactivity, short reaction time and simplicity of procedure. In addition, it can be used at very low temperatures and no by-products are formed after it reacts which seems crucial for the synthesis of unstable products as well as for reactions that involve rearrangement of intermediates. The different oxide derivatives isolated were characterized by NMR and mass spectrometry and when it was possible, X-ray analysis were carried out. The thermal decomposition of each of them was studied and was found to be very complex as none of these decomposition mixture is straight-forward. The mechanism of decomposition of the oxide derivatives of polysulfides is discussed in Chapter 4.

3.3.5. General

All these compounds can be synthesized in reasonable yields by electrophilic oxidation or non-oxidative synthetic procedures . They are very odorous and relatively unstable at room temperature (except di-*t*-butyl trisulfide-1,1-dioxide **(145)**) which seriously complicates their isolation and characterization. Finally, the oxidative reactivity of this class of compounds was qualitatively determined by following the reaction by tlc and it was found to decrease with the number of oxygen atoms bonded to the trisulfide **(Figure 9)**.

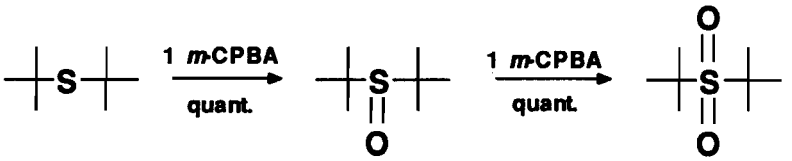
$$R_2S_3O > R_2S_3O_2 > R_2S_3O_3 > R_2S_3O_4$$

Figure 9: Oxidative Reactivity of the Oxide Derivatives of di-*t*-Butyl Trisulfide.

3.4. Extension to the Oxidation of other Polysulfides

3.4.1. Oxidation of Sulfides

The procedure of the oxidation of di-*t*-butyl trisulfide was extended to the synthesis of oxide derivatives of di-*t*-butyl sulfide. The one and two equivalent *m*-CPBA oxidation of di-*t*-butyl sulfide **(118a)** afforded almost quantitative yields of di-*t*-butyl sulfoxide **(120a)** and di-*t*-butyl sulfone **(121)** respectively **(equation 72)**.



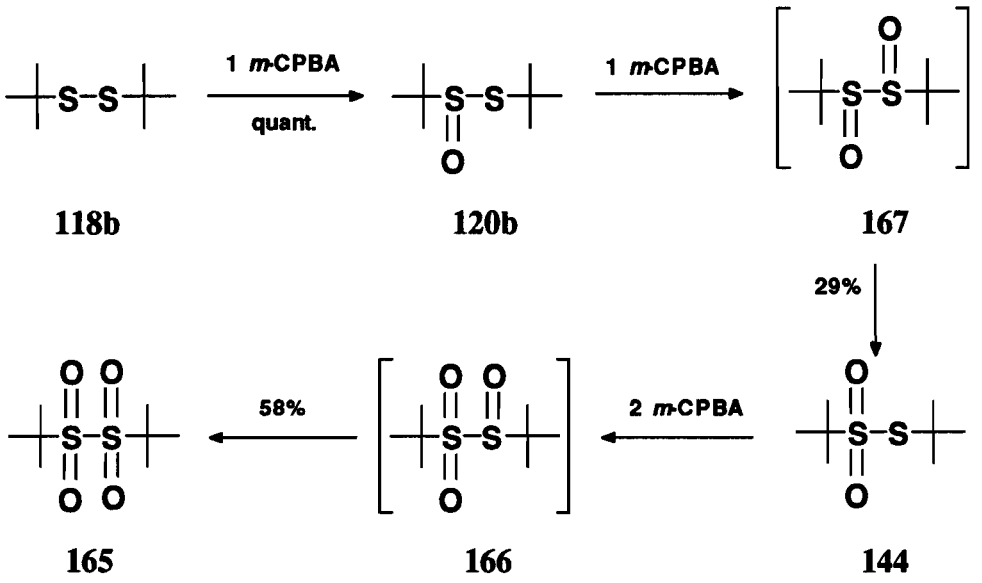
118a **120a** **121** **(eq. 72)**

The oxidation of sulfides has been extensively studied using many different oxidizing agents.[4]

3.4.2. Oxidation of Disulfides

The oxidation of disulfides has been thoroughly studied as described in Chapter 1. However, most of the research has been focussed on the detection of the *vic*-disulfoxide moiety **80**. The synthesis of disulfide-1,1,2-trioxide (sulfinyl sulfone) **82** and disulfide-1,1,2,2-tetraoxide (*vic*-disulfone) **83** has also been reported mainly for aryl derivatives.[127]

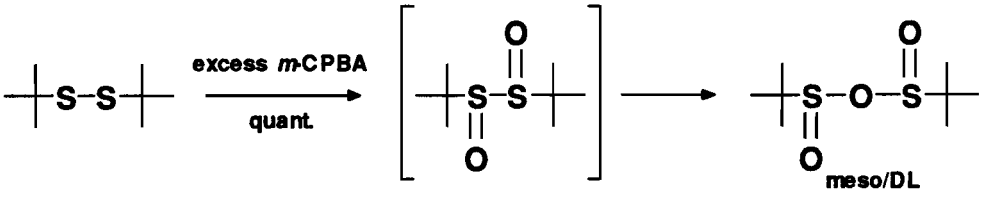
In the present study, the oxidation of di-*t*-butyl disulfide **(118b)** was achieved using *m*-CPBA and DMD. Using one equivalent of electrophilic agent under the usual conditions gave a very high yield of the corresponding disulfide-1-oxide (thiosulfinate) **120b**. The subsequent oxidation with another equivalent of oxidizing agent gave di-*t*-butyl disulfide-1,1-dioxide (di-*t*-butyl thiosulfonate) **(144)** in fair yield using DMD and variable results were obtained when *m*-CPBA was used (a detailed study is presented in Chapter 4). Further oxidation of **144** using 2 equivalents of electrophilic oxidizing agent afforded the di-*t*-butyl disulfide-1,1,2,2-tetraoxide (di-*t*-butyl *vic*-disulfone) **(165)**. Di-*t*-butyl disulfide-1,1,2-trioxide **(166)** was certainly an intermediate but could not be isolated at room temperature as reported in the literature **(Scheme 34)**.[127h,l]



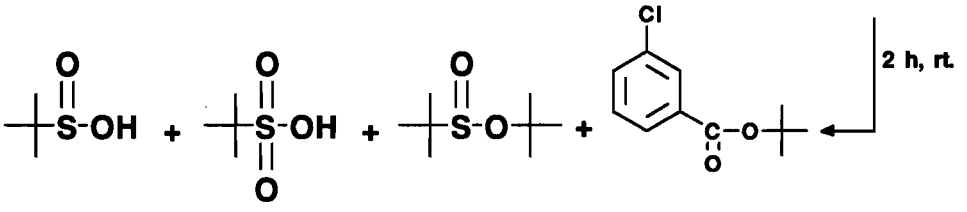
SCHEME 34

Direct oxidation of **118b** using excess oxidizing agent only afforded a high yield of *t*-butyl sulfinic anhydride **(168)** when the reaction was carried out at low temperature (<0°C). Compound **168** rapidly decomposed to a variable mixture of *t*-butyl sulfinic acid

(**163**) and *t*-butyl sulfonic acid (**164**). Significant amounts of *t*-butyl-*meta*-chlorobenzoate (**146**) and *t*-butyl *t*-butylsulfinate (**147**) were also isolated when the reaction mixture was kept at room temperature before work-up. The formation of these decomposition products is probably due to rearrangement problems of the di-*t*-butyl disulfide-1,2-dioxide (di-*t*-butyl *vic*-disulfoxide) (**167**)[203] (a detailed study is presented in Chapter 4) (**Scheme 35**).



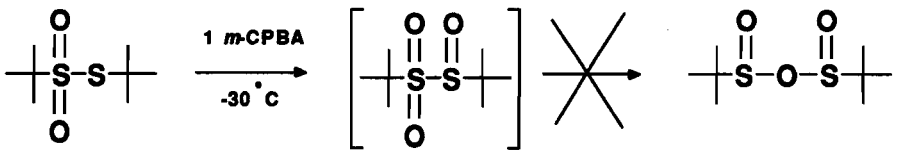
118b **167** **168**



163 **164** **147** **146**

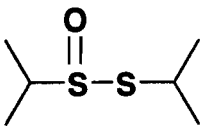
SCHEME 35

However, when the 1 equivalent oxidation of **144** was carried out at low temperature (-30°C), di-*t*-butyl disulfide-1,1,2-trioxide (**166**) was detected and characterized by ^{1}H and ^{13}C NMR. The low temperature decomposition study of the disulfide-1,1,2-trioxide **166** did not give any *t*-butyl sulfinic anhydride (**168**) (**equation 73**). A full discussion on the detection and decomposition of **166** is presented in Chapter 4.

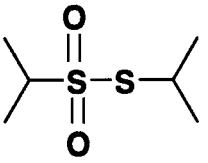


144 **166** **168** **(eq. 73)**

A similar study has been carried out on diisopropyl disulfide; diisopropyl thiosulfinate (diisopropyl disulfide-1-oxide) (**123b**) and the corresponding thiosulfonate (diisopropyl disulfide-1,1-dioxide) (**169**) were isolated in good yield using one and two equivalents respectively of DMD or *m*-CPBA. Although DMD oxidation was slightly more efficient, very good results were obtained using *m*-CPBA in contrast with the results obtained with the *t*-butyl derivative.



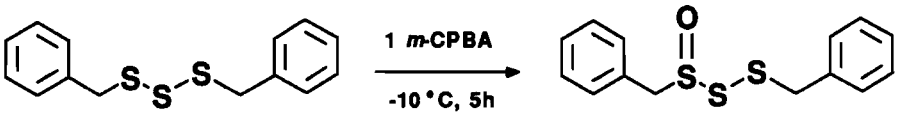
123b



169

3.4.3. Oxidation of Trisulfides

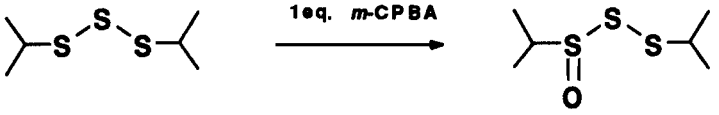
The oxidation procedures described earlier have been applied to other linear and cyclic trisulfides. The oxidation of benzyl trisulfide (**115d**) at low temperature afforded a high yield of the corresponding trisulfide-1-oxide **170** using 1 equivalent of *m*-CPBA. Compound **170** was found to have a low stability at room temperature and gave a complex mixture that could not be determined with certainty (**equation 74**).



(eq. 74)

115d **170 (91%)**

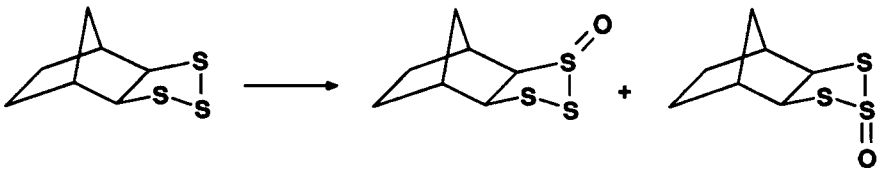
The one equivalent *m*-CPBA oxidation of diisopropyl trisulfide (**171**) afforded a moderate yield of the corresponding trisulfide-1-oxide **172** in a regiospecific manner (**equation 75**). Compound **172** was found to be relatively unstable (less than 48 h at room temperature).



(eq. 75)

171 **172 (72%)**

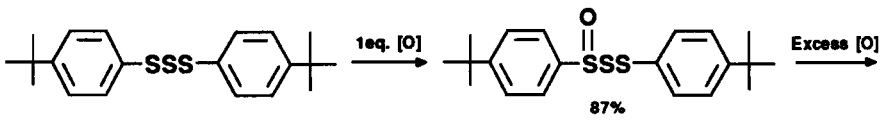
The results obtained by Bartlett and Ghosh by *m*-CPBA oxidation of norbornentrithiolane[183] (*exo*-3,4,5-trithiatricyclo[5.2.1.0]decane[201]) **(138)** were confirmed using DMD as oxidizing agent **(equation 47)**.



(eq. 47)

138 **139** **140**

The oxidation of aryl trisulfides has also been attempted. Di(*p*-*t*-butyl-phenyl) trisulfide **(115c)** has been oxidized by 1 equivalent of *m*-CPBA and DMD and gave regiospecific addition to the external sulfur to form di(*p*-*t*-butyl-phenyl) trisulfide-1-oxide **(173)**. Further oxidation using an excess of both oxidizing agents was unsuccessful and only afforded the unreacted starting material **(equation 76)**.



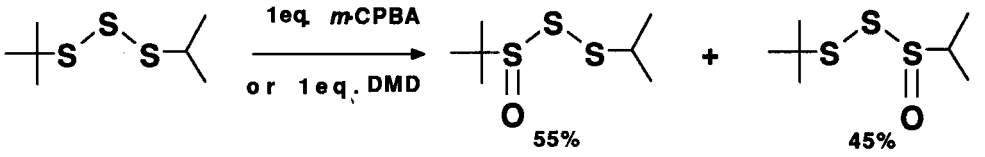
173 (eq. 76)

115c **173**

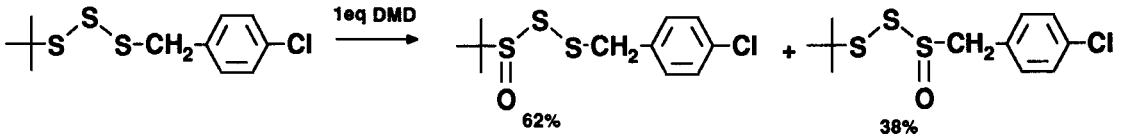
Compound **173** is very stable at room temperature contrary to its *t*-butyl analog (no decomposition was observed after 6 months at room temperature). It is also surprising that the dioxide derivative of **115c** is not formed by direct oxidation. It is believed that none of the sulfur atoms of **173** is nucleophilic enough to react with electrophilic oxidizing agents.

The synthesis of a pure unsymmetrical trisulfide-1-oxide was also attempted by direct oxidation. As reported in Chapter 1 and discussed in Chapter 2, the oxidation of an unsymmetrical disulfide is more or less regioselective depending on the substituents. However, it has never been reported as a regiospecific reaction. In order to examine this more carefully, the oxidations of *t*-butyl-isopropyl trisulfide **(116a)** and *t*-butyl-*p*-chloro-benzyl trisulfide **(116d)** have been carried out using different electrophilic oxidizing agents. The oxidation of **116a,d** afforded both possible unsymmetrical trisulfide-1-oxides in high yields (>90%). Using *m*-CPBA or DMD as oxidizing agent, the analysis of the ratios of the 1-oxides formed revealed that the attack was slightly favored at the sulfur

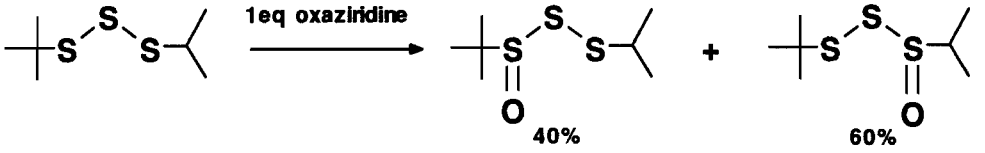
adjacent to the *t*-butyl group. By contrast, the oxidation of **116a** with 2-benzenesulfonyl-3-*p*-nitrophenyl oxaziridine[217] afforded the reverse stereoselectivity (**Scheme 36**).



116a



116d



116a

SCHEME 36

Although the regioselectivity of such a reaction is low, the sulfur adjacent to a tertiary substituent is preferred compared to secondary and primary using conventional electrophilic oxidizing agents as suggested in Chapter 2. Using an oxaziridine, the reaction takes place at the sulfur attached to the less substituted group, presumably because of steric hindrance. Even here, the regioselectivity is rather low.

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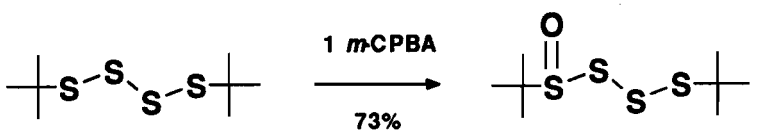
217 F. A. Davis, R. T. Reddy, W. Hava and P. J. Carroll, *J. Am. Chem. Soc.*, **114**, 1428 (1992); and references cited therein. The sample of oxaziridine used was obtained courtesy of D. Trojan.

3.4.4. Oxidation of Tetrasulfides

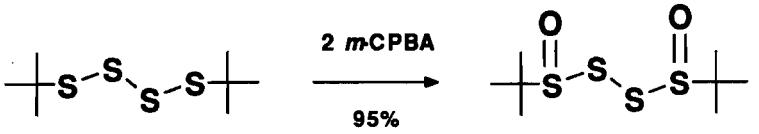
The oxidation has also been extended to tetrasulfides. Using one equivalent of *m*-CPBA, di-*t*-butyl tetrasulfide (**118d**) was converted to di-*t*-butyl tetrasulfide-1-oxide (**120d**) in fair yield (**equation 77**).



(eq. 77)

118d **120d**

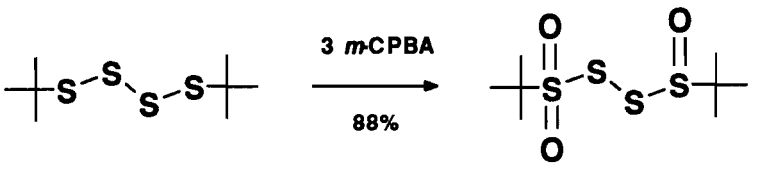
The 2 equivalent *m*-CPBA oxidation of **118d** afforded a very high yield of di-*t*-butyl tetrasulfide-1,4-dioxide (**174**) as a solid (**equation 78**). The two diastereoisomers of **174** were observed by ^{1}H and ^{13}C NMR. As its trisulfide analog, compound **174** is unstable at room temperature (<12 h) and its decomposition is discussed in Chapter 4.



(eq. 78)

118d **174 meso/d,l**

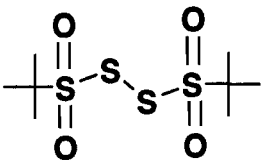
Finally, di-*t*-butyl tetrasulfide (**118d**) was oxidized using 3 equivalents of *m*-CPBA and gave a fair yield of di-*t*-butyl tetrasulfide-1,1,4-trioxide (**175**) (**equation 79**). The analysis of the crude mixture showed that the reaction was very clean and no intermediate could be detected. By analogy with the trisulfide analog, the formation of **175** is expected to proceed by the oxidation of **174** at the sulfinyl sulfur. If the internal sulfenyl sulfur was oxidized, compound **175** would be obtained by the rearrangement of a very reactive 1,2-*vic*-disulfoxide. In all cases studied here and reported in the literature,[134c] such rearrangements are not very clean and always deliver at least traces of sulfinic (**163**) and sulfonic (**164**) acid that could not be detected in the preparation of **175**. The synthesis and decomposition of **175** is discussed in Chapter 4.



(eq. 79)

118d **175**

Di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide **(159)** was isolated from the decomposition of compound **130, 157** and **161** as stated earlier.



159

Compound **159** was fully characterized and recrystallization from hexanes afforded suitable crystals for X-ray analysis. Figure **10** represents the ORTEP drawing of **159** and Table **14** the selected bond lengths and angles. The crystallography data obtained for compound **159** are very similar to the one observed for its trisulfide analog **161**. Compound **159** also presents a mirror of symmetry in the middle of the S(2)-S(3) bond. The S-S bond lengths of **159** are 0.02Å longer than the one of the trisulfide analog. There is a big difference (0.12Å) between the external and the internal S-S bond lengths of **159**. However the molecule remains relatively stable at room temperature (no decomposition after 5 months). The bond angles are smaller for **159** than they were in the corresponding trisulfide which is probably due to the release of strain generated by the additional sulfur.

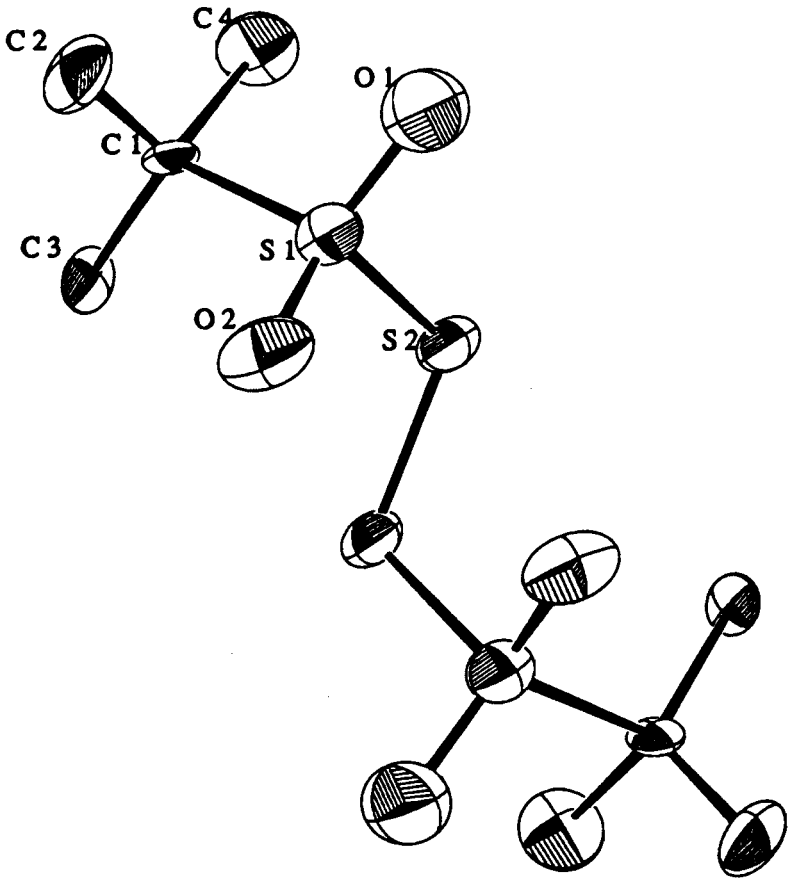


Figure 10: ORTEP Drawing of di-*t*-Butyl Tetrasulfide-1,1,4,4-Tetraoxide (159)

Table 11: Bond lengths, valency angles and torsion angles for 159[a]

Bond Lengths (Å)			
S(2)-S(1)	2.1293(16)	S(2)-S(3)	2.0037(22)
S(1)-O(1)	1.438(3)	S(1)-O(2)	1.428(3)
S(1)-C(1)	1.820(4)		
Valency Angles (°)			
S(1)-S(2)-S(3)	104.30(7)	O(1)-S(1)-O(2)	119.49(24)
S(2)-S(1)-O(1)	102.49(16)	S(2)-S(1)-O(2)	109.17(14)
S(2)-S(1)-C(1)	106.10(16)		
S(1)-C(1)-C(2)	108.7(4)		
S(1)-C(1)-C(3)	104.5(4)		
S(1)-C(1)-C(4)	108.2(3)		
Torsion Angles (°)			
S(3)-S(2)-S(1)-C(1)	90.6(1)	S(1)-S(2)-S(3)-S(4)	90.9(1)
O(1)-S(1)-S(2)-S(3)	155.6(2)	O(2)-S(1)-S(2)-S(3)	27.9(1)

[a]. Estimated σ's refer to the last digit.

The electrophilic oxidation of di-*t*-butyl tetrasulfide afforded new compounds[197] that were characterized by NMR spectroscopy. Their synthesis and characterization is very similar to their trisulfides analogs. However, they are more stable than their trisulfide analogs which is somewhat surprising (discussed in Chapter 4).

3.4.5. Conclusions

The procedure of oxidation of di-*t*-butyl trisulfide developed in the first part of this Chapter was easily extended to the preparation of other alkyl polysulfide-polyoxides. Primary, secondary and tertiary alkyl trisulfide-1-oxides were prepared and their stability was shown to be directly correlated to their degree of substitution. The general behaviour (regiochemistry, stability and characterization) of alkyl polysulfide-polyoxides seems to be very similar to the one of their trisulfide analogs (discussed in Chapter 4). However, the electrophilic oxidation of cyclic trisulfides is somewhat different from the one of linear chain trisulfides because the oxidation of some trithiolanes is not regiospecific and the 1- and 2-oxide analogs are formed. Finally, the oxidation of aryl trisulfides is also somewhat different from the one presented here. Although the regiochemistry of such a reaction agrees with what is found for di-*t*-butyl trisulfide, it is surprising that no more oxidation takes place on the 1-oxide derivative, while tetraoxides of the alkyl analogs have been isolated and identified.

CHAPTER 4. INTERMEDIATES AND MECHANISMS OF THE DECOMPOSITION OF ALKYL POLYSULFIDE-POLYOXIDES

4.1. Introduction

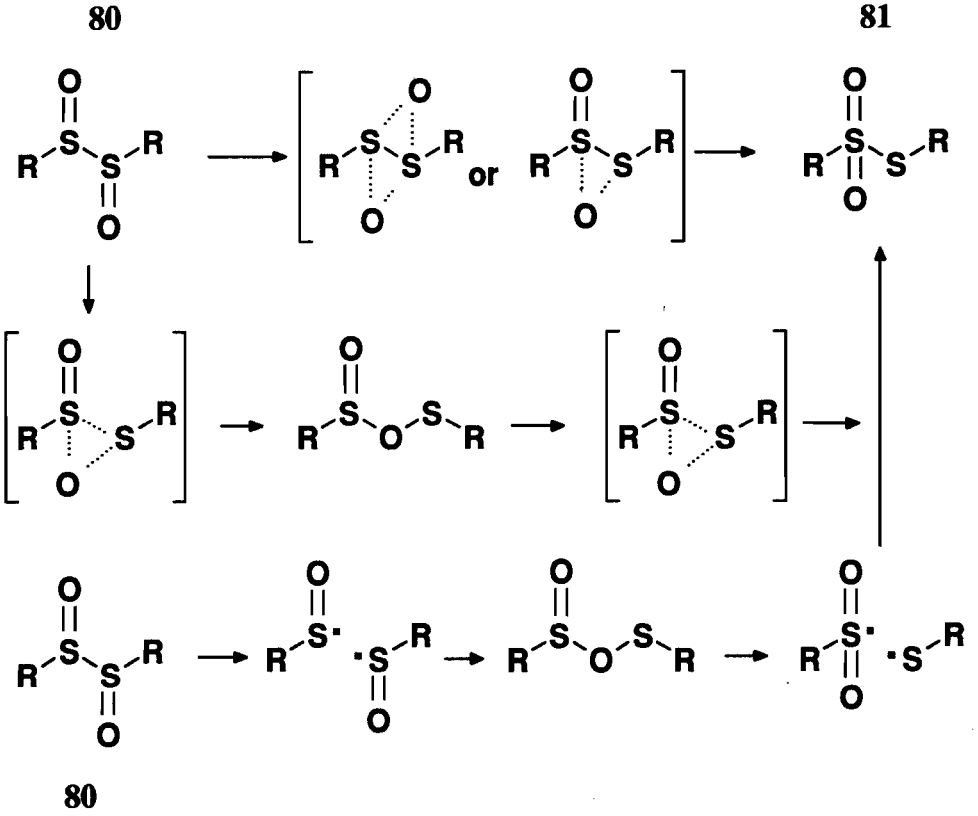
The synthesis and the mechanisms of formation of a wide variety of polysulfide-polyoxides have been described in the previous Chapter. The study has been centered on the di-*t*-butyl derivatives but it was successfully extended to the oxidation of other alkyl, aryl and cyclic analogs. The comparison of various oxidation reactions using different substrates as well as the use of other synthetic procedures led us to the proposal of several mechanisms of reaction that involve the formation of very reactive intermediates. Although the oxidation of symmetrical polysulfides is in most cases regiospecific and very effective, the actual isolation of these compounds in pure form is quite complex because most of them decompose rapidly at room temperature.

Their strong odor, low stability and similar chemical properties make them very difficult to separate and characterize. The control of the reaction conditions and the number of oxidant equivalents used is crucial in the preparation and handling of most of these polysulfide-polyoxides. In the present Chapter, the detection of some reaction intermediates using low temperature NMR is presented as well as a general decomposition behaviour of this class of compounds *via* detailed decomposition studies of some of them.

4.1.1. Preparation of Disulfide-1,1-Dioxides (Thiosulfonates)

The oxidation of disulfides has been extensively studied and thoroughly reviewed in Chapter 1. Among the disulfide-polyoxides, the preparation of thiosulfonates **81** is the one that created the most interest because of mechanistic aspects (formation of *vic*-disulfoxides **80**), chemical properties and practical applications. Very recently, the

chemistry of thiosulfonates **81** was very well reviewed.[218] As stated earlier, the most common method for the synthesis of symmetrical thiosulfonates **81** is the oxidation of the corresponding thiosulfinates **79** or even disulfides. Using electrophilic oxidizing agents, the oxidation of alkyl thiosulfinates **79** was shown to proceed through the exclusive formation of *vic*-disulfoxides **80** and rearrangement to the corresponding thiosulfonates **81** as described in the second part of Chapter 1. Kinetic and labeling experiments as well as the use of unsymmetrical alkyl, aryl and cyclic starting materials have led to the proposal of several mechanisms for the formation of thiosulfonates **81** as detailed in Chapter 1. **Scheme 37** summarizes the various mechanisms proposed in the literature.[81]



SCHEME 37

Although many of the mechanistic studies concluded that formation of *vic*-disulfoxides **80**, the major breakthrough in this area, was the detection of **80** at low temperature (Chapter 1).

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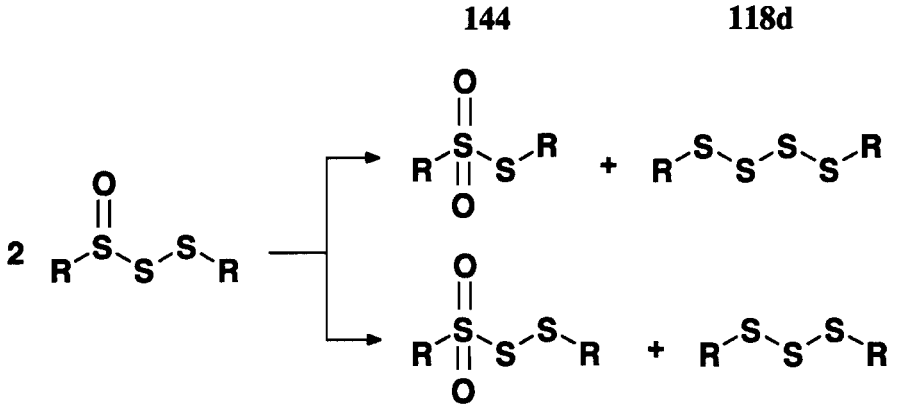
218 N. F. Zefirov, N. V. Zyk, E. K. Beloglazkina and A. G. Kutateladze, *Sulfur Reports*, **14**, 223 (1993).

4.1.2. Decomposition of Trisulfide-Polyoxides

The synthesis of only a few trisulfide-polyoxides has been reported as described in the introduction of Chapter 3. Most of these studies were limited due to the low stability of the products formed. Thus, in most cases, the oxidation reactions were carried out on trisulfides bearing bulky substituents such as *t*-butyl groups, in order to obtain relatively stable oxidation products.

Steudel[197] was the first to isolate di-*t*-butyl trisulfide-1-oxide (**120c**) by direct oxidation of the corresponding trisulfide (**118c**). The thermal decomposition of **120c** afforded the corresponding trisulfide **118c**, tetrasulfide **118d**, disulfide-1-oxide (thiosulfinate) **120b**, disulfide-1,1-dioxide (thiosulfonate) **144** and trisulfide-1,1-dioxide **145**. The formation of some of these decomposition products was explained by the disproportionation of di-*t*-butyl trisulfide-1-oxide (**120c**) (**Scheme 38**).



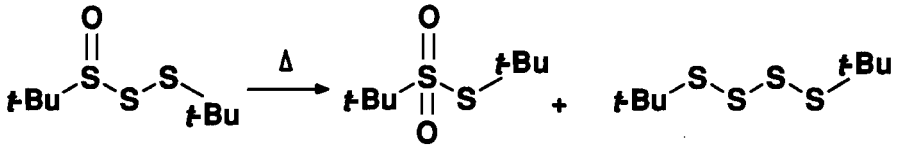
120c **145** **118c**

SCHEME 38

However, the relative concentration of each of these decomposition products is not reported and the mechanism proposed does not account for all the products isolated from the thermal decomposition of **120c**.

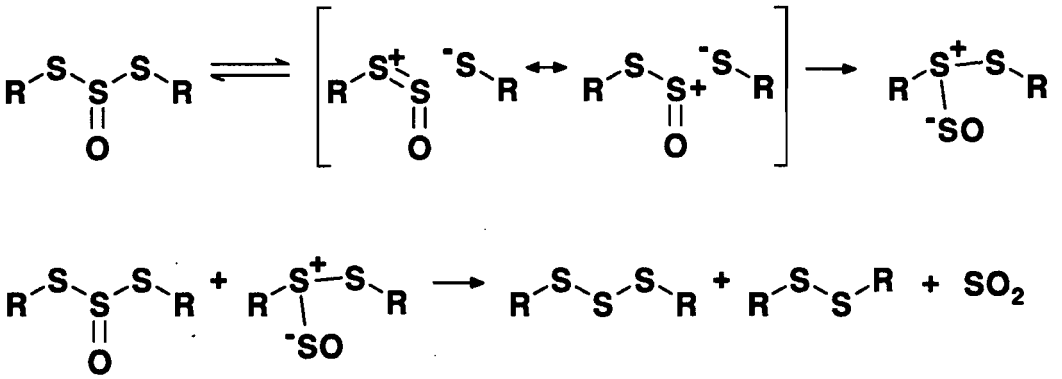
A few years later, Bleeker[204] reported the preparation of di-*t*-butyl trisulfide-1-oxide (**120c**) from *t*-butyl hydrodisulfide (**148**) and *t*-butyl sulfinyl chloride (**149**) (Chapter 3); however, he was unable to purify the product. On attempted distillation and chromatography **120c** gave di-*t*-butyl tetrasulfide (**118d**) (60%) and di-*t*-butyl disulfide-

1,1-dioxide (thiosulfonate) **(144)** **(equation 80)**; no decomposition mechanism was proposed.



120c **144** **118d** (eq. 80)

The synthesis of di-*t*-butyl trisulfide-2-oxide **(156)** was reported by Field and Lacefield[179] from *t*-butyl mercaptan and thionyl chloride (Chapter 3). Following the same procedure, they were able to prepare a wide variety of symmetrical trisulfide-2-oxides **150** as well as unsymmetrical analogs. A detailed thermal decomposition study was also reported which allowed them to draw the following conclusions. The di-*t*-butyl derivative, **156**, is the most stable of the compounds they had synthesized. When heated, 2 moles of trisulfide-2-oxide **150** decompose cleanly to give an equimolar mixture of disulfide, trisulfide and sulfur dioxide (as shown in Scheme 22). The decomposition of diphenyl trisulfide-2-oxide follows first-order kinetics in refluxing carbon tetrachloride. The decomposition is strongly catalyzed by sulfur dioxide and when unsymmetrical trisulfide-2-oxides are used, scrambling of the groups occurs. Finally, they suggested *via* irradiation experiments, that the decomposition seems more likely to be heterolytic than homolytic. From all these results they proposed the following mechanism for the thermal decomposition of trisulfide-2-oxides **150** **(Scheme 39)**.



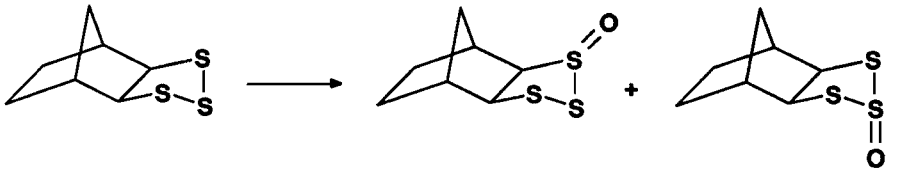
150

SCHEME 39

The mechanism proposed is consistent with the results observed previously. However, the last step of the mechanism that should involve a transfer of oxygen to form the disulfide and the SO_2 moiety is not very clear.

4.1.3. Cyclic Trisulfide-Polyoxides

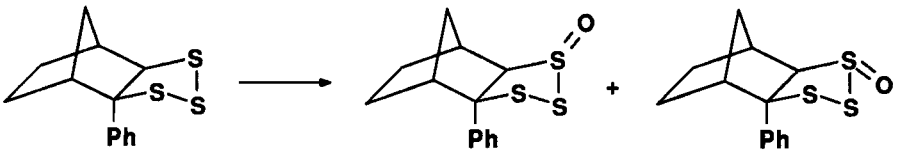
The oxidation of cyclic trisulfide (trithiolane) was first reported by Ghosh and Bartlett[200] as described in Chapter 3. Using norbornanetrithiolane **(138)**, they reported one of the first non-regiospecific *m*-CPBA oxidations and the corresponding trithiolane-2-oxide **140** was obtained as major product (55%) **(equation 47)**. Ozonation of **138** gave **140** as sole product.



(eq. 47)

138 **139** **140**

However, oxidation of the phenyl derivative **(176)** exclusively afforded the *exo* and *endo* 1-oxides **(177a-b)** **(equation 81)**.

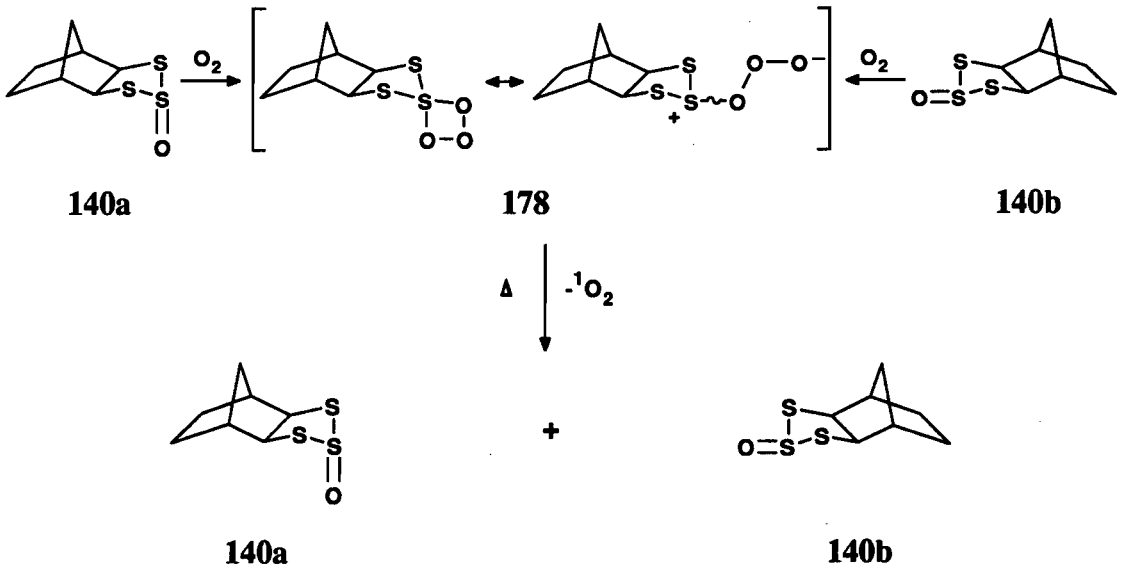


(eq. 81)

176 **177a** **177b**

A crystallography study was reported and proved that only the *endo*-norbornanetrithiolane-2-oxide **140a** was formed by either *m*-CPBA oxidation or ozonisation. However, they reported the O_2-catalyzed isomerization of **140a** to its *exo* analog **140b**. To explain this result, they proposed that **140a** and **140b** react with O_2 to produce a trioxide analog **178** that is in equilibrium between its cyclic and linear forms. Although the attempts to trap $^1O_2$ were unsuccessful, they proposed that intermediate **178**

should be stable at -78°C but would decompose at warmer temperatures affording the 2 possible isomers (**Scheme 40**).

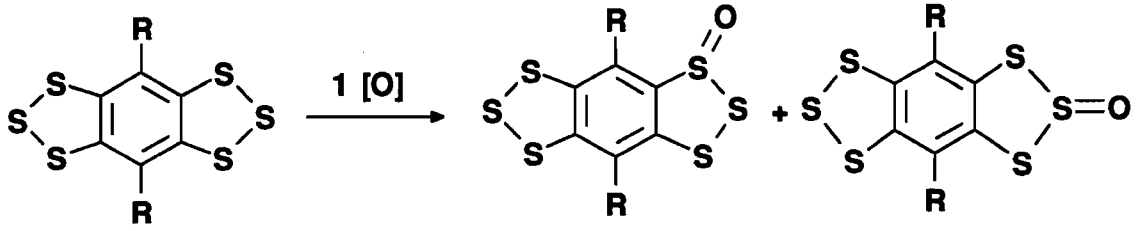


140a **178** **140b**

140a **140b**

SCHEME 40

A similar study has been reported by Sato and coworkers.[202] They reported the oxidation of two 4,8-dialkylbenzobistrithioles **141** to a mixture of the corresponding 1-oxide **142** and 2-oxide **143** as described in the introduction of Chapter 3 (**Scheme 14**). Using several oxidizing agents, it was shown that the relative percentage of 1- and 2-oxides depends on the oxidizing agent used, the reaction affording only the 2-oxide **143** when *N*-iodosuccinimide was employed.

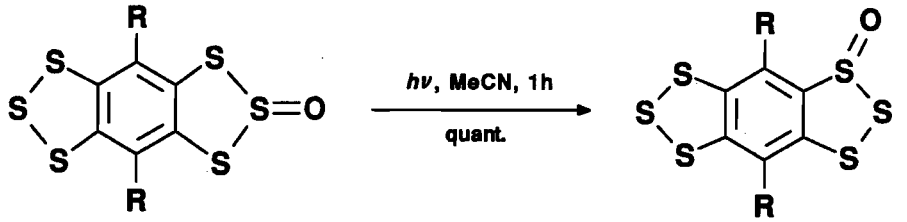


141 **142** **143**

R = Me, (Et)	**[O] = *m*-CPBA**	**55%, (68%)**	**19%, (18%)**
	[O] = NBS	**60%, (65%)**	**>3%, (>3%)**
	[O] = NIS	**none**	**42%, (41%)**

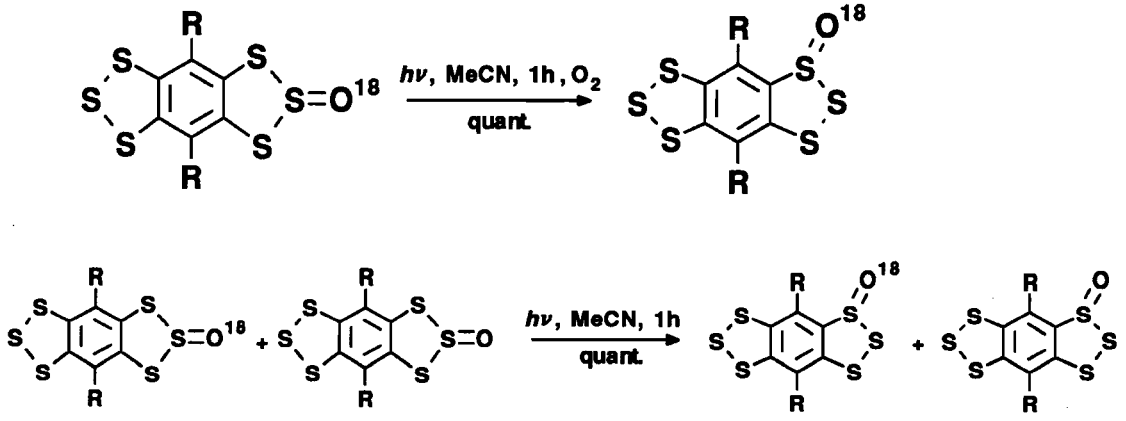
SCHEME 14

In a separate project, they have shown that the 2-oxide **143** was quantitatively converted to the 1-oxide analog **142** under specific photochemical conditions (**equation 82**).



143 **142** (eq. 82)

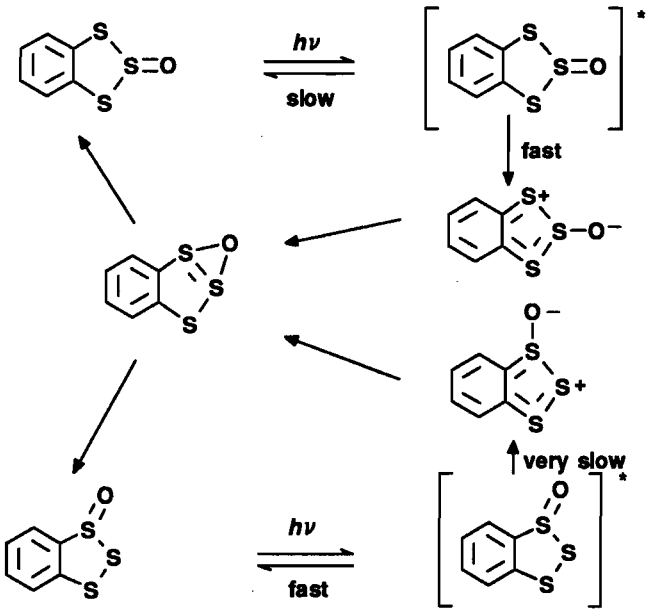
Other experiments proved that such a conversion is not reversible, does not occur under thermal conditions, is not catalyzed by acids and does not occur if the trithiolane is not bridged to an aromatic system. Using ^{18}O-labelled 2-oxide **143**, they observed that the percentage of marker remains steady in the course of the photochemical rearrangement in the presence of O_2 and that there was no cross-over between the labelled molecules and the unlabelled ones (**Scheme 41**).



$[^{18}O] = 55\%$

SCHEME 41

From these results they concluded that this photochemical oxygen migration proceeds intramolecularly. They proposed a mechanism for these photochemical rearrangements without ring opening although a mechanism that involves ring opening could not be ruled out (**Scheme 42**).



SCHEME 42

Although the formation and decomposition of thiosulfinates **79** and thiosulfonates **81** has been extensively studied as described in Chapter 1, not much has been done on the chemistry of their trisulfide analogs. The few studies that are reported here were always limited by the reactivity of the product formed and the complexity of the decomposition mixtures as well as the similarity of the final products. However, in the present thesis most of the di-*t*-butyl polysulfide-polyoxides were isolated and characterized as described in Chapter 3. These results provide a good opportunity to elaborate a mechanistic study of the formation and the decomposition of some of these polysulfide-polyoxides.

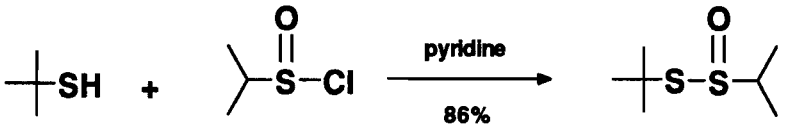
4.2. Formation and Decomposition of Alkyl Disulfide-Polyoxides

4.2.1. Disulfide-1-Oxides (Thiosulfinates) 79

As mentioned earlier, the chemistry of thiosulfinates **79** has been extensively studied and reviewed. The synthesis of symmetrical thiosulfinates is commonly carried out in high yield using either electrophilic or nucleophilic oxidizing agents as described in the previous Chapters. However, the oxidation of unsymmetrical disulfides is not regiospecific and gives in most cases the 2 possible thiosulfinates (Chapter 2). For this matter, non-oxidative synthetic procedures are employed. The decomposition of most of the thiosulfinates **79** is believed to be a simple disproportionation leading to the formation of the corresponding thiosulfonate **81** and disulfide. Depending on the substituents, aryl or alkyl, the mechanism involved was shown to be homolytic or heterolytic respectively. All these results are detailed in the second part of Chapter 1.

In the present study, primary **123c**, secondary **123b** and tertiary **120b** symmetrical alkyl thiosulfinates (see Chapter 3) were prepared in high yield by direct oxidation using various oxidizing agents especially dimethyldioxirane (DMD). DMD behaves as any electrophilic oxidizing agent[211] but it presents the advantage to be very efficient and does not require any workup of the reaction mixture.

The synthesis of an unsymmetrical thiosulfinate,[110] *t*-butyl isopropyl disulfide-2-oxide **(179)**, was achieved in high yield by reacting *t*-butyl mercaptan and isopropyl sulfinyl chloride[219] **(180)** in the presence of pyridine at low temperature **(equation 83)**.



180 **179** **(eq. 83)**

219 I. B. Douglass and R. V. Norton, *J. Org. Chem.*, **33**, 2104 (1968).

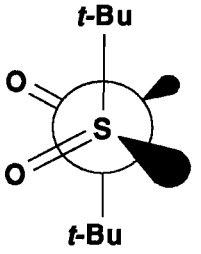
4.2.2. Disulfide-1,2-Dioxides (*vic*-Disulfoxides) 80

4.2.2.1. Literature Inconsistencies

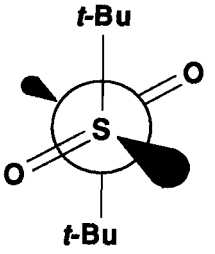
The detection of *vic*-disulfoxide **80** as intermediate in the electrophilic oxidation of thiosulfinates **79** to thiosulfonates **81** has been one of the most challenging projects in this area of sulfur chemistry. A highlight of the most interesting results is presented in the second part of Chapter 1. The present study focuses on the special case of the detection of di-*t*-butyl disulfide-1,2-dioxide (**167**) as well as its decomposition. This work has been essentially covered by Freeman and Angeletakis.[134,203b]

In 1981, they reported[134c] the detection of di-*t*-butyl-1,2-dioxide (**167**) at -40°C using low temperature NMR spectroscopy. It was shown that compound **167** was stable at this temperature and rapidly decomposed when the temperature was elevated to -20°C where no trace of **167** could be detected.

Due to the chirality of the sulfoxides moieties, the NMR spectra of **167** should present signals corresponding to the two diastereoisomers of **167a,b (Figure 11)**. However, only one of the two possible diastereoisomers appears in the spectra.



167a: d,l



167b: meso

Figure 11

In separate studies,[134d,e] they reported the detection of other alkyl disulfide-1,2-dioxides (primary and secondary alkyl) using the same low temperature technique. In these last cases, the diastereomeric disulfide-1,2-dioxides were reported and could be clearly identified on the spectrum presented. In another study reported by Harpp and Folkins,[135] the diastereomeric signals of several bridged bicyclic disulfide-1,2-dioxides were reported and observable at low temperature. In one case, *vic*-disulfoxides were shown to exist (*ca.* 10%) at temperature up to 30°C.

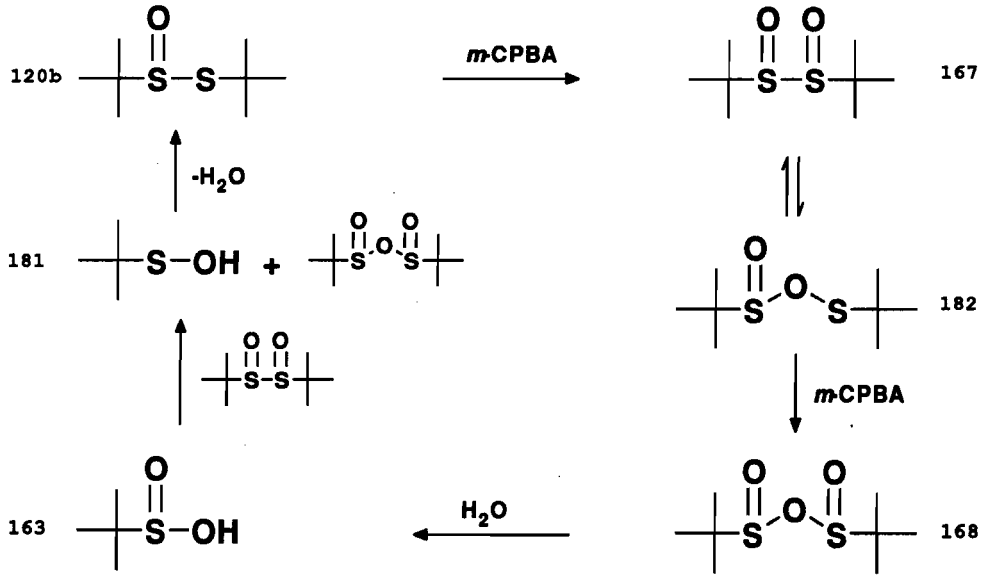
In contrast to the oxidation of primary, secondary and cyclic disulfide-1-oxides, the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) affords only one of the two possible diastereoisomers. Although Freeman and Angeletakis[134e] and Freeman and Lee[203b] have mentioned that the low temperature *m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) gives the diastereomeric di-*t*-butyl disulfide-1,2-dioxide (**167**), the only article referenced in both cases is the one in 1981[134c] where they clearly showed and reported that only *one* of the two possible diastereoisomers was obtained; they gave no further comments.

In addition, the low temperature oxidation of **120b** does not give any di-*t*-butyl disulfide-1,1-dioxide (**144**) (thiosulfonate) but a mixture of diastereomeric *t*-butyl sulfinic anhydrides (**168a,b**) and unreacted di-*t*-butyl disulfide-1-oxide (**120b**).[134a,c] Once again, the low temperature electrophilic oxidation of all the other disulfide-1-oxides mentioned earlier leads to the formation of the corresponding disulfide-1,1-dioxides as major rearrangement products.

From these observations, it is clear that the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) is quite different from the one of primary, secondary and cyclic alkyl disulfide-1-oxides and it would be of interest to understand these differences.

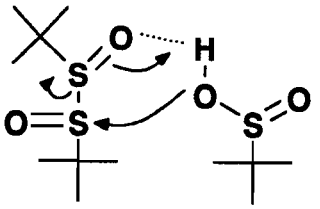
Concerning the low temperature oxidation of di-*t*-butyl disulfide-1-oxide (**120b**), the reaction was reported[134c] to be conducted at -40°C. After filtration and ^{13}C NMR acquisition (both at -40°C), the spectrum obtained was interpreted as a mixture of starting material **120b**, one of the two possible diastereoisomers of disulfide-1,2-dioxides **167** and diastereomeric *t*-butyl sulfinic anhydrides (**168a,b**). After 15 min at -30°C, the main difference was the decrease of the disulfide-1,2-dioxide **167** and the presence of small amounts of supposed *t*-butyl sulfenic acid (**181**). After 15 min at -20°C, compounds **167** and **181** had completely vanished. After 3 hours at room temperature, one of the two diastereoisomers of *t*-butyl sulfinic anhydrides (**168a** or **b**) had disappeared and small amounts of *t*-butyl sulfinic acid (**163**) and *t*-butyl sulfonic acid (**164**) could be detected.

These results were explained by attack of the electron rich sulfenyl sulfur giving the disulfide-1,2-dioxide **167** which is believed to be in equilibrium with the corresponding *O,S*-sulfenyl sulfinate (**182**) at -40°C. They suggested that compound **182** could then be oxidized by *m*-CPBA which would explain the presence of unreacted starting materials **120b** and the formation of sulfinic anhydride **168 (Scheme 43)**.

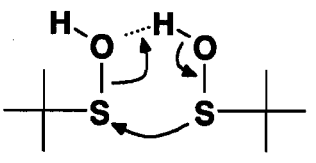


SCHEME 43

However, no trace of *O,S*-sulfenyl sulfinate **182** could be detected at -40°C. This observation led to the proposal of another possible decomposition path that would involve the reaction of the sulfinic acid **163** with the disulfide-1,2-dioxide **167** to give the corresponding sulfinic anhydride **168** and sulfenic acid **181** according to intermediate **183**. A characteristic reaction of sulfenic acids is dehydration to disulfide-1-oxide **184**.

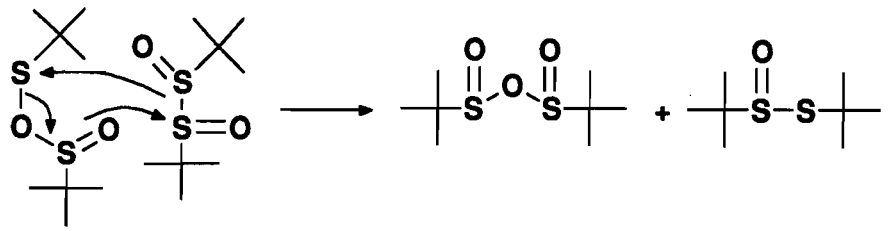


183



184

Finally, the presence of **120b** and **168** as well as the decomposition of **181** was explained by the reaction between **167** and **182** that are supposed to be in equilibrium, according to **equation 84**.

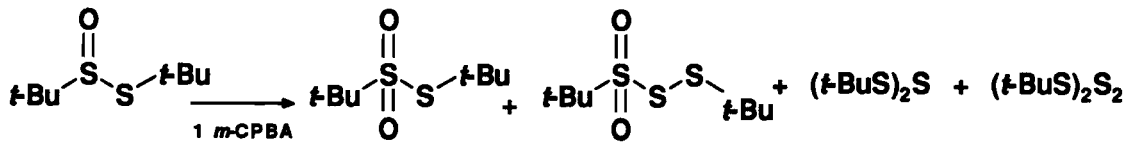


(eq. 84)

182 **167** **168** **120b**

All these possible mechanisms are summarized in Scheme **43** which was presented in the corresponding article.[134c] The main problem is the proposal of an equilibrium between the disulfide-1,2-dioxide **167** and the *O,S*-sulfenyl sulfinate **182** because none of the corresponding signals could be detected by NMR at -40°C and *all* the mechanisms proposed involve the presence of **182**. Scheme **43** is also inconsistent because the formation of **120b** and **168** is explained by the reaction of disulfide-1,2-dioxide **167** with sulfinic acid **163** while compound **163** is reported to be formed by the reaction of the same sulfinic anhydride **168** with adventitious water. This is somewhat of a "Catch 22" unless several decomposition mechanisms are taking place simultaneously.

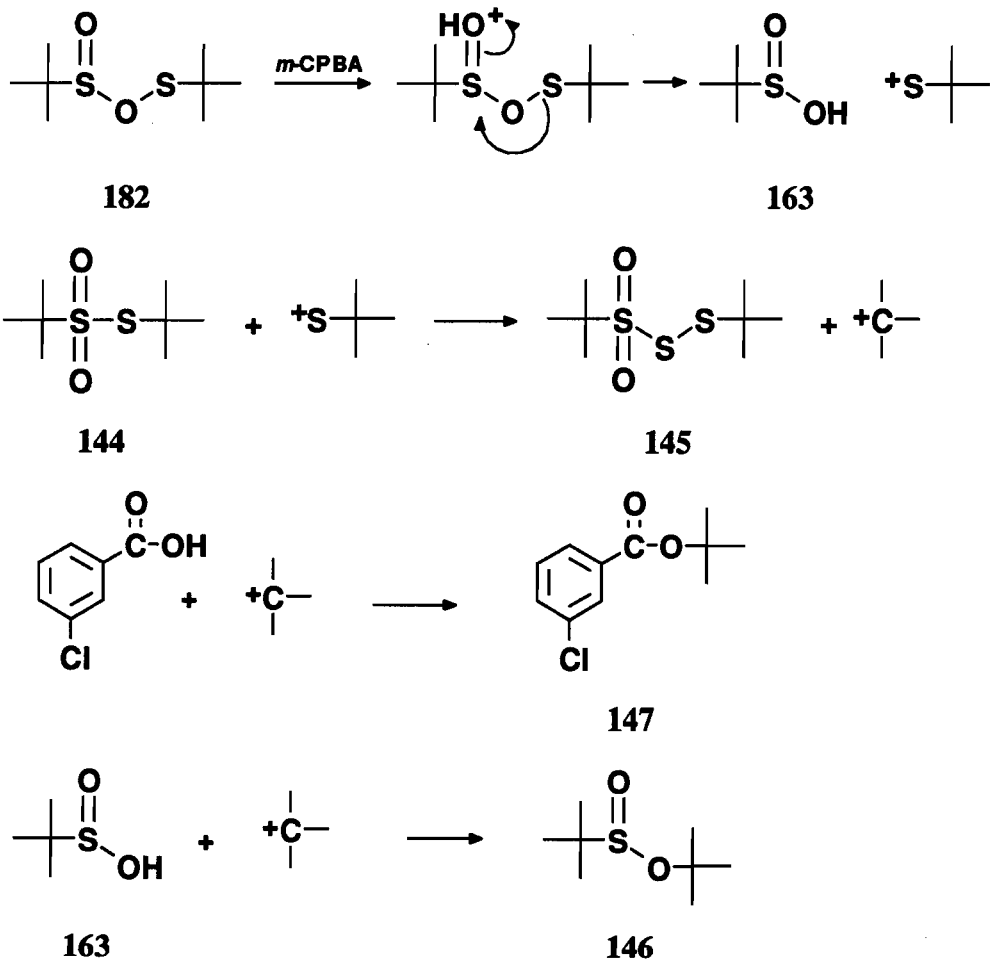
In 1988, Freeman and Lee[203b] reported another study on the 1 and 2 equivalent *m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (**120b**). The reactions were carried out at 0°C under similar conditions to the one reported earlier for the low temperature experiments. Using 1 equivalent of oxidizing agent, they isolated and characterized di-*t*-butyl disulfide-1,1-dioxide (**144**) (24%), di-*t*-butyl trisulfide-1,1-dioxide (**145**) (75%) and small amounts of the corresponding tri- and tetrasulfide**118c,d** (**Scheme 44**).



120b **144** **145** **118c** **118d**

SCHEME 44

In the second part of the article, a discussion on the possible mechanisms involved in the 1 and 2 equivalents oxidation of **120b** is presented. The following scheme summarizes the various paths that would account for most of the decomposition products **(Scheme 45)**.



SCHEME 45

In contrast with what was reported in 1981,[134a-c] Freeman and Lee[203b] were able to isolate some di-*t*-butyl disulfide-1,1-dioxide **(144)** (24%) as reported by other research groups.[220] A conclusion would be that **144** is not formed by the rearrangement of the di-*t*-butyl disulfide-1,2-dioxide **(167)**. However, many other studies[134,135] have shown, using other substrates, that the formation of disulfide-1,1-dioxides comes from the

220 a) H. Asakawa, Kamiya, S. Takey, *Takeda Kenkyusho Ho*, **29**, 610 (1970); *Chem. Abstr.*, **74**, 125603 (1971); b) J. L. Kice, T. W. S. Lee, *J. Am. Chem. Soc.*, **100**, 5094 (1978); c) J. L. Kice, T. W. S. Lee, S. Pan, *J. Am. Chem. Soc.*, **102**, 4448 (1980).

rearrangement of disulfide-1,2-dioxides. Another explanation of this unique behaviour of the di-*t*-butyl derivative could be that the reaction is temperature and solvent dependent.

The mechanism proposed in Scheme **45** is inconsistent with the one reported in 1981 (Scheme **43**). In the first case, they proposed an acid catalyzed dissociation of the elusive *O,S*-sulfenyl sulfinate **182** to electrophilic *t*-butyl sulfenium ion (*t*-BuS$^+$) and sulfinic acid **163** as opposed to the *m*-CPBA oxidation of *O,S*-sulfenyl sulfinate **182** to sulfinic anhydride **168** which is then hydrolyzed or reacted with the disulfide-1,2-dioxide **167**.

This two articles are irreconcilable; the di-*t*-butyl derivative presents unique behaviour that still remains complex and definitely needs more study. Other inconsistencies have been noticed in various articles but as they are not directly related to the *t*-butyl case it would be inappropriate to detail them here.

4.2.2.2. Formation and Decomposition of di-*t*-Butyl Disulfide-1,2-Dioxide (167)

Although the work reported by Freeman[134,203b] was remarkable in terms of the first detection of *vic*-disulfoxides and the development of "high tech" low temperature experiments, there is a need for a reinvestigation of part of their studies. The main problems concern the di-*t*-butyl derivative and can be summarized as follows:

1/ Only one of the two possible diastereoisomers of di-*t*-butyl disulfide-1,2-dioxides (**167**) is formed when di-*t*-butyl disulfide-1-oxide (**120b**) is oxidized by *m*-CPBA at low temperature.

2/ The mechanisms proposed for the rationalization of the rearrangement products of di-*t*-butyl disulfide-1,2-dioxide (**167**) are inconsistent as described earlier.

3/ In contrast with other disulfide-1-oxides, only traces of di-*t*-butyl disulfide-1,2-dioxide (**144**) could be detected from the low temperature oxidation of the corresponding disulfide-1-oxide **120b**. Under similar conditions, various ratios of **144** have been isolated.[134a,b,d,203,220]

Low Temperature Experiment

In the first part of the present study, it was decided to reinvestigate the low temperature oxidation of di-*t*-butyl disulfide-1-oxide (**120b**). The procedure used is unavoidably somewhat different from the one reported by Freeman and Angeletakis.[134] The oxidation of **120b** has been carried out using exactly 1 equivalent of *m*-CPBA (>99% as opposed to commercially available 80-85% as reported in the related articles). Considering that the di-*t*-butyl disulfide-1,2-dioxide (**167**) formed should be stable at -40°C, the reaction was stirred for 4 days at -55°C. Freeman and Angeletakis waited only 1 h before filtration which is surprising because all the other experiments carried out at warmer temperatures were run for at least 3 h before completion.[134a,b,d,203,220] Working at a lower temperature, one would imagine that the oxidation would be slower. The reaction was conducted in deuterated chloroform and most of the unreacted *m*-CPBA and *m*-CBA formed were not soluble at this temperature. The reaction mixture was then filtered using a customized device (described in the experimental Chapter) that allowed the filtration to take place at temperature lower than -40°C (the equipment employed is much simpler than the one described by Freeman and Angeletakis[134e]). Under the same conditions, the solution was transferred into a 5 mm NMR tube which was stored in dry ice. Freeman and Angeletakis used 10 mm NMR tubes claiming that the temperature rises above -40°C during the 30-60 seconds interval required for the transfer of the NMR tube from the dry ice/2-propanol bath to the probe of the spectrometer. The use of the 10 mm NMR tube generates the problem of installing a special probe which does not usually allow the recording of both ^{1}H and ^{13}C NMR spectra. To avoid this problem and still use a 5 mm NMR probe, the spectrometer (Jeol 270) was cooled to -100°C and the sample was kept in dry ice. The transfer of the NMR tube from the dry ice to the probe of the spectrometer was done in 30-60 seconds, the probe temperature remained below -60°C and the sample was still frozen (Mp. of $CDCl_3$ = -64°C). Then, the temperature of the spectrometer was set to -45°C, the temperature of the sample was allowed to stabilize for 30 min and the ^{1}H and ^{13}C NMR spectra were recorded at various temperatures (**Figure 12**).

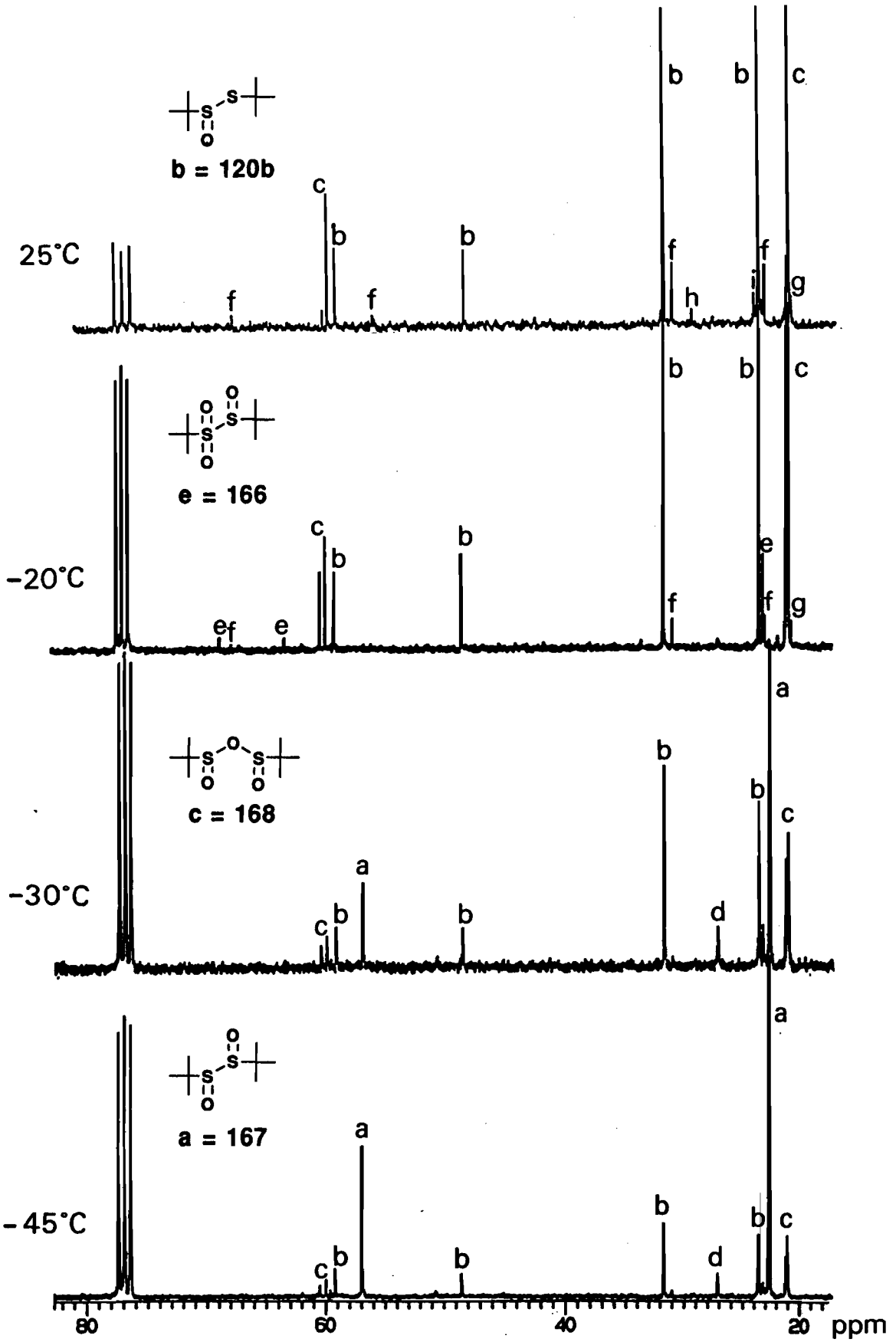


Figure 12: ^{13}C NMR Spectra at Several Temperatures of the Product Mixture from the *m*-CPBA Oxidation of 120b.

Analysis of the NMR Spectra

The ^{1}H and ^{13}C NMR spectrum obtained at -45°C show the presence of di-*t*-butyl disulfide-1,2-dioxide (**167**) as major compound (>80%) as well as an equimolar mixture of di-*t*-butyl disulfide-1-oxide (**120b**), *t*-butyl sulfinic anhydride (**168**) and small amounts of *t*-butyl sulfenic acid (**181**). On warming to -30°C, the di-*t*-butyl disulfide-1,2-dioxide (**167**) slowly decomposed to an equimolar mixture of **120b** and **168**, the intensity of **167** remaining unchanged. At -20°C, the disulfide-1,2-dioxide **167** and the sulfenic acid **181** had completely disappeared and small amounts of di-*t*-butyl disulfide-1,1,2-trioxide (**166**) could be detected in a separate experiment. Finally, after 10 min at room temperature, the product mixture was composed of di-*t*-butyl disulfide-1-oxide (**120b**) (45%), one of the two diastereoisomers of *t*-butyl sulfinic anhydride (**168**) (30%), di-*t*-butyl disulfide-1,1-dioxide (**144**) (7%) and small amounts of *t*-butyl sulfinic acid (**163**), *t*-butyl sulfonic acid (**164**) and di-*t*-butyl trisulfide-1,1-dioxide (**145**) as well as traces of undefined compounds. All these results can be seen on the spectra presented in Figure **12** and the chemical shifts of all the compounds identified in this low temperature experiment have been reported in **Table 15** and were derived from parallel synthesis or consistent literature reports.

Table 15: ^{13}C and ^{1}H NMR Chemical Shifts of the di-*t*-Butyl Derivatives Observed[a]

Entry	Compound	Spectra	C	CH_3	H	C'	CH_3'	H'
181	*t*-BuSOH[221]	**d**	50.85	27.39	1.31			
163	*t*-BuS(O)OH	**g**	57.46	21.42	1.19			
164	*t*-BuS(O)$_2$OH[b]	**i**	58.07	24.49	1.43			
118b	*t*-BuSSBu-*t*		45.87	30.54	1.28			
120b	*t*-BuS(O)SBu-*t*	**b**	59.35	24.18	1.53	48.65	32.21	1.35
167	*t*-BuS(O)S(O)Bu-*t*[c]	**a**	57.08	22.95	1.29			
144	*t*-BuS(O)$_2$SBu-*t*	**f**	68.01	23.65	1.59	56.31	31.45	1.44
166	*t*-BuS(O)$_2$S(O)Bu-*t*[d]	**e**	69.28	23.74	1.50	63.68	23.80	1.47
168a	*t*-BuS(O)OS(O)Bu-*t*[d]		60.52	21.37	1.28			
168b	Diastereoisomers	**c**	60.07	21.53	1.26			

[a] All the spectra were recorded in $CDCl_3$; [b] partially soluble in $CDCl_3$; [c] The spectra were obtained at -45°C; [d] The spectra were obtained at -20°C.

221 J. R. Shelton and K. E. Davis, *Int. J. Sulfur Chem.*, **8**, 205 (1973).

The ratios of the intermediates were determined from the integration of the various proton NMR spectra as well as from the intensity of the carbon signals that were shown by calibration experiments to correspond to their relative molar concentration (within 10%) when simple acyclic disulfide-polyoxides bearing the same alkyl group are compared.

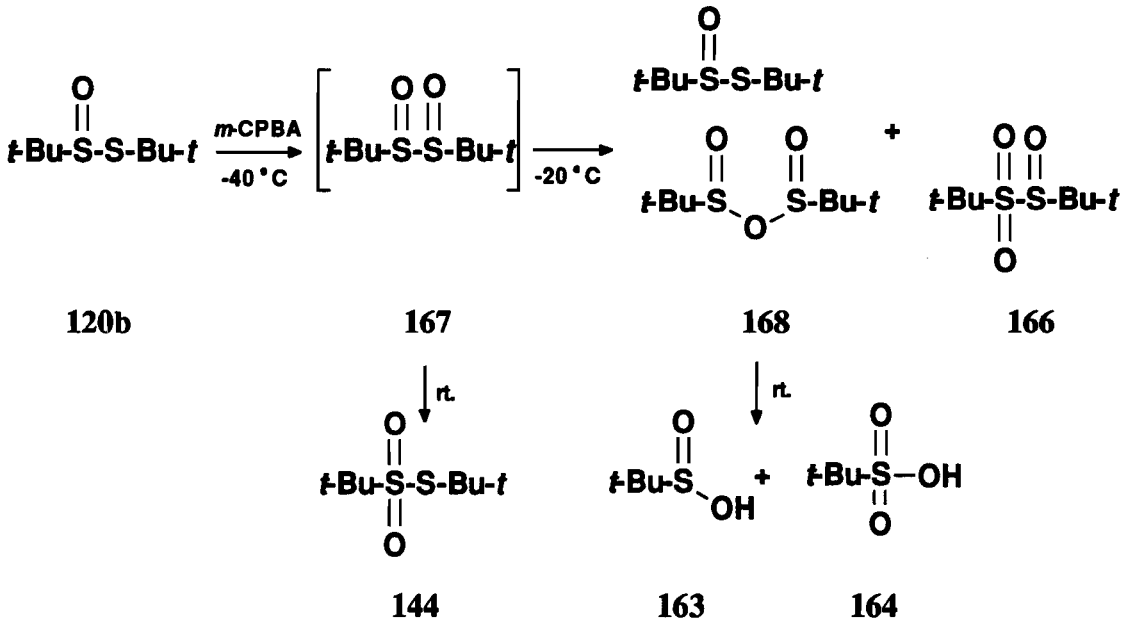
Determination of the Influential Parameters

The low temperature oxidation of di-*t*-butyl disulfide-1-oxide **(120b)** has been repeated several times using excess *m*-CPBA or commercially available 80-85% *m*-CPBA, for different reaction times (1 h to 4 days), in anhydrous conditions and in the presence of water; the spectra were recorded at slightly different temperatures (stepwise by 5°C). Finally, several types of decomposition have been examined (stepwise from -40 to 25°C and direct decomposition from -40 to 25°C).

It would be too long to detail each of these experiments (a typical procedure is described above), but a general behaviour as well as the influential parameters can be highlighted. Although good results can be obtained with 80-85% *m*-CPBA as reported by Freeman and Angeletakis,[134] it is preferable to use a pure oxidizing agent in order to add exactly 1 equivalent and be sure of the anhydrous conditions. The use of excess *m*-CPBA (2 equivalents) for a relatively long period of time (12 h) does not affect the reaction products. The study of the reaction time has shown that the reaction was almost completed after 2 h at -45°C. Carrying out the reaction over 4 days showed that the di-*t*-butyl disulfide-1,2-dioxide **(167)** was very stable under these low temperature conditions. The formation of **167** does not seem to be affected by the presence of water. However, more *t*-butyl sulfenic acid **(181)** has been detected under aqueous conditions, although some **181** was also found when the reaction was carried out under inert atmosphere. The formation of *t*-butyl sulfenic acid seems to be independent of the decomposition of disulfide-1,2-dioxide as it is present at -45°C, its low concentration remaining relatively constant until it decomposes (see spectra above). Compound **167** seems to be stable up to temperatures ranging from -40°C to -35°C. The decomposition is very fast above -25°C (<5 min). No real difference was observed between the stepwise decomposition and the direct one but the presence of water as well as the presence of residual *m*-CPBA or *m*-CBA substantially altered the ratios of decomposition products but no general behaviour could be found.

Mechanistic Study

The above results allowed the determination of the optimum conditions for this reaction now defined as 1 equivalent of pure *m*-CPBA, a temperature lower than -40°C at all times, reaction times greater than 12 h and an anhydrous, inert medium. Under these specific conditions, the results obtained are explicable in terms of exclusive formation of one of the two possible diastereoisomers of di-*t*-butyl disulfide-1,2-dioxides (**167**) as shown on the spectrum recorded at -45°C. According to the procedure employed and the spectrum obtained at -45°C, the conversion of di-*t*-butyl disulfide-1-oxide (**120b**) to **167** was at least 90%. In addition, no trace of *m*-CPBA, *m*-CBA or water could be detected in the spectrum. The decomposition of **167** afforded an equimolar mixture of **120b** and **168** as well as small amounts of di-*t*-butyl disulfide-1,1,2-trioxide (**166**). A possible explanation would be the complete formation of disulfide-1,2-dioxide **167** followed, at warmer temperatures, by the disproportionation of 2 moles of **167** into 1 mole of disulfide-1-oxide **120b** and 1 mole of sulfinic anhydride **168**. As a consequence, the spectrum obtained at -20°C only presents an equimolar mixture of **120b** and **168** as well as traces of **166**. The other products observed at room temperature come from the decomposition of the reactive *t*-butyl sulfinic anhydride **168** as shown in Chapter 3 (**Scheme 46**).

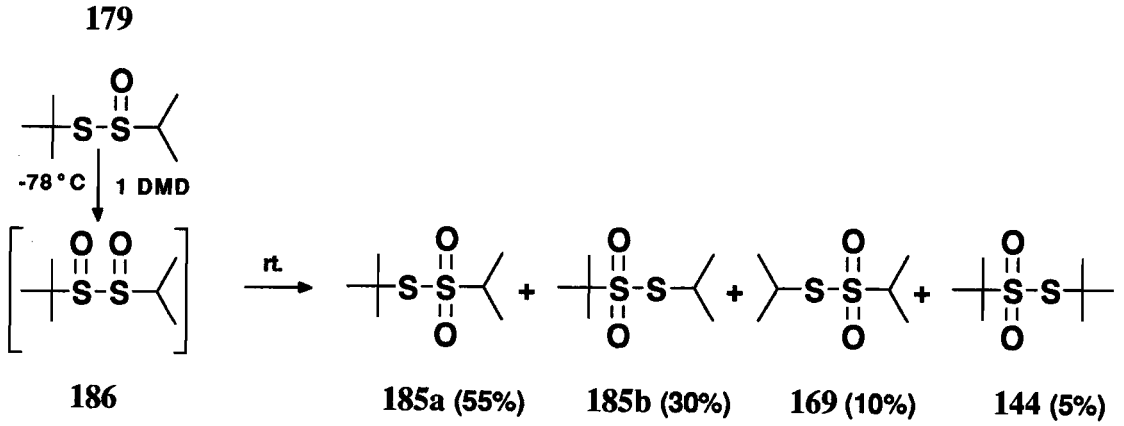


SCHEME 46

These results agree well with those reported by Freeman and Angeletakis.[134c] However, the spectra reported[134c] were misinterpreted because the reaction was incomplete after 1 h and the temperature chosen (-40°C) was too close to the decomposition temperature of the disulfide-1,2-dioxide **167**. As a result, their reaction mixtures always included significant amounts of sulfinic anhydride **168** and disulfide-1-oxide **120b** known as the decomposition products of **167** as well as unreacted **120b**. These side-products seriously complicated the analysis of the reaction path.

The decomposition study reported here was facilitated by the almost complete formation of the di-*t*-butyl disulfide-1,2-dioxide (**167**). The previous results have clearly shown that the disproportionation of **167** afforded mainly the corresponding disulfide-1-oxide **120b** and sulfinic anhydride **168**. However, the detailed decomposition mechanism is not clear because only one of the two possible diastereoisomers of **167** is formed and no *t*-butyl disulfide-1,1-dioxide (**144**) can be observed at -20°C.

In a separate experiment, *t*-butyl isopropyl disulfide-2-oxide (**179**) was oxidized using 1 equivalent of DMD at low temperature. The reaction products were a mixture of the four possible dialkyl disulfide-1,1-dioxides **144, 169, 185a-b (Scheme 47)**.

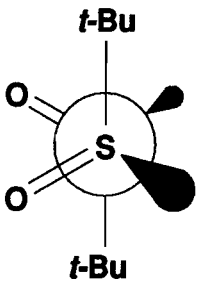


SCHEME 47

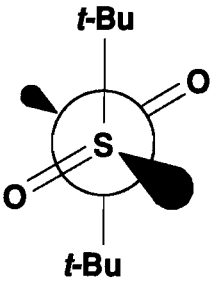
Assuming that there is exclusive formation of the corresponding disulfide-1,2-dioxide (**186**), the analysis of the reaction products (mixed disulfide-1,1-dioxides) implies the cleavage of **186**. In addition, the percentage of each product presented in Scheme **47** is very different and are representative of preferred cleavage and recombination. This observation is more in favor of a heterolytic cleavage rather than a homolytic one. Similar studies[105,133] described in Chapter 1 provided the same conclusion.

As stated earlier, the oxidation of other alkyl disulfide-1-oxides always afforded the two diastereoisomers of the corresponding disulfide-1,2-dioxides; their decompositions gave the disulfide-1,1-dioxides as major product. However, the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) affords only one of the two possible diastereoisomers of the 1,2-dioxides **167** and its decomposition gives almost none of the expected 1,1-dioxide **144**, but a clean mixture of products that can not be rationalized by a straight-forward mechanism.

In the case of the di-*t*-butyl derivative, the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) is believed to only afford the kinetically favored disulfide-1,2-dioxide **167a** or **b**. This possibility is supported by the results observed for the di-*t*-butyl trisulfide-1,3-dioxide (Chapter 3).



167a: d,l

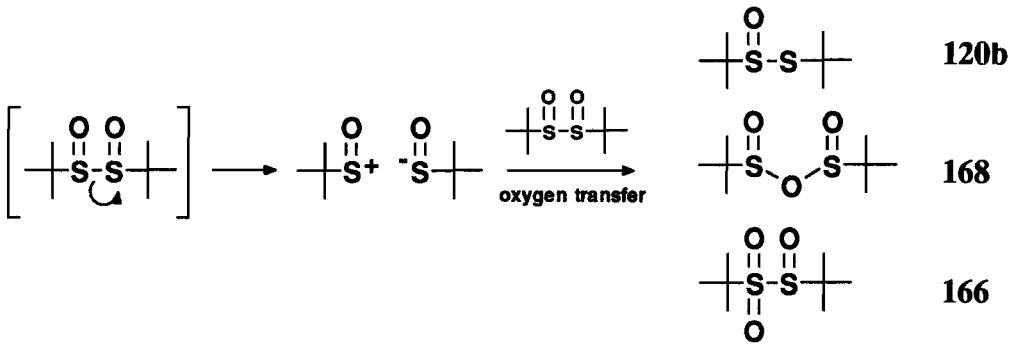


167b: meso

On warming, heterolytic cleavage of the disulfide-1,2-dioxide **167** should afford two very interesting ambident species (*t*-BuS^{+}(=O) (**187a**) and *t*-BuS^{-}(=O) (**187b**)) whose existence is supported by literature evidence[222] (Schleyer and coworkers reported clear evidence of a sulfinyl cation and sulfinyl anion in different systems). The synthesis of *t*-butyl sulfinyl chloride (**149**) and *t*-butyl sulfenic acid (**181**) also demonstrate the ambident character of the sulfinyl moiety. In contrast to the other alkyl derivatives, the *t*-butyl sulfinyl ions **187a-b** are so sterically hindered that their recombination apparently is slower than their reaction with another molecule of di-*t*-butyl disulfide-1,2-dioxide (**167**) which is supposed to be less hindered under these specific conditions[226] (see next section). As a consequence, the formation of the second diastereoisomer of **167** does not occur and thus, there is no formation of di-*t*-butyl disulfide-1,1-dioxide (**144**). Another possible explanation would be that the kinetically favored product is also the

222 a) P. R. Schreiner, P. V. R. Schleyer and R. K. Hill, *J. Org. Chem.*, **58**, 2822 (1993); b) P. R. Schreiner, P. V. R. Schleyer and R. K. Hill, *J. Org. Chem.*, **59**, 1849 (1994); and references cited therein.

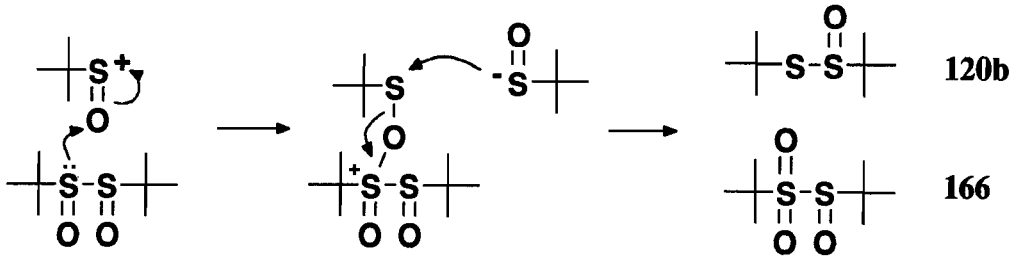
thermodynamic compound. Due to the steric hindrance of the *t*-butyl groups, only one of the diastereomeric disulfide-1,2-dioxides **167** is formed and if it is the thermodynamically favored diastereoisomer, the other one will not be observed. The formation of disulfide-1-oxide **120b** as well as the diastereomeric sulfinic anhydride **168** or the disulfide-1,1,2-trioxide **166** can be explained by an oxygen transfer mechanism between one molecule of disulfide-1,2-dioxide **167** and the *t*-butyl sulfinyl ions **187a-b** **(Scheme 48)**.



167

SCHEME 48

The rationalization of the oxygen transfer reaction led us to the proposal of three possible mechanisms. The first possibility would be the lone pair of electrons of the sulfinyl sulfur of **167** attacking the oxygen of the sulfinyl cation (*t*-BuS^{+}(=O)). The intermediate formed could then react with the remaining sulfinyl anion (*t*-BuS^{-}(=O)) giving the **120b** and **166** **(Scheme 49)**.

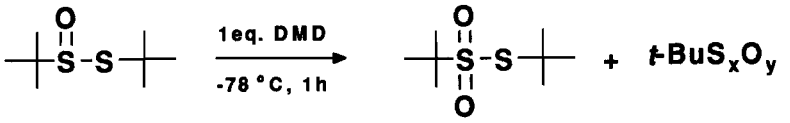


167

SCHEME 49

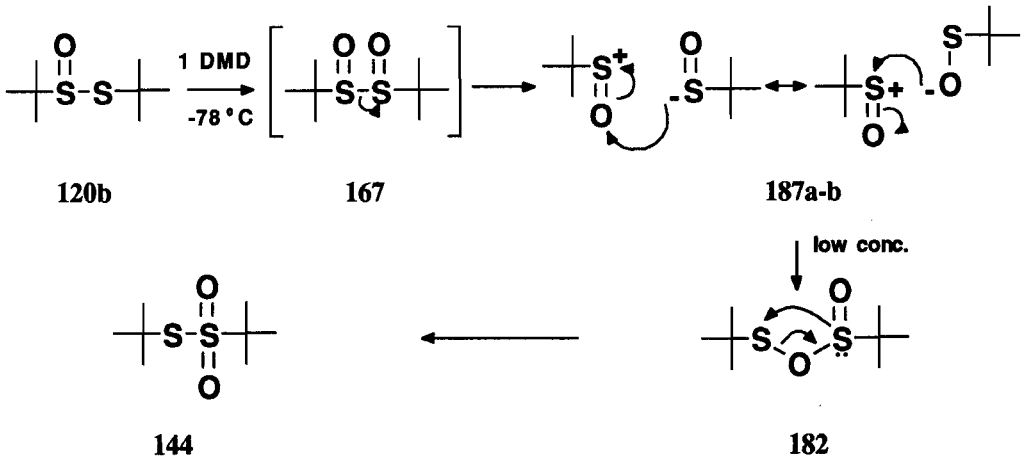
This first mechanism is an extrapolation of electrophilic oxidation. However, it does not account for the formation of sulfinic anhydride **168**.

The 1 equivalent DMD oxidation of di-*t*-butyl disulfide-1-oxide **(120b)** was carried out at -78°C in acetone and anhydrous conditions until no trace of **120b** could be detected by tlc. This reaction afforded a relatively high yield (83%) of the expected di-*t*-butyl disulfide-1,1-dioxide **(144)** while a typical *m*-CPBA oxidation of **120b** in methylene chloride always gives a low yield of **144 (equation 89)**.



120b **144 (83%)** **(eq. 89)**

In all the DMD oxidation experiments reported here, the oxidizing agent was a 0.04-0.08 M solution of dimethyldioxirane in acetone. Thus, the DMD oxidation reactions were always carried out at low concentration ([**120b**] ~ 0.02 M) compared to the one reported here and by others[134a,b,d,203,220] using other oxidizing agents ([**120b**] ~ 0.2 M). For the specific case reported here, the reagent concentration of the DMD oxidation is about 10 times that of a typical *m*-CPBA oxidation. According to the mechanism reported earlier, the DMD oxidation should give the exclusive formation of the corresponding disulfide-1,2-dioxide **167** (the low temperature experiment could not be carried out because of the dilution problem and inevitable presence of acetone). On warming to room temperature, cleavage of the 1,2-dioxide **167** should afford the ambident *t*-butyl sulfinyl ions **187a-b** (*t*-BuS$^+$(=O) and *t*-BuS$^-$(=O)). At such reagent concentration, these ions react together before they meet another molecule of disulfide-1,2-dioxide **167**. The recombination of these two sulfinyl ions affords the expected disulfide-1,1-dioxide probably *via* the formation of *O,S*-sulfenyl sulfinate **182 (Scheme 52)**.

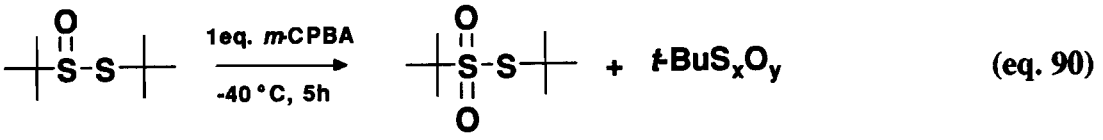


120b **167** **187a-b**

144 **182**

SCHEME 52

Accordingly, in a separate experiment, the oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) was carried out using 1 equivalent of *m*-CPBA under similar conditions (low concentration) to those reported for the DMD oxidation of **120b** ([**120b**] = 0.01 M, -78°C, CH_2Cl_2). Analysis of the reaction mixture afforded a moderate yield (64%) of the expected di-*t*-butyl disulfide-1,1-dioxide (**144**) (**equation 90**).



(eq. 90)

[**120b**] = 0.01 M **144**

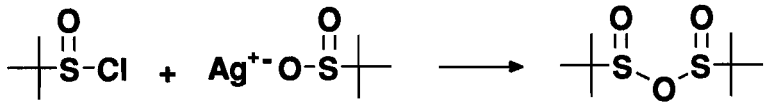
Finally, Freeman and Angeletakis[134c] reported that only traces of di-*t*-butyl disulfide-1,1-dioxide (**144**) were formed by the low temperature *m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (**120b**). As stated earlier, the similar experiment reported here showed significant amounts of disulfide-1,1-dioxide **144** (7%) at the end of the decomposition. A consistent explanation of such a difference lies in the fact that their reaction mixtures were much more concentrated than ours (5-10 times) as they were using 10 mm NMR tubes and obtained almost noiseless ^{13}C NMR spectra by only acquiring 200 transients.

The results presented in this section give clear evidence of the special behaviour of the di-*t*-butyl derivatives. Low temperature experiments, use of unsymmetrical starting material as well as various solvents and working at different concentrations allows the proposal of a mechanism that is consistent with the results observed for the low temperature decomposition of di-*t*-butyl disulfide-1,2-dioxide (**167**) as well as for the formation of di-*t*-butyl disulfide-1,1-dioxide (**144**) by direct oxidation.

4.2.4. Characterization of di-*t*-Butyl Disulfide-Tri- and Tetraoxides

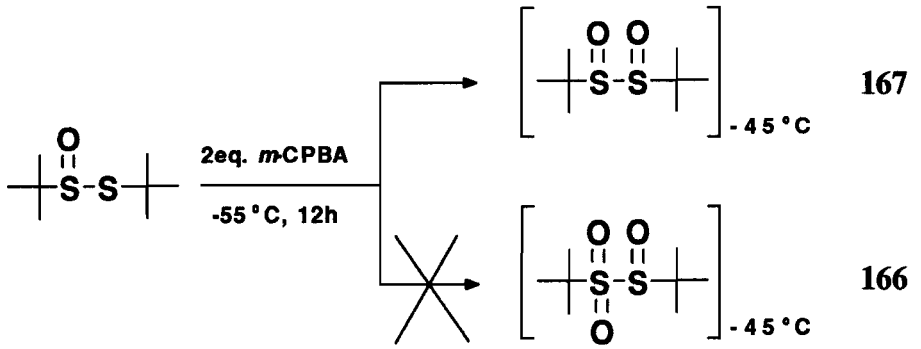
To our knowledge, di-*t*-butyl disulfide-1,1,2-trioxide (**166**) and di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) have never been isolated, detected or characterized. The synthesis of other alkyl and aryl disulfide-1,1,2-trioxides **82** was reported[127e,f,l] by reacting the corresponding sulfinyl chloride with the sodium salt of the sulfinic acid. However, using *t*-butyl sulfinyl chloride (**149**) and silver *t*-butyl sulfinate, the only

compound isolated[127h] was not the expected *t*-butyl disulfide-1,1,2-trioxide **(166)** but the corresponding anhydride **168** probably because of steric hindrance or thermodynamic control, i.e., **168** is more stable than **166** as suggested by Freeman[127l] **(equation 91)**.



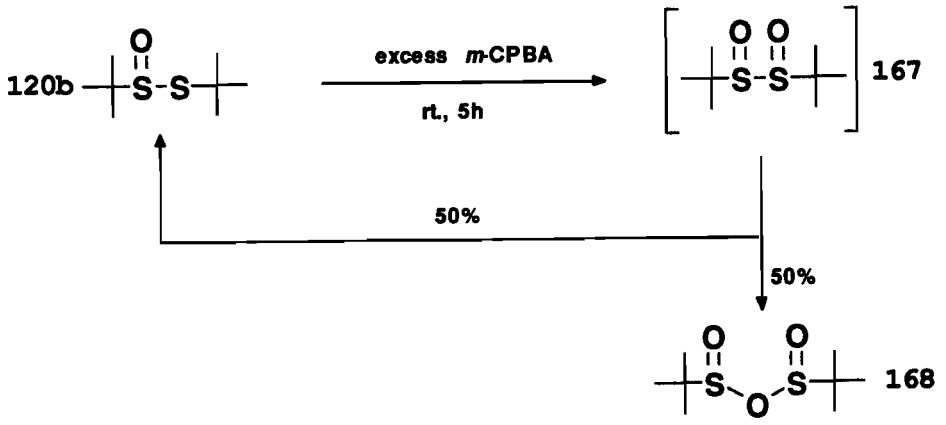
149 **168** **(eq. 91)**

As stated earlier, small amounts of supposed di-*t*-butyl-disulfide-1,1,2-trioxide **166** were detected in the low temperature decomposition of the corresponding disulfide-1,2-dioxide **167**. The chemical shifts observed were tentatively assigned to **166** by analogy with the ones of other di-, tri- and tetrasulfide derivatives as well as with the ones of the tri- and tetrasulfide analogs **157** and **175** (see Table 16). From these results, it was thought that the di-*t*-butyl disulfide-1,1,2-trioxide **(166)** might be detected at low temperature. However, the low temperature oxidation of di-*t*-butyl disulfide-1-oxide **(120b)** using 2 equivalents of *m*-CPBA only afforded the corresponding disulfide-1,2-dioxide **167** and no trace of **166** could be detected at -45°C as reported in the previous section. A possible explanation is the exclusive formation of 1,2-dioxide **167** (Figure **12**) that should then react with the other equivalent of *m*-CPBA. The formation of disulfide-1,1,2-trioxide **166** would imply the attack of a sulfinyl sulfur at the elctrophilic oxygen of the peracid. As shown in Chapter 3, the electrophilic oxidation of a sulfinyl sulfur at -55°C is very slow and considering that the di-*t*-butyl disulfide-1,2-dioxide is rather sterically hindered, it is not surprising that no reaction takes place under these specific conditions **(equation 92)**.



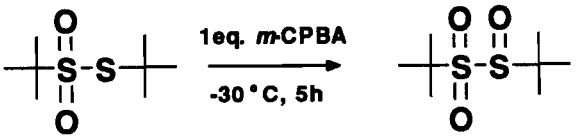
120b **167** **166** **(eq. 92)**

Direct oxidation of the di-*t*-butyl disulfide-1-oxide (**120b**) at higher temperature using more than 2 equivalents of *m*-CPBA afforded only the sulfinic anhydride **168** as reported in Chapter 3 (**equation 73**). In this case, the disulfide-1,2-dioxide **167** formed is not stable at this temperature and decomposes to an equimolar mixture of **120b** and **168** as seen previously. The disulfide-1-oxide **120b** present in the reaction mixture can then be re-oxidized by the excess *m*-CPBA forming **167** which decomposes to **120b** and **168**; this process could proceed until all the oxidizing agent has been used (**Scheme 53**).



SCHEME 53

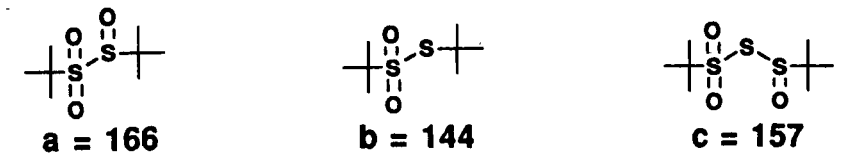
Knowing that small amounts of di-*t*-butyl disulfide-1,1,2-trioxide (**166**) could be detected at -20°C, and that sulfenyl sulfurs are usually much more nucleophilic than sulfinyl sulfurs, the synthesis of **166** was attempted by direct oxidation of di-*t*-butyl disulfide-1,1-dioxide (**144**) using 1 equivalent of pure *m*-CPBA at -30°C for 5 h according to the low temperature experiment procedure previously described (**equation 93**).



(eq. 93)

144 **166**

The ^{1}H and ^{13}C NMR spectrum (**Figure 13**) were recorded at -30°C and interpreted as an 85% conversion of di-*t*-butyl disulfide-1,1-dioxide (**144**) to di-*t*-butyl disulfide-1,1,2-trioxide (**166**). Small amounts of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) are also detected because the disulfide-1,1-dioxide **144** used contained some di-*t*-butyl trisulfide-1,1-dioxide (**145**).



a = 166 b = 144 c = 157

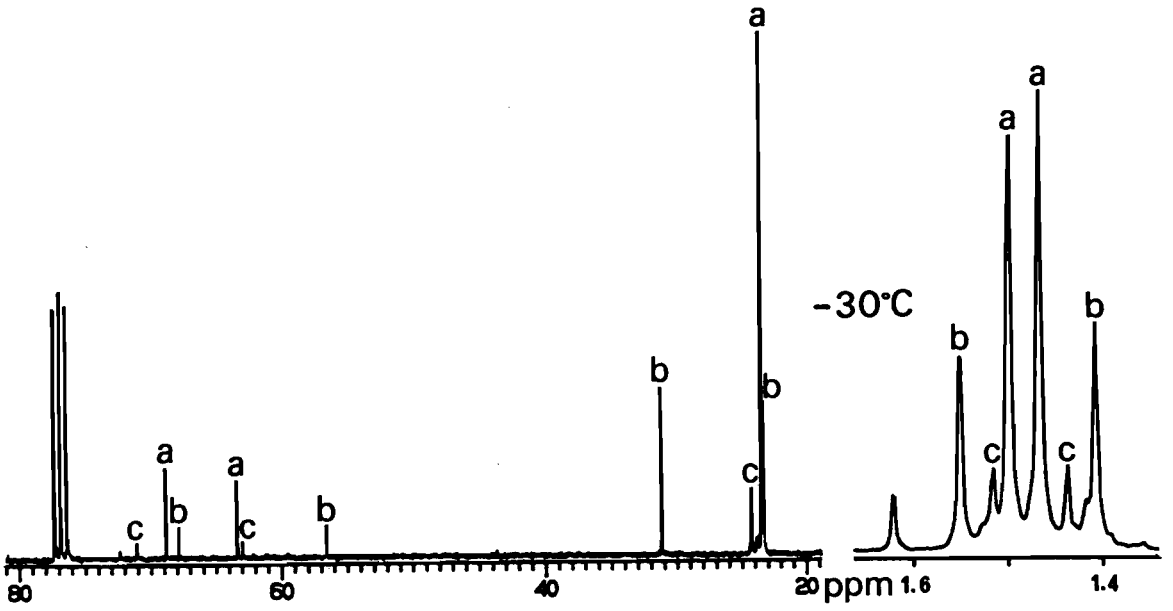
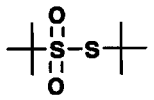
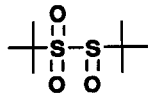
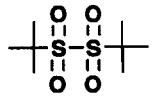
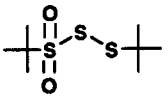
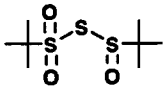
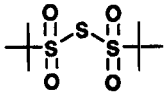


Figure 13: Low Temperature ^{13}C and ^{1}H NMR Spectra of di-*t*-Butyl Disulfide-1,1,2-Trioxide (166).

In contrast with what is reported in Chapter 2, this oxidation is controlled by steric effects because compound **145** was completely converted to **157** while only 85% conversion was observed with the disulfide analogs. The chemical shifts of the compounds detected in this low temperature experiment are reported in **Table 16.**

Table 16: ^{1}H and ^{13}C NMR Chemical Shifts of the Compounds Observed in the Low Temperature Detection of di-*t*-Butyl Disulfide-1,1,2-Trioxide (166).[a]

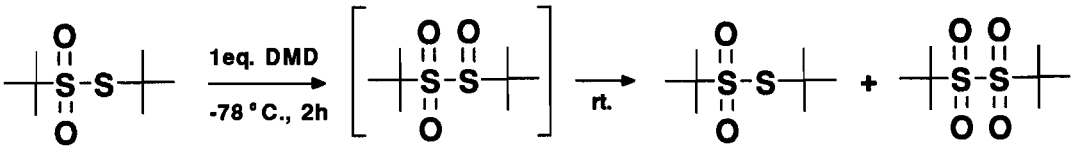
Entry	Compound	Spectra	C	CH_3	H	C'	CH_3'	H'
144		**b**	68.01	23.65	1.592	56.31	31.45	1.448
166[b]		**a**	69.28	23.74	1.501	63.68	23.80	1.473
165			72.67	24.60	1.633			
145			70.06	24.18	1.465	49.95	29.86	1.395
157		**c**	71.38	23.99	1.551	63.08	24.51	1.463
161			73.45	24.15	1.545			

[a] All the spectra were recorded in $CDCl_3$; [b] These spectra were obtained at -30°C.

The decomposition study of the di-*t*-butyl disulfide-1,1,2-trioxide (**166**) was also investigated. Although *t*-butyl sulfinic acid (**163**) and *t*-butyl sulfonic acid (**164**) (known as the decomposition products of *t*-butyl sulfinic anhydride (**168**)) were detected, the stepwise (10°C) decomposition of **166** from -30°C to room temperature was very messy and did not allow the determination of a clear mechanism. However, significant amounts of di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) were detected at various temperatures. The presence of **165** suggests that the mechanism proposed previously, ionic cleavage and oxygen transfer (steric hindrance in the recombination) could be extrapolated to the decomposition of di-*t*-butyl disulfide-1,1,2-trioxide (**166**).

The possibility of such a decomposition mechanism was also supported by the results obtained from a separate experiment. The oxidation of pure di-*t*-butyl disulfide-1,1-dioxide (**144**) was attempted using 1 equivalent of DMD at -78°C and was shown to

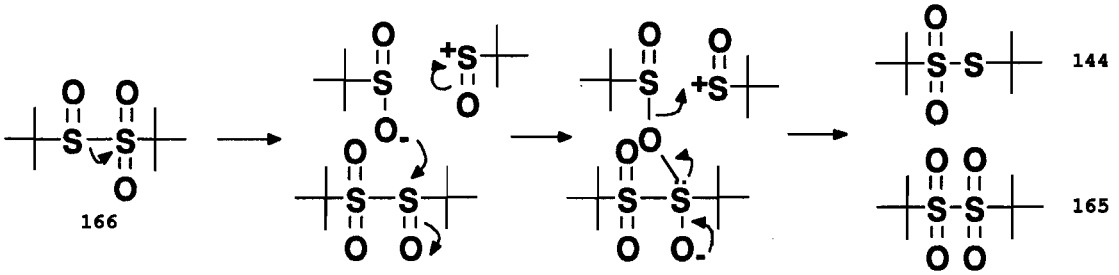
give cleaner decomposition products. Under these conditions, no trace of di-*t*-butyl disulfide-1,1,2-trioxide (**166**) was detected at room temperature. The reaction mixture presented a 60/40 mixture of di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) and di-*t*-butyl disulfide-1,1-dioxide (**144**) (**Scheme 54**).



144 **166** **144** **165**

SCHEME 54

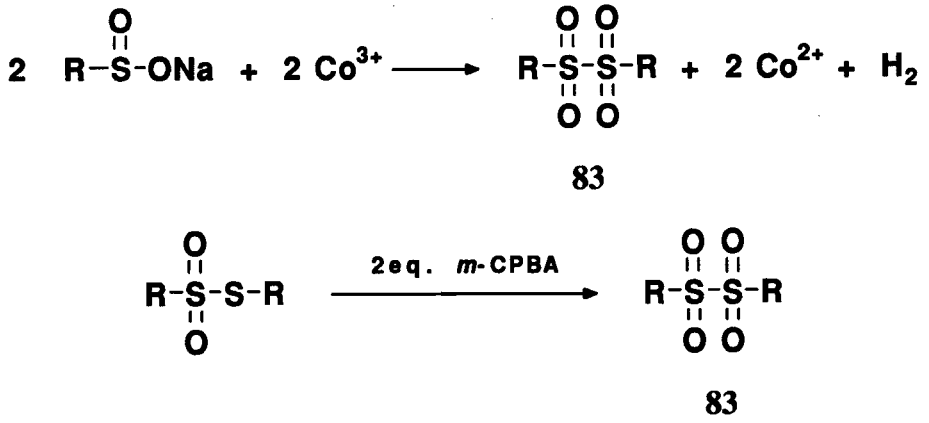
Considering that the low temperature oxidation of **144** gave 85% of disulfide-1,1,2-trioxide **166**, that the sulfenic sulfur of **144** must be much more nucleophilic than the sulfinic sulfur of **166** and that the steric effect is in favor of the formation of the 1,1,2-trioxide **166** rather than 1,1,2,2-tetraoxide **165**, the oxidation of di-*t*-butyl disulfide-1,1-dioxide (**144**) by DMD at low temperature should afford the exclusive formation of **166**. By analogy with the results obtained for the low temperature oxidation of di-*t*-butyl disulfide-1-oxide (**120b**), the disulfide-1,1,2-trioxide **166** formed should give the ionic intermediates on warming. It is difficult to predict whether *t*-butyl sulfonyl cation **188a** and *t*-butyl sulfinyl anion (**187b**) or the reverse are formed. However, sulfinyl and sulfonyl groups are known to be good leaving groups[127k] and under these dilute conditions, the reaction of the ions formed with another molecule of starting material should eventually give the products observed as the formation of 1,1,2-trioxide **166** is not favored . However, as will be described later, the recombination of the sulfonyl ion **188** should be sterically very difficult with respect to the recombination of sulfinyl ions. As a consequence, the oxygen transfer mechanism is still a good explanation for the formation of these decomposition products (**Scheme 55**).



SCHEME 55

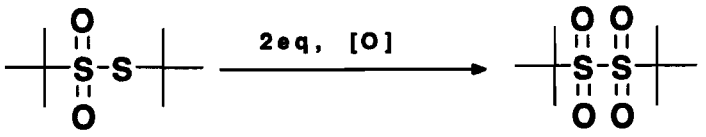
If the mechanism presented above is correct only 50% of disulfide-1,1,2,2-tetraoxide **165** should have been obtained. The 60% of **165** observed can be explained by the NMR integration errors which were earlier reported to be about 10%. Possibly the discrepancy could be related to an excess of oxidizing agent or a combination of both.

Although almost nothing is known about the chemistry of the alkyl *vic*-disulfone (alkyl disulfide-1,1,2,2-tetraoxide) (**83**), the synthesis of a few aryl and alkyl disulfide-1,1,2,2-tetraoxides has been reported by oxidation of the corresponding sodium sulfinate with cobalt(III) sulfate[127g] or by direct peracid oxidation of the corresponding disulfide-1,1-dioxide[127k,l] (**Scheme 56**).



SCHEME 56

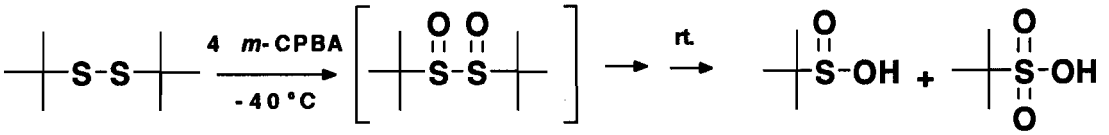
The oxidation of di-*t*-butyl disulfide-1,1-dioxide (**144**) using 2 equivalents of *m*-CPBA or DMD afforded a low to moderate yield of the corresponding disulfide-1,1,2,2-tetraoxide **165** as reported in Chapter 3 (**equation 94**).



(eq. 94)

144 **[O] = *m*-CPBA 38%** **165**
[O] = DMD 63%

Using *m*-CPBA, the oxidation reaction was very slow and after 8 days at -20°C a low yield of di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) was isolated. However, the DMD oxidation afforded a fair yield of the desired **165** in less than 12 h from -78°C to room temperature. Direct oxidation of di-*t*-butyl disulfide with 4 equivalents of *m*-CPBA at -40°C were unsuccessful and mainly afforded *t*-butyl sulfinic acid (**163**) and *t*-butyl sulfonic acid (**164**) for reasons stated earlier (**Scheme 57**).



118b **167** **163** **164**

SCHEME 57

The further investigation of the formation and decomposition of the di-*t*-butyl disulfide polyoxides allowed the characterization of new products, the explanation of odd results and the proposal of consistent general mechanisms. In comparison with the well studied disproportionation of thiosulfinates (disulfide-1-oxides), clear evidence of a similar disproportionation for the decomposition of di-*t*-butyl disulfide-1,2-dioxide (**167**) and di-*t*-butyl disulfide-1,1,2-trioxide (**166**) are reported here. In contrast to a previous report,[134c] the general mechanism proposed here accounts for most of the results observed (detection of only one diastereoisomer of **167**, decomposition products and intermediates). Finally, the use of DMD was shown to present great advantages over peracids in this specific case of the *t*-butyl disulfide-polyoxides where steric and electronic effects are very important.

4.3. Decomposition Study of Alkyl Trisulfide-Monoxides

The synthesis and characterization of a variety of alkyl trisulfide-1-oxide (R-S(O)SS-R) has been described in Chapter 3. The electrophilic oxidation of primary, secondary and tertiary alkyl trisulfides as well as aryl trisulfides was shown to be regiospecific and to proceed in high yield. In contrast, the peracid oxidation of trithiolane derivatives afforded the corresponding 1- and 2-oxides and the electrophilic oxidation of unsymmetrical alkyl trisulfides gave the corresponding 1- and 3-oxides although steric effects and electronic effects could be clearly shown. Parallel experiments have shown that in our hands, alkyl trisulfide-2-oxides (R-SS(O)S-R) could not be obtained by direct oxidation using a wide variety of different types of oxidizing agents (nucleophilic and electrophilic) (Chapter 3). However, direct oxidation of certain trithiolanes afforded the corresponding trithiolane-2-oxides in various ratios depending on the oxidizing agent used as reported in the introduction of Chapter 3.

A general method of synthesis of trisulfide-2-oxides (R-SS(O)S-R) has been reported by Field[179] and was found to be very efficient in all the cases reported. Following this procedure, the synthesis of primary, secondary, tertiary alkyl, cyclic[200,202] and aryl trisulfide-2-oxides[179] for both symmetrical and unsymmetrical analogs were very successful.

In contrast to the disulfide-1-oxides (thiosulfinates) **79**, the alkyl trisulfide-1-oxides (R-S(O)SS-R) were found to have a relatively low stability at room temperature, the stability decreasing with the degree of substitution (tertiary > secondary > primary). To our knowledge, no real decomposition study of this class of compounds has been reported yet, although various decomposition products were determined by different groups of researchers.[197,204] However, as described in Chapter 3, the decomposition of this class of compounds is quite complex; no straight-forward mechanism could be advanced. By contrast, the decomposition of trisulfide-2-oxides (R-SS(O)S-R) is very clean and was very well investigated as reported in the introduction of this Chapter. However, parts of the mechanism proposed remains unclear because it was not detailed by Field.[179]

Considering the complexity of the decomposition mixtures and that very little is known about the decomposition of trisulfide-monoxides, it was decided to further investigate the decomposition of this class of compounds focusing on the di-*t*-butyl derivatives that created the most controversy.

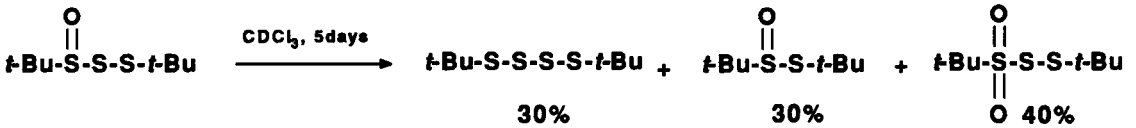
4.3.1. di-*t*-Butyl Trisulfide-1-Oxide (120c)

As described in Chapter 3, di-*t*-butyl trisulfide-1-oxide (**120c**) was obtained in moderate yield and high purity by direct oxidation of the corresponding trisulfide **118c**. The purification of compound **120c** was difficult because of the low stability of this class of compounds.

4.3.1.1. Decomposition Products

The decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) under various conditions afforded contradictory complex mixtures of products that could not be completely rationalized.[197,204] In the present study, the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) is further investigated under standardized conditions.

The first part this study has been focussed on the determination of the identity and amounts of the decomposition products of **120c**. Many attempts using pure *t*-butyl trisulfide-1-oxide (**120c**) (>96% by proton NMR) have shown that the decomposition mixture was quite messy, but afforded as major compounds (>80%) di-*t*-butyl tetrasulfide (**118d**), di-*t*-butyl trisulfide-1,1-dioxide (**145**) and di-*t*-butyl disulfide-1-oxide (**120b**). The decomposition of **120c** was carried at different temperatures (rt., 50°C, 100°C), in different solvents (benzene-d_6, chloroform-*d*, acetone-d_6, acetonitrile-d_3), at different concentrations (5 mg/mL to 50 mg/mL) and in various decomposition conditions (dark, inert atmosphere). Although the relative concentration of the final products significantly varied according to the purity of the starting material and the solvent used (*vide infra*), the reaction mixtures were found in most cases to be close to an equimolar mixture of the three products (**Scheme 19**).



120c **118d** **120b** **145**

SCHEME 19

The relative concentrations of the decomposition products were determined after separation by silica gel chromatography or by the relative integrals observed on ^{13}C NMR. A satisfactory integral could not be obtained by proton NMR owing to overlapping peaks. However, calibration experiments have shown that the relative integral of this specific mixture corresponds to their respective relative molar concentrations within *ca.* 7%. The deviation from the average 1:1:1 mixture of the three decomposition products can be rationalized by the fact the reaction is not clean (at least 10% of other derivatives), the inherent error of the NMR calculations or the inevitable loss of compound using silica gel chromatography. The quantification of the decomposition products has been attempted using gc analysis. Unfortunately, the compounds decompose readily on the capillary column used.

Although small amounts of di-*t*-butyl trisulfide **(118c)** and di-*t*-butyl disulfide-1,1-dioxide (thiosulfonate) **(144)** have been detected in rare occasions, the results observed here are somewhat in contrast with the ones reported in the literature.[197,204] However, their decomposition conditions were different from ours. The products of the decomposition of di-*t*-butyl trisulfide-1-oxide **(120c)** as well as their relative concentrations have been determined. The decomposition mechanism remains unclear as these products in the literature can not easily be rationalized and a further mechanistic investigation similar to the one reported by Field and Lacefield[179] was undertaken.

4.3.1.2. Kinetic Study

Because further understanding of the decomposition of trisulfide-1-oxides (R-S(O)SS-R) would explain the formation of the previously reported products and because of interest in the decomposition itself, kinetic studies were undertaken. Considering the complexity of the decomposition mixture and the results reported in Chapter 3, the kinetic experiments were carried out on di-*t*-butyl trisulfide-1-oxide **(120c)** by ^{13}C and ^{1}H NMR. However, most the proton NMR kinetic experiments could not be interpreted owing to overlapping peaks.

The concentrations of di-*t*-butyl trisulfide-1-oxide **(120c)** employed were approximately 0.3 mol L^{-1} for ^{13}C kinetic experiments and 0.01 mol L^{-1} for proton experiments. The NMR tubes were filled under a nitrogen atmosphere and sealed. These decomposition experiments were carried out at 45°C and the time between acquisition

was set to 1 h. In order to know if there was any influence of solvent polarities upon the rates of the decomposition, the kinetic experiments were carried out in benzene-d_6, chloroform-d, acetone-d_6 and acetonitrile-d_3. In all cases, the decomposition was completed within 12 hours. The rate constants were calculated from the slope of $\ln_{rel.conc.}$ vs time plots, assuming first-order kinetics (**Figure 14**). The relative concentration (rel.conc.) of starting material and products were calculated by comparing their signal intensities to the one of *t*-butyl chloride which was used as an internal standard. In all the cases studied, no reaction with the internal standard could be detected.

Following this procedure reasonably good agreement with first-order kinetics were obtained. A typical rate profile of the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) is shown in Figure 14.

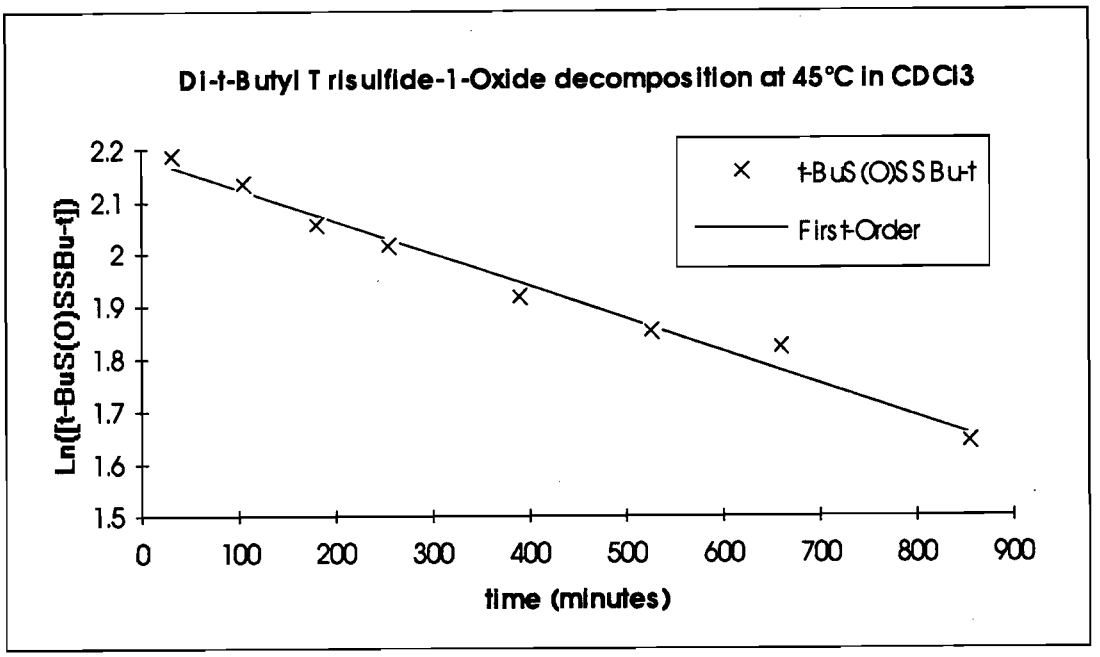


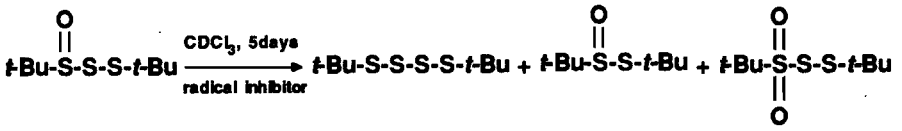
Figure 14: First Order Rate Plot for the Decomposition of di-*t*-Butyl Trisulfide-1-Oxide (120c)

The use of four different solvents did not afford consistent results. Although most of the plots of the $\ln_{rel.conc.}$ vs time were linear, the rates of decomposition varied with the solvent polarities and even from one experiment to another.

Overall, the kinetic study was somewhat unsuccessful. It was impossible to obtain reliable rates of decomposition and the calculation of the enthalpy and the entropy of the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) could not be done. Finally, the use of solvents of different polarities did not give the desired information on the influence of the polarity on the rate of the decomposition and thus, on the type of mechanism

(heterolytic or homolytic). However, most of the data obtained, reasonably agreed with first-order kinetics and by analogy with other studies,[179] the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) can be postulated to follow a first-order process with the cleavage of the trisulfide-1-oxide **120c** as the rate determining step.

The use of solvents of different polarities did not afford a clear answer on whether the cleavage was homolytic or heterolytic. Parallel experiments have shown that in the presence of radical inhibitors (benzoquinone or 4-*t*-butyl catechol) or light/dark effects, the decomposition was still taking place at similar rates and afforded the same decomposition products (**equation 95**).



(eq. 95)

120c **118d** **120b** **145**

By analogy with the decomposition of alkyl polysulfide-polyoxides previously reported and according to the results presented here, the cleavage of di-*t*-butyl trisulfide-1-oxide (**120c**) seems to be more likely to be heterolytic than homolytic. According to previous reports[81,92a,133,203] and considering the decomposition products formed, the ionic cleavage of this trisulfide-1-oxide should occur at a S-S bond. Due to the presence of an oxygen atom on the sulfur chain and considering that crystallography studies[227] have shown that the S(O)-S bond is longer than the S-S and $S(O)_2$-S, it is reasonable to suggest that the rate determining step is the ionization of the S(O)-S bond. This cleavage should afford a cation and an anion. Considering that the oxygen atom is more electronegative than the sulfur atom, that sulfinyl chlorides[219] are generally more stable than chloro disulfides,[206] and by analogy with previous reports,[81,203,222] the ionic cleavage of di-*t*-butyl trisulfide-1-oxide (**120c**) is believed to afford the *t*-butyl sulfinyl cation (**187a**) and the *t*-butyl disulfide anion (**189**) (**equation 96a**).

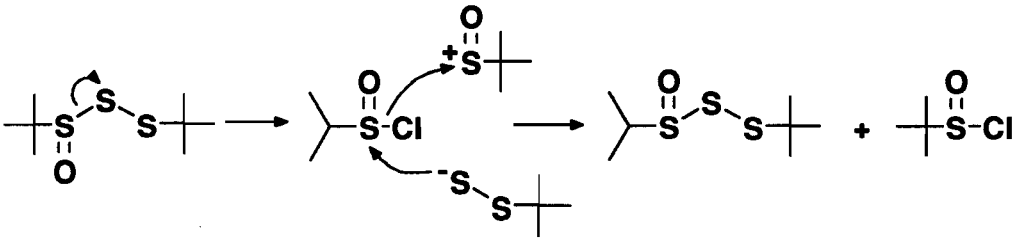
(eq. 96a)

120c **187a** **189**

227 See Chapter 3 and references therein.

Several attempts to confirm the postulated cleavage of di-*t*-butyl trisulfide-1-oxide (**120c**) were carried out by decomposition of **120c** in the presence of a wide variety of trapping agents in the conditions earlier reported. The use of di(p-*t*-butyl phenyl) trisulfide-1-oxide (**173**), excess di-*t*-butyl trisulfide (**118c**), dimethyl sulfoxide, phenyl acetylene, 2,3-dimethyl-1,3-butadiene, dimethyl thiocarbamyl chloride and dimethyl carbamyl chloride were unsuccessful in our hands. Under these specific conditions, normal decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) occurred in most cases implying that the trapping agents used were not reactive enough. In the rare cases where the trapping agents (dimethyl sulfoxide and 2,3-dimethyl-1,3-butadiene) participated in the decomposition, the reaction mixture was very complex and could not be analyzed using available techniques. However, using isopropyl sulfinyl chloride (**180**) as a trapping agent, significant amounts of *t*-butyl sulfinyl chloride (**149**) (~20%) could be detected (the ^{1}H and ^{13}C NMR chemical shifts of the trapped intermediates **149** were compared to those of a pure sample of *t*-butyl sulfinyl chloride (**149**)). The formation of *t*-butyl sulfinyl chloride (**149**) was easily detected as its NMR chemical shifts are very different from those of the other decomposition products.

The clear evidence of formation of *t*-butyl sulfinyl chloride (**149**) confirms the cleavage earlier reported as it involves the formation of the *t*-butyl sulfinyl cation (**187a**) which reacts with chloride anion. Careful analysis of the other decomposition products also gives clear evidence of the reaction of the *t*-butyl disulfide anion (**189**) with isopropyl sulfinyl chloride (**180**) to form *t*-butyl isopropyl trisulfide-3-oxide (**190**) as all its decomposition products were detected in the reaction mixture (the decomposition of *t*-butyl isopropyl trisulfide-3-oxide (**190**) is described later) (**Scheme 58**).



120c **190** **149**

SCHEME 58

Further analysis of the reaction mixture by NMR and silica gel chromatography were consistent with the previous results and clearly showed the decomposition products of di-*t*-butyl trisulfide-1-oxide (**120c**) and *t*-butyl isopropyl trisulfide-3-oxide (**190**) as well as mixed decomposition products (these results will be presented and discussed in the next section).

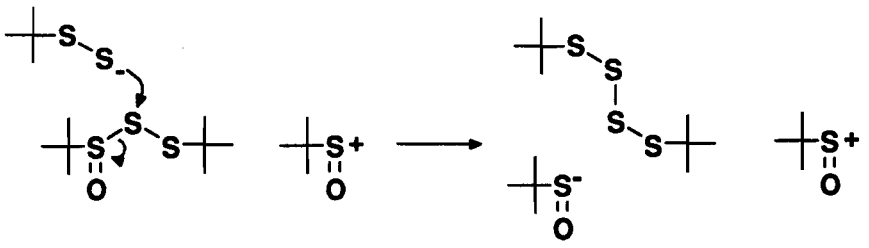
4.3.1.3. Decomposition of An Unsymmetrical Trisulfide-1-Oxide

The main features of the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**), that must be accounted for by any mechanism, are as follows. (1) The decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) affords a 1:1:1 mixture of di-*t*-butyl tetrasulfide (**118d**), di-*t*-butyl trisulfide-1,1-oxide (**144**) and di-*t*-butyl disulfide-1-oxide (**120b**). (2) The decomposition is approximated by first-order kinetics. (3) The decomposition is significantly influenced by heat but not by light and even takes place in the presence of radical inhibitor. (4) *t*-Alkyl trisulfide-1-oxide **120c** is far more stable than sec-alkyl **172** or primary alkyl trisulfide-1-oxide **170**. (6) The decomposition is not clean, implying that competing rearrangements take place.

First, the rate determining cleavage of **120c** into an ion pair is suggested, leading to the formation of *t*-butyl sulfinyl cation (**187a**) and *t*-butyl disulfide anion (**189**) (**equation 96a**).

120c **187a** **189** (eq. 96a)

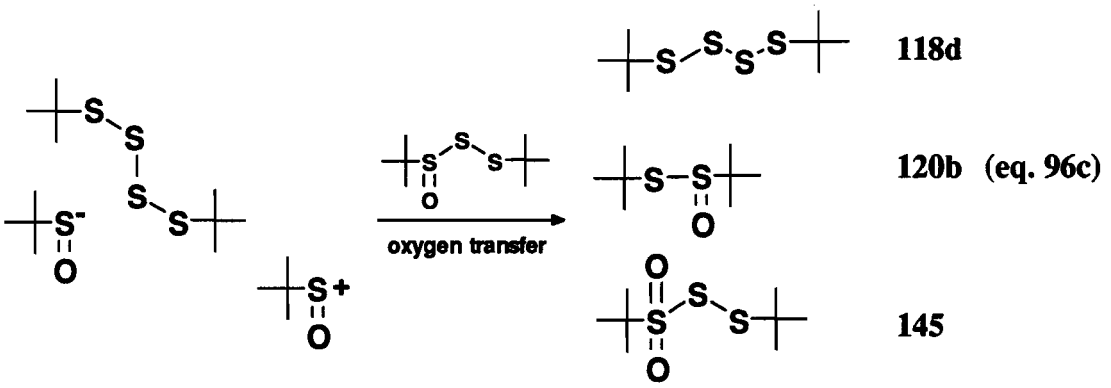
These pair of ions can obviously recombine and give back the starting material or eventually react with a second molecule of trisulfide-1-oxide **120c**. In this last case, the *t*-butyl disulfide anion (**189**) can attack the electron-poor sulfinyl sulfur atom and give back a molecule of starting material. Another possibility is the attack on the internal sulfur which is also quite electrophilic as seen previously. Cleavage of the weakest bond (S-S(O)) should give the first decomposition product, di-*t*-butyl tetrasulfide (**118d**) as well as *t*-butyl sulfinyl anion (**187b**). The formation of *t*-butyl sulfinyl anion (**187b**) is supported by literature reports[222] as described in the decomposition of di-*t*-butyl disulfide-1,2-dioxide (*vic*-disulfoxide) (**167**) (**equation 96b**).



(eq. 96b)

120c **187a** **187b** **118d**

Therefore, the reaction mixture is composed of starting material **120c**, di-*t*-butyl tetrasulfide (**118d**), and this pair of very interesting ambident ions **187a-b**. In the first part of this Chapter, it was shown that these ambident ions do not easily recombine to give di-*t*-butyl disulfide-1,1-dioxide (**144**) because of steric effects.[226] As a consequence, they react faster with a third molecule of starting material **120c** by an oxygen transfer mechanism that should afford the two final decomposition products (**equation 96c**).



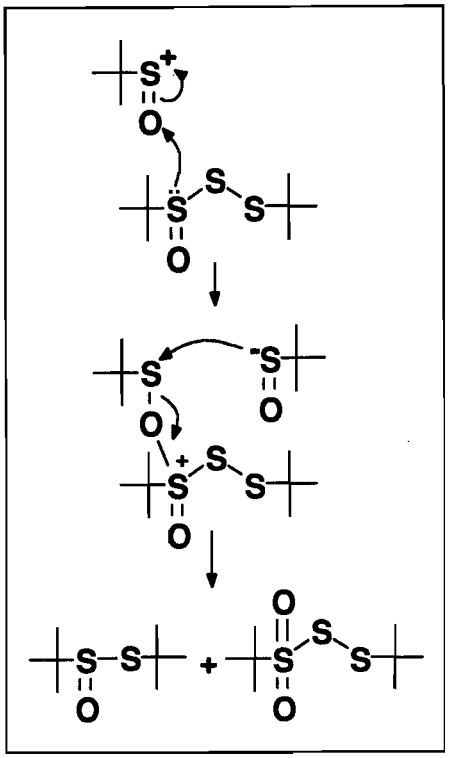
118d

120b (eq. 96c)

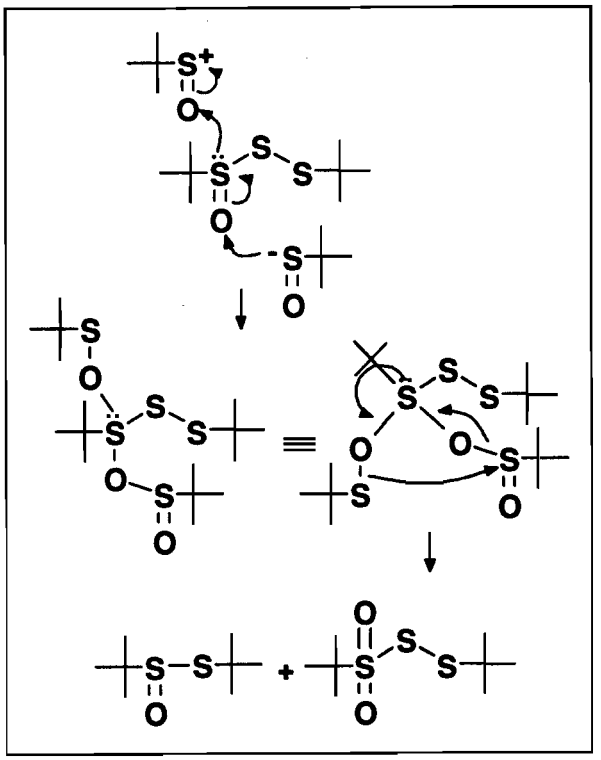
145

187b **118d** **187a**

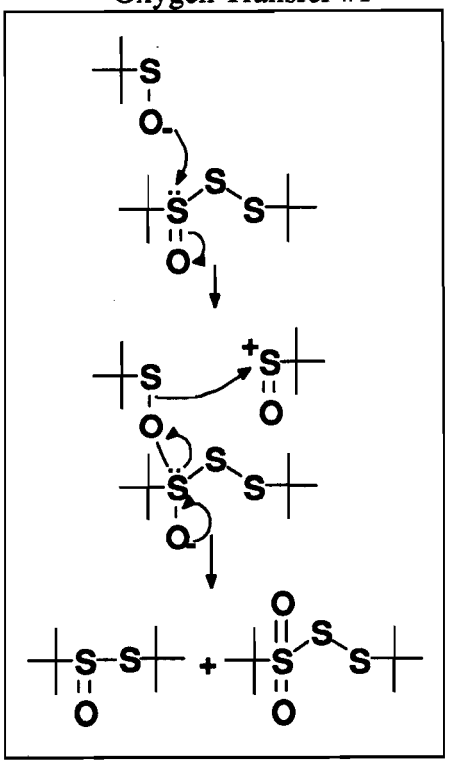
The four oxygen transfer mechanisms earlier proposed, can be applied to the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) and are illustrated on **Scheme 59**. Once again, none of these oxygen transfer mechanisms can be ruled out. However, some of them are less likely to happen. First, it has been shown in Chapter 3 that the 1 equivalent peracid oxidation of di-*t*-butyl trisulfide-1-oxide (**120c**) affords exclusively the corresponding trisulfide-1,3-dioxide **130** (**equation 59**). Therefore, the reaction of the trisulfide-1-oxide **120c** with the *t*-butyl sulfinyl cation **187a** (electrophilic mechanism, # 1 above) should take place at the 3 position which is the most nucleophilic but no trace of trisulfide-1,3-dioxide **130** has ever been detected in these decomposition experiments. However, we are in the presence of ionic species and the reaction at position 1 affords the thermodynamically favored product namely di-*t*-butyl trisulfide-1,1-dioxide (**145**).



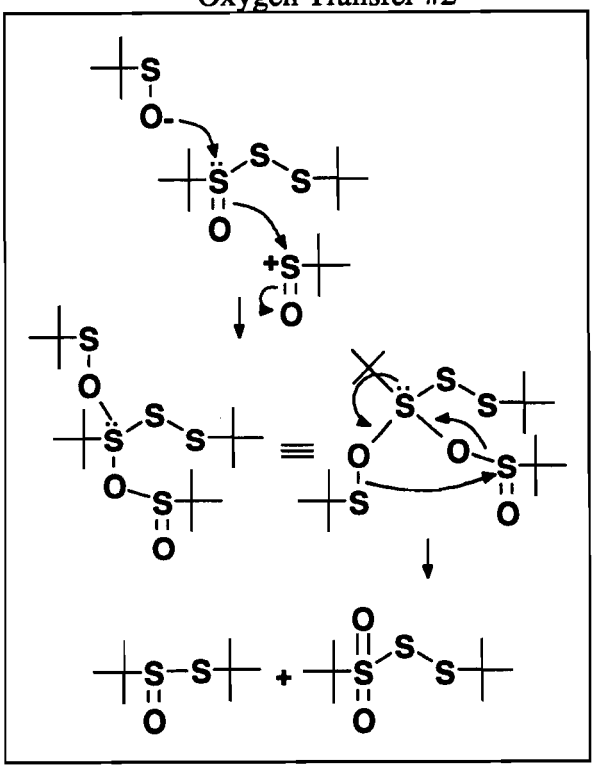
Oxygen Transfer #1



Oxygen Transfer #2



Oxygen Transfer #3



Oxygen Transfer #4

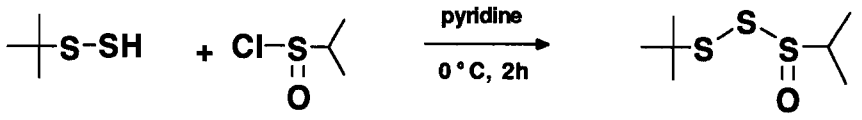
SCHEME 59

It was also shown in Chapter 3 that the nucleophilic oxidation of di-*t*-butyl trisulfide-1-oxide (**120c**) did not afford any trace of di-*t*-butyl trisulfide-1,1-dioxide (**145**). Therefore, the reaction of trisulfide-1-oxide **120c** with the sulfinyl anion **187b** (nucleophilic mechanism, # 3 above) is somewhat contradictory with the results previously reported. However, this type of nucleophilic oxidation might be milder than the ones reported earlier and under these specific conditions, there may not be any bond cleavage.

Mechanism # 3 remains a reasonable pathway. Mechanisms # 2 and # 4 involving a tetrasubstituted intermediate, are also possible explanation for the decomposition products of di-*t*-butyl trisulfide-1-oxide (**120c**), however the termolecular pathway is less likely than mechanism # 3.

At this point in the study on the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**), it was believed that the analysis of the decomposition products of an unsymmetrical trisulfide-1-oxide (R-S(O)SS-R') could help to confirm the likelihood of this rather complex decomposition mechanism (bond cleavage, formation of terasulfide and oxygen transfer rearrangement).

The synthesis of *t*-butyl isopropyl trisulfide-3-oxide (**190**) was achieved by reaction of *t*-butyl hydrodisulfide (**148**) with isopropyl sulfinyl chloride (**180**) in the presence of pyridine (**equation 97**).



(eq. 97)

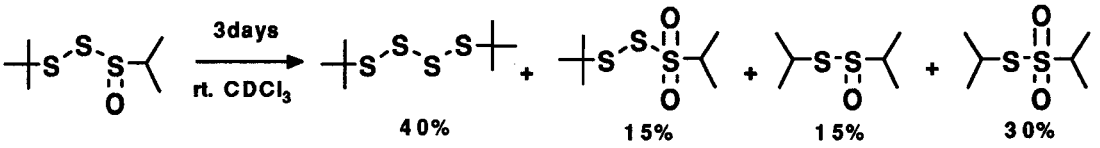
148 **180** **190**

To our knowledge this is the first synthesis of an unsymmetrical alkyl trisulfide-1-oxide. Compound **190** was found to be even less stable than di-*t*-butyl trisulfide-1-oxide (**120c**) but could still be purified by column chromatography.

According to the mechanism suggested for the decomposition of di-*t*-trisulfide-1-oxide (**120c**), the decomposition products of *t*-butyl isopropyl trisulfide-3-oxide (**190**) should be di-*t*-butyl tetrasulfide (**118d**), *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) and diisopropyl disulfide-1-oxide (**123b**). No scrambling of the alkyl groups should be observed if the mechanism proposed is valid. However, considering that the oxidation of

diisopropyl disulfide-1-oxide (**123b**) gives a high yield of the corresponding disulfide-1,1-dioxide **169** in contrast to the oxidation of di-*t*-butyl disulfide-1-oxide (**120c**), it can be envisioned that significant amounts of diisopropyl disulfide-1,1-dioxide (**169**) could be detected as the rearrangement of the ambident ions formed should be more sterically favored than in the *t*-butyl case.[226]

The decomposition of *t*-butyl isopropyl trisulfide-3-oxide (**190**) was carried out several times under similar conditions to the ones reported for the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**). In this case, the decomposition was very clean compared to the one earlier reported and afforded all the expected products (**Scheme 60**).

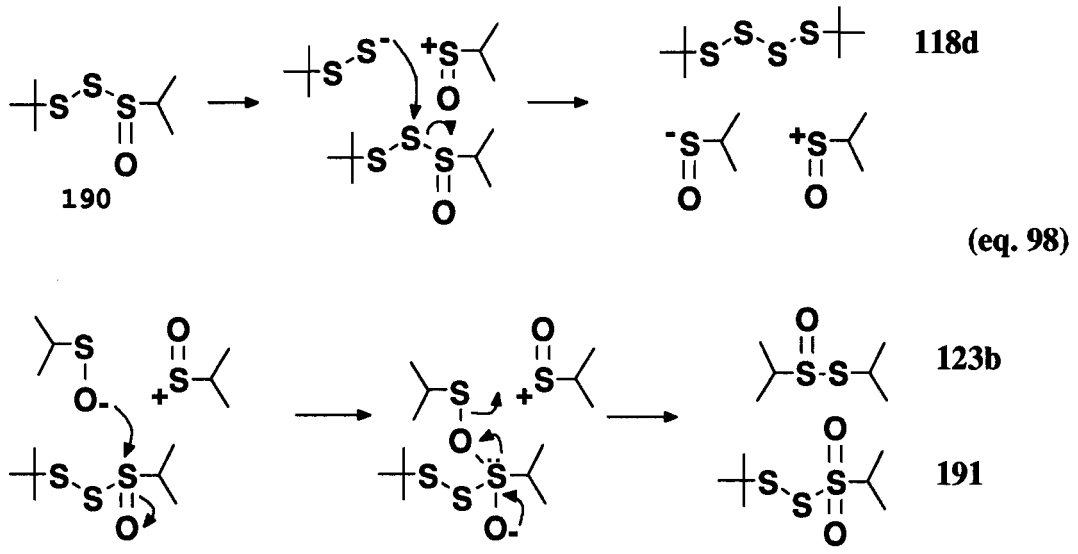


190 **118d** **191** **123b** **169**

SCHEME 60

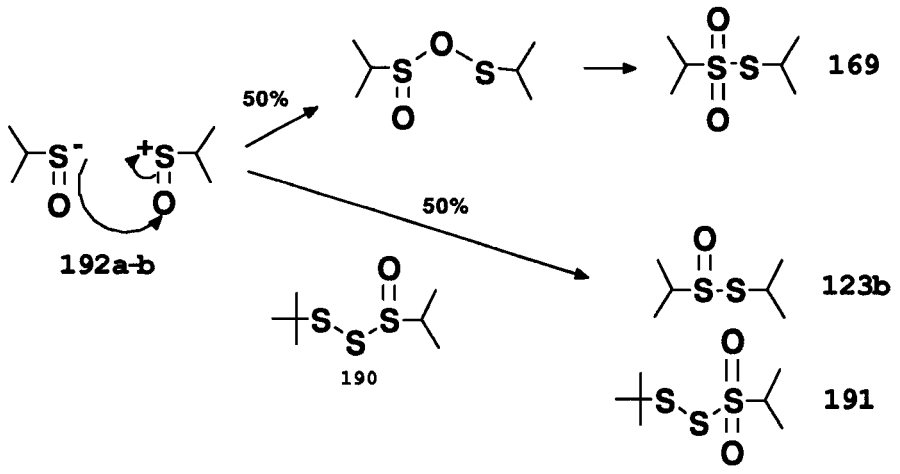
The relative concentration of each of the final products was estimated from the ^{13}C NMR as the proton NMR presented considerable overlapping and clear separations could not be obtained by silica gel chromatography. However, it is clear that di-*t*-butyl tetrasulfide (**118d**) is the only polysulfide formed and is the major decomposition product (no unsymmetrical tetrasulfide could be detected by NMR and gc analysis). The unique formation of tetrasulfide **118d** implies the formation of two ambident isopropyl ions **192a-b**. In this case, the recombination of ions **192a-b** to form diisopropyl disulfide-1,1-dioxide (**169**) is in competition with their reaction with another molecule of *t*-butyl isopropyl trisulfide-3-oxide (**190**). This reaction was previously proposed to be an oxygen transfer that should only deliver *t*-butyl trisulfide-3,3-dioxide (**191**) and diisopropyl disulfide-1-oxide (**123b**). Any other mechanism than oxygen transfer should give scrambling of the alkyl groups. A careful analysis of the NMR spectrum as well as the separation of part of the reaction mixture by silica gel chromatography gave clear evidence of the sole formation of *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) and di-isopropyl disulfide-1-oxide (**123b**) (the other possible scrambling products have been obtained in separate experiments and have clearly different NMR signals which would have been easily identified if they were present). Moreover, the relative concentration of

the final products of the oxygen transfer reaction was estimated to be a 1:1 mixture of **191** and **123b** by comparing the intensities of the secondary carbon signals (CH). These results are consistent with the oxygen transfer mechanism **(equation 98)**.



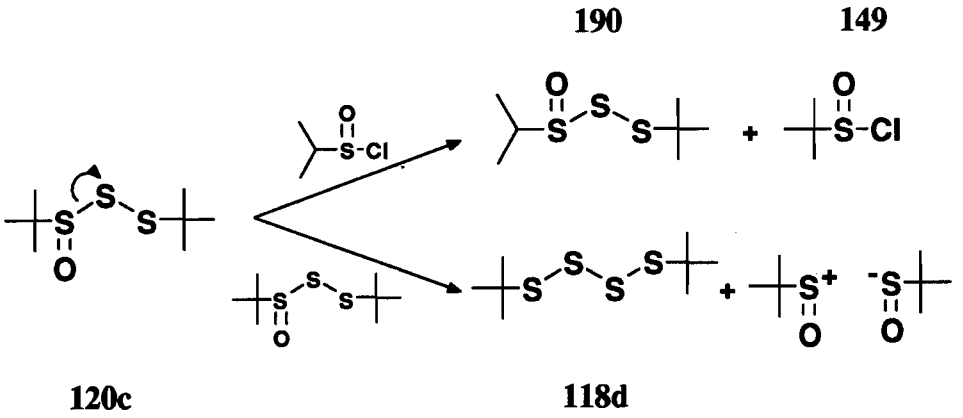
(eq. 98)

Finally, the competition between the recombination of the pair of ions **192a-b** that gives diisopropyl disulfide-1,1-dioxide **(169)** and the oxygen transfer mechanism was estimated to be *ca.* 50/50 by comparing the relative intensities of the secondary carbon signals of diisopropyl disulfide-1,1-dioxide **(169)** with the ones of diisopropyl disulfide-1-oxide **(123b)** plus *t*-butyl isopropyl trisulfide-3,3-dioxide **(191)** **(Scheme 61)**.



SCHEME 61

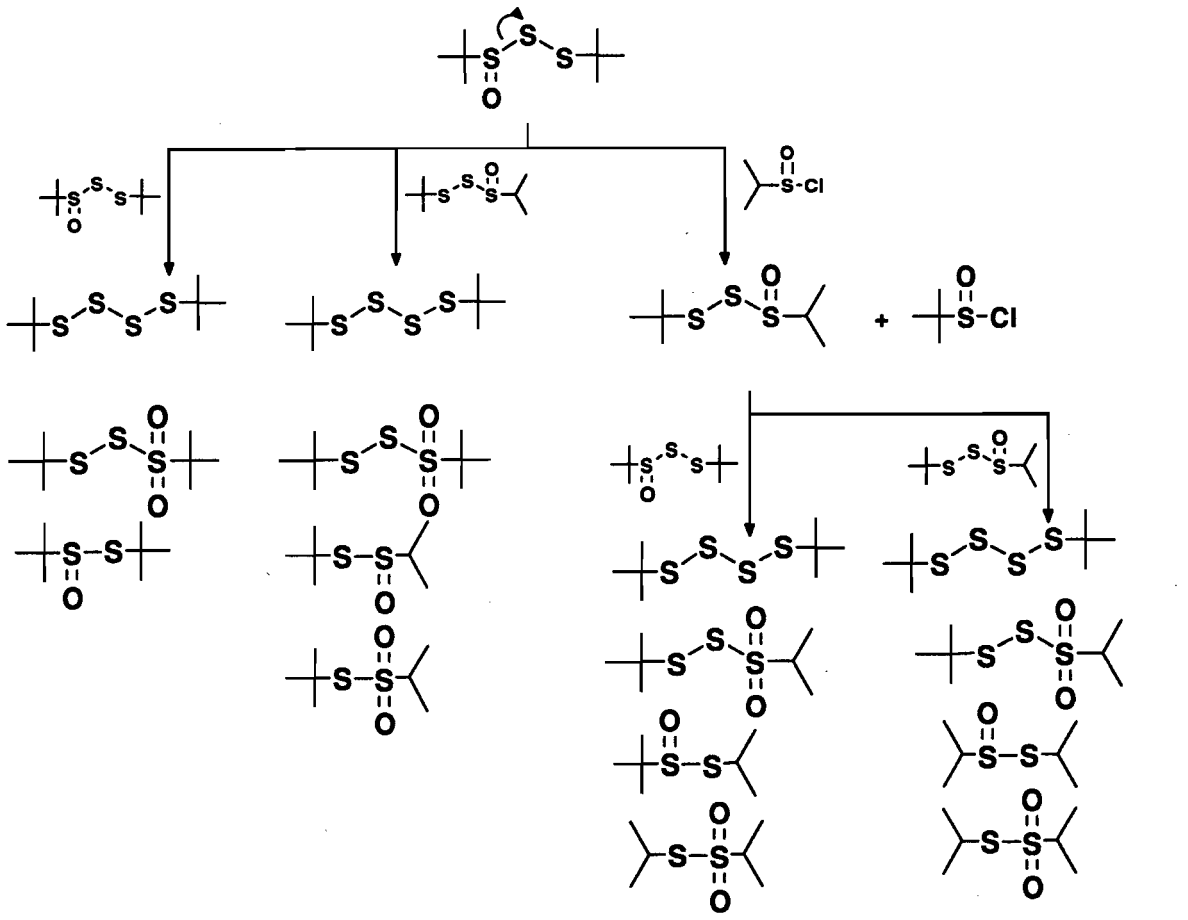
The decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) in the presence of 0.5 equivalents of isopropyl sulfinyl chloride (**180**) was reported earlier. The complexity of the reaction mixture as well as the impossibility to isolate all these compounds by chromatography did not allow a complete analysis. However, the competition between the normal decomposition of **120c** and the reaction with isopropyl sulfinyl chloride (**180**) could be clearly seen and is rationalized by the use of only 0.5 equivalents of sulfinyl chloride **180** (using 1 equivalent of **180,** a large excess was found in the final reaction mixture that considerably prevented the analysis of the spectra) (**Scheme 62**).



SCHEME 62

The competition among the normal decomposition of **120c**, the reaction with **180**, the recombination of ions **192a-b** as well as the oxygen transfer reaction can be clearly seen in **Scheme 63.**

The formation of all these compounds can be rationalized by the mechanism proposed earlier except for the formation of small quantities of di-*t*-butyl disulfide (**118b**) and diisopropyl disulfide (**122**) that have only been detected when using this trapping agent. Although quantification of product could not really be done, major and minor compounds could easily be defined which gives an idea about the various competition involved in these decomposition experiments (**Table 17**).

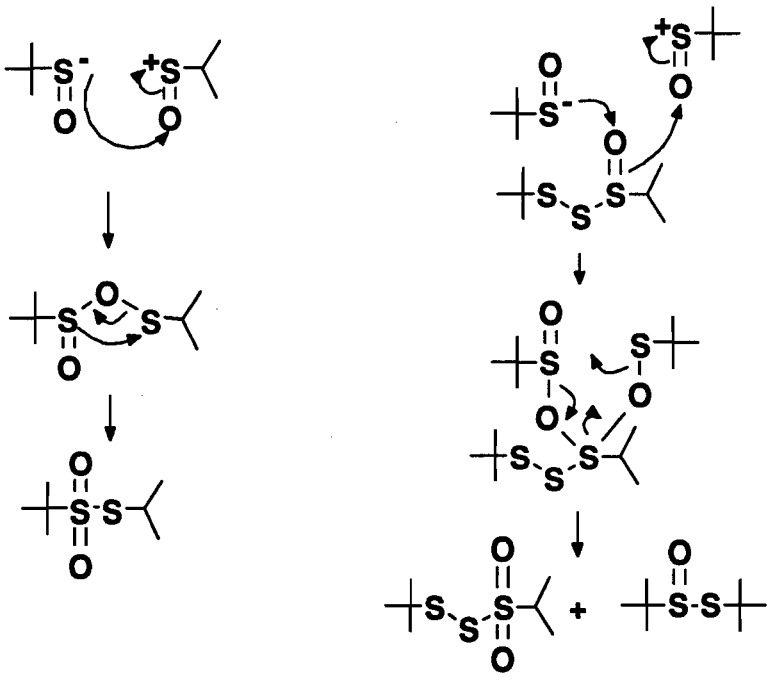


SCHEME 63

Table 17: di-*t*-Butyl Trisulfide-1-Oxide and Isopropyl Sulfinyl Chloride Study

Entry	Compound	Quantity	Entry	Compound	Quantity
118d	*t*-BuSSSSBu-*t*	major	**144**	*t*-BuS(O)$_2$SBu-*t*	traces
145	*t*-BuS(O)$_2$SSBu-*t*	major	**120b**	*t*-BuS(O)SBu-t	moderate
191	*t*-BuSSS(O)$_2$Pr-i	moderate	**193**	*t*-BuS(O)SPr-i	traces
185a	*t*-BuS(O)$_2$SPr-i	moderate	**179**	*t*-BuSS(O)Pr-i	none
169	i-PrSS(O)$_2$Pr-i	small	**123b**	i-PrSS(O)Pr-i	traces
185b	*t*-BuSS(O)$_2$Pr-i	traces	**149**	*t*-BuS(O)Cl	moderate

The fact that more di-*t*-butyl trisulfide-1,1-dioxide (**145**) is formed than *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) implies that the normal decomposition of **120c** is favored over the reaction with sulfinyl chloride **180**. The fact that very small quantities or none of *t*-butyl isopropyl disulfide-1-oxide (**193**), *t*-butyl isopropyl disulfide-2-oxide (**179**), *t*-butyl isopropyl disulfide-2,2-dioxide **185a** and diisopropyl disulfide-1,1-dioxide (**169**) could be detected can be interpreted as follows. Due to the preferred normal decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**), more ambident *t*-butyl sulfinyl pair of ions **187a-b** than isopropyl ones **192a-b** are present in solution. Therefore, the isopropyl sulfinyl cation **192a** formed has more chance to react with the *t*-butyl sulfinyl anion **187b** rather than with another. Therefore, it explains the major formation of *t*-butyl isopropyl disulfide-1,1-dioxide **185a** according to the mechanism proposed in the first part of the present Chapter (the formation of di-*t*-butyl disulfide-1,1-dioxide (**144**) is inhibited by steric hindrance). Similarly, the oxygen transfer reaction has more chance to occur with *t*-butyl sulfinyl ions **187a-b** than isopropyl sulfinyl ions **192a-b**. As a result, more di-*t*-butyl disulfide-1-oxide (**120b**) is formed than the other possible disulfide-1-oxides. All these products were isolated or identified in parallel synthesis such as the 1 equivalent DMD oxidation of *t*-butyl isopropyl disulfide-2-oxide (**179**) earlier reported (the products were characterized by NMR) (**Scheme 64**).



SCHEME 64

4.3.1.4. Mechanistic Conclusions

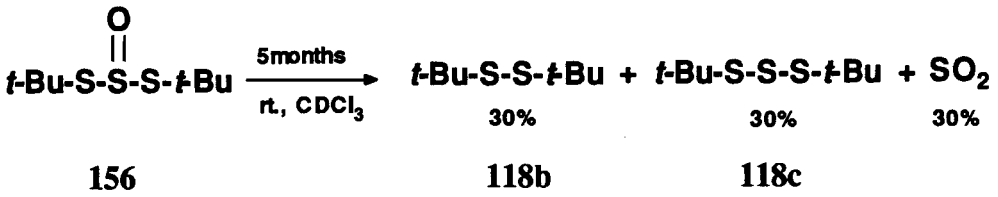
As can be seen, the decomposition of trisulfide-1-oxide **(120c)** does not proceed through a straight-forward mechanism. With no intent of proposing the exact mechanism or assuming that all compounds of this class decompose by the same pattern, the mechanism suggested here is consistent with the experimental data. While the kinetic experiments were somewhat inconsistent, the use of trapping agents confirmed the suggested cleavage of the starting material at the S(O)-S bond. The heterolytic mechanism is supported by the decomposition experiments in the presence of radical inhibitors, the effects of heat and light as well as by the obvious steric hindrance which should not be that strong in the case of an homolytic mechanism. Finally, the use of an unsymmetrical trisulfide-1-oxide **190** as well as the careful analysis of the results obtained from the decomposition of di-*t*-butyl trisulfide-1-oxide **(120c)** in the presence of isopropyl sulfinyl chloride **(180)** are completely consistent with the involvement of ambident ions and the oxygen transfer mechanism.

4.3.2. Decomposition of di-*t*-Butyl Trisulfide-2-Oxide

A detailed study of the decomposition of trisulfide-2-oxides (R-SS(O)-R) has been reported by Field and Lacefield[179] and is described in the introduction of this Chapter. The main points for the decomposition of trisulfide-2-oxides were reported as follows: (1) 2 moles of trisulfide-2-oxide decompose cleanly to give an equimolar mixture of the corresponding disulfide, trisulfide and sulfur dioxide (e.g.: Scheme 22); (2) the decomposition is first-order, at least for di-phenyl trisulfide-2-oxide; (3) simultaneous decomposition of two different trisulfide-2-oxides or of an unsymmetrical trisulfide-2-oxide results in the scrambling of groups; (4) the reaction is induced by heat but not significantly by light; (5) *t*-alkyl trisulfide-2-oxides are far more stable than sec-alkyl or primary alkyl trisulfide-2-oxides and (6) the decomposition is catalyzed by sulfur dioxide.

As reported in Chapter 3, di-*t*-butyl trisulfide-2-oxide **(156)** was synthesized according to the Field procedure[179] and could not be prepared by direct oxidation of the corresponding trisulfide **118c**. Compound **156** appeared to be relatively stable at room temperature (5 months). Its decomposition was studied at various temperatures and afforded in all cases an equimolar mixture of di-*t*-butyl disulfide **(118b)**, di-*t*-butyl

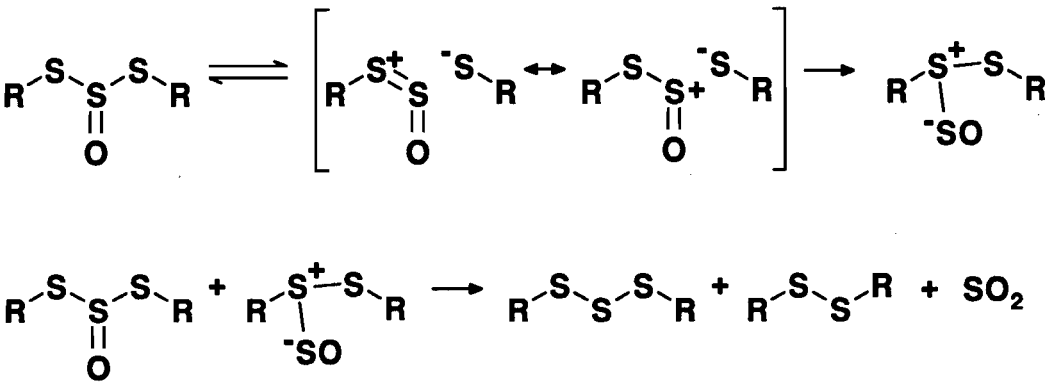
trisulfide (**118c**) and sulfur dioxide (the actual percentage of SO_2 was not measured) (**Scheme 22**).



156 **118b** **118c**

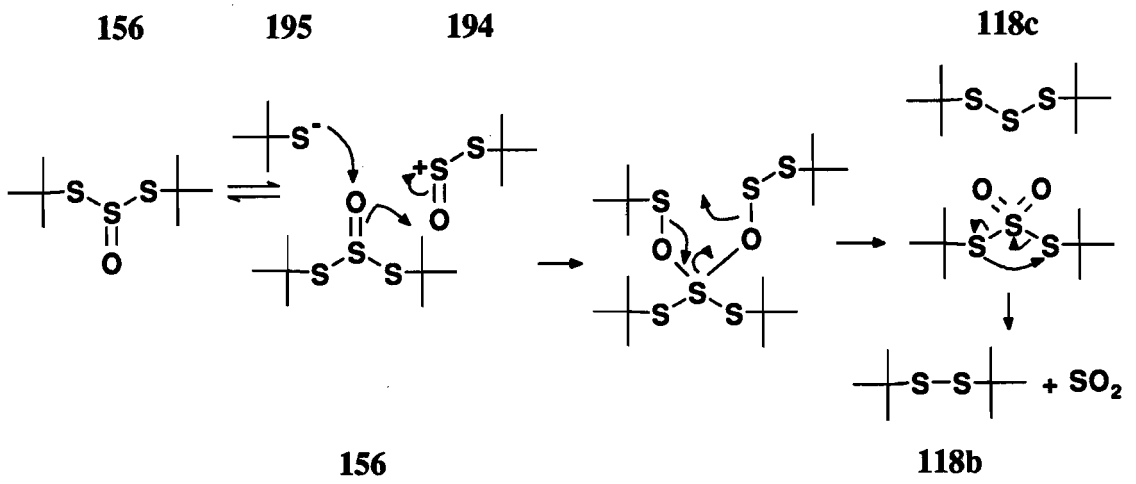
SCHEME 22

The mechanism reported by Field and Lacefield[179] is consistent with the experimental results obtained. However, they did not really propose a detailed mechanism but rather gave a summary of the general characteristics of the decomposition of trisulfide-2-oxides (R-SS(O)S-R). The first-order kinetics imply that the rate determining step is unimolecular which ruled out a simple disproportionation mechanism. As previously mentioned, their decomposition study concluded that ionic cleavage of the starting material at the S(O)-S bond gives a thiosulfinyl cation and a sulfenyl anion followed by a rapid reduction of a second molecule of starting material affording the three known products. This mechanism is very similar to that proposed earlier for the decomposition of trisulfide-1-oxides (R-S(O)SS-R) (**Scheme 39**).



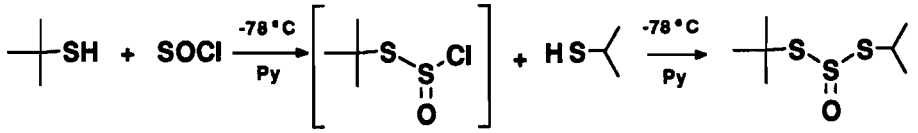
SCHEME 39

The first step involves the ionic cleavage of di-*t*-butyl trisulfide-2-oxide (**156**) at the S(O)-S bond to give *t*-butyl thiosulfinyl cation (**194**) and *t*-butyl sulfenyl anion (**195**). In the presence of another molecule of di-*t*-butyl trisulfide-2-oxide (**156**), the oxygen transfer reaction should afford the di-*t*-butyl trisulfide (**118c**) and di-*t*-butyl trisulfide-2,2-dioxide (**162**). The synthesis of **162** has been attempted by direct nucleophilic oxidation and non-oxidative synthetic procedures but was unsuccessful in our hands (Chapter 3). Compound **162** is believed to decompose immediately to an equimolar mixture of di-*t*-butyl disulfide (**118b**) and sulfur dioxide which are the two final decomposition products (**Scheme 65**).



SCHEME 65

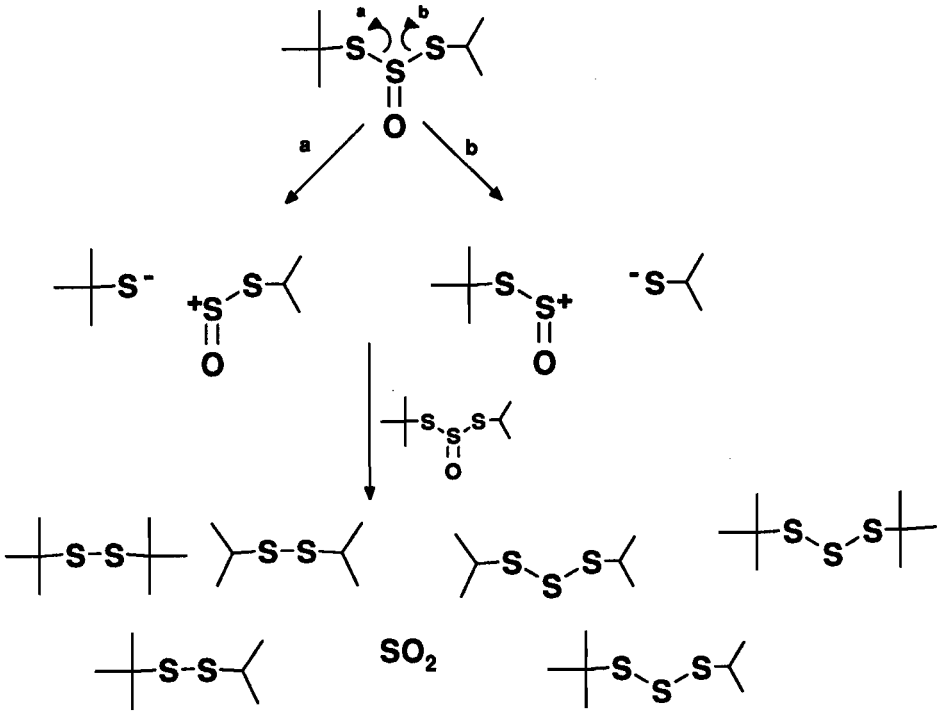
The mechanism proposed earlier can easily be applied to the decomposition of di-*t*-butyl trisulfide-2-oxide (**156**) and remains consistent with the results and the general characteristics reported by Field and Lacefield.[179] The decomposition study of the unsymmetrical *t*-butyl isopropyl trisulfide-2-oxide (**196**) that was synthesized according to Field's procedure (**equation 99**) showed scrambling of the alkyl groups.



(eq. 99)

196

This is rationalized by the fact that cleavage of **156** can take place on both side of the sulfinyl sulfur atom and the oxygen transfer can then take place with any of the ions present in solution **(Scheme 66)**.



SCHEME 66

The relative concentration of the final products could not be determined by NMR spectroscopy or silica gel chromatography.

4.4. Formation and Decomposition Study of Alkyl Trisulfide-Dioxides

As described in Chapter 3, several alkyl trisulfide-dioxides (R-S_3O_2-R') were isolated and characterized. A wide variety of trisulfide-1,1-dioxides (R-$S(O)_2$SS-R) have been reported and were prepared by non-oxidative, synthetic procedures. However, it has been shown that direct electrophilic oxidation of trisulfides (R-SSS-R) or trisulfide-1-oxides (R-S(O)SS-R) does not afford the corresponding trisulfide-1,1-dioxides except in rare cases where the intermediate formed readily decomposes to give some trisulfide-1,1-dioxide.[198] By analogy with the oxidation of disulfides,[218] the nucleophilic oxidation of trisulfide-1-oxides should have given the desired trisulfide-1,1-dioxides. In our hands, these nucleophilic oxidation experiments were unsuccessful. Trisulfide-1,1-dioxides were found to be relatively stable and were isolated as decomposition products of various polysulfide-polyoxides.

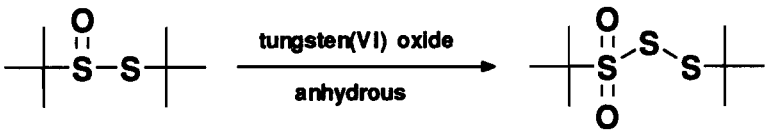
The electrophilic oxidation of trisulfide-1-oxides has been postulated to take place at the central sulfur giving the corresponding trisulfide-1,2-dioxides (R-S(O)S(O)S-R) that would rapidly rearrange to the 1,1-dioxide derivatives.[198] However, no clear evidence of this mechanism has been reported. To our knowledge, trisulfide-1,2-dioxides have never been detected.

The more electron rich sulfur atom of a trisulfide-1-oxide is believed to be the external sulfenyl sulfur which should preferentially react with the oxidizing agent to give the trisulfide-1,3-dioxide analog. Such compounds were first postulated by Steudel[197] and clear evidence of diastereomeric trisulfide-1,3-dioxides **(130)** is given in Chapter 3.

Although various trisulfide-1,1-dioxides have been reported, very little is known about their chemical properties or their preparation by direct oxidation. In addition, almost nothing has been reported on trisulfide-1,3- and 1,2-dioxides. Therefore, it was decided to further investigate this class of compounds, focusing on the di-*t*-butyl derivative.

4.4.1. Alkyl Trisulfide-1,1-Dioxides

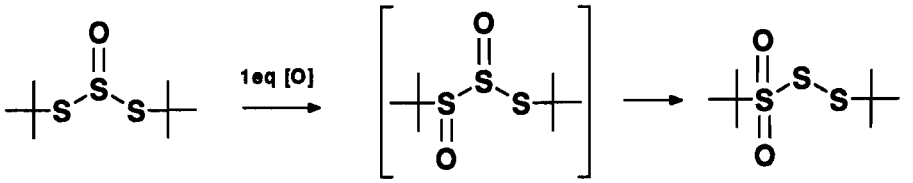
Di-*t*-butyl trisulfide-1,1-dioxide (**145**) has been isolated from the decomposition of various di-*t*-butyl trisulfide-polyoxides probably because **145** is one of the most stable of the *t*-butyl analogs (Chapter 3). Evans[203a] reported that the peracid oxidation of di-*t*-butyl disulfide-1-oxide (**120b**) in the presence of anhydrous tungsten(VI) oxide affords high yield of the corresponding trisulfide-1,1-dioxide **145** **(equation 100)**.



(eq. 100)

120b **145**

As described in Chapter 3, the peracid oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) gives a high yield of di-*t*-butyl trisulfide-1,1-dioxide (**145**) using DMD and moderate yields were observed using *m*-CPBA **(equation 61)**.



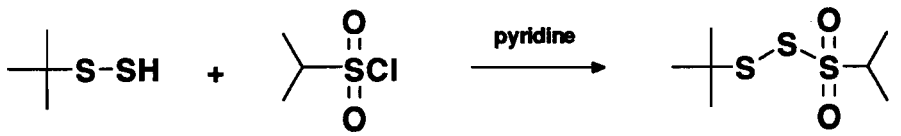
(eq. 61)

156 **158** **145**

[O] = *m*-CPBA 48%
[O] = DMD 85%

Such a conversion provides further demonstration of the formation of trisulfide-1,2-dioxide (**158**) which rapidly rearranges to the di-*t*-butyl trisulfide-1,1-dioxide (**145**).

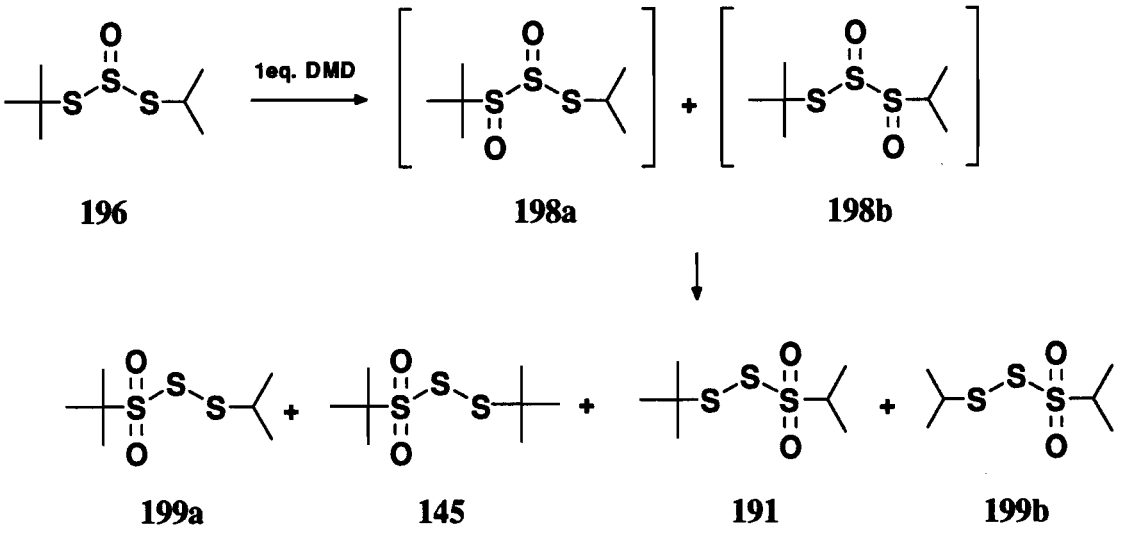
An unsymmetrical trisulfide-1,1-dioxide ($R\text{-}S(O)_2SS\text{-}R'$) has also been prepared by the reaction of *t*-butyl hydrodisulfide (**148**) with isopropyl sulfonyl chloride[219] (**197**) in the presence of pyridine. Pure *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) was isolated in low yield by chromatography. Compound **191** was found to be relatively stable at room temperature (>2 months) **(equation 101)**.



148 **197** **191**

t-Butyl isopropyl trisulfide-3,3-dioxide (**191**) was also isolated from the decomposition of the corresponding trisulfide-3-oxide **190**.

The direct oxidation of *t*-butyl isopropyl trisulfide-2-oxide (**196**) using 1 equivalent of DMD was not regioselective. A careful analysis of the reaction mixture (a detailed discussion is presented later) suggest the formation of the 2 possible trisulfide-1,2-dioxides (**198a-b**) which rearrange to give a mixture of the two symmetric **145**, **199a** and the two unsymmetric trisulfide-1,1-dioxides **191**, **199b** (**Scheme 67**).



196 **198a** **198b**

199a **145** **191** **199b**

SCHEME 67

The formation of trisulfide-1,1-dioxides by *m*-CPBA oxidation of the corresponding trisulfide-2-oxides was not very clean in most cases. As reported in the previous section, the solvent and reagent concentration are very important in all the reactions that involve rearrangements of intermediates. In contrast, the DMD oxidation proceeds in high yield and affords clean products probably because of better reaction conditions (low concentration, no side products).

4.4.2. Alkyl Trisulfide-1,2-Dioxides

As discussed in the previous section, the formation of di-*t*-butyl trisulfide-1,1-dioxide (**145**) by oxidation of the corresponding trisulfide-2-oxide (**156**) implies the formation of di-*t*-butyl trisulfide-1,2-dioxide (**158**) as an intermediate. By analogy with the low temperature detection of di-*t*-butyl disulfide-1,2-dioxide (**167**), it might be possible to detect its trisulfide analog **158**. However, di-*t*-butyl trisulfide-1,2-dioxide (**158**) should be even less stable than the corresponding disulfide **167** because of the extra sulfur atom that should favor the cleavage of the S(O)-S(O) bond.

The low temperature oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) was carried out according to the procedure described previously for the detection of di-*t*-butyl disulfide-1,2-dioxide (**167**). The reaction was carried at -60°C for 12 h. The reaction mixture was filtered and transferred to the NMR spectrometer at the same temperature. The ^{13}C and ^{1}H NMR were recorded at various temperatures from -60°C to room temperature (**Figure 15**). Although, the spectra obtained are not as clean as the ones previously recorded, significant amounts of di-*t*-butyl trisulfide-1,2-dioxide (**158**) can be detected at -60°C. Compound **158** is barely stable at this temperature, rapidly decomposes at -50°C and only traces can be observed at -40°C. As expected, di-*t*-butyl trisulfide-1,2-dioxide (**158**) is far less stable than its disulfide analog **167** which was very stable at -40°C. However, clear evidence for such an intermediate could be obtained by comparing its NMR signals and its behaviour with the ones of the disulfide analog **167**. The ^{13}C NMR signals of di-*t*-butyl trisulfide-1,2-dioxide (**158**) could be clearly identified as they are consistent with the NMR signals of the various di-*t*-butyl trisulfide-polyoxides as well as with the ones of di-*t*-butyl disulfide-1,2-dioxide (**167**).

The presence of the two diastereoisomers of di-*t*-butyl trisulfide-1,2-dioxides **158a-b** could not be defined with certainty due to the small quantities of 1,2-dioxide **158** formed and the complexity of the reaction mixture. The analysis of the spectrum obtained at -60°C revealed that some starting material **156** (~30%) was not oxidized under these conditions. Large quantities (~45%) of unknown compounds could also be detected. The study of the decomposition of di-*t*-butyl trisulfide-1,2-dioxide **158** from -60°C to -40°C, clearly show that these unknown compounds correspond to the decomposition products of **158**.

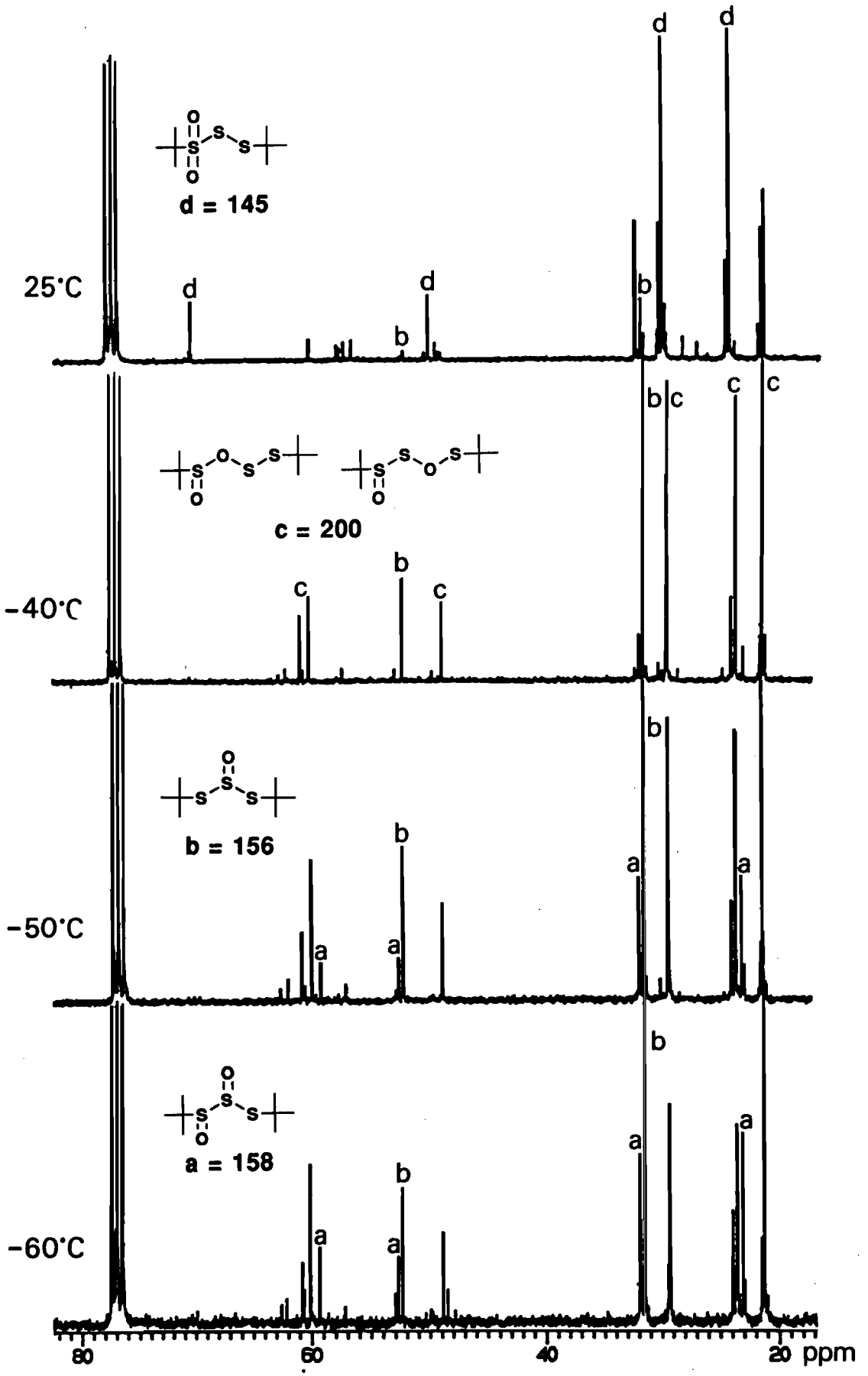
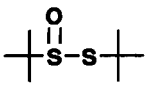
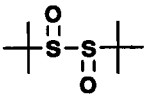
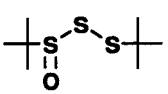
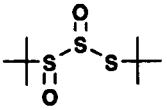
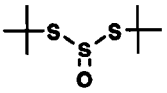


Figure 15: ^{13}C NMR Spectra at Several Temperatures of the Product Mixture of the *m*-CPBA Oxidation of di-*t*-Butyl Trisulfide-2-Oxide (156).

Table 18 clearly shows that the signals of the disulfide-1,2-dioxide **167** and the trisulfide-1,2-dioxide **158** are very similar. In both cases, the *t*-butyl group attached to the sulfinyl sulfur has its chemical shifts at slightly higher field than the ones in the corresponding 1-oxides **120b-c**. Finally, the chemical shifts observed for the *t*-butyl bonded to the sulfenyl sulfur of **158** are slightly lower field than the ones of the corresponding 2-oxide **156**. These results are consistent with the NMR study reported in Chapter 3. The ^{1}H NMR were very difficult to interpret owing to problems with overlapping signals.

Table 18: ^{13}C and ^{1}H NMR Chemical Shifts of 158 and its Related Derivatives[a,b]

Entry	Compound	Spectra	C	CH_3	H	C'	CH'_3	H'
120b			59.35	24.18	1.530	48.65	32.21	1.351
167[c]			57.08	22.95	1.294			
120c			60.67	23.79	1.385	48.73	29.80	1.390
158[c]		**a**	59.34	23.06	1.393	52.77	31.91	1.293
156		**b**	52.10	31.80	1.545			

[a] Recorded using deuterated chloroform ($CDCl_3$) as NMR solvent; [b] Relaxation time (t_1) used: t_1= 2s; [c] The spectra were obtained at low temperature and do not represent a specific diastereoisomer.

In order to further understand these spectra and to optimize the reaction conditions, this low temperature experiment was repeated several times using excess *m*-CPBA (2 equivalents), at different temperatures, in a different solvent (CD_2Cl_2), and for various reaction times (4 h to 4 days).

The analysis of these results revealed that the oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) was not even complete using 2 equivalents of *m*-CPBA at -60°C for 4 days. This result points out the lack of reactivity of the substrate at this temperature. At warmer

temperatures (>-60°C), no di-*t*-butyl trisulfide-1,2-dioxide (**158**) can be observed which emphasizes the low stability of **158**. As mentioned previously, this trisulfide-1,2-dioxide **158** is barely stable at -60°C and a large quantity of decomposition products could be observed. To avoid this stability problem and increase the reactivity of the substrate, the low temperature experiment was attempted using methylene chloride-d_2 which has a lower freezing point (-93°C) and is more polar than $CDCl_3$. The reaction was carried out at -80°C but did not afford good results because of low conversion (<30%), variation of the chemical shifts and overlapping of the solvent and the reaction products peaks. From these results, it was concluded that the temperature was too low to allow a suitable conversion of the starting material **156** and too high for the di-*t*-butyl trisulfide-1,2-dioxide (**158**) to be stable enough to detect.

The study of the decomposition of di-*t*-butyl trisulfide-1,2-dioxide (**158**) is complicated by the remaining starting material and the impossibility of detecting undecomposed **158**. However, the main final decomposition product (spectrum at room temperature) is mainly di-*t*-butyl trisulfide-1,1-dioxide (**145**) which is consistent with the preparation of **145** reported in the previous section. Analysis of the spectra from -60°C to room temperature revealed the presence of 8 carbon and 4 proton signals corresponding to 4 different *t*-butyl groups. The chemical shifts observed are in favor of a diastereomeric unsymmetrical di-*t*-butyl derivative or two very closely related unsymmetrical di-*t*-butyl analogs **200**. These signals were observable in various ratios up to room temperature (**Figure 16**).

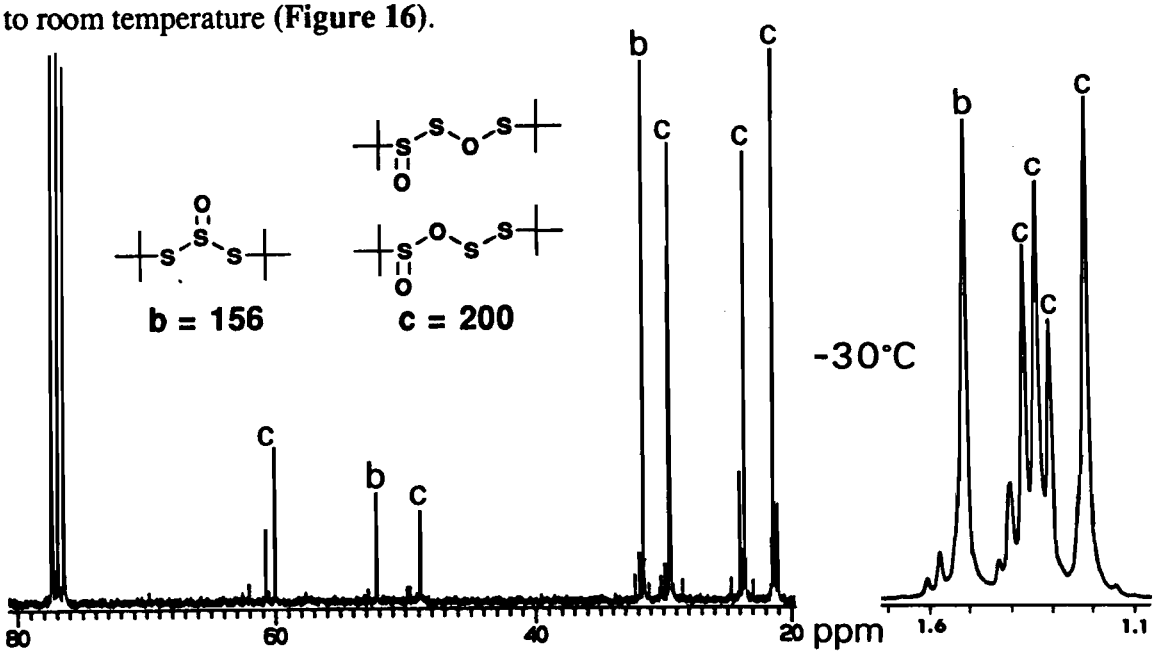
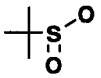


Figure 16: ^1H and ^{13}C NMR Spectra of Intermediates 200.

A NMR comparison of the different classes of di-*t*-butyl polysulfide-polyoxides is presented in the conclusion of this Chapter. This study clearly reveals that the chemical shifts of a given *t*-butyl group can be unambiguously interpreted depending on which sulfur it is bonded to (sulfenyl, sulfinyl, sulfonyl or sulfinate). The only exception encountered is the di-*t*-butyl disulfide-1,1-dioxide **(144)** where one of the tertiary carbon signals is out of the normal range. This carbon NMR study was used to assign the unknown signals observed in the decomposition of di-*t*-butyl trisulfide-1,2-dioxide **(158)**. These unknown chemical shifts and the ranges of the different types of di-*t*-butyl derivatives are presented in **Table 19**.

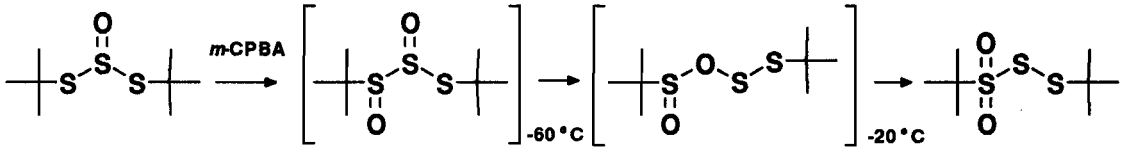
Table 19: ^{1}H and ^{13}C NMR of 200 and Chemical Shifts Ranges (δ ppm) of the *t*-Butyl Groups Bonded to Differently Oxidized Sulfur[a]

Compound	C	CH_3	H	C'	CH'_3	H'
200[b]	60.81	21.36	1.368	48.91	29.56	1.305
	60.10	23.63	1.337	48.86	29.48	1.217
	60 - 61	21 - 22	1.1 - 1.2			
	59 - 64	24 - 26	1.3 - 1.6			
	68 - 74	23 - 26	1.4 - 1.6			
				48 - 53	29 - 33	1.3 - 1.5

[a] All the spectra were recorded in $CDCl_3$; [b] The spectra were obtained at -60°C.

This comparison clearly shows that the decomposition intermediates **200** present two slightly different *t*-butyl groups bonded to a sulfenyl sulfur (~ 49 and ~ 29.5 ppm), another one bonded to a sulfinate sulfur (~ 60 and 21.5 ppm) and the last one corresponds to a moiety in between a *t*-butyl sulfinyl and a *t*-butyl sulfinate (~ 60 and ~ 23.5 ppm). Considering that the trisulfide-1,1-dioxide **145** is the main decomposition product and that no diastereoisomer should be observed, the unknown **200** are believed to be two closely related unsymmetrical di-*t*-butyl analogs.

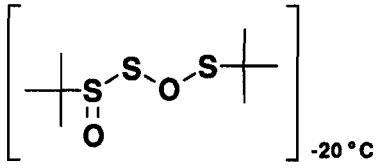
Although the structure of these intermediates can not be determined with certainty, it is clear that di-*t*-butyl trisulfide-1,2-dioxide (**158**) is formed under these low temperature conditions and that the final decomposition product is mainly di-*t*-butyl trisulfide-1,1-dioxide (**145**). Therefore, considering the mechanism proposed earlier for the decomposition of the disulfide-1,2-dioxide **167** and according to the NMR study, a consistent intermediate would be the *t*-butyl sulfinic *t*-butyl thiosulfenic anhydride (**200a**) which is the expected intermediate of the rearrangement of di-*t*-butyl trisulfide-1,2-dioxide (**158**) to di-*t*-butyl trisulfide-1,1-dioxide (**145**) (**Scheme 68**).



156 **158** **200a** **145**

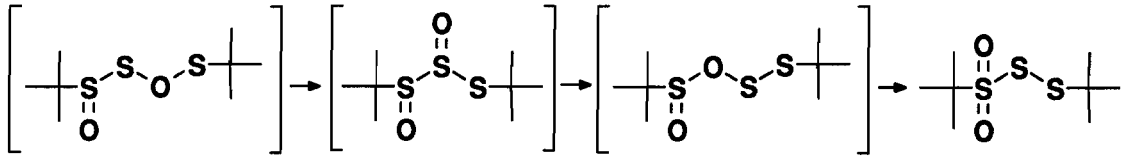
SCHEME 68

The only unsymmetrical *t*-butyl derivative closely related to intermediate **200a** that would match the required chemical shifts would be the *t*-butyl sulfenic *t*-butyl thiosulfinate anhydride (**200e**).



200e

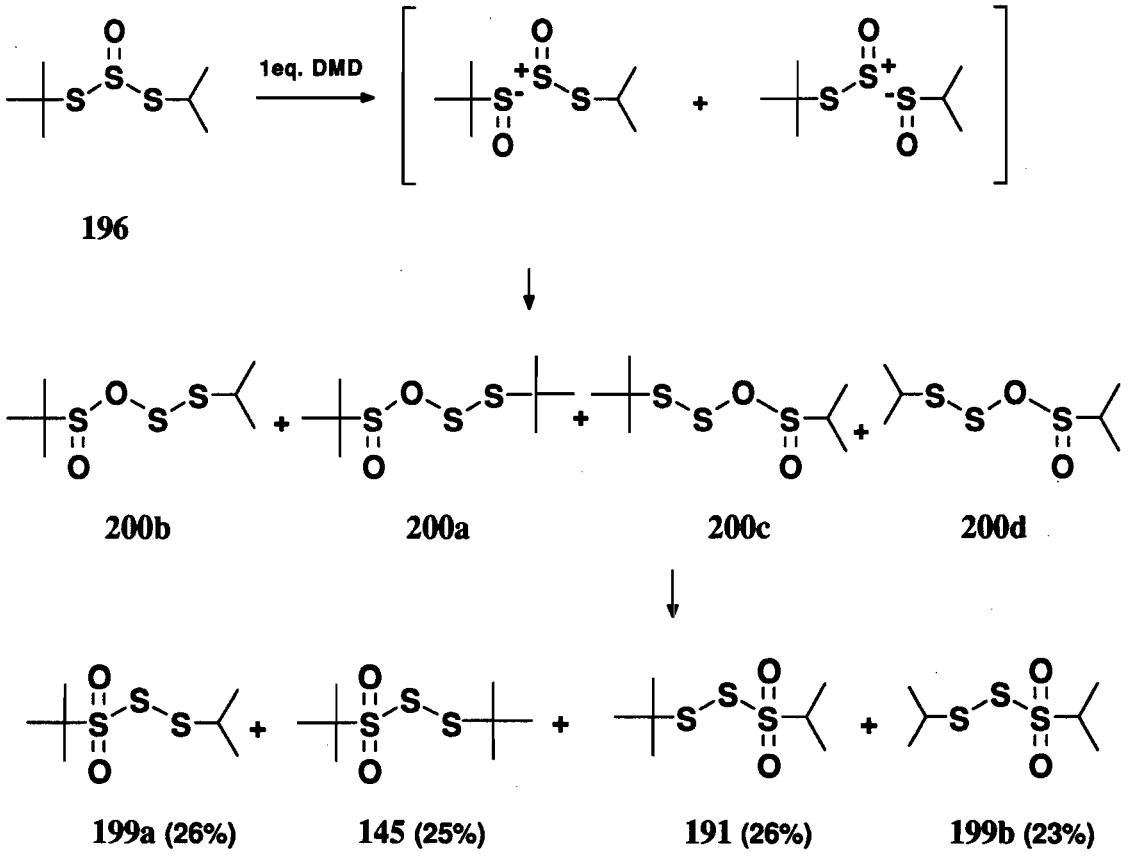
It is conceivable that intermediate **200e** rearranges to give back the trisulfide-1,2-dioxide **158**. At this temperature, **158** would immediately redecompose to a mixture of **200a** and **200e**. Considering that intermediate **200a** gives the trisulfide-1,1-dioxide **145**, the final decomposition mixture should be mainly composed of **145** (**Scheme 68b**).



200e **158** **200a** **145**

SCHEME 68b

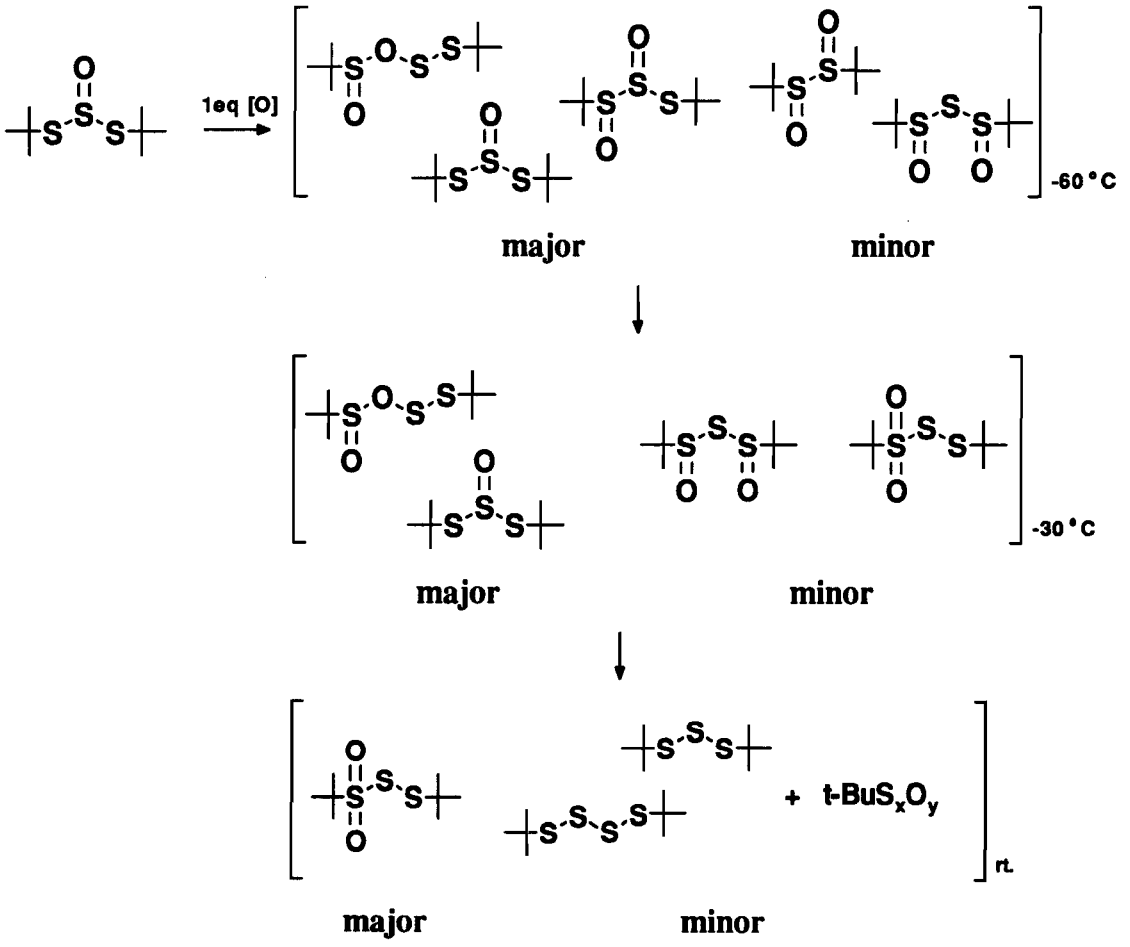
The 1 equivalent DMD oxidation of *t*-butyl isopropyl trisulfide-2-oxide (**196**) reported in the previous section (**Scheme 67**), afforded an almost equimolar mixture of the two symmetrical and two unsymmetrical possible trisulfide-1,1-dioxides (**145, 199a, 191, 199b**). These results can be rationalized by proposing that under these reaction conditions, both *t*-butyl isopropyl trisulfide-1,2- (**198a**) and 2,3-dioxides (**198b**) are formed. The formation of large quantities of both symmetrical trisulfide-1,1-dioxides **145** and **199a** is consistent with the previously proposed cleavage of the S(O)-S(O) bonds, random recombination of ions (less steric hindrance here because of the extra sulfur) should eventually give the four possible sulfinyl thiosulfenyl anhydrides **200a-d** which should rearrange to the four possible trisulfide-1,1-dioxides (**145, 199a, 191, 199b**) (**Scheme 69**).



SCHEME 69

Although compounds **200a-d** are the logical intermediates of the conversion of trisulfide-2-oxide to trisulfide-1,1-dioxides, their existence could not be reported with certainty as they were always mixed with other undefined intermediates **200e** that prevent from a clear interpretation of the spectra.

It is also surprising that small quantities of di-*t*-butyl disulfide-1,2-dioxide **(167)** and di-*t*-butyl trisulfide-1,3-dioxide **(130)** were detected while the di-*t*-butyl trisulfide-2-oxide **(156)** used did not contain any traces of the corresponding polysulfides **118b-c** or polysulfide-1-oxides **120b-c**. However, it was observed that the remaining trisulfide-2-oxide **156** was not stable under these conditions and probably participates in the decomposition of the trisulfide-1,2-dioxide **158**. Considering the complexity of the mechanism reported earlier, it is not so surprising that many different di-*t*-butyl derivatives are observed (di-*t*-butyl tri- **(118c)** and tetrasulfide **(118d)** were also observed) **(Scheme 70)**.



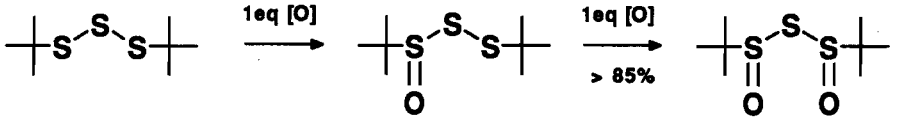
SCHEME 70

To our knowledge, this is the first detection of a trisulfide-1,2-dioxide. However, the rearrangement of this trisulfide-1,2-dioxide to the corresponding trisulfide-1,1-dioxide could not be fully understood because under these conditions, the detection of the

trisulfide-1,2 dioxide is temperature controlled. Therefore, it considerably limits the decomposition study as other derivatives are always present in the reaction mixture. Low temperature experiments using stronger oxidizing agents such as DMD should afford better results. We were unable to develop a suitable technique for the low temperature DMD oxidation.

4.4.3. Alkyl Trisulfide-1,3-Dioxides

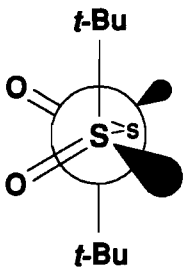
As described in Chapter 3, the 1 equivalent electrophilic oxidation of di-*t*-butyl trisulfide-1-oxide (**120c**) and the 2 equivalent electrophilic oxidation of di-*t*-butyl trisulfide (**118c**) afforded a high yield of di-*t*-butyl trisulfide-1,3-dioxide (**130**). Although very little is known about this class of compounds and considering that the existence of such derivatives has been questioned,[198] the diastereomeric mixture of di-*t*-butyl trisulfide-1,3-dioxides (**130**) was isolated and characterized. Unfortunately, low temperature crystallography was unsuccessful. However, the NMR data of **130** are completely consistent with those of the other di-*t*-butyl polysulfide-polyoxides (**equation 102**).



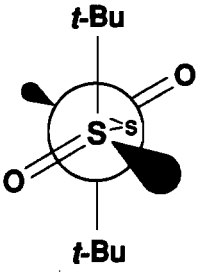
118c **120c** **130** **(eq. 102)**

These results clearly show that the external sulfenyl sulfur which is supposed to be the most electron rich atom of **130** reacts regiospecifically with electrophilic oxidizing agents to afford the di-*t*-butyl trisulfide-1,3-dioxide (**130**). Compound **130** has been shown to have a relatively low stability but could still be isolated at room temperature.

Due to the presence of two sulfinyl moieties in a molecule of trisulfide-1,3-dioxide **130**, two diastereoisomers of di-*t*-butyl trisulfide-1,3-dioxides (**130a-b**) are observed in ^{1}H and ^{13}C NMR.



130a: d,l

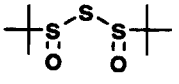
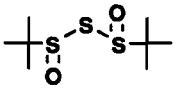


130b: meso

As described in Chapter 3, there seems to be kinetic and thermodynamic diastereoisomers. On one specific occasion, ^{1}H and ^{13}C NMR of the reaction mixture afforded only one of the two diastereoisomers. After 3 h at room temperature an equimolar mixture of the 2 diastereoisomers was observed and after 6 h only the second diastereoisomer could be observed as well as small quantities of a decomposition product (**Figure 17**). The kinetic product was suggested to be the d,l diastereoisomer **130a** and the thermodynamic product was meso **130b**. The energy difference was calculated to be 15.5 kcal/mol.[215]

The ^{13}C and ^{1}H NMR chemical shifts of the d,l and the meso diastereomeric di-*t*-butyl trisulfide-1,3-dioxides have been reported in **Table 20**. It can be noticed that the difference between the diastereomeric tertiary carbon signals (~ 0.4 ppm) is greater than the one between the methyl peaks (> 0.01 ppm). However, the two diastereoisomers can be clearly identified by carbon and proton NMR.

Table 20: ^{1}H and ^{13}C NMR Chemical Shifts (δ ppm) of 130[a,b]

Entry	Compound	Spectra	C	CH_3	H	C'	CH'_3	H'
130a		**a**	62.39	24.17	1.410			
130b		**b**	62.02	24.18	1.422			

[a] Recorded using deuterated chloroform ($CDCl_3$) as NMR solvent; [b] Relaxation time (t_1) used: t_1= 2s;

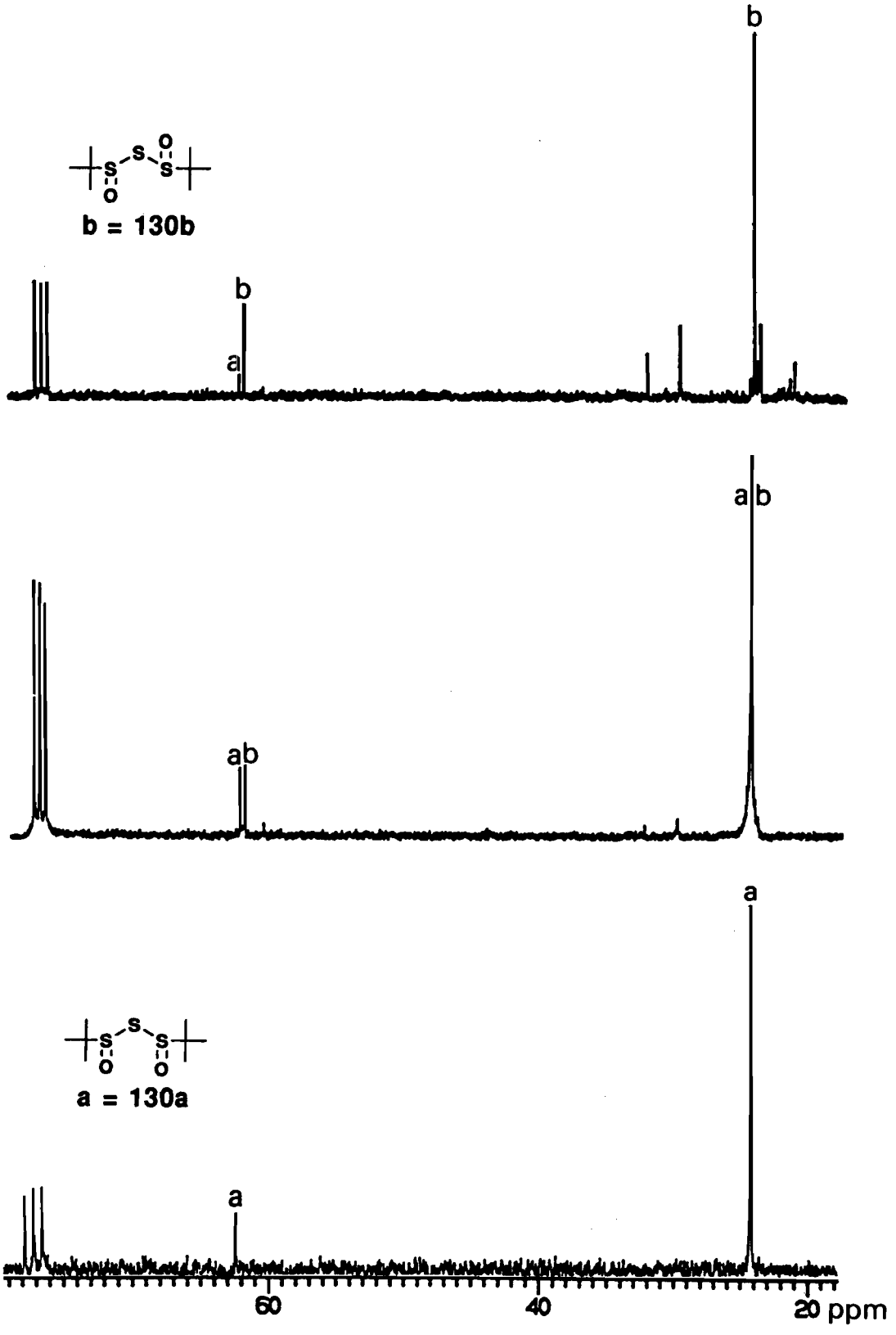
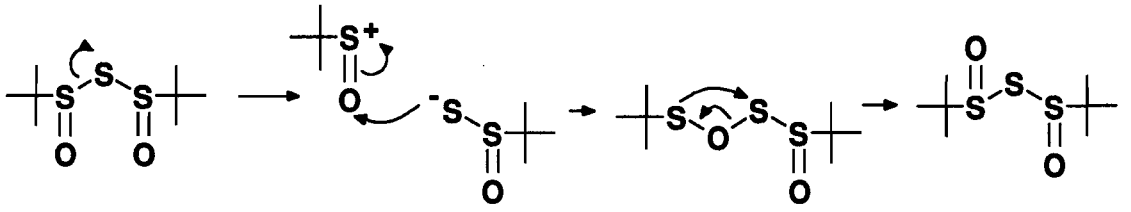


Figure 17: ^{13}C NMR Spectra of the Conversion of 130a to 130b.

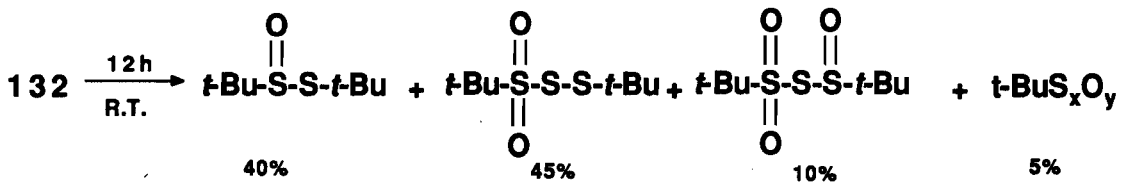
The formation of only one of the two diastereoisomers is consistent with the mechanism proposed earlier for the formation of di-*t*-butyl di- (**167**) and trisulfide-1,2-dioxide (**158**). The conversion of the kinetic to the thermodynamic diastereoisomer implies the cleavage and recombination of di-*t*-butyl trisulfide-1,3-dioxide (**130**). This cleavage can be heterolytic or homolytic. However, considering that there is a preferred recombination to give the thermodynamic diastereoisomer and by analogy with previous mechanistic studies, this cleavage is believed to proceed through the ionic cleavage of the S-S(O) bond affording the *t*-butyl sulfinyl cation (**187a**) and the *t*-butyl disulfide-1-oxide anion (**201**). Recombination of these two ions should give the thermodynamic diastereoisomer **130a** believed to be the meso form (**Scheme 71**).



130b **187a** **201** **130a**

SCHEME 71

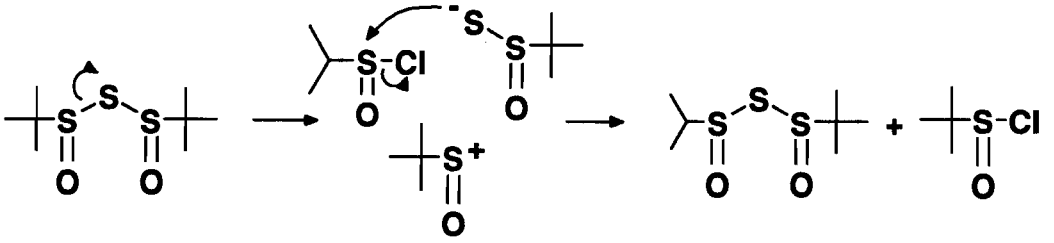
As described earlier, di-*t*-butyl trisulfide-1,3-dioxide (**130**) is barely stable at room temperature and can not be kept in the freezer for more than a week. The decomposition of **130** was also investigated and afforded a very complex mixture. Various attempts in slightly different conditions have shown that the two main decomposition products were the corresponding disulfide-1-oxide **120b** and trisulfide-1,1-dioxide **145**. Significant quantities of di-*t*-butyl trisulfide-1,1,3-trioxide **157** were detected in most cases as well as a wide variety of the other di-*t*-butyl polysulfide-polyoxides. The spectra were too crowded to be fully interpreted and silica gel chromatography did not allow a useful separation (**Scheme 24**).



120b **145** **157**

SCHEME 24

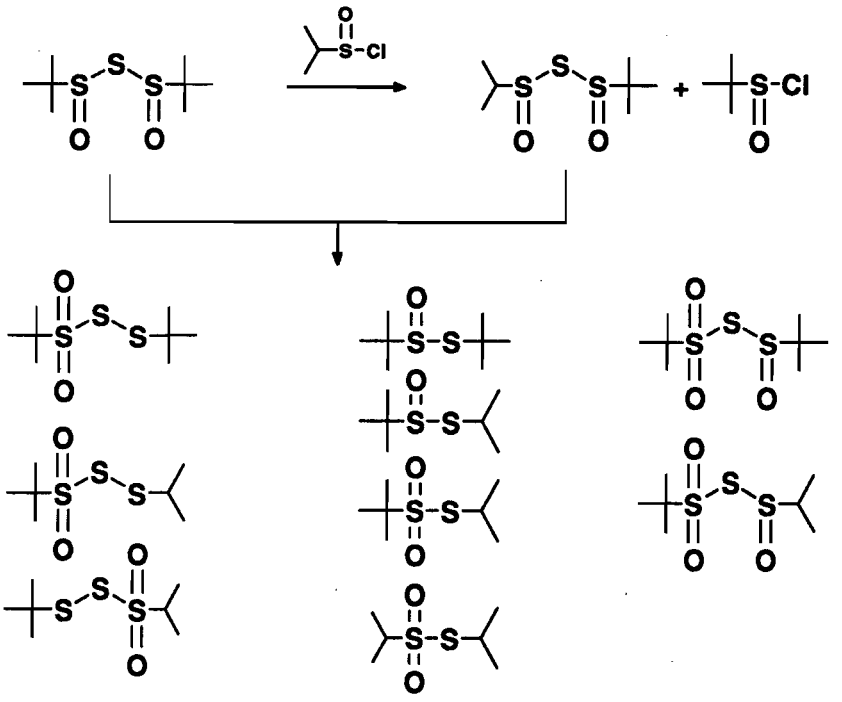
In a separate experiment, the decomposition of di-*t*-butyl trisulfide-1,3-dioxide (**130**) was carried out in the presence of 1 equivalent of isopropyl sulfinyl chloride (**180**) as trapping agent. Although the final decomposition mixture was even more complex, *ca.* 40% of *t*-butyl sulfinyl chloride (**149**) could be clearly identified by ^{13}C and ^{1}H NMR. The detection of *t*-butyl sulfinyl chloride (**149**) confirms the previous hypothesis of ionic cleavage of the trisulfide-1,3-dioxide at the S-S(O) bond. Under these conditions, the *t*-butyl disulfide-1-oxide anion (**201**) formed can react with isopropyl sulfinyl chloride (**180**) to give the unsymmetrical *t*-butyl isopropyl trisulfide-1,3-dioxide (**202**) and the *t*-butyl sulfinyl cation (**187a**) can then react with the remaining chloride ion affording the observed *t*-butyl sulfinyl chloride (**149**) (**Scheme 72**).



130 **180** **187a** **201** **202** **149**

SCHEME 72

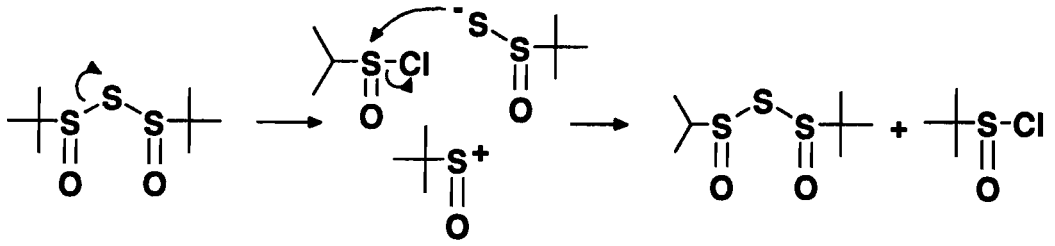
Although *t*-butyl isopropyl trisulfide-1,3-dioxide (**202**) could not be detected, significant amounts of its decomposition products, *t*-butyl isopropyl trisulfide-1,1-dioxide (**199b**) and *t*-butyl isopropyl disulfide-1,1-dioxide (**185a**), were identified as well as other derivatives issued from the normal decomposition and the mixed decomposition (**Scheme 73**).



SCHEME 73

The results observed in this decomposition study are even more complex than the ones observed previously. Therefore, it is very difficult to give a detailed decomposition mechanism. However, using the mechanistic principles developed in the previous cases these results can be reasonably rationalized.

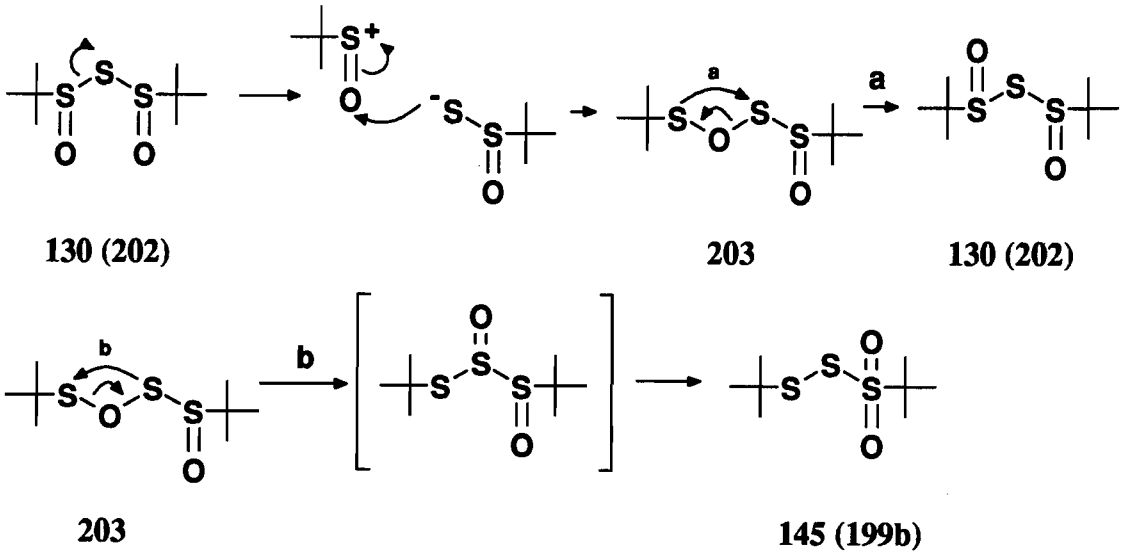
First, good evidence of the cleavage of the S-S(O) bond is given by the formation of *t*-butyl sulfinyl chloride **(149)** and *t*-butyl isopropyl-1,3-dioxide **(202)** **(Scheme 72a)**. This scheme is repeated to provide a better understanding of the decomposition mechanism.



130 **180** **187a** **201** **202** **149**

SCHEME 72a

The formation of trisulfide-1,1-dioxides **145** and **199b** can be explained by the recombination of these ions to form an intermediate **203** similar to **200** reported in the decomposition trisulfide-1,2-dioxides. Rearrangement of such an intermediate could give back the trisulfide-1,3-dioxide **130** and **202** as shown previously or eventually afford the trisulfide-1,2-dioxides that would immediately be converted to the trisulfide-1,1-dioxide **145** and **199b**. This theory is suggested because chemical shifts in the region of this type of intermediates **203** were detected (see NMR study at the end of this Chapter) (**Scheme 72b**).

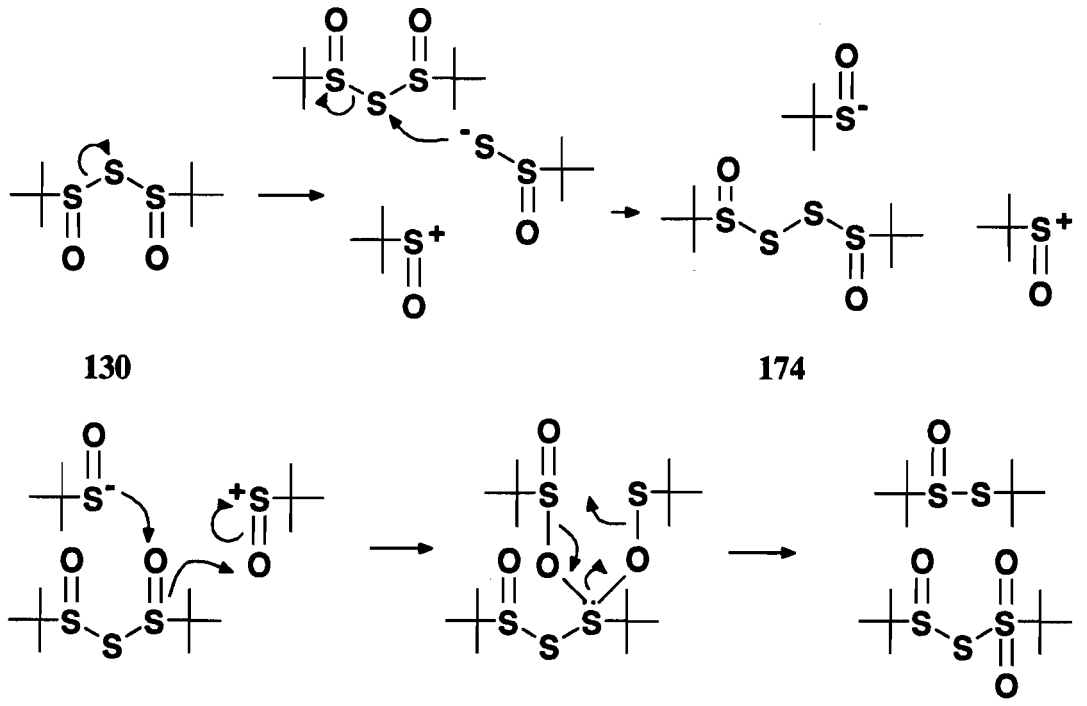


130 (202) **203** **130 (202)**

203 **145 (199b)**

SCHEME 72b

Finally, the formation of trisulfide-1,1,3-trioxide **157** suggests that an oxygen transfer reaction also take place in this case. This would also account for the formation of disulfide-1-oxides **120b** and **193**. The formation of tetrasulfide-1,4-dioxide **(174)** is also possible and would also account for the formation of disulfide-1,1-dioxide **185a** and **169** (low intensity NMR signals in the region of 1,4-dioxide **174** could be detected) (**Scheme 72c**).

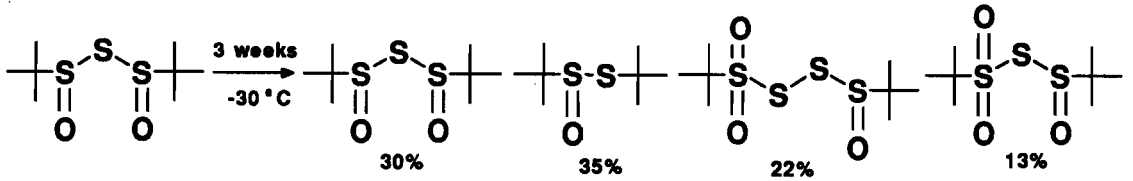


130 174

120b 157

SCHEME 72c

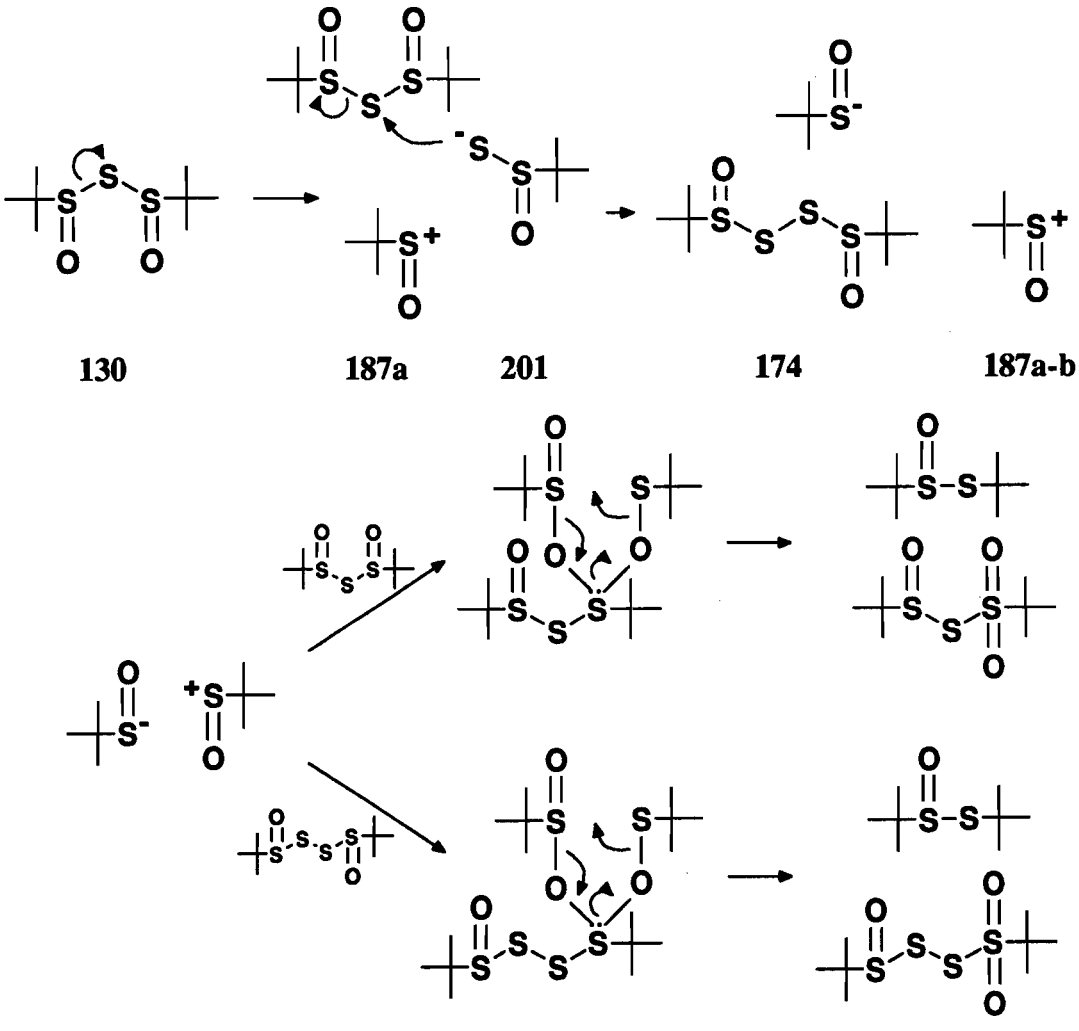
As mentioned earlier, di-*t*-butyl trisulfide-1,3-dioxide **(130)** is not stable at -30°C when stored in the freezer. The determination of the products of the decomposition of at this temperature confirmed the previous results. After 3 weeks in the freezer, the decomposition mixture presented 30% of the thermodynamic diastereoisomer of di-*t*-butyl trisulfide-1,3-dioxide **(130)**, 35% of di-*t*-butyl disulfide-1-oxide **(120b)**, 22% of di-*t*-butyl tetrasulfide-1,1,4-tetraoxide **(175)** and 13% of trisulfide-1,1,3-trioxide **157** **(Scheme 24a)**.



130a-b 130b 120b 175 157

SCHEME 24a

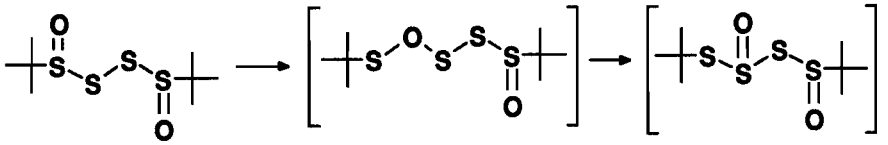
This low temperature study allowed the detection of the decomposition intermediates and the ratios and products observed are completely consistent with the mechanism previously proposed. It is clear that the decomposition of the trisulfide-1,3-dioxides **130a-b** proceeds through the ionic cleavage of the S(O)-S bond. The reaction of the disulfide-1-oxide anion **201** formed with another molecule of **130** affords the tetrasulfide-1,4-dioxide **174** and *t*-butyl sulfinyl anion **(187b)** (traces of **174** could be detected). The ambident sulfinyl ions **187a-b** formed in the two previous step react with the tetrasulfide-1,4-dioxide **174** or the trisulfide-1,3-dioxide **130** by an oxygen transfer reaction affording the corresponding trioxides **175** or **157** respectively. The difference in reactivity of **174** (22%) and **130** (13%) can be explained by steric and electronic effects as the tetrasulfide derivative is less hindered and has an extra sulfur atom **(Scheme 72d)**.



SCHEME 72d

A number of different mechanisms can take place and it is probably a combination of all of them that delivers this rather complex mixture. In addition, products such as trisulfide-1,1,3-trioxide **(157)** and tetrasulfide-1,4-dioxide **(174)** can participate in the decomposition and even further complicate the study. As a consequence, the more stable compounds, trisulfide-1,1-dioxide **145** and disulfide-1-oxide **120b**, are the major products observed at room temperature because they are thermodynamically favored.

As described in Chapter 3, the synthesis of di-*t*-butyl tetrasulfide-1,4-dioxide **(174)** afforded similar results in terms of diastereomeric signals (see NMR study at the end of this Chapter). However, the tetrasulfide analog seems to be significantly more stable at room temperature (>2 days). The decomposition of di-*t*-butyl tetrasulfide-1,4-dioxide **(174)** also afforded a rather complex mixture but no trace of tri- or tetrasulfide-1,1-dioxide could be detected. This observation suggests that the sulfur chain is too long to allow the oxygen migration suggested earlier **(equation 103)**.



174 **(eq. 103)**

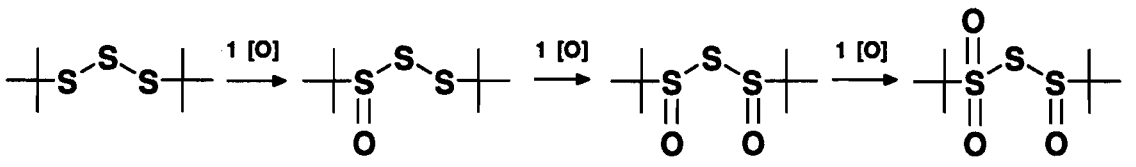
4.5. Formation and Decomposition Study of Alkyl Trisulfide-Tri- and Tetraoxides

The synthesis and characterization of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) and 1,1,3,3-tetraoxide (**161**) (Chapter 3) has been achieved by electrophilic oxidation. The analysis of the reaction mixtures, the oxidation of various substrates as well as low temperature experiments, have shown that contrary to current belief,[198] the oxidation was taking place regiospecifically at the external sulfinyl sulfur rather than the internal sulfenyl sulfur. In all the cases studied here, the central sulfur was found to be surprisingly non-reactive as concluded by other researchers.[200]

4.5.1. Alkyl Trisulfide-1,1,3-Trioxides

To our knowledge, the isolation of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) is the first example of this class of compounds. The structure of the molecule has been confirmed by crystallography and the NMR data reported for this trisulfide-1,1,3-trioxide **157** are consistent with the ones of the other di-*t*-butyl polysulfide-polyoxides (see NMR study at the end of this Chapter).

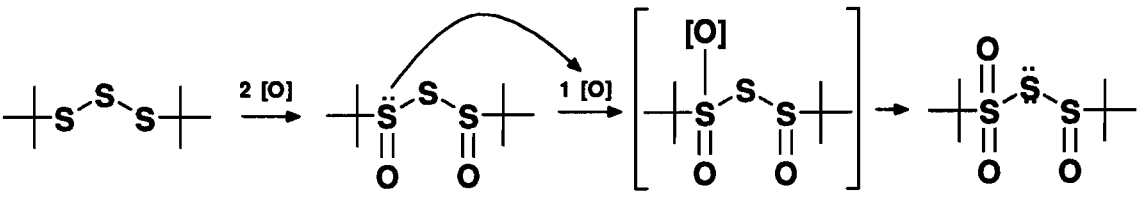
The preparation of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) is detailed in Chapter 3 and was achieved by electrophilic oxidation of the corresponding trisulfide **118c**, trisulfide-1-oxide **120c** and trisulfide-1,3-dioxide **130** using 1, 2 and 3 equivalents respectively. Although compound **157** could not be separated by column chromatography, pure trisulfide-1,1,3-trioxide **157** could be obtained in high yield by recrystallisation when the exact number of equivalents of oxidizing agent was employed **(Scheme 74).**



118c **120c** **130** **157**

SCHEME 74

The formation of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has been shown to proceed through the attack of the external sulfinyl sulfur to the electrophilic oxidizing agent (**Scheme 30**).

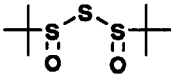
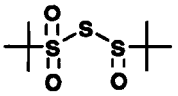


118c **130** **157**

SCHEME 30

Various experiments ruled out the supposedly preferred oxidation at the central sulfur.[198] To confirm these results, the 1 equivalent *m*-CPBA oxidation of di-*t*-butyl trisulfide-1,3-dioxide (**130**) was followed by ^{1}H and ^{13}C NMR at low temperature. The reaction was carried out at -40°C and the 50% conversion NMR spectrum was recorded at the same temperature according to the low temperature technique previously reported (**Figure 18**). The analysis of these three spectra clearly shows that the pure di-*t*-butyl trisulfide-1,3-dioxide (**130**) is slowly converted to the trisulfide-1,1,3-trioxide **157** (spectrum -40°C) and the complete reaction mainly affords the desired **157** (**Table 21**).

Table 21: ^{1}H and ^{13}C NMR Chemical Shifts (δ ppm) of 130 and 157[a,b]

Entry	Compound	Spectra	C	CH_3	H	C'	CH'_3	H'
130a		**a**	62.39	24.17	1.410			
130b			62.02	24.18	1.422			
157		**b**	71.38	23.99	1.551	63.08	24.51	1.463

[a] Recorded using deuterated chloroform ($CDCl_3$) as NMR solvent; [b] Relaxation time (t_1) used: t_1= 2s; [c] **130a** and **130b** represent the two diastereoisomers of **130**.

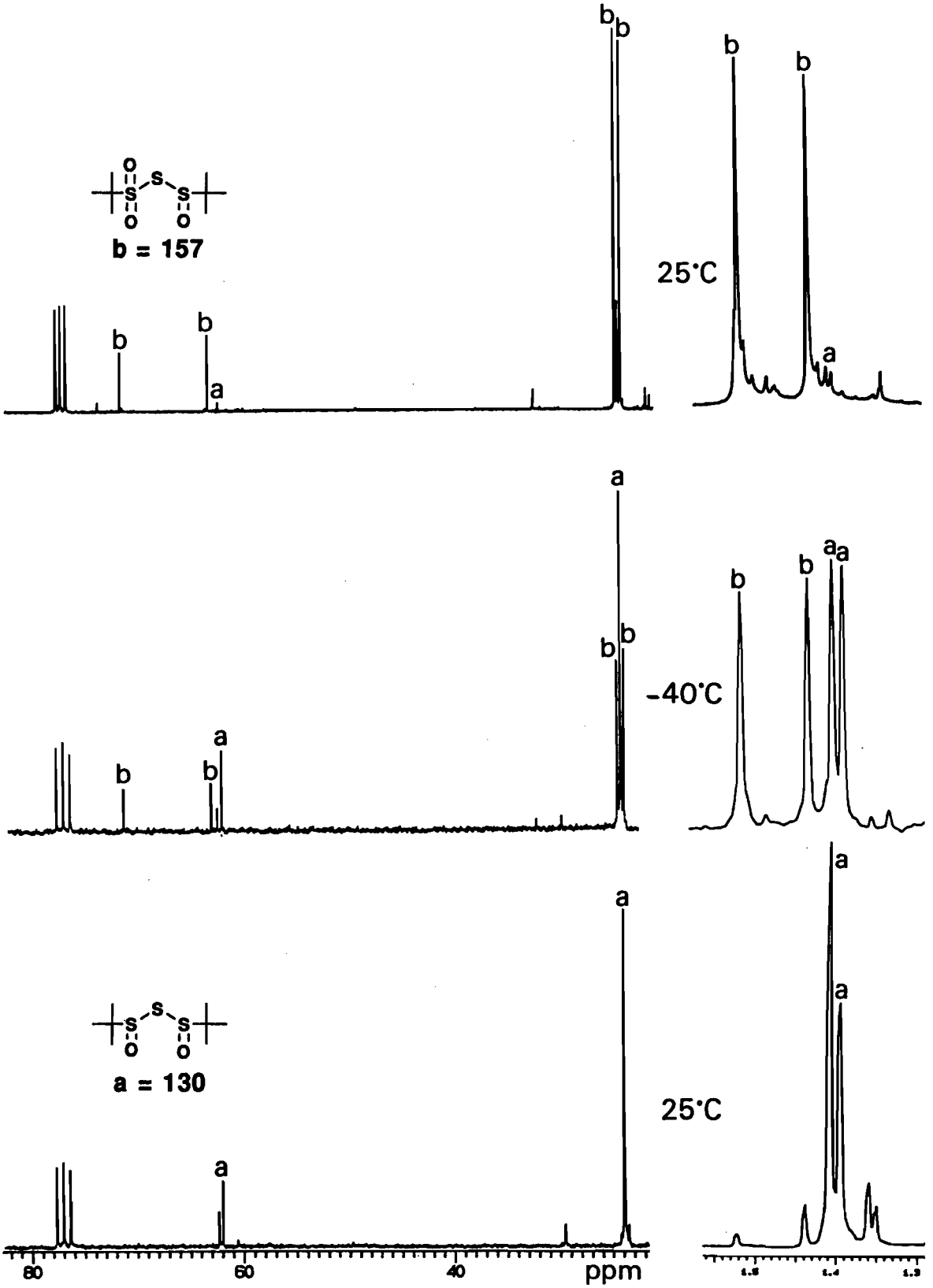
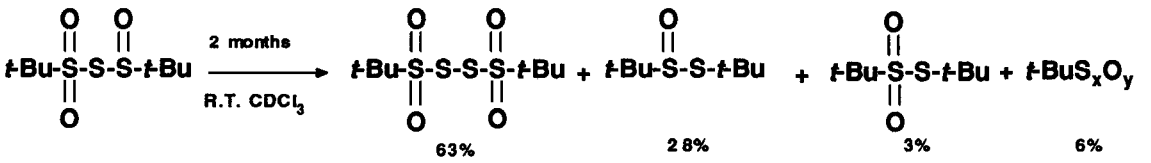


Figure 18: ^{13}C and ^{1}H NMR Spectra of the Conversion of 130 to 157 at Various temperatures.

In contrast to the previously reported low temperature experiments, the reaction mixture obtained at -40°C is very clean and no intermediates can be detected. Therefore, if the reaction was taking place at the central sulfur, the very reactive di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) should be formed and would then rearrange to the corresponding trisulfide-1,1,3-trioxide **157**. By analogy with the previously reported results, the spectra recorded at -40°C should at least show the presence of some intermediate if the trisulfide-1,2,3-trioxide **160** was not stable enough at this temperature. In addition, all the reactions that involve a rearrangement of this type give complex mixtures of final products in contrast with the results observed here.

As reported in Chapter 3, di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) is not very stable at room temperature (less than 2 weeks). However, it is much more stable than its disulfide analog **166**. The presence of an extra sulfur probably reduces the steric hindrance of the molecule and **157** is therefore more stable than **166**. Silica gel chromatography and a careful analysis of the NMR spectrum of the reaction mixture of the decomposition of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) revealed the presence of several decomposition products. The decomposition of **157** was found to be cleaner than those of most of the other derivatives. The major product is di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**). Moderate quantities of di-*t*-butyl disulfide-1-oxide (**120b**) were detected as well as small amounts of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**), di-*t*-butyl disulfide-1,1-dioxide (**144**), *t*-butyl sulfinic (**163**) and sulfonic acid (**164**) plus traces of another undefined di-*t*-butyl derivative believed to be *t*-butyl sulfonic anhydride (**206**) (*vide infra*) (**Scheme 27**).

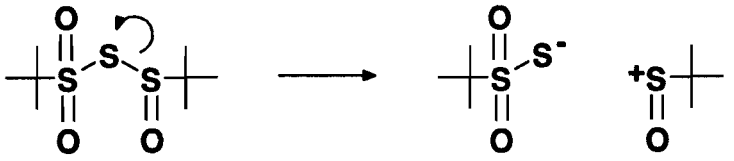


157 **159** **120b** **144**

SCHEME 27

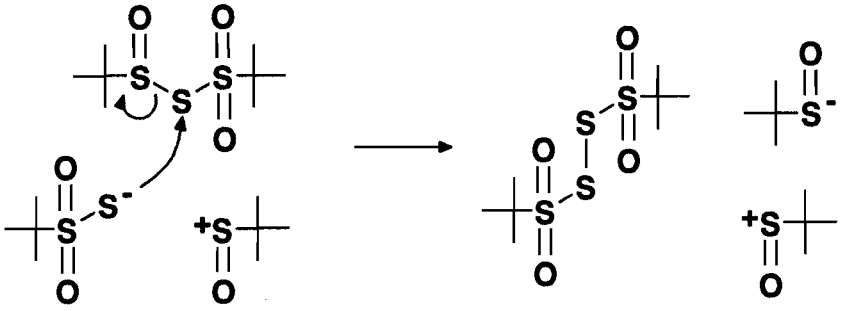
The mechanism proposed earlier can be applied to the decomposition of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) and most of the products can be rationalized.

By analogy with the previous decomposition studies, the ionic cleavage of a molecule of **157** should afford the *t*-butyl sulfinyl cation (**187a**) and the *t*-butyl thiosulfonate anion (**204**) as the S(O)-S is the longest bond of the S-S linkages (**equation 104a**).



157 **204** **187a** **(eq. 104a)**

The *t*-butyl thiosulfonate anion (**204**) can react with another molecule of trisulfide-1,1,3-trioxide **157** to eventually give di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) and the *t*-butyl sulfinyl anion **187b** (**equation 104b**).

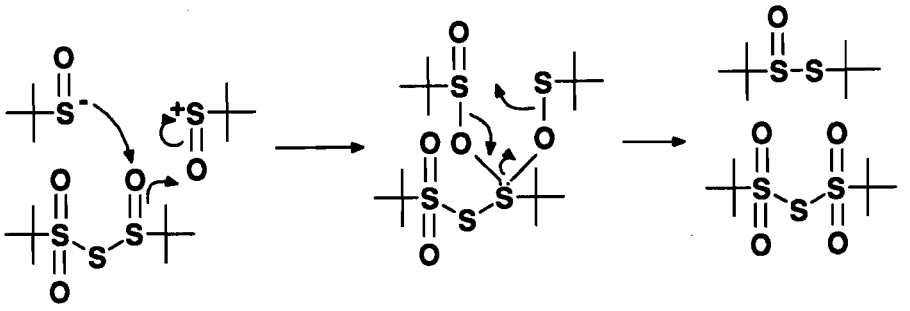


204 **159** **187a-b** **(eq. 104b)**

At that point, the two ambident *t*-butyl sulfinyl ions **187a-b** can react with each other and give di-*t*-butyl disulfide-1,1-dioxide (**144**) or react with another molecule of trisulfide-1,1,3-trioxide **157** according to the oxygen transfer mechanism reported earlier and then afford di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) and di-*t*-butyl disulfide-1-oxide (**120b**). As discussed previously, the oxygen transfer reaction is favored over the formation of disulfide-1,1-dioxide **144** because of steric effects. However, in this case di-*t*-butyl trisulfide-1,1,3-trioxide **157** is also somewhat hindered and there is competition between the two paths as small quantities of disulfide-1,1-dioxide **144** are observed (**equation 104c**).

187a-b

120b



(eq. 104c)

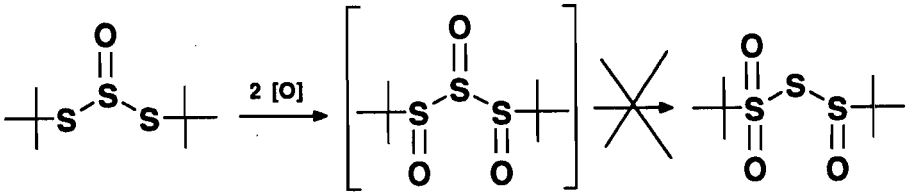
157

161

The di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) formed is not stable under these conditions and gives di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) and the presumed sulfonic anhydride **206** as will be described at the end of this section. The formation of the sulfinic (**163**) and sulfonic (**164**) acids is explained by the reaction of the ambident ions **187a-b** with the remaining *m*-CBA.

4.5.2. Alkyl Trisulfide-1,2,3-Trioxides

As reported in Chapter 3, the low temperature detection of di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) has been attempted by the 2 equivalent *m*-CPBA oxidation of di-*t*-butyl trisulfide-2-oxide (**156**). Considering the previous results, it was clear that this trisulfide-1,2,3-trioxide **160** would be very difficult to detect. However, the main interest of such an experiment was to confirm the mechanism proposed for the formation of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**). The formation of trisulfide-1,2,3-trioxide **160** is more favored in this case than it is in the oxidation of trisulfide-1,3-trioxide (**130**). The external sulfur atoms have been shown on many occasions to be much more reactive toward electrophilic oxidizing agents than the corresponding internal sulfur atom. Therefore, if any trisulfide-1,2,3-trioxide **160** would exist, it has a greater chance to be formed by the oxidation of trisulfide-2-oxide **156** than by the oxidation of 1,3-dioxide **130**. In addition, if the oxidation of **130** proceeded through the formation of trisulfide-1,2,3-trioxide **160**, compound **160** should rearrange cleanly and rapidly to the corresponding trisulfide-1,1,3-trioxide **157** as shown in the previous section. However, no trace of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has never been detected in any of the experiments carried out (**equation 65**).



(eq. 65)

156 **157**

[O] = *m*-CPBA ($CDCl_3$, -60°C, 6 h)
[O] = DMD (Acetone, <-80°C, 5 h)

The low temperature oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) has been carried out under the exact same conditions as the one reported for the detection of di-*t*-butyl trisulfide-1,2-dioxide (**158**) (-60°C, $CDCl_3$, 12 h). Considering the results reported for the detection of **158**, it would be surprising to find any di-*t*-butyl trisulfide-1,2,3-trioxide **160** as *t*-butyl trisulfide-1,2-dioxide **158** would be even less reactive toward the oxidizing agent than **156** and the trisulfide-1,2,3-trioxide **160** formed would be less stable than **158** at this temperature. As expected, no clear NMR signals of trisulfide-1,2,3-trioxide **160** could be detected under these specific conditions.

Several other oxidation experiments at various temperatures, using different oxidizing agents, for various reaction times concluded similarly. The extreme conditions were the 2.5 equivalents DMD oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) at -78°C for more than 5 h. Even under these conditions, no trace of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) has been detected in the final reaction mixture **(see equation 65)**

However, under these low temperature conditions, the ^{13}C and ^{1}H NMR spectra obtained at -60°C presented interesting results. In contrast with the 1 equivalent oxidation of trisulfide-2-oxide **156**, the excess *m*-CPBA (4 equivalents) of di-*t*-butyl trisulfide-2-oxide (**156**) was complete as no more **156** could be detected. No trace of trisulfide-1,2-dioxide **158** could also be detected and the higher field tertiary carbon signals (*t*-butyl sulfenyl signal) of the intermediates **200** earlier proposed to be *t*-butyl sulfinic *t*-butyl thiosulfenic anhydride (**200a**) and its related structure **200e** had almost completely disappeared. In addition, new peaks could be clearly detected (**Figure 19**).

A careful analysis of these results suggests that di-*t*-butyl trisulfide-2-oxide (**156**) was completely oxidized to its 1,2-dioxide **158** analog. At this temperature, di-*t*-butyl trisulfide-1,2-dioxide (**158**) is barely stable and gives large quantities of the postulated intermediate **200a**. The fact that no trace of trisulfide-1,2-dioxide **158** could be observed suggests that **158** might have reacted with the excess *m*-CPBA to give the trisulfide-1,2,3-trioxide **160** that readily decomposed at this temperature.

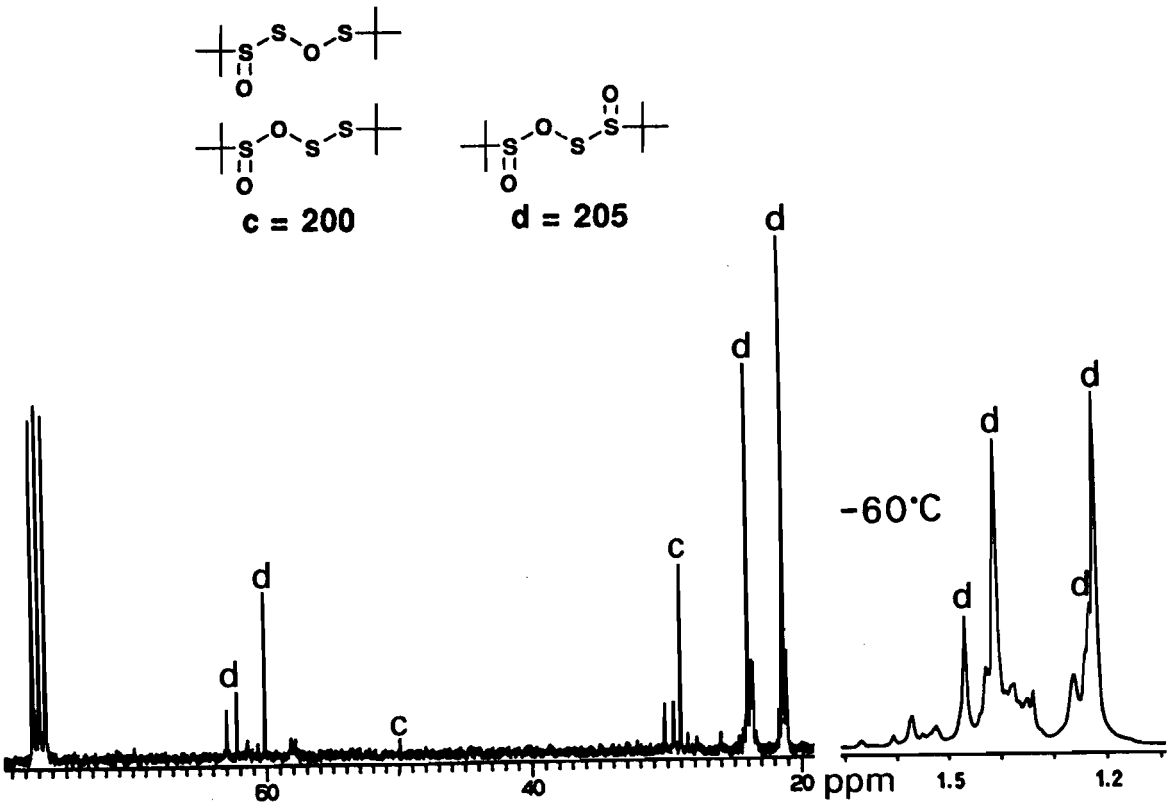
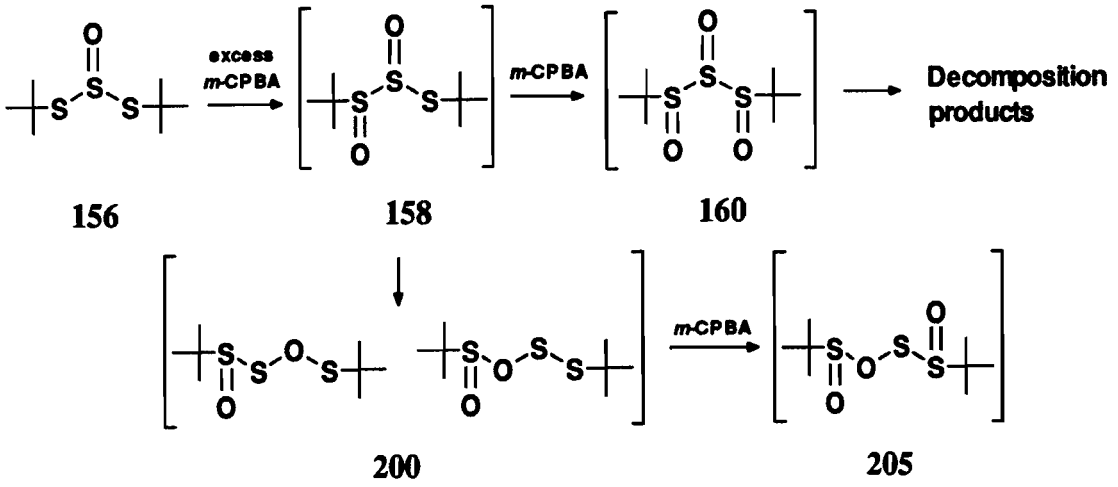


Figure 19: ^{13}C NMR of the Excess *m*-CPBA Oxidation of 156 at -60°C.

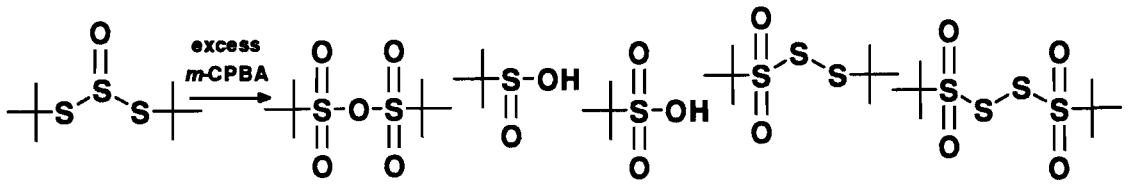
Only small amounts of the presumed intermediates **200** could be detected, but similar, clear NMR signals could be observed except for the *t*-butyl sulfenyl (*t*-Bu-S) peaks that had disappeared. Therefore, it seems reasonable that intermediates **200** were oxidized by the excess *m*-CPBA to afford another intermediate **205** as the oxidation is expected to take place at the external sulfenyl sulfur for reasons stated earlier (**Scheme 75**).



SCHEME 75

The NMR spectra obtained could not be completely rationalized according to the intermediates proposed. As shown previously, these anhydride derivatives **200** and **205** can give complex mixtures that are often difficult to interpret. In addition, the use of excess *m*-CPBA at such temperature requires a relatively high dilution of the reaction mixture as *m*-CPBA and *m*-CBA are not soluble under these conditions. As a consequence, the resolution of the corresponding ^{13}C NMR spectrum is lower as the acquisition time has to be relatively short (<2 h) under this low temperature condition.

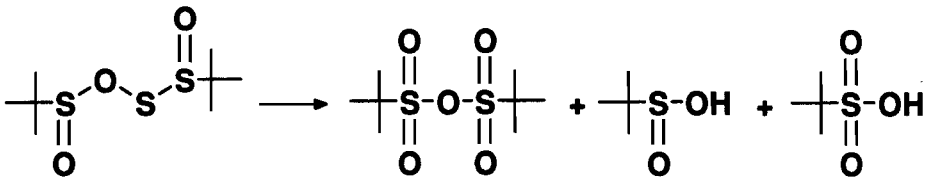
The final decomposition mixture was mainly composed of *t*-butyl sulfinic (**163**) and sulfonic acid (**164**), di-*t*-butyl trisulfide-1,1-dioxide (**145**), di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) as well as large quantities of presumed *t*-butyl sulfonic anhydride (**206**) as will be discussed in the next section (**Scheme 76**).



156 **206** **163** **164** **145** **159**

SCHEME 76

The formation of di-*t*-butyl trisulfide-1,1-dioxide (**145**) signals the presence of remaining *t*-butyl sulfinic *t*-butyl thiosulfenic anhydride **200a**. The formation of **163** and **164** and the chemical shifts reported for intermediate **205** are consistent with the results observed for *t*-butyl sulfinic anhydride (**168**). As described earlier, the decomposition of **168** does not give any di-*t*-butyl disulfide-1,1,2-trioxide **166**, but a mixture of hydrolyzed products. Similarly, the intermediate **205** suggested here does not give any traces of trisulfide-1,1,3-trioxide **157** but a rather complex mixture of related products (sulfinic **163** and sulfonic **164** acids as well as the presumed sulfonic anhydride **206**) (**Scheme 77**).



205 **206** **163** **164**

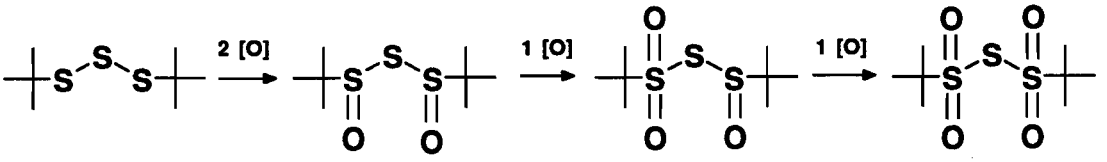
SCHEME 77

In a separate experiment, the reaction mixture was filtered at -60°C and pentane was added. A precipitate formed immediately and was found to be mainly di-*t*-butyl sulfone (**121**). This is the only time that such a compound was isolated in any of the decomposition studies carried out. The formation of di-*t*-butyl sulfone (**121**) implies a reaction at the tertiary carbon of the *t*-butyl group.

The formation, rearrangement and decomposition of di-*t*-butyl trisulfide-1,2,3-trioxide (**160**) is far from being solved and considering the results obtained for the corresponding trisulfide-1,2-dioxide **158**, it will be difficult to resolve this problem. However, the main objective was to show that the formation of di-*t*-butyl trisulfide-1,1,3-trioxide (**160**) proceeds through the electrophilic oxidation of the external sulfinyl sulfur rather than the internal sulfenyl sulfur. Clear evidence of such a mechanism has been obtained in the present study.

4.5.3. Alkyl Trisulfide-1,1,3,3-Tetraoxides

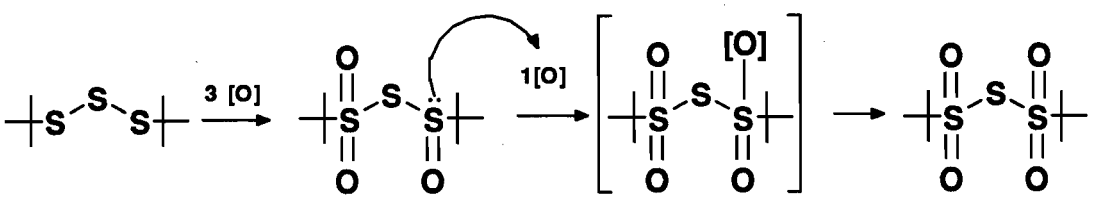
As described in Chapter 3, the synthesis of di-*t*-butyl trisulfide-1,1,3,3-trioxide (**161**) has been achieved by direct oxidation of various substrates using the appropriate number of equivalent of electrophilic oxidizing agent (**Scheme 78**).



118c **130** **157** **161**

SCHEME 78

By analogy with the preparation of the disulfide analogs **165** and considering the mechanism of formation of trisulfide-1,1,3-trioxide **157** previously reported, the conversion of **157** to the corresponding trisulfide-1,1,3,3-tetraoxide **161** is believed to proceed through the oxidation of the sulfinyl sulfur rather than the internal sulfenyl sulfur (**Scheme 33**).

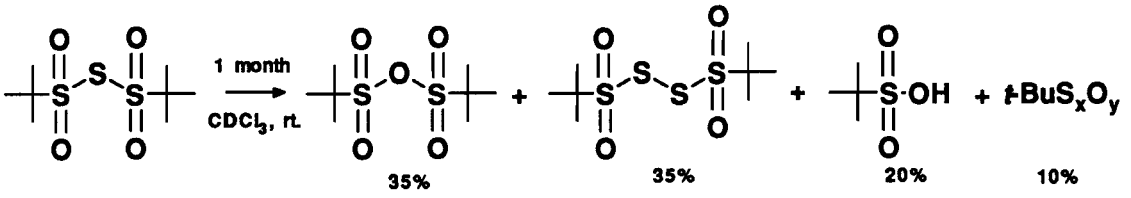


118c **157** **161**

SCHEME 33

Further oxidation of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) was shown to be impossible under these conditions. This result emphasizes the non-reactivity of the central sulfenyl sulfur towards electrophilic oxidizing agents.

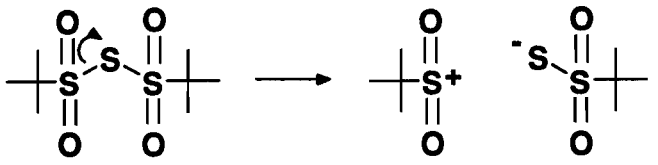
The decomposition of di-*t*-butyl tetrasulfide-1,1,3,3-tetraoxide **161** at room and elevated temperatures has also been investigated. In both cases, the same decomposition products were found. The main products were an equimolar mixture of the di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) and the presumed *t*-butyl sulfonic anhydride (**206**) as well as significant amounts of *t*-butyl sulfonic acid **164**. Very small quantities of sulfinic acid **163**, di-*t*-butyl disulfide-1,1-dioxide **144** and other derivatives were also detected (**Scheme 32**).



161 **206** **159** **164**

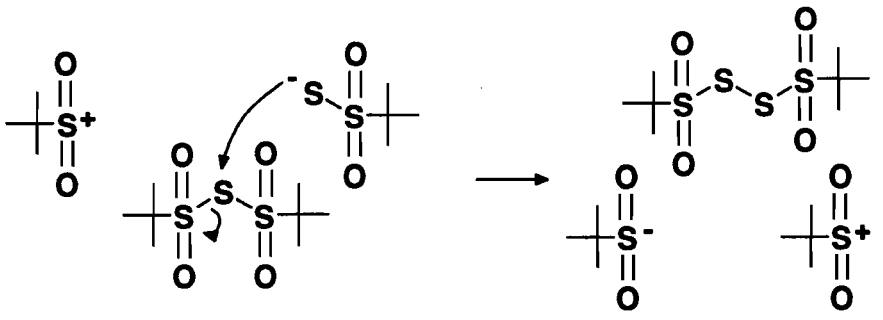
SCHEME 32

Once again, the formation of these decomposition products can be rationalized by the various mechanisms proposed in this Chapter. By analogy with the previous studies, the first step of the decomposition of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) should be the ionic cleavage of **161** affording the *t*-butyl sulfonyl cation **188a** and the *t*-butyl thiosulfonate anion (**204**) (**equation 105a**).



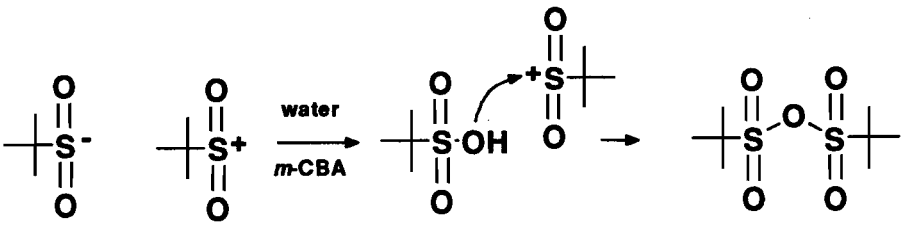
161 **188a** **204** **(eq. 105a)**

The *t*-butyl thiosulfonate anion **(204)** formed could eventually react with another molecule of trisulfide-1,1,3,3-tetraoxide **161** to give the corresponding tetrasulfide-1,1,4,4-tetraoxide **159** and generate the *t*-butyl sulfonyl anion **188b (equation 105b)**.



161 **204** **188b** **159** **188a** **(eq. 105b)**

The two ambident *t*-butyl sulfonyl ions **188a-b** should not react together to form the expected di-*t*-butyl disulfide-1,1,2,2-tetraoxide **165** because of steric hindrance. Considering that the ambident sulfinyl ions **187a-b** do not easily recombine for the same reasons, it is not surprising that the corresponding sulfonyl ions **188a-b** do not react with each other. In this case, the oxygen transfer is impossible and the reaction with trisulfide-1,1,3,3-tetraoxide **161** or tetrasulfide-1,1,4,4-tetraoxide **159** would lead to already existing products as di-*t*-butyl disulfide-1,1,2,2-tetraoxide **165** is sterically disfavored. As a consequence, the *t*-butyl sulfonyl ions **(188a-b)** are converted to sulfonic acid **164** probably because of residual *m*-CBA or traces of water. The *t*-butyl sulfonic acid **(164)** formed can then react with the remaining *t*-butyl sulfonyl cation **(188a)** to give the proposed *t*-butyl sulfonic anhydride **(206) (equation 105c)**.



(eq. 105c)

188a-b **164** **206**

The *t*-butyl sulfonic anhydride (**206**) could not be identified with certainty as it could not be separated by chromatography. The parallel synthesis of **206** was attempted by dehydration of *t*-butyl sulfonic acid **164** but was unsuccessful in our hands.[228] However, the chemical shifts recorded are consistent with *t*-butyl sulfonic anhydride (**206**) as can be seen in the NMR study presented in the conclusion of this Chapter. Compound **206** was only detected in decomposition experiments where sulfonyl ions (**188a-b**) are supposed to be formed and is therefore, probably derived from the reaction of such ions. The small amounts of the other decomposition products reflect the difficult recombination of these ambident ions.

The isolation of di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (**159**) has also been reported in Chapter 3. The characterization of **159** was very similar to its trisulfide analog **161**, but the tetrasulfide-1,1,4,4-tetraoxide **159** was found to be very stable at room temperature (unchanged after 6 months). A possible explanation would be that **159** is less hindered than its trisulfide analog **161** or because the cleavage of a molecule of **159** would not lead to the formation of any stable compound.

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228 M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).

4.6. Conclusions

The results presented in this Chapter are directly related to the synthesis and characterization of the alkyl polysulfide-polyoxides that are described in Chapter 3. The main interest of this study is to present a global overview of the oxidative reactivity of alkyl polysulfide-polyoxides. Although this work has been centered on the di-*t*-butyl derivatives, it was successfully extended in most cases to differently substituted analogs. The di-*t*-butyl derivative was chosen because of the great advantage of being a critical analog as was shown on many occasions. In several cases, the stability induced by the adjacent *t*-butyl groups allowed the isolation and characterization of poorly documented compounds. In other cases, the inherent steric hindrance of the *t*-butyl groups seriously complicated the reaction path and allowed a better understanding of the mechanisms involved by emphasizing the influential parameters. In addition, the characterization of the different derivatives was greatly facilitated by the relatively simple NMR signals of the *t*-butyl group. Although differently substituted derivatives have been synthesized, this study was rather focused on the *t*-butyl oxide derivatives of various polysulfides. This turned out to be determinant in the understanding of very complex decomposition mixtures and the proposal of a rational mechanism as the results reported are surprisingly congruent from one series to another. As a result, the general understanding of this class of compounds could be applied to the study of other analogs and can be summarized as follows.

4.6.1. Formation and Stability of Alkyl Polysulfide-Polyoxides

The oxidation of symmetrical polysulfides was shown to be regiospecific with preferred attack at the sulfenyl sulfur. However, the internal sulfur was found to be surprisingly non-reactive towards electrophilic oxidizing agents. As a result, contrary to current belief,[198] the oxidation of an external sulfinyl sulfur atom was shown in specific cases to be favored over the internal sulfenyl sulfur.

In general, the stability of the compounds bearing a sulfinyl moiety is lower than the one bearing a sulfonyl moiety except in specific cases where the steric effects are very important. This observation is supported by the crystallography study that reveals

that the S(O)-S bond is longer than the corresponding $S(O)_2$-S one. The rationalization of such behaviour is rather difficult but it could be because the two oxygen atoms on the same sulfur cancel each other's effects. Another possibility might come from the decomposition of these derivatives. In most cases, the formation of ambident ions was postulated. Considering that the recombination of ambident *t*-butyl sulfinyl anion was shown to be controlled by steric effects, it is conceivable that the recombination of the corresponding ambident sulfonyl ions would would be even more retarded.

4.6.2. Decomposition Principles of Alkyl Polysulfide-Polyoxides

The alkyl polysulfide-polyoxides have been shown to be relatively unstable except in rare cases. The decomposition is not very clean in general and affords complex mixtures that are often quite difficult to rationalize by the usual theories. The rate determining step of the decomposition of these derivatives was suggested to be a heterolytic cleavage of the starting material. The subsequent reaction of the ions formed would lead in most cases to the formation of ambident ions. Depending on the substrate and the reaction conditions, the recombination of these ions is controlled by steric effects and is often in competition with an oxygen transfer reaction with another molecule.

The general mechanism proposed is supported by clear evidence obtained from kinetic and low temperature experiments, uses of radical inhibitors and trapping agents as well as study of the decomposition of unsymmetrical derivatives that clearly show the rearrangements of the two alkyl groups. Moreover, the mechanism proposed is consistent with all the cases studied under very different decomposition conditions (temperature, concentration and solvents).

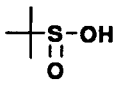
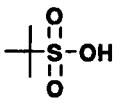
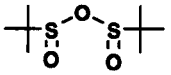
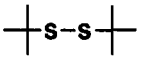
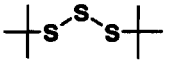
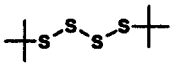
4.6.3. NMR Study of Alkyl Polysulfide-Polyoxides

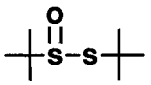
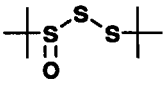
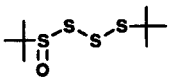
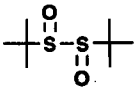
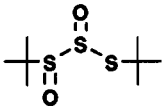
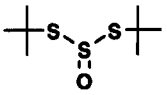
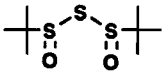
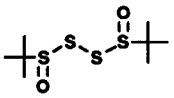
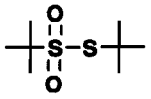
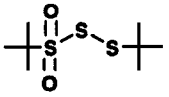
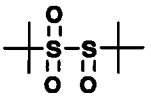
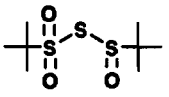
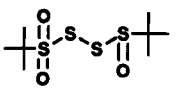
The characterization of the different derivatives was essentially carried out by NMR spectroscopy. The *t*-butyl trisulfide-polyoxides were fully characterized by the appropriate techniques considering that most of these compounds are relatively unstable. All of them were submitted to crystallographic analysis and the structure of 5 of them was definitely confirmed. Unfortunately, the two low temperature X-rays were unsuccessful. The use of mass spectrometry was not very helpful as only very small

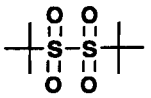
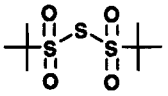
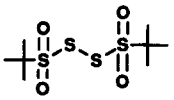
parent peaks could be obtained even under chemical ionization conditions. However, the results obtained showed specific fragmentation in some cases. All these oxide derivatives readily decomposed under gas chromatographic analysis. Finally, the melting points were measured in all appropriate cases. In most cases the sample melted over a 20°C range suggesting that the compound decomposed in the capillary tube.

The techniques of choice to study this class of compounds were found to be ^{1}H and ^{13}C NMR because they give reliable chemical shifts and can easily be used at various temperatures. Once the structure of one series of oxide derivatives has been confirmed by crystallography, the structures of the oxide derivatives of the other series were defined by NMR spectroscopy as there is a very good correlation among the compounds of this class as was shown in Chapter 3 and is presented here (**Table 22**).

Table 22: ^{1}H and ^{13}C NMR Chemical Shifts (δ ppm) of *t*-Butyl Trisulfide-Polyoxides[a,b,c]

Entry	Compound	C	CH_3	H	C'	CH'_3	H'
163		57.46	21.42	1.196			
164[e]		58.07	24.49	1.432			
168a		60.52	21.37	1.284			
168b		60.07	21.53	1.261			
118b					45.87	30.54	1.280
118c					48.91	29.88	1.347
118d					49.01	30.16	1.382

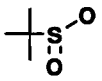
120b		59.35	24.18	1.531	48.65	32.21	1.353
120c		60.67	23.79	1.385	48.73	29.80	1.390
120d		60.60	23.82	1.330	49.91	29.76	1.321
167[d]		57.08	22.95	1.294			
158[d]		59.34	23.06	1.393	52.77	31.91	1.293
156					52.10	31.80	1.545
130a		62.39	24.17	1.410			
130b		62.02	24.18	1.422			
174a		61.51	23.50	1.410			
174b		61.20	23.77	1.368			
144		68.01	23.65	1.596	56.31	31.45	1.441
145		70.06	24.18	1.465	49.95	29.86	1.395
166[d]		69.28	23.74	1.499	63.68	23.80	1.474
157		71.38	23.99	1.551	63.08	24.51	1.463
175		71.16	23.72	1.519	62.33	23.84	1.453

165		72.67	24.60	1.633
161		73.45	24.15	1.545
159		72.10	24.18	1.527

[a] Recorded using deuterated chloroform ($CDCl_3$) as NMR solvent; [b] Relaxation time (t_1) used: t_1= 2s; [c] a and b represent the two diastereoisomers; [d] The spectrum was obtained at low temperature and does not represent a specific diastereoisomer; [e] Partially soluble in $CDCl_3$.

From the results presented in Table 22, one can see that the chemical shifts of each of these compounds is very consistent with the others. As a consequence, the chemical shifts of a given *t*-butyl group can be unambiguously interpreted depending on which sulfur it is bonded to (sulfenyl, sulfinyl, sulfonyl or sulfinate) (**Table 23**).

Table 23: ^1H and ^{13}C NMR Chemical Shifts Ranges (δ ppm) of the *t*-Butyl Groups Bonded to Differently Oxidized Sulfur[a,b]

Fonctionality	C	CH_3	H	C'	CH'_3	H'
	60 - 61	21 - 22	1.1 - 1.2			
	59 - 64	24 - 26	1.3 - 1.6			
	68 - 74	23 - 26	1.4 - 1.6			
				48 - 53	29 - 33	1.3 - 1.5

The only exception encountered is the di-*t*-butyl disulfide-1,1-dioxide **(144)** where one of the tertiary carbon signals is out of the normal range. These results are presented in Table **22**. Four types of *t*-butyl groups have been defined according to the degree of oxidation of the sulfur it is bonded to (sulfenyl, sulfinyl, sulfonyl or sulfinate). Specific ranges of chemical shifts are given for each type of *t*-butyl group.

The results presented in Table **23** clearly show that the structure of other analogs can be easily determined by comparing the chemical shifts observed with the ranges reported here. The preparation and characterization of a wide variety of isopropyl analogs revealed that similar ranges can be applied to other alkyl analogs.

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

1/ The synthesis of symmetrical and unsymmetrical di-, tri- and tetrasulfides has been further investigated. The development of a new set of conditions for the reaction of polysulfide chlorides with mercaptans allowed the isolation of various polysulfides in high yield and purity. This procedure presents the advantage to be a one vessel reaction that can be carried out in less than 2 hours using commercially available chemicals. Although the best results were obtained using hindered polysulfide chlorides, the preparation of primary alkyl polysulfides has also been reported even if slightly different conditions were used in rare cases.

2/ The study of the oxidative reactivity of alkyl polysulfides confirmed the non regiospecificity of the electrophilic oxidation of polysulfides. The oxidation of an equimolar mixture of di-*t*-butyl mono-, di-, tri- and tetrasulfides allowed the quantification of the sulfur chain length effects. Sulfides were found to react much faster than disulfides which are slightly more reactive than tri- and tetrasulfides. Using differently substituted disulfides, the quantification of the alkyl substitution effect revealed that the oxidation of the tertiary alkyl analog was favored over the secondary and primary derivatives. The predominance of these two factors was also determined by comparative experiments. The sulfur-chain length effect is more important when the number of sulfur atoms is less or equal to 2. The substitution effect dominated for sulfur atoms > 2.

3/ A wide variety of polysulfide-polyoxides were synthesized by direct oxidation and non-oxidative procedures. The nucleophilic oxidation of hindered polysulfides was unsuccessful in our hands. However, the electrophilic oxidation of symmetrical and unsymmetrical primary, secondary, tertiary alkyl, cyclic and aryl polysulfides afforded the corresponding 1-oxide derivatives using several oxidizing agents (meta-chloroperbenzoic acid, peracetic acid, dimethyl dioxirane and an oxaziridine). Using different quantities of oxidizing agent, many barely known analogs have been isolated such as diastereomeric trisulfide-1,3-dioxides, diastereomeric tetrasulfide-1,4-dioxides, trisulfide-1,1,3-trioxide and tetrasulfide-1,1,4-trioxide for example. Other unknown derivatives (di-*t*-butyl disulfide-1,1,2-trioxide and di-*t*-butyl

trisulfide-1,2-dioxide) were clearly detected by low temperature oxidation experiments. In all cases, dimethyl dioxirane was found to be the oxidizing agent of choice. Several unsymmetrical polysulfide-polyoxides have been isolated by non-oxidative procedures especially an unsymmetric trisulfide-1-oxide (*t*-butyl isopropyl trisulfide-3-oxide).

4/ X-ray crystallography of most of the di-*t*-butyl trisulfide-polyoxides confirmed the structure of the key compounds. All the other polysulfide-polyoxides were characterized by NMR spectroscopy and the chemical shifts were found to be very consistent from one to another. A thorough NMR and crystallographic study of the di-*t*-butyl polysufide-polyoxide class of compounds revealed the influence of the number and the position of the oxygen atoms on the sulfur-chain as well as the similarity among the di-, tri- and tetrasulfide analogs. NMR spectroscopy was found to be a very reliable tool for the characterization of this class of compounds.

5/ The oxidation of various substrates and the use of low temperature oxidation experiments allowed the determination of several pathways. The existence of trisulfide-1,2-dioxides (*vic*-disulfoxides) was shown by the detection of such intermediates at low temperature and by the preparation of trisulfide-1,1-dioxides by electrophilic oxidation of the corresponding trisulfide-2-oxides. In all cases but trithiolanes, the oxidation was found to be regiospecific delivering only one product. The oxidation of di-*t*-butyl trisulfide-1-oxide gave stereospecifically the d,l di-*t*-butyl trisulfide-1,3-dioxide which rapidly converted to the thermodynamically favored meso diastereoisomer at room temperature. The d,l and meso diastereoisomers were assigned according to molecular modeling calculations. Although sulfenyl sulfur atoms were found to be more electron rich than sulfinyl sulfur atoms in most cases, clear evidence of the non-reactivity of the internal sulfenyl sulfur towards electrophilic oxidizing agents was reported here. As an example the oxidation of di-*t*-butyl trisulfide-1,3-dioxide was shown to take place at the external sulfinyl sulfurs rather than the internal sulfenyl sulfur.

6/ Finally, the decomposition of this class of compounds was thoroughly investigated and the decomposition products of most of the these polysulfide-polyoxides determined. Using kinetic and low temperature experiments, light/dark effects, radical inhibitors, trapping agents, solvent and concenttration effects and unsymmetrical analogs, a general mechanism for the decomposition of di-*t*-butyl

polysulfide-polyoxides was proposed. The rate determining step is clearly consistent with the ionic cleavage of one S-S bond of the starting material. The reaction of the ions formed with another molecule of starting material generally provide one of the decomposition products and a pair of ambident sulfinyl or sulfonyl ions. Because of the hindrance, these ions do not recombine but rather react with another molecule of starting material by an oxygen transfer mechanism that seems to involve a tetra substituted sulfur intermediate. Rearrangement of this intermediate gives the remaining decomposition product. Although this decomposition mechanism is complex, it was found to be consistent with all the cases studied here.

CHAPTER 5. EXPERIMENTAL

5.1. General Methods

Chemical reagents were obtained from commercial sources and used directly unless otherwise stated. Di-*t*-butyl trisulfide (99%) was provided by Elf Atochem N. A. Inc., King of Prussia, Pennsylvania and used as such.

All the solvents that were used were stored over 3Å molecular sieves which had previously been activated by heating at 400°C overnight and cooled in a desiccator. Hexanes and methylene chloride were distilled from concentrated sulfuric acid (H_2SO_4) and anhydrous phosphorus pentoxide (P_2O_5) respectively. Hexanes were also passed through an alumina column. Petroleum ether was low boiling (35-60°C); ether refers to anhydrous diethyl ether in all cases.

Pyridine and triethylamine were distilled from potassium hydroxide and stored over activated 3Å molecular sieves. Sulfur dichloride (SCl_2) was distilled from 0.1% phosphorus pentachloride and the fraction boiling from 58-60°C was used immediately.[229] Sulfur monochloride (S_2Cl_2) was distilled from charcoal and sulfur and the fraction boiling from 137-139°C was used immediately.[230] Thionyl chloride ($SOCl_2$) and sulfuryl chloride (SO_2Cl_2) were freshly distilled before using. The *m*-CPBA **(119)** used was purified by washing the commercial 80-85% or 50-60% material with a phosphate buffer, drying, filtering and evaporating at reduced pressure. The solid was then recrystallized from methylene chloride to afford 99% *m*-CPBA.[231] Dimethyldioxirane **(124)** was prepared according to the literature procedure.[232] It was stored in the freezer over 3Å molecular sieves and used within a week. The purity was checked by gc analysis prior to use. The dropwise additions of dimethyldioxirane were

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229 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, Pub., 1, p. 1121 (1967).

230 L. F. Fieser and M. Fieser, *Op. Cit.*, p. 1122.

231 N. N. Shartz and J. H. Blumberg, *J. Org. Chem.*, **29**, 1496 (1976).

232 a) R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989); b) M. Singh and R. W. Murray, *J. Org. Chem.*, **57**, 4263 (1992).

always carried out using a pressure-equalized dropping funnel equipped with a dry ice-cooling jacket.

Melting points (Mp.) were obtained in open capillaries on a Gallenkamp melting point apparatus and are uncorrected. Thin Layer Chromatography was performed on 0.25 mm Merck silica gel plates (60F-254) with polyester backing and visualized by UV light and a 10% aqueous sulfuric acid solution of ammonium molybdate-cerium sulfate developing dip. Silica gel chromatography was carried out on Merck Kieselgel 60 (230-400 mesh) and alumina chromatography on Fisher Scientific Neutral Alumina (80-200 mesh) that had previously been dried. In both cases flash column procedures[233] were used. Gas chromatography was performed on a Varian Associates (VA) model 3700 gas chromatograph equipped with a model 4270 printing integrator and an FID detector. Separation was achieved using a 15 m glass capillary column bonded with 3% silicone OV-101.

^{1}H NMR spectra were recorded at 200 MHz (Varian XL-200 and Varian Gemini 200), at 270 MHz (Jeol 270-CPF) and at 300 MHz (Varian XL-300) with the solvents noted. Multiplicity assignments are reported using the following abbreviations: s for singlet, d for doublet, t for triplet, q for quartet, h for heptet and m for multiplet. ^{13}C NMR were recorded on the same instruments (50.3 MHz, 67.9 MHz and 75.4 MHz). In both cases, the chemical shifts (δ) are reported in parts per million relative to TMS.

Low resolution electron impact (EI) and chemical ionization (CI) mass spectra were obtained using a DuPont Instruments 21-492B equipped with a 70-eV ionizing energy source and used in direct-inlet mode.

X-ray crystallography was performed by Dr. Rosemary C. Hynes at the Department of Chemistry, McGill University, Montreal, Quebec, Canada. Solution and refinement were done using NRCVAX system program.[234]

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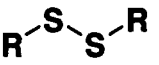
233 W. C. Still, M. Khan and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

234 a) E. J. Gabe, Y. Lepage, J.-P. Charland, F. L. Lee, P. S. White, *J. Appl. Crystallogr.*, **22**, 384 (1989); b) *International Tables For X-ray Crystallography*, Vol. IV, Kynoch Press, Birmingham, England (1974); c) C. K. Johnson, ORTEP, A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, Oak Ridge Tennessee (1976); d) A. C. Larson, *Crystallographic Computing*, Munksgaard, Copenhagen, p. 293 (1970); e) D. Rogers, *Acta Cryst.*, **A37**, 734 (1981).

5.2. Chapter 2

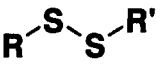
5.2.1. General Procedure for the Preparation of Disulfides

Preparation of Symmetric Disulfides (104):



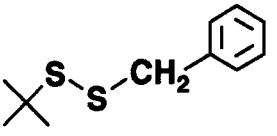
A solution of thiol (20 mmol) and pyridine (20 mmol) in ether (50 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfuryl chloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 1 h after the addition was complete. It was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. In all cases studied, no further purification was necessary. Characterization data are reported in Table **1**.[192]

Preparation of Unsymmetric Disulfides (105):



A solution of the first thiol (10 mmol) and pyridine (10 mmol) in ether (25 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfuryl chloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 0.5 h after the addition was complete. The second thiol (10 mmol) and pyridine (10 mmol) in 25 mL of ether was added dropwise over 0.5 h at -78°C and the reaction mixture was stirred for an additional 0.5 h. The reaction mixture was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. Characterization data and purification methods are reported in Table **1**.[192]

Preparation of *t*-Butyl Benzyl Disulfide (105c):

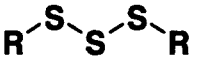


To a stirred solution of benzyl disulfide (2.46 g, 10 mmol) and pyridine (1 mL) in ether (25 mL) was added dropwise at room temperature over 0.5 h a solution of sulfuryl chloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 0.5 h after the

addition was complete. A solution of *t*-butyl mercaptan (20 mmol) and pyridine (20 mmol) in 25 mL of ether was added dropwise over 0.5 h at room temperature and the reaction mixture was stirred for an additional 0.5 h. The reaction mixture was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. No further purification was necessary. Characterization data are reported in Table **1**.[192]

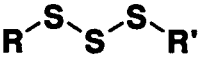
5.2.2. General Procedure for the Preparation of Trisulfides

Preparation of Symmetric Trisulfides (115):



A solution of thiol (20 mmol) and pyridine (20 mmol) in ether (50 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfur dichloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 1 h after the addition was complete. It was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. In all cases studied, no further purification was necessary. Characterization data are reported in Table **2**.[192]

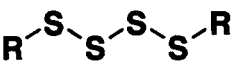
Preparation of Unsymmetric Trisulfides (116):



A solution of the first thiol (10 mmol) and pyridine (10 mmol) in ether (25 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfur dichloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 0.5 h after the addition was complete. The second thiol (10 mmol) and pyridine (10 mmol) in 25 mL of ether was added dropwise over 0.5 h at -78° C and the reaction mixture was stirred for an additional 0.5 h. The reaction mixture was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. Characterization data and purification methods are reported in Table **2**.[192]

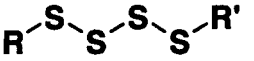
5.2.3. General Procedure for the Preparation of Tetrasulfides

Preparation of Symmetric Tetrasulfides (117a):



A solution of thiol (20 mmol) and pyridine (20 mmol) in ether (50 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfur monochloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 1 h after the addition was complete. It was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. In all cases studied, no further purification was necessary. Characterization data are reported in Table **3**.[192]

Preparation of Unsymmetric Tetrasulfides (117b):



A solution of the first thiol (10 mmol) and pyridine (10 mmol) in ether (25 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfur monochloride (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 0.5 h after the addition was complete. The second thiol (10 mmol) and pyridine (10 mmol) in 25 mL of ether was added dropwise over 0.5 h at -78°C and the reaction mixture was stirred for an additional 0.5 h. The reaction mixture was then transferred to a separatory funnel, washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. Characterization data and purification methods are reported in Table **3**.[192]

5.2.4. Oxidative Reactivity Study

Oxidation of di-*t*-Butyl Polysulfides Using 0.25 Equivalent *m*-CPBA:

To a stirred solution of di-*t*-butyl sulfide (99 mg, 0.68 mmol), di-*t*-butyl disulfide (112 mg, 0.63 mmol), di-*t*-butyl trisulfide (149 mg, 0.71 mmol) and di-*t*-butyl tetrasulfide (171 mg, 0.71 mmol) in 50 mL of methylene chloride was added dropwise

0.72 mmol of *m*-CPBA dissolved in 25 mL of methylene chloride. The reaction was stirred at room temperature and under nitrogen for 2 h. The *m*-CBA formed was removed by washing the reaction mixture with 2x20 mL portions of water, 3x20 mL portions of 1 N NaOH solution and with 20 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The relative quantities of the reaction products are reported in Table **4**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

Oxidation of di-*t*-Butyl Polysulfides Using 1.0 Equivalent *m*-CPBA:

To a stirred solution of di-*t*-butyl sulfide (97 mg, 0.66 mmol), di-*t*-butyl disulfide (114 mg, 0.64 mmol), di-*t*-butyl trisulfide (134 mg, 0.64 mmol) and di-*t*-butyl tetrasulfide (148 mg, 0.61 mmol) in 50 mL of methylene chloride was added dropwise 2.55 mmol of *m*-CPBA dissolved in 50 mL of methylene chloride. The reaction was stirred at room temperature and under nitrogen for 2 h. The *m*-CBA formed was removed by washing the reaction mixture with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The relative quantities of the reaction products are reported in Table **5**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

Oxidation of Alkyl Disulfides Using 0.33 Equivalent *m*-CPBA:

To a stirred solution of di-*t*-butyl disulfide (112 mg, 0.63 mmol), diisopropyl disulfide (84 mg, 0.56 mmol) and benzyl disulfide (165 mg, 0.67 mmol) in 50 mL of methylene chloride was added dropwise 0.68 mmol of *m*-CPBA dissolved in 25 mL of methylene chloride. The reaction was stirred at room temperature and under nitrogen for 2 h. The *m*-CBA formed was removed by washing the reaction mixture with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The relative quantities of the reaction products are reported in Table **6**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

Comparative Studies Using 0.50 Equivalent of *m*-CPBA:

To a stirred solution of di-*t*-butyl disulfide (121 mg, 0.68 mmol) and benzyl sulfide (160 mg, 0.65 mmol) in 50 mL of methylene chloride was added dropwise 0.68 mmol of *m*-CPBA dissolved in 25 mL of methylene chloride. The reaction was stirred at room temperature and under nitrogen for 2 h. The *m*-CBA formed was removed by washing the reaction mixture with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The relative amounts of the reaction products are reported in Table **7**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

The same procedure was repeated using 0.56 mmol of di-*t*-butyl trisulfide and 0.60 of benzyl disulfide with 0.61 mmol of *m*-CPBA. The relative amounts of the reaction products are reported in Table **7**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

Comparative Studies Using 0.50 Equivalent of Dimethyldioxirane:

To a stirred solution of di-*t*-butyl disulfide (130, 0.73 mmol) and benzyl sulfide (179 mg, 0.73 mmol) in 20 mL of acetone was added dropwise 11 mL of a 0.07 M solution of dimethyldioxirane in acetone. The reaction was stirred at -78°C and under nitrogen for 1 h. The reaction mixture was dried with $MgSO_4$, filtered and evaporated. The relative quantities of the reaction products are reported in Table **7**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

The same procedure was repeated using 0.56 mmol of di-*t*-butyl trisulfide and 0.50 mmol of benzyl disulfide with 11.5 mL of a 0.05 M solution of dimethyldioxirane. The relative quantities of the reaction products are reported in Table **7**. The ^1H NMR and ^{13}C NMR of these compounds are reported in the experimental part of Chapter **3**.

5.3. General Oxidation Procedures

5.3.1. ***Procedure 1:*** ***m*-CPBA (119) oxidation.** A typical experimental procedure is the *m*-CPBA oxidation of di-*t*-butyl trisulfide (**118c**) to di-*t*-butyl trisulfide-1-oxide (**120c**) (the characterization of **120c** is presented later). A solution of *m*-CPBA (0.98 g, 5.71 mmol, 1.1 eq) in methylene chloride (25 mL) was added dropwise to an ice cooled solution of di-*t*-butyl trisulfide (**118c**) (1.09 g, 5.19 mmol) in CH_2Cl_2 (15 mL) during 0.5 h under nitrogen. After stirring for 3 h at 0°C, the mixture was concentrated to 10 mL by roto-evaporation. The solution was cooled to -78°C and the *m*-CBA that crystallized (0.85 g, 5.48 mmol, 96%) was collected. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on alumina using a 13% ethyl acetate/hexanes solution to give di-*t*-butyl trisulfide-1-oxide (**120c**) (1.08 g, 4.77 mmol, 92%) as a white solid. In the following *m*-CPBA oxidations, the reaction temperature, the reaction time and the number of equivalents of *m*-CPBA may vary and are reported. The method of separation can also be different depending on the compound prepared.

5.3.2. ***Procedure 2:*** **Peracetic acid (CH_3CO_3H) oxidation.** A typical experimental procedure is the CH_3CO_3H oxidation of di-*t*-butyl trisulfide (**118c**) to di-*t*-butyl trisulfide-1-oxide (**120c**) (the characterization of **120c** is presented later). A solution of peracetic acid (40%) (0.97 g, 5.13 mmol, 1.1 eq) in methylene chloride (25 mL) was added dropwise to an ice cooled solution of di-*t*-butyl trisulfide (**118c**) (0.98 g, 4.66 mmol) in CH_2Cl_2 (15 mL) during 0.5 h under nitrogen. After stirring for 5 h at 0°C, the solvent was removed *in vacuo* to give an oily residue that was chromatographed on alumina using a 13% ethyl acetate/hexanes solution to give di-*t*-butyl trisulfide-1-oxide (**120c**). In the following CH_3CO_3H oxidations, the reaction temperature, the reaction time and the number of equivalents of CH_3CO_3H may vary and are reported. The method of separation can also be different depending on the compound prepared.

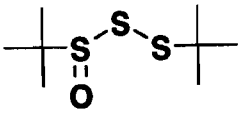
5.3.3. ***Procedure 3:*** **DMD (124) oxidation.** A typical experimental procedure is the DMD oxidation of di-*t*-butyl trisulfide (**118c**) to di-*t*-butyl trisulfide-1-oxide (**120c**) (the characterization of **120c** is presented later). A 0.07 M solution of DMD (**124**) in acetone (34 mL, 2.38 mmol, 1 eq) was added dropwise to a cooled solution (-78°C) of di-*t*-butyl trisulfide (**118c**) (0.5 g, 2.38 mmol) in acetone (10 mL) during 30 min under

nitrogen. After stirring for 1 h at -78°C, the solvent was removed *in vacuo* to give di-*t*-butyl trisulfide-1-oxide (**120c**) (0.53 g, 2.33 mmol, 98%) as a solid. In the following DMD oxidations, the reaction time and the number of equivalents of DMD may vary and are reported. The method of separation is indicated when necessary.

5.4. Chapter 3

5.4.1. di-*t*-Butyl Trisulfide-1-Oxide (120c)

5.4.1.1. Synthesis of di-*t*-butyl trisulfide-1-oxide (120c)



***m*-CPBA oxidation of di-*t*-butyl trisulfide (118c).** Di-*t*-butyl trisulfide-1-oxide (**120c**) was prepared as described in procedure 1. **Mp.** 61-63°C (lit.[197] 63-65°C). **^{1}H** and **^{13}C NMR** are reported in Table **12**. **MS** (EI, 70 eV, 30°C) m/z (rel. intensity) 226 ($M^{+\cdot}$, 1.1); 178 ($M^{+\cdot}$-S=O, 3.5); 170 (*t*-BuS(O)SS$^{+\cdot}$, 6.0); 106 (*t*-BuS(O)$^{+\cdot}$, 20.8); 90 ($C_4H_{10}S^{+\cdot}$, 18.4); 57 (*t*-Bu$^+$, 100); 41 ($C_3H_5^{+\cdot}$, 62.1).

Peracetic acid oxidation of di-*t*-butyl trisulfide (118c). Di-*t*-butyl trisulfide-1-oxide (**120c**) (0.93 g, 4.11 mmol, 88%) was prepared as described in procedure 2. Analytical data were identical to the one previously reported.

Dimethyl dioxirane (DMD) oxidation of di-*t*-butyl trisulfide (118c). Di-*t*-butyl trisulfide-1-oxide (**120c**) was prepared as described in procedure 1. Analytical data were identical to the one previously reported.

Reaction of *t*-butyl hydrodisulfide (148) with *t*-butyl sulfinyl chloride (149).[204] A solution of *t*-butyl sulfinyl chloride (**149**) (0.481 g, 3.44 mmol, 1 eq) in methylene chloride (25 mL) was added dropwise to an ice cooled solution of *t*-butyl hydrodisulfide (**148**)[213] (0.42 g, 3.44 mmol) and pyridine (0.28 g, 3.44 mmol, 1 eq) in CH_2Cl_2 (20 mL) during 0.5 h under nitrogen. After stirring for 12 h at 0°C, the reaction mixture was washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and

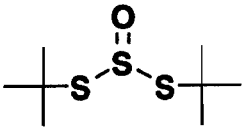
with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on alumina using a 13% ethyl acetate/hexanes solution to give di-*t*-butyl trisulfide-1-oxide **(120c)** (0.528 g, 2.34 mmol, 68%) the remaining compounds being di-*t*-butyl tetrasulfide **(118d)**. Analytical data were identical to the one previously reported.

5.4.1.2. Decomposition of di-*t*-butyl trisulfide-1-oxide (120c)

The decomposition of di-*t*-butyl trisulfide-1-oxide (120c) (34 mg, 0.15 mmol) in $CDCl_3$ was followed by ^1H and ^{13}C NMR at room temperature. After 5 days no traces of **120c** could be detected. The decomposition products were identified as **118d** (30%), **120b** (30%) and **145** (40%); there quantities were calculated from the intensity observed on ^{13}C NMR because the ^1H NMR presented too much overlap of signals. A reference solution of **118d** (33 mg, 0.14 mmol), **120b** (31 mg, 0.16 mmol) and **145** (27 mg, 0.11 mmol) confirmed that the intensity of the signals on ^{13}C NMR were proportional to the ratio of each compound of the sample at ± 7%. Other similar calibration experiments using different derivatives were caried out. In all cases, a good agreement between the ^{13}C NMR intensity and the relative concentrations of the derivatives employed was found within 5-10%. Similar results have been reported.[133]

5.4.2. di-*t*-Butyl Trisulfide-2-Oxide (156)

5.4.2.1. Synthesis of di-*t*-butyl trisulfide-2-oxide (156)



Reaction of *t*-butyl mercaptan with sulfuryl chloride.

Di-*t*-butyl trisulfide-2-oxide **(156)** was prepared using the procedure of Field and Lacefield.[179a] Compound **156** was isolated as a colorless solid (90%); **Mp.** 50-52°C (lit.[179a] 51-51.5°C). **^1H and ^{13}C NMR** are reported in Table **12.** **MS** (EI, 70 eV, 30°C) m/z (rel. intensity) 226 ($M^{+\cdot}$, 1.3); 210 ($M^{+\cdot}$-O, 1.2); 178 ($M^{+\cdot}$-S=O, 3.8); 170 (*t*-BuSS(O)$S^{+\cdot}$, 11.1); 154 (*t*-BuSSS$^{+\cdot}$, 2.0); 90 ($C_4H_{10}S^{+\cdot}$, 19.0); 57 (*t*-Bu^+, 100); 41 ($C_3H_5^{+\cdot}$, 42.1).

Attempted nucleophilic oxidation of di-*t*-butyl trisulfide (118c). The oxidation of di-*t*-butyl trisulfide **(118c)** (0.4-0.6 g, 1.9-2.86 mmol) was attempted using H_2O_2/1N NaOH,[209] *t*-BuOOH/1N NaOH,[209] KO_2[209] and $KMnO_4$[200] according to the literature procedures. The reactions were followed by tlc and gc. When no reaction had taken place under the reported conditions, the reaction mixture was refluxed until partial decomposition of the starting material had taken place giving a mixture of polysulfides. In all cases, the final products were a mixture of di-*t*-butyl di-, tri- and tetrasulfides that were characterized by NMR spectrometry and gc analysis. Using 1 equivalent of $NaIO_4$,[100f] the reaction products were an equimolar mixture of **118c** and **118b**. Using 1.5 equivalents of $NaIO_4$,[100f] the reaction products were **118c** (70%), **118b** (15%) and **118d** (15%). Finally, using 2 equivalents of $NaIO_4$,[100f] the reaction products were **118c** (80%) and **118d** (20%).

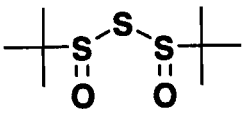
Attempted photochemical oxidation of di-*t*-butyl trisulfide (118c). Molecular oxygen (O_2) was bubbled through a stirred solution of di-*t*-butyl trisulfide **(118c)** (2.02 g, 9.62 mmol) in dodecane (15 mL) that was heated at 135°C. After 2 weeks under these conditions, the reaction mixture was analyzed by NMR and gc and presented a 8:2 ratio of di-*t*-butyl tri- **(118c)** and tetrasulfides **(118d)** which is equivalent to the thermal decomposition of di-*t*-butyl trisulfide at this temperature.[214]

5.4.2.2. Decomposition of di-*t*-butyl trisulfide-2-oxide (156)

The decomposition of di-*t*-butyl trisulfide-2-oxide (41 mg, 0.18 mmol) in $CDCl_3$ was followed by ^1H and ^{13}C NMR at room temperature. After 5 months no traces of **156** could be detected. The decomposition products were identified by ^1H NMR and gc as an equimolar mixture of **118b** (50%) and **118c** (50%). The decomposition of **156** (145 mg, 0.64 mmol) at 100°C in CCl_4 gave the same decomposition mixture within 19 h (identify by NMR and gc). The condenser employed was equipped with a trap of wet pH paper. Clear evidence of sulfur dioxide evolution were given by the strongly acidic coloration of the pH paper by the end of the decomposition.

5.4.3. di-*t*-Butyl Trisulfide-1,3-Dioxide (130)

5.4.3.1. Synthesis of di-*t*-butyl trisulfide-1,3-dioxide (130)



***m*-CPBA oxidation of di-*t*-butyl trisulfide (118c).** Compound **118c** (0.53 g, 2.52 mmol) was oxidized using *m*-CPBA (12h, -40°C, 2.5 eq) according to procedure 1. The solvent was removed at -10°C *in vacuo* (2.5 mm Hg) using a dry ice condenser roto-evaporator to give an oily residue. Di-*t*-butyl trisulfide-1,3-dioxide (**130**) (0.58 g, 2.42 mmol, 96%) crystallized from *n*-pentane in the freezer; **Mp.** 60-85°C (**130** probably decomposition before it reached its melting point). ^{1}**H** and ^{13}**C NMR** chemical shifts are reported in Table **12** (the sample was run at low temperature (-20°C) or at room temperature using very concentrated samples (100 mg)). Compound **130** was not stable enough to give consistent results on MS.

Peracetic acid oxidation of di-*t*-butyl trisulfide (118c). Compound **118c** (0.51 g, 2.43 mmol) was oxidized using peracetic acid (40%) (12h, -20°C, 2.5 eq) according to procedure 2. The solvent was removed *in vacuo* to give an oily residue. Di-*t*-butyl trisulfide-1,3-dioxide (**130**) (0.35 g, 1.46 mmol, 60%) crystallized from *n*-pentane in the freezer; the remaining compounds being unreacted **118c**. Analytical data were identical to the one previously reported.

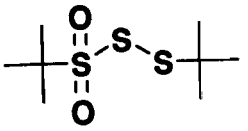
DMD oxidation of di-*t*-butyl trisulfide (118c). Compound **118c** (0.53 g, 2.52 mmol) was oxidized using DMD (0.05 M) (1.5h, -78°C, 2.1 eq) according to procedure 3. The solvent was removed at 0°C *in vacuo* (2.5 mm Hg) to give di-*t*-butyl trisulfide-1,3-dioxide (**130**) as a solid (0.60 g, 2.47 mmol, 98%); **Mp.** 60-85°C (**130** probably decomposition before it reached its melting point). Analytical data were identical to the one previously reported.

5.4.3.2. Decomposition of di-*t*-butyl trisulfide-1,3-dioxide (130)

The decomposition of di-*t*-butyl trisulfide-1,3-dioxide (**130**) (87 mg, 0.36 mmol) in $CDCl_3$ was followed by ^{1}H and ^{13}C NMR at room temperature. After 12 h no traces of **130** could be detected. The decomposition products were identified by ^{1}H and ^{13}C NMR

as a mixture of **145** (45%), **120b** (40%), **157** (10%), **159** (2%) and other undefined *t*-butyl derivatives (3%).

5.4.4. di-*t*-Butyl Trisulfide-1,1-Dioxide (145)



5.4.4.1. Synthesis of di-*t*-butyl trisulfide-1,1-dioxide (145)

Attempted nucleophilic oxidation of di-*t*-butyl trisulfide-1-oxide (120c). The oxidation of di-*t*-butyl trisulfide-1-oxide (**120c**) (0.4-0.6 g, 1.77-2.65 mmol) was attempted using H_2O_2/1N NaOH,[209] *t*-BuOOH/1N NaOH,[209] KO_2,[209] $KMnO_4$[200] and $NaIO_4$[100f] according to literature procedures. In all cases, the final products were a mixture of di-*t*-butyl di-, tri- and tetrasulfides that were characterized by NMR spectrometry and gc analysis.

***m*-CPBA oxidation of di-*t*-butyl trisulfide-2-oxide (156).** The oxidation of **156** (0.93 g, 4.11 mmol) was carried out using *m*-CPBA (-40°C, 5 h, 1.4 eq) according to procedure 1. Silica gel column chromatography using a 10% ethyl acetate/hexanes solution afforded the desired di-*t*-butyl trisulfide-1,1-dioxide (**145**) (0.48 g, 1.97 mmol, 48%) as a colorless solid; **Mp.** 58-65°C (lit.[116] 56.5-62.5°C). **^{1}H and ^{13}C NMR** are reported in Table **12. MS** (EI, 70 eV, 30°C) m/z (rel. intensity) 242 ($M^{+\cdot}$, 0.4); 178 ($M^{+\cdot}$-$S(O)_2$, 6.6); 122 (*t*-$BuS(O)_2^{+\cdot}$, 13.8); 90 ($C_4H_{10}S^{+\cdot}$, 16.3); 64 ($S(O)_2$, 19.9); 57 (*t*-Bu^+, 100); 41 ($C_3H_5^{+\cdot}$, 46.1).

Peracetic acid oxidation of di-*t*-butyl trisulfide-2-oxide (156). The oxidation of **156** (1.09 g, 4.82 mmol) was carried out using CH_3CO_3H (40%) (-20°C, 5 h, 1.4 eq) according to procedure 2. Silica gel column chromatography using a 10% ethyl acetate/hexanes solution afforded the desired di-*t*-butyl trisulfide-1,1-dioxide (**145**) (0.41 g, 1.69 mmol, 35%) as a colorless solid. Analytical data were identical to the ones previously reported.

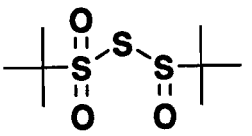
DMD oxidation of di-*t*-butyl trisulfide-2-oxide (156). The oxidation of **156** (0.98 g, 4.33 mmol) was carried out using DMD (0.05 M) (-78°C, 2 h, 1.2 eq) according to procedure 3. Silica gel column chromatography using a 10% ethyl acetate/hexanes

solution afforded the desired di-*t*-butyl trisulfide-1,1-dioxide (**145**) (0.89 g, 3.68 mmol, 85%) as a colorless solid. Analytical data were identical to the ones previously reported.

5.4.4.2. Decomposition of di-*t*-butyl trisulfide-1,1-dioxide (145)

The decomposition of di-*t*-butyl trisulfide-1,1-dioxide (**145**) (87 mg, 0.36 mmol) in $CDCl_3$ was followed by ^1H and ^{13}C NMR at room temperature. After 6 months under these conditions no decomposition occurred. The decomposition of **145** (198 mg, 0.82 mmol) at 80°C in CCl_4 gave di-*t*-butyl disulfide (**118b**) as sole product after 15 h (identify by NMR and gc). The condenser employed was equipped with a trap of wet pH paper. Clear evidence of sulfur dioxide evolution were given by the strongly acidic coloration of the pH paper by the end of the decomposition.

5.4.5. di-*t*-Butyl Trisulfide-1,1,3-Trioxide (157)



5.4.5.1. Synthesis of di-*t*-butyl trisulfide-1,1,3-trioxide (157)

***m*-CPBA oxidation of di-*t*-butyl trisulfide (118c).** The oxidation of **118c** (1.05 g, 5.00 mmol) was carried out using *m*-CPBA (-40°C,12 h, 3.5 eq) according to procedure 1. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) (1.02 g, 3.95 mmol, 79%) crystallized from *n*-pentane in the freezer as colorless needles; **Mp.** 80-100°C (**157** probably decomposed before reaching its melting point). **^1H and ^{13}C NMR** are reported in Table **12**. **MS** (CI (NH_3), 70 eV, 100°C) m/z (rel. intensity) 276 ($M(NH_4)^+$, 4.6); 260 ($M(NH_4)^+$-O, 3.6); 228 ($M(NH_4)^+$-S=O, 8.3); 172 (*t*-$BuS(O)_2SNH_4^+$, 7.0); 140 (*t*-$BuS(O)_2NH_4^+$, 47.6); 123 (*t*-$BuS(O)_2H_2^+$, 45.0); 57 (*t*-Bu^+, 100).

Peracetic acid oxidation of di-*t*-butyl trisulfide (118c). The oxidation of **118c** (0.93 g, 4.43 mmol) was carried out using CH_3CO_3H (-20°C, 12 h, 3.5 eq) according to procedure 2. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) (0.51 g, 1.99 mmol, 45%) crystallized from *n*-pentane in the freezer as colorless needles. The analytical data were identical to the ones previously reported.

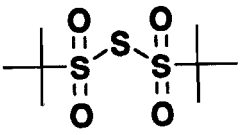
DMD oxidation of di-*t*-butyl trisulfide (118c). The oxidation of **118c** (0.56 g, 2.66 mmol) was carried out using DMD (0.08 M) (-78°C, 6 h, 3.2 eq) according to procedure 3. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) (0.617 g, 2.39 mmol, 90%) crystallized from *n*-pentane in the freezer as colorless needles. The analytical data were identical to the ones previously reported.

DMD oxidation of di-*t*-butyl trisulfide-1,1-dioxide (145).. The oxidation of **145** (0.50 g, 2.06 mmol) was carried out using DMD (0.08 M) (-78°C, 2 h, 1 eq) according to procedure 3. Roto-evaporation of the solvent afforded di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) (0.49 g, 1.92 mmol, 93%) as a colorless solid. Analytical data were identical to the ones previously reported.

5.4.5.2. Decomposition of di-*t*-butyl trisulfide-1,1,3-trioxide (157)

The decomposition of di-*t*-butyl trisulfide-1,1,3-trioxide (**157**) (31 mg, 0.12 mmol) in $CDCl_3$ was followed by ^1H and ^{13}C NMR at room temperature. After 2 weeks under these conditions, no traces of **157** could be detected. The decomposition products were identified by ^1H and ^{13}C NMR as a mixture of **159** (63%), **120b** (28%), **144** (3%) as well as 6% of a mixture of **161**, **163**, **164** and **206**.

5.4.6. di-*t*-Butyl Trisulfide-1,1,3,3-Tetraoxide (161)



5.4.6.1. Synthesis of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (161)

***m*-CPBA oxidation of di-*t*-butyl trisulfide (118c).** The oxidation of **118c** (0.92 g, 4.38 mmol) was carried out using *m*-CPBA (-40°C, 12 h, 4.5 eq) according to procedure 1. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (0.63 g, 2.32 mmol, 53%) was crystallized from *n*-pentane in the freezer as colorless needles; **Mp.** 85-105°C (**161** probably decomposed before reaching its melting point). **^1H and ^{13}C NMR** are reported in Table **12**. **MS** (CI (NH_3), 70 eV, 100°C) m/z (rel. intensity) 292 ($M(NH_4)^+$, 0.6); 260 ($M(NH_4)^+$-S, 3.6); 228 ($M(NH_4)^+$-$S(O)_2$, 6.3); 172 (*t*-$BuS(O)_2SNH_4^+$, 9.3); 140 (*t*-$BuS(O)_2NH_4^+$, 100.0); 123 (*t*-$BuS(O)_2H_2^+$, 82.5).

Peracetic acid oxidation of di-*t*-butyl trisulfide (118c). The oxidation of **118c** (0.42 g, 2.00 mmol) was carried out using CH_3CO_3H (-20°C, 12 h, 4.5 eq) according to procedure 2. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (0.14 g, 0.50 mmol, 25%) was crystallized from *n*-pentane in the freezer as colorless needles. Analytical data were identical to the ones previously reported.

DMD oxidation of di-*t*-butyl trisulfide (118c). The oxidation of **118c** (0.39 g, 1.86 mmol) was carried out using DMD (0.07 M) (-78°C, 6 h, 4.2 eq) according to procedure 3. The solvent was removed *in vacuo* at room temperature and di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (0.32 g, 1.19 mmol, 64%) was crystallized from *n*-pentane in the freezer as colorless needles. Analytical data were identical to the ones previously reported.

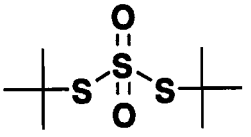
DMD oxidation of di-*t*-butyl trisulfide-1,1,3-trioxide (157).. The oxidation of **157** (0.617 g, 2.39 mmol) was carried out using DMD (0.07) (-78°C, 6 h, 1 eq) according to procedure 3. Roto-evaporation of the solvent afforded di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (0.52 g, 1.86 mmol, 78%) as a colorless solid. Analytical data were identical to the ones previously reported.

5.4.6.2. Decomposition of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (161)

The decomposition of di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) (37 mg, 0.13 mmol) in $CDCl_3$ was followed by ^1H and ^{13}C NMR at room temperature. After 1 month under these conditions, no traces of **161** could be detected. The decomposition products were identified by ^1H and ^{13}C NMR to be **159** (35%), **206** (35%), **164** (20%) as well as a mixture of **163**, **144**, **120b** and other *t*-butyl derivatives (10%)

5.4.7. Attempted Synthesis of Other di-*t*-Butyl Trisulfide-Polyoxides

Attempted preparation of di-*t*-butyl trisulfide-2,2-dioxide (162) by nucleophilic oxidation of di-*t*-butyl trisulfide-2-oxide (156). The oxidation of di-*t*-butyl trisulfide-2-oxide (**156**) (0.4-



0.5 g, 1.77-2.21 mmol) was attempted using H_2O_2/1N NaOH,[209] *t*-BuOOH/1N NaOH,[209] KO_2,[209] $KMnO_4$[200] and $NaIO_4$[100f] under the experimental conditions described in the literature. The reactions were followed by tlc and gc. When no reaction had taken place under the reported conditions, the reaction mixture was refluxed until partial decomposition of the starting material to a mixture of polysulfides. In all cases, the final products were a mixture of di-*t*-butyl di-, tri- and tetrasulfides that were characterized by NMR spectrometry and gc analysis.

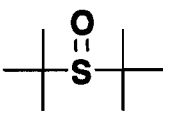
Attempted preparation of penta and hexaoxide derivatives of di-*t*-Butyl trisulfide by electrophilic oxidation of di-*t*-butyl trisulfide (118c). A variety of oxidation reactions of di-*t*-butyl trisulfide (**118c**) (0.5-1.0 g, 2.38-4.76 mmol) were attempted using excess *m*-CPBA (-40°C and rt., 12 h, 6-10 eq) and DMD (-78°C, 12 h, 6-10 eq) according to the procedures 1 and 3. In all cases, roto-evaporation of the solvent afforded di-*t*-butyl trisulfide-1,1,3,3-tetraoxide (**161**) as main product and no trace of penta or hexaoxide could be detected.

Attempted oxidation of di-*t*-butyl trisulfide-2-oxide (156) by 2, 3 and 4 equivalents of electrophilic oxidizing agent. A variety of oxidation reactions of di-*t*-butyl trisulfide-2-oxide (**156**) (0.3-0.5 g, 2.38-4.76 mmol) were attempted using *m*-CPBA (-40°C, 6-12 h, 2, 3 and 4 eq) and DMD (-78°C, 4 h, 2, 3 and 4 eq) according to procedures 1 and 3. Roto-evaporation of the solvent afforded various ratios of *t*-butyl sulfinic acid (**163**), *t*-butyl sulfonic acid (**164**), *t*-butyl-3-chlorobenzoate (**146**) and *t*-butyl *t*-butylsulfinate (**147**)[134c] as well as **145** and **120b**. The reaction products were identified by NMR spectroscopy, silica gel column chromatography and parallel synthesis (*vide infra*). In all cases, attempts to separate the reaction mixtures were unsuccessful.

5.4.8. Extension to the Oxidation of Other Polysulfides

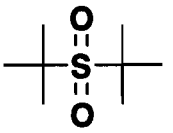
5.4.8.1. Oxidation of Sulfides

Preparation of di-*t*-butyl sulfoxide[235] (120a) by *m*-CPBA oxidation of di-*t*-butyl sulfide (118a). The oxidation of **118a** (1.1 g, 7.53 mmol)



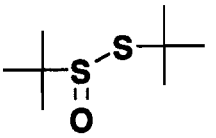
235 J. R. Shelton and K. E. Davis, *J. Am. Chem. Soc.*, **89**, 718 (1967).

was carried out using *m*-CPBA (rt., 1 h, 1.2 eq) according to procedure 1. A quantitative yield of di-*t*-butyl sulfoxide (**120a**) was obtained. **^{1}H NMR** ($CDCl_3$) δ: 1.34 (s, 18H) ppm. **^{13}C NMR** ($CDCl_3$) δ: 57.38, 25.36 ppm. **MS** (CI (NH_3), 70 eV, 30°C) m/z (rel. intensity) 163 ($MH^{+\cdot}$, 100.0); 107 ($MH^{+\cdot}$-*t*-Bu, 28.6).

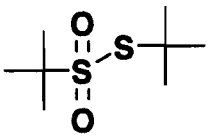


Preparation of di-*t*-butyl sulfone (121) by *m*-CPBA oxidation of di-*t*-butyl sulfoxide (120a). The oxidation of **120a** (0.52 g, 3.21 mmol) was carried out using *m*-CPBA (rt., 2 h, 1.2 eq) according to procedure 1. A high yield of di-*t*-butyl sulfone (**121**) was obtained (0.56 g, 3.15, 98%). **Mp.** 90-105°C; **^{1}H NMR** ($CDCl_3$) δ: 1.48 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 64.69, 25.96 ppm.

5.4.8.2. Oxidation of Disulfides



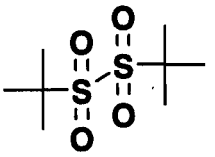
Preparation of di-*t*-butyl disulfide-1-oxide (120b). Compound **120b** was prepared in almost quantitative yield by Freeman's[203b] procedure. Similar results were obtained using DMD following procedure 3. **^{1}H NMR** ($CDCl_3$) δ: 1.38 (s, 9H) 1.56 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 59.35, 48.56, 32.25, 24.19 ppm.



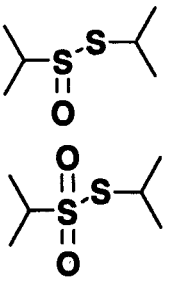
Preparation of di-*t*-butyl disulfide-1,1-dioxide (144). Compound **144** was prepared in low yield by Freeman's[203b] procedure. However, the 1 equivalent DMD (-78°C, 6h, 1 eq) oxidation of **120b** and the 2 equivalents DMD (-78°C, 6h, 2 eq) oxidation of **118b** gave a high yield of **144** (83%, 75% respectively) under the conditions described in procedure 3. In all cases, compound **144** was purified by silica gel chromatography using benzene as solvent. Anhydrous conditions were crucial in both cases. **^{1}H NMR** ($CDCl_3$) δ: 1.45 (s, 9H) 1.60 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 68.09, 56.39, 31.53, 23.73 ppm. The experiments related to the solvent and reagent concentration dependence are reported in the experimental part of Chapter 4.

Attempted preparation of di-*t*-butyl disulfide-1,1,2-trioxide (166). The preparation of di-*t*-butyl disulfide-1,1,2-trioxide (**166**) and di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) was attempted by oxidation of the corresponding disulfide **118b** (0.8-1.2 g, 4.49-6.74 mmol) using *m*-CPBA (0°C to -40°C, 1-8 days, 3-5 eq) according to procedure 1. Evaporation of the solvent *in vacuo* and at low temperature (10°C) gave the

diastereomeric mixture of di-*t*-butyl-sulfinic anhydride (**168**). **168a**: **^{1}H NMR** ($CDCl_3$) δ: 1.18 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 60.43, 21.51 ppm.. **168b**: **^{1}H NMR** ($CDCl_3$) δ: 1.17 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 60.07, 21.37 ppm. After 2 h at room temperature **168** was converted to a mixture of *t*-butyl sulfinic (**163**) acid, *t*-butyl sulfonic acid (**164**), *t*-butyl *m*-chlorobenzoate (**146**) and *t*-butyl *t*-butyl sulfinate (**147**). Compounds **163** and **164** were identified by ^{1}H and ^{13}C NMR from the crude mixture and were characterized from parallel synthesis (experimental of Chapter 4) as well as literature reports.[134c] **163**: **^{1}H NMR** ($CDCl_3$) δ: 1.19 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 57.46, 21.42 ppm; **164**: **^{1}H NMR** ($CDCl_3$ partly soluble) δ: 1.43 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 58.07, 24.49 ppm. Compound **146** and **147** were obtained by silica gel column chromatography. Elution with 13% ethyl acetate/hexanes gave **146** and further elution with 25% ethyl acetate/hexanes afforded **147**. **146** (9%) **^{1}H NMR** ($CDCl_3$) δ: 1.60 (s, 9H), 7.31 (m, 4H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 164.46, 134.30, 133.78, 132.40, 129.51, 129.48, 127.53, 81.67, 28.12 ppm; **147** (19%): **^{1}H NMR** ($CDCl_3$) δ: 1.42 (s, 9H), 1.15 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 82.55, 56.76, 29.40, 21.60 ppm. (The procedure of low temperature NMR detection of **166** is reported in the experimental part of Chapter 4)



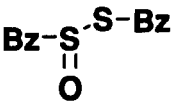
Preparation of di-*t*-butyl disulfide-1,1,2,2-tetraoxide (165). The preparation of di-*t*-butyl disulfide-1,1,2,2-tetraoxide (**165**) was achieved by oxidation of **144** (0.82 g, 3.74 mmol) using *m*-CPBA (-20°C, 8 days, 2.5 eq) according to procedure 1. Evaporation of the solvent *in vacuo* and silica gel chromatography using a 25% ethyl acetate/hexanes solution afforded the desired **165** (0.53, 2.20 mmol, 58%) as a solid. The same experiment was repeated using DMD (-78°C, 6 h, 2.5 eq) and gave **165** (76%) according to procedure 3; **Mp.** 63-92°C (**165** probably decomposed before reaching its melting point); **^{1}H NMR** ($CDCl_3$) δ: 1.63 (s, 18H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 72.67, 24.60 ppm.



Preparation of diisopropyl disulfide-1-oxide (123b) and diisopropyl disulfide-1,1-dioxide (169). Compounds **123b** and **169** were obtained using *m*-CPBA according to the known procedure[127k] (similar to procedure 1). The oxidation was also achieved using 1 and 2 equivalents of DMD according to procedure 3. **123b** (quant.): **^{1}H NMR** ($CDCl_3$) δ: 3.51 (h, 1H), 3.09 (h, 1H), 1.38 (dd, 6H), 1.27 (dd, 6H)

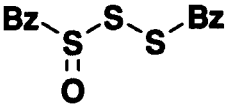
ppm; ^{13}C NMR ($CDCl_3$) δ: 55.08, 38.11, 24.45, 24.24, 16.38, 15.53 ppm. **169** (93%): ^{1}H NMR ($CDCl_3$) δ: 3.62 (h, 1H), 3.31 (h, 1H) 1.42 (d, 6H), 1.48 (d, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ: 63.48, 42.92, 24.24, 16.28 ppm.

Preparation of benzyl disulfide-1-oxide (123c). Compound **123c** was prepared by oxidation of the commercially available benzyl disulfide (**122c**) using the procedure described for the synthesis of **120b**. ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, 10H), 4.31 (s, 2H), 4.27 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 134.68, 133.85, 130.33, 130.24, 129.83, 128.29, 128.02, 127.42, 62.03, 36.22 ppm.

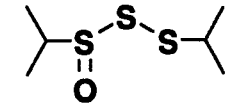


5.4.8.3. Oxidation of Trisulfides

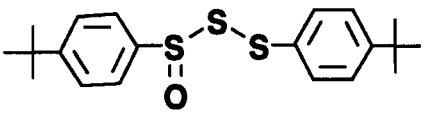
Preparation of benzyl trisulfide-1-oxide (170). The oxidation of benzyl tridulfide (**115d**) (0.42 g, 1.51 mmol) was carried out using *m*-CPBA (-20°C, 5h, 1.1 eq.) according to procedure 1. Low temperature (5°C) evaporation under high vacuum (1 mm of Hg) afforded a quantitative yield of benzyl trisulfide-1-oxide (**170**) which was significantly decomposed after 2 h at room temperature. **Mp.**: 50-70°C (**170** probably decomposed before reaching its melting point); ^{1}H NMR ($CDCl_3$) δ: 7.34 (m, 10H), 4.31 (d, 2H), 4.12 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 135.76, 130.34, 130.27, 129.56, 128.81, 128.70, 128.58, 127.84, 62.29, 45.20 ppm.



Preparation of diisopropyl trisulfide-1-oxide (172). The oxidation of diisopropyl trisulfide (**171**) (0.54 g, 2.97 mmol) was carried out using *m*-CPBA (0°C, 2h, 1.1 eq) according to procedure 1. The crude product was chromatographed over silica gel with benzene and afforded **172** (72%) as a liquid. ^{1}H NMR ($CDCl_3$) δ: 3.16 (m, 2H), 1.25 (m, 12H) ppm; ^{13}C NMR ($CDCl_3$) δ: 55.33, 42.37, 22.28, 22.21, 16.15, 15.53 ppm.



Oxidation of norbornentrithiolane (138). The oxidation of norbornentrithiolane[200] (**138**) (0.760 g, 4 mmol) was achieved using DMD (0.07) (-78°C, 2 h, 1 eq) according to procedure 3. The crude mixture was chromatographed over silica gel with 25% ethyl acetate/pentane and afforded similar results to those reported by Bartlett and Ghosh.[200]



Preparation of di(*p*-*t*-butyl-phenyl) trisulfide-1-oxide (173). The oxidation of di(*p*-*t*-butyl-phenyl) trisulfide **(115c)** (0.82 g, 2.26 mmol) using *m*-CPBA (0°C, 2h, 1.1 eq) or DMD (-78°C, 1h, 1 eq) afforded **173** (87%, 88% respectively) by crystallization from hexanes according to procedures 1 and 3; **Mp.** 128-130°C. **^{1}H NMR** ($CDCl_3$) δ: 7.29 (q, 4H), 7.43 (q, 4H), 1.32 (s, 9H), 1.30 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 157.52, 154.98, 140.11, 136.27, 127.38, 126.42, 125.63, 124.53, 35.21, 34.89, 31.09, 31.00 ppm.

Attempted oxidation of di(p-*t*-butyl-phenyl) trisulfide-1-oxide (173). Further oxidation of **173** using excess *m*-CPBA or DMD (rt., 24h, 2 eq) according to procedure 1 and 3 only gave unreacted **173**.

Attempted preparation of *t*-butyl isopropyl trisulfide-1-oxide.

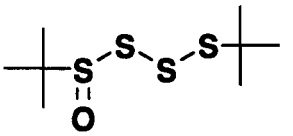
The oxidation of *t*-butyl isopropyl trisulfide **(116a)** (0.50 g, 2.55 mmol) using *m*-CPBA (0°C., 2 h, 1.2 eq) and DMD (0.06 M) (-78°C, 6h, 2 eq) according to procedures 1 and 3 resulted in a mixture of *t*-butyl isopropyl trisulfide-1-oxide (55%) and *t*-butyl isopropyl trisulfide-3-oxide (45%) that could not be separated. The percentage of each of them was determined by measuring the integration ratios on proton NMR in $CDCl_3$. ***t*-Butyl isopropyl trisulfide-1-oxide: ^{1}H NMR** ($CDCl_3$) δ: 3.05 (h, 1H), 1.40 (s, 9H), 1.32 (dd, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 59.98, 42.25, 23.32, 22.07, 21.96 ppm. ***t*-Butyl isopropyl trisulfide-3-oxide: ^{1}H NMR** ($CDCl_3$) δ: 3.05 (h, 1H), 1.40 (s, 9H), 1.32 (dd, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 55.45, 48.12, 29.56, 16.17, 15.35 ppm.

The oxidation of **116a** was also attempted using 2-benzenesulfonyl-3-*p*-nitrophenyl oxaziridine under the experimental conditions described in the literature.[217] Both isomers, *t*-butyl isopropyl trisulfide-1-oxide (40%) and *t*-butyl isopropyl trisulfide-3-oxide (60%), were obtained. The ratios of each of them were measured by proton NMR in $CDCl_3$.

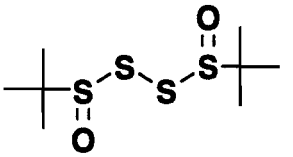
Attempted preparation of *t*-butyl-*p*-chlorobenzyl trisulfide-1-oxide. The oxidation of *t*-butyl-*p*-chlorobenzyl trisulfide **(116d)** (0.41 g, 1.47 mmol) using DMD (0.06 M) (-78°C, 1h, 1 eq) according to procedure 3 resulted in a mixture of *t*-butyl-*p*-chlorobenzyl trisulfide-1-oxide (62%) and *t*-butyl-*p*-chlorobenzyl trisulfide-3-oxide (38%) that could not be separated. The percentage of each of them was determined by measuring the integration ratios on proton NMR in $CDCl_3$. ***t*-Butyl-*p*-chlorobenzyl trisulfide-1-oxide: ^{1}H NMR** ($CDCl_3$) δ: 7.25 (m, 4H), 4.01 (s, 2H), 1.39 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ:

60.42, 44.10, 23.58 ppm. ***t*-Butyl-*p*-chlorobenzyl trisulfide-3-oxide:** **^{1}H NMR** ($CDCl_3$) δ: 7.25 (m, 4H), 4.31 (s, 2H), 1.40 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 61.32, 48.85, 29.96 ppm.

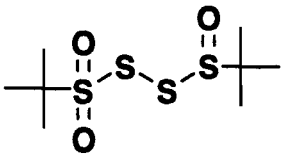
5.4.8.4. Oxidation of Tetrasulfides



Preparation of di-*t*-butyl tetrasulfide-1-oxide (120d). The oxidation of di-*t*-butyl tetrasulfide (**118d**) (1.05 g, 4.34 mmol) was carried out using *m*-CPBA (0°C, 2 h, 1.2 eq) according to procedure 1. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on alumina using a 13% ethyl acetate/hexanes solution to give di-*t*-butyl tetrasulfide-1-oxide (**120d**) (0.82 g, 3.17 mmol, 73%) as a solid; **Mp.** 65-68°C (lit.[197] 68-78°C). **^{1}H NMR** ($CDCl_3$) δ: 1.33 (s, 9H) 1.32 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$) δ: 60.60, 49.91, 29.76, 23.82 ppm.

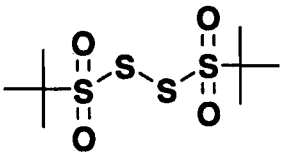


Preparation of di-*t*-butyl tetrasulfide-1,4-dioxide (174). The oxidation of di-*t*-butyl tetrasulfide (**118d**) (0.50 g, 2.06 mmol) was carried out using *m*-CPBA (-40°C, 6 h, 2.2 eq) according to procedure 1. The solvent was removed at low temperature (-20°C) under high vacuum (2.5 mm Hg) to give a diastereomeric mixture of di-*t*-butyl tetrasulfide-1,4-dioxide (**174**) (0.53 g, 1.96 mmol, 95%) as a pale yellow solid that was recrystallized in the freezer from a 5% CH_2Cl_2/*n*-pentane solution; **Mp.** 50-70°C (**174** probably decomposed before reaching its melting point) **^{1}H NMR** ($CDCl_3$) δ: 1.41 (s, 9H) 1.37 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$) δ: 61.51, 61.20, 23.77, 23.50 ppm.



Preparation of di-*t*-butyl tetrasulfide-1,1,4-trioxide (175). The oxidation of di-*t*-butyl tetrasulfide (**118d**) (0.47 g, 1.94 mmol) was carried out using *m*-CPBA (-40°C, 6 h, 3.5 eq) according to procedure 1. The solvent was removed at low temperature (-20°C) under high vacuum (2.5 mm Hg) to give di-*t*-butyl tetrasulfide-1,1,4-trioxide (**175**) (0.49 g, 1.71 mmol, 88%) as a pale yellow solid that was recrystallized in the freezer from a 20% CH_2Cl_2/*n*-pentane solution. **Mp.** 85-100°C (**175** probably decomposed before reaching its melting point). **^{1}H NMR** ($CDCl_3$) δ: 1.52 (s, 9H) 1.45 (s, 9H) ppm. **^{13}C NMR** ($CDCl_3$) δ: 71.16, 62.33, 23.84, 23.72 ppm.

Isolation of di-*t*-butyl tetrasulfide-1,1,4,4-tetraoxide (159). Compound **159** was isolated from the decomposition of **130, 157** and **161** by silica gel column chromatography using a 25% solution of ethyl acetate/hexanes. It was recrystallized in hexanes. **Mp.** 80-130°C (**159** probably decomposed before reaching its melting point); **^{1}H NMR** ($CDCl_3$) δ: 1.53 (s, 18H) ppm. **^{13}C NMR** ($CDCl_3$) δ: 72.10, 24.18 ppm.

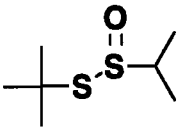


5.5. Chapter 4

5.5.1. Unsymmetrical *t*-Butyl Isopropyl Polysulfide-Polyoxides

5.5.1.1. *t*-Butyl isopropyl polysulfide-monoxides

Preparation of *t*-butyl isopropyl disulfide-2-oxide (179). The synthesis of **179** was achieved by a slightly modified version of the procedure reported by Block.[92a] A solution of isopropyl sulfinyl chloride (**180**) (0.631 g, 5 mmol) in 25 mL of ether was added dropwise over a 1 h period under nitrogen to an ice cooled solution of *t*-butyl mercaptan (0.449 g, 5 mmol) and pyridine (0.400 g, 5 mmol) in 50 mL of ether. A heavy white precipitate formed during addition. After stirring for an additional 1 h at 0°C, the reaction mixture was washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on silica gel using a 20% ethyl acetate/hexanes solution to give *t*-butyl isopropyl disulfide-2-oxide (**180**) (0.756 g, 4.20 mmol, 84%) as a liquid. The first fraction was di-*t*-butyl trisulfide-2-oxide (**156**). **179**; **^{1}H NMR** ($CDCl_3$) δ: 3.17 (h, 1H), 1.50 (s, 9H), 1.32 (dd, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 55.28, 48.68, 32.13, 16.49, 15.84 ppm.



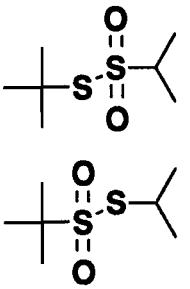
Preparation of *t*-butyl isopropyl trisulfide-3-oxide (190). The synthesis of **190** was achieved by a slightly modified version of the procedure reported by Bleeker.[204] A solution of isopropyl sulfinyl chloride (**180**) (0.631 g, 5 mmol) in 25 mL of ether was added dropwise over a 1 h period under nitrogen to an ice cooled solution of *t*-butyl hydrodisulfide (**148**) (0.610 g, 5 mmol) and pyridine (0.400 g, 5 mmol) in 50 mL of ether. A heavy white precipitate formed during addition. After stirring for an additional 5 h at 0°C, the reaction mixture was washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on silica gel using a 13% ethyl acetate/hexanes solution. The first fraction was di-*t*-butyl tetrasulfide (**118d**) (10%); the second fraction *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) (8%) (*vide infra*); the third fraction was *t*-butyl isopropyl trisulfide-3-oxide (**190**) (0.795 g, 3.75 mmol, 75%) as a liquid. The last fraction was diisopropyl disulfide-1-oxide (**123b**) (7%). **190**; **^{1}H NMR** ($CDCl_3$) δ: 3.05 (h, 1H), 1.40 (s, 9H), 1.32 (dd, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 55.45, 48.12, 29.56, 16.17, 15.35 ppm.

Decomposition of *t*-butyl isopropyl trisulfide-3-oxide (190). The decomposition of **190** (70 mg, 0.33 mmol) in $CDCl_3$ was followed by ^{1}H and ^{13}C NMR at room temperature. After 4 days under these conditions, no traces of **190** could be detected. The decomposition products were identified by ^{1}H and ^{13}C NMR to be *t*-butyl tetrasulfide (**118d**) (40%), *t*-butyl isopropyl trisulfide-3,3-dioxide (**191**) (15%), diisopropyl disulfide-1-oxide (**123b**) (15%) and diisopropyl disulfide-1,1-dioxide (**169**) (30%). The decomposition was repeated at 45°C for 12 h using 300 mg of *t*-butyl isopropyl trisulfide-3-oxide (**190**). The reaction mixture was partially separated by silica gel chromatography using a 10% ethyl acetate/hexanes solution. The results obtained were similar to the one previously reported at room temperature.

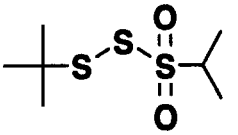
Preparation of *t*-butyl isopropyl trisulfide-2-oxide (196). Compound **196** was prepared according to Field's procedure.[179a] *t*-Butyl isopropyl trisulfide-2-oxide (**196**) was purified by column chromatography using a 13% ethyl acetate/hexanes solution as eluent and gave a colorless oil (82%); **196**; **^{1}H NMR** ($CDCl_3$) δ: 3.49 (m, 1H), 1.45 (s, 9H), 1.37 (dd, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 51.54, 39.84, 31.62, 24.05, 23.25 ppm.

Decomposition of *t*-butyl isopropyl trisulfide-2-oxide (196). The decomposition of **196** (65 mg, 0.31 mmol) in CCl_4 was reflux for 12 h until no traces of **196** could be detected by tlc. The decomposition products were identified by ^1H and ^{13}C NMR to be a scrambled mixture of the possible symmetrical and unsymmetrical di- and trisulfides. These results were confirmed by gc analysis.

5.5.1.2. *t*-Butyl isopropyl polysulfide-dioxides

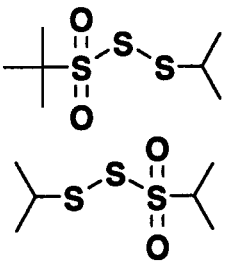


DMD oxidation of *t*-butyl isopropyl disulfide-2-oxide (179). The DMD (0.06 M, -78°C, 1.2 eq) oxidation of *t*-butyl isopropyl disulfide-2-oxide (**179**) (0.756 g, 4.20 mmol) was carried out according to procedure 3. After evaporation of the solvent, the crude mixture was analysed by ^1H and ^{13}C NMR and presented a mixture of the four possible symmetrical and unsymmetrical disulfide-1,1-dioxides, **185a** (55%), **185b** (30%), **169** (10%), **144** (5%). These percentages were estimated from the crude NMR spectrum according to the calibration experiments reported earlier. Silica gel chromatography using 10% ethyl acetate/hexanes as eluent gave a mixture of *t*-butyl isopropyl disulfide-1,1-dioxide (**185b**) (85%) and di-*t*-butyl disulfide-1,1-dioxide (**144**) (15%) as a first fraction and *t*-butyl isopropyl disulfide-2,2-dioxide (**185a**) (83%) and di isopropyl disulfide-1,1-dioxide (**169**) (17%) as second fraction. The similarity of the ^{13}C NMR signals between the symmetrical and unsymmetrical disulfide-dioxides and the very different ratio of the two derivatives in each fraction allowed a clear NMR characterization of the unsymmetrical disulfide-dioxide; **185b**; **^1H NMR** ($CDCl_3$) δ: 3.63 (h, 1H), 1.46 (s, 9H), 1.42 (d, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 68.57, 43.41, 24.55, 23.74 ppm. **185a**; **^1H NMR** ($CDCl_3$) δ: 3.29 (h, 1H), 1.51 (s, 9H), 1.39 (d, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 63.88, 55.17, 31.05, 16.04 ppm. *t*-Butyl isopropyl disulfide-1,1-dioxide (**185b**) was also isolated from the decomposition of di-*t*-butyl trisulfide-1-oxide (**120c**) in the presence of isopropyl sulfinyl chloride (**179**) (*vide infra*).



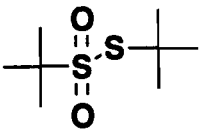
Preparation of *t*-butyl isopropyl trisulfide-3,3-dioxide (191). Isopropyl sulfonyl chloride (**197**) was most conveniently prepared according to the Douglass procedure[220] using four equivalents of acetic anhydride. A solution of isopropyl sulfonyl chloride (**197**) (0.257 g, 1.81 mmol) in 15 mL of ether was added dropwise over a 1 h period under nitrogen to an ice cooled solution of *t*-butyl hydrodisulfide (**148**) (0.221 g, 1.81 mmol) and pyridine (0.160 g, 2

mmol) in 25 mL of ether. After stirring for an additional 5 h at room temperature, the reaction mixture was washed with 2x25 mL portions of water, 3x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $MgSO_4$, filtered and evaporated. The solvent was removed *in vacuo* to give an oily residue that was chromatographed on silica gel using a 13% ethyl acetate/hexanes solution to give *t*-butyl isopropyl trisulfide-3,3-dioxide **(191)** (0.090 g, 0.39 mmol, 22%) as a liquid. The first fraction was *t*-butyl tetrasulfide **(118d)** (65%). **191**; **^{1}H NMR** ($CDCl_3$) δ: 3.52 (h, 1H), 1.42 (d, 6H), 1.38 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 61.85, 50.17, 30.34, 17.02 ppm.



DMD oxidation of *t*-butyl isopropyl trisulfide-2-oxide (196). The DMD (0.05 M, -78°C, 1.2 eq) oxidation of *t*-butyl isopropyl trisulfide-2-oxide **(196)** (1.053 g, 4.97 mmol) was carried out according to procedure 3. After evaporation of the solvent, the crude mixture was analysed by ^{1}H and ^{13}C NMR and presented a close to equimolar mixture of the four possible symmetrical and unsymmetrical trisulfide-1,1-dioxides, **199a** (26%), **145** (25%), **191** (26%) and **199b** (23%). These percentages were estimated from the crude NMR spectrum according to the calibration experiments reported earlier. Silica gel chromatography using 10% ethyl acetate/hexanes as eluent gave a mixture of *t*-butyl isopropyl trisulfide-1,1-dioxide **(199a)** (85%) and di-*t*-butyl trisulfide-1,1-dioxide **(145)** (15%) as a first fraction and *t*-butyl isopropyl trisulfide-3,3-dioxide **(191)** (83%) and diisopropyl trisulfide-1,1-dioxide **(199b)** (17%) as second fraction. The similarity of the ^{13}C NMR signals between the symmetrical and unsymmetrical trisulfide-dioxides and the previous characterization of one of the two derivatives in each fraction allowed a clear NMR characterization of the unknown trisulfide-dioxides; **199a**; **^{1}H NMR** ($CDCl_3$) δ: 3.38 (h, 1H), 1.48 (s, 9H), 1.39 (d, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 70.28, 43.32, 24.02, 21.92 ppm. **199b**; **^{1}H NMR** ($CDCl_3$) δ: 3.36 (h, 1H), 3.58 (s, 1H), 1.41 (d, 6H), 1.36 (d, 6H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 60.30, 42.88, 21.92, 16.36 ppm. *t*-Butyl isopropyl trisulfide-1,1-dioxide **(199a)** was also isolated from the decomposition of di-*t*-butyl trisulfide-1,3-dioxide **(130)** in the presence of isopropyl sulfinyl chloride **(179)**

5.5.2. Preparation of di-*t*-Butyl Disulfide-1,1-Dioxide (144)



5.5.2.1. Solvent Effect

***m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (120b) in acetic acid.** A solution of *m*-CPBA (0.487 g, 2.83 mmol, 1.1 eq) in 10 mL of freshly distilled acetic acid was added dropwise to an ice cooled solution of **120b** (0.5 g, 2.58 mmol) and *t*-butyl chloride (0.120 g, 1.3 mmol) in 5 mL of acetic acid under abhydrous conditions. *t*-Butyl chloride was used as an internal standard. After stirring for 2 h, the reaction mixture was evaporated and the NMR of the crude mixture showed no trace of di-*t*-butyl disulfide-1,1-dioxide (**144**) but *t*-butyl sulfinic acid (**163**) as major compound (87%). The chemical shifts observed for **163** were similar to those reported in the literature.[134c] **163**: **^{1}H NMR** ($CDCl_3$) δ: 1.19 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 57.46, 21.42 ppm.

***m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (120b) in methylene chloride.** A solution of *m*-CPBA (0.487 g, 2.83 mmol, 1.1 eq) in 10 mL of anhydrous CH_2Cl_2 was added dropwise to an ice cooled solution of **120b** (0.5 g, 2.58 mmol) and *t*-butyl chloride (0.120 g, 1.3 mmol) in 5 mL of anhydrous CH_2Cl_2 under nitrogen. *t*-Butyl chloride was used as an internal standard. After stirring for 5 h at 0°C, the reaction mixture was kept at -78°C for 30 minutes. The *m*-CBA that crystallized was collected and the NMR of the crude mixture showed 19% of di-*t*-butyl disulfide-1,1-dioxide (**144**) plus a complex mixture of compounds reported earlier. The chemical shifts observed for **144** were similar to those reported earlier as well as in the literature.[203]

***m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (120b) in toluene.** A solution of *m*-CPBA (0.487 g, 2.83 mmol, 1.1 eq) in 10 mL of dried toluene was added dropwise to an ice cooled solution of **120b** (0.5 g, 2.58 mmol) and *t*-butyl chloride (0.120 g, 1.3 mmol) in 5 mL of toluene under nitrogen. *t*-Butyl chloride was used as an internal standard. After stirring for 7 h at 0°C, the reaction mixture was kept at -78°C for 30 minutes. The *m*-CBA that crystallized was filtered and the NMR of the crude mixture showed 37% of di-*t*-butyl disulfide-1,1-dioxide (**144**), 10% of unreacted **120b** plus a complex mixture of compounds reported earlier. The chemical shifts observed for **144** were similar to those reported earlier as well as in the literature.[203]

***m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (120b) in 50/50 carbon tetrachloride and *n*-pentane.** A solution of *m*-CPBA (0.487 g, 2.83 mmol, 1.1 eq) in 10 mL of dried CCl_4 was added dropwise to an ice cooled solution of **120b** (0.5 g, 2.58 mmol) and *t*-butyl chloride (0.120 g, 1.3 mmol) in 5 mL of dried *n*-pentane under nitrogen. *t*-Butyl chloride was used as an internal standard. After stirring for 3 days at room temeperature and 2 h at reflux, the reaction mixture was kept at -78°C for 30 minutes. The *m*-CBA that crystallized was filtered and the NMR of the crude mixture showed 48% of di-*t*-butyl disulfide-1,1-dioxide (**144**), 10% of unreacted **120b** plus a complex mixture of compounds reported earlier. The chemical shifts observed for **144** were similar to those reported earlier as well as in the literature.[203]

5.5.2.2. Concentration effect

DMD oxidation of di-*t*-butyl disulfide-1-oxide (120b) in acetone. A 0.05 M dried solution of DMD (20mL, 1 eq) in acetone was added dropwise to an ice cooled solution of **120b** (0.2 g, 1.03 mmol) and *t*-butyl chloride (0.046 g, 0.5 mmol) in 30 mL of dried acetone. *t*-Butyl chloride was used as an internal standard and the relative concentration of **120b** was 0.023 M. After stirring for 1 h at -78°C the solvent was evaporated and the NMR of the crude mixture showed 83% of di-*t*-butyl disulfide-1,1-dioxide (**144**) plus a complex mixture of compounds reported earlier. The chemical shifts observed for **144** were similar to those reported earlier as well as in the literature.[203]

***m*-CPBA oxidation of di-*t*-butyl disulfide-1-oxide (120b) at low concentration in methylene chloride.** A solution of *m*-CPBA (0.195 g, 1.13 mmol, 1.1 eq) in 50 mL of anhydrous CH_2Cl_2 was added dropwise to an ice cooled solution of **120b** (0.2 g, 1.03 mmol) and *t*-butyl chloride (0.046 g, 0.5 mmol) in 50 mL of anhydrous CH_2Cl_2 under nitrogen. *t*-Butyl chloride was used as an internal standard and the relative concentration of **120b** was 0.01. The reaction mixture was stirred for 12 h at -78°C. The *m*-CBA that crystallized was filtered and the NMR of the crude mixture showed 64% of di-*t*-butyl disulfide-1,1-dioxide (**144**) plus a complex mixture of compounds reported earlier as well as significant quantities of residual *m*-CBA. The chemical shifts observed for **144** were similar to those reported earlier as well as in the literature.[203]

5.5.3. NMR Rate Measurements

The kinetic experiments were performed on a XL300 spectrometer at 45°C and using *t*-butyl chloride (0.5 eq) as internal standard. A 5 mm NMR tube containing a solution of di-*t*-butyl trisulfide-1-oxide (**120c**) and the internal standard in various solvents (benzene-d_6, chloroform-*d*, acetone-d_6 acetonitrile-d_3) was allowed to equilibriate at 45°C in the NMR probe for 15 mins. ^{1}H or ^{13}C NMR spectra were acquired (32 or 1024 transients respectively) at various intervals over a period of 12 h. The rates were calculated by measuring the peak heights of product formed or reactant consumed and the peak height of the internal standard. Considering that the concentration of *t*-butyl chloride was known and constant, the concentration of the different products and reagent were easily obtained at any time. Plotting the $\ln_{rel.conc.}$ vs time, the first order rate could be calculated from the slope of the linear plots obtained.

Some of these experiments were repeated using traces of radical inhibitors (benzoquinone or 4-*t*-butyl catechol). In both cases, normal decomposition of di-*t*-butyl trisulfide-1-oxide (**120**) was observed.

5.5.4. Trapping Experiments

Decomposition of di-*t*-butyl trisulfide-1-oxide (120c) in the presence of 0.5 equivalent of isopropyl sulfinyl chloride (180). The decomposition of a solution of di-*t*-butyl trisulfide-1-oxide (**120c**) (300 mg, 1.33 mmol) and isopropyl sulfinyl chloride (**180**) (84 mg, 0.66 mmol, 0.5 eq) in 10 ml of $CHCl_3$ was carried out at room temperature for a week or 50°C for 12 h. The ^{1}H and ^{13}C NMR of the crude mixtures were similar in both cases. The partial separation of the reaction mixtures by silica gel chromatography and the careful analysis of the crude NMR spectra allowed the detection of the decomposition products of di-*t*-butyl trisulfide-1-oxide (**120c**), *t*-butyl isopropyl trisulfide-3-oxides (**190**), the mixed decomposition as well as *t*-butylsulfinyl chloride (**149**). Pure samples of **149** were prepared according to literature procedures.[116,204] **149**; **^{1}H NMR** ($CDCl_3$) δ: 1.36 (s, 9H) ppm; **^{13}C NMR** ($CDCl_3$) δ: 64.24, 22.23 ppm. The various decomposition products are reported in Table 17 and were determined by comparison of the detected signals with those of previously characterized compounds.

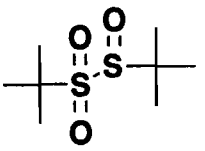
The relative concentration of these decomposition products were estimated according to the calibration experiments reported earlier.

Decomposition of di-*t*-butyl trisulfide-1,3-dioxide (130) in the presence of 1 equivalent of isopropyl sulfinyl chloride (180). The decomposition of a solution of di-*t*-butyl trisulfide-1,3-dioxide **(130)** (300 mg, 1.24 mmol) and isoprpoyl sulfinyl chloride **(180)** (156 mg, 1.24 mmol, 1 eq) in 10 ml of $CHCl_3$ was carried out at room temperature for 12 h. The ^1H and ^{13}C NMR of the crude mixtures clearly revealed the formation of *t*-butyl sulfinyl chloride **(149)** (~40%). The partial separation of the reaction mixtures by silica gel chromatography and the careful analysis of the crude NMR spectra allowed the detection of the decomposition products of di-*t*-butyl trisulfide-1,3-dioxide **(130)**, *t*-butyl isopropyl trisulfide-1,3-dioxides (could not be detected) and the mixed decomposition. The various decomposition products are reported in Scheme 72 and were determined by comparison of the detected signals with those of previously characterized compounds in most cases. The relative concentration of these decomposition products were estimated according to the calibration experiments reported earlier.

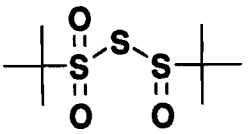
5.5.5. Low Temperature Oxidation Experiments

General procedure for the low temperature *m*-CPBA oxidation experiments. A typical procedure is the detection of di-*t*-butyl disulfide-1,2-dioxide **(167)**. The oxidation of di-*t*-butyl disulfide-1-oxide **(120b)** (150 mg, 0.77 mmol) dissolved in 0.5 mL of dry $CDCl_3$ was achieved by the slow addition of pure anhydrous *m*-CPBA (>99%) (133 mg, 0.77 mmol, 1 eq) partially dissolved in 2 mL of $CDCl_3$. The reaction mixture was stirred for 4 days at -55°C under nitrogen using a cooling system. The reaction was carried out in deuterated chloroform and most of the *m*-CPBA and *m*-CBA formed were not soluble at this temperature. The reaction mixture was then filtered using a customized piece of equipment that allowed the filtration to take place at a temperature lower than -40°C. The filtration equipment was a two-necked flask (5 mL) placed in the cooling bath. One outlet was connected to the vacuum hose and the other to a coarse filtration Schlenk device that was surrounded by a jacket filled with dry ice. Using a pipette that had previously been stored in dry ice, the reaction mixture was quickly transferred to the bottom of the Schlenk tube. Because of a moderate vaccum, the

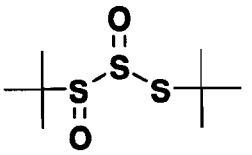
solution went through the filtrate before it had frozen. After removal of the jacket, Schlenk and vacuum hose, the reaction mixture was transferred into a 5 mm NMR tube that was kept in dry ice (transfer by frozen pipette). The spectrometer (Jeol 270) was cooled to -100°C and the sample was kept in dry ice. The transfer of the NMR tube from the dry ice to the probe of the spectrometer was done in 30-60 seconds, the temperature of the probe remained below -60°C and the sample was still frozen (**Mp.** of $CDCl_3$ = -64°C). Then, the temperature of the spectrometer was set to -45°C, the temperature of the sample was allowed to stabilize for 0.5 h and the ^1H and ^{13}C NMR spectra were recorded at various temperatures.



Low temperature detection of di-*t*-butyl disulfide-1,1,2-trioxide (166). The oxidation of di-*t*-butyl disulfide-1,1-dioxide **(144)** (200 mg, 0.95 mmol) dissolved in 0.5 mL of dry $CDCl_3$ was achieved by the slow addition of pure anhydrous *m*-CPBA (>99%) (164 mg, 0.95 mmol, 1 eq) partially dissolved in 2 mL of $CDCl_3$. After 5 h at -30°C the reaction mixture was treated as previously described.



Low temperature detection of di-*t*-butyl trisulfide-1,1,3-trioxide (157). The oxidation of di-*t*-butyl trisulfide-1,3-dioxide **(130)** (200 mg, 0.83 mmol) dissolved in 0.5 mL of dry $CDCl_3$ was achieved by the slow addition of pure anhydrous *m*-CPBA (>99%) (167 mg, 0.97 mmol, 1.1 eq) partially dissolved in 2 mL of $CDCl_3$. After 1 h at -40°C the reaction mixture was treated as previously described.

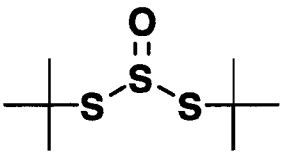


Low temperature detection of di-*t*-butyl trisulfide-1,2-dioxide (158). The oxidation of di-*t*-butyl trisulfide-2-oxide **(156)** (170 mg, 0.75 mmol) dissolved in 0.5 mL of dry $CDCl_3$ was achieved by the slow addition of pure anhydrous *m*-CPBA (>99%) (194 mg, 1.12 mmol, 1.5 eq) partially dissolved in 2.5 mL of $CDCl_3$. After 4 days at -60°C the reaction mixture was treated as previously described.

Attempted low temperature detection of di-*t*-butyl trisulfide-1,2,3-trioxide (160). The oxidation of di-*t*-butyl trisulfide-2-oxide **(156)** (170 mg, 0.75 mmol) dissolved in 0.5 mL of dry $CDCl_3$ was achieved by the slow addition of pure anhydrous *m*-CPBA (>99%) (516 mg, 3.0 mmol, 4 eq) partially dissolved in 4 mL of $CDCl_3$. After 4 days at -60°C the reaction mixture was treated as described previously.

APPENDIX I.

X-RAY STRUCTURE DETERMINATION[234] OF DI-*t*-BUTYL TRISULFIDE-2-OXIDE (156)



- **Crystal Data for the Structure Determination of 156** **(Table XR-1)**
- **Atomic Coordinates and Temperature Factors for 156** **(Table XR-2)**
- **Distances and Angles for 156** **(Table XR-3)**

Intensity data were collected at room temperature on a AFC6S Rigaku diffractometer controlled by TEXRAY software using the θ/2θ scan mode.

Table XR-1. Crystal data for the structure determination of 156.

Chemical Formula	$C_8H_{18}OS_3$
Formula Weight	226.41
X-ray crystal dimension (mm)[a]	0.50 x 0.40 x 0.30
Radiation	Cu
Crystal system	tetragonal
Space group	$P4_32_12$
Lattice constants	
a (Å)	13.301(3)
b (Å)	
c (Å)	14.800(3)
V (Å^3)	2619.3(8)
Z	8
F (000)	985.35
Density (calc'd) (g cm^{-3})	1.149
μ (mm^{-1})	4.81
λ (Å)	1.54056
2θ max (°)	90.0
h, k, l ranges	0 12, 0 8, 0 13
No. of reflections measured	1382
No. of unique reflections	1065
No. of reflections with $I_{net} > 2.5\sigma(I_{net})$	679
For significant reflections	RF = 0.076[b], R_W = 0.086[d], G_OF = 2.92[d]
Maximum shift / σ ratio	0.035
Deepest hole in D-map (e / Å^3)	-0.240
Highest peak in D-map (e / Å^3)	0.270
Drop of standard intensities	1.7% for each crystal
Method of structure determination	Solved by direct methods
Method of structure refinement	NRCVAX system programs

[a] cell dimensions were obtained from 25 reflections with 2θ angle in the range 48.00 - 60.00°.

[b] $RF = \Sigma (F_o - F_c) / \Sigma (F_o)$

[c] $R_w = (\Sigma [w(F_o - F_c)^2 / \Sigma (wF_o^2)])^{½}$

[d] $G_oF = (\Sigma[w(F_o - F_c)^2 / (\#\text{ reflections} - \#\text{ parameters})])^{½}$

Table XR-2. Atomic coordinates (x, y, z) and temperature factors (B_{eq}) for compound **156**. Estimated σs refer to the last digit.

Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
S 2	0.1453(5)	0.9012(5)	0.0022(5)	9.1(4)
S 1	0.1341(6)	0.7465(5)	-0.0044(5)	10.0(5)
S 3	0.2144(6)	0.8891(5)	0.1251(4)	10.1(5)
O	0.2217(18)	0.9394(16)	-0.0685(12)	15.3(17)
C 1	0.0394(21)	0.7311(23)	-0.0968(21)	9.0(17)
C 2	0.0355(24)	0.615 (3)	-0.1052(18)	12.9(23)
C 3	-0.051 (3)	0.768 (3)	-0.0666(24)	20.8(34)
C 4	0.072 (4)	0.778 (3)	-0.1829(16)	20.3(36)
C 5	0.2347(22)	1.0248(20)	0.1554(15)	7.9(15)
C 6	0.301 (4)	1.076 (3)	0.0926(23)	21.7(34)
C 7	0.269 (3)	1.0263(23)	0.2437(21)	18.0(31)
C 8	0.147 (3)	1.085 (3)	0.143 (3)	18.0(30)

Beq is the mean of the principal axes of the thermal ellipsoid.

Calculated Hydrogen Atom Parameters

	x	y	z	Biso
H 2C	0.096	0.570	-0.132	13.4
H 2A	0.018	0.577	-0.043	13.4
H 2B	-0.027	0.589	-0.145	13.4
H 3C	-0.055	0.720	-0.008	22.0
H 3A	-0.040	0.847	-0.051	22.0
H 3B	-0.103	0.738	-0.115	22.0
H 4C	0.082	0.858	-0.176	21.0
H 4A	0.140	0.749	-0.212	21.0
H 4B	0.015	0.766	-0.234	21.0
H 6C	0.374	1.043	0.093	22.6
H 6A	0.274	1.075	0.024	22.6
H 6B	0.311	1.155	0.107	22.6
H 7C	0.220	0.987	0.289	18.7
H 7A	0.336	0.981	0.240	18.7
H 7B	0.294	1.098	0.269	18.7
H 8C	0.114	1.086	0.076	18.0
H 8A	0.087	1.050	0.182	18.0
H 8B	0.147	1.159	0.170	18.0

Hydrogen positions calculated assuming C-H of 1.08A. Biso(H) is from Uiso(H) = 0.01 + Ueq(C).

Table XR-3: Bond Distances, Valency and Dihedral Angles of Compound **156**. Estimated σs refer to the last digit.

Bond Distances(A) and Angles(Degrees)

S(2)-S(1)	2.066(9)	C(1)-C(3)	1.37(5)
S(2)-S(3)	2.045(10)	C(1)-C(4)	1.48(4)
S(2)-O	1.544(22)	C(5)-C(6)	1.45(4)
S(1)-C(1)	1.87(3)	C(5)-C(7)	1.38(4)
S(3)-C(5)	1.88(3)	C(5)-C(8)	1.42(4)
C(1)-C(2)	1.55(5)		

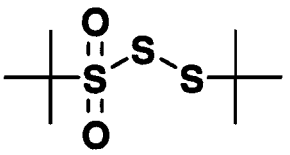
S(1)-S(2)-S(3)	89.8(4)	C(2)-C(1)-C(4)	110(3)
S(1)-S(2)-O	110.1(9)	C(3)-C(1)-C(4)	112(3)
S(3)-S(2)-O	109.5(9)	S(3)-C(5)-C(6)	112.7(22)
S(2)-S(1)-C(1)	101.1(10)	S(3)-C(5)-C(7)	106.6(19)
S(2)-S(3)-C(5)	101.6(8)	S(3)-C(5)-C(8)	112.7(21)
S(1)-C(1)-C(2)	100.9(19)	C(6)-C(5)-C(7)	113(3)
S(1)-C(1)-C(3)	108.1(22)	C(6)-C(5)-C(8)	98(3)
S(1)-C(1)-C(4)	112.8(25)	C(7)-C(5)-C(8)	112(3)
C(2)-C(1)-C(3)	110(3)		

Torsion Angles in Degrees

S 3	S 2	S 1	C 1	164.5(11)	O	S 2	S 1	C 1	-84.9(13)
S 1	S 2	S 3	C 5	-178.8(10)	O	S 2	S 3	C 5	70.0(12)
S 2	S 1	C 1	C 2	177.0(23)	S 2	S 1	C 1	C 3	-66.8(21)
S 2	S 1	C 1	C 4	58.6(18)	S 2	S 3	C 5	C 6	-63.0(19)
S 2	S 3	C 5	C 7	171.9(24)	S 2	S 3	C 5	C 8	47.8(17)

APPENDIX II.

X-RAY STRUCTURE DETERMINATION[234] OF DI-*t*-BUTYL TRISULFIDE-1,1-DIOXIDE (145)



- **Crystal Data for the Structure Determination of 145** **(Table XR-4)**
- **Atomic Coordinates and Temperature Factors for 145** **(Table XR-5)**
- **Distances and Angles for 145** **(Table XR-6)**

Intensity data were collected at room temperature on a AFC6S Rigaku diffractometer controlled by TEXRAY software using the θ/2θ scan mode.

Table XR-4. Crystal data for the structure determination of **145**.

Chemical Formula	$C_8H_{18}O_2S_3$
Formula Weight	242.41
X-ray crystal dimension (mm)[a]	0.33 x 0.30 x 0.30
Radiation	Cu
Crystal system	monoclinic
Space group	$P2_1/c$
Lattice constants	
a (Å)	10.7495(23)
b (Å)	11.872(3)
c (Å)	11.1591(20)
β (°)	113.399(15)
V (Å^3)	1307.0(5)
Z	4
F (000)	519.96
Density (calc'd) (g cm^{-3})	1.232
μ (mm^{-1})	4.91
λ (Å)	1.54056
2θ max (°)	110.0
h, k, l ranges	-11 10, 0 12, 0 11
No. of reflections measured	2046
No. of unique reflections	1638
No. of reflections with $I_{net} > 2.5\sigma(I_{net})$	1208
For significant reflections	RF = 0.054[b], R_W = 0.057[d], G_OF = 2.40[d]
Maximum shift / σ ratio	0.030
Deepest hole in D-map (e / Å^3)	-0.260
Highest peak in D-map (e / Å^3)	0.300
Drop of standard intensities	4.1% for each crystal
Method of structure determination	Solved by direct methods
Method of structure refinement	NRCVAX system programs

[a] cell dimensions were obtained from 25 reflections with 2θ angle in the range 60.00 - 80.00°.

[b] $RF = \Sigma (F_o - F_c) / \Sigma (F_o)$

[c] $R_w = (\Sigma [w(F_o - F_c)^2 / \Sigma (wF_o^2)])^{½}$

[d] $G_oF = (\Sigma[w(F_o - F_c)^2 / (\#\text{ reflections} - \#\text{ parameters})])^{½}$

Table XR-5. Atomic coordinates (x, y, z) and temperature factors (B_{eq}) for compound **145**. Estimated σs refer to the last digit.

Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
S 1	0.84592(17)	0.97434(14)	0.18926(17)	5.90(10)
S 2	0.64987(17)	1.02549(16)	0.16860(17)	7.10(11)
S 3	0.64139(18)	0.99303(15)	0.34192(17)	6.48(11)
O 1	0.8264 (6)	0.9324 (5)	0.0638 (5)	11.2 (4)
O 2	0.9017 (4)	0.9017 (4)	0.3017 (5)	8.8 (3)
C 1	0.9482 (6)	1.1023 (5)	0.2211 (6)	5.9 (4)
C 2	0.8854 (8)	1.1809 (6)	0.1066 (6)	9.0 (5)
C 3	1.0878 (8)	1.0619 (8)	0.2337 (8)	10.8 (6)
C 4	0.9566 (8)	1.1533 (6)	0.3471 (6)	8.0 (4)
C 5	0.5553 (6)	0.8557 (5)	0.3224 (6)	5.5 (3)
C 6	0.4231 (8)	0.8551 (8)	0.2112 (8)	11.6 (6)
C 7	0.5439 (10)	0.8378 (7)	0.4487 (8)	11.9 (7)
C 8	0.6419 (8)	0.7643 (6)	0.3010 (7)	8.8 (5)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

calculated hydrogen atom parameters

	X	Y	Z	Biso
H 2A	0.947	1.255	0.118	9.4
H 2B	0.870	1.141	0.015	9.4
H 2C	0.789	1.209	0.104	9.4
H 3A	1.076	1.023	0.143	11.9
H 3B	1.152	1.134	0.240	11.9
H 3C	1.135	1.004	0.314	11.9
H 4A	1.013	1.231	0.364	8.7
H 4B	0.856	1.176	0.339	8.7
H 4C	1.006	1.098	0.429	8.7
H 6A	0.381	0.771	0.192	11.4
H 6B	0.347	0.915	0.211	11.4
H 6C	0.441	0.868	0.124	11.4
H 7A	0.505	0.754	0.446	13.7
H 7B	0.642	0.829	0.528	13.7
H 7C	0.476	0.893	0.471	13.7
H 8A	0.740	0.765	0.382	10.0
H 8B	0.601	0.682	0.303	10.0
H 8C	0.658	0.777	0.212	10.0

Hydrgen positions were calculated assuming C-H distance of 1.08A. Biso(H) is from Uiso(H)=0.01 + Ueq(C)

Table XR-6: Bond Distances, Valency and Dihedral Angles of Compound **145**.
Estimated σs refer to the last digit.

Bond distances (A) and Angles (degree)

S(1)-S(2)	2.1159(24)	C(1)-C(2)	1.507(9)
S(1)-O(1)	1.421(5)	C(1)-C(3)	1.528(10)
S(1)-O(2)	1.442(5)	C(1)-C(4)	1.500(9)
S(1)-C(1)	1.825(6)	C(5)-C(6)	1.469(10)
S(2)-S(3)	2.0093(24)	C(5)-C(7)	1.478(9)
S(3)-C(5)	1.845(6)	C(5)-C(8)	1.509(10)

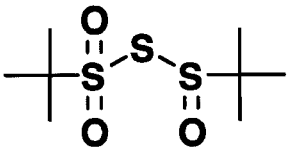
S(2)-S(1)-O(1)	104.0(3)	S(1)-C(1)-C(4)	109.0(4)
S(2)-S(1)-O(2)	108.57(20)	C(2)-C(1)-C(3)	111.4(6)
S(2)-S(1)-C(1)	106.20(23)	C(2)-C(1)-C(4)	112.7(6)
O(1)-S(1)-O(2)	119.7(3)	C(3)-C(1)-C(4)	110.4(6)
O(1)-S(1)-C(1)	109.0(3)	S(3)-C(5)-C(6)	112.0(5)
O(2)-S(1)-C(1)	108.5(3)	S(3)-C(5)-C(7)	104.0(5)
S(1)-S(2)-S(3)	105.31(10)	S(3)-C(5)-C(8)	110.0(4)
S(2)-S(3)-C(5)	105.56(20)	C(6)-C(5)-C(7)	112.7(6)
S(1)-C(1)-C(2)	108.5(4)	C(6)-C(5)-C(8)	108.3(6)
S(1)-C(1)-C(3)	104.5(5)	C(7)-C(5)-C(8)	109.8(6)

Torsion angles

O 1	S 1	S 2	S 3	145.6(3)	O 2	S 1	S 2	S 3	17.1(2)
C 1	S 1	S 2	S 3	-99.5(2)	S 2	S 1	C 1	C 2	-60.4(3)
S 2	S 1	C 1	C 3	-179.4(5)	S 2	S 1	C 1	C 4	62.6(3)
O 1	S 1	C 1	C 2	51.1(4)	O 1	S 1	C 1	C 3	-67.9(4)
O 1	S 1	C 1	C 4	174.1(6)	O 2	S 1	C 1	C 2	-177.0(5)
O 2	S 1	C 1	C 3	64.1(4)	O 2	S 1	C 1	C 4	-53.9(4)
S 1	S 2	S 3	C 5	-97.4(2)	S 2	S 3	C 5	C 6	-54.8(4)
S 2	S 3	C 5	C 7	-176.8(5)	S 2	S 3	C 5	C 8	65.7(3)

APPENDIX III.

X-RAY STRUCTURE DETERMINATION[234] OF DI-*t*-BUTYL TRISULFIDE-1,1,3-TRIOXIDE (157)



- **Crystal Data for the Structure Determination of 157** **(Table XR-7)**
- **Atomic Coordinates and Temperature Factors for 157** **(Table XR-8)**
- **Distances and Angles for 157** **(Table XR-9)**

Intensity data were collected at room temperature on a AFC6S Rigaku diffractometer controlled by TEXRAY software using the θ/2θ scan mode.

Table XR-7. Crystal data for the structure determination of **157.**

Chemical Formula	$C_8H_{18}O_3S_3$
Formula Weight	258.41
X-ray crystal dimension (mm)[a]	0.30 x 0.30 x 0.07
Radiation	Graphite-monochromated CuK_α
Crystal system	monoclinic
Space group	$P2_1$
Lattice constants	
a (Å)	5.9004(17)
b (Å)	11.9502(15)
c (Å)	9.1617(14)
β (°)	95.927(24)
V (Å^3)	642.55(22)
Z	2
F (000)	276.74
Density (calc'd) (g cm^{-3})	1.336
μ (mm^{-1})	0.54
λ (Å)	0.70930
2θ max (°)	46.9
h, k, l ranges	-6 6, 0 13, 0 10
No. of reflections measured	1189
No. of unique reflections	1006
No. of reflections with $I_{net} > 2.5\sigma (I_{net})$	871
For significant reflections	RF = 0.055[b], R_W = 0.053[d], G_OF = 2.42[d]
Maximum shift / σ ratio	0.001
Deepest hole in D-map (e / Å^3)	-0.360
Highest peak in D-map (e / Å^3)	0.390
Drop of standard intensities	3.5% for each crystal
Method of structure determination	Solved by direct methods
Method of structure refinement	NRCVAX system programs

[a] cell dimensions were obtained from 25 reflections with 2θ angle in the range 25.00 - 30.00°.

[b] $RF = \Sigma (F_o - F_c) / \Sigma (F_o)$

[c] $R_w = (\Sigma [w(F_o - F_c)^2 / \Sigma (wF_o^2)])^{1/2}$

[d] $G_oF = (\Sigma[w(F_o - F_c)^2 / (\#\text{ reflections} - \#\text{ parameters})])^{1/2}$

Table XR-8. Atomic coordinates (x, y, z) and temperature factors (B_{eq}) for compound 157. Estimated σs refer to the last digit.

Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
S 1	0.7032(4)	0.23381	0.46768(23)	3.90(11)
S 2	0.5309(4)	0.2429 (3)	0.25631(22)	4.18(11)
S 3	0.7823(4)	0.1728 (3)	0.1313 (3)	4.62(12)
O 1	0.5213(11)	0.2279 (9)	0.5587 (6)	5.8 (4)
O 2	0.8654(14)	0.1490 (9)	0.4696 (8)	6.8 (4)
O 3	0.8809(12)	0.2650 (9)	0.0485 (7)	7.3 (4)
C 1	0.8492(15)	0.3680 (9)	0.5031 (10)	3.2 (4)
C 2	1.0129(19)	0.3866 (11)	0.3911 (12)	5.5 (5)
C 3	0.6675(16)	0.4584 (10)	0.4988 (11)	4.6 (5)
C 4	0.9746(20)	0.3559 (11)	0.6562 (11)	5.8 (6)
C 5	0.5824(17)	0.0951 (11)	-0.0024 (10)	4.3 (5)
C 6	0.4195(16)	0.1739 (12)	-0.0849 (10)	5.2 (5)
C 7	0.7478(19)	0.0409 (12)	-0.1022 (12)	6.2 (6)
C 8	0.4630(21)	0.0074 (10)	0.0815 (12)	6.1 (6)

Beq is the mean of the principal axes of the thermal ellipsoid.

Calculated Hydrogen Atom Paramters

	x	y	z	Biso
H 2A	0.938	0.384	0.278	6.6 (37)
H 2B	1.053	0.473	0.388	6.6 (69)
H 2C	1.130	0.316	0.396	6.6 (29)
H 3A	0.788	0.526	0.508	5.4 (18)
H 3B	0.554	0.477	0.402	5.4 (29)
H 3C	0.551	0.447	0.582	5.4 (35)
H 4A	1.072	0.279	0.665	6.5 (42)
H 4B	0.848	0.327	0.723	6.5 (23)
H 4C	1.047	0.437	0.682	6.5 (24)
H 6A	0.321	0.141	-0.181	6.1 (39)
H 6B	0.501	0.246	-0.130	6.1 (39)
H 6C	0.280	0.191	-0.022	6.1 (28)
H 7A	0.870	0.093	-0.157	7.1 (49)
H 7B	0.867	-0.011	-0.043	7.1 (20)
H 7C	0.661	0.029	-0.213	7.1(119)
H 8A	0.342	0.031	0.156	7.1 (15)
H 8B	0.590	-0.041	0.144	7.1 (41)
H 8C	0.353	-0.055	0.023	7.1 (37)

Hydrogen positions calculated assuming C-H of 1.08A. Biso(H) Uiso(H) = Ueq(C) + 0.01.

Table XR-9: Bond Distances, Valency and Dihedral Angles of Compound **157**. Estimated σs refer to the last digit.

Bond Distances(A) and Angles(Degrees)

S(1)-S(2)	2.095(3)	C(1)-C(2)	1.497(14)
S(1)-O(1)	1.427(7)	C(1)-C(3)	1.520(14)
S(1)-O(2)	1.393(9)	C(1)-C(4)	1.524(14)
S(1)-C(1)	1.834(10)	C(5)-C(6)	1.494(16)
S(2)-S(3)	2.136(4)	C(5)-C(7)	1.546(15)
S(3)-O(3)	1.490(10)	C(5)-C(8)	1.515(16)
S(3)-C(5)	1.860(11)		

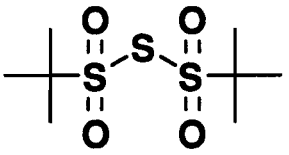
S(2)-S(1)-O(1)	102.7(3)	S(1)-C(1)-C(3)	107.4(6)
S(2)-S(1)-O(2)	108.5(3)	S(1)-C(1)-C(4)	104.8(8)
S(2)-S(1)-C(1)	107.0(3)	C(2)-C(1)-C(3)	112.3(9)
O(1)-S(1)-O(2)	120.9(6)	C(2)-C(1)-C(4)	111.0(8)
O(1)-S(1)-C(1)	107.9(5)	C(3)-C(1)-C(4)	111.4(8)
O(2)-S(1)-C(1)	108.9(5)	S(3)-C(5)-C(6)	110.4(9)
S(1)-S(2)-S(3)	100.23(14)	S(3)-C(5)-C(7)	101.7(7)
S(2)-S(3)-O(3)	108.2(4)	S(3)-C(5)-C(8)	107.9(7)
S(2)-S(3)-C(5)	96.9(3)	C(6)-C(5)-C(7)	112.1(8)
O(3)-S(3)-C(5)	106.7(5)	C(6)-C(5)-C(8)	112.6(9)
S(1)-C(1)-C(2)	109.5(7)	C(7)-C(5)-C(8)	111.4(11)

Torsion Angles in Degrees

O 1	S 1	S 2	S 3	-153.7(4)	O 2	S 1	S 2	S 3	-24.5(4)
C 1	S 1	S 2	S 3	92.8(3)	S 2	S 1	C 1	C 2	-59.8(5)
S 2	S 1	C 1	C 3	62.4(5)	S 2	S 1	C 1	C 4	-179.0(7)
O 1	S 1	C 1	C 2	-169.8(9)	O 1	S 1	C 1	C 3	-47.5(6)
O 1	S 1	C 1	C 4	71.1(7)	O 2	S 1	C 1	C 2	57.2(7)
O 2	S 1	C 1	C 3	179.5(9)	O 2	S 1	C 1	C 4	-61.9(7)
S 1	S 2	S 3	O 3	-107.2(4)	S 1	S 2	S 3	C 5	142.6(4)
S 2	S 3	C 5	C 6	60.0(6)	S 2	S 3	C 5	C 7	179.2(8)
S 2	S 3	C 5	C 8	-63.4(6)	O 3	S 3	C 5	C 6	-51.4(6)
O 3	S 3	C 5	C 7	67.8(7)	O 3	S 3	C 5	C 8	-174.8(10)

APPENDIX IV.

X-RAY STRUCTURE DETERMINATION[234] OF DI-*t*-BUTYL TRISULFIDE-1,1,3,3-TETRAOXIDE (161)



- **Crystal Data for the Structure Determination of 161** **(Table XR-10)**
- **Atomic Coordinates and Temperature Factors for 161** **(Table XR-11)**
- **Distances and Angles for 161** **(Table XR-12)**

Intensity data were collected at room temperature on a AFC6S Rigaku diffractometer controlled by TEXRAY software using the θ/2θ scan mode.

Table XR-10. Crystal data for the structure determination of **161.**

Chemical Formula	$C_8H_{18}O_4S_3$
Formula Weight	274.41
X-ray crystal dimension (mm)[a]	0.50 x 0.25 x 0.20
Radiation	Cu
Crystal system	Orthorhombic
Space group	Pbnb
Lattice constants	
a (Å)	9.3517(10)
b (Å)	10.5713(12)
c (Å)	13.3309(12)
V (Å^3)	1317.89(24)
Z	4
F (000)	589.24
Density (calc'd) (g cm^{-3})	1.383
μ (mm^{-1})	5.05
λ (Å)	1.54056
2θ max (°)	110.0
h, k, l ranges	0 9, 0 11, 0 14
No. of reflections measured	943
No. of unique reflections	820
No. of reflections with $I_{net} > 2.5\sigma(I_{net})$	726
For significant reflections	RF = 0.043[b], R_W = 0.054[d], G_OF = 3.39[d]
Maximum shift / σ ratio	0.071
Deepest hole in D-map (e / Å^3)	-0.330
Highest peak in D-map (e / Å^3)	0.390
Drop of standard intensities	2% for each crystal
Method of structure determination	Solved by direct methods
Method of structure refinement	NRCVAX system programs

[a] cell dimensions were obtained from 25 reflections with 2θ angle in the range 80.00 - 100.00°.

[b] $RF = \Sigma (F_o - F_c) / \Sigma (F_o)$

[c] $R_w = (\Sigma [w(F_o - F_c)^2 / \Sigma (wF_o^2)])^{½}$

[d] $G_oF = (\Sigma[w(F_o - F_c)^2 / (\#\text{ reflections} - \#\text{ parameters})])^{½}$

Table XR-11. Atomic coordinates (x, y, z) and temperature factors (B_{eq}) for compound **161**. Estimated σs refer to the last digit.

Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
S 1	3/4	0.35712(12)	0.25000	3.98(6)
S 2	0.93492(10)	0.24154(9)	0.24868(6)	3.67(5)
O 1	0.9051 (3)	0.12219(23)	0.20639(19)	4.83(12)
O 2	1.0361 (3)	0.3229 (3)	0.19891(20)	5.51(14)
C 1	0.9903 (4)	0.2257 (3)	0.3792 (3)	3.76(16)
C 2	0.8759 (6)	0.1496 (6)	0.4336 (3)	5.50(24)
C 3	1.0106 (7)	0.3559 (5)	0.4239 (4)	6.1 (3)
C 4	1.1306 (5)	0.1517 (6)	0.3742 (4)	5.53(24)
H 2A	0.906 (5)	0.137 (4)	0.498 (5)	8.0 (13)
H 2B	0.783 (6)	0.214 (5)	0.429 (5)	9.2 (15)
H 2C	0.859 (5)	0.062 (5)	0.406 (4)	7.4 (13)
H 3A	1.034 (6)	0.347 (5)	0.498 (5)	10.1 (15)
H 3B	0.922 (5)	0.411 (5)	0.419 (3)	7.6 (13)
H 3C	1.088 (5)	0.399 (4)	0.375 (3)	7.2 (13)
H 4A	1.159 (6)	0.125 (4)	0.439 (4)	8.4 (14)
H 4B	1.209 (5)	0.216 (4)	0.343 (4)	7.6 (13)
H 4C	1.122 (4)	0.083 (4)	0.336 (3)	5.4 (11)

Beq is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically. For hydrogens, Beq = Biso.

Table XR-12: Bond Distances, Valency and Dihedral Angles of Compound **161**.
Estimated σs refer to the last digit.

Bond Distances(A) and Angles(Degrees)

S(1)-S(2)	2.1175(12)	C(2)-H(2B)	1.11(6)
S(1)-S(2)a	2.1175(12)	C(2)-H(2C)	1.01(5)
S(2)-O(1)	1.410(3)	C(3)-H(3A)	1.01(7)
S(2)-O(2)	1.440(3)	C(3)-H(3B)	1.01(5)
S(2)-C(1)	1.823(4)	C(3)-H(3C)	1.08(5)
C(1)-C(2)	1.522(6)	C(4)-H(4A)	0.95(5)
C(1)-C(3)	1.511(6)	C(4)-H(4B)	1.08(5)
C(1)-C(4)	1.529(6)	C(4)-H(4C)	0.89(5)
C(2)-H(2A)	0.91(6)		

S(2)-S(1)-S(2)a	109.52(7)	H(2A)-C(2)-H(2B)	112(4)
S(1)-S(2)-O(1)	111.00(12)	H(2A)-C(2)-H(2C)	105(4)
S(1)-S(2)-O(2)	101.29(13)	H(2B)-C(2)-H(2C)	114(4)
S(1)-S(2)-C(1)	106.08(12)	C(1)-C(3)-H(3A)	109(3)
O(1)-S(2)-O(2)	118.67(17)	C(1)-C(3)-H(3B)	113(3)
O(1)-S(2)-C(1)	110.83(16)	C(1)-C(3)-H(3C)	103.7(24)
O(2)-S(2)-C(1)	107.96(17)	H(3A)-C(3)-H(3B)	106(4)
S(2)-C(1)-C(2)	107.7(3)	H(3A)-C(3)-H(3C)	118(4)
S(2)-C(1)-C(3)	109.1(3)	H(3B)-C(3)-H(3C)	105(4)
S(2)-C(1)-C(4)	104.4(3)	C(1)-C(4)-H(4A)	111(3)
C(2)-C(1)-C(3)	112.5(4)	C(1)-C(4)-H(4B)	106.1(22)
C(2)-C(1)-C(4)	110.7(4)	C(1)-C(4)-H(4C)	111(3)
C(3)-C(1)-C(4)	112.0(4)	H(4A)-C(4)-H(4B)	110(4)
C(1)-C(2)-H(2A)	107(3)	H(4A)-C(4)-H(4C)	107(4)
C(1)-C(2)-H(2B)	101(3)	H(4B)-C(4)-H(4C)	110(4)
C(1)-C(2)-H(2C)	114(3)		

symmetry equivalent: 1.500-x y 0.500-z

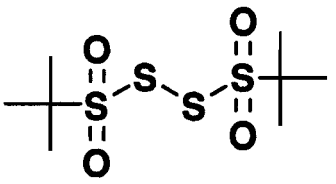
S(2)a	0.56508	0.24154	0.25132

Torsion Angles in Degrees

S 2′	S 1	S 2	O 1	25.5(1)	S 2′	S 1	S 2	O 2	152.4(1)
S 2′	S 1	S 2	C 1	-95.0(1)	S 2	S 1	S 2′	O 1′	25.5(1)
S 2	S 1	S 2′	O 2′	152.4(1)	S 2	S 1	S 2′	C 1′	-95.0(1)
S 1	S 2	C 1	C 2	67.1(2)	S 1	S 2	C 1	C 3	-55.3(2)
S 1	S 2	C 1	C 4	-175.2(3)	O 1	S 2	C 1	C 2	-53.5(3)
O 1	S 2	C 1	C 3	-175.9(4)	O 1	S 2	C 1	C 4	64.2(3)
O 2	S 2	C 1	C 2	175.0(4)	O 2	S 2	C 1	C 3	52.6(3)
O 2	S 2	C 1	C 4	-67.3(3)	S 1	S 2′	C 1′	C 2′	67.1(2)
S 1	S 2′	C 1′	C 3′	-55.3(2)	S 1	S 2′	C 1′	C 4′	-175.2(3)
O 1′	S 2′	C 1′	C 2′	-53.5(3)	O 1′	S 2′	C 1′	C 3′	-175.9(4)
O 1′	S 2′	C 1′	C 4′	64.2(3)	O 2′	S 2′	C 1′	C 2′	175.0(4)
O 2′	S 2′	C 1′	C 3′	52.6(3)	O 2′	S 2′	C 1′	C 4′	-67.3(3)

APPENDIX V.

X-RAY STRUCTURE DETERMINATION[234] OF DI-*t*-BUTYL TETRASULFIDE-1,1,4,4-TETRAOXIDE (159)



- **Crystal Data for the Structure Determination of 159** **(Table XR-13)**
- **Atomic Coordinates and Temperature Factors for 159** **(Table XR-14)**
- **Distances and Angles for 159** **(Table XR-15)**

Intensity data were collected at room temperature on a AFC6S Rigaku diffractometer controlled by TEXRAY software using the θ/2θ scan mode.

Table XR-13. Crystal data for the structure determination of **159**.

Chemical Formula	$C_8H_{18}O_4S_4$
Formula Weight	306.46
X-ray crystal dimension (mm)[a]	0.50 x 0.50 x 0.10
Radiation	Graphite-monochromated CuK_α
Crystal system	monoclinic
Space group	C2c
Lattice constants	
a (Å)	12.4036(21)
b (Å)	5.7613(13)
c (Å)	20.007(4)
β (°)	97.745(15)
V (Å^3)	1416.7(5)
Z	4
F (000)	649.96
Density (calc'd) (g cm^{-3})	1.437
μ (mm^{-1})	0.64
λ (Å)	0.70930
2θ max (°)	55.0
h, k, l ranges	-16 16, 0 7, 0 26
No. of reflections measured	1708
No. of unique reflections	1637
No. of reflections with $I_{net} > 2.5\sigma(I_{net})$	1315
For significant reflections	RF = 0.057[b], R_W = 0.068[d], G_oF = 3.58[d]
Maximum shift / σ ratio	0.014
Deepest hole in D-map (e / Å^3)	-0.430
Highest peak in D-map (e / Å^3)	0.400
Drop of standard intensities	0.17% for each crystal
Method of structure determination	Solved by direct methods
Method of structure refinement	NRCVAX system programs

[a] cell dimensions were obtained from 25 reflections with 2θ angle in the range 27.00 - 35.00°.

[b] $RF = \Sigma (F_o - F_c) / \Sigma (F_o)$

[c] $R_w = (\Sigma [w(F_o - F_c)^2 / \Sigma (wF_o^2)])^{1/2}$

[d] $G_oF = (\Sigma[w(F_o - F_c)^2 / (\#\text{ reflections} - \#\text{ parameters})])^{1/2}$

Table XR-14. Atomic coordinates (x, y, z) and temperature factors (B_{eq}) for compound **159**. Estimated σs refer to the last digit.

Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
S 1	0.45861(9)	0.74783(24)	0.20340(5)	3.50(5)
S 2	0.53994(8)	0.99905(21)	0.15023(5)	2.95(4)
O 1	0.4563 (3)	1.0691 (7)	0.09720(16)	5.40(18)
O 2	0.5892 (3)	1.1684 (6)	0.19679(15)	4.47(15)
C 1	0.6443 (3)	0.8418 (8)	0.11297(19)	3.04(17)
C 2	0.5900 (6)	0.6592 (11)	0.0660 (3)	5.0 (3)
C 3	0.7013 (5)	1.0274 (13)	0.0761 (3)	4.8 (3)
C 4	0.7207 (5)	0.7305 (13)	0.1696 (3)	4.7 (3)
H 2A	0.535 (5)	0.549 (10)	0.084 (3)	7.2 (16)
H 2B	0.560 (4)	0.727 (10)	0.030 (3)	5.1 (15)
H 2C	0.652 (4)	0.578 (10)	0.047 (3)	5.8 (14)
H 3A	0.648 (4)	1.086 (8)	0.0382 (24)	4.4 (12)
H 3B	0.728 (5)	1.139 (11)	0.104 (3)	8.1 (21)
H 3C	0.761 (4)	0.965 (8)	0.0589 (21)	4.1 (11)
H 4A	0.753 (3)	0.829 (8)	0.2041 (21)	3.3 (11)
H 4B	0.777 (5)	0.671 (11)	0.155 (3)	7.4 (17)
H 4C	0.673 (5)	0.621 (11)	0.192 (3)	7.8 (17)

Beq is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically. For hydrogens, Beq = Biso.

Table XR-15: Bond Distances, Valency and Dihedral Angles of Compound **159**. Estimated σs refer to the last digit.

Bond Distances(A) and Angles(Degrees)

S(1)-S(1)a	2.0037(22)	C(2)-H(2B)	0.85(5)
S(1)-S(2)	2.1293(16)	C(2)-H(2C)	1.02(6)
S(2)-O(1)	1.438(3)	C(3)-H(3A)	0.99(5)
S(2)-O(2)	1.428(3)	C(3)-H(3B)	0.88(7)
S(2)-C(1)	1.820(4)	C(3)-H(3C)	0.93(5)
C(1)-C(2)	1.508(7)	C(4)-H(4A)	0.94(5)
C(1)-C(3)	1.527(7)	C(4)-H(4B)	0.86(6)
C(1)-C(4)	1.518(7)	C(4)-H(4C)	1.02(7)
C(2)-H(2A)	1.04(6)		

S(1)a-S(1)-S(2)	104.30(7)	H(2A)-C(2)-H(2B)	110(5)
S(1)-S(2)-O(1)	102.49(16)	H(2A)-C(2)-H(2C)	114(4)
S(1)-S(2)-O(2)	109.17(14)	H(2B)-C(2)-H(2C)	99(5)
S(1)-S(2)-C(1)	106.10(16)	C(1)-C(3)-H(3A)	107(3)
O(1)-S(2)-O(2)	119.49(24)	C(1)-C(3)-H(3B)	111(4)
O(1)-S(2)-C(1)	108.63(19)	C(1)-C(3)-H(3C)	110(3)
O(2)-S(2)-C(1)	109.99(21)	H(3A)-C(3)-H(3B)	112(5)
S(2)-C(1)-C(2)	108.7(4)	H(3A)-C(3)-H(3C)	109(4)
S(2)-C(1)-C(3)	104.5(4)	H(3B)-C(3)-H(3C)	104(5)
S(2)-C(1)-C(4)	108.2(3)	C(1)-C(4)-H(4A)	117(3)
C(2)-C(1)-C(4)	110.6(5)	C(1)-C(4)-H(4B)	111(4)
C(3)-C(1)-C(4)	112.0(5)	C(1)-C(4)-H(4C)	104(3)
C(1)-C(2)-H(2A)	117(3)	H(4A)-C(4)-H(4B)	101(5)
C(1)-C(2)-H(2B)	107(4)	H(4A)-C(4)-H(4C)	105(4)
C(1)-C(2)-H(2C)	104(3)	H(4B)-C(4)-H(4C)	116(5)

		1.000-x	y	0.500-z
symmetry equivalent:				
S(1)a	0.54139	0.74783	0.29660	

Torsion Angles in Degrees

S 1′	S 1	S 2	O 1	-155.6(2)	S 1′	S 1	S 2	O 2	-27.9(1)
S 1′	S 1	S 2	C 1	90.6(1)	S 2	S 1	S 1′	S 2′	90.9(1)
S 1	S 2	C 1	C 2	60.1(3)	S 1	S 2	C 1	C 3	-179.4(4)
S 1	S 2	C 1	C 4	-60.0(3)	O 1	S 2	C 1	C 2	-49.4(3)
O 1	S 2	C 1	C 3	71.0(3)	O 1	S 2	C 1	C 4	-169.5(4)
O 2	S 2	C 1	C 2	178.1(4)	O 2	S 2	C 1	C 3	-61.5(3)
O 2	S 2	C 1	C 4	58.0(3)	S 1	S 1′	S 2′	O 1′	-155.6(2)
S 1	S 1′	S 2′	O 2′	-27.9(1)	S 1	S 1′	S 2′	C 1′	90.6(1)