(TITLE FOR SPINE)

REDUCTIVE CLEAVAGE OF ACETALS
BY BH_3 AND BY $HCo(CO)_4$

THE REDUCTIVE CLEAVAGE OF ACETALS AND RELATED COMPOUNDS BY BORANE AND BY HYDROCOBALT TETRACARBONYL

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When a debater's point is not impressive, he brings forth many arguments.

Talmud Jerushalmi, Berakot 2:3

ABSTRACT

Acetals were found to be reducible by borane (BH_3) in tetrahydrofuran and by trimethylamine-borane in acetic acid. The borane reduction was first-order in acetal, and approximately third-order in borane; it apparently proceeded via a carbonium ion mechanism.

Simple aliphatic acetals, when heated with hydrocobalt tetracarbonyl ($HCo(CO)_4$), gave a complex mixture of products, but when the acetal carbon atom bore a phenyl substituent, only the products of reductive cleavage were obtained. *p*-Methoxybenzyl alcohol (I) and *p*-methoxybenzyl methyl ether (II) both yielded the same products on reduction with $HCo(CO)_4$, except that I gave bis-[2-(4-methoxyphenyl)ethyl] ether where II gave 1-methoxy-2-(4-methoxyphenyl)ethane. Ether formation, which also occurs during benzaldehyde reduction, is now explained in terms of acetal formation and reductive cleavage, both catalysed by $HCo(CO)_4$. Otherwise, all the new products are explicable by current knowledge.

In reductive cleavage of 1,3-dimethoxyphthalan with $HCo(CO)_4$, preferential attack occurred on the ring oxygen, while with borane it occurred on an *exo*-oxygen.

RESUME

On a trouvé que les acétals sont réduits par le borane (BH_3) dans le tétrahydrofuranne et par le triméthylamine-borane dans l'acide acétique. La réduction au borane est de premier ordre pour l'acétal, et approximativement de troisième ordre pour le borane; la réaction parait procéder par un mécanisme d'ion carbonium.

Les acétals aliphatiques simples, lorsque chauffés en présence d'hydrure de cobalt tetracarbonyle ($HCo(CO)_4$) donnent un mélange de produits. Cependant lorsque le carbone acétalique a pour substituent un groupe phényl, les produits du clivage réductif sont les seuls obtenus. L'alcool p-méthoxybenzylique et l'éther méthyl p-méthoxybenzylique, lorsque réduits avec $HCo(CO)_4$, donnent les mêmes produits, sauf que le premier donne l'éther bis-2-(4-méthoxyphényl)éthylique et que le second donne le 1-méthoxy-2-(4-méthoxyphényl)éthane. La formation d'éthers, qui se produit aussi lors de la réduction du benzaldehyde, est maintenant expliquée par la formation d'acétals suivi de clivages réductifs, les deux phenomènes étant catalysés par $HCo(CO)_4$. Les connaissances actuelles peuvent expliquer la formation de tous les autres produits nouveaux.

Une attaque préférentielle sur l'oxygène du cycle se produit lors du clivage réductif du 1,3-diméthoxyphthalan avec $HCo(CO)_4$, alors que la réaction avec le borane, l'attaque se fait à l'oxygène exo.

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TABLE OF CONTENTS

Page

CHAPTER 1 - INTRODUCTION

CHAPTER 2 - THE REDUCTIVE CLEAVAGE OF ACETALS BY BORANE (BH_3)

CHAPTER 3 - TRIMETHYLAMINE-BORANE AS A REDUCING AGENT FOR ACETALS

Page

CHAPTER 4 - THE REDUCTIVE CLEAVAGE OF ACETALS BY $HCo(CO)_4$

CHAPTER 5 - SOLUTIONS OF PURE $HCo(CO)_4$ IN HYDROCARBONS - THEIR REACTION WITH ACETALS

CHAPTER 6 - REDUCTIVE CLEAVAGE OF p-METHOXYBENZYL ALCOHOL AND ITS ETHERS

CHAPTER 6 (continued)

CHAPTER 7 - THE REDUCTIVE CLEAVAGE OF AN ALDAL BY BORANE AND BY $HCo(CO)_4$

CHAPTER 8 - EXPERIMENTAL SECTION

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND SYMBOLS

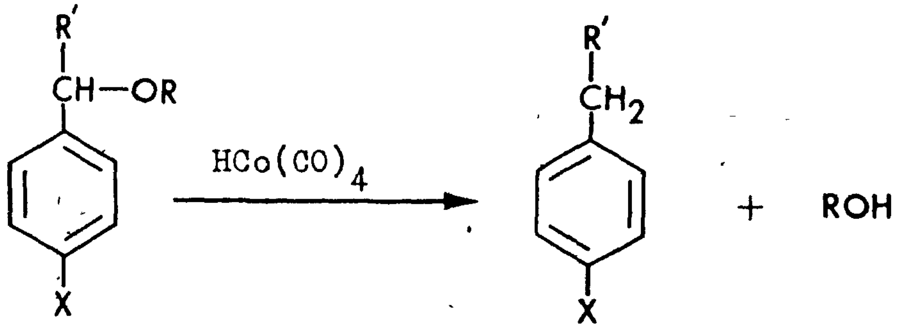
Ac	Acetyl
DCC	Dicyclohexylcarbodiimide
DMF	N,N'-Dimethylformamide
Me	Methyl
Ph, Ø	Phenyl
NTP	Normal temperature and pressure (273°K, 760 mm Hg)
THF	Tetrahydrofuran
TMS	Tetramethylsilane
ppm	Parts per million
Hz	Hertz
J	Nuclear spin-spin coupling constant
δ	Chemical shift (in ppm downfield from TMS)
p.m.r.	Proton magnetic resonance
i.r.	Infrared
b.p.	Boiling point
m.p.	Melting point
m.m.p.	Mixed melting point
g.l.c.	Gas liquid chromatography
g.c.-m.s.	Gas chromatography - mass spectrometry
c	Cis-
t	Trans-
psig	Pounds per square inch above atmospheric pressure
λ	Wavelength (cm^{-1})
μ	Wavelength (microns)

CHAPTER 1

INTRODUCTION

1.1 General Remarks

A recent search (1) for a soluble agent that would promote the hydrogenolytic cleavage of benzyl ethers has revealed hydrocobalt tetracarbonyl ($HCo(CO)_4$) to be effective for this purpose (Eq.1.1). When the ether bore a para substituent, X, which was electron-releasing , e.g. -OMe — the reaction occurred easily at 150-180°C, and gave high yields (90-100%) of reduced product. When the X-group was H, very little reduction occurred below 200°C.



1.1

The reaction appeared to be specific to ethers of this type. However, when it was applied to the delignification of wood*, a process in which the key step is thought to be benzyl ether cleavage (see Appendix 5), the residual cellulose was greatly reduced in molecular weight (as measured by viscosity and by gel permeation chromatography).

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* Several publications (2-4) describe the use of cobalt carbonyl catalysts for the hydrogenolysis of wood or lignin.

The work presented here was initiated to examine in greater detail the reaction of p-methoxybenzyl ethers with $HCo(CO)_4$, in order to ascertain the mechanism of the reductive cleavage, and thus to permit a choice of conditions which might minimise the reaction with cellulose. The mechanism of this reaction with $HCo(CO)_4$ is likely to be similar to that already proposed for p-methoxybenzyl alcohol (96, 98). A detailed examination, discussed in Chapter 6, of the products obtained from this alcohol and from its methyl ether provided confirmatory evidence for the postulated mechanism. These results soon led to the recognition that p-methoxybenzyl ethers are vinylogs of acetals, and consequently their reduction is a special case of acetal reduction. Hence the scope of the work was broadened at this point to become a study of the reaction of $HCo(CO)_4$ with acetals and related compounds.

It is worth noting here that the glycosidic links of cellulose are also acetals, consequently this study has a bearing both on delignification and on cellulose depolymerisation by $HCo(CO)_4$.

While the reactions of aliphatic acetals with catalytically generated $HCo(CO)_4$ have been studied before, no-one has previously pointed out the remarkably different behaviour of acetals having an α-phenyl group. This, and the reasons for it, are discussed in Chapter 4. The realization that $HCo(CO)_4$ catalyses both the formation (fast) and reduction (slow) of acetals has enabled us to propose a solution to unexplained observations reported in the literature: the formation of ethers during the reduction of aldehydes (see 4.6).

It is always difficult to determine the active species for a catalytic system involving many compounds in equilibrium; cobalt carbonyl catalysts are no exception. The case for $HCo(CO)_4$* as the active agent in acetal cleavage is here

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* Or a species readily derived from it under ambient conditions.

supported by a series of experiments in which solutions of pure $HCo(CO)_4$ in organic solvents were employed (Chapter 5). Used in stoichiometric amounts, under conditions close to ambient, this reagent caused reductive cleavages similar to those obtained under more drastic conditions with catalytic amounts of cobalt carbonyls.

While pondering the mechanism of the reductive cleavages mentioned above, an intermediate hydrocobalt tricarbonyl was considered, and this hypothetical species was noted to be coordinatively unsaturated, like borane (BH_3). This consideration eventually led to the discovery of the reductive cleavage of acetals by borane — a completely new reaction of wide applicability, which may prove to have practical advantages over other reactions currently used to convert acetals into ethers. As this is the most significant discovery made during the course of the work it is discussed first, in Chapter 2.

Chapter 7 deals with the behaviour of an aldal — 1,3-dimethoxyphthalan — in both reducing systems, hydrocobalt tetracarbonyl and borane.

Before proceeding with discussion of the results obtained, a brief survey of the methods available for acetal synthesis is presented. This is followed by a brief resumé of the previously known systems for reductive cleavage of acetals. The preparation and properties of diborane are discussed in Chapter 2, those of hydrocobalt tetracarbonyl in Chapters 4 and 5.

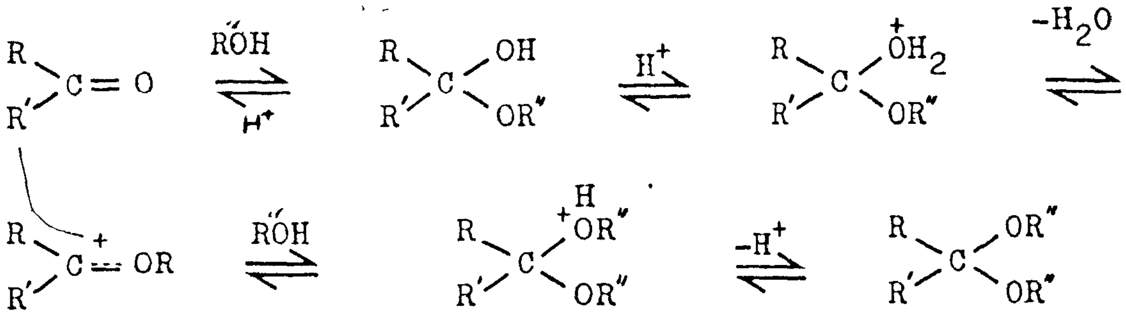
1.2 Nomenclature

The designation 'acetal' is used here not only for compounds derived from aldehydes, but as a general term encompassing also ketals and formals (ref.6, p.310). The term 'borane' is used in this work for solutions or compounds of diborane in which the molecule is considered to be completely dissociated into BH_3 units.

1.3 General Methods for the Preparation of Acetals

The methods available for acetal synthesis are discussed in detail in references 5 and 6.

In the present research most of the starting materials were prepared by variations of the common procedure whereby a carbonyl compound is condensed with an alcohol in the presence of an acid catalyst. The reaction comprises a series of equilibria proceeding first to the hemiacetal, and then, <u>via</u> an oxocarbonium ion, to the acetal (Eq. 1.2).



1.2

Sometimes good yields of acetal result from simply mixing the reagents (7, 8). Usually, however, some means of forcing the equilibria to the right must be employed, such as removal of the water formed in the reaction by means of drying agents or by azeotropic distillation with benzene or toluene using a Dean-Stark water separator (9). Equilibrium is achieved rapidly, except for compounds which yield highly destabilized carbonium ions, e.g. chloral.

When the carbonyl compound is volatile*, azeotropic distillation of water cannot be used, and transacetalation is a useful alternative: an acetal and an alcohol are mixed in the presence of an acid catalyst, whereupon alcohol interchange takes place. Removal of the more volatile alcohol by distillation (often as an azeotrope with benzene) can generally

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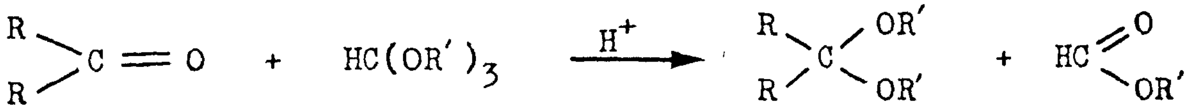
* The volatility of formaldehyde and acetaldehyde may be overcome by using the trimeric or polymeric forms.

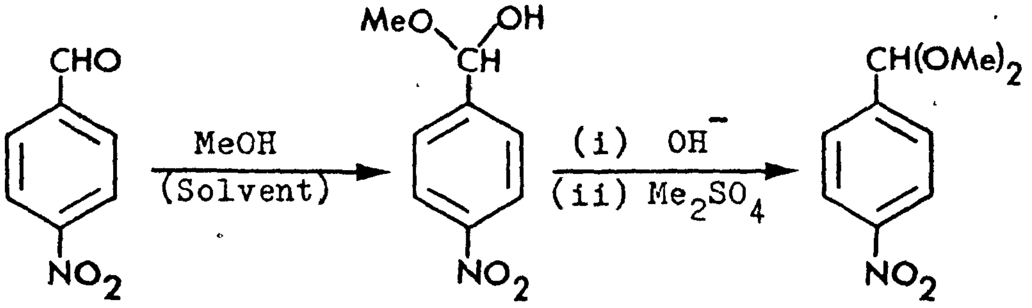
be achieved without loss of starting acetal, and thus the reaction is driven to completion (10). The mechanism is simply the last two equilibria in Equation 1.2. This method of synthesis is limited by the need for a starting material which is an acetal of the required carbonyl compound.

Orthoesters will convert almost any carbonyl compound into its acetal (Eq.1.3). This method is most useful for producing methyl and ethyl acetals (11), for which the orthoesters are commercially available. The acetals so formed may then be used as starting materials for transacetalation.



1.3

Base-catalysed acetal formation is successful with those carbonyl compounds which yield large quantities of hemiacetal in alcoholic solution (12). The reaction, an example of which is shown in Equation 1.4, has been applied so far only to carbohydrates and to very electron-poor carbonyl groups (e.g. benzil, ninhydrin and α-halogenated ketones), though it should also be successful with most simple aldehydes.



1.4

Other general methods not employed in this work are:

i. Acid-catalysed addition of alcohols (14, 15) or orthoesters (16) to acetylenes in the presence of mercuric ion or BF_3;

ii. Acid-catalysed addition of alcohols (17), acetals (18) or orthoesters (19, 20) to α,β-unsaturated ethers;

iii. Displacement of an alkoxy group from an orthoester by H-(diisobutylaluminum hydride) (21) or R-(Grignard or Reformatsky reagent) (22, 23);

iv. Alcoholysis of α-halo ethers — a reaction chiefly useful in carbohydrate chemistry (24);

v. Treatment of a gem-dihalide with an alcohol in the presence of a strong base (25, 41).

1.4 The Choice of Acetals Studied

Many of the acetals studied were chosen because their reductive cleavage by the $LiAlH_4$-$AlCl_3$ system had previously been investigated (26, 27), and thus they provide a means of comparing the new reactions with one that is well known. With two exceptions, compounds capable of *cis*-*trans* isomerism were avoided, as it seemed possible (28) that the results might depend on the *cis*-*trans* ratio of the mixture.

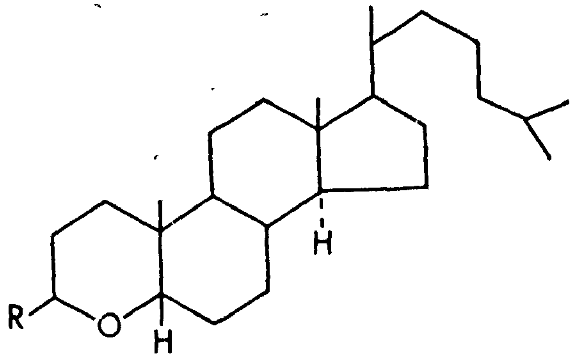
1.5 A Survey of Methods for the Hydrogenolysis of Acetals

Acetal groups in alkaline media are resistant to most reagents, including the strongest reducing agents. This resistance disappears if one of the oxygen atoms of the acetal becomes positively charged, either by protonation or by Lewis acid attack.

Table 1.1 shows the published methods for homogeneous hydrogenolysis of acetals. Except for Entries 5 and 8, all yields of reduced product — i.e. ether — are reported to be good (70% or over).

The active species of the "mixed hydride" reagents, Entries 3 and 4, are thought to be a hydridoaluminum chloride (37, 38) and a hydridoboron fluoride (34) respectively.

It is quite surprising that borane has not been tried before; its efficacy is certainly suggested by Entries 2 to 7 in Table 1.1. Indeed the system used by Pettit and Dias (Entry 5) to reduce hemiacetal 1 (R=OH) to the ether 1 (R=H) and acetal 2 (R=OMe) to ether 2 (R=H) — yields 44% and 47% respectively — may possibly proceed via borane; though more likely a hydridoboron fluoride is involved. (Jones (36) has shown that the reduction of alicyclic ketones by trimethylamine-borane/excess boron trifluoride mixture does not involve borane. The latter gives a quite different axial-equatorial product distribution.)



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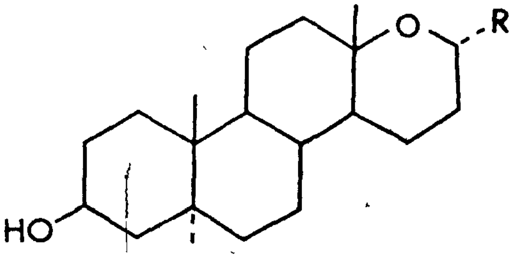

2

A number of patents (130-133) describe the cleavage of simple aliphatic acetals by $HCo(CO)_4$. The products are complicated by a concomitant hydroformylation reaction and further discussion is therefore reserved until Chapter 4.

While there are no reported homogeneous cleavages of acetals by other transition-metal catalysts akin to $HCo(CO)_4$, acetal hydrogenolysis by heterogeneous catalysis is well-known. For example, acetals of benzaldehyde (39, 40) and of benzophenone (41), are readily reduced by hydrogen in the presence of nickel and palladium catalysts. The stability of various sugar acetals to hydrogenolysis has been reviewed by de Belder (42), who noted that whereas benzylidene groups are vulnerable to hydrogenolysis in the presence of a palladium catalyst, isopropylidene, cyclohexylidene, ethylidene and methylidene acetals are not affected. Isopropylidene acetals can be hydrogenolysed under vigorous conditions in the presence of a copper chromite catalyst (43).

Ketals having β-hydrogens are readily reduced under mild conditions in the presence of acids and a rhodium catalyst (44). However this reaction proceeds <u>via</u> the α,β-unsaturated ether and is consequently an olefin reduction rather than the reductive cleavage of an acetal (Eq.1.5).

$$R_2CH\text{-}CH(OR)_2 \quad \overset{H^+}{\xrightleftharpoons{-ROH}} \quad R_2C{=}CHOR \quad \xrightarrow[Rh]{H_2} \quad R_2CHCH_2OR \qquad 1.5$$

TABLE 1.1

Reagents Available for Homogeneous Hydrogenation of Acetals

Entry #	Reagent	Postulated Active Species	Conditions	Reference
1	Triethylsilane $+ZnCl_2$		Ambient	29
2	Decaborane		120-130°	30
3	$LiAlH_4-AlCl_3$	$AlHCl_2$, AlH_2Cl	Ambient	27, 28, 31, 32
4	$LiAlH_4-BF_3$	BHF_2, BH_2F	Ambient	33, 34
5	$NaBH_4$-Excess BF_3		Ambient	35
6	Diisobutyl-aluminum hydride		Ambient to 80°	21
7	Aluminum hydride		Ambient	37
8	$Co_2(CO)_8/H_2/CO$	$HCo(CO)_4$	110-200°, 100-1000 Atm.	130-133

CHAPTER 2

THE REDUCTIVE CLEAVAGE OF ACETALS BY BORANE (BH_3)

2.1 Introduction

The reductive cleavage of acetals by borane (BH_3) discovered in the course of this work, may prove to have practical advantages over previously known methods of reducing acetals to ethers. Borane solutions in tetrahydrofuran (THF), readily available commercially, are stable when kept cold over long periods of time, and thus no preparation is required*. The boric acid product obtained after hydrolysis at the end of the reaction is readily removed by extraction with water, or by volatilisation as trimethyl borate. This procedure contrasts with mixed hydride systems containing aluminum, where either dilute acid must be used to decompose the aluminum complexes, or, if water is used, the aluminum hydroxide must be removed by filtration. Borane is, moreover, a milder, more selective reducing agent than mixed hydrides. For example, carbon-halogen bonds, cleaved by mixed hydrides, are stable to borane (53).

Consider Table 2.1 which shows the wide range of applicability of borane for reducing acetals. In each of the experiments described, an excess of borane was used, and the conditions were adjusted so that the reaction went to completion. Yields of ethers and hydroxyethers were good, with two exceptions: acetophenone diethyl ketal (Expt.2), from

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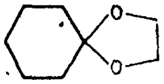
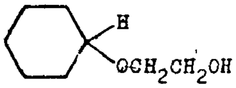
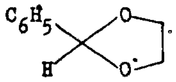
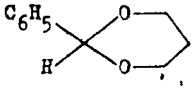
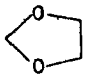
* Trimethylamine-borane ($Me_3\overset{+}{N}-\overset{-}{B}H_3$), also found to be effective for reducing reactive acetals when employed in acetic acid solution (Chapter 3), is a crystalline solid stable towards water. In certain reactions it may prove even more convenient.

TABLE 2.1

Reductive Cleavage of Simple Acetals and Ketals with Borane

Ex. #	Compound Reduced	Product	Yield, %	Reaction Time,[e] Hours
1	$C_6H_5CH(OMe)_2$	$C_6H_5CH_2OMe$	99[a], (90)[c]	24
2	$C_6H_5C(OEt)_2Me$	$C_6H_5CH(OEt)Me$	40[a], (35)	1[f]
3	$(Me)_2C(OC_4H_9\text{-}n)_2$	$Me_2CHOC_4H_9\text{-}n$	58[a]	48
4			90[b], (80)	15 (at 35°)
5		$C_6H_5CH_2OCH_2CH_2OH$	94[b], (85)	19
6		$C_6H_5CH_2O(CH_2)_3OH$	96[b], (92)	40
7		$MeOCH_2CH_2OH$	16[b,d]	24 (at 57°)

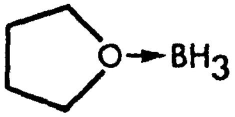
(a) Yields obtained by gas chromatographic analysis (±5%) of the crude reaction mixture after excess borane was decomposed. (b) By g.l.c. analysis of the ether extract. (c) Figures in parentnesis represent yields obtained after distillation. (d) 78% starting material remains. (e) At ambient temperature unless otherwise stated. (f) Reaction mixture became hot (50°) immediately after mixing. Mixing at -78°C and allowing to warm slowly to ambient temperature did not produce better yields.

which a large amount of non-distillable oily residue was obtained, and 1,3-dioxolane (Expt.7) in which the acetal (concentration 0.67M) apparently did not compete well with the THF solvent*.

For discussion of the details of acetal cleavage by borane, this chapter is divided into two main sections; the first (2.4) concerns the organic chemistry of acetal cleavage, the second (2.5) deals with the behaviour of the <u>borane</u> part of the borane-acetal complex. Initially, however, it is useful to summarize the preparation and relevant chemistry of the borane reagent.

2.2 The Nature and Preparation of "Borane in Tetrahydrofuran"

~~Dibor~~ane (B_2H_6) is a gas which is spontaneously inflammable in air, and consequently is difficult to handle in routine organic reactions. It is only slightly soluble in common hydrocarbon and ether solvents, with one exception: it dissolves readily in THF, where it evidently exists as the addition compound 3 (50, 51).



3

Solutions of borane (BH_3) in THF are prepared by treating sodium borohydride in diglyme with boron trifluoride etherate and passing the B_2H_6 gas, generated according to Equation ~~2.1~~, into THF (52).

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[*] The reaction of borane with THF at elevated temperatures has been studied previously (45, 49). On addition of water to the product of Expt.7, no hydrogen was evolved. G.l.c. of the product showed several peaks besides those of starting material and methyl cellosolve; one of them was due to n-butanol, presumably formed by reductive cleavage of THF (49).

$$3NaBH_4 + 4BF_3 = 2B_2H_6\uparrow + 3NaBF_4$$

2.1

$$B_2H_6 + 2\ THF \longrightarrow 2\ THF\cdot BH_3$$

Alternatively, a suspension of sodium borohydride in THF is treated with the requisite amount of boron trifluoride etherate, and the precipitated sodium borofluoride is filtered off.

2.3 Carbon-Oxygen Bond Cleavage by Borane in THF

The cleavage of C-O bonds by borane in THF is a well established phenomenon. It occurs, for example, during the following reductions*:

a) carboxylic acids (46-48), esters (45, 46) and lactones (46) to alcohols,

b) hindered esters and lactones to ethers (35),

c) amides to amines (53-55),

d) epoxides to alcohols (45, 56),

e) cleavage of THF to n-butanol, and 1-methyltetrahydrofuran to 2-pentanol (49),

f) p-dimethylaminobenzaldehyde and p-anisyl cyclopropyl ketone to hydrocarbons (57),

g) xanthol and xanthone to xanthene (58, 59), benzanthrone to benzanthrene (59), and benzhydrol to diphenylmethane (59).

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* Long and Freeguard (60) have reported that borane could be made to cleave ethers by addition of iodine:

$$6PhOMe + 3I_2 + B_2H_6 \longrightarrow 2B(OPh)_3 + 6MeI + 3H_2\uparrow$$

The iodine was rapidly decolourised and hydrogen was evolved. Bromine reacted similarly. It seems likely that these cleavages are actually reactions of BI_3 and BBr_3. Certainly, BBr_3 is well known for its cleavage of ethers yielding, as above, alkyl halide and borate (61, 62).

Of these examples, acetal cleavage most closely resembles the tetrahydrofuran reductions in example (e). These reductions were accomplished by heating the reagents at 60^{o} in a sealed tube for 2 to 3 days. The author (49) did not propose a mechanism for the reduction.

2.4 The Organic Chemistry of Acetal Cleavage by Borane

2.4.1 Modification of the Acetal Structure : Its Effect on the Rate and Position of Cleavage

i) The Effect of Substituents at C_2 and at C_4 on the Reaction Rate.

The relative rates of reductive cleavage of pairs of cyclic acetals having different substituents were compared by competitive reactions in which a mixture of two acetals (10mmol of each) was added to an excess of 1M borane in THF (see Table 2.2). After a short interval, the reaction was stopped and the products were hydrolysed by adding sodium carbonate solution. Gas chromatographic analysis of an ether extract of the mixture indicated the extent of reduction of each acetal. The rates of reduction of the two acetals should be directly proportional to the amounts of reduction products formed, with the following provisos (27):

a) the acetal molecule must participate in the rate-determining step,

b) the extent of reduction must be small so that the acetal concentration remains practically constant,

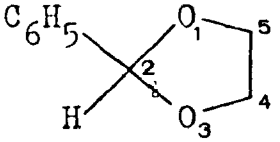
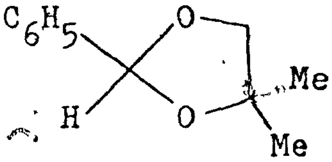
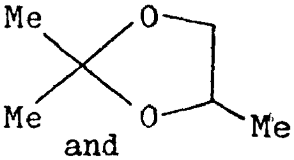
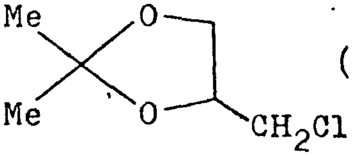
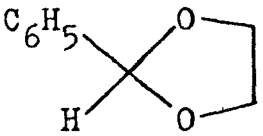
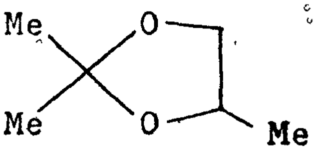
c) the reduction step must be irreversible,

d) little or no product must be lost by further reaction.

The first proviso is shown to be fulfilled in Section 2.5, and point (d) is satisfied by the good yields of product obtained. While there is no evidence for (c), oxidation of an ether in an excess of borane is hard to envisage.

TABLE 2.2

Competitive Reduction of Acetals by Borane in THF[a]

Expt. No.		Substrate		Total Products Formed, mmol	Reaction Time, min.
8^b			(4)	0.31,0.31[c]	20
9^b			(5)	2.3,2.4[c]	20
10	(a)		(6)	0.22	35
		and			
	(b)		(7)	0.025	
11	(a)		(4)	1.2	35
		and			
	(b)		(6)	0.24	

---

a) A mixture of two acetals (10 mmol of each) and 3ml of THF was added to 45ml of approximately 1M borane in THF at 0^{o}C.

b) Analysis of the products of competitive reduction was not possible in this case, so separate experiments were conducted simultaneously under identical conditions.

c) Duplicate experiments; borane solution diluted to about 0.8M to reduce the reaction rate.

Table 2.2 shows the results of competitive reductions of pairs of acetals with different substituents at C_4 and C_2.

Substitution of two methyl groups at C_4 on 2-phenyl-1,3-dioxolane increases the rate of cleavage of the acetal about seven fold (Experiments 8 and 9)*. On the other hand, substitution of an electron-withdrawing group at C_4 has the reverse effect (Experiment 10). The two acetals <u>6</u> and <u>7</u> in this experiment were chosen to be sterically very similar, but to have substituents with opposite inductive effects.

The activating effect of phenyl or pentamethylene substituents at C_2 is apparent from the conditions required for completion of reduction in Experiments 4, 5 and 7 (Table 2.1). Moreover, Experiment 11 (Table 2.2) shows that 2-phenyl-1,3-dioxolane (<u>4</u>) reacts faster than 2,2,4-trimethyl-1,3-dioxolane (<u>6</u>). Since the effect of a methyl group at C_4 is activating, a phenyl substituent at C_2 must be more activating than two methyl groups.**

In summary, the presence at C_2 or C_4 of electron-donating substituents speeds the reaction; phenyl substituents at C_2 also speed the reaction, whereas an electron-withdrawing substituent at C_4 slows the reaction.

---

* A competitive reduction of <u>4</u> and <u>5</u> was not possible owing to overlapping peaks on the gas chromatogram. Separate experiments (Ex.8 and 9) were therefore conducted simultaneously under identical conditions.

** In support of their carbonium-ion mechanism for mixed hydride reduction of acetals, Leggetter and Brown (27) compared their results with those of Kreevoy and Taft (63) who had studied the rate of acid-catalysed hydrolysis for a variety of simple C_2-substituted acetals. Generally similar trends were present, but there is an unexplained discrepancy: Kreevoy and Taft found two methyl substituents at C_2 to be more powerfully activating than a phenyl group, Leggetter and Brown found the reverse order — as is also found here with borane reduction.

ii) The Effect of Substituents at C_4 on the Direction of Cleavage

Table 2.3 illustrates how some substituents at C_4 on the dioxane and dioxolane rings influence the position of cleavage. The results presented in Tables 2.1, 2.2 and 2.3 are all strikingly similar to those obtained by other workers (26, 27) with the $LiAlH_4$-$AlCl_3$ reagent, and indicate that the course of borane cleavage may closely resemble the oxocarbonium-ion mechanism postulated for the mixed hydride reagent.

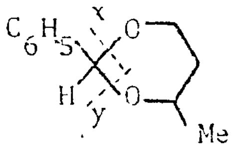
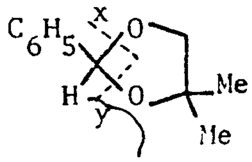
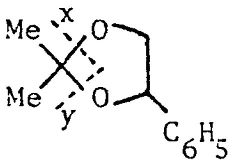
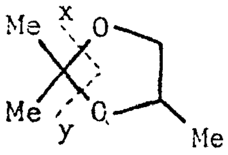
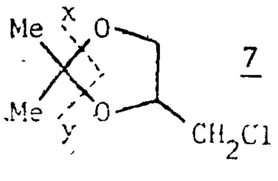
Preferential attack of borane at O_1 of the dioxane and dioxolane rings to give the most stabilized oxocarbonium ion (Scheme 2.1) would explain the results of Experiments 12, 13 and 15 (Table 2.3).

The cleavage of the C_2-O_3 bond which predominated in the reduction of 2,2-dimethyl-4-chloromethyl-1,3-dioxolane (7) (Experiment 16) is explicable by noting that the inductive effect of the substituent at C_4 is opposite to that of the corresponding substituents in the previous examples. Under the influence of an electron-attracting group, the most stable carbonium ion would be obtained, as illustrated in Scheme 2.2, by preferential borane attack at O_3. Thus it appears that electronic factors control the direction of cleavage — at least when steric hindrance is not extreme — for, had steric factors been important in the reaction of 7, the preferred attack would have been at O_1, as in Experiment 15, but the preference would have been even greater because of the bulk of the chlorine atom near O_3.

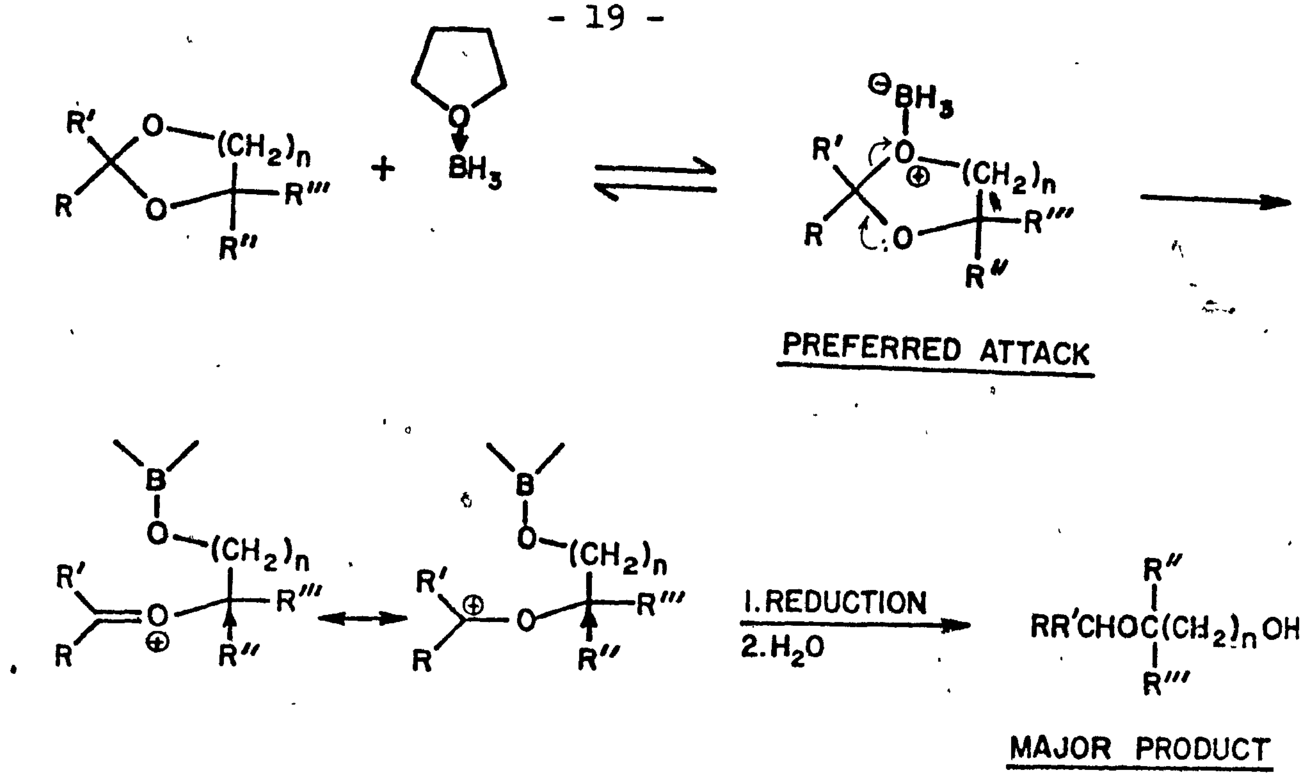
The very small influence observed here of a phenyl group at C_4 (Experiment 14) has also been noted in the mixed hydride reactions (27).

Overall, the results presented in this section provide strong evidence for the intermediacy of an oxocarbonium ion in acetal cleavage by borane.

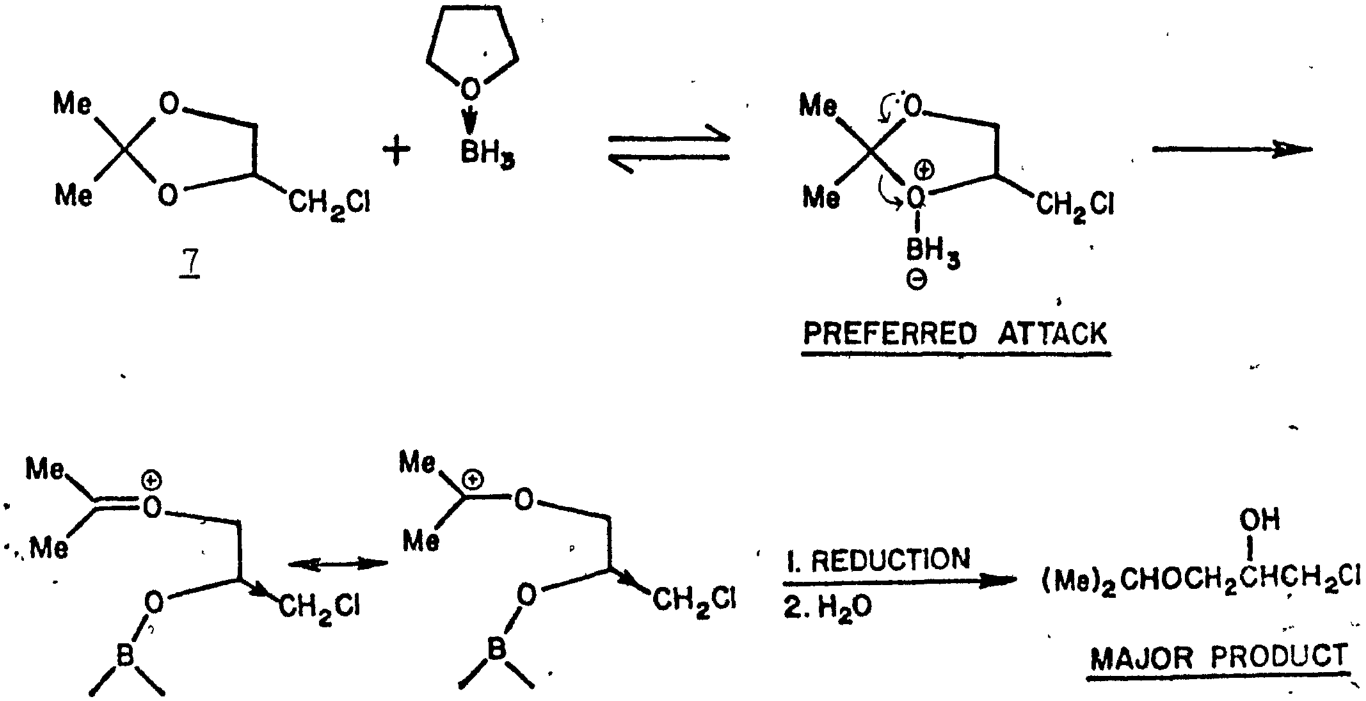
Table 2.3 Reductive cleavage of C_4-substituted dioxanes and dioxolanes

Expt. No.	Compound Reduced	Products Obtained	Yield,⁽¹⁾ %	Total Recovery of Product, %
12		$C_6H_5CH_2O\underset{Me}{C}HCH_2CH_2OH$ (cleavage at x) $C_6H_5CH_2OCH_2CH_2\underset{Me}{C}HOH$ (cleavage at y)	82 18	92
13	 5	$C_6H_5CH_2O\overset{Me}{\underset{Me}{C}}CH_2OH$ (cleavage at x) $C_6H_5CH_2OCH_2\overset{Me}{\underset{Me}{C}}OH$ (cleavage at y)	97 3	89
14		$C_6H_5\underset{OiPr}{C}HCH_2OH$ (cleavage at x) $C_6H_5\overset{OH}{C}HCH_2O\text{-}iPr$ (cleavage at y)	58 42	88
15	 6	$iPrO\overset{Me}{C}HCH_2OH$ (cleavage at x) $iPrOCH_2\overset{Me}{C}HOH$ (cleavage at y)	80 20	75
16	 7	$iPrO\overset{CH_2Cl}{C}HCH_2OH$ (cleavage at x) $iPrOCH_2\overset{CH_2Cl}{C}HOH$ (cleavage at y)	15 85	88

(1) The percentage of the isolated reduction product that is primary or secondary (tertiary) alcohol, as analysed by gas chromatography



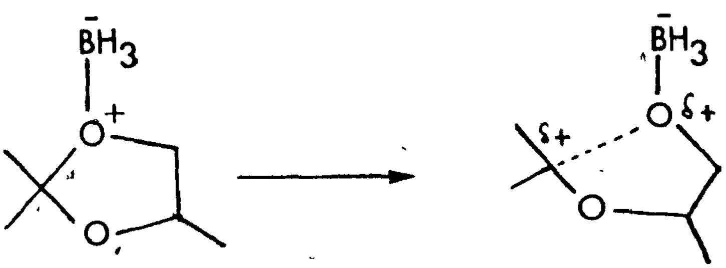
SCHEME 2.1



SCHEME 2.2

2.5 The Behaviour of the Borane Moiety during Acetal Cleavage

The behaviour of the borane moiety during acetal cleavage may be visualised by considering that as the C-O bond breaks (Scheme 2.3), the boron atom receives a greater share of the electrons from the hitherto strongly polarized O-B bond, and thus tends to become an alkoxyborohydride ion. It is unlikely, however, that such a species could exist uncoordinated in the presence of excess borane, for Brown* has observed that borohydride ion reacts with diborane in diglyme solution to give a complex ion, $B_2H_7^-$. Since alkoxyborohydride ions are more powerful nucleophiles than borohydride**, one expects reduction of borane by $ROBH_3^-$ species to proceed to a greater extent than reduction by BH_4^-.



Scheme 2.3

During acetal cleavage, energetically favourable complex formation (or complete hydride transfer) between the incipient alkoxyborohydride ion and neighbouring borane molecules can be anticipated. Since complex borohydride ion formation will reduce the overall activation energy for C-O cleavage, it is likely that the two processes will occur simultaneously. The observations presented in the following section provide evidence for this hypothesis.

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* Reference 46, page 86.

** Reference 46, page 246.

2.5.1 Kinetic Studies of the Reaction between Acetals and Borane in THF

Two acetals, one simple (benzaldehyde dimethylacetal) and one cyclic (2-phenyl-1,3-dioxolane), were chosen to exemplify the kinetics of the reaction between acetals and borane in THF. The procedure used for benzaldehyde dimethylacetal was as follows: standard dilutions of borane taken from a stock solution (1.15M) were made with dry THF. When the solution had equilibrated in a constant temperature bath for a few minutes, sufficient acetal was added to bring the concentration to 0.025M. The ratio of borane to acetal was deliberately made as high as possible so that the concentration of the former would be virtually constant throughout the reaction, thus simplifying the kinetics by reducing the rate Equation 2.1 to Equation 2.2 (pseudo first-order conditions).

$$\frac{d(\text{Product})}{dt} = k\,[\text{acetal}]^m\,[BH_3]^n \qquad 2.1$$

$$\frac{d(\text{Product})}{dt} = k_{obsd}\,[\text{acetal}]^m \qquad 2.2$$

$$k_{obsd} = k\,[BH_3]^n \qquad 2.3$$

After fixed time intervals samples of the reaction mixture were removed, quenched by addition of aqueous sodium carbonate, and the organic material was analysed by g.l.c. The experimental points are plotted out as curves in Fig.2.1. Many more points at longer times were obtained for the two lower curves. Fig.2.2 shows the same results plotted according to the integrated first-order equation:

$$k_{obsd} = \frac{1}{t}\log_e\frac{A}{A-x} \qquad 2.4$$

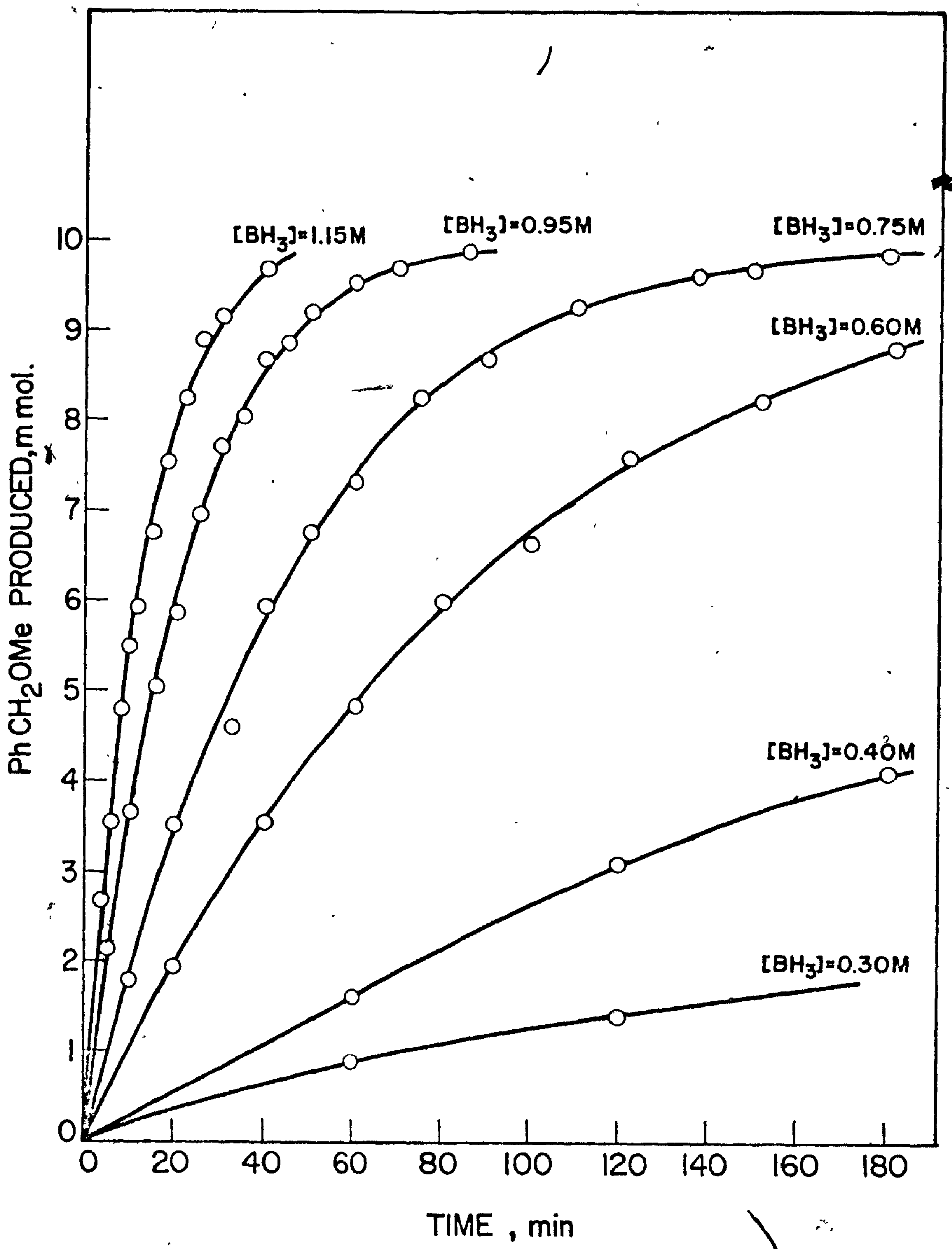

Fig.2.1 The reductive cleavage of ØCH(OMe)$_2$ (10 mmol) with borane in THF at 17°C.

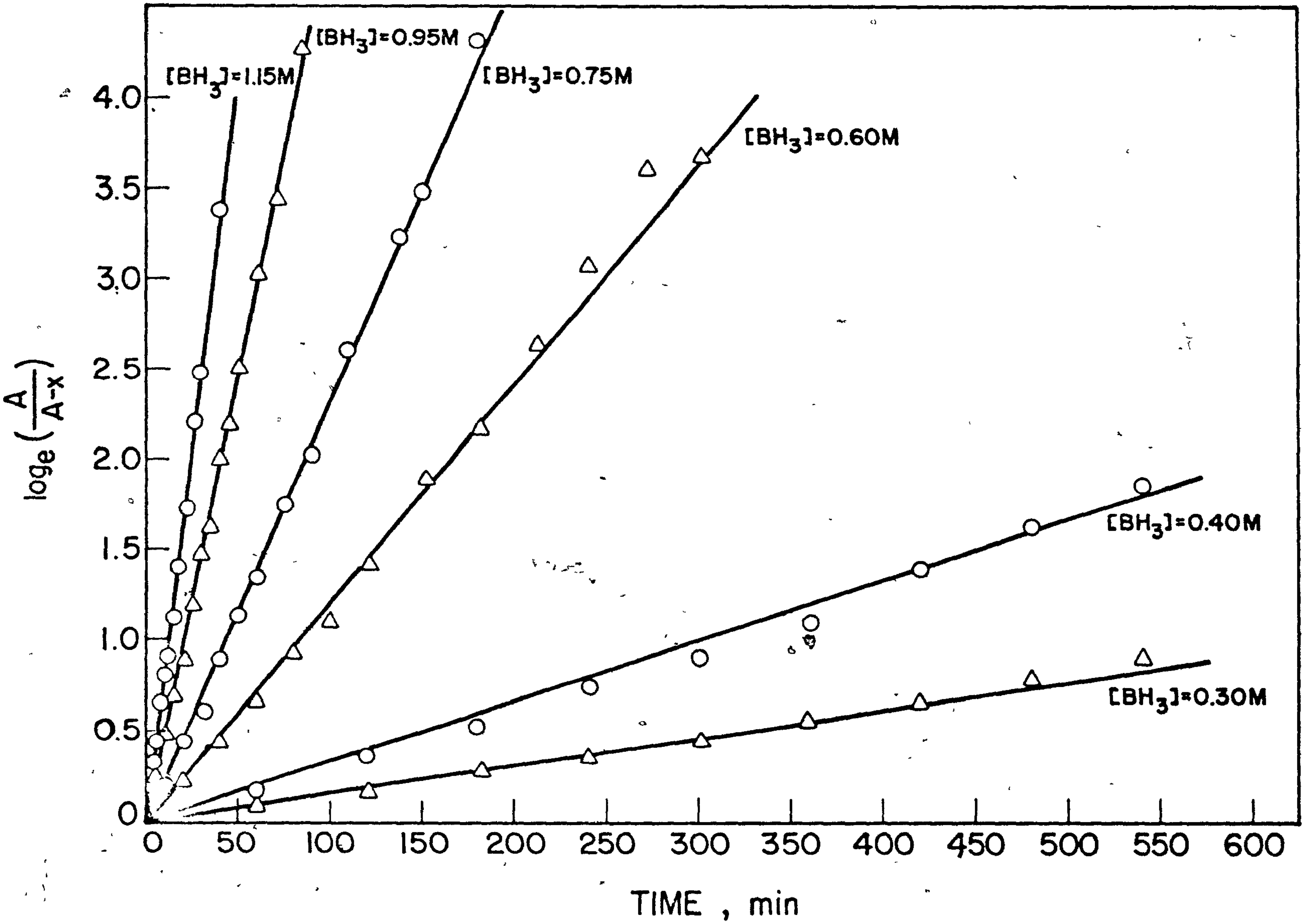

Fig.2.2 Pseudo first-order plot for the reaction of ØCH(OMe)$_2$ with borane in THF.

where A is the initial acetal concentration and x is the product concentration at time t*.

The majority of the experimental points lie very close to straight lines of zero intercept and we may conclude that the reduction is first-order in acetal. Towards the end of the reaction the plots exhibit a slight tendency to zero order.

The slopes of the pseudo-first-order graphs yielded the rate constants k_{obsd}. The dramatic effect of reducing the borane concentration can be seen from the values of k_{obsd} and the half-life periods shown in Table 2.4. A log-log plot of k_{obsd} <u>versus</u> borane concentration yielded the graph shown in Fig.2.3 — a straight line of slope 2.9**, This is the value of n (Eq.2.3). The y intercept of the graph yielded a k value of 5.4×10^{-2} min^{-1} $mole^{-2.9}$. The values for the rate constant k given in Table 2.4 were calculated from Equation 2.3 using $n = 2.9$.

Thus, within error limits, the reductive cleavage of benzaldehyde dimethylacetal appeared to be third-order in borane. Such a high order in borane was unexpected, and further experiments were therefore initiated to check this observation. This time a fresh batch of borane and a different acetal, 2-phenyl-1,3-dioxolane (4), were employed. After cleavage and hydrolysis, this acetal yields an alcohol which gives a slightly tailing peak in the gas chromatograph, causing some difficulty in analysing very small amounts of product. For this reason it was necessary to work with higher (0.208M) concentrations of acetal. Since the borane was no longer in large excess, pseudo first-order conditions did not obtain; therefore, the initial reaction rate was used to determine the order of reaction. Table 2.5 shows the initial rates over the region zero to 0.5mmol

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* For a discussion of the methods of determining the order of a reaction see ref.65.

** A slope of 2.91 was calculated by the least squares method; standard error around the fitted line = 0.058.

TABLE 2.4

Rates of Reduction of 0.025M Benzaldehyde Dimethylacetal by Borane in THF at 17°

Borane Conc. M	Half-life, min.	k_{obsd}, min^{-1}	k, min^{-1} $mole^{-2.9}$
1.15	9	0.079	5.7×10^{-2}
0.95	14	0.049	5.7×10^{-2}
0.75	30	0.023	5.3×10^{-2}
0.60	57	0.012	5.3×10^{-2}
0.40	200	0.0035	5.0×10^{-2}
0.30	400	0.0017	5.7×10^{-2}

TABLE 2.5

Rates of Reduction of 0.208M 2-Phenyl-1,3-dioxolane (4) by Borane in THF at 0°

Borane Conc., M	Time taken to form 0.5 mmol. Product, Δt, min.	Initial Rate**, $\frac{dx}{dt}$, mmol/min.
1.15*	6	0.085
0.95	10	0.052
0.75	19	0.026
0.60	33	0.015
0.40	117	0.0043
0.30	243	0.0020

---

* The nominal concentration of the stock solution from which accurate dilutions were made.

** An approximation made here is that over the range 0-0.5mmol reacted $\frac{\Delta x}{\Delta t} = \frac{dx}{dt}$

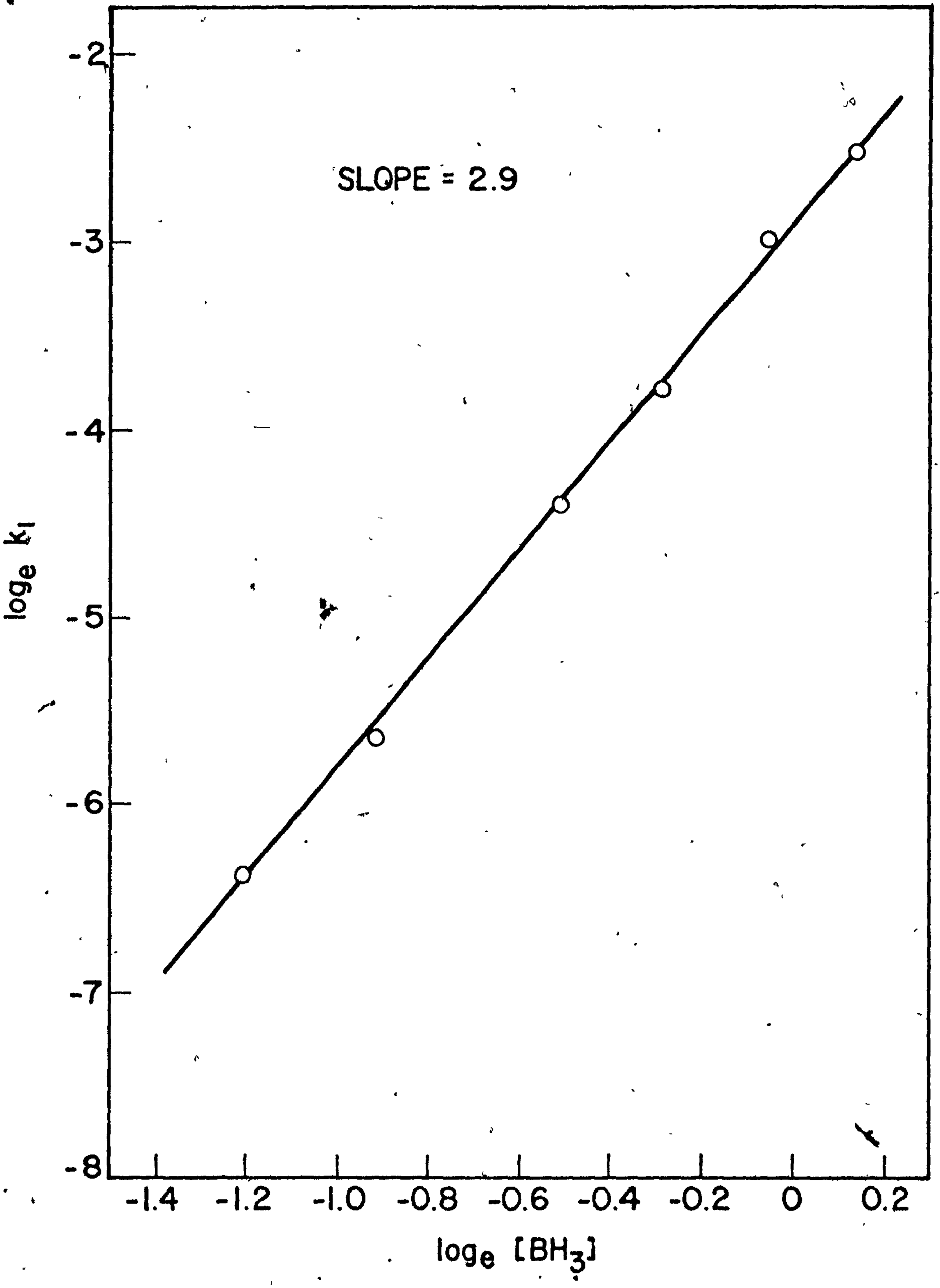


Fig.2.3 A log-log plot of the pseudo first-order rate constant against borane concentration.

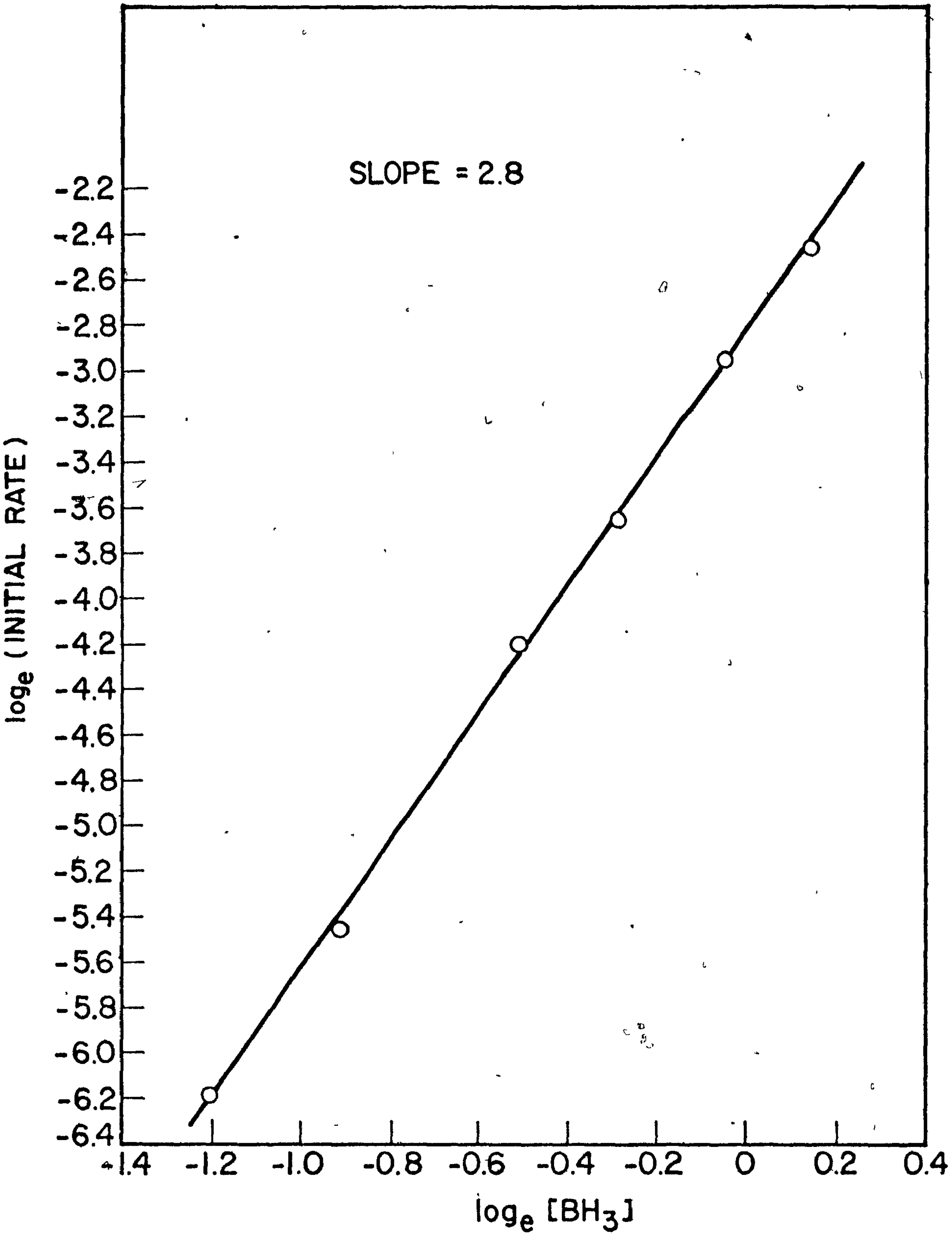


Fig.2.4 A log-log graph of the initial reaction rate versus borane concentration for 2-phenyl-1,3-dioxolane reduction.

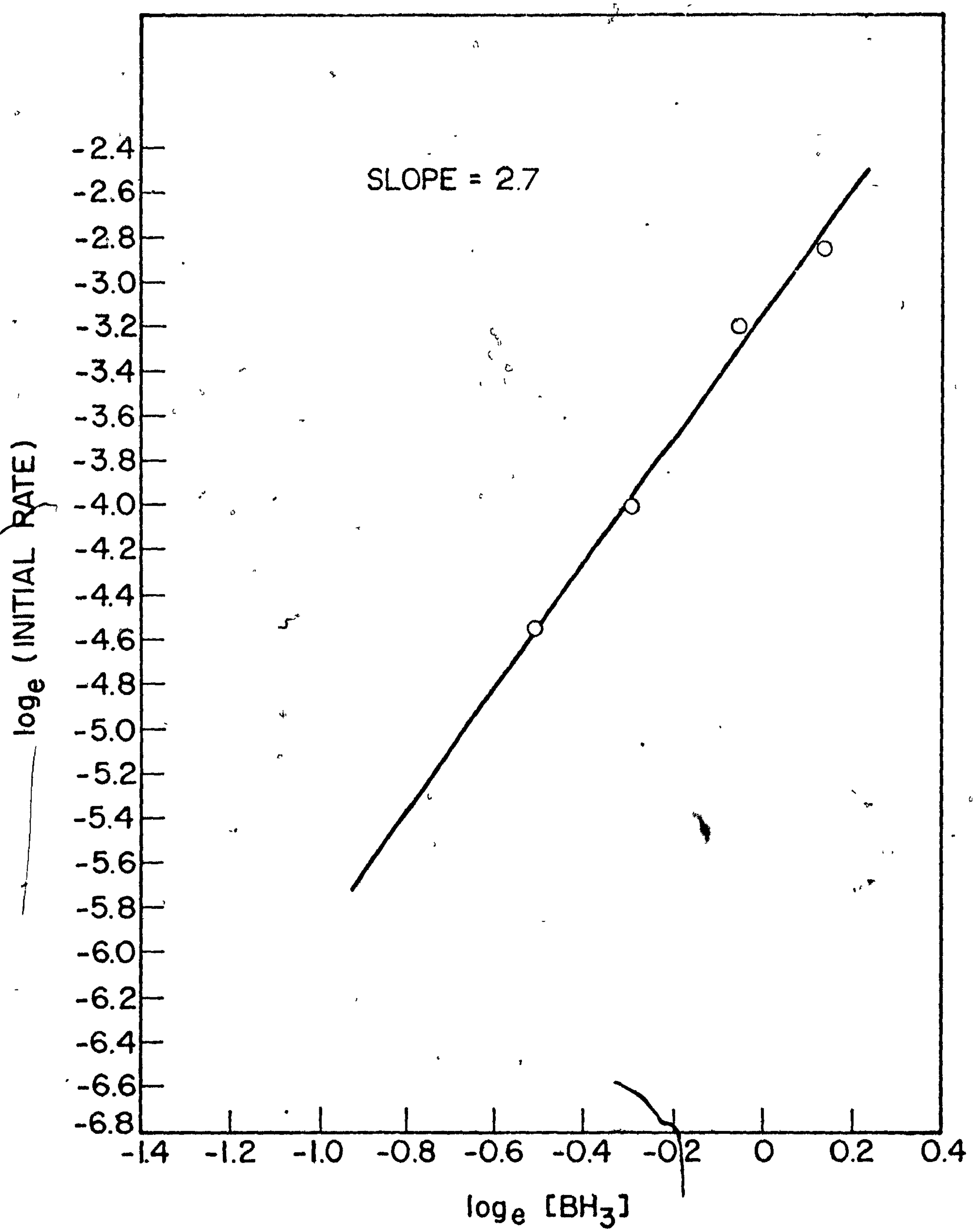


Fig.2.5 A log-log graph of the initial reaction rate versus borane concentration for the reduction of redistilled 2-phenyl-1,3-dioxolane.

of product formed (5% of total reaction), and Fig.2.4 shows the graph of $\log_e$ (initial rate) <u>versus</u> $\log_e [BH_3]$. The slope of 2.8[*] agrees well with that found for benzaldehyde dimethylacetal. As a double check, some of these experiments were repeated using redistilled acetal and a third batch of borane in THF. The results gave a $\log_e$ (initial rate) <u>versus</u> $\log_e [BH_3]$ graph of slope 2.7[**] (Fig.2.5).

2.5.2 The Mechanistic Implications of the Observed Kinetics

How can the observed kinetics — particularly the high order in borane — be explained? It was mentioned at the beginning of Section 2.5 that the transition state for acetal cleavage might involve more than one borane moiety[***]. To understand more clearly how this could occur, it is useful to examine the known chemistry of simple borohydride anions.

Metal hydrides reduce diborane to borohydride (Eq.2.5),

$$2\ M^+H^- + B_2H_6 \longrightarrow 2\ M^+BH_4^- \qquad 2.5$$

but in an ether solvent with an excess of diborane further reaction occurs (66) (Eq.2.6)[****].

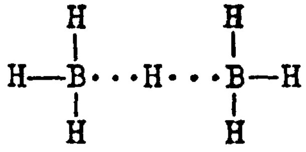
$$M^+BH_4^- + \tfrac{1}{2}B_2H_6 \longrightarrow M^+B_2H_7^- \qquad 2.6$$

---

[*] Calculated slope; 2.80, standard error; 0.045.

[**] Calculated slope; 2.73, standard error; 0.12 — within error limits these slopes are the same.

[***] Klein and Dunkelblum (64) found the reduction of carbonyl groups to be 3/2 order in 'B_2H_6' (THF solution) — thus showing this reduction to be much more complex than the originally proposed internal hydride transfer by a single borane unit (46).

[****] The ion $B_2H_7^-$ has been formulated  $\mathrm{H{-}\overset{H}{\underset{H}{B}}\cdots H\cdots\overset{H}{\underset{H}{B}}{-}H}$ (67) and is thought also to be bound to the solvent (68).

The overall equation of the reaction then becomes:

$$M^+H^- \quad + \quad B_2H_6 \longrightarrow M^+B_2H_7^- \qquad 2.7$$

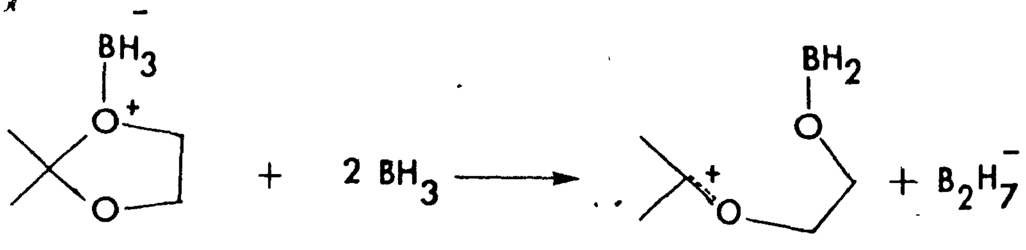
Alkoxyborohydride ions are more powerful hydride donors than BH_4^- owing to the availability of $p\pi$-$p\pi$ double bonding in the alkoxyborane $\underline{8}$ resulting from hydride donation (46) (Eq.2.8).

$$RO\bar{B}H_3 \xrightarrow{-H^-} \underset{\underline{8}}{RO{-}BH_2} \longleftrightarrow R{-}\overset{+}{O}{=}\overset{-}{B}H_2 \qquad 2.8$$

Therefore, it is not unreasonable to expect that in THF solution with an excess of borane the alkoxyborohydride ion would react as in Equation 2.9, which is analogous to Equation 2.7.

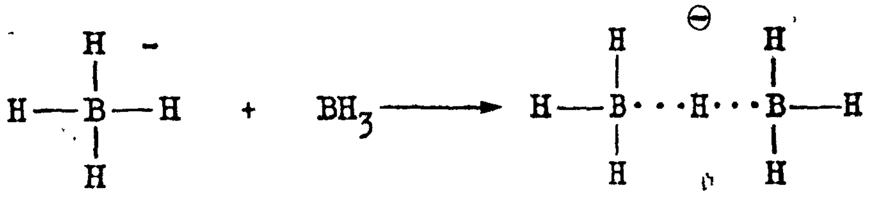
$$RO\bar{B}H_3 \quad + \quad B_2H_6 \longrightarrow ROBH_2 \quad + \quad B_2H_7^- \qquad 2.9$$

The reaction shown in Equation 2.9 would be energetically favourable, since even BH_4^- will reduce borane to $B_2H_7^-$. If this reaction occurs concomitantly with C-O cleavage of an acetal (Eq.2.10) the overall activation energy will be reduced because <u>instead of a high energy alkoxyborohydride ion resulting from cleavage, a much lower energy species — $B_2H_7^-$ will be formed.</u>



2.10

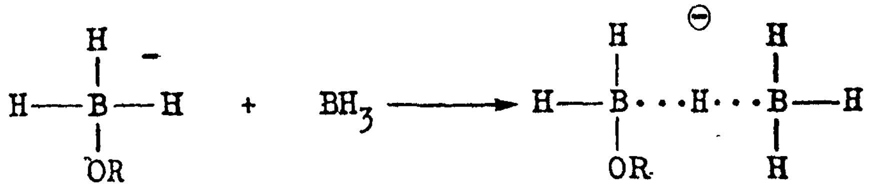
Let us examine this possibility in greater detail. The BH_4^- reduction of borane has been formulated as in Equation 2.11, writing $B_2H_7^-$ as a singly hydrogen-bridged ion (67).



$$BH_4^- + BH_3 \longrightarrow [H_3B\cdots H\cdots BH_3]^{\ominus}$$

2.11

By analogy with Equation 2.11, alkoxyborohydride reduction will first yield complex ion 9 (Eq.2.12).

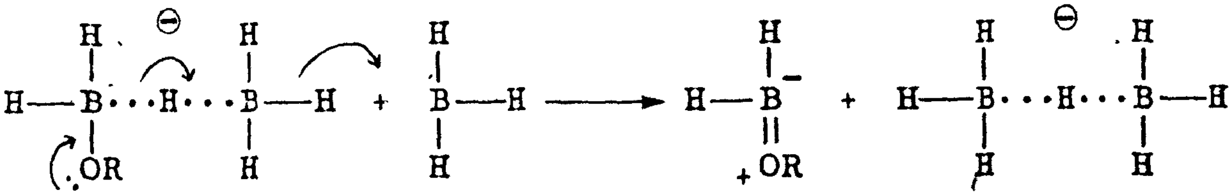


$$H_3B(OR)^- + BH_3 \longrightarrow [H_2(RO)B\cdots H\cdots BH_3]^{\ominus}$$

9

2.12

It seems likely, however, that in the presence of excess borane further reaction will occur (Eq.2.13) to yield an alkoxyborane (which is stabilised by pπ-pπ bonding) and $B_2H_7^-$ (the most stable borohydride anion under these conditions).

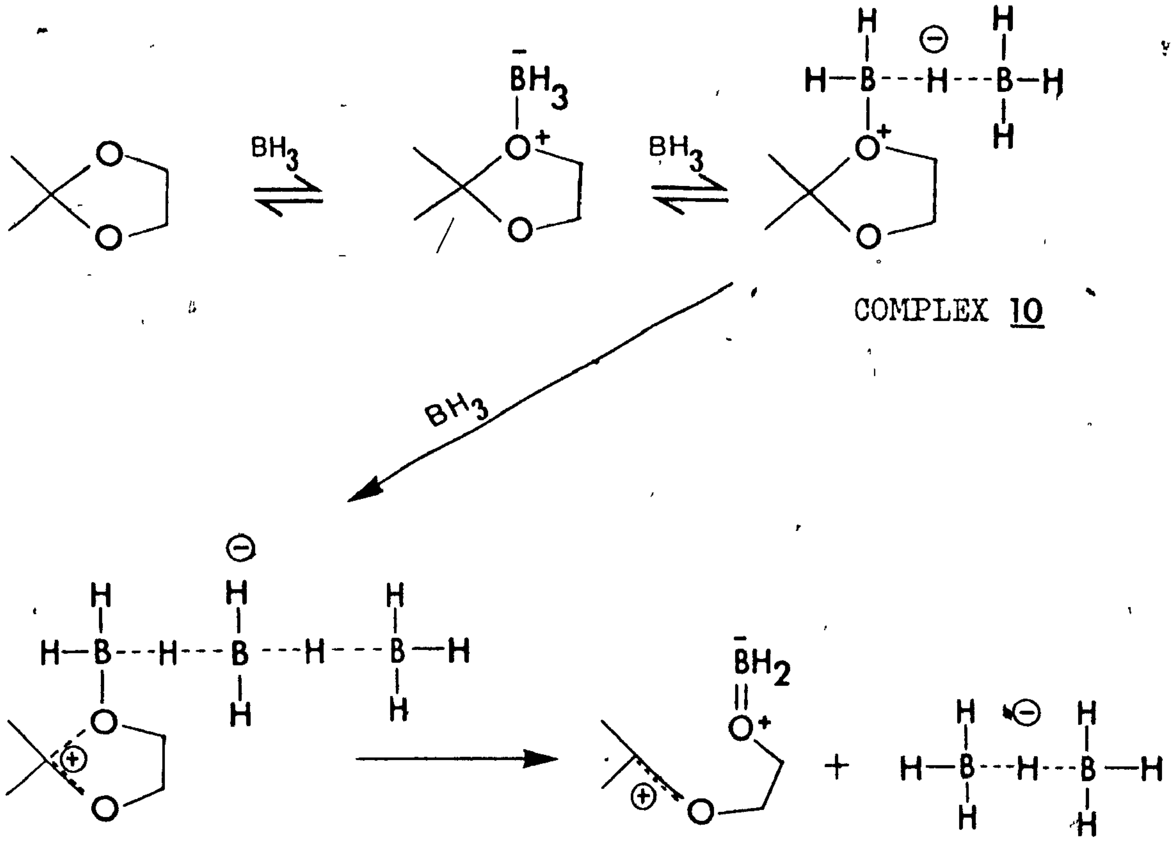


$$[H_2(RO)B\cdots H\cdots BH_3]^{\ominus} + BH_3 \longrightarrow H_2\bar{B}{=}\overset{+}{O}R + [H_3B\cdots H\cdots BH_3]^{\ominus}$$

9

2.13

If we now apply these ideas to acetal cleavage, we obtain Equation 2.14 (which is simply an expansion of Eq.2.10).

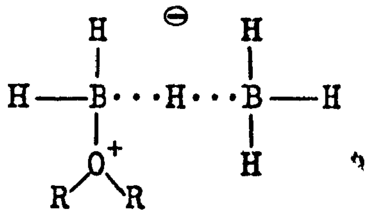


COMPLEX 10

TRANSITION STATE

2.14

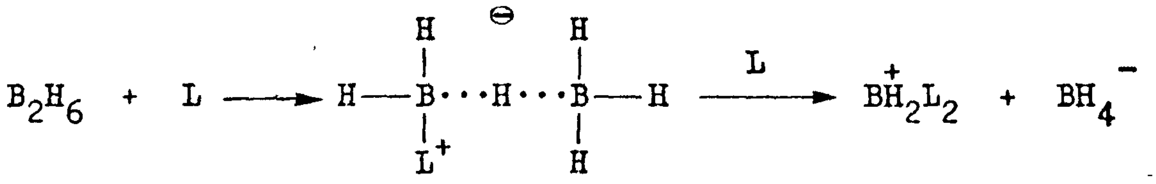
So far the argument is speculative, but the literature does contain some analogies. In order to explain the equivalence of the protons observed in ^{11}B n.m.r. spectra of B_2H_6 in diethyl ether and in diglyme, Gaines (69) has postulated the existence of species 11.



11

Infra-red studies (70) have shown that 5-membered, 2-substituted acetals have similar basicities to diglyme; consequently, if species 11 forms in diglyme, complex 10 can be expected in acetal-borane mixtures. Obviously, however, when the more basic THF is also present, the concentration of 10 will be small.

The second analogy, though a little more remote, concerns the transition state. Addition of diborane to excess base (L) at low temperatures causes unsymmetrical cleavage via a singly hydrogen-bridged intermediate 12 (71) (Eq.2.15).

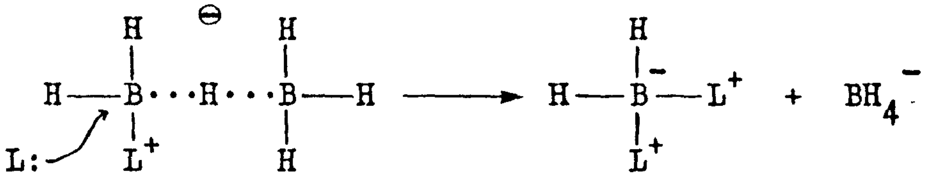


$$B_2H_6 + L \longrightarrow H{-}\overset{H}{\underset{L^+}{B}}\cdots\overset{\ominus}{H}\cdots\overset{H}{\underset{H}{B}}{-}H \xrightarrow{L} \overset{+}{B}H_2L_2 + BH_4^-$$

12

2.15

The second step presumably involves attack of a second molecule of base upon the intermediate 12 as in Equation 2.16, electron donation to boron displacing a BH_4^- ion.

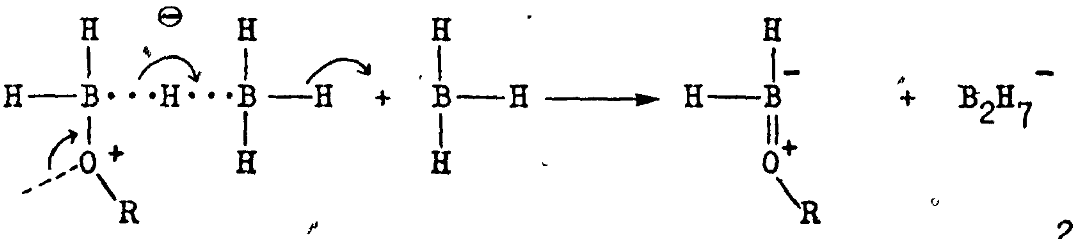


$$L{:} \; H{-}\overset{H}{\underset{L^+}{B}}\cdots\overset{\ominus}{H}\cdots\overset{H}{\underset{H}{B}}{-}H \longrightarrow H{-}\overset{H}{\underset{L^+}{\overset{-}{B}}}{-}L^+ + BH_4^-$$

12

2.16

Now compare the proposed mechanism of acetal cleavage (Eq.2.17):



$$H{-}\overset{H}{\underset{\overset{+}{O}-R}{B}}\cdots\overset{\ominus}{H}\cdots\overset{H}{\underset{H}{B}}{-}H + \overset{H}{\underset{H}{B}}{-}H \longrightarrow H{-}\overset{H}{\underset{\overset{+}{O}-R}{\overset{-}{B}}} + B_2H_7^-$$

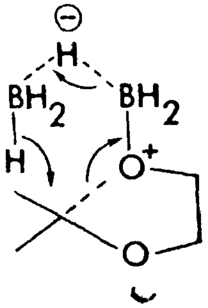
2.17

Here, it is pπ-pπ bond formation (rather than a second base molecule) which displaces the borohydride ion. In the presence of excess borane, $B_2H_7^-$ would be more readily formed than BH_4^-. Otherwise the reactions are analogous.

A final analogy concerns the hydride exchange between $B_2H_7^-$ and B_2H_6 which is known from n.m.r. observations to be rapid at room temperature (69). This exchange must pass through a transition state similar to that shown in Equation 2.14.

Thus, insofar as the reactions described here are generally applicable, they explain how the reduction of acetals can be third-order in borane.

It is not clear at present whether the orders 2.9 and 2.8 in borane found here represent third-order reactions within experimental error, or whether perhaps there is a contribution from a transition state involving only two borane molecules, e.g. 13. If some acetal were cleaved via transition state 13, the observed order in borane would obviously be less than 3.0.



13

2.5.3 The Reaction of Borane with Excess Acetal

In this experiment the tables were turned — an excess of acetal, not borane, was employed. Thus, from the yield of reduced product it is possible to determine whether all three hydrogens of borane are available for acetal reduction*. The analysis results revealed that for every available hydrogen atom initially present in the borane solution, one molecule of

---

* Brown and Korytnyk (48) have shown that the third hydrogen of borane reacts very slowly with ketones and nitriles.

acetal was reduced to ether after 18 hours at 30° *. Consequently, under these conditions, all three hydrogens of borane are available for acetal reduction.

2.6 Selectivity in Borane Reductions

In reference 46, page 250, H.C. Brown states: "....carboxylic acid and aldehyde groups possess reactivities that would be competitive with the hydroboration reaction. Fortunately ... aldehyde groups can be protected as the acetals."

It is clear from the work presented in this thesis that this protection will not be complete under all experimental conditions. However, it will generally be easy to effect selective hydroborations on molecules possessing both olefinic double bonds and acetal groups provided that low temperatures are employed and an excess of borane is avoided. The rate of hydroboration is immeasurably fast even at temperatures below zero, whereas cyclic acetal cleavage requires hours at 30-50° for completion. Selectivity could be further improved by using dilute THF solutions, since acetal reduction is close to third-order in borane and hydroboration of olefins is first-order in diborane (64).

Descriptions of such selective reductions are to be found in the literature. For example, Lehmann (72) has been successful in the hydroboration of carbohydrate derivatives having a double bond and isopropylidene groups. He employed a slight excess of borane for two hours at room temperature. Likewise hydroboration of unsaturated steroids has been accomplished when ketal groups were present (73).

Carboxylic acid groups are also extremely reactive to borane (46, 48) and selective reduction in presence of acetals should present no problem. However, no generalisations can be

---

* Details are given in 8.2.3.

made for more slowly reacting groups like nitriles, epoxides and esters. For these compounds, selective reduction in the presence of acetals will depend on the particular structures concerned.

CHAPTER 3

TRIMETHYLAMINE-BORANE AS A REDUCING AGENT FOR ACETALS

3.1 Introduction

Trimethylamine-borane (74) is one of a series of amine-borane complexes whose properties resemble those of borohydrides rather than borane. For example, such complexes reduce quinones and acid chlorides (75) and slowly reduce ketones (fast if boron trifluoride is present) (36). They do not reduce nitro, carboxyl, carbethoxy and sulphonamido groups, but trimethylamine-borane can reduce amides to amines in some instances (77). The complexes reduce Schiff's bases to amines when glacial acetic acid is used as solvent (76, 77). Billman and McDowell (77) found that with trimethylamine-borane, the amine product became acetylated under these conditions; no acetylation occurred in absence of trimethylamine-borane.

The rate of reduction by amine-borane complexes decreases in the series methylamine > dimethylamine > trimethylamine (75).

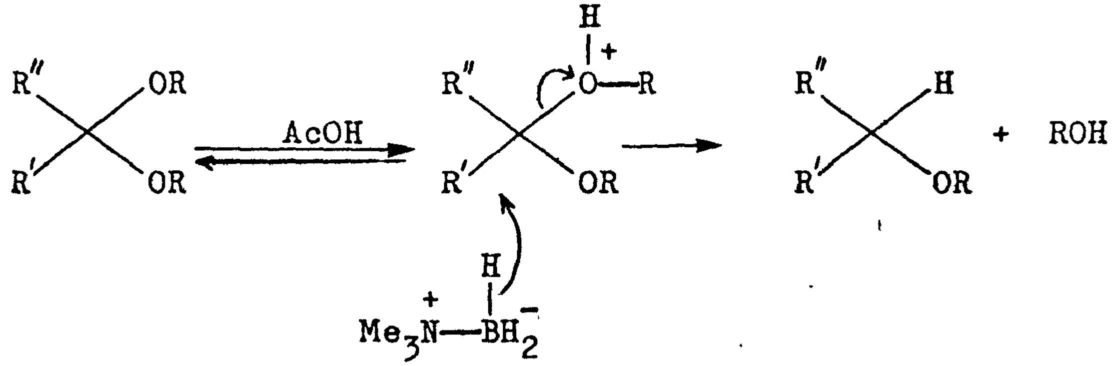
Amine-borane complexes can effect the hydroboration of olefins (78-80) but only at elevated temperatures where, it is thought, the complexes are partially dissociated (79).

3.2 The Reduction of Acetals

Towards the end of this work, we discovered that acetals are reduced by trimethylamine-borane in glacial acetic acid. The first acetal examined, benzaldehyde dibenzylacetal, gave good yields of the normal cleavage products under mild conditions (Table 3.1, Experiment 2). Further examination, however, (Experiments 4 and 5) showed that the reductions were more complex than they had first appeared to be.

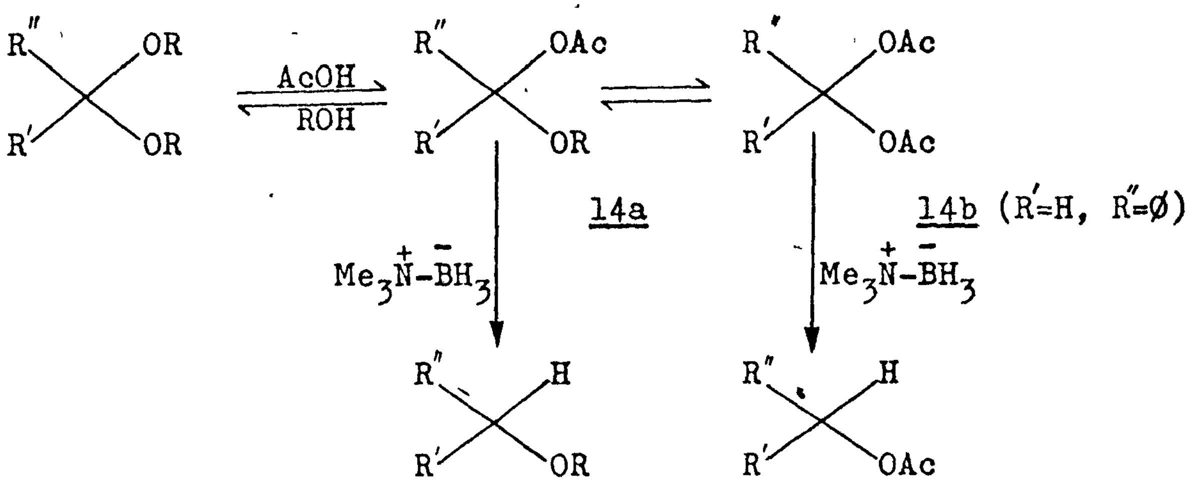
3.2.1 The Reduction of Benzaldehyde Dibenzylacetal (23)

Compound 23 was not reduced by trimethylamine-borane in diglyme solution, even at 100° (Table 3.1, Experiment 1); the presence of acetic acid thus appears to be crucial. However, the rôle played by the acetic acid is not clear. It may, as Fieser and Fieser suggest (81), serve simply to liberate borane from the complex, but in view of the extreme reactivity of borane with carboxyl groups (47), the formation of free borane in glacial acetic acid solution does not seem likely. An alternative explanation is that the acetic acid protonates the substrate, which is then attacked by the amine-borane complex acting as a hydride donor (Eq.3.1).



3.1

A second possibility is that the reaction is actually a reduction by trimethylamine-borane (Eq.3.2)* of a first-formed hemiacetal acetate (14a).



3.2

As applied to compound 23, the equation shows how the reduction of an intermediate benzaldehyde diacetate (14b), which would also be expected in acetic acid solution, would yield one of the observed products — benzyl acetate. There are other routes to this product; for example, a blank experiment revealed that pure benzyl alcohol is partly acetylated by the solvent alone under the reaction conditions (Table 3.1, Experiment 3). However, the sum of the benzyl alcohol and the benzyl acetate yields exceeds 100 mole percent, based on the starting acetal (Experiment 2), thus providing evidence for the formation of some benzyl acetate via an intermediate diacetate of the type 14b.

---

* The reaction of acids and acetals to yield aldehyde diacetates like 14b is briefly mentioned in ref.5(p.443). The latter compounds are more usually prepared from the aldehydes, or from acetylenes (82).

The formation of 14a would be analogous to the preparation of 1-O-cyclohexylmethanoyl-2-acetyl-β-D-glucose by treatment of β-D-glucose-1,2-ethyl orthoacetate with cyclohexylcarboxylic acid (83).

A steady evolution of hydrogen gas was evident throughout the reduction, and could result from solvent attack on the species $Me_3\overset{+}{N}-BH_2$ remaining after the hydride transfer step.

3.2.2 The Reduction of Cyclohexanone Ethylene Ketal (13a)

The reduction of 13a with an equimolar amount of trimethylamine-borane was slow at room temperature, and even at 50° was only 62% complete after 24 hours (Table 3.1, Experiment 4). A small sample of the reaction mixture was shaken with concentrated aqueous sodium carbonate, extracted with benzene, and the extract was washed with water. G.l.c. analysis of the extract revealed unreacted starting material, the expected products 2-cyclohexyloxyethanol and its acetylated form (1-acetoxy-2-cyclohexyloxyethane), and, in addition, a small amount of a high boiling component. The latter, after isolation, was identified from its p.m.r. spectrum as 1,2-dicyclohexyloxyethane*.

During the isolation of the product compounds, the reaction mixture was shaken with concentrated aqueous sodium carbonate and extracted with ether. The extract was dried over anhydrous sodium carbonate and distillation was attempted without having washed the extract with water. The first distillate fraction consisted of a mixture of unreacted ketal and trimethylamine-borane, the latter crystallising in the receiver. Thereafter only a small amount of 2-cyclohexyloxyethanol and its acetate distilled. A large quantity of liquid remained in the distillation flask, and when water was added, white crystals of boric acid separated, indicating that the bulk of the product alcohol had been present as its borate.

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* By comparison with Experiment 5, cyclohexyl acetate was also expected and was therefore carefully sought; none was found. Any ethylene glycol present among the products would have dissolved in the aqueous sodium carbonate, thus escaping detection.

The boric acid formed was removed as the volatile trimethyl borate by repeatedly adding methanol and evaporating, after which 2-cyclohexyloxyethanol was readily distillable, leaving 1,2-dicyclohexyloxyethane (<u>13c</u>) as residue.

3.2.3 The Reduction of 2-Phenyl-1,3-dioxane (<u>4a</u>)

During the reduction of <u>4a</u> (25 mmol) with trimethylamine-borane (25 mmol), the volume of the evolved hydrogen was measured; it amounted to 29 mmol. Gas evolution ceased after 70 hours at 50°, and 99% of the starting acetal was found to be consumed, with almost all of it appearing as reduction products (Experiment 5). The stoichiometry suggests that only one active hydrogen atom of trimethylamine-borane is available for reduction, the other two appearing as hydrogen gas as the reaction proceeds.

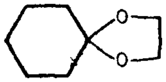
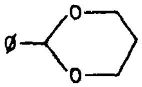
During the isolation of the organic products, boric acid (1.05g, 68%) was once again obtained as a by-product of decomposition of the borate complexes with water. Some 1,3-propanediol was also recovered from an aqueous extract of the product mixture. The identity of all the product compounds was confirmed by comparison of physical properties with those of authentic materials.

The only satisfactory explanation the author can devise for the formation of the diethers 1,2-dicyclohexyloxyethane (<u>13c</u>) and 1,3-dibenzyloxypropane (<u>4c</u>) involves a transacetalation reaction between product alcohol and starting material to yield acyclic acetals (<u>13b</u>, <u>4b</u>), which yield the diethers by reductive cleavage (Schemes 3.1 and 3.2). Similar transacetalations between product alcohols and starting acetals under acidic conditions are discussed more fully in the next chapter, where diethers were also discovered among the products of the reaction of acetals with $HCo(CO)_4$.

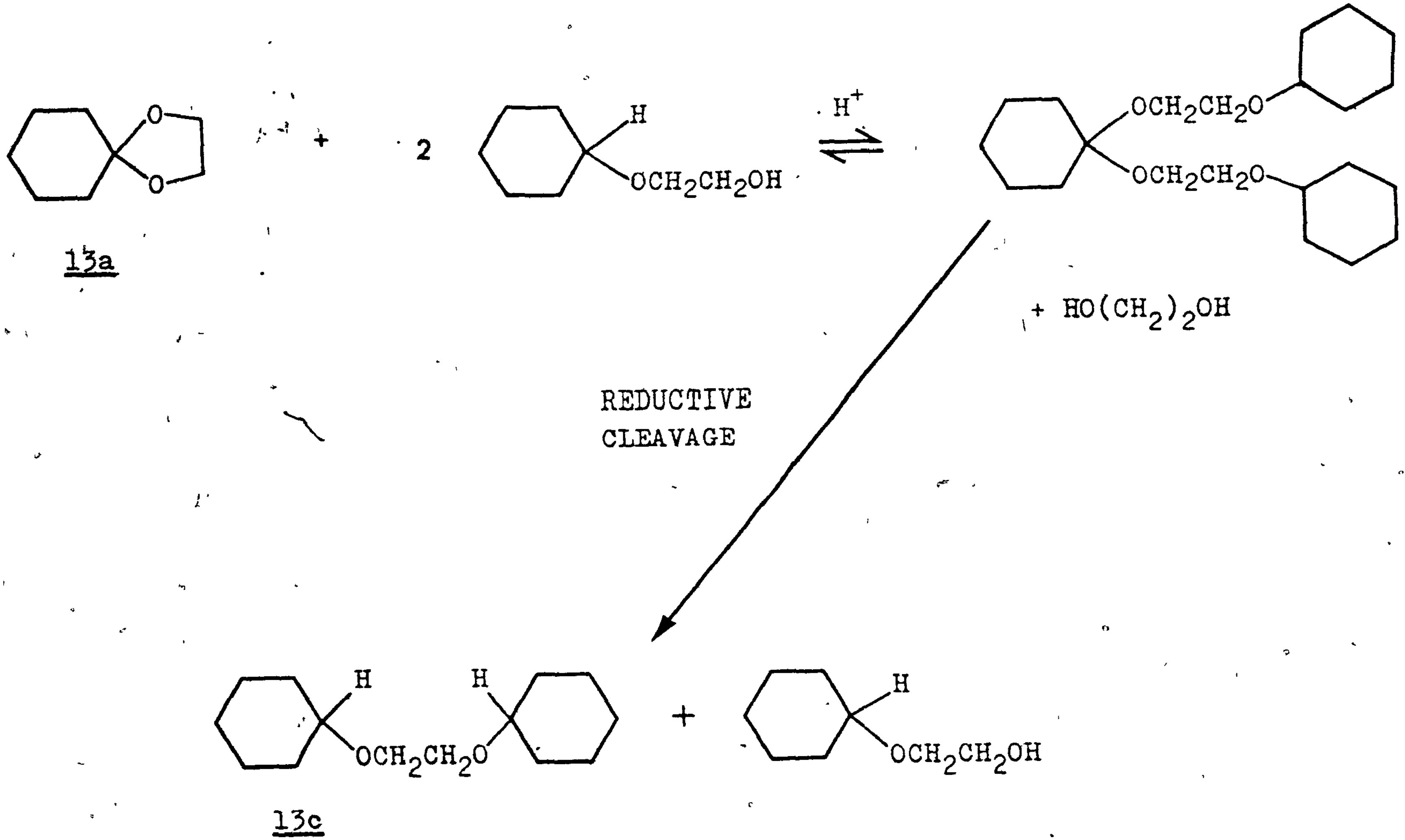
For the moment, let us merely note that the transacetalation reaction explains the formation of both diether and free diol (Experiment 5).

TABLE 3.1

The Reduction of Acetals by Trimethylamine-Borane[a]

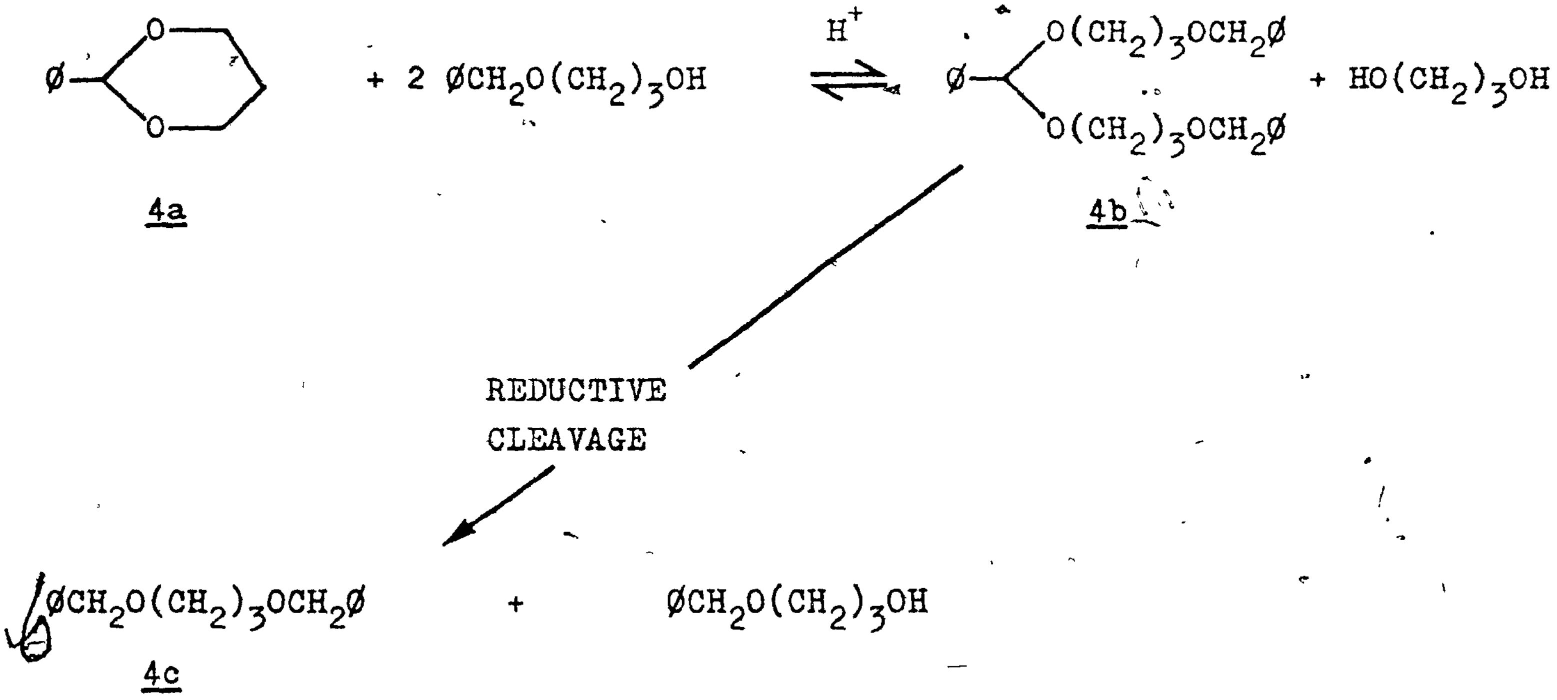
Ex. #	Starting Material	Solvent	Conditions	Products Found, %			Starting Acetal Remaining, %
1	$\text{Ø}CH(OCH_2\text{Ø})_2$ (23)	Diglyme[b]	100°, 72h.	Nil			96
2	$\text{Ø}CH(OCH_2\text{Ø})_2$ (23)	Acetic acid	27°, 52h.[c]	dibenzyl ether benzyl alcohol benzyl acetate	92[d] 90 13	(88)[e] (91) (12)	0
3	$\text{Ø}CH_2OH$	Acetic acid	26°, 52h. Me_3N-BH_3 omitted	benzyl alcohol benzyl acetate	90 10		-
4	 (13a)	Acetic acid	50°, 24h.	2-cyclohexyloxyethanol 1-acetoxy-2-cyclohexyloxyethane (13c) 1,2-dicyclohexyloxyethane	50 5 7	(41) (2) (3)	38 (29)
5	 (4a)	Acetic acid	50°, 70h.	3-benzyloxy-1-propanol 1-acetoxy-3-benzyloxypropane (4c) 1,3-dibenzyloxypropane benzyl acetate 1,3-propanediol	40 38 19 2 -	(35) (31) (23) (2) (18)	1

(a) 25 mmol of acetal and trimethylamine-borane used throughout. (b) Purified according to ref.215. (c) G.l.c. revealed the reaction to be 97% complete after 23h. (d) Yields are given in mole percent based on the starting material; analysis by g.l.c. (e) Isolated yields are given in parentheses.



13a
+
2
H
OCH2CH2OH
H+
OCH2CH2O
OCH2CH2O
+ HO(CH2)2OH
REDUCTIVE
CLEAVAGE
H
H
OCH2CH2O
13c
+
H
OCH2CH2OH

SCHEME 3.1


Ø
O
O
+ 2 ØCH2O(CH2)3OH
H+
Ø
O(CH2)3OCH2Ø
O(CH2)3OCH2Ø
+ HO(CH2)3OH
4a
4b
REDUCTIVE CLEAVAGE
ØCH2O(CH2)3OCH2Ø
+
ØCH2O(CH2)3OH
4c

SCHEME 3.2

CHAPTER 4

THE REDUCTIVE CLEAVAGE OF ACETALS BY $HCo(CO)_4$

4.1 Hydrocobalt Tetracarbonyl and the Oxo Process

In 1938 Roelen (84, 85) discovered the oxo reaction — the conversion of olefins into higher aldehydes by hydrogen and carbon monoxide in the presence of a catalyst containing cobalt (Eq.4.1). Under more drastic conditions, aldehydes are reduced to alcohols.

$$R\text{-}CH{=}CH\text{-}R' + H_2 + CO \xrightarrow[\text{100-140}^{\circ}]{\text{cobalt catalyst}} RCH_2CH(R')CHO + R'CH_2CH(R)CHO \qquad 4.1$$

Although a conventional Fischer-Tropsch catalyst* was used in the early experiments, Roelen soon realised that the active catalyst was a soluble cobalt carbonyl. This conclusion was later confirmed by Adkins and Krsek (88) who used dicobalt octacarbonyl ($Co_2(CO)_8$) as catalyst. During the nineteen fifties and sixties, considerable evidence accumulated indicating that $HCo(CO)_4$, rather than $Co_2(CO)_8$, was the active species (88-94).

Nowadays the oxo process is of great commercial importance; about 2.7 million tons of oxo products (chiefly butyraldehydes obtained from propylene) were manufactured in 1970 (95). In step with the commercial development of the oxo process, a great deal of fundamental work has been done on it and on related reactions, and several reviews have been published (96-107).

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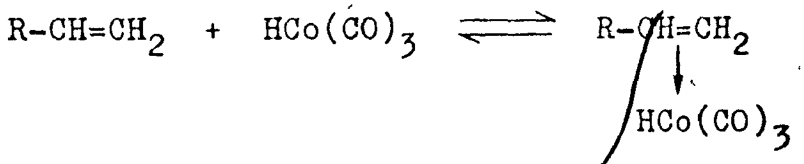
* Cobalt-thoria-magnesia-kieselguhr (100:5:8:200).

Although $HCo(CO)_4$ is strongly acidic* (108-112) only <u>cis</u>-addition to olefins occurs under <u>oxo</u> conditions (92, 103, 114, 267, 268). Moreover, the direction of addition can be Markownikoff or anti-Markownikoff depending upon conditions (92). To reconcile these facts and also to explain the inverse dependence of the hydroformylation rate on the partial pressure of carbon monoxide (115), Heck and Breslow (92, 116) have postulated hydrocobalt tricarbonyl ($HCo(CO)_3$) to be the true active species under most conditions — formed as in Equation 4.2.

$$\tfrac{1}{2}Co_2CO_8 + H_2 \rightleftharpoons HCo(CO)_4 \rightleftharpoons HCo(CO)_3 + CO \qquad 4.2$$

The species $HCo(CO)_3$ has not been detected, but in catalytic systems the most reactive species are often present at the lowest concentrations and are consequently the most difficult to identify (117). $HCo(CO)_3$ is a coordinately unsaturated species which, in additions to olefins, would be expected to behave rather like diborane (Eq.4.3).



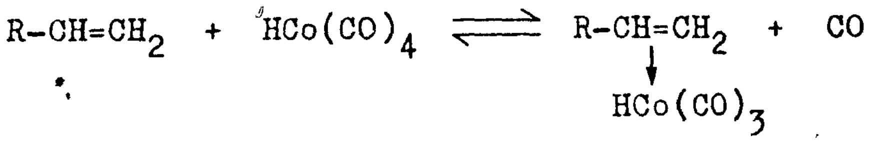
$$R\text{-}CH{=}CH_2 + HCo(CO)_3 \rightleftharpoons \underset{\displaystyle HCo(CO)_3}{R\text{-}\overset{}{CH{=}CH_2}\big\downarrow} \qquad 4.3$$

---

* The acidic properties of $HCo(CO)_4$ are somewhat mysterious. Though of mineral acid strength, $HCo(CO)_4$ is not very soluble in water (saturated solution = 0.056M at room temperature (111)) and is readily extracted by organic solvents! The acidity of this substance derives from the stability of $Co(CO)_4^-$; an anion of inert gas structure, isoelectronic with $Ni(CO)_4$, but possessing a negative charge which strengthens metal-ligand bonding.

The low solubility of $HCo(CO)_4$ in water is especially puzzling since the free energy of solution of the gas in water has been calculated to be about -135Kcal/Mole (113) — consequently solution should be a highly favoured process.

An alternative explanation is that coordination of the olefin to $HCo(CO)_4$ (115) occurs with simultaneous displacement of a CO ligand (Eq.4.4).



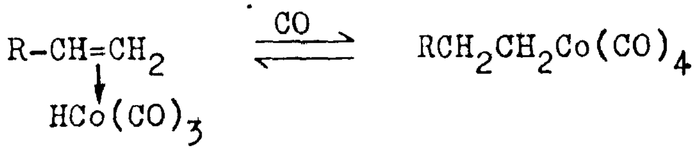
$$\mathrm{R{-}CH{=}CH_2} + \mathrm{HCo(CO)_4} \rightleftharpoons \underset{\substack{\downarrow \\ \mathrm{HCo(CO)_3}}}{\mathrm{R{-}CH{=}CH_2}} + \mathrm{CO}$$

4.4

According to this scheme free $HCo(CO)_3$ would not be present, but the inhibiting action of carbon monoxide would still be operative.

A general concensus has been reached about the remaining steps of the oxo reaction. They are:

(i) conversion of the π-alkyl to a σ-alkyl complex with hydride transfer (Eq.4.5).



$$\underset{\substack{\downarrow \\ \mathrm{HCo(CO)_3}}}{\mathrm{R{-}CH{=}CH_2}} \xrightleftharpoons{\mathrm{CO}} \mathrm{RCH_2CH_2Co(CO)_4}$$

4.5

(ii) CO insertion by a mechanism analogous (118) to the well studied alkylmanganese pentacarbonyl insertion (119, 120) (Eq.4.6).

$$\mathrm{RCH_2CH_2Co(CO)_4} \xrightleftharpoons{\mathrm{CO}} \mathrm{RCH_2CH_2COCo(CO)_4}$$

4.6

(iii) a reduction step involving either molecular hydrogen or a second molecule of $HCo(CO)_4$.

4.2 Aldehyde Reduction

Some authors consider hydrocobalt tricarbonyl also to be the active species in aldehyde reduction by hydrogen in the presence of cobalt carbonyl catalysts (121, 122). Again, the evidence here is the inverse dependence of reaction rate on P_{co} and also the appearance of formate esters, in considerable yield (10-30%), along with the product alcohol (Eq.4.7).

$$\mathrm{RCHO} \xrightarrow[\text{cobalt catalyst} \atop 150\text{-}200^{\circ}]{\mathrm{H_2,\ CO}} \mathrm{RCH_2OH} + \mathrm{RCH_2OCHO} \qquad 4.7$$

The formate, which is not formed by esterification of the alcohol, is believed to result from CO-insertion into the cobalt-oxygen bond in an intermediate $RCH_2OCo(CO)_3$ (106, 121).

4.3 Miscellaneous Reactions of $HCo(CO)_4$

The reactions of $HCo(CO)_4$ with aromatic compounds having nitrogen-nitrogen bonds or carbon-nitrogen multiple bonds have been extensively reviewed by Rosenthal and Wender (123). Aromatic oximes and nitriles, phenylhydrazones and Schiff's bases of aromatic carbonyl compounds, azines and azo compounds are all reduced and carbonylated to various extents. Temperatures in excess of 200° favour carbonylated products such as substituted ureas and phthalimidines. Amines are produced only at temperatures in the range 120-150° (124).

Polynuclear aromatic hydrocarbons are partially reduced (125).

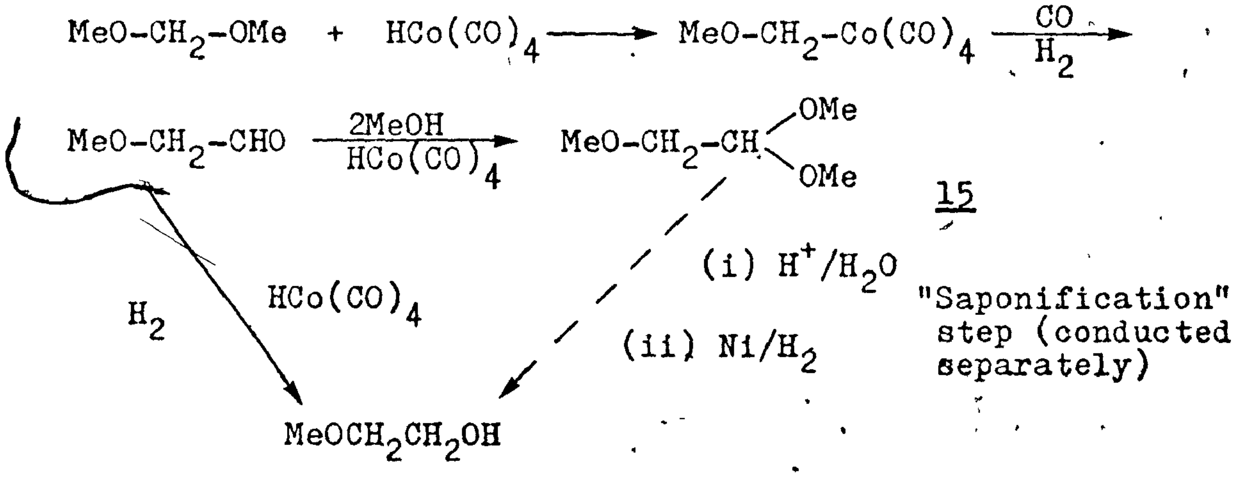
Benzyl alcohols react with catalytically produced $HCo(CO)_4$ to give hydrocarbons chiefly, but also some hydroformylated products (126-128). Benzhydrol and triphenylcarbinol yield only the reduced products, di- and triphenylmethane, respectively. This reaction has been studied in detail by Wender et al. (129) who found the reaction rate to be independent of carbon monoxide pressure, and concluded that the mechanism probably involves protonation of the alcohol by $HCo(CO)_4$, followed by cleavage of the oxonium ion and reduction of the resulting carbonium ion.

4.4 A Literature Survey of the Reaction between $HCo(CO)_4$- and Acetals

Out of eight reports of reactions between cobalt carbonyl catalysts, synthesis gas, and acetals, five concern acetals of formaldehyde. German workers (130, 131) using formaldehyde dimethylacetal were looking chiefly for hydroformylated products, since their aim was to develop a cheap synthesis of ethylene glycol. Some reduction product, dimethyl ether, was obtained (130) but ethylene glycol monomethyl ether (<u>14</u>) and methoxyacetaldehyde dimethylacetal (<u>15</u>), in equimolar amounts, were the main products detected (131).

The latter compound was converted into the desired product <u>14</u> by a reductive saponification. Overall yields of <u>14</u> based on the starting acetal were 15-25%.

The reaction is believed to proceed as in Scheme 4.1 (131):



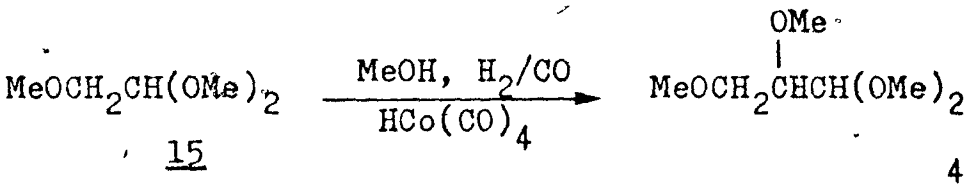
<u>14</u>

Scheme 4.1

1,1-diethoxyethane reacts similarly (134).

American workers (132, 133) who reacted formaldehyde dimethylacetal under higher pressures and temperatures for shorter reaction times than the Germans, claimed 90-100% yields of <u>15</u> when an excess of methanol was present. Curiously, when formaldehyde diethylacetal was employed, in the presence of an excess of ethanol, only 5.7% yield of 1,1,2-triethoxyethane was obtained (132).

Compound 15 will react further under more drastic conditions and in the presence of methanol to form 1,1,2,3-tetramethoxypropane in 81% yield (133) (Eq.4.8).

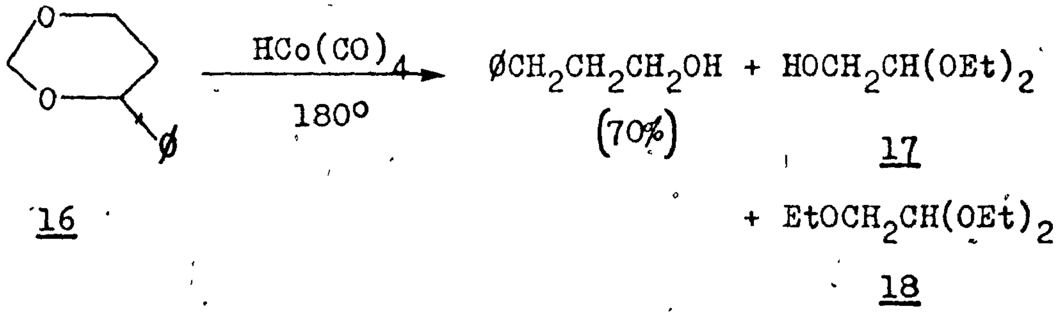


$$\underset{\underline{15}}{\mathrm{MeOCH_2CH(OMe)_2}} \xrightarrow[\mathrm{HCo(CO)_4}]{\mathrm{MeOH,\ H_2/CO}} \mathrm{MeOCH_2}\overset{\mathrm{OMe}}{\overset{|}{\mathrm{C}}}\mathrm{HCH(OMe)_2}$$

4.8

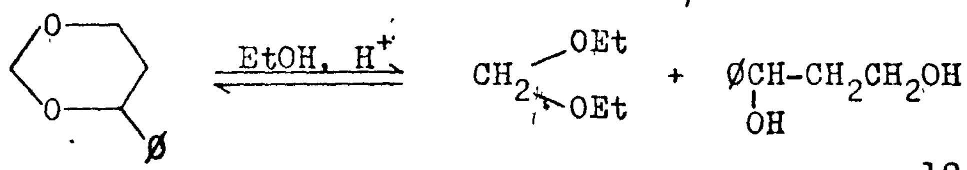
[N.B. Implicit in the data presented so far in this Section, is the observation that $HCo(CO)_4$ catalyses acetal formation. Acetals have also been found among the products of the oxo process, and several instances of $HCo(CO)_4$-catalysed transacetalations between aldehydes and orthoesters are known (86, 87, 100, 135-139).]

A Japanese paper purports to describe the reaction of 4-phenyl-1,3-dioxane (16) with $HCo(CO)_4$ for 4.5 hours at 180° (140); 3-phenyl-1-propanol was obtained in yields of 70% or more and the eliminated carbon atom reappeared, hydroformylated, as glycolic aldehyde diethylacetal (17) and as 1,1,2-triethoxyethane (18) (Eq.4.9).



4.9

Although the authors gave few experimental details, the ethanol solvent employed was described as "94%". This alcohol would contain sufficient water for complete hydrolysis of the starting material. In any case, under the catalytic action of $HCo(CO)_4$ extensive ethanolysis is bound to occur (Eq.4.10).



16

19

4.10

Since reaction of the ethanolysis products shown in Equation 4.10 with $HCo(CO)_4$ can be expected to yield exactly the products detected by the authors*, there is certainly room for doubt that the reaction they were observing was that of cyclic acetal (16). Hydrogenolysis of 16 in a 1,4-dioxane solvent yielded neither 17, nor 18, but an increased yield of 3-phenyl-1-propanol was reported. However the failure of the authors to realise the importance of using dry, alcohol free, solvents can only cast doubt on this observation as well, especially as in benzene solution no reaction took place.

Only one example has been described (see ref.103, p.106) of the reaction of $HCo(CO)_4$ with a benzylidene group. A 4,6-O-benzylidene pyranose sugar derivative was treated with $Co_2(CO)_8$ under an equimolar mixture of hydrogen and carbon monoxide; the products contained both the 4-O-benzyl and the 6-O-benzyl derivatives. The reaction was complicated by a concurrent hydrolysis.

Methyl cellobioside, when treated with cobalt carbonyl catalyst and synthesis gas for eight hours at 180° in the presence of water, was reported to yield 7% of the product of reductive cleavage at C_1: 1,5-anhydro-D-glucitol (1). The value of this observation is reduced, however, because

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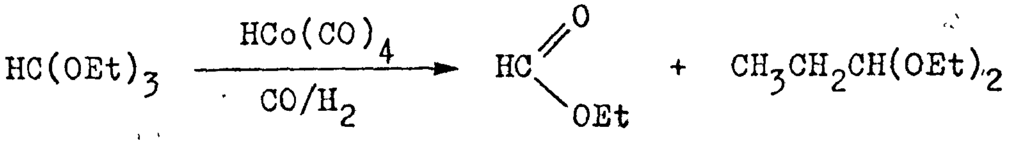
*Reduction of 3-hydroxy-3-phenyl-1-propanol (19) by $HCo(CO)_4$ can safely be assumed to yield chiefly 3-phenyl-1-propanol (by comparison with Table 4.5, Entries 3 and 4). The Japanese workers themselves (140) decided that 17 somehow formed via the intermediacy of formaldehyde diethyl acetal. Compound 18 can form as in Scheme 4.1, identification was by chromatography only, no products were isolated, and the source of the comparison compound was not mentioned.

In a reaction allied to acetal cleavage, orthoesters react with carbon monoxide and hydrogen in the presence of $Co_2(CO)_8$ at 100° (141). The products here, however, are rather different. For example, ethyl orthoformate yields propionaldehyde diethylacetal and also ethyl formate (Eq.4.11).



4.11

4.5 Results and Discussion

Aliphatic and aromatic acetals react differently with $HCo(CO)_4$. The difference is evident from the results shown in Tables 4.1 and 4.2 or, more dramatically, by comparing the g.l.c. chart of the products of benzaldehyde dibenzylacetal reduction, which indicates only two compounds to be present (Fig.4.1), with the corresponding charts for acetone n-butyl ketal (Fig.4.2) and propionaldehyde diethylacetal (Fig.4.3).

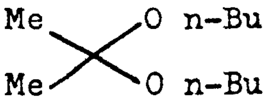
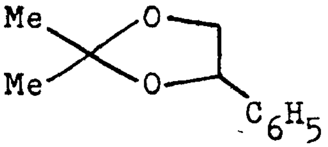
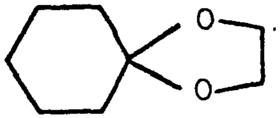
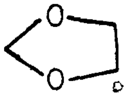
4.5.1 Aliphatic Acetals

The reason for the proliferation of products with the aliphatic acetals is that these acetals, having hydrogens on an adjacent carbon atom, readily undergo elimination to the α,β-unsaturated ethers in the presence of an acid catalyst. Indeed this is a preparative route to α,β-unsaturated ethers (ref.6, p.337).

The α,β-unsaturated ether, once formed, can react in many ways. A few possibilities are outlined in Schemes 4.2 and 4.3.

TABLE 4.1

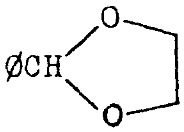
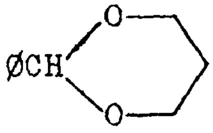
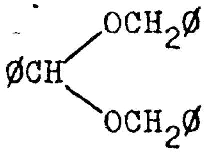
The Reaction of Some Aliphatic Acetals with $HCo(CO)_4$

Acetal	Number of Products Detected[a]	Yield of Ether $\begin{matrix}R'\\R\end{matrix}\!>CHOR''$, %[a]	Starting Material Remaining, %[a]	Reaction Temp. and Time[b]
$CH_3CH_2CH(OEt)_2$	7 major[c] >30 minor[d]	0	0	180°, 2h.
	9 major >20 minor +n-Butanol	8	0	180°, 3h.
	5 major[e] 1 minor	0	20	170°, 22h.
	Nil	0	90	195°, 2h.
$CH_2(OMe)_2$	6 major[f] + methanol	25	0	180°, 4h.
	5 major[g] 5 minor	20	5	180°, 3h.

(a) Analysis by g.l.c. (b) Under 2400 psig of synthesis gas ($2H_2$:1CO). (c) >5% of total area. (d) In the range 0.5 - 5% of the total area. (e) One of which corresponded to 2-phenylethanol, isolated in 32% yield. (f) Including dimethyl ether and ethylene glycol monomethyl ether. (g) The largest of which (25% of the total area) had the same retention time as diethylene glycol.

TABLE 4.2

Reaction of Some Aromatic Acetals with HCo(CO)$_4$

Ex #	ACETAL	PRODUCT	YIELD OBTAINED, %	UNREACTED STARTING MATERIAL, %	CONDITIONS 2400 psi (initial), H$_2$/CO(2:1)
1	ØCH(OMe)$_2$	ØCH$_2$OMe	96^a(83)^b	0	160°, 2h.
2	ØC(OEt)$_2$Me	ØCH(OEt)Me	93(81)^b	0	170°, 3h.
		ØCH$_2$Me	4		
		EtOH	106		
3	ØC I$_2$CH(OMe)$_2$	ØCH$_2$CH$_2$OMe +8 minor products	65(53)^b	0	180°, 2h.
4		ØCH$_2$OCH$_2$CH$_2$OH	37(28)^c	3	210°, 6h.
		ØCH$_2$OCH$_2$CH$_2$OCH$_2$Ø	50(41)^c		
		ØCH$_3$	9		
5		ØCH$_2$O(CH$_2$)$_3$OH	26(18)^c	30(28)^c	164°, 4h.
		ØCH$_2$O(CH$_2$)$_3$OCH$_2$Ø	40(37)^c		
		ØCH$_3$	2		
6	 ØCH(OCH$_2$Ø)$_2$	ØCH$_2$OCH$_2$Ø	95	0	128°, 1h.
		ØCH$_2$OH	92		

(a) Analysis by g.l.c. using "bracketing" standards of authentic samples. Figures in parentheses are yields of isolated material.
(b) By distillation
(c) By SiO$_2$ chromatography

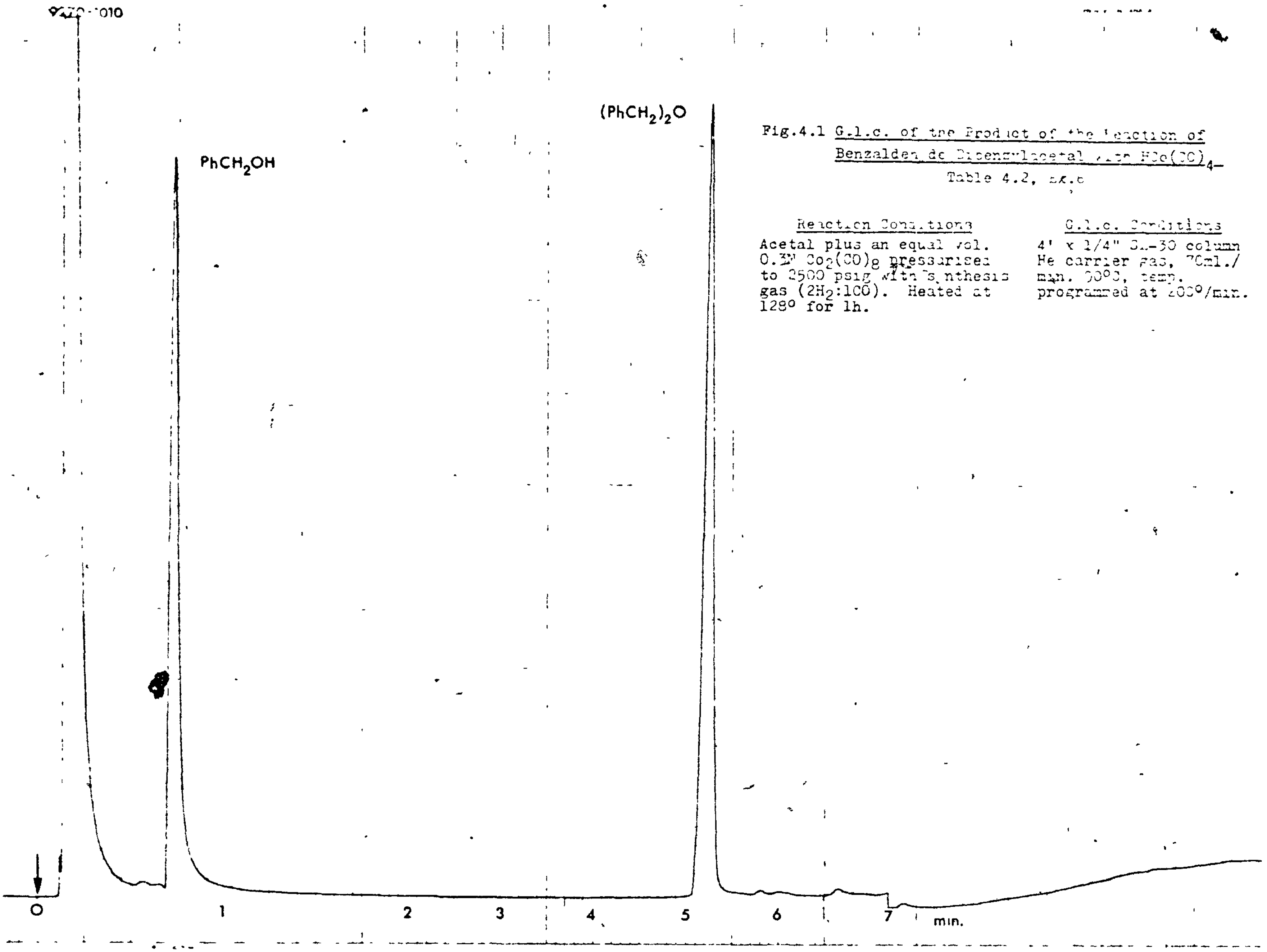


Fig.4.1 G.l.c. of the Product of the Reaction of Benzaldehyde Dibenzylacetal with HCo(CO)$_4$ — Table 4.2, Ex.6

Reaction Conditions

Acetal plus an equal vol. 0.3M Co$_2$(CO)$_8$ pressurised to 2500 psig with synthesis gas (2H$_2$:1CO). Heated at 128° for 1h.

G.l.c. Conditions

4' x 1/4" SE-30 column He carrier gas, 70ml./min. 90°C, temp. programmed at 20°/min.

Fig.4.2 G.l.c. of Products of Reaction of Propionaldehyde Diethylacetal with $HCo(CO)_4$

Reaction Conditions

Acetal plus equal vol. 0.3M $Co_2(CO)_8$ in benzene pressurised to 2430 psig with synthesis gas ($2H_2$:1CO). Heated at 180° ± 5° for 2h.

G.l.c. Conditions

4' x 1/4" SE-30 column
He carrier gas, 70ml./min.
80°C, temp. programmed at
20C°/min.

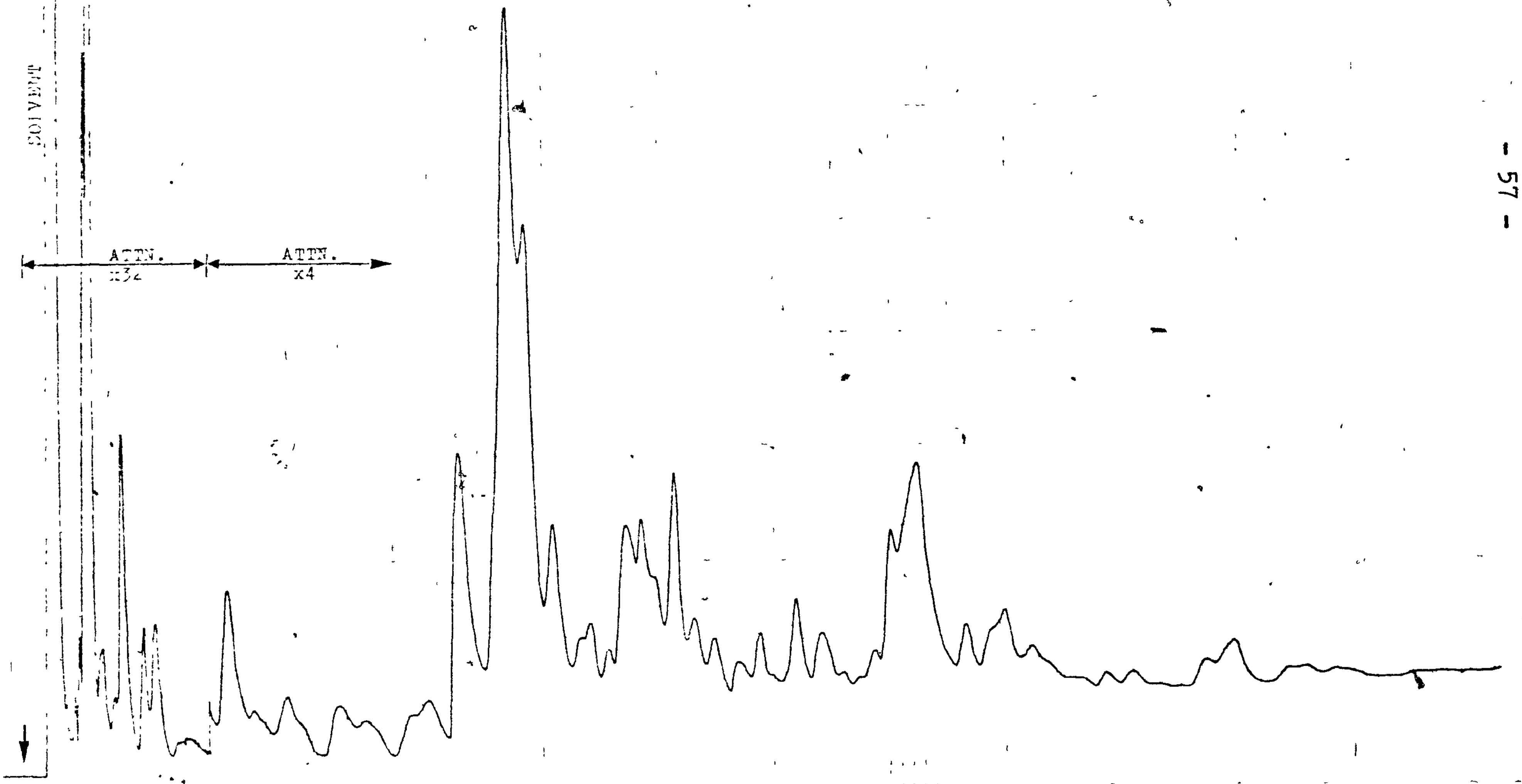


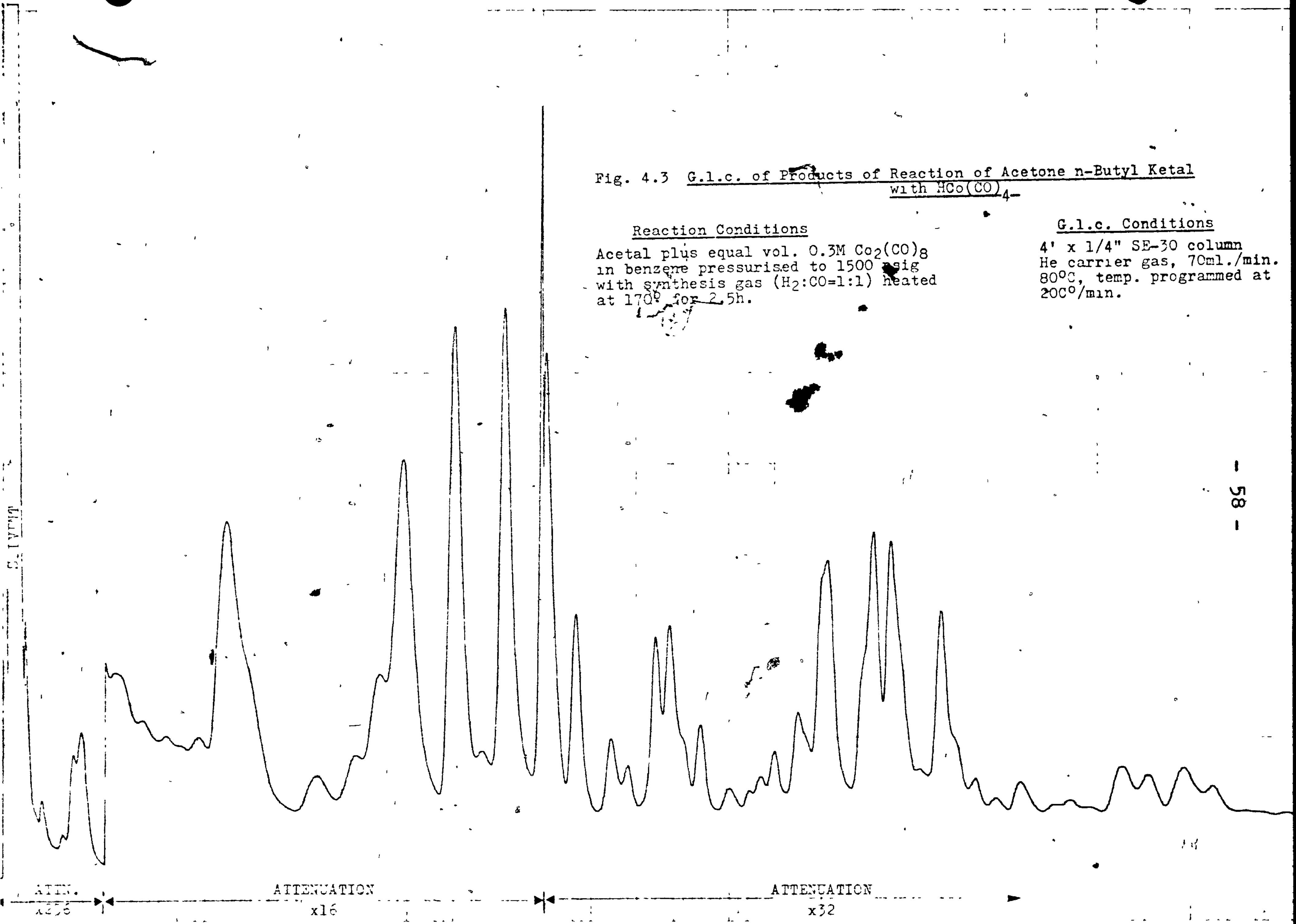
Fig. 4.3 G.l.c. of Products of Reaction of Acetone n-Butyl Ketal with $HCo(CO)_4$

Reaction Conditions

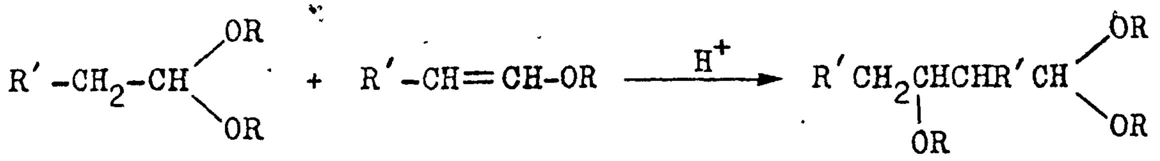
Acetal plus equal vol. 0.3M $Co_2(CO)_8$ in benzene pressurised to 1500 psig with synthesis gas (H_2:CO=1:1) heated at 170° for 2.5h.

G.l.c. Conditions

4' x 1/4" SE-30 column
He carrier gas, 70ml./min.
80°C, temp. programmed at 20C°/min.



Condensation with more acetal

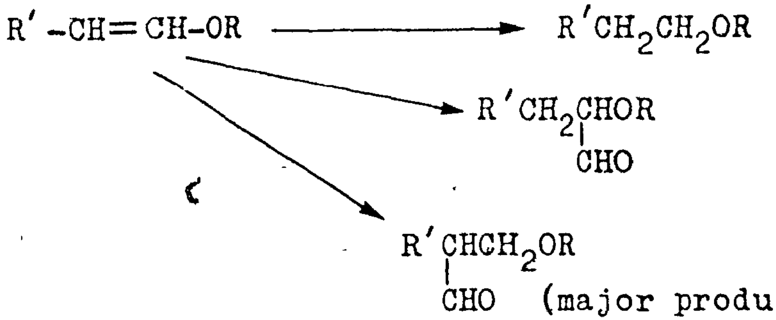


(ref.6, p.322).

N.B. The product is an acetal and can undergo further condensations.

Scheme 4.2

Reaction with $HCo(CO)_4$



(major product if R'=H, ref.97, p.290)

Scheme 4.3

The aldehyde products can either:

(i) react with alcohols present in solution, yielding acetals which can react further, or

(ii) be themselves reduced to alcohols which, by undergoing acetalation or alcohol interchange, can yield even more types of acetals.

When heated in the reaction vessel under the same conditions used in the experiments described in Table 4.2, but with omission of the catalyst, acetone n-butyl ketal proved to be stable and was recovered unchanged. However, when a few crystals of p-toluene-sulphonic acid were added and the reaction was repeated, all the ketal was destroyed and the g.l.c. chart showed five major products and six minor ones.

Whereas considerations of entropy make it reasonable to expect cyclic acetals to be less reactive than simple ones*, the special inertness of cyclohexanone ethylene ketal is probably related to the increased energy required to form the necessary carbonium ion on account of the eclipsing involved in going from sp^3 to sp^2 hybridisation. Similar eclipsing makes cyclohexanone a relatively reactive ketone (142).

The inability of formals to yield α,β-unsaturated ethers makes their reaction products simpler. This is undoubtedly one reason why formals are the best studied of all acetals in their reactions with $HCo(CO)_4$. The products to be expected from formaldehyde dimethyl acetal were outlined in Section 4.4.

4.5.2 Aromatic Acetals

Experiments 1 and 2 in Table 4.2 show that simple aromatic acetals give good yields of reduction products with $HCo(CO)_4$. Much milder conditions than those shown were later found to effect this cleavage: benzaldehyde dimethylacetal is over 95% reduced after 30 mins. at 130°. The ethylbenzene obtained in Experiment 2 and the toluene found in Experiments 4 and 5 probably result from slight reductive cleavage of the benzyl ether products. This small amount of cleavage agrees with the findings of Li (1).

In the absence of catalyst, 2-phenyl-1,3-dioxane was found to be perfectly stable under the reaction conditions, and, being unable to form an α,β-unsaturated ether by elimination, it was also stable under the same conditions in the presence of p-toluenesulphonic acid (unlike acetone n-butyl ketal).

Because of a report (144) that benzaldehyde diethyl acetal undergoes disproportionation at 200° in the presence

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* E.g. formaldehyde diethyl acetal hydrolyses 10^4 times faster than the pentaerythritol acetal of formaldehyde (143).

of thorium oxide (Eq.4.12), it was also thought necessary to perform a blank experiment with benzaldehyde dimethylacetal (30) under the reaction conditions.

$$\text{ØCH(OEt)}_2 \xrightarrow[\text{ThO}_2]{200^\circ} \text{ØCH}_2\text{OEt} + \text{MeCHO} \qquad 4.12$$

In the absence of catalyst, compound (30) was unchanged after 3½ hours at 160°.

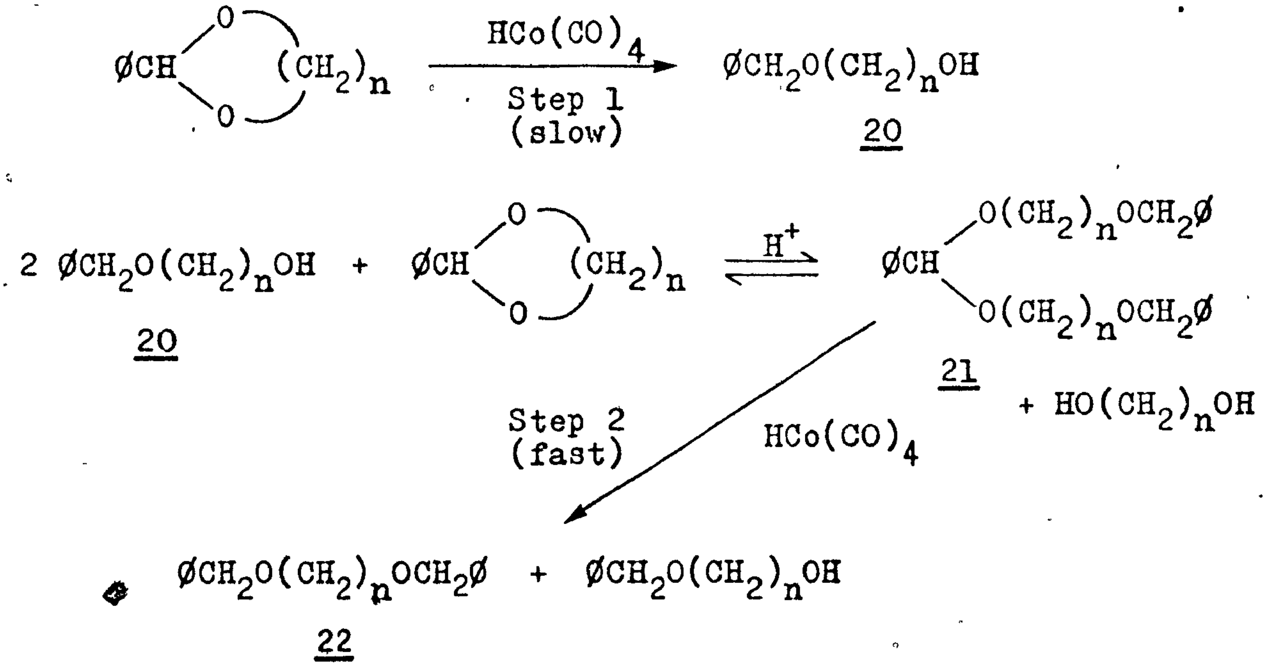
Cleavage of cyclic acetals (Experiments 4 and 5, Table 4.2) differs from that of simple acetals:

(i) by being slower — as comparison of the conditions and starting material recovery shows; and

(ii) by yielding a di-benzyl ether as main product.

The Formation of Di-ethers

Consider the following mechanism for di-ether formation during acetal reduction: as the cleavage proceeds and product alcohol begins to accumulate, transacetalation with unreacted starting material occurs to yield a new acyclic acetal 21 (Scheme 4.2).



Scheme 4.2

Provided that the simple acetal 21 cleaves at a rate comparable to that of the cyclic starting material and that transacetalation is fast, a large amount of the alcohol 20 will be converted into the diether 22.

Two items of evidence have been obtained to support this hypothesis.

1. In view of the rather meagre literature documentation of $HCo(CO)_4$ catalysis of acetal formation and transacetalation, it was thought advisable to demonstrate the $HCo(CO)_4$-catalysed formation of acetals of benzaldehyde.

2. An acyclic acetal of benzaldehyde was shown to cleave faster than a related cyclic one — a fact already implied by the conditions required for the reductions shown in Table 4.2 (p.55).

These experiments were conducted as follows.

1. Benzaldehyde with a ten-molar excess of dry methanol was heated for a very short time at 85° with the catalyst (Experiment 1, Table 4.3). G.l.c. showed a yield of 70% of benzaldehyde dimethylacetal, which was then isolated in a yield of 55%.

When longer times and higher temperatures were employed (Experiment 2), the composition of the product closely resembled that obtained from pure benzaldehyde dimethylacetal (Experiment 1, Table 4.2).

2. It is not always possible to use "competitive reactions" (as was done with BH_3) to compare the reactivities of two different acetals with $HCo(CO)_4$. If the alcohol moieties of the acetals to be compared are different, complications involving transacetalation prevent unambiguous interpretation of the results of competitive reactions. In this event it is necessary to rely on separate reactions conducted under conditions made as similar as possible.

Thus benzaldehyde dimethyl acetal (10 mmol) was heated with catalyst under synthesis gas to 118°, then was cooled.

TABLE 4.3

Reductions of Benzaldehyde-Alcohol Mixtures with $HCo(CO)_4$[a]

Exp #	Substrate[b]	Molar Ratio Benzaldehyde /Alcohol	Reaction Time, hrs.	Reaction Temperature, °C	Product Yield[c] by G.l.c.,	%
1	Benzaldehyde + Methanol	1:10	0.2	85±5	Benzaldehyde dimethylacetal	70(55)[d]
					Benzaldehyde	23
					Benzyl methyl ether	7
2	Benzaldehyde + Methanol	1:4	1.4	161±2	Benzyl methyl ether	90(79)[d]
					Benzyl alcohol	1 (1)
					Dibenzyl ether	1 (1)
3	Benzaldehyde + Benzyl alcohol	1:2	1.8	158±2	Dibenzyl ether	87(92)
					Benzyl alcohol	45(32)
4	Benzaldehyde + p-Chlorobenzyl alcohol	1:2	2.0	162±3	p-Chlorobenzyl benzyl ether	75(70)
					Benzyl alcohol	10 (7)
					Dibenzyl ether	5 (1)
					p-Chlorobenzyl alcohol	51(41)
5	Benzaldehyde + Benzyl alcohol	1:3	0.25	85±5	Benzaldehyde	80
					Benzaldehyde dibenzylacetal	15(14)[d]
					Dibenzyl ether	2
					Benzyl alcohol	e

(a) Aldehyde moles/Co_2CO_8 moles=24; $[Co_2(CO)_8]$=0.3M; Synthesis gas ($2H_2$:1CO) pressure=2500psig. (b) Added to catalyst only after reaction temperature attained. (c) Isolated yields (SiO_2 chromatography) in parentheses. (d) This compound was isolated by distillation. (e) Detected but not quantified.

The product consisted of 96.5% of benzyl methyl ether and 3.5% of unchanged starting material. When 2-phenyl-1,3-dioxolane (4) was treated identically (the temperature profile differed by no more than two Centigrade degrees from that of the previous experiment) the product comprised 58% of diether (22, n=2), 32% of 2-(benzyloxy)ethanol (20, n=2) and 10% of unchanged starting material.

Although the second experiment is complicated by trans-acetalation, which destroys a good deal of cyclic acetal, the detection of the remaining 10% of cyclic acetal (vs. 3.5% for ØCH(OMe)$_2$ under the same conditions) shows that this cyclic acetal, at least, is slower to react than its simple counterpart.

Earlier in this chapter it was noted that acetals able to form α,β-unsaturated ethers by elimination generally yield a multitude of products with $HCo(CO)_4$. It is therefore surprising that the acetals used in Experiments 2 and 3, Table 4.2, gave high yields of reduction products*. The explanation is that here the double bond formed by elimination is conjugated to the aromatic ring and such double bonds are reduced, not hydroformylated, by $HCo(CO)_4$ (98 and ref.107, p.171). This is especially true when there are other substituents on the double bond — thus styrene itself gave only 25% of ethylbenzene and the remainder was hydroformylated, but α-methyl styrene gave 69% of isopropylbenzene and only 9% of hydroformylated material (90). Therefore, any α,β-unsaturated ether formed in Experiments 2 and 3 will mostly be reduced to the same ether product which would have resulted from a reductive cleavage of the acetal.

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* E.g. phenacetaldehyde dimethylacetal yields the α,β-unsaturated ether when passed over a catalyst at a high temperature, exactly as do aliphatic acetals (ref.5, p.437).

4.6 Ether Formation during the Reduction of Aldehydes by $HCo(CO)_4$

The recognition that $HCo(CO)_4$ catalyses both the formation and the reductive cleavage of aromatic acetals has enabled us to propose a solution to a problem in the literature.

Benzaldehyde is known to form large quantities (often over 50%) of dibenzyl ether when heated with $HCo(CO)_4$ for 2 hours or less at temperatures of 180-200° (146, 147). The ratio (benzyl alcohol/benzyl ether) in the product strongly depends on the initial concentration of the aldehyde (146). Wender *et al.* (147) at first thought the ether was formed by dehydration of benzyl alcohol, but in subsequent work (127) found that under the same conditions — though for a somewhat longer time — benzyl alcohol yielded only toluene and phenethyl alcohol. The same two products were the only ones isolated by Ziesecke (148) in numerous experiments with benzyl alcohol and cobalt catalysts under varied conditions. Dawydoff heated benzyl alcohol and $HCo(CO)_4$ for 5 hours at 200°C but obtained only a 2% yield of dibenzyl ether (146).

Thus, the formation of dibenzyl ether in benzaldehyde reductions has remained unexplained.

The similarity between this dibenzyl ether formation and the formation of di-ether during the cleavage of cyclic acetals suggests that they follow a similar mechanism — i.e., as benzyl alcohol forms in the presence of $HCo(CO)_4$, it reacts with benzaldehyde to yield benzaldehyde dibenzylacetal (23) (Scheme 4.4). This acetal is then cleaved by $HCo(CO)_4$ and forms dibenzyl ether and benzyl alcohol*.

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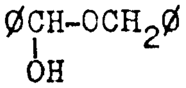
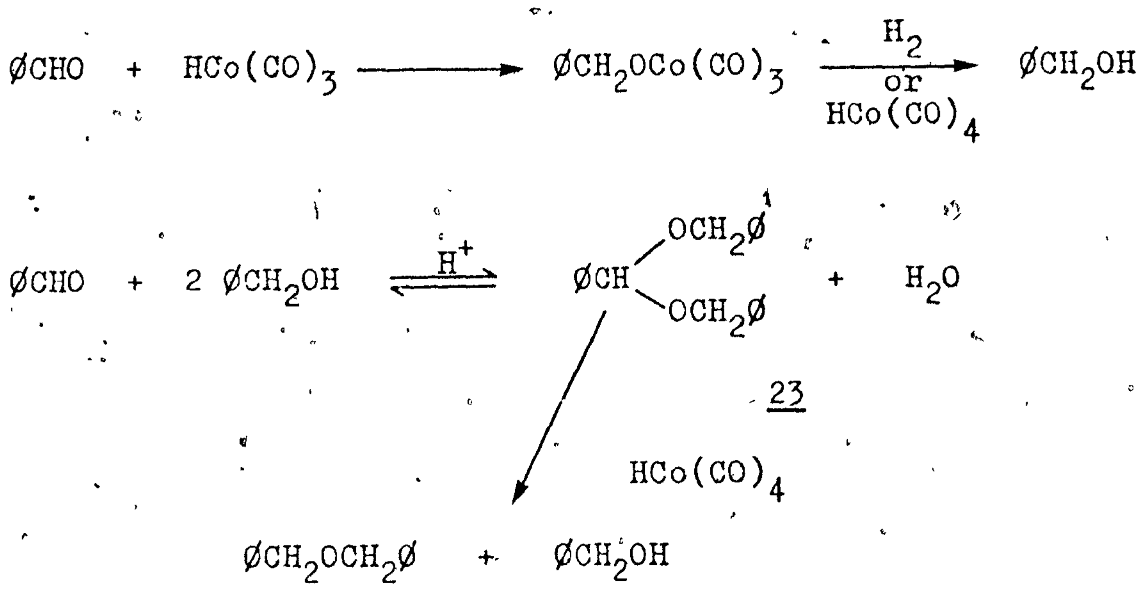
* Reductive cleavage of the intermediate hemiacetal



$\phi\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}OCH_2\phi$

to yield dibenzyl ether and water is also a possibility which cannot be ruled out at present.

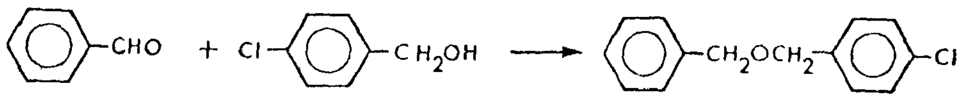


Scheme 4.4.

According to Scheme 4.4 three moles of benzaldehyde are required (directly and indirectly) to form one mole of intermediate 23. Consequently the average rate of ether formation will be roughly proportional to the cube of the concentration of starting material. The rate of benzyl alcohol formation, however, will be proportional only to the first power of the concentration of starting material. Thus Scheme 4.4 explains the experimental finding that the yield of ether decreases rapidly upon dilution of the starting material, and then benzyl alcohol becomes the chief product (146).

Support for the Scheme is provided by Table 4.3, Experiment 3, wherein benzaldehyde was treated with two equivalents of benzyl alcohol and gave, under milder conditions than Wender <u>et</u> <u>al</u>. employed, a nearly quantitative yield of dibenzyl ether, and almost half the benzyl alcohol was recovered unchanged.

Experiment 4 resembled the previous experiment except that p-chlorobenzyl alcohol was used. The chief product was p-chlorobenzyl benzyl ether (Eq.4.13), but some reduction of benzaldehyde to benzyl alcohol did occur, with subsequent formation of a little dibenzyl ether.



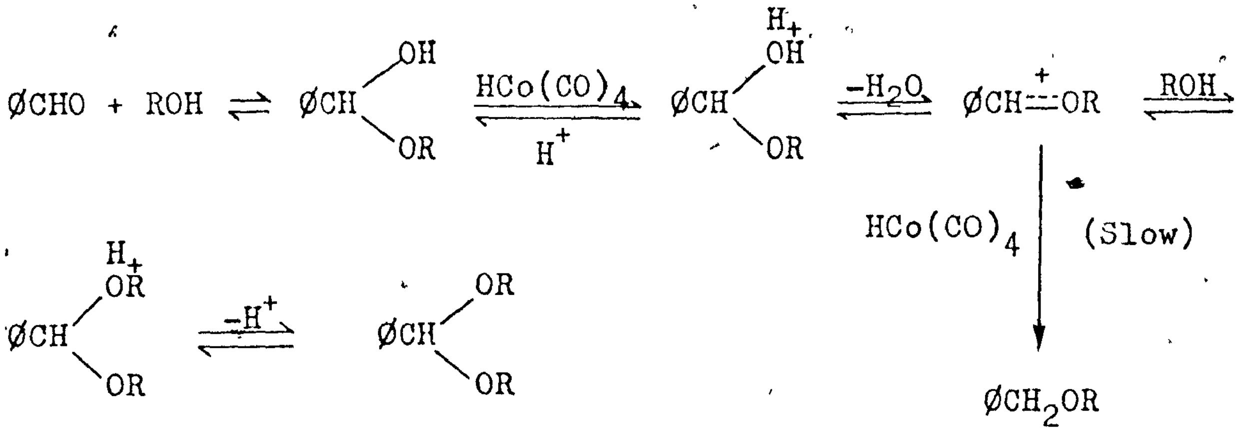
4.13

No bis-(p-chlorobenzyl) ether was formed. Clearly, then, the ether derives from 1 molecule of aldehyde and 1 molecule of alcohol.

Evidence for the role of benzaldehyde dibenzylacetal (23) as an intermediate in ether formation was obtained when it was isolated in 14% yield from a mixture of benzaldehyde and benzyl alcohol treated under mild conditions with catalyst (Experiment 5, Table 4.3). Under more drastic conditions this acetal gave a good yield of dibenzyl ether, as expected (Experiment 6, Table 4.2).

4.7. The Mechanism of Acetal Cleavage with $HCo(CO)_4$

It is reasonable to anticipate a carbonium-ion mechanism for the reduction of acetals with $HCo(CO)_4$. As we know that acetal formation is catalysed by $HCo(CO)_4$, we can deduce that this catalyst must be capable of generating carbonium ions from hemiacetals by protonation (see Chapter 1). Hence, we would also anticipate the facile formation of carbonium ions from acetals. The most straightforward mechanism for acetal formation and reduction is illustrated in Scheme 4.5.



Scheme 4.5

Reduction of similarly generated carbonium ions is the generally accepted mechanism in the reaction of p-methoxybenzyl alcohol (a related compound — see Chapter 6) with $HCo(CO)_4$ (96, 98). Such carbonium ions apparently also play a role in the reduction of benzhydrols (98, 129) and in the generation of hydroformylation products from formaldehyde dimethyl acetal (140).

The reduction step in Scheme 4.5 must be relatively slow or isolation of the acetal from aldehyde, alcohol and $HCo(CO)_4$ mixtures (Experiments 1 and 5, Table 4.3) would not be possible. Evidence for the rôle of a carbonium ion in the reductive cleavage of acetals was obtained by comparing the rates of cleavage of the benzyl acetals of substituted benzaldehyde in competitive reactions (Table 4.4). Low reaction temperatures were necessary to avoid cleavage of all the acetal before the autoclave could be cooled (the apparatus had no direct liquid-sampling facility). Before its contents were mixed, the autoclave was heated to 100°C to convert much of the $Co_2(CO)_8$ into $HCo(CO)_4$, thus preventing complete dependence of the reaction rate upon the slow rate of formation of $HCo(CO)_4$ at the reaction temperature. The figures shown in Table 4.4, while not providing an exact quantitative measure of the reactivity of the acetals, clearly indicate that an electron-releasing group in the *para* position enhances the reduction rate, and an electron-withdrawing substituent diminishes the rate — just as Wender and co-workers have found for benzhydrols (129).

TABLE 4.4

Competitive Reductions of Pairs of Acetals of the Type p-X-$C_6H_4CH(OCH_2Ph)_2$[a]

X	Reaction Temperature, °C	Starting Material[b] Unreacted, %	Product Ether[b] Formed, %
MeO	75	12	59
+			
H		74	7
H	80	41	42
+			
Cl		65	16

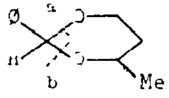
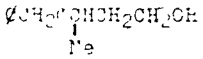
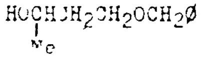
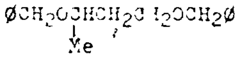
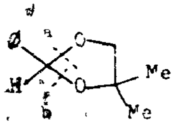
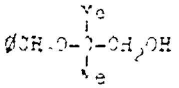
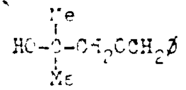
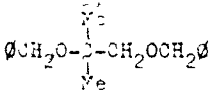
(a) Procedure as described in 8.4.1 but with 1 mmol of each acetal + 5 ml hexane in the ampoule. Catalyst equilibrium established by heating at 90-100° for 25 mins. before mixing the contents at the reaction temp. and allowing the autoclave to cool to ambient (~ 2h.). (b) Analysed by g.l.c.

4.8 The Influence of Substituents at C_4 on Cyclic Acetals

Table 4.5 shows the yields of products obtained from cleavage of two C_4-substituted acetals with $HCo(CO)_4$. In Experiment 20, the detection of the secondary alcohol in greater yield than the primary does not necessarily imply that the former is the predominant product of cleavage. The major product is diether, and it may be that the primary alcohol reacts faster than the secondary in the transacetalation reaction which leads to diether. In other words, a possible interpretation is that primary alcohol is rapidly converted into diether, thus leaving the secondary alcohol predominant in the alcohol fraction.

TABLE 4.5

The Influence of Substituents at C_4 on the Direction of Acetal Cleavage by $HCo(CO)_4$

Exp #	Starting Material	Structure of Products	Yield of Products*, %		Recovery of Starting Material*, %	Conditions
20	 (cis isomer)	Cleavage at (a)		(20)	37(32)	165°, 2hrs.
		 $\text{Ø}CH_2O\underset{Me}{C}HCH_2CH_2OH$	3			
		Cleavage at (b)				
		 $HO\underset{Me}{C}HCH_2CH_2OCH_2\text{Ø}$	18			
		Di-ether				
		 $\text{Ø}CH_2O\underset{Me}{C}HCH_2CH_2OCH_2\text{Ø}$	33	(29)		
21	 **5**	Cleavage at (a)		(29)	56(40)	160°, 4hrs.
		 $\text{Ø}CH_2O-\overset{Me}{\underset{Me}{C}}-CH_2OH$	4			
		Cleavage at (b)				
		 $HO-\overset{Me}{\underset{Me}{C}}-CH_2OCH_2\text{Ø}$	27			
		Di-ether				
		 $\text{Ø}CH_2O-\overset{Me}{\underset{Me}{C}}-CH_2OCH_2\text{Ø}$	6	(7)		

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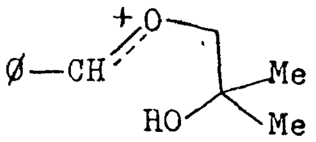
* Yields determined by gas chromatography, figures in parentheses are isolated yields (SiO_2 chromatography).

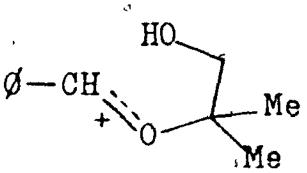
1

This argument is not tenable for Experiment 21 where little diether was formed and primary alcohol plus diether was barely one-third of the yield of secondary alcohol. Clearly then, in this latter case, predominant cleavage of 5 occurred at the C_2-O_3 link.

The result of Experiment 21 appears, at first sight, to be strong evidence AGAINST a carbonium-ion mechanism; cleavage at b requires the formation of the less stable oxocarbonium ion 24; cleavage at a yields oxocarbonium ion 25 which is stabilised by the presence of α-methyl groups.



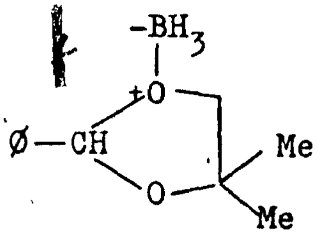
24 (cleavage at b)



25 (cleavage at a)

We saw in Chapter 2 that borane cleaved this acetal predominantly at a and also that there was strong evidence that the borane cleavage proceeded via a carbonium ion.

How is it possible, in the reaction with $HCo(CO)_4$, to reconcile the preponderance of C_2-O_3 cleavage of 5 with the expected carbonium-ion mechanism? The answer may lie in solvation. Little solvation of the initial borane-acetal complex (26) is expected because the positive and negative centers are bonded to each other. In contrast, the protonated acetal (27) resulting from attack by $HCo(CO)_4$ on 5, would be strongly solvated.



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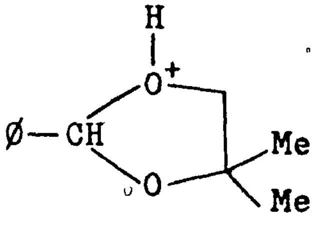

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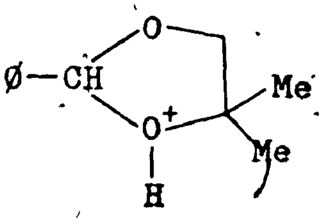

28

It is clear from an inspection of models that for steric reasons solvation of <u>27</u> will take place more extensively than solvation of <u>28</u>, especially since under the conditions employed the "solvent" consists of unprotonated acetal or its reduction product — i.e. the "solvent" is a bulky molecule*. Since the solvation energy may be large, the poorly solvated species <u>28</u>, even though leading to an apparently higher-energy carbonium ion (<u>24</u>), may have the lowest activation energy. It is also important to consider the effect of solvation on the carbonium ions <u>24</u> and <u>25</u>. Intermediate <u>24</u> is best stabilised by solvation, whereas <u>25</u> is best stabilised by inductive effects; hence these intermediates may be of similar energy.

It may thus be argued that the positive effect of solvation on the activation energy is greater for <u>27</u> than for <u>28</u>, and the result is preferential C_2-O_3 cleavage.

Explanations of the result of Experiment 21 invoking protonation as rate-determining step seem rather unlikely in view of (i) the strong acidity of $HCo(CO)_4$ (equivalent to a mineral acid, (108-112)) and (ii) the rapid build-up of acetal** in mixtures of aldehyde and alcohol with the catalyst.

4.9 <u>Carbon Monoxide Insertion in Cobalt Carbonyls</u>

In the presence of carbon monoxide, primary alkyl cobalt carbonyls are in equilibrium with acyl cobalt carbonyls <u>via</u> an insertion reaction (Eq.4.14) probably achieved by a 1,2 shift of

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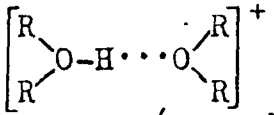
[*] Solvation of protonated ether molecules by unprotonated ether molecules is a well-known phenomenon; stable complex ions of the type  are known (149). Increasing the bulk of the R groups (even by simply going from Et- to n-Bu-) decreases an ether's ability to coordinate polar molecules(150).

[**] Formation of acetal requires hemi-acetal protonation.

the alkyl group from cobalt to carbon (101, 118).

$$RCo(CO)_n + CO \rightleftharpoons RCOCo(CO)_n \qquad 4.14$$

The chemical (92, 151) and spectroscopic (93) evidence that acyl cobalt tetracarbonyls are formed during the <u>oxo</u> reaction, likely explains why all non-branched olefins give good yields of aldehydes in the commercial process.

Hydrogenation, always a competing reaction in the <u>oxo</u> process*, is of little significance for unbranched olefins, but can become dominant if the olefin is branched, or conjugated (157).

4.9.1 The Effect of Substituent Electronegativity

The electronegativity of the R group in Equation 4.14 has an important influence on CO-insertion; strongly electronegative groups prevent this reaction (ref.105, p.240). For instance, unlike methyl cobalt carbonyl, cyanomethylcobalt carbonyl (<u>29</u>) does not insert CO at $0^{o}C$ (152).

$$N\equiv C\text{-}CH_2\text{-}Co(CO)_4$$

<u>29</u>

Butyl vinyl ether and allyl ethyl ether give considerable amounts of reduction products with $HCo(CO)_4$; the corresponding olefins give only aldehydes (153).

Electronegative R-groups can be expected to stabilise both metal-alkyl and metal-acyl bonds, but particularly the former. Hence, with a more electron-withdrawing R group, the equilibrium in Equation 4.14 will be displaced to the left.

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* An overall reaction scheme for both hydrogenation and hydroformylation has been proposed (157, 159).

The equilibrium constant for the formation of acyl

$$RMn(CO)_5 + CO \overset{k}{\rightleftharpoons} RCOMn(CO)_5 \qquad 4.15$$

manganese carbonyls (Eq.4.15) has been found to decrease in the order $R=C_2H_5 > CH_3 > C_6H_5$; the rate of the forward reaction (k) varied likewise (154):

$$R = C_2H_5 > C_6H_5 \approx CH_3 \gg C_6H_5CH_2, CF_3$$

When $R=C_6H_5CH_2$, no acyl-derivative could be detected at equilibrium.

Relative to phenyl, this benzyl effect is remarkable*; it may be due to increased crowding at the α-carbon atom in going from sp^2 to sp^3 hybridisation.

4.9.2 Steric Effects

The rules formulated by Keulemans, Kwantes and van Bavel (155) — later slightly modified by Wender et al. (156) — for hydroformylation with cobalt catalysts, state that "addition of a formyl group to a tertiary carbon atom does not occur at all ... Addition of a formyl group adjacent to a tertiary carbon atom is strongly hindered, but may yet occur to a small extent." More recent experimental evidence bears this out — Wender and co-workers found that when isobutylene was hydroformylated, 97% of the CO insertion occurred at the primary carbon to yield isovaleraldehyde or its reaction products (156). Subsequently Marko found that hydrogenation to isobutane was the main reaction taking place, with hydroformylation a poor second (157). Observations have shown that two isomeric butylcobalt carbonyls are formed during the

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* It has also been observed in cobalt carbonyls (118).

reaction — i.e. both Markownikoff and anti-Markownikoff hydrometallation occur — *but only the primary butylcobalt carbonyl inserts CO appreciably.*

Earlier in this Chapter the reduction of α-methyl styrene to isopropylbenzene and a small amount of hydroformylated material was mentioned. It turns out that the hydroformylation product is exclusively β-phenylbutyraldehyde (158), once again supporting the rules of Keulemans, Kwantes and van Bavel.

The invariable fate of tertiary alkyl cobalt carbonyls under *oxo* process conditions is reduction to the hydrocarbon. This can occur by activation of molecular hydrogen by an alkylcobalt tricarbonyl (Eq.4.16) (159).

$$RCo(CO)_4 \overset{-CO}{\rightleftharpoons} \cancel{RCo(CO)}_3 \overset{H_2}{\rightleftharpoons} RCoH_2(CO)_3 \longrightarrow RH + HCo(CO)_3 \tag{4.16}$$

or *via* another molecule of $HCo(CO)_4$ (101, 160, 161).

The reason benzhydryl and tertiary alkylcobalt carbonyls fail to undergo CO insertion is probably steric (129). Table 4.6 lends support to this idea. When bulky phenyl groups are α-substituents, secondary cobalt carbonyls do not insert CO (Entry 2). One phenyl and one methyl group apparently provide almost sufficient hindrance to prevent CO insertion (Entries 3, 4). A similarly hindered cobalt carbonyl formed by addition of $HCo(CO)_4$ to *cis*-stilbene is known to undergo hydrogenolysis to diphenylethane (162). As can be seen from Entries 5 and 6, when the α-substituent is a single aryl group, hydroformylation is considerable. (The reaction conditions of Entry 4 differ somewhat from the others of Table 4.6 since the starting material was the acetophenone, the alcohol having been formed *in situ*.)

Although Wender's group reacted *p*-methoxybenzyl alcohol in the temperature range of 70-95°C and obtained large amounts

TABLE 4.6

Hydroformylation versus Reduction for Some α-Substituted Alcohols and Acetals

Entry #	Starting Material	Postulated Structure of Intermediate Cobalt Carbonyl	Hydroformylated Product, %	Reduced Product, %	Reference
1	ϕ_3COH	$\phi_3C\text{-}Co(CO)_4$	0	100	129
2	ϕ_2CHOH	$\phi_2CH\text{-}Co(CO)_4$	0	100	127, 129
3	$\phi\underset{Me}{CH}OH$	$\phi\underset{Me}{CH}\text{-}Co(CO)_4$	0	100	127, 129 146
4	$\underline{p}\text{-}MeOC_6H_4\underset{Me}{CH}OH^b$	$\underline{p}\text{-}MeOC_6H_4\underset{Me}{CH}\text{-}Co(CO)_4$	6	91	98, 127
5	$\underline{p}\text{-}MeOC_6H_4CH_2OH$	$\underline{p}\text{-}MeOC_6H_4CH_2\text{-}Co(CO)_4$	21	68	This work, Chapter 6
6	$X\text{-}C_6H_4CH_2OH^c$	$X\text{-}C_6H_4CH_2\text{-}Co(CO)_4$	50-20	25-65	128
7	$\phi CH(OR)_2$	$\phi\overset{OR}{CH}\text{-}Co(CO)_4$	0	100	This work Chapter 4
8	$CH_2(OMe)_2$	$MeOCH_2\text{-}Co(CO)_4$	Major Product	Minor Product or Not Detected	130-133
9	$R\ CH_2CH(OMe)_2$	$R\ CH_2\overset{OMe}{CH}\text{-}Co(CO)_4$	R =H 18 R =OMe 81	Not Detected Not Detected	134 133

(a) $Co_2(CO)_8$ catalyst, synthesis gas, 125-200°C. (b) formed in situ by reduction of p-methoxyacetophenone. (c) X = p-alkyl, p-benzyl, p-chloro or 2,4,6 trimethyl.

of homologated product and polymer (128), these data are omitted from Table 4.6. Reaction at higher temperatures produces little or no polymer, and the homologated/reduced product ratio is in line with that observed for other substituted benzyl alcohols (see Chapter 6). Wender's group later reduced p-methoxybenzyl alcohol at 140°C but unfortunately did not analyse the products (162).

In this work no formylation products were detected in the reduction cleavage of α-aryl acetals — the reduction products (ethers) have been obtained in yields approaching 100%. This observation (Entry 7) is consistent with the other data in Table 4.6. The cobalt tetracarbonyls derived from benzylidene acetals resemble most closely in steric hindrance those shown in Entries 3 and 4.

Cobalt carbonyls derived from formals, or acetals with an α-alkyl substituent undergo a considerable amount of CO insertion (Entries 8 and 9).

SUMMARY

The acidic nature of $HCo(CO)_4$ catalyses both the formation of acetals and their subsequent decomposition.

The reduction of benzylidene acetals to ethers appears to be a special case of the reaction between $HCo(CO)_4$ and acetals. In general, reduction of the intermediate carbonium ion is so slow that it occurs only if other possible routes are blocked.

Structural features of the acetal necessary to achieve this blocking are (i) an absence of hydrogen atoms adjacent to the acetal group (elimination cannot then occur), (ii) the presence of a bulky substituent on the acetal carbon atom (hydrogenation is then favoured over CO insertion).

CHAPTER 5

SOLUTIONS OF PURE $HCo(CO)_4$ IN HYDROCARBONS - THEIR REACTION WITH ACETALS

5.1 Preparation of $HCo(CO)_4$ Solutions

Solutions of $HCo(CO)_4$ in hydrocarbon solvents are readily prepared according to the method of Kirch and Orchin (151): A solution of dicobalt octacarbonyl in a hydrocarbon solvent is first disproportionated by adding a base (e.g. dimethylformamide), according to Equation 5.1.

$$3Co_2(CO)_8 + 12\ \text{Base} \longrightarrow 2\left[Co(\text{Base})_6\right]^{++} \left[Co(CO)_4\right]^{-}_{2} + 8CO \qquad 5.1$$

The salt thus formed is next decomposed by adding strong aqueous acid (usually hydrochloric) and the $HCo(CO)_4$ so produced dissolves in the hydrocarbon layer to yield a lemon-yellow solution which is washed with air-free water and is dried by addition of anhydrous sodium sulphate (153). For work with acetals, a second drying step over a molecular sieve was found to be essential to prevent complete hydrolysis of the substrate.

All these operations, except the disproportionation, must be performed with complete exclusion of air, since $HCo(CO)_4$ is rapidly oxidised by atmospheric oxygen to $Co_2(CO)_8$. The most convenient apparatus is a pear-shaped flask filled with carbon monoxide, and having a side-arm closed by a serum cap. Liquids are added and removed through the side-arm by means of a syringe. Sodium sulphate, contained in a horizontally positioned flask connected to a second side-arm, is added by tilting the apparatus.

Solutions of $HCo(CO)_4$ cannot be kept, even at 0°C, and must be used within an hour or two of preparation. The rate of decomposition (Eq.5.2) is said to vary approximately as the square of the concentration (111).

$$2\ HCo(CO)_4 \longrightarrow Co_2(CO)_8 + H_2 \qquad 5.2$$

A 1M solution in hexane has a half-life of "a few minutes" at 25°C; a 0.02M solution has a half-life of about 5 hours (111)*.

The solutions are conveniently analysed gasometrically by decomposing the $HCo(CO)_4$ with aqueous potassium iodide/iodine solution and measuring the carbon monoxide evolved (163) (Eq.5.3).

$$2\ HCo(CO)_4 + 3I_2 \xrightarrow{H_2O} 2CoI_2 + 8CO + 2HI\ (aq.) \qquad 5.3$$

5.2 The Reductive Cleavage of Acetals by $HCo(CO)_4$ Solutions

During the course of the present research, the $HCo(CO)_4$ solutions prepared as described above were found to bring about reductive cleavage of acetals under conditions close to ambient (Eq.5.4).

$$PhCH(OR)_2 + 2\ HCo(CO)_4 = PhCH_2OR + ROH + Co_2(CO)_8 \qquad 5.4$$

This finding supports the rôle of $HCo(CO)_4$ as active species in the catalytic reaction (Chapter 4). Table 5.1 shows the results obtained for the reduction of two acetals of benzaldehyde by $HCo(CO)_4$ solutions. Experiments 1, 2 and 3 show that increasing solvent polarity greatly increases the rate of the reaction of benzaldehyde dibenzyl acetal (23) with $HCo(CO)_4$ (see also Fig.5.1). The yield of ether produced is

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* Whereas the gas-phase decomposition is undoubtedly 2nd-order (111); these data, taken from the same source, do not offer convincing evidence that the same is true for the reaction in

not greatly affected by the solvent. Experiment 4 does show a higher yield; it differs from Experiment 3 by having half the amount of $HCo(CO)_4$. Consequently, acetal is present in excess and the yield is based on $HCo(CO)_4$. The improvement of yield presumably results from reduced loss of $HCo(CO)_4$ by the reaction in Equation 5.2.

Experiments 5 and 6 illustrate the effect of adding chlorobenzene to the reaction mixtures. The reaction mixture in Experiment 6, because of chlorobenzene addition, was three times more dilute than that in Experiment 5, but still reacted slightly faster (Fig.5.2).

The increase in reaction rate produced by polar solvents may be taken as evidence for a polar intermediate in acetal cleavage, as proposed in the previous chapter (Section 4.7). A polar solvent could promote the cleavage of an oxonium ion by solvation of the incipient oxocarbonium ion.

A comparison of Experiments 5 and 7, or 8 and 9 shows that while the rate of reaction of $HCo(CO)_4$ is greatly accelerated by a modest increase in temperature, the yield of ether is not significantly altered. This could mean that the reactions shown in Equations 5.2 and 5.4 have similar activation energies.

Except for Experiment 7, analysis of the ether product was restricted to g.l.c. because of the small quantities involved. Large quantities of $HCo(CO)_4$ solutions are difficult and expensive to work with.

The major experimental difficulty encountered was the removal of traces of water from the $HCo(CO)_4$ preparation so that acetal hydrolysis would not occur. Simply drying for an hour over sodium sulphate left so much water that hydrolysis was the only reaction observed. When a second drying step over molecular sieve was introduced, hydrolysis of the acetal was reduced to an acceptable level (15–30%). Further attempts eliminate hydrolysis were unsuccessful, owing to the limited stability of the $HCo(CO)_4$ solutions. A better approach to this problem in future would be to devise a synthesis of $HCo(CO)_4$ which does not require water.

The (reversible) removal of some acetal by a hydrolytic side-reaction should not invalidate the results of acetal cleavage shown in Table 5.1, because: (i) the benzaldehyde hydrolysis product is not reduced under the experimental conditions employed (benzaldehyde, but not benzyl alcohol was detected at the end of Experiments 8 and 9); (ii) an excess of acetal was detected at the end of each experiment.

5.3 Cobalt Recovery

After removal of a small sample for g.l.c. analysis, the product of Experiment 1 was cooled in a dry-ice/acetone mixture and the bright orange crystals of $Co_2(CO)_8$ were filtered off. Roasting these at 750°C yielded Co_3O_4 equivalent to 55% of the original cobalt. This method of separating $Co_2(CO)_8$ works well with stoichiometric olefin reductions, and gives a cobalt recovery of about 80% (151). In acetal reductions, therefore, some cobalt must remain in solution. The clear yellow colour of the filtrate confirms the removal of $Co_2(CO)_8$, which gives almost black solutions. Incomplete cobalt recovery has been previously noted in stoichiometric reduction of aldehydes to alcohols with $HCo(CO)_4$ (164).

TABLE 1

The reaction of Acetals with $HCo(CO)_4$ under Stoichiometric Conditions

Exp. #	Acetal[a]	(mmole)	$HCo(CO)_4$ (mmole)	Solvent (Vol., ml)	Approx. Reaction Time (hrs.)[b]	Temp.	Ether Product[c] (Mole %)
1	23	(1.0)	2.5	C_6H_{14} (26)	212-260	22°	43[d]
2	23	(0.5)	1.2	C_6H_{14}(3) + C_6H_6 (10)	94-117	22°	60
3	23	(1.0)	2.3	C_6H_{14}(5) + THF (10)	1-2	22°	53
4	23	(1.0)	1.3	C_6H_{14}(5) + THF (10)	1-2	22°	70
5	23	(1.0)	2.4	C_6H_6 (5.3)	25-92	22°	47
6	23	(1.0)	1.9	C_6H_6(6) + C_6H_5Cl (10)	44-104	22°	55
7	23	(1.0)	1.9	C_6H_6 (6)	2-10	37°	51(43)[e]
8	30	(0.6)	1.9	C_6H_6(6)	2-10	37°	35[f]
9	30	(0.55)	2.4	C_6H_6(5.3)	20-50	22°	38[f]

(a) 23 = $\phi CH(OCH_2\phi)_2$, 30 = $\phi CH(OCH_3)_2$

(b) Until $HCo(CO)_4$ no longer detectable (by smell or by pptn. with nickel tri-o-phenanthroline complex).

(c) Yield calculation is based on Eq.5.4. Benzyl alcohol was also detected in Experiments 1-7 but as it is formed by hydrolysis as well as by reduction it was not quantified.

(d) $Co_2(CO)_8$ isolated as orange crystals, mp.50-51°C., by cooling the hexane solution to -78°C. Calcination yielded 108 mg. Co_3O_4, equivalent to 1.35 mmole $Co(CO)_4$.

(e) Isolated yield (SiO_2 chromatography).

(f) Benzaldehyde, but no benzyl alcohol detected.

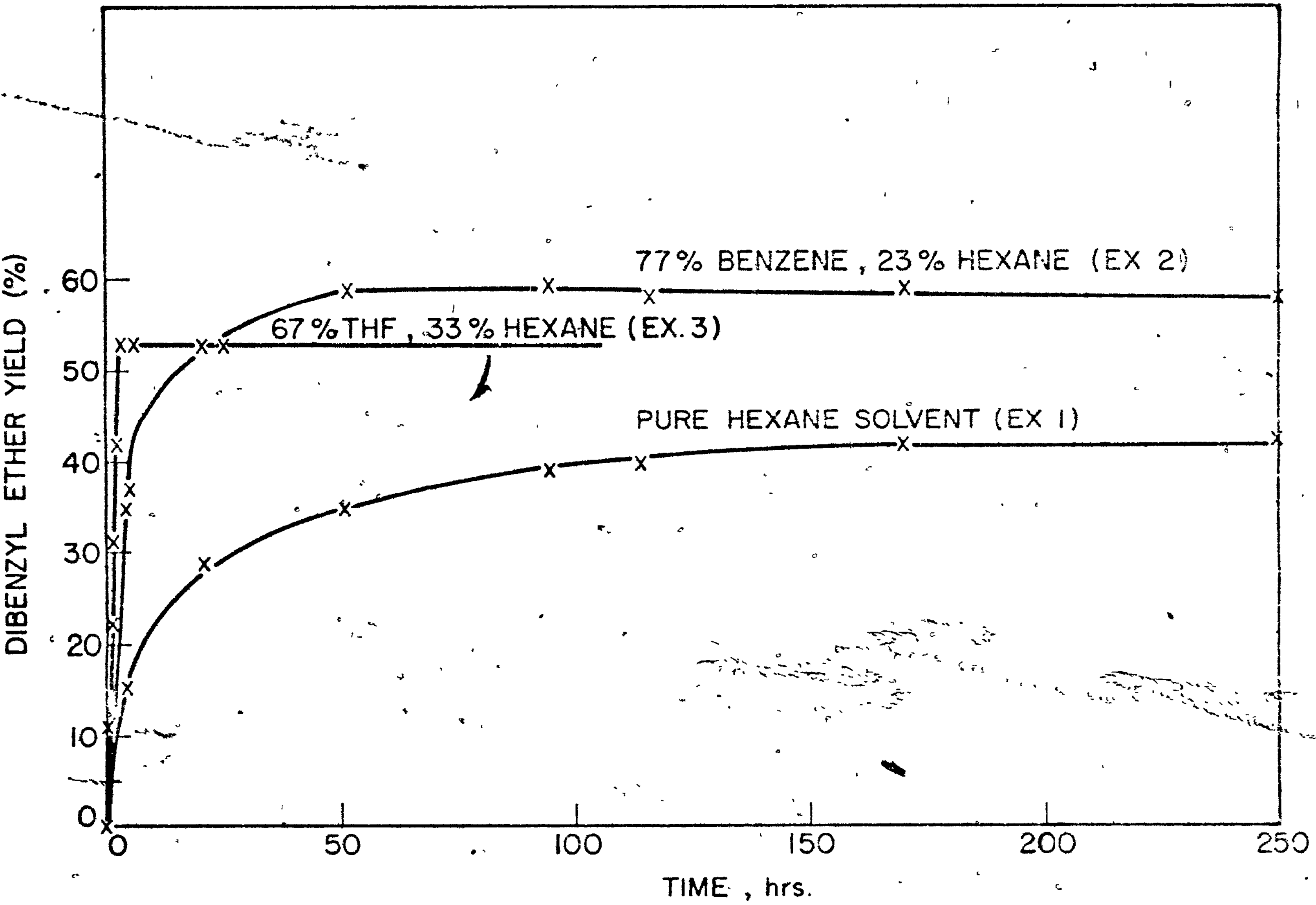


Fig.5.1 The reduction of benzaldehyde dibenzylacetal (23) by $HCo(CO)_4$ solutions in various solvents at 25°.

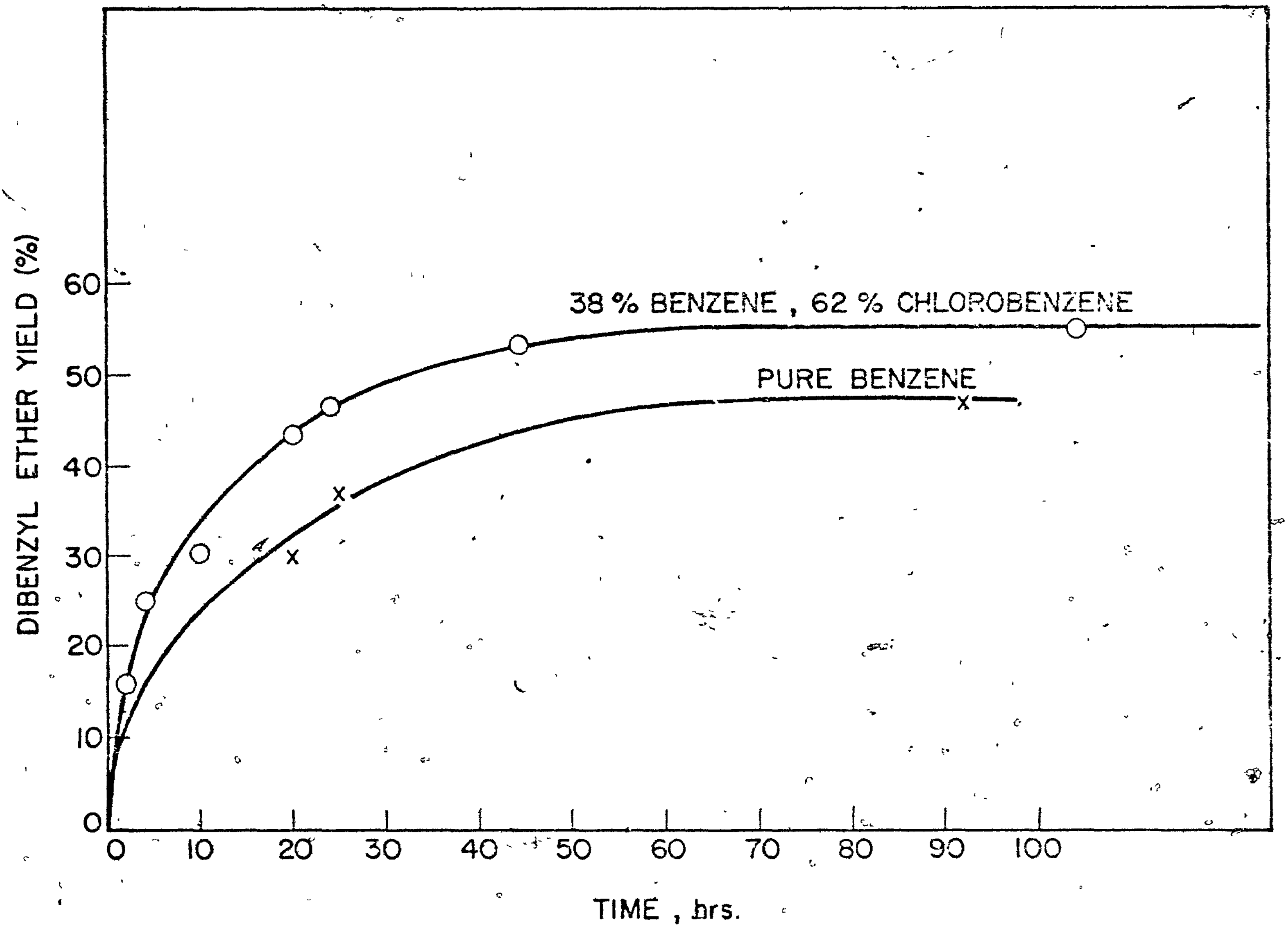
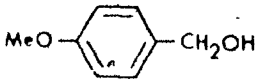


Fig.5.12. The reduction of benzaldehyde dibenzylacetal by $HCo(CO)_4$ solutions in benzene with and without added chlorobenzene.

KEY TO CHAPTER 6

31

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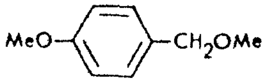
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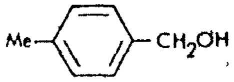
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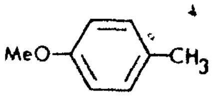
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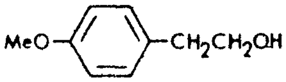
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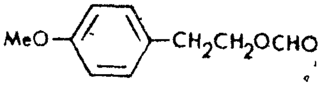
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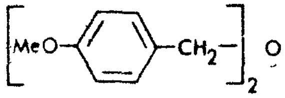
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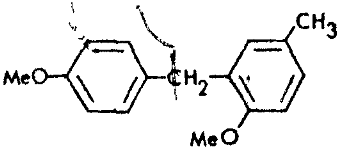
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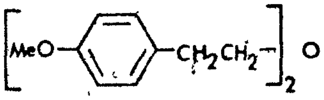
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ethyl ether

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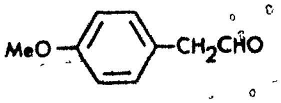
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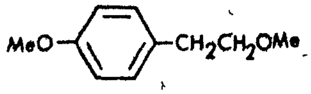
p-methoxyphenethyl methyl
ether

CHAPTER 6

REDUCTIVE CLEAVAGE OF p-METHOXYBENZYL ALCOHOL AND ITS ETHERS

Our interest in p-methoxybenzyl ethers stems from the existence of similar structures in lignin; we were working from the hypothesis that a homogeneous reductive cleavage of the benzyl ether cross-links would render lignin soluble, but would not simultaneously attack cellulose. The benzyl ether model compounds were used in the search for suitable reducing agents. (For details of studies with lignin and cellulose see Appendix 5).

As this chapter is necessarily rather complex, a summary is presented next in order to outline the main points.

6.1 Summary

The catalytic reduction of p-methoxybenzyl alcohol (31) by $HCo(CO)_4$ has been re-examined. The anomalous behaviour of this alcohol noted by Wender et al. is probably due to its ability to react at low temperatures where the catalyst-forming reactions are slow in attaining equilibrium.

Chromatographic analysis revealed many products not observed by earlier workers. Apart from ether 39, all products are explicable from current knowledge of the chemistry of the catalyst.

Reduction of p-methoxybenzyl methyl ether (32) gave products similar to those of the alcohol (31), except that p-methoxyphenethyl methyl ether (41) appeared and no 39 was formed.

A mechanism for the formation of ethers 39 and 41 is proposed and some supporting evidence is provided.

p-Methoxybenzyl ethers were also reduced by stoichiometric amounts of $HCo(CO)_4$ under conditions close to ambient. Reduction was slower and yields were less than with acetals. Polar solvents accelerated the reaction.

Excess borane in THF reduced p-methoxybenzyl methyl ether in 75% yield at 135°; yields were low at temperatures near ambient.

6.2 Reduction with Catalytically Generated $HCo(CO)_4$

The reaction of catalytically produced $HCo(CO)_4$ with various benzyl alcohols has been extensively studied by Wender, Orchin *et al.* (93, 126-127); the stoichiometric reduction of benzyl alcohol by the same material at ambient temperature and pressure has also been investigated (89, 164).

Comparatively little is known, however, of the behaviour of benzyl *ethers* with this reagent. Dibenzyl ether itself is resistant to reduction by $HCo(CO)_4$ even at 200°C (17). In fact, this ether has been obtained as a major product in reductions of benzaldehyde by $HCo(CO)_4$ (146, 147). Benzyl ethers also appear as major products in the hydrogenolysis of the cyclic acetals of benzaldehyde (see Chapter 4, Table 4.2). C.M. Li (1) has recently found that p-substituted benzyl ethers vary greatly in reactivity towards $HCo(CO)_4$, depending on the nature of the substituent: if the p-substituent is H, the ethers are virtually inert to the catalyst up to 190°C; if the p-substituent is $-OCH_3$, the ethers readily undergo hydrogenolysis (Eq.1.1) well below this temperature*. Indeed p-methoxybenzyl ethers are even hydrogenolysed under stoichiometric conditions at 40-50°C as discussed in Section 6.4.

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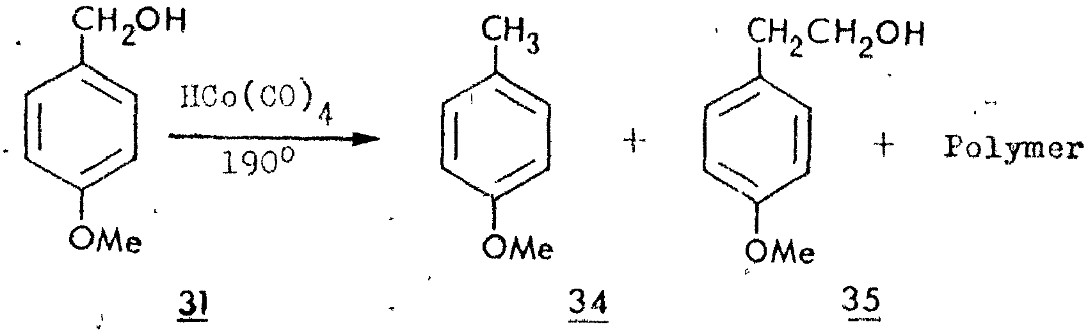
* The strongly activating effect of p-methoxy groups on reductive cleavages was also observed for benzyl alcohols by Wender and co-workers (128) working with $HCo(CO)_4$, and by others using hydride reducing agents (167, 168). The effect has been taken to indicate that a carbonium ion is an intermediate in the reaction.

6.2.1 Reduction of p-Methoxybenzyl Alcohol (31)

In the study by Wender's group (128) of the reaction of various p-substituted benzyl alcohols with catalytically produced $HCo(CO)_4$ at 190°C, the majority of alcohols examined yielded 41-63% of hydrocarbon and 16-36% of homologated alcohol, the ratio homologated product/hydrocarbon being in the region 0.3-0.7. p-Methoxybenzyl alcohol, however, was anomalous, yielding 16% of hydrocarbon, 44% of homologated alcohol, and about 34% of high boiling polymer (Eq.6.1).



6.1

The procedure used by these workers was as follows: the autoclave was charged with the mixed reagents, pressurised with synthesis gas at 25°C and then the temperature was raised to 190°C in 110 minutes. It was noted that in some instances gas absorption began before the final temperature was reached, especially with p-methoxybenzyl alcohol, which started to absorb gas at 70°C, and had taken up one mole of gas per mole of alcohol by the time the temperature reached 92°C.

It occurred to us that the anomalous product ratio from p-methoxybenzyl alcohol might be a consequence of reaction at such low temperatures. (The next most reactive alcohol — p-methylbenzyl — starts to react only at about 130°C (128)).

In order to test this possibility the following modification of Wender's conditions was made: quantities were scaled down by a factor of 13 and the p-methoxybenzyl alcohol was kept in a small open ampoule separate from the catalyst-benzene mixture. After the pressurised autoclave had been heated to a constant 177°C (60 mins.) the apparatus was tilted to mix all the contents. There was an immediate temperature rise of several degrees, and the gas pressure remained constant (signifying absorption). Analysis of the products by g.l.c. gave 71% of hydrocarbon and 24% of homologated compounds (Table 6.1, Experiment 1). Practically no polymeric materials were found. The ratio of homologated compounds to hydrocarbons is 0.33, in line with that found for other alcohols which react at this temperature.

For an alcohol which reacts only at higher temperatures (e.g. >130°) the method of addition of the reactants is unimportant. Thus in Experiment 3, Table 6.1, p-methylbenzyl alcohol (33) and catalyst were premixed and heated to 185° in 85 minutes; in Experiment 2, the alcohol was placed in the ampoule and added only after the reaction temperature (185°) had been attained. Despite the difference in technique, there was no significant difference in the products from these two experiments*.

The anomalous result obtained by Wender et al. for p-methoxybenzyl alcohol is apparently due to the alcohol being reactive enough to be attacked by $HCo(CO)_4$ even at 70°C. The equilibrium in Equation 6.2 is reached rather slowly at this temperature**, and the unusual behaviour of p-methoxybenzyl alcohol may result from the low concentration of $HCo(CO)_4$ present — which would favour side reactions rather than reduction of a carbonium-ion intermediate.

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* The yield of homologated material was, however, somewhat lower than Wender et al. obtained. The reason for this is not clear.

** At 100°, but under rather lower gas pressure, equilibrium concentration of $HCo(CO)_4$ is reached only after 45 mins.(94).

T[illegible]

Reactions of Catalytically Pr[illegible] $HCo(CO)_4$ with p-Methoxybenzyl Alcohol and its Methyl Ether

Ex. #	Substrate	Mole Ratio of Substrate to $Co_2(CO)_8$	Catalyst Concentration, M	Reaction Time, h	Reaction Temp., °C	Products Obtained, %		Unreacted Starting Material	Ratio of Unsaturated Product to Hydrocarbon	Ratio of Formate to Alcohol	Polymeric Product[f] %
1[a]	31	39[b]	0.31[b]	2.5	181±4	(34) p-Methylanisole (35) p-[illegible] (36) p-[illegible] ([illegible]) [illegible] ether (38) [illegible][j] (39) [p-[illegible]]	71[i] ([illegible])[e] 13 (17) 1.1 (1.3) [illegible] } ([illegible]) [illegible] 2.7 (2.5)	0	0.33	0.28	4
2[a]	33	39	0.31	2.0	185±2	p-[illegible]ene p-$MeOC_6H_4CH_2CH_2OH$ p-[illegible] (40) p-MeO[illegible]	51 (41) 13 (13) 1.0 (1.5) 0.6 (0.7)	19(14)	0.27	0.10	Not analysed
3[c]	33	39	0.31	2.0	185±4	p-[illegible] p-$MeOC_6H_4CH_2CH_2OH$ p-$MeOC_6H_4CH_2CH_2OCHO$ p-MeO[illegible]	54 13 1.4 0.6	18	0.2[illegible]	0.10	Not Analysed
4[c]	31	39	0.31	5.0	85	p-Methylanisole p-$MeOC_6H_4CH_2CH_2OH$ p-$MeOC_6H_4CH_2CH_2OCHO$	5.4 3.3 [illegible].0	32	1.0	0.[illegible]1	44
5[c]	31	39	0.31	5.0	104	p-Methylanisole p-$MeOC_6H_4CH_2CH_2OH$ p-$MeOC_6H_4CH_2CH_2OCHO$	6.3 4.4 2.0	31	1.0	0.45	[illegible]
6[a]	31	39	0.31	4.5[g], 6[h]	104	p-Methylanisole p-$MeOC_6H_4CH_2CH_2OH$ p-$MeOC_6H_4CH_2CH_2OCHO$	13 [illegible].7 [illegible].3	.73	0.46	0.32	8

(a) Substrate added only after reaction temp. attained. (b) Equal to that used by Wender et al. (128). (c) Substrate and catalyst premixed and heated from ambient. (d) G.l.c. analysis based on total starting material. (e) Isolated yields (Silica chromatography) are given in parentheses. (f) Material which did not distill at 200°, 0.2 mm pressure, includes compound 39. Yield is based on total starting material. (g) Time taken for slow addition. (h) Heating period after addition. (i) p-Methoxyphenyl(p-methoxy, p-tolyl) methane (33). (j) Identified by p.m.r., also semicarbazone m.p. 228-230° (not recryst.). Lit. (130) m.p. 234°. (k) Dimers not analysed.

[illegible] (cont'd)

Ex. #	Substrate	Mole Ratio of Substrate to $Co_2(CO)_8$	Catalyst Concentration, [illegible]	Reaction Time, h	Reaction Temp., °C	Products Obtained	Unreacted Starting Material %	Ratio of [illegible] to [illegible]	Ratio of Formate to Alcohol	Polymeric Product wt %
[illegible]	31	39[b]	0.31[b]	2.5	181±4	(34) p-[illegible] 71[i] ([illegible])[e] (35) p-[illegible] 23 (17) (36) p-[illegible] [illegible].2 (1.3) (37) Di[illegible] ether [illegible] (38) [illegible]methane[i] [illegible] ([illegible]) (39) [p-[illegible]]$_2$O [illegible]2.0 (2.5)	0	0.33	0.28	4
7[a]	31	7.7	1.6	10[g], 1.5[h]	104±3	p-[illegible] 17 p-[illegible] p-[illegible] [illegible].9	[illegible]8	0.28	0.20	45
8[a]	31	39	0.03	2.0	182±2	p-[illegible] 55 p-[illegible] 1.[illegible] p-[illegible] [illegible].9 Di[illegible] ether 3 [illegible]arylmethane[i] 0.[illegible]	11	0.19	0.30	0
9[a]	32	39	0.31	2.0	181±[illegible]	p-[illegible] 7[illegible] (75) p-[illegible] ([illegible]) p-Me[illegible] Trace (41) p-[illegible] 11 (11) [illegible]arylmethane[i] .4 (1.1)	0.3	0.23	0	3
10[a]	31 + Methanol (1.1 molar ratio)	39	0.31	2.2	181±4	p-[illegible] p-[illegible] p-Me[illegible] 1.[illegible] p-Me[illegible] [illegible] Di[illegible] ether 1.[illegible] [illegible]arylmethane[i] 1 [p-Me[illegible]]$_2$O 1.6	1.[illegible]	0.39	0.0[illegible]	8

(a) Substrate added only after reaction temp. attained. (c) Equal to that used for [illegible]. (b) [illegible] (c) Substrate and catalyst premixed and heated from ambient. (d) G.l.c. analysis based on total starting material. (e) Isolated yields [illegible] chromatography are given in parentheses. (f) Material which did not distill at 200°, 0.2 mm pressure, includes compound 37. [illegible] Yield is based on total starting material. (g) Time taken for slow addition. (h) Heating period after addition. (i) p-Methoxyphenyl(p-methoxy-m-tolyl)methane [illegible]. [illegible] identified by p.m.r., also semicarbazone m.p. 228-230° (not recryst.). Lit. (180) m.p. 234°. (k) [illegible] not analysed

$$Co_2CO_8 + H_2 \rightleftharpoons 2\ HCo(CO)_4 \qquad 6.2$$

Reactions at low temperatures were further investigated in Experiments 4, 5 and 6. In experiments 4 and 5 the p-methoxybenzyl alcohol and catalyst were mixed, synthesis gas (2H$_2$:1CO) was added, and the autoclave was heated rapidly (30 mins.) to temperatures of 85° and 104° respectively. Even after 5 hours both experiments yielded over 30% of unreacted alcohol, the monomeric product had a 1:1 homologated product/hydrocarbon ratio, but most of the product was polymeric material. Experiment 6 was performed under the same conditions as Experiment [illegible], but the p-methoxybenzyl alcohol was not pre-mixed with catalyst; it was added gradually at 104°C from a small ampoule so constructed that one or two drops shook out each time the autoclave was inverted. Even more unreacted alcohol (7[illegible]%) was obtained from this experiment, but, significantly, the material that did react formed less polymer and had a homologated product/hydrocarbon ratio (0.46) much closer to that obtained in high temperature reactions. This result appears to support the idea that it is the slow attainment of equilibrium in Equation 6.2 which causes both the "abnormal" product ratio, and the formation of polymeric product when p-methoxybenzyl alcohol reacts with HCo(CO)$_4$ at low temperatures; drop-wise addition of substrate compensates somewhat for the slow attainment of equilibrium.

The small yields of product obtained in Experiments 4, 5 and 6 may be the result of incomplete regeneration of HCo(CO)$_4$ at the low reaction temperatures (85°, 104°). When the quantity of catalyst was increased, more substrate reacted (Experiment 7).

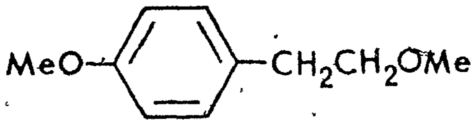
Experiments 1 and 8 are practically identical except for dilution, and the main effects are:

i) a decreased homologated product/hydrocarbon ratio and,

ii) a drastically diminished quantity of dimeric material produced.

6.2.2 Reduction of p-Methoxybenzyl Methyl Ether (32)

Experiment 9 was done under the same conditions as Experiment 1 but the starting material was p-methoxybenzyl methyl ether (32). The percentage of homologated products was lower with the ether. One reason for this may be the increased polarity of the solvent due to methanol formed as the reaction proceeds; water formed in the benzyl alcohol reactions plays little, if any, rôle because it is insoluble in benzene. Of the dimers, only the diarylmethane (38) was formed, but the most remarkable difference was the appearance of 1-methoxy-2-(4-methoxyphenyl)ethane (41).



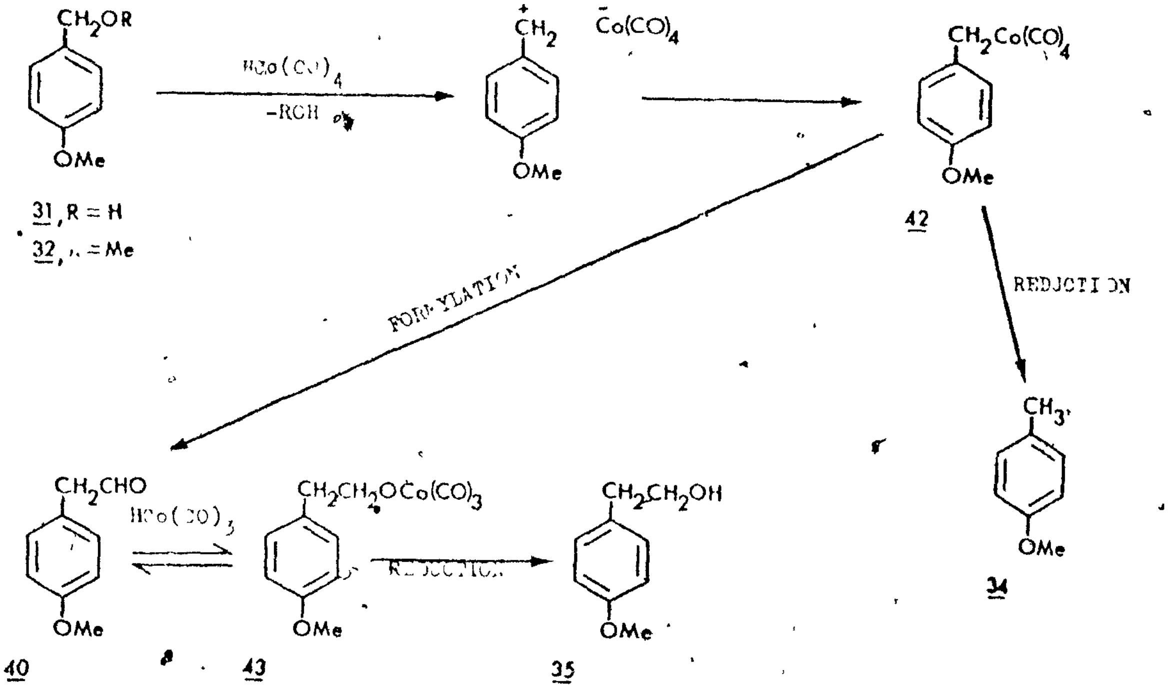
41

As the yields of the major products in Experiments 1 and 9 are closely similar, it seems likely that the cleavage of this benzyl ether follows a mechanism similar to that proposed for benzyl alcohols — i.e. Scheme 6.1, R=Me. However, the new product 41 must be accounted for.

As we believe the first step of the reaction to be protonation and methanol cleavage, the terminal methyl group of 41 must be derived from free methanol in solution. This conclusion was proven correct by conducting a reduction of p-methoxybenzyl alcohol (31) in the presence of added methanol; compound 41 was produced (Experiment 10). Its yield was smaller than in Experiment 9 — probably because 31 liberated water during the reaction. Further discussion of this topic is reserved for Section 6.2.4 (p.97).

6.2.3 The Mechanisms of Formation of the Many Products Shown in Table 6.1

The formation of p-methyl anisole (34) and p-methoxyphenethyl alcohol (35) has been discussed by other workers, who generally believe (96) that both products stem from a common intermediate 42 (Scheme 6.1).



Scheme 6.1 The Published Mechanism for p-Methoxybenzyl Alcohol Reduction (R=H) (compiled from refs.96, 121, 127 and 128).

(i) p-Methoxyphenethyl Formate (36)

This substance was isolated from the reaction mixture by chromatography on silica gel, and was identified from its p.m.r. spectrum and by the detection of p-methoxyphenethyl alcohol (35) after alkaline hydrolysis. When a sample of the latter alcohol was esterified with formic acid and dicyclohexylcarbodiimide (DCC), the product had properties (g.l.c., p.m.r. spectrum, ref. index) identical to those of the material obtained from Experiment 1.

Although there are no previous reports of formates being produced from benzyl alcohols and cobalt carbonyl catalysts, they are not unexpected. Formates are well known as products of the reduction of aldehydes under oxo process conditions (96, 122, 146, 169-171) and, as illustrated in Scheme 6.1, an aldehyde is believed to be an intermediate in the homologation of benzyl alcohols (127)*.

It has been argued that formates may result from the $HCo(CO)_4$-catalysed esterification of the homologated alcohols (102). That the bulk of the product is not produced in this way was demonstrated as follows: a mixture of p-methoxyphenethyl alcohol (35), p-methyl anisole (34), and water (in the same proportions as the products of Experiment 1) was heated under synthesis gas to 180°C. The mixture was then added to cobalt carbonyl catalyst and maintained at 180° for 2 hours. A trace of formate (less than 0.17% yield) was detected by g.l.c. — this was less than a thirtieth of the amount obtained in Experiment 1.

The mechanism of aldehyde reduction with cobalt carbonyl catalysts is still not settled (121, 122, 129) but the high formate yields always obtained suggest the presence of an intermediate containing an oxygen-cobalt bond. This may result from attack by the coordinately unsaturated hydrocobalt tricarbonyl ($HCo(CO)_3$) first postulated by Heck and Breslow (116) (see Sections 4.1, 4.2). Marko has found evidence from kinetic studies that this is so (121). Thus it seems likely that the formate isolated in our experiments resulted from 43 (Scheme 6.1) by insertion of a ligand CO molecule into the Co-O bond, followed by reduction.

Paralleling Marko's observations (170) we found the formate/alcohol ratio to be highest at low temperatures

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* B.R. James in his review (ref.107, p.179) states the opposite! The reviewer has misinterpreted the original paper (127) wherein it is shown that an aldehyde is not an intermediate in HYDROCARBON formation from aromatic alcohols.

(Experiments 4, 5 and 6, Table 6.1) and also to decrease when the catalyst concentration was raised (Experiment 7). If methanol was present or could be formed (Experiments 9, 10) the ratio was greatly reduced.

As the mechanism of reduction of intermediates such as 43 is still not decided (121, 122, 129) an explanation of the significance of the above findings is not yet possible.

(ii) Dianisyl Ether (37)

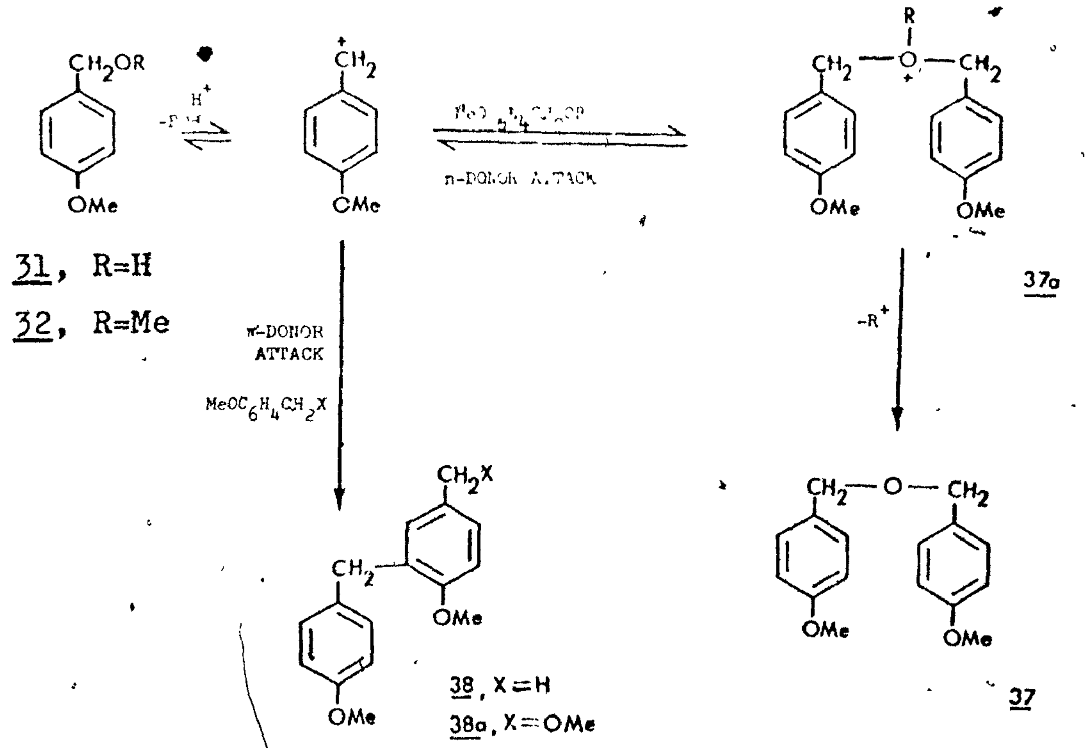
This product is known to be formed from p-methoxybenzyl alcohol by the action of mineral acids (172, 173, 177, 178). As $HCo(CO)_4$ is a strong acid (108-112), the occurrence of dianisyl ether among the products of reduction is not surprising. It was formed in only small amounts and was identified from its p.m.r. spectrum, and then found to have the same retention times, on two g.l.c. columns, as a pure sample prepared according to reference 173.

(iii) 3-Methyl-6,4'-dimethoxydiphenylmethane (38), "Diarylmethane"

In those experiments where this and the previous compound were formed together, no separation was achieved either on the silica gel column or by distillation. Compound 38 was identified from the p.m.r. spectrum of the mixture by subtraction of the simple dianisyl ether spectrum. This identification was confirmed by synthesising 38 by an alternative route. Subsequently this compound was obtained in a pure form from the $HCo(CO)_4$ cleavage of p-methoxybenzyl methyl ether (32), a reaction which does not produce dianisyl ether.

Similar diarylmethanes have been obtained previously by (i) mild acidolysis of a benzyl ether (175), and (ii) by treatment of a benzyl ether with a Lewis acid (176).

In attempting to synthesise 38 by treating a solution of p-methoxybenzyl alcohol, in a large excess of p-methyl anisole, with concentrated sulphuric acid, mixtures of dianisyl ether and the diarylmethane were always obtained, the relative proportions depending on the dilution of the alcohol. These mixtures, which resembled those formed during $HCo(CO)_4$ treatment of the alcohol, were difficult to separate. The need for separation was avoided by starting with p-methoxybenzyl methyl ether (32) rather than the alcohol 31 in which event no 37 was formed. Scheme 6.2 shows a mechanism for the formation of 37 and 38. It is clear that loss of R^+ from 37a will occur readily if R=H. However, if R=Me, loss of R^+ is less facile, and equilibrium will soon be established, whereupon all further reaction will occur by attack of the carbonium ion on the aromatic nucleus and will yield 38, either directly as in the synthesis (X=H), or after reductive cleavage of a dimeric benzyl ether 38a.



Scheme 6.2

The same explanation applies to Experiment 9 (Table 6.1) in which p-methoxybenzyl methyl ether (32), when reacted with $HCo(CO)_4$ yielded 38 but not 37.

(iv) Bis-[2-(4-methoxyphenyl)ethyl] ether (39)

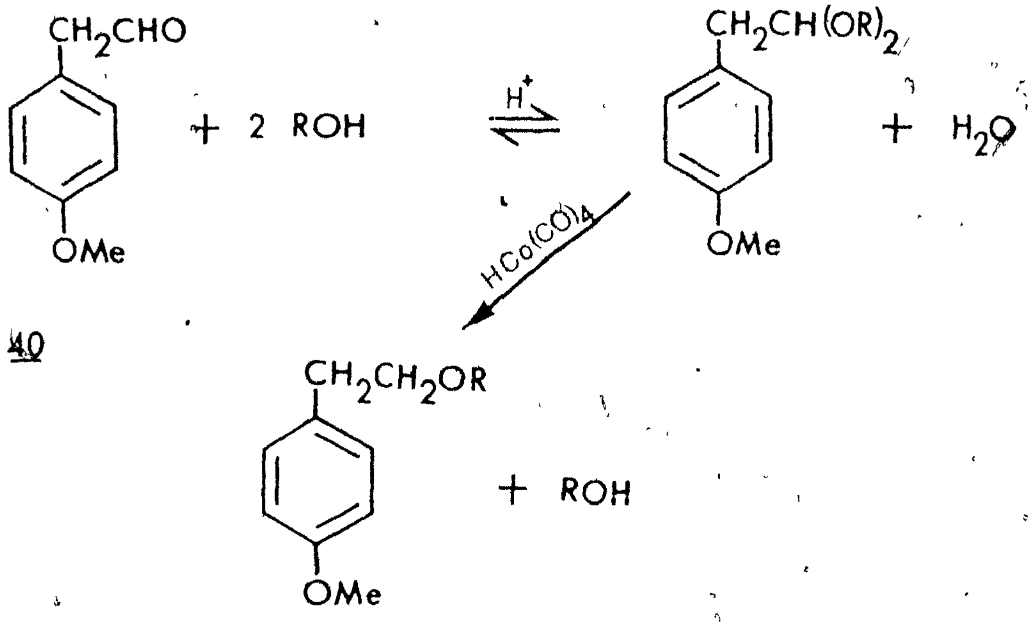
This material, obtained as a small quantity of colorless oil from Experiment 1, was identified from its p.m.r. spectrum. The identification was confirmed when an ether having the same properties was synthesised in good yield by treating p-methoxyphenethyl alcohol (35) with $H_2SO_4 \cdot 3H_2O$ at 140°C — a modification of the method used by Senderens to prepare bis-(2-phenethyl)ether (37).

When 35 was heated with $HCo(CO)_4$, under the same conditions as Experiment 1, no 39 was formed. Thus 35 was not dehydrated by $HCo(CO)_4$ under these reaction conditions. (A similar experiment with methanol present likewise yielded neither 39 nor 41.)

6.2.4 The Mechanism of Ether Formation

In Chapter 4, the formation of dibenzyl ether during benzaldehyde reductions was discussed. The proposed mechanism involved reaction of the first-formed benzyl alcohol with unreacted aldehyde to yield an acetal which was subsequently cleaved.

By analogy, the ether products 39 and 41 most likely result from cleavage of acetals formed between the intermediate p-methoxyphenacetaldehyde (40) and alcohols in the reaction mixture (Scheme 6.3). We have seen that 41 is formed when free methanol is added to $HCo(CO)_4$-p-methoxybenzyl alcohol reaction mixtures (Experiment 10), or if methanol can be produced in the initial attack (Experiment 9). Furthermore, as the reaction proceeds and homologated alcohol 35 begins to accumulate, this can also react with 40 yielding an acetal, cleavage of which yields 39.



40

39, R = p-$MeOC_6H_4CH_2CH_2$–
41, R = Me

Scheme 6.3

Evidence for Scheme 6.3 and the rôle of 40 as an intermediate in benzyl alcohol and ether cleavages was provided by the following experiments: p-methoxyphenacetaldehyde (40), when added[*] to the $HCo(CO)_4$ catalyst mixture, yielded most of the products found in Experiment 1 — i.e. p-methoxyphenethyl alcohol (35) (11%), p-methoxyphenethyl formate (36) (7%), bis-[2-(4-methoxyphenyl)ethyl] ether (39) (17%), and p-methyl anisole (34) (4%). No starting material was recovered; the remaining material was polymeric. As an intermediate in benzyl alcohol and ether cleavage, 40 would be present only at low concentrations and thus would be less prone to polymerise.

Wender et al. obtained only polymeric materials when attempting a similar reaction with phenacetaldehyde (127). Less polymer may have resulted had they mixed the reagents at 130° or above.

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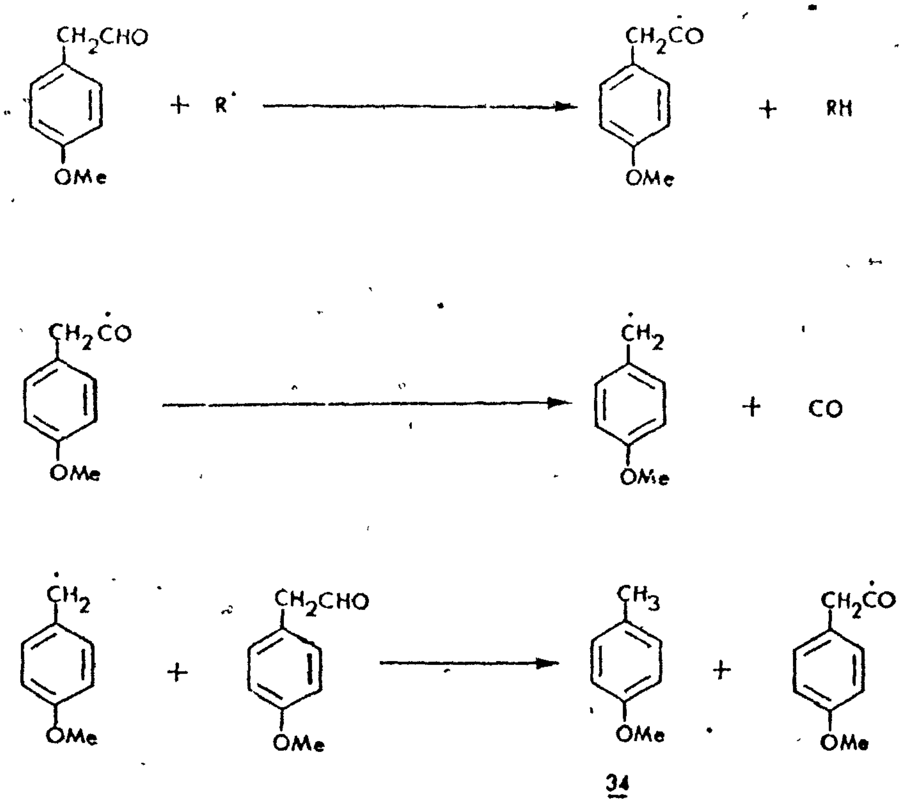
[*] Addition at 130°, temperature raised to 180° in 25 minutes, maintained at 180° for 3 hours.

The reduction of 40 described above was repeated in the presence of 4 equivalents of methanol. Only traces of formate 36 and ether 39 were produced, the major product was p-methoxyphenethyl methyl ether (41) (26%) along with 35 (20%) and 34 (4%). The higher yields here are no doubt due to rapid acetal formation, thus decreasing the amount of aldehyde available for polymerisation. The decrease of the yields of ether 39, and formate 36 by methanol addition was also apparent in Experiment 9 (Table 6.1). The first was due to competition between methanol and alcohol 35 in acetal formation (Scheme 6.3), the second was possibly a solvent effect, modifying CO-insertion by intermediate 43 (Scheme 6.1).

The small quantity of p-methyl anisole (34) formed from p-methoxyphenacetaldehyde (40) probably resulted from a free-radical decomposition (Scheme 6.4).



Scheme 6.4

A similar decarbonylation of β-phenylisovaleraldehyde has been observed to proceed almost to completion at 130° in the presence of a trace of peroxide catalyst (181).

6.3 The Relationship between p-Methoxybenzyl Ethers and Acetals

Since p-methoxybenzyl ethers may be regarded as vinylogs of acetals (Fig.6.1), their reactivity towards $HCo(CO)_4$ is not surprising in view of the facile acetal cleavages described in Chapter 4.

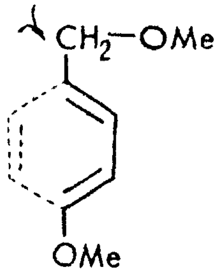
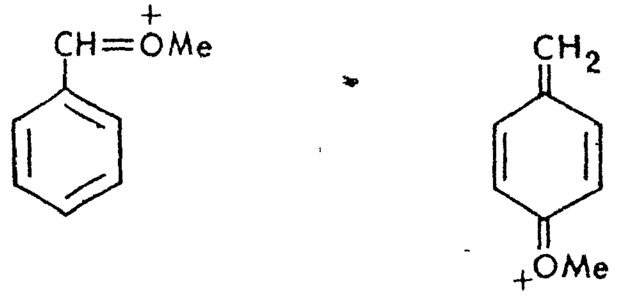


Fig.6.1 p-Methoxybenzyl methyl ether, showing its vinylogous relationship to an acetal.

Nevertheless, reductive cleavage of p-methoxybenzyl methyl ether is considerably slower than that of the corresponding acetal. For example, in direct contrast to acetals, at room temperature this ether is practically inert to hydrocarbon solutions of $HCo(CO)_4$ (Section 6.4.1) and to borane in THF (Section 6.5). The difference is readily explained in terms of the stabilities of the intermediate carbonium ions; the canonical forms of these ions are of comparable energy except for the oxonium ion form (Fig.6.2).



(a) (b)

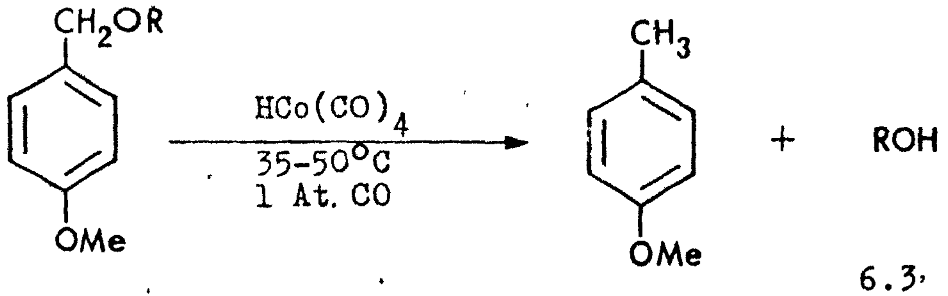
Fig.6.2 Oxonium ion from (a) benzaldehyde dimethylacetal and (b) a p-methoxybenzyl ether.

The latter is quinonoid for p-methoxybenzyl ethers, but aromatic for acetals.

Clearly the acetal carbonium ion is the more stable of the two types.

6.4 The Reduction of p-Methoxybenzyl Ethers with Stoichiometric Amounts of $HCo(CO)_4$.

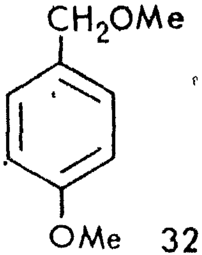
Solutions of $HCo(CO)_4$ in hydrocarbon solvents, prepared as described in Sections 5.1 and 8.4.1, reacted with p-methoxybenzyl ethers to yield p-methyl anisole (Eq.6.3). Some, but not all, of the cobalt was recovered as $Co_2(CO)_8$.



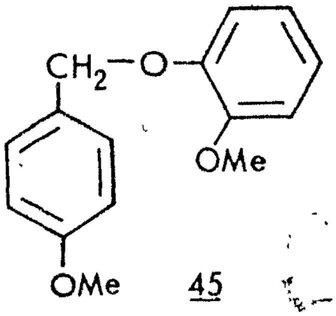
6.3

The yields in this reaction were much lower than those obtained in the analogous reactions of acetals (Section 5.1), presumably owing to the lower reactivity of the ether*.

The two ethers chosen for study — p-methoxybenzyl methyl ether (32), and p-anisyl guaiacyl ether (45) — gave different results which are described in the following two sections.



32



45

6.4.1 p-Methoxybenzyl Methyl Ether (32)

Table 6.2 shows the results of reductive cleavage of 32 by $HCo(CO)_4$ in a range of solvents. The $HCo(CO)_4$ solutions were prepared in hexane and consequently the solvent mixtures all contained 33% of hexane besides the solvent listed.

Addition of a polar solvent accelerated the decomposition of $HCo(CO)_4$ in the reaction mixture. This was indicated by (i) the rapid (in minutes) blackening of the solution followed by much gas evolution as dicobalt octacarbonyl produced was attacked by the basic solvent**, (ii) the relatively short time before $HCo(CO)_4$ became undetectable by smell or by precipitation with nickel-(o-phenanthroline) complex (163).

---

* If the reaction is slow, most of the $HCo(CO)_4$ will decompose according to: $2\ HCo(CO)_4 \longrightarrow H_2 + Co_2(CO)_8$

** Reaction mixtures in acetonitrile solution at first darken (formation of $Co_2(CO)_8$) and then revert to a pale orange color with rapid gas evolution. Reactions of many basic solvents, including acetonitrile, with $Co_2(CO)_8$ have been described by Heiber and Sedlmeier (182).

TABLE 6.2

Reductive Cleavage of p-Methoxybenzyl Methyl Ether (32) by 0.14M $HCo(CO)_4$ Solutions

Exp. #	Solvent[a]	Reaction Temp., °C	Approximate[b] Reaction Time, hours	Final Yield of p-Methylanisole (34), mole %
1	Benzene	22	27-93	0.3
2	Hexane	36-40	8-10	1.6 (0.5% cleavage after 1 hour)
3	Hexane	40-45	7-10	1.6[c]
4	Benzene	40-45	2.5-6	3.0
5	THF	40-45	0.5-1.0	0.6
6	Acetone	36-40	0.5-0.8	1.4
7	Acetone	47-51	0.5-0.8	1.6
8	Acetonitrile	40-45	0.5-1.0	2.9
9	Dimethylsulfoxide	Solvent reduced by $HCo(CO)_4$		

(a) The solvent listed (10 ml.) was added to 1 mmol of ether in each flask, followed by 5 ml. hexane containing 2.1 mmol $HCo(CO)_4$. All 'solvents', therefore, contained at least 33% hexane. (b) Until $HCo(CO)_4$ was no longer detectable, by smell or by precipitation with nickel-(o-phenanthroline) complex. (c) $Co_2(CO)_8$ recovery equivalent to 1.4 mmol of cobalt.

Hexane solutions at 40°C took two to three hours to become fully black and very little gas evolution occurred.

While speeding $HCo(CO)_4$ decomposition, polar solvents did not affect the yield of reduced product in a predictable way (compare Experiments 3, 5 and 8, Table 6.2). However, the rate of cleavage-product formation was increased by polar solvents. For example, with acetone-hexane solvent, all $HCo(CO)_4$ had disappeared after 50 minutes at 38±2° (Experiment 6) and 1.4% cleavage was obtained. In pure hexane after 1 hour, only 0.5% cleavage had occurred, several hours later the value reached 1.6% (Experiment 2). Apparently polar solvents accelerate ether reduction and $HCo(CO)_4$ decomposition about equally.

6.4.2 p-Anisyl Guaiacyl Ether, or, 2-(4-Methoxybenzyloxy)-anisole (45)

A marked effect of solvent on the yield of p-methyl anisole (34) was evident when 45 was the substrate ether (Table 6.3). In polar solvents, the rate of reduction was also increased.

Since both ethers 32 and 45 show a considerable increase of cleavage rate in polar solvents, it is possible that solvent assists in the cleavage*. To confirm this notion will require thorough kinetic studies and an investigation of inversion/retention at the benzyl carbon (after partial deuteration).

The difference in magnitude of the solvent effect for the two ethers is surprising because, on the basis of the foregoing discussion, the ethers would be expected to cleave via carbonium-ion type transition states (46, 47) of very similar energy.

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* S_N2 reactions of the type $RX^+ + Y^- \longrightarrow RY + X$ and S_N1 reactions of the type $RX^+ \longrightarrow R^+ + X$ exhibit negative solvent effects (183).
Acidolysis of α-phenethyl phenyl ether by HCl, an S_Ni reaction, showed only a very small positive solvent effect (184).
Nucleophilic solvent assistance is reviewed briefly in ref.166.

TABLE 6.3

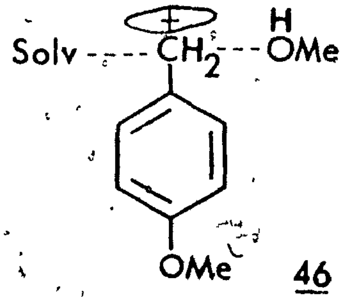
The Reaction of Anisyl Guaiacyl Ether (45)[a] with Stoichiometric Amounts of $HCo(CO)_4$

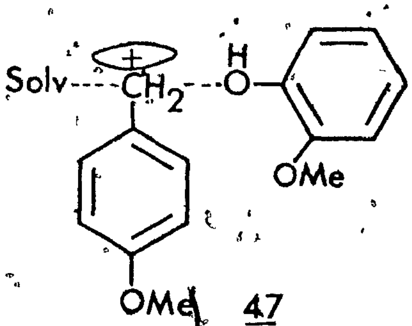
Exp. #	Reaction Temp, °C	Solvent	Mole Ratio 45 /$HCo(CO)_4$ [b]	Approx. Reaction Time, min.	p-Methylanisole(34)[c] Yield, %
1	45-50	C_6H_6(100%)	0.7[d]	-	6.5
2	45-50	C_6H_6(32%), Me_2CO(68%)	0.6	-	26[e]
3	45-50	C_6H_{14}(40%), C_6H_6(60%)	1.0	350	1.4 (0.2% cleavage) (after 40 mins)
4	45-50	C_6H_{14}(40%), THF (60%)	1.0	200	3.4 (1.1% cleavage) (after 26 mins)
5	45-50	C_6H_{14}(40%), Me_2CO(60%)	1.0	60	9.0 (5.6% cleavage) (after 9 mins.)

(a) With the exception of Experiment 1, ether concentration employed was 0.06-0.05M.
(b) Analysed according to ref.208.

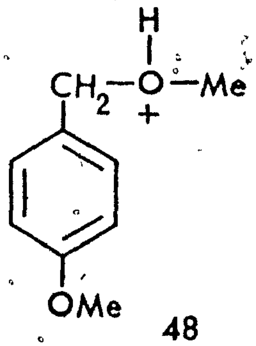
(c) Based on the equation: $MeOC_6H_4CH_2OR + 2\ HCo(CO)_4 \longrightarrow MeOC_6H_4CH_3 + ROH + Co_2(CO)_8$

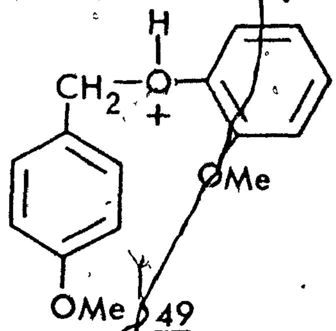
(d) Ether concentration 0.11M.
(e) 65% recovery of starting material, m.p. 93-94°, mixed m.p. with pure 45, 94-96°.


46


47

An explanation, admittedly speculative, may be found in the differing degrees of solvation of the protonated ethers 48 and 49.


48


49

The argument runs as follows: for steric reasons, 49 is less stabilised by solvation than 48, and requires less activation energy to reach the transition state 47*. Consequently, it reacts faster (this argument parallels that given in Section 4.8 for acetals) and competes more effectively with $HCo(CO)_4$ decomposition to give higher yields.

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* Solvation of both transition states 46 and 47 is likely to be small because of the dispersed charge.

6.4.3 CO-Insertion under Stoichiometric Conditions

During all the studies of stoichiometric reduction of p-methoxybenzyl ethers with $HCo(CO)_4$, no products resulting from carbon monoxide-insertion were detected. Other workers who treated benzyl alcohol in a like manner also observed only the reduction product, toluene (89, 164).

In this respect the stoichiometric reaction differs from the catalytic one, where at least 25% of the product is hydroformylated (see Table 6.1 and ref. 128). The difference could be ascribed to inhibition of the weak CO-insertion by the low partial pressure of CO under stoichiometric conditions (straight-chain olefins in which CO-insertion is always the dominant reaction continue to insert CO under stoichiometric conditions (89, 115, 164)). An additional factor may be the rapid reduction of intermediate 42* by the excess of $HCo(CO)_4$ present under stoichiometric conditions. Under catalytic conditions, by contrast, $HCo(CO)_4$ is probably present only at very low concentrations.

6.5 The Reduction of p-Methoxybenzyl Methyl Ether (32) with Borane in THF

The reduction of 32 by borane is a very slow reaction compared with reduction of the isomeric benzaldehyde dimethyl acetal. Only a trace of p-methylanisole (34) was formed after a reaction mixture containing 32 (0.2M) and borane in THF (1M) had stood for 1½ hours at 25°C. After 18 hours in a water bath at 40-50°C the mixture yielded only 7%** of 34; the bulk of the starting material was unchanged. A 75% yield of 34 was obtained**,

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* P.93.

** G.l.c. analysis.

however, when 32 was treated with an excess of borane in THF and heated to 135° for 5 hours, under 700 psig of hydrogen[*].

Under mild conditions 34 was the only product detected, but at elevated temperatures some side products were evident in the gas chromatogram; these may derive from cleavage of the solvent by borane[**].

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[*] Thakar and Subba Rao have effected reductions of some aromatic alcohols and ketones to hydrocarbons under similar conditions (59).

[**] For example, see ref.49.

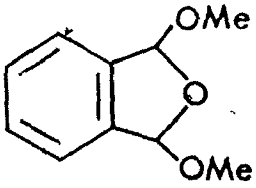
CHAPTER 7

THE REDUCTIVE CLEAVAGE OF AN ALDAL BY BORANE AND BY $HCo(CO)_4$

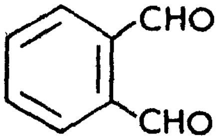
7.1 Introduction

The results of reactions of borane and $HCo(CO)_4$ with simple acetals suggested examination of the more complex case of a cyclic aldal having both a ring oxygen and exocyclic oxygen atoms open to attack.

For these studies 1,3-dimethoxyphthalan was chosen — a choice dictated by the necessity of having an aromatic substituent in order to obtain a 'clean' reaction with $HCo(CO)_4$ and by the ease of synthesis of 50.



50



51

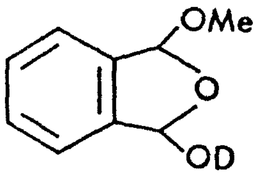
7.2 Preparation of 1,3-Dimethoxyphthalan

The compound 1,3-dimethoxyphthalan (50) was first prepared by Schmitz in 1958 (185) by adding a methanolic solution of o-phthalaldehyde (51) and dimethyl sulphate to aqueous sodium hydroxide. Schmitz reported this to be the first example of synthesis of an acetal from the aldehyde itself under alkaline conditions. In fact it is probably an example of hemi-acetal methylation — a well known reaction (186).

o-Phthalaldehyde (51) has long been known to form a monohydrate (187), and its proposed hemialdal structure was supported by polarographic (188) and u.v. spectral (189) measurements.

Final confirmation of this structure is nowadays very easily achieved by means of nuclear magnetic resonance: Figures 7.1 and 7.2 show the p.m.r. spectra of 51 in carbon tetrachloride and D_2O respectively. Fig.7.1 is the expected aromatic aldehyde spectrum; Fig.7.2 shows that in D_2O about 90% of the material has been converted into the hemialdal form (the aldehyde form shows as a singlet at δ 10.82 and also in the small signals centred on δ 8.37)*.

Similarly a solution of 51 in MeOD exhibits over 85% conversion into the dialdehyde methanolate (52) 45 minutes after mixing (Fig.7.3). No aldehyde was detectable in a second p.m.r. spectrum of the same solution taken 65 hours later; only 52 and a trace of 50 were evident.



52

Clearly then, in Schmitz's synthesis, the "methanolic solution of o-phthalaldehyde" starting material contains mostly the dialdehyde methanolate (undeuterated 52).

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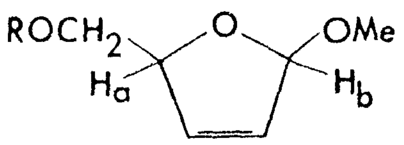
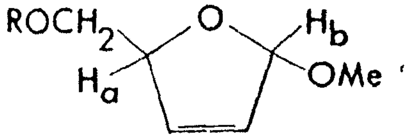
[*] A considerable downfield shift is evident for the aldehyde signals shown in Fig.7.2 when compared to Fig.7.1. At least part of this shift is caused by the use of an external TMS reference for the D_2O spectrum.

7.3 The Properties of 1,3-Dimethoxyphthalan (50)

Schmitz did not realise the possibility of stereoisomerism in 50*. It was discovered later by Aso and Tagami (191): they observed in the p.m.r. spectrum of their product in carbon tetrachloride solution a single methoxyl peak and two peaks for the methine protons at δ 5.81 and 6.05 ppm. Although they were unable to separate the isomers, the authors assigned the methine signals on theoretical grounds as being due to the cis and trans configurations respectively. The isomers were found to be present in the ratio 60 cis:40 trans. In making their assignment, Aso and Tagami assumed the ether ring of 50 to be in an envelope form. Doubt is cast on this assumption by the work of Lemieux et al. (192) who showed from p.m.r. studies that the compounds 53 and 54 have ether rings which are approximately planar (as models had indicated). Models similarly show the ether ring of 50 to be planar.



53 $J_{A-B} = 1.2$ Hz



54 $J_{A-B} = 4.4$ Hz

R = Bz, Ac, H

Our preparation of 1,3-dimethoxyphthalan (50) yielded the same isomer ratio as obtained by Aso and Tagami (Fig.7.4) and under high resolution in CCl_4 solution the two separate methoxyl signals were observed. By repeated chromatography on silica gel small quantities of pure isomers were obtained.

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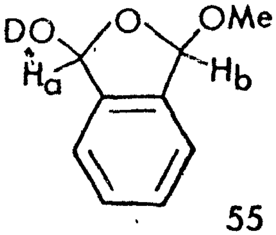
* This is a common failing; Rieche and Schultz described 1,3-dimethylphthalan and 1,3-diphenylphthalan apparently without considering that their product might be a mixture of isomers (190). Powell and Rexford (269) made the same omission with 1,3-diethoxyphthalan, as did Weygand et al. with 6-bromo-1,3-dimethoxyphthalan (270).

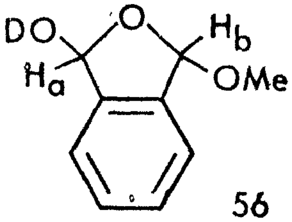
Complete separation was not achieved but the first and last fractions eluted contained relatively pure isomers. The first eluting isomer gave the downfield methine signal (Fig.7.5); the slower moving isomer gave the upfield methine signal (Fig.7.6). The trans-isomer, having a lower dipole moment than the cis, would be expected to elute first; this result therefore supports the assignment of Aso and Tagami. Regrettably, an insufficient quantity of the pure isomers was available for dipole moment measurements.

When the separated isomers were allowed to stand for a day or two in contact with silica gel they reverted to the 60:40 cis-trans mixture, which appears to be the equilibrium ratio. The predominance of the cis-configuration at equilibrium has not yet been explained.

A more detailed examination of Fig.7.3 gives additional support to the assignment of Aso and Tagami — the methine region of this spectrum shows 6 lines; a pair of doublets at δ 6.53 and 6.32 ppm, J=2 Hz, and two singlets at 6.02 and 6.28 ppm resulting from cis- and trans-dialdehyde methanolates 55 and 56.



55



56

The isomer which yields the downfield signals also shows a methine coupling (J_{A-B}) of 2 Hz. It is reasonable to conclude that the more strongly coupled isomer is trans on the basis of the work by Lemieux et al. (192), who measured J_{A-B} in compounds 53 and 54, and found the trans isomer to show strong coupling, the cis weak.

Because of the close structural similarity of the dialdehyde methanolates 55 and 56 and the 1,3-dimethoxyphthalans (50), assignment of the downfield methine signal to the trans isomer of the former supports the similar assignment for 50 made by Aso and Tagami (191).

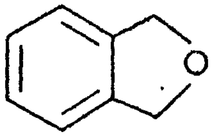
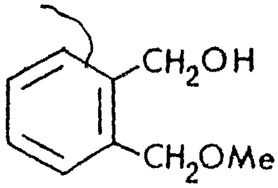
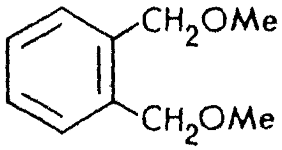
Contrastingly, Lemieux et al. found the β-D-furanoside 53 (R=H) to give a methine signal at lower fields than those of the α- or trans-isomer 54 (R=H) (192). This is surprising since α-D-furanosides generally give anomeric proton signals at lower fields than the β-anomers. However, Lemieux et al. were obliged to measure their spectra in $(CD_3)_2SO$, as this was the only solvent out of a total of seven which brought about a separation of all the signals (271). Consequently, their unusual observation may be the result of a solvent effect, in which the $(CD_3)_2SO$ shifts the two isomers to different extents.

7.4 The Reductive Cleavage of 1,3-Dimethoxyphthalan (50) by Borane (BH_3)

When a sample of the equilibrium mixture of 50 (60% cis, 40% trans) was treated with borane in THF, three products resulted — see Table 7.1.

TABLE 7.1

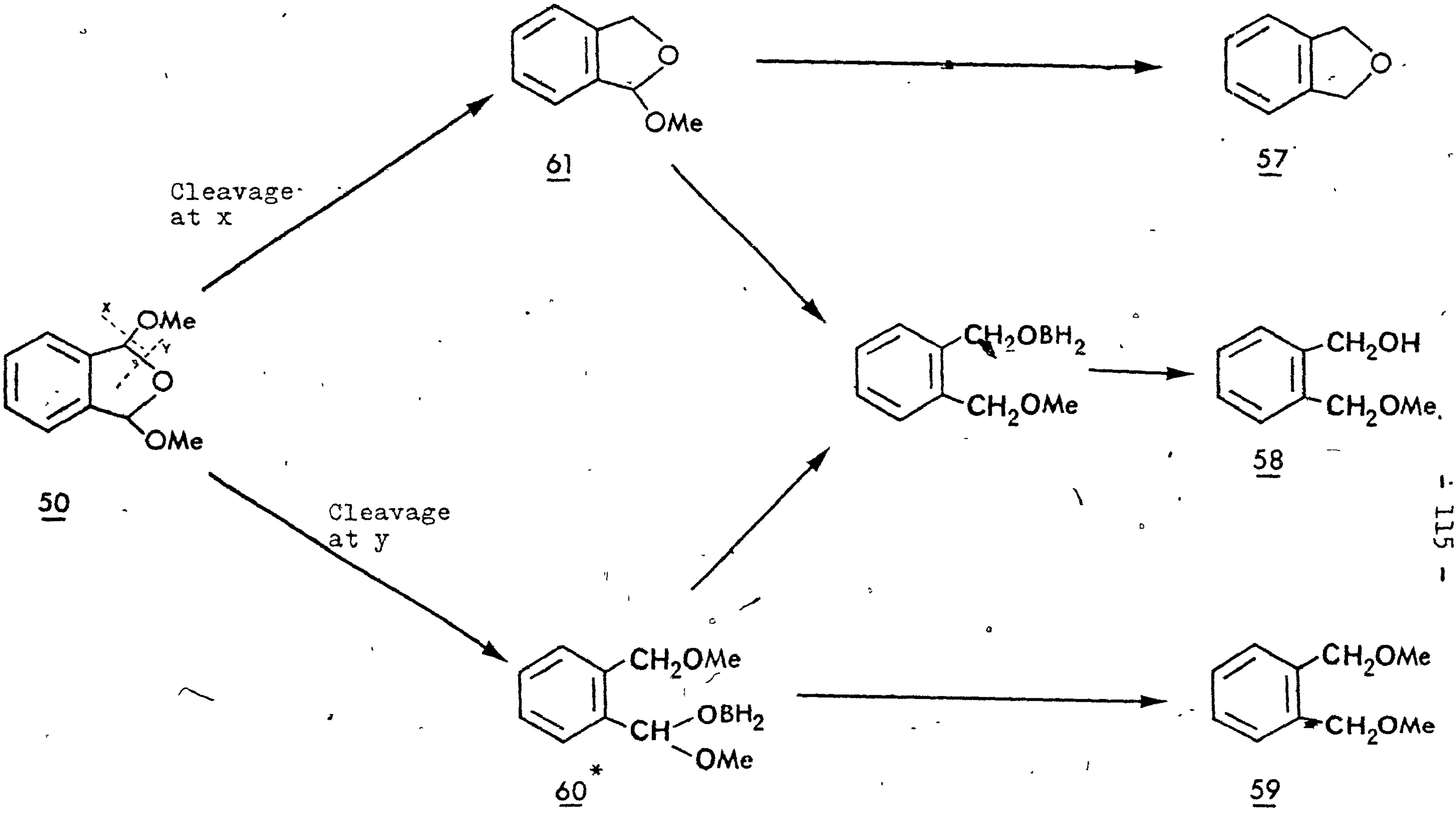
Products Obtained from 1,3-Dimethoxyphthalan (50) and Borane[a]

Product Structure	Yield, % (by g.l.c.)	Isolated[b] Yield, %
 (57)	72	60
 (58)	28	16
 (59)	0.4	0

(a) 25 mmoles BH_3 (1M) in THF added to 10 mmols of 50 under nitrogen. Mixture heated at 40°C for 7 hours.
(b) by distillation.

Compounds 58 and 59 were identified by their p.m.r. spectra, and the structures were confirmed by comparison of the properties of the isolated materials with authentic samples — a procedure followed for most of the products described in this chapter. Phthalan (57), however, was considered sufficiently well characterised by both its physical and chemical properties (notably the facile oxidation to the peroxide) not to require synthesis.

Scheme 7.1 indicates how the compounds in Table 7.1 can be formed. Phthalan (57) can only result from initial borane attack on an exocyclic oxygen; 59 can only result from initial



SCHEME 7.1 Product Formation during BH_3 Cleavage of 1,3-Dimethoxyphthalan (50)

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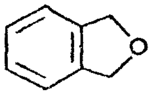
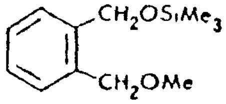
* The formation of alcohols and ethers from hemiacetal borohydrides, like 60, has been discussed previously in reference to ester reduction by BH_3 (35, 45).

attack on the ring oxygen; whereas 58 can be formed by either route. Despite this ambiguity, the 72% yield of phthalan indicates cleavage of the exocyclic oxygens on both 50 and 61 to be the preferred *modus operandi* of borane.

The borane reduction of 50 was repeated on a small scale (50-60mg.) using a series of incompletely separated isomer mixtures, each treated identically. The results of g.l.c. analysis of the silylated product are shown in Table 7.2.

TABLE 7.2

G.l.c. Analysis of Reduction Products from a Range of Isomer Mixtures of 50

Isomeric Composition of Starting Material[a]	 % of Total Area	 % of Total Area
90%t : 10%c	72	28
89%t : 11%c (i)[b]	75	25
(ii)	75	25
40%t : 60%c (equilibrium mixture)	72	28
22%t : 78%c	74	26
14%t : 86%c	76	24

(a) Determined by p.m.r. (b) Repeated g.l.c. analyses.

No trend can be seen in the ratio of the major products as the isomer ratio is changed. The conclusion, therefore, is either that the *cis*- and *trans*-isomers give identical amounts of *exo*- and *endo*-cleavage, or that the borane equilibrates the isomers much faster than they are cleaved.

7.5 The Reductive Cleavage of 1,3-Dimethoxyphthalan (50) by $HCo(CO)_4$

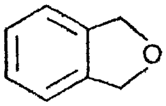
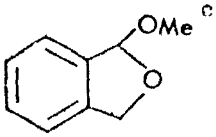
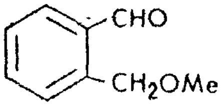
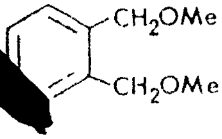
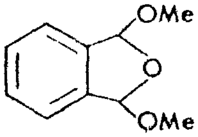
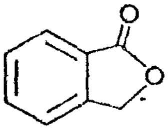
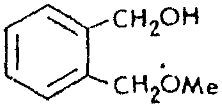
On reaction with $HCo(CO)_4$ the cleavage products of 50 are much more complex than those obtained with borane. After 90 minutes at 160±5° with catalytically generated $HCo(CO)_4$, the g.l.c. of the product showed seven major peaks, three of which overlapped (Table 7.3). One of the latter peaks changed position upon silylation, revealing itself to be 58. The remaining compounds were identified after separation on a silica gel column. The starting material, much of which was unreacted, suffered considerable hydrolysis on the column and was partially obtained as o-phthalaldehyde (51); none of this compound was evident in the original g.l.c.

The first thing to notice about Table 7.3 is the relatively large quantity of α,α'-dimethoxy-o-xylene (59) produced, and the low yield of phthalan (57), compared to the borane cleavage products. Next it should be noted that for every molecule of 59 formed, an oxygen atom is lost, presumably as water. Under the prevailing acidic conditions, this water may be expected to react immediately with unchanged starting material (50) and hydrolyse it to o-phthalaldehyde (51). The mysterious appearance of phthalide 62 was explained when this compound was obtained along with phthalan as a product of the reaction of $HCo(CO)_4$ and 51 (see Appendix 3 for further discussion of the reduction of 51). Scheme 7.2 is a rationalisation of the formation of the six product compounds in Table 7.3. It is basically the same as Scheme 7.1 with the addition of side-reactions involving free water and methanol. These side-reactions can occur with $HCo(CO)_4$ because, in contrast to borane, it is inert towards active hydrogen atoms.

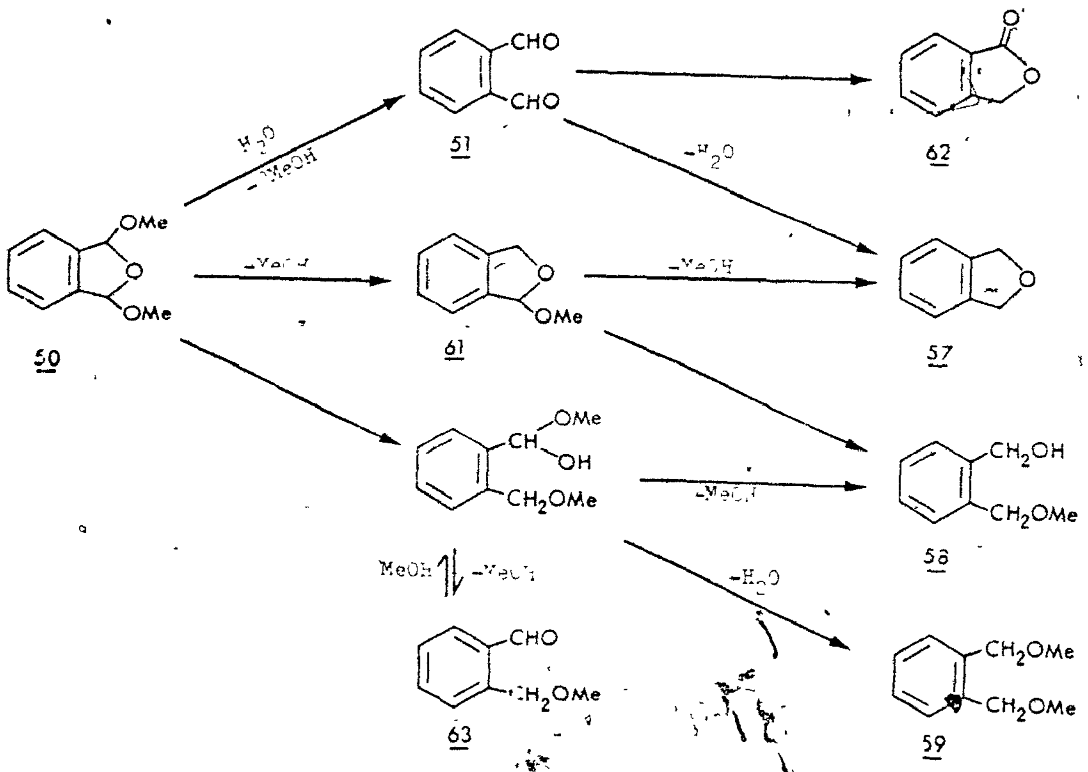
Aldehyde 63 appears to be a new compound, its structure was determined by p.m.r. spectroscopy and confirmed chemically by (i) preparation and analysis of the semicarbazone;

TABLE 7.3

Products Obtained by Reductive Cleavage of 1,3-Dimethoxyphthalan (50) with Mo(CO)$_4$[a]

Symbol	Product	G.l.c.[b] Retention Time(min)	% Total Area	% Total Area after Silylation	Isolated Yield (% Theory)
57		0.9	7	8	1
61	 [c]	1.7	4	4	4
63		2.2	23	22	19
59		2.5	20	19	17
50		2.8	40	37	30[d]
62		2.85			3
58		2.8		5	-

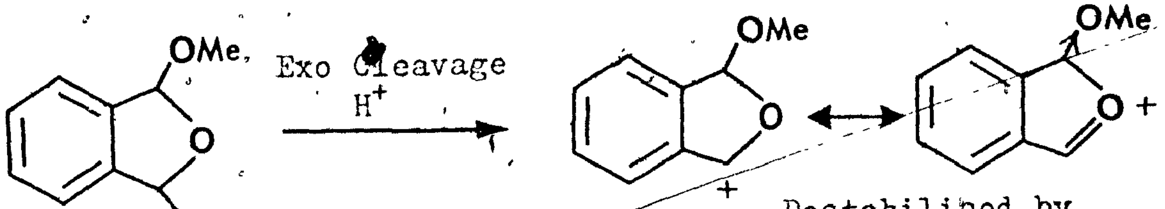
(a) At 160±5°C for 90 mins. (b) G.l.c. oven temp. 100°C — see Section 8.1 for full details. (c) This compound gave a p.m.r. spectrum consistent with the formula shown, but polymerised before further measurement were made. (d) Includes 9% obtained as the hydrolysis product, o-phthalaldehyde (51).



SCHEME 7.2 Product Formation in the HCo(CO)$_4$ Cleavage of 1,3-Dimethoxyphthalan (50)

(ii) reduction with sodium borohydride to 58; and (iii) formation of the corresponding benzoic acid — a known compound — by autoxidation in air.

The strong preference for attack on the ring oxygen shown by $HCo(CO)_4$ can be explained in terms of the destabilisation of the oxo-carbonium ion resulting from *exo*-cleavage (Scheme 7.3).



Destabilised by
(i) Increased ring strain
(ii) Inductive effect

Scheme 7.3

Neither of the destabilising effects operates if the attack is on the ring oxygen.

The preference of borane for *exo*-attack may be dictated by steric factors which would have little influence on protonation by $HCo(CO)_4$.

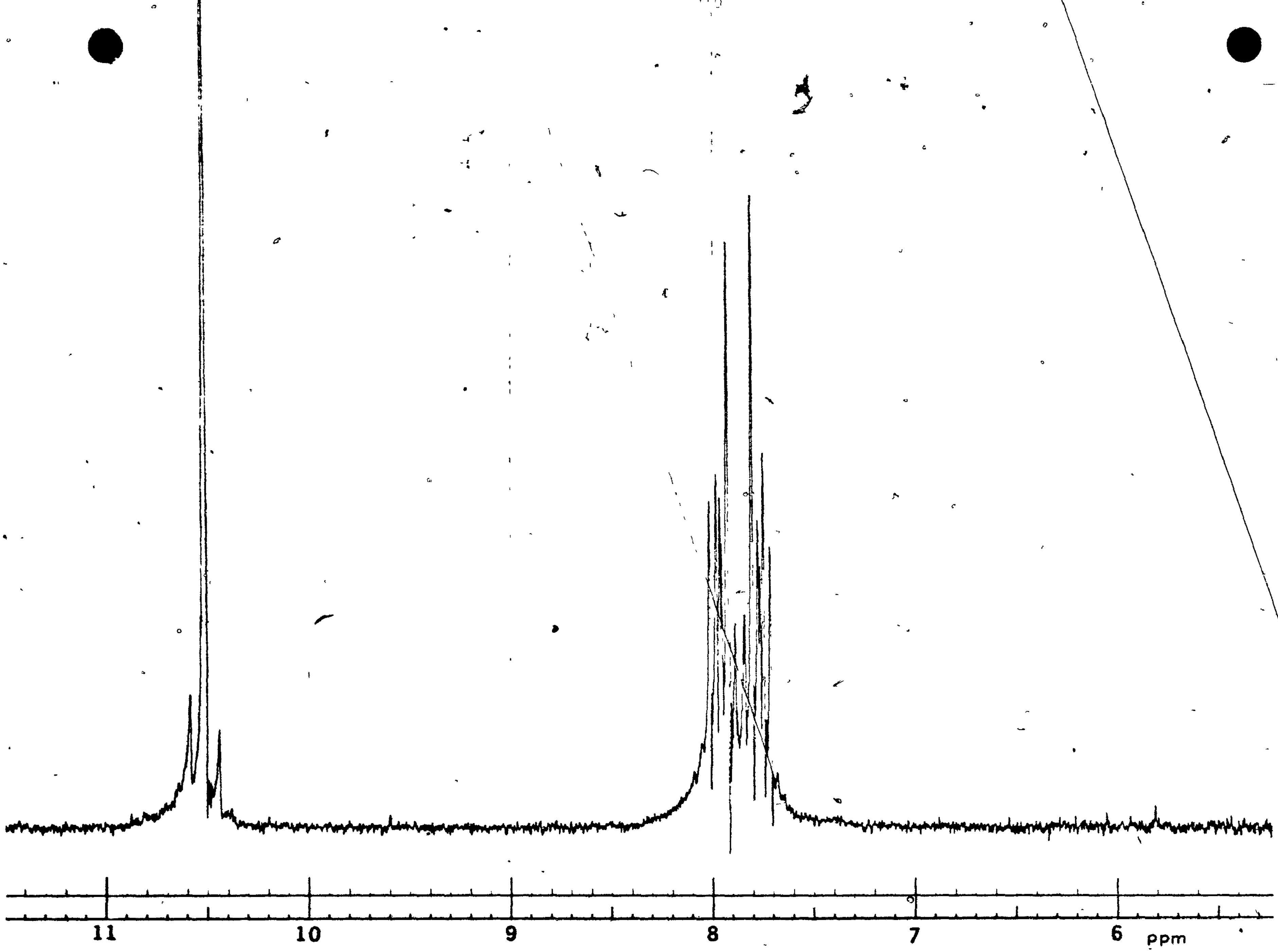


Fig.7.1 P.m.r. spectrum of o-phthalaldehyde in CCl_4 solution, showing aromatic and, downfield, aldehyde protons.

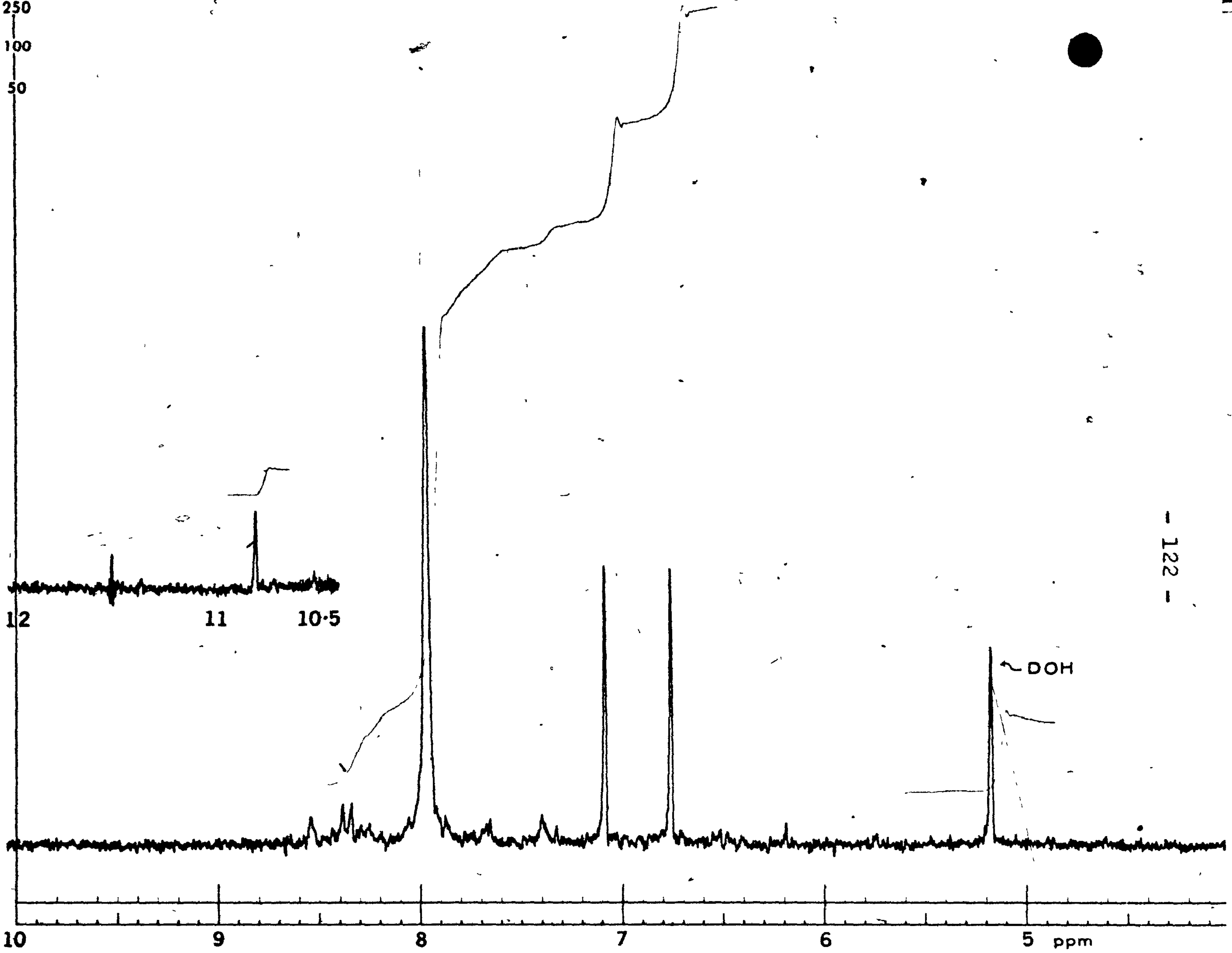


Fig.7.2 P.m.r. spectrum of *o*-phthalaldehyde; 3.7% solution in D_2O (External TMS). Most of the material is in the hemialdal form (*cis*- and *trans*-methine protons at δ 6.76, 7.10), about 10% aldehyde remains δ 10.82, 8.37.

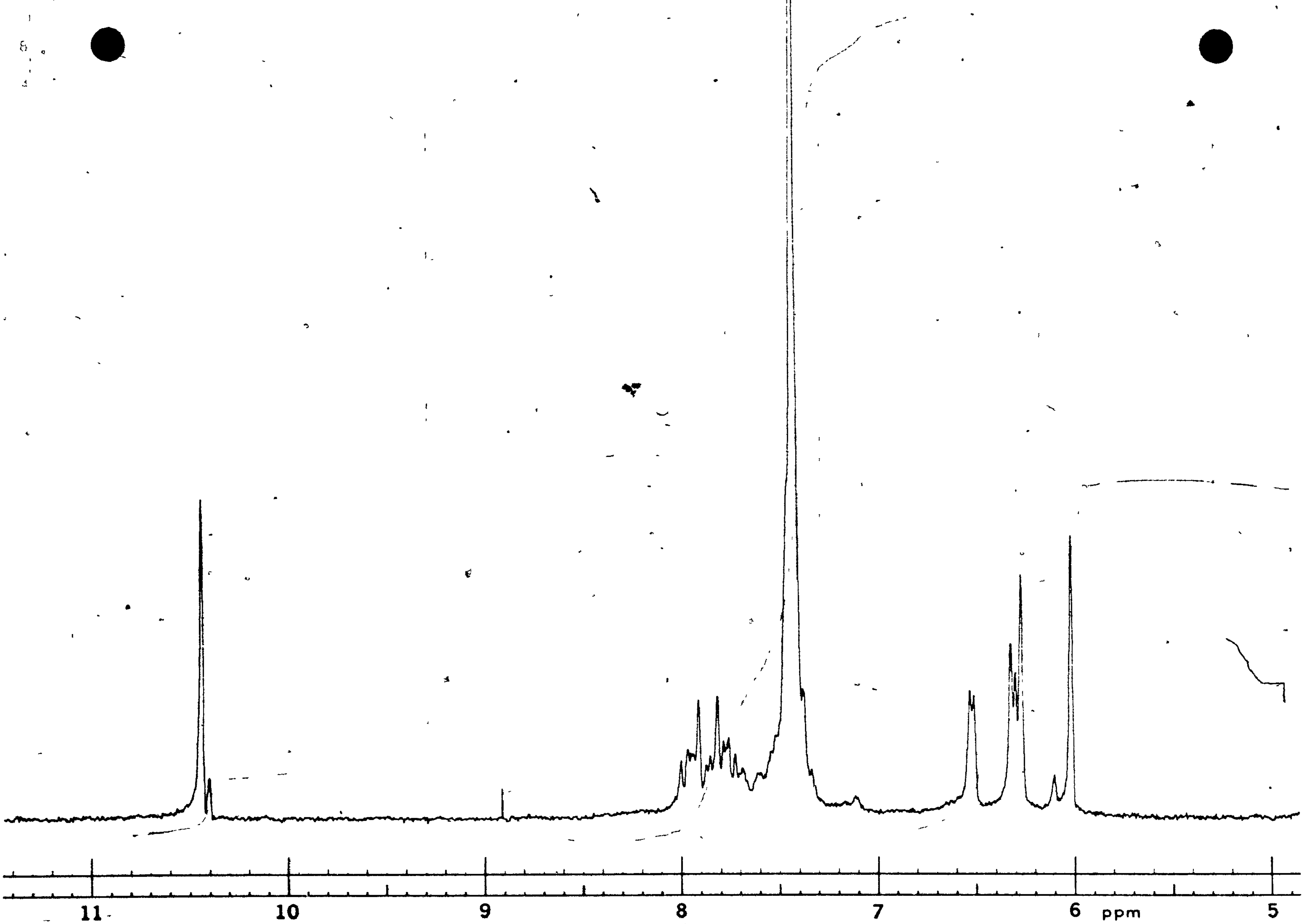


Fig.7.3 P.m.r. spectrum of *o*-phthalaldehyde solution, 24% b.w. in methanol-d_1. This spectrum, taken shortly after the solution was made, shows a significant amount of aldehyde (δ 10.45, s, and 7.9,m). The six large peaks in the region 6-7ppm are due to the methine protons of the dialdehyde methanolates, the *trans*-isomer of which exhibits long-range coupling.

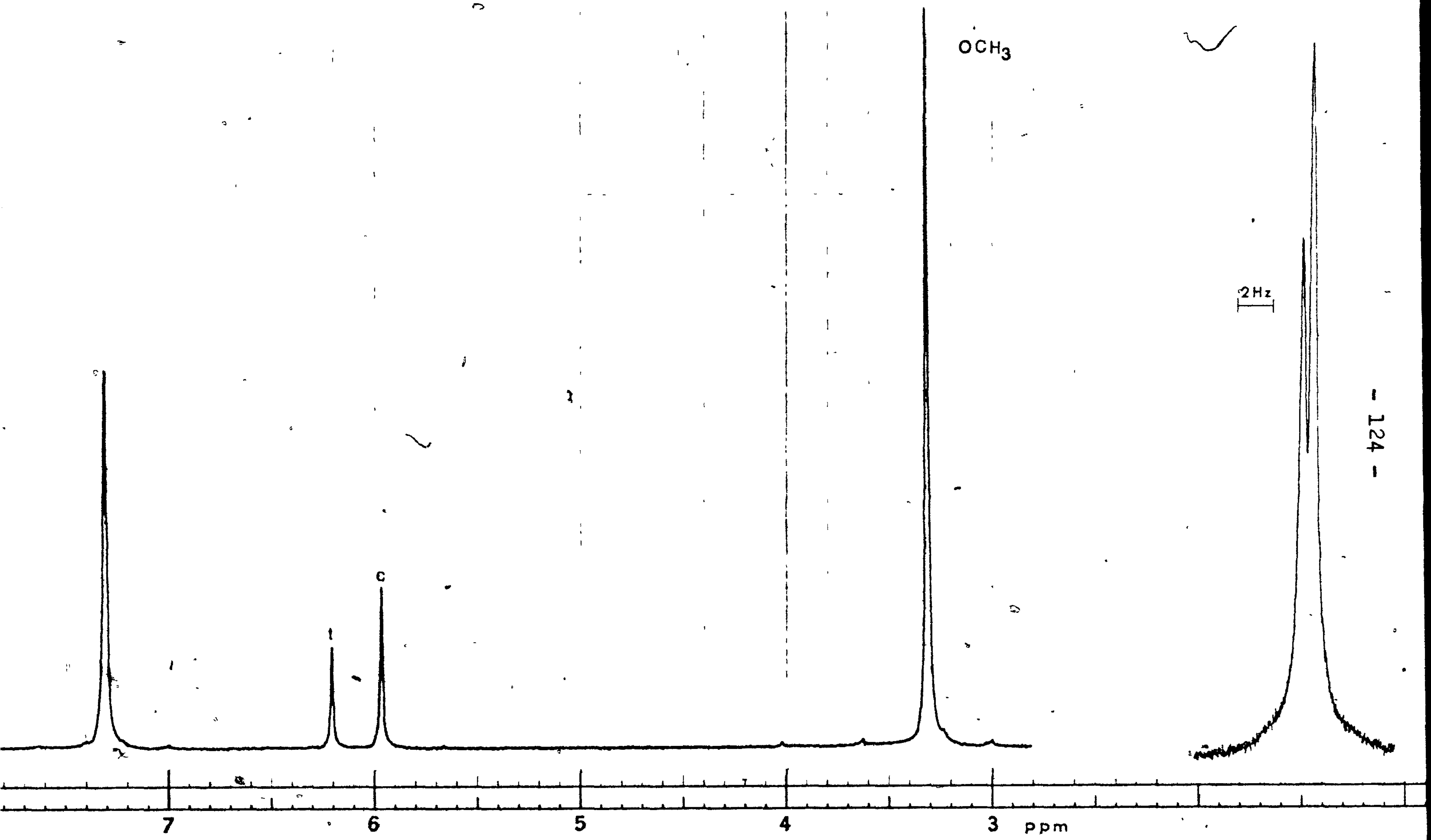


Fig.7.4 P.m.r. spectrum of the product of 1,3-dimethoxyphthalan synthesis (CCl$_4$ solution). The cis- and trans-isomers, measured from the methine proton signals near 6ppm, were present in the ratio 60:40. The inset shows the methoxyl signal scanned at 0.1 Hz sec^{-1}, 100 Hz sweep width. The trans-methoxyl is 0.005ppm downfield from the cis.

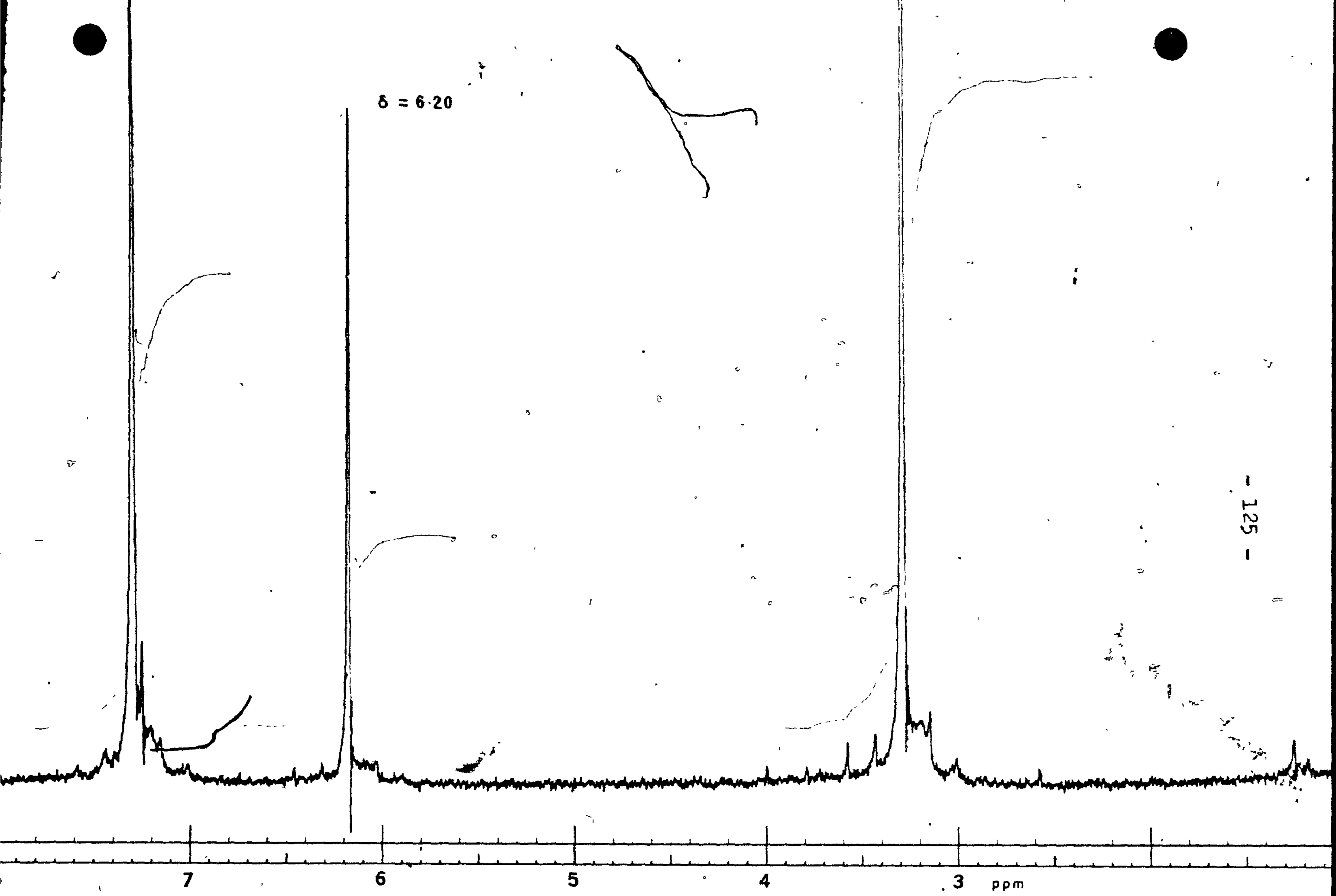


Fig.7.5 P.m.r. spectrum of the isomer of 1,3-dimethoxyphthalan which elutes first from silica gel, (*trans*).

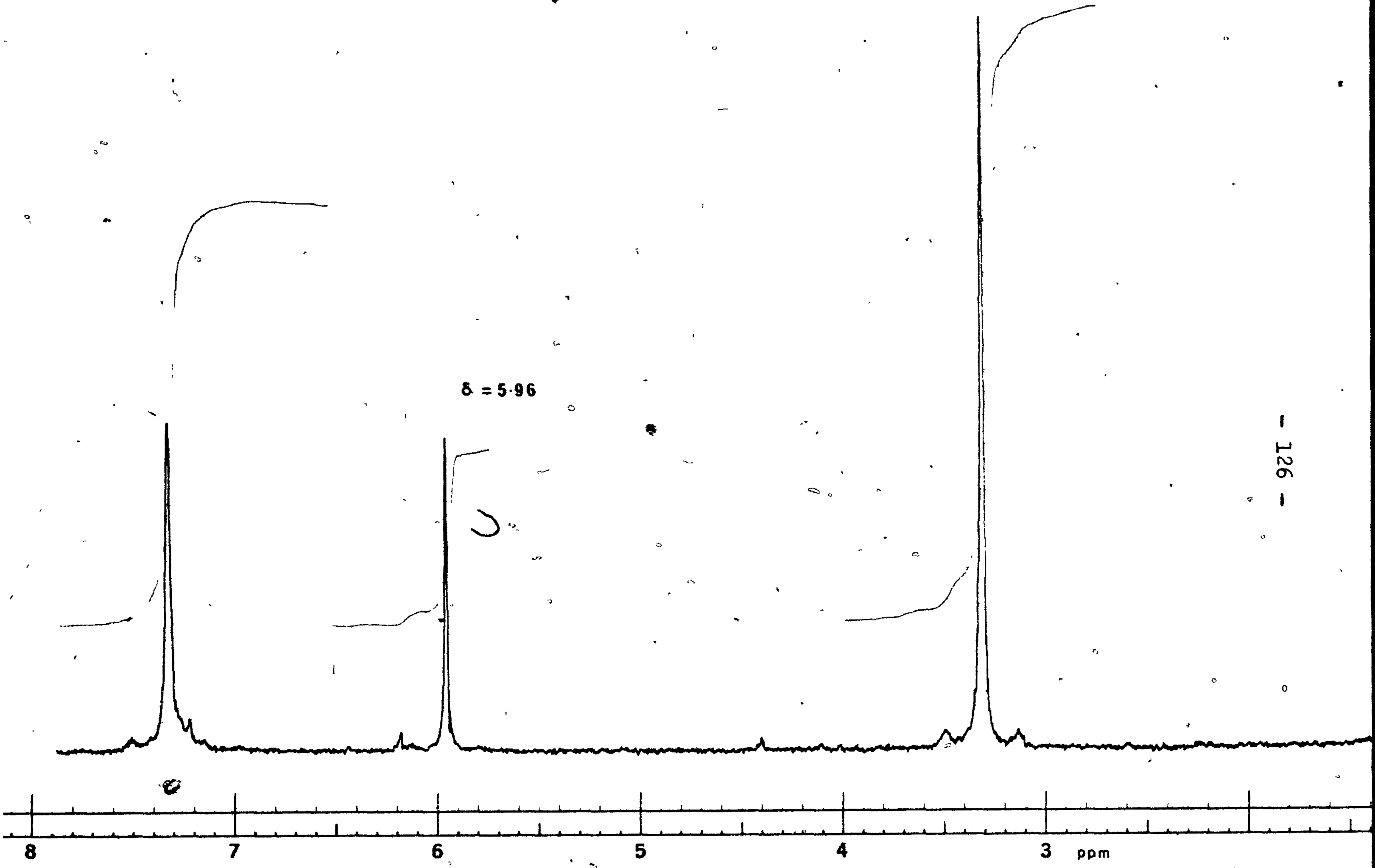


Fig.7.6 P.m.r. spectrum of the isomer of 1,3-dimethoxyphthalan which elutes second from silica gel, (<u>cis</u>).

CHAPTER 8

EXPERIMENTAL SECTION

8.1 General Methods

The purity of the starting materials and the isolated products was determined by gas liquid chromatography (g.l.c.) and, when the compound was previously reported, by refractive index or melting point (m.p.). The identity of already known compounds was confirmed by comparison of physical properties, infrared and proton magnetic resonance (p.m.r.) spectra with those of the authentic compounds (synthesised, if necessary, according to the literature).

When hitherto unknown compounds were revealed by the p.m.r. spectrum of a product fraction, a microanalysis* of a sample of the compound or of a derivative was obtained. An alternative synthesis of the compound in question was devised, and the product so obtained was compared with the sample first isolated, using all the aforementioned criteria. In some instances, chemical properties and gas chromatography-mass spectroscopy (g.c.-m.s.) were used to confirm the proposed structures.

Gas chromatographic analyses were done on a Hewlett-Packard F & M model 402 instrument, equipped, in most cases, with 120 cm glass column packed with 4% SE-30 on Chromosorb WAWDMCS. The products of Experiment 15, Table 2.3, required a 180 cm column for adequate separation, and the volatile product of Experiment 7, Table 2.1, could only be separated from the THF solvent by using a 120 cm Porapak R column. A helium carrier-gas flow-rate of 60 ml/min. was maintained,

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* Schwarzkopf Microanalytical Laboratory, New York City.

and column-oven temperatures ranged between 50° and 250° depending upon sample volatility. A flame-ionisation detector was used throughout.

Isolation of product compounds was occasionally possible by distillation, but generally silica gel chromatography (0.08 mm. silica; Macherey, Nagel and Co.) was most effective. Benzene with increasing amounts of diethyl ether (up to 15% by volume) was used as eluent. After the components of a product mixture had been isolated and identified, the recovery of each component was checked by quantitative g.l.c. analysis of the original mixture using "bracketing standards" of each pure component. The mixed isomeric hydroxyethers obtained in the experiments shown in Tables 2.3 and 4.5 were not completely separated by SiO_2 chromatography, but in some cases small amounts of the isomers were obtained pure and could be characterised. Fortunately, the g.l.c. analysis in these instances could be confirmed both qualitatively and quantitatively by p.m.r. spectroscopy of the mixture, as the pure isomers (prepared as described below) had distinctly different p.m.r. spectra.

P.m.r. spectra were measured on a Varian HA-100 spectrometer, using tetramethylsilane (TMS) as field/frequency lock*. Unless otherwise stated, spectra were taken in carbon tetrachloride (CCl_4) solution at 30°, using an upfield sweep of 1 Hz/sec. Chemical shifts (δ) are given in p.p.m. downfield from TMS to the centre of the multiplets, the spectrometer being regularly recalibrated by means of a precision frequency counter. The apparent coupling constants are the directly observed line spacings (in Hz.). Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. P.m.r. spectra were obtained for every compound prepared, and always agreed with the expected structures. Integration of a p.m.r. spectrum yields only the relative numbers of non-equivalent protons in

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* In methanol-d_1, the solvent provided the lock signal. With D_2O as solvent, an external TMS capillary was employed.

the molecule. The values reported in this work are sometimes a multiple of the numbers found from the integral. The value of this multiple is obtained by valency and/or molecular weight considerations.

Infrared spectra were measured in CCl_4 solution on a Unicam SP200G spectrometer.

Mass spectra were recorded on an LKB 9000 g.c.-m.s. unit at an ionising potential of 70 eV with an ion source temperature of 200°.

Melting points were taken on a Fisher-Johns apparatus and, like the boiling points quoted here, are uncorrected.

Refractive indices were measured on an Abbé refractometer (Zeiss).

8.2 Reductions with Borane in THF

8.2.1 Procedure

The reduction of 2-phenyl-4-methyl-1,3-dioxane (Experiment 12, Table 2.3) is representative of the general experimental procedure. The acetal (3.56 g, 20 mmol) was cooled to 0° and borane in THF (30 ml of "1 M" solution (Alfa Inorganics), approx. 30 mmol), previously cooled to -10°, was pipetted in. The mixture was swirled, kept for 10 min. in an ice-bath, then allowed to warm to room temperature. After 24 hours, the extent of the reaction was tested as follows: three drops of solution were removed, treated with an equal volume of water* and the mixture was shaken with a little benzene. A gas chromatogram of the benzene layer showed that some starting material remained. To complete the reaction the mixture was heated at 40°±5° for 24 hours, when gas chromatography showed all starting material to have reacted**. Next the reaction

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* Acetone n-butyl ketal (Ex.3, Table 2.1) was completely hydrolysed by this procedure.

** All cyclic acetals except 2-phenyl-1,3-dioxolane (<u>4</u>) required a heating period to complete the reaction.

mixture was cooled, and water was added dropwise, causing effervescence. Slow addition of water was continued until effervescence ceased, and then more water (30-40 ml.) was added to dissolve the precipitated boric acid and to hydrolyse the boric esters. The aqueous solution was extracted several times with ether, and the combined extracts were washed with water, dried (Na_2SO_4) and evaporated. A little dry methanol was added and the mixture was evaporated, this procedure being repeated to remove any remaining traces of boric acid as the volatile methyl borate. The residue was distilled, yielding 3.3g (92%) of mixed alcohols b.p. 107-110^o at 1 mm.

Analysis by g.l.c., with calibration standards prepared from authentic samples of the isomeric hydroxyethers, gave the results shown in Table 2.3. Complete separation of the isomers was not achieved but a small amount of each in pure form was obtained by chromatography on silica gel. The p.m.r. spectra and refractive indices of the pure fractions so obtained confirmed the identification of the g.l.c. peaks. The p.m.r. spectrum of the mixture confirmed the g.l.c. analysis.

8.2.2 Details of the Kinetic Studies of the Reaction between Borane and Acetals

A solution of borane was diluted to the required concentration with dry tetrahydrofuran* (THF), placed in a constant-temperature bath and the acetal (10 mmol) was added. The solution in the reaction flask was stirred with a magnetic stirrer and was protected by a calcium chloride tube. Aliquots (0.2 ml.) removed after fixed times were dropped into saturated aqueous sodium carbonate (0.2 ml.) to quench the reaction.

G.l.c. analysis of the samples so obtained was effected with an oven temperature of 110^o; other conditions were as described in 8.1. The g.l.c. system gave a slightly greater

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* Dried over sodium, distilled, and stored in the dark over clean sodium wire.

molar response for the acetal than for its cleavage product. Therefore, in order to relate g.l.c. areas to mole percentages in the sample, response factors were required. These were readily determined by comparing the areas produced by equimolar injections of acetal and of product. In this way it was found that the percentage area due to benzyl methyl ether required multiplication by 1.06 to yield mole percent relative to the acetal 30. Likewise the response factor for 2-benzyloxyethanol was 1.02 relative to 4.

As the mole percentage of product, calculated from the ratio of the product peak area to the total area, was independent of the size of the injected sample, the results were highly replicable. Four injections of the same sample (Fig.2.2, $[BH_3]$= 0.6M curve, 60 min. sample) indicated the following amounts of benzyl methyl ether: 4.93, 4.81, 4.69 and 4.93 (mmol) — a relative standard deviation of ±2.4%.

8.2.3 The Reaction of Borane with Excess Benzaldehyde Dimethylacetal (30)

Borane (12.2 mmol) in THF (10 ml.) was added to an excess of acetal 30 (53 mmol) in a flask attached to a gas burette. There was an exothermic reaction and some hydrogen (3.1 mmol) was evolved. As the reaction proceeded, aliquots (2 ml.) were withdrawn by syringe through a septum for

i) analysis of boron and hydrogen content*,

ii) g.l.c. analysis of the organic fraction.

The results are shown in Table 8.1. Analysis of the standard borane solution prior to reaction showed it to have the empirical formula $BH_{2.7}$. Therefore the borane taken initially

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[*] Hydrogen was estimated as H_2 by adding water to the borane solution in a flask attached to a gas burette. Mannitol in excess was then added to the boric acid residue in the flask, and the mixture was titrated with potassium hydroxide to phenolphthalein end-point (193). One mole of hydroxide is consumed per mole of boric acid present.

TABLE 8.1

The Reaction of Borane[a] with Excess Acetal[b] at 30°

Time, min	H_2 Evolved by Aliquot, mmol	H_3BO_3 in Aliquot, mmol	Borane Empirical Formula	Hydride Available for Reduction, mmol	Reduction[c] Product Formed, mmol
Prior to Addition of Acetal	3.7	1.4	$BH_{2.7}$	33	0
0[d]	-	-	$BH_{2.5}$	30	0
20	2.3	1.4	$BH_{1.6}$	20	12
40	1.1	1.4	$BH_{0.8}$	10	17
80	0.62	1.3	$BH_{0.5}$	6	22
160	0.22	1.4	$BH_{0.16}$	2	26
1115	0	1.4	BH_0	0	30

(a) 12.2 mmol of "$BH_{2.7}$" in 10 ml of THF. (b) 53 mmol of benzaldehyde dimethyl acetal. (c) $PhCH_2OMe$ as analysed by gas chromatography. (d) When the reagents were mixed, 3.1 mmol of H_2 was evolved, possibly because of moisture in the system, thus diminishing the hydride available for reduction.

contained 33.0 mmol of hydride. Discounting the initial hydrogen evolution, 30 mmol of hydride are theoretically available for reduction. After 18 hours at 30°C, a sample of reaction mixture yielded no hydrogen gas upon addition of water and 30 mmol of benzyl methyl ether were found to have been produced. Therefore all the hydrogens of borane were consumed in the reduction of excess acetal at 30°C.

8.2.4 Source of the Acetals and Ketals described in Chapter 2

Benzaldehyde dimethyl acetal (30) was prepared in 35% yield according to Fischer and Giebe (7). B.p. 97.5° at 30 mm. Lit. (7) b.p. 198-199° at 762 mm.

Acetophenone diethyl ketal was prepared according to Fuson and Burness (194). B.p. 103° at 16 mm; n_D^{20} 1.4781. Lit. (194) b.p. 101.5 at 15 mm; n_D^{20} 1.4773.

Acetone di-n-butyl ketal — The method of Howard and Lorette (10) was used, yield 70%. B.p. 80-80.5° at 10 mm; $n_D^{23.5}$ 1.4117. Lit. (10) b.p. 83° at 18 mm; n_D^{25} 1.4105 and b.p. (195) 64-64.5° at 3 mm; n_D^{20} 1.4120.

Cyclohexanone ethylene ketal (13a) and the following four compounds were all synthesized by Salmi's method (196). B.p. 69-70° at 12 mm, n_D^{20} 1.4592. Lit. (196) b.p. 73° at 16 mm; n_D^{20} 1.4583.

2-Phenyl-1,3-dioxolane (4) Yield 66%, b.p. 123-124° at 26 mm; n_D^{22} 1.5264. Lit. (27) b.p. 116° at 20 mm, (197) b.p. 129° at 25 mm; n_D^{18} 1.5285.

2-Phenyl-1,3-dioxane (4a) Yield 85%, b.p. 126-127° at 15 mm; m.p. 46-48°. Lit. (198) b.p. 125° at 14 mm; m.p. 49-51°.

2-Phenyl-4-methyl-1,3-dioxane B.p. 134-135° at 18 mm; n_D^{25} 1.5145. Lit. (199) b.p. 134-135° at 15 mm, (197) b.p. 162° at 40 mm; n_D^{18} 1.5165. The p.m.r. spectrum indicates that this compound is a single pure isomer (presumably *cis*, e,e — see ref.201 and discussion in Appendix 1). The methyl group appears as a sharp doublet at δ 1.2 and the proton at C_2 is a singlet at δ 5.3.

2-Phenyl-4,4-dimethyl-1,3-dioxolane (5) Yield 93%, b.p. 99.5-101.5° at 10 mm; n_D^{25} 1.5005. Lit. (27) b.p. 85° at 5 mm; n_D^{25} 1.5015. Whereas the alcohols used for the previous syntheses were commercially available, in this case it was necessary to synthesize 2-methyl-1,2-propanediol. The method of Leggetter and Brown (27) was employed.

2,2-Dimethyl-4-phenyl-1,3-dioxolane and the following two compounds were prepared according to the method of Fischer and Pfähler (200). Yield 85%, b.p. 104-105° at 13 mm; n_D^{22} 1.5016. Lit. (202) b.p. 95-96° at 10 mm.

2,2,4-Trimethyl-1,3-dioxolane (6) Yield 14%, b.p. 98-100° at 758 mm; n_D^{22} 1.3952. Lit. (27), b.p. 99° at 700 mm, (203) 98-99° at 760 mm.

2,2-Dimethyl-4-chloromethyl-1,3-dioxolane (7) Yield 42%, b.p. 76-77° at 38 mm; n_D^{22} 1.4341. Lit (27) b.p. 78° at 40 mm, (200) n_D^{15} 1.4375.

1,3-Dioxolane was purchased (Eastman Kodak Co.).

Formaldehyde dimethyl acetal was obtained from Baker Chemical Co.

8.2.5 Source of Authentic Samples of the Reduction Products described in Chapter 2.

Benzyl methyl ether, 2-benzyloxyethanol and 2-methoxyethanol were obtained from Eastman Kodak Co.

α-Methylbenzyl ethyl ether was prepared according to Mislow (204).

Isopropyl n-butyl ether was synthesized by the method of Henstock (205), b.p. 109° at 763 mm. Lit. (205) b.p. 108° at 738 mm.

2-Cyclohexyloxyethanol — The synthesis of Eliel et al. (26) was employed. Overall yield 18%; b.p. 115-118° at 28 mm; n_D^{22} 1.4602. Lit. (26) b.p. 100° at 14 mm; n_D^{25} 1.4605.

3-Benzyloxy-1-propanol was made according to ref.207. B.p. 130°

at 10 mm; n_D^{26} 1.5110. Lit. (207) b.p. 114° at 0.9 mm; n_D^{20} 1.5184, (208) b.p. 155° at 23 mm.

3-Benzyloxy-1-butanol was prepared according to Stork *et al*. (209). Since these authors did not give details, the procedure employed is described. Sodium was added to benzyl alcohol (10.8 g, 0.1 mol) in 50 ml of xylene. When the reaction terminated, excess sodium was removed, ethyl crotonate (5.7 g, 0.05 mol) was added with stirring, and the mixture was heated for 5 hours at 90°. The pasty mixture was cooled in ice water and acidified with a slight excess of 5% sulphuric acid. Ether (60 ml) was added and the mixture was stirred until all solid had dissolved. G.l.c. of the ether extract showed two major products which were assumed to be the benzyl and ethyl esters of 3-benzyloxybutanoic acid. Fractional distillation of the extract yielded a fairly pure fraction of the benzyl ester, b.p. 100-105° at 0.35 mm; n_D^{25} 1.5370, λ_{max} 1740 cm^{-1}; p.m.r. spectrum shows two types of benzyl protons: δ 5.0 (s, 2H), δ 4.4 (m, 2H). This material was reduced with $LiAlH_4$ and yielded benzyl alcohol (identified by g.l.c.) and 3-benzyloxy-1-butanol (1.5 g, 17%) b.p. 108-109° at 1mm; n_D^{24} 1.5095. The p.m.r. spectrum of the benzyl protons showed an AB pattern; δ_A 4.32, δ_B 4.46, J_{AB}=-12 Hz. Lit. (28) b.p. 98-107° at 1 mm.

4-Benzyloxy-2-butanol was obtained in 82% yield by $LiAlH_4$ reduction of 4-benzyloxy-2-butanone (Fluka) as described by Eliel *et al*. (26). The product was purified by chromatography on silica gel after which infrared spectroscopy showed no trace of carbonyl absorption; n_D^{26} 1.5051. Lit. (26) n_D^{20} 1.5080.

2-Benzyloxy-2-methyl-1-propanol and the following two compounds were prepared according to Leggetter and Brown (27). B.p. 132-134° at 9 mm; n_D^{25} 1.5115. Lit. (27) b.p. 102° at 3.5 mm; n_D^{25} 1.5088.

1-Benzyloxy-2-methyl-2-propanol b.p. 106-107° at 7 mm; n_D^{25} 1.4997. Lit. (27) b.p. 106° at 6 mm; n_D^{25} 1.4997.

2-Isopropoxy-2-phenylethanol b.p. 122-123.5° at 13 mm; n_D^{25} 1.5030. Lit. (27) b.p. 94° at 3 mm; n_D^{25} 1.4982.

2-Isopropoxy-1-phenylethanol was obtained as a gift from Dr. R.K. Brown.

2-Isopropoxy-1-propanol and the following compound were made by the method of Chitwood and Freure (210). B.p. 145-146° at 763 mm; n_D^{23} 1.4149. Lit. (210) b.p. 143-144° at 760 mm; n_D^{20} 1.4094.

1-Isopropoxy-2-propanol b.p. 144-144.5° at 764 mm; $n_D^{23.5}$ 1.4070, Lit. (210) b.p. 137-138° at 760 mm; n_D^{20} 1.4070.

3-Chloro-2-isopropoxy-1-propanol was obtained as a gift from Dr. Brown (see ref.27).

1-Chloro-3-isopropoxy-2-propanol Synthesis of this compound according to Leggetter and Brown (27) failed, but success was achieved *via* a different set of conditions (211). B.p. 90-92° at 23-24 mm; n_D^{23} 1.4398. Lit. (211) b.p. 87-87.5° at 20 mm; n_D^{25} 1.4370.

8.3 Reductions with Trimethylamine-Borane

8.3.1 The Reduction of Benzaldehyde Dibenzylacetal (23)

Trimethylamine-borane (Matheson, Coleman and Bell, 1.84 g, 25 mmol) was dissolved in glacial acetic acid, and 23 (7.6 g, 25 mmol) was added. The mixture was stirred in a constant-temperature bath at 27° for two days and small samples were removed periodically to check the progress of the reaction (g.l.c.). Slow evolution of gas occurred during the first 24 hours of the reaction.

After two days the mixture was poured into 100 ml. of saturated aqueous sodium carbonate solution, which was then extracted twice with ether. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated, yielding 8.06 g. of mixed product.

A 2.0 g. quantity of this mixture was chromatographed on a silica gel column, yielding the following fractions:

(i) dibenzyl ether, 1.082 g (88%); n_D^{20} 1.5604; p.m.r.; δ 4.43 (4 H, s), 7.2 (10 H, m). G.l.c., i.r. identical to those of the purchased sample (Aldrich).

(ii) benzyl acetate, 0.117 g. (12.6%); n_D^{20} 1.5020, λ_{max} 1745 cm^{-1}. Lit. (213) n_D^{20} 1.5032. G.l.c., i.r. identical to purchased sample (Anachemia).

(iii) benzyl alcohol, 0.11 g. (11%), n_D^{20} 1.5400. Lit. (214), n_D^{20} 1.5402. G.l.c., i.r. identical to those of the purchased sample (Aldrich).

8.3.2 The Reduction of Cyclohexanone Ethylene Ketal (<u>13a</u>)

Most of the experimental details of this reduction were given in Section 3.2.2 and Table 3.1.

The first fraction of product distillate, 1.7 g, b.p. 70-100°C at 16 mm., after removal of unreacted trimethylamine-borane by silica gel chromatography yielded:

(i) unreacted starting acetal, 1.02 g. (29%), n_D^{23} 1.4600. Lit. (196) n_D^{20} 1.4583;

(ii) 2-cyclohexyloxyethanol, 0.44 g;

(iii) 1-acetoxy-2-cyclohexyloxyethane, 0.043 g.

After decomposition of the borate in the reaction products, a second distillate fraction (1.25 g, b.p. 101-105° at 16 mm) was obtained. Upon chromatography this yielded:

(i) 2-cyclohexyloxyethanol, 1.05 g;

(ii) 1-acetoxy-2-cyclohexyloxyethanol, 0.060 g.

In total 1.49 g. (41%) 2-cyclohexyloxyethanol, n_D^{23} 1.4629 was obtained. Lit. (26) n_D^{25} 1.4605.

The total recovery of 1-acetoxy-2-cyclohexyloxyethanol was 0.103 g (2.2%); λ_{max} 1750 cm^{-1}; g.l.c., p.m.r., and i.r. were all identical to the authentic sample.

Traces of 2-cyclohexyloxyethanol were eliminated from the distillation residue by chromatography and the relatively non-polar 1,2-dicyclohexyloxyethane (0.043 g) so obtained had the following properties: n_D^{25} 1.4696, p.m.r.; δ 3.5 (4 H, s, $O-CH_2-CH_2-O$), 3.25 (2 H, m, methine protons), 1.0-2.0 (20 H, m, ring methylene protons). The equivalence of the methylene protons at 3.5 confirms the symmetrical structure of the molecule. G.l.c. and i.r. results were identical to those of the product obtained by an alternative synthetic route (8.3.4).

8.3.3 The Reduction of 2-phenyl-1,3-dioxane (4a)

The reductive cleavage of 4a was accomplished in a similar way to that of benzaldehyde dibenzylacetal (Section 8.3.1) except that the evolution of hydrogen gas was measured in this instance (655 ml at NTP; 29 mmol). The reaction products were isolated by removing the acetic acid solvent on a rotary evaporator, and partitioning the residue between water and benzene. The aqueous layer was evaporated to dryness and the solid residue was stirred with ether (20 ml) and filtered. The boric acid crystals were washed (50 ml of ether) and dried, yield of H_3BO_3: 1.05 g (68%). Evaporation of the ether filtrate yielded 1,3-propanediol (0.35 g, 18%).

The benzene layer was evaporated to give 4.04 g of crude product, 2.5 g of which was chromatographed on silica gel. The following fractions were obtained:

(i) benzyl acetate, 0.044 g (2%), n_D^{24} 1.4980, λ_{max} 1745 cm^{-1}.

(ii) 1,3-dibenzyloxypropane (64), 0.52 g (13%), n_D^{24} 1.5350, g.l.c., p.m.r. and i.r. identical to those of the authentic material (Section 8.4.3);

(iii) 1-acetoxy-3-benzyloxypropane, 0.99 g (31%), n_D^{26} 1.4896, g.l.c., p.m.r. and i.r. identical to those of the authentic material (Section 8.3.4);

(iv) 3-benzyloxy-1-propanol, 0.91 g (35%), n_D^{22} 1.5124, g.l.c., p.m.r. and i.r. identical to those of the authentic material (Section 8.2.5).

8.3.4 Sources of Reagents and Authentic Product Compounds for the Foregoing Reductions

Diglyme (Eastman) was dried and purified by a reduced pressure distillation from lithium aluminum hydride under nitrogen (215).

Glacial acetic acid (Anachemia, reagent grade) was not specially purified.

Benzaldehyde dibenzylacetal (23) was prepared by Salmi's method (196), yield 65%. B.p. 163-166° at 0.04-0.05 mm; n_D^{24} 1.5765. Lit. (216) b.p. "about 168°" at 0.1 mm, (217) 170° at 0.2 mm; n_D^{20} 1.5776.

The sources of several of the product compounds were previously discussed in Section 8.2.5.

1-Acetoxy-2-cyclohexyloxyethanol was prepared in 81% yield by treating 2-cyclohexyloxyethanol (1.02 g, 7 mmol), prepared as described in Section 8.2.5, with an excess of pyridine and acetic anhydride at room temperature. After two days the volatile components were removed on a rotary evaporator at 70° and the residue was purified by chromatography on silica gel. Yield of product 1.08 g, n_D^{23} 1.4465, λ_{max} 1750 cm^{-1}, p.m.r.; δ 4.10 (2 H, t, $-CH_2OAc$), 3.55 (2 H, t, $-CH_2OR$), 3.25 (1 H, m, methine), 2.00 (3H, s, acetoxy), 2.0-1.0 (10 H, m, ring $-CH_2-$).

Anal. Calc. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.51

Found : C, 63.9; H, 9.74

1,2-Dicyclohexyloxyethane was prepared in very small yield by a Williamson synthesis: sodium (7 g, 0.3 mol) was dissolved in cyclohexanol (30 g, 0.3 mol) diluted with xylene (200ml). A mixture of xylene (50 ml) and 1,2-dibromoethane (28 g, 0.15 mol) was added to the stirred sodium cyclohexyloxide mixture over a period of 2 hours. The mixture was refluxed for 2 hours, cooled, and the precipitated sodium bromide was filtered off. A g.l.c. analysis of the xylene solution revealed only cyclohexanol and a trace of the high boiling product*. The cyclohexanol was distilled off and the distillation residue was applied to a silica gel column. The yield of 1,2-dicyclohexyloxyethane so obtained was 0.034 g (0.1%), p.m.r.; δ 3.5 (4 H, s, $-OCH_2-$), 3.25 (2 H, m, methine), 2.0-1.0 (20 H, m, ring, CH_2).

The synthesis of 1,3-dibenzyloxypropane is described in Section 8.4.3.

1-Acetoxy-3-benzyloxypropane was prepared from 3-benzyloxy-1-propanol (Section 8.2.5) in 97% yield by treating it with excess pyridine and acetic anhydride at room temperature. After 2 days, the volatile components were removed on a rotary evaporator and the residue was purified by silica gel chromatography. The product had λ_{max} 1744 cm^{-1}; n_D^{25} 1.4903. Lit. (218) $n_D^{22.5}$ 1.4913.

8.4 Acetal Cleavage with Catalytic Amounts of $HCo(CO)_4$

8.4.1 Procedure

The reductive cleavage of 2-phenyl-1,3-dioxane (4a) (Table 4.2, Experiment 5) is representative of the general procedure. A stainless steel autoclave, having a removable glass liner and internal volume (with the liner in place) of 255 ml., was employed. A quantity of acetal 4a (4.33 g) was supported in a small open ampoule above the catalyst mixture (0.44 g $Co_2(CO)_8$ in 3.8 ml benzene) inside the liner. After purging with carbon monoxide, the autoclave was pressurised to 2400 psig with a 2:1 H_2/CO mixture and the temperature was raised to 160°C in 45 minutes. At this temperature the autoclave was tilted to mix the acetal and the catalyst, and

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* Elimination was doubtless the chief reaction.

heating was continued at $165\pm5^{\circ}$ for 4 hours. The autoclave was then cooled to room temperature, and vented, and the contents were made up to 50 ml in benzene. A g.l.c. analysis of this solution revealed the following components: unchanged starting material, 28%; 3-benzyloxy-1-propanol 26%; 1,3-dibenzyloxypropane 40%[*] as major constituents; toluene (1.8%) and a trace of benzaldehyde ($<1\%$) were also evident.

A 40 ml. portion of the benzene solution was now evaporated under reduced pressure (30°C, ~ 15 mm. Hg) and the residue was allowed to stand open to the atmosphere for 24 hours to permit the catalyst to oxidise. (A repreat g.l.c. analysis after this procedure showed that catalyst oxidation did not affect the organic materials.) A little benzene was next added to the product and the resulting mixture, consisting of dissolved organic material and suspended oxidised catalyst, was applied to a silica gel column. The fractions thus obtained in order of elution[**] were as follows:

(i) 1,3-dibenzyloxypropane (<u>64</u>), 0.99 g (37%); $n_D^{22.3}$ 1.5361; authentic sample[***] $n_D^{22.2}$ 1.5386; g.l.c. retention time and p.m.r. spectrum were identical to those of the synthesised sample;

(ii) 2-phenyl-1,3-dioxane (<u>4a</u>) - starting material, 1.04 g (30%); m.p. $46\text{-}47^{\circ}$, mixed m.p. with starting material $46\text{-}47.5^{\circ}$;

(iii) 3-benzyloxy-1-propanol, 0.59 g (18%); n_D^{20} 1.5168. Lit. (26) n_D^{20} 1.5184; g.l.c. retention time and p.m.r. spectrum were identical to those of a synthesised sample[****].

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[*] The quantitative analysis of this compound was actually made from a second, later g.l.c. analysis, after the compound had been isolated and identified.

[**] Benzene eluent for the first two fractions, benzene +15% by volume ether for fraction (iii).

[***] See Section 8.4.3 for the synthesis of this compound.

[****] Described in Section 8.2.5.

Finally, a 'blank' reaction was necessary in order to be sure that the catalyst was indeed responsible for the reduction and not, say, molecular hydrogen acting upon a carbonium ion. Accordingly, the experiment described above was repeated but a little p-toluenesulphonic acid* (0.05 g) was substituted for the dicobalt octacarbonyl. A g.l.c. analysis of the product showed no reduction products, only starting material and a trace of benzaldehyde.

8.4.2 Source of the Starting Materials Described in Chapter 4.

Many of the acetals and ketals used in Chapter 4 were the same as those described in Chapters 2 and 3. Their sources were discussed in Sections 8.2.4 and 8.3.4.

Propionaldehyde diethylacetal was prepared in 46% yield according to reference 212. B.p. 124-125° at 757 mm; n_D^{22} 1.3890. Lit. (212) b.p. 123° at 740 mm; $n_D^{25.5}$ 1.3872.

Phenylacetaldehyde dimethylacetal was prepared in 53% yield according to reference 8. B.p. 84-84.5° at 6 mm; n_D^{24} 1.4930. Lit. (8) b.p. 219-221° at 754 mm.

p-Methoxybenzaldehyde dibenzylacetal - The method of Gualtieri et al. (219) was used, but some decomposition of this reactive acetal was found (p.m.r.) to occur during distillation. B.p. 192-198° at 0.2-0.25 mm. Lit. (219), b.p. 195° at 0.25 mm. Moreover, decomposition in the injection port of the g.l.c. caused difficulty in estimating the purity of the product by this technique. Since all contaminants are relatively volatile, however, a pure product was obtained without distillation of the acetal. After the reaction, the mixture was stirred with a large excess of aqueous potassium carbonate, the upper layer was separated, washed twice with water, and the volatile materials were removed under reduced pressure. After 2 hours in an oil bath at 120° under 0.08 mm pressure, the residual

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* This material completely destroyed acetone n-butyl ketal under similar conditions (Section 3.5.1).

pale yellow oil was completely pure p-methoxybenzaldehyde dibenzylacetal as far as could be detected by p.m.r., yield 85%; n_D^{20} 1.5756. This product is pure enough for most purposes, but if necessary, the yellow colour may be removed by silica gel chromatography.

p-Chlorobenzaldehyde dibenzylacetal - This compound does not appear to have been previously reported. It was prepared from p-chlorobenzaldehyde (Eastman, practical, 40 g. 0.28 mol.) and benzyl alcohol (130 g. 1.2 mol.) with p-toluenesulphonic acid (0.1 g.) as catalyst. The water produced was removed as benzene-water azeotrope, using 300 ml. of benzene and a Dean-Stark separator. After 3 hours of refluxing, no further water was obtained, and the reaction mixture was stirred with excess saturated aqueous sodium carbonate solution. The upper layer was separated, washed with water, and distilled under reduced pressure. The final fraction of distillate, b.p. 196-198° at 0.1 mm was the pure acetal; yield, 76 g (80%); n_D^{20} 1.5816; p.m.r.; δ 4.40 (4 H, s, benzyl methylenes), 5.51 (1 H, s, methine), 7.2 (14 H, m, aromatic protons).

Anal. Calc. for $C_{21}H_{19}ClO_2$: C, 74.4; H, 5.65; Cl, 10.5

Found : C, 74.4; H, 5.63; Cl, 10.7

8.4.3 Source of Authentic Samples of the Reduction Products Described in Chapter 4.

Products not discussed in earlier sections were obtained as follows:

Ethylbenzene - purchased from Eastman Kodak Co.

Phenethyl methyl ether was synthesised from phenethyl alcohol, methyl iodide and silver oxide, according to ref.222. The sweet-smelling product was purified by chromatography on silica gel. Yield 60%, $n_D^{23.5}$ 1.4962. Lit. (223) n_D^{21} 1.5001.

1,2-Dibenzyloxyethane was prepared by a Williamson synthesis in which 2-benzyloxyethanol (Eastman, 10 g, 0.066 mol) was stirred with excess (2 g) sodium and xylene (25 ml) for 24 hours. Excess sodium was removed, benzyl chloride (5.3 g, 0.041 mol) was added, and the mixture was boiled under reflux for 4 hours. The precipitated sodium chloride was filtered off, and the filtrate was distilled under vacuum. Yield 5.3 g (53%), b.p. 123-125° at 0.05-0.07 mm; n_D^{26} 1.5436. Lit. (224) b.p. 139° at 0.1 mm.

<u>1,3-Dibenzyloxypropane</u> (<u>64</u>) was made from 3-benzyloxy-1-propanol (preparation described in 8.2.5) by a Williamson synthesis as described above. Yield, 65%; b.p. 145-146° at 0.03 mm; $n_D^{22.2}$ 1.5386; p.m.r.; δ 7.19 (10 H, m, aromatic), 4.35 (4 H, s, Ph-CH_2-O-), 3.46 (4 H, t, -O-CH_2-C), 1.81 (2 H, quintet, C-CH_2-C).

Anal. Calc. for $C_{17}H_{20}O_2$: C, 79.7; H, 7.87.

Found : C, 79.7; H, 7.96.

<u>1,3-Dibenzyloxybutane</u> (<u>65</u>) was prepared by Williamson synthesis from 0.7 g of 3-benzyloxy-1-butanol (Section 8.2.5). The crude product was purified by chromatography on a short (25 cm) silica gel column and yielded 0.77 g (73%) of 1,3-dibenzyloxybutane, $n_D^{24.5}$ 1.5320; p.m.r.; δ 7.20 (10 H, m, aromatic), 4.39 (2 H, AB quartet, $\delta_A = 4.31$, $\delta_B = 4.47$, $J_{AB} = -11$ Hz, $PhCH_2O$ — on assymetric C_3), 4.36 (2 H, s, $PhCH_2O$ — on C_1), 3.5 (3 H, m, protons on C_1 and C_3), 1.7 (2 H, m, protons on C_2), 1.13 (3 H, d, J = 6 Hz, methyl).

Anal. Calc. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.20

Found : C, 79.5; H, 8.07

<u>1,2-Dibenzyloxy-2-methylpropane</u> (<u>66</u>) - a Williamson synthesis starting from 2-benzyloxy-2-methyl-1-propanol (Section 8.2.5) was again successful. The product was purified by silica gel chromatography as above, n_D^{25} 1.5280; p.m.r.; δ 7.22 (10 H, m, aromatic), 4.44 and 4.46 (4 H, two s, $PhCH_2O$-), 3.34 (2 H, s, -OCH_2-C), 1.24 (6 H, s, methyl).

Anal. Calc. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.20

Found : C, 79.2; H, 8.01

Compounds 64, 65 and 66 have not been prepared before. A word of caution concerning their analysis is in order. Dibenzyl ethers in air form peroxides quite rapidly, and unless they are stored under nitrogen or analysed within a few days of purification, the carbon and hydrogen analysis is invariably much too low. Samples of dibenzyl ethers kept open to air turn completely into crystalline solids (peroxides?) after several months.

G.l.c. analysis of the diether product obtained in Experiment 21, Table 4.5 revealed two impurities in addition to a compound having the same retention time as 1,2-dibenzyloxy-2-methylpropane (66). The p.m.r. spectrum of the product was identical to that of authentic 66, except for the appearance of four small additional signals. However the impurities evidently had a large effect upon the refractive index, which was n_D^{25} 1.5450 (c.f. n_D^{25} 1.5280 for synthesised 66).

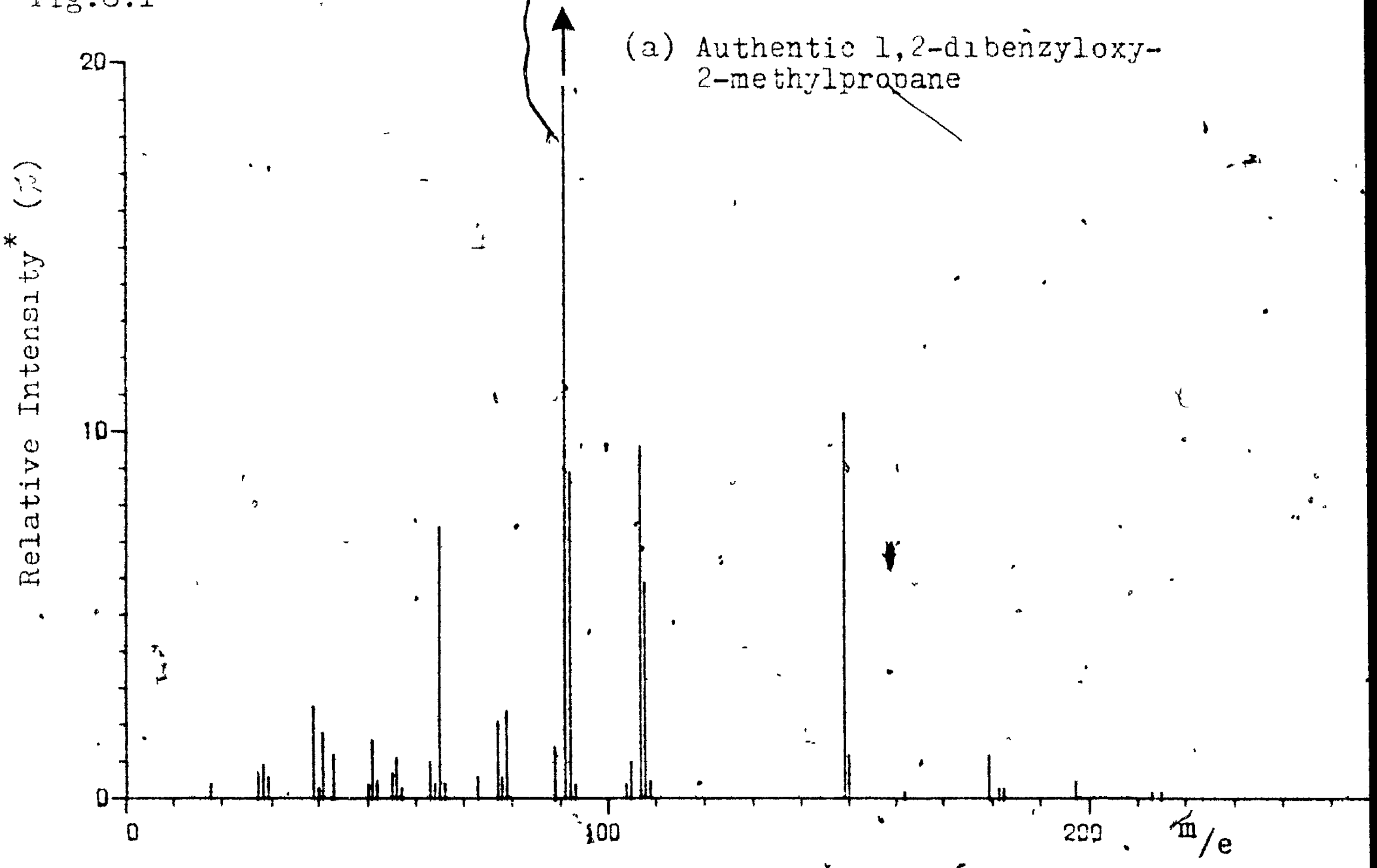
In order to confirm the identity of the product of Experiment 21, g.c.- m.s. was employed. Fig.8.1 shows the mass spectra of (a) authentic 66 prepared by Williamson synthesis, and (b) the least polar product fraction obtained in Experiment 21. With the exception of minor peaks; more of which are included in spectrum (a) because the sample used was more concentrated, the two spectra are the same, thus confirming the identity of the product.

The spectra are dominated by the peak at m/e 91 ($PhCH_2^+$ and/or tropylium) which is the base peak.

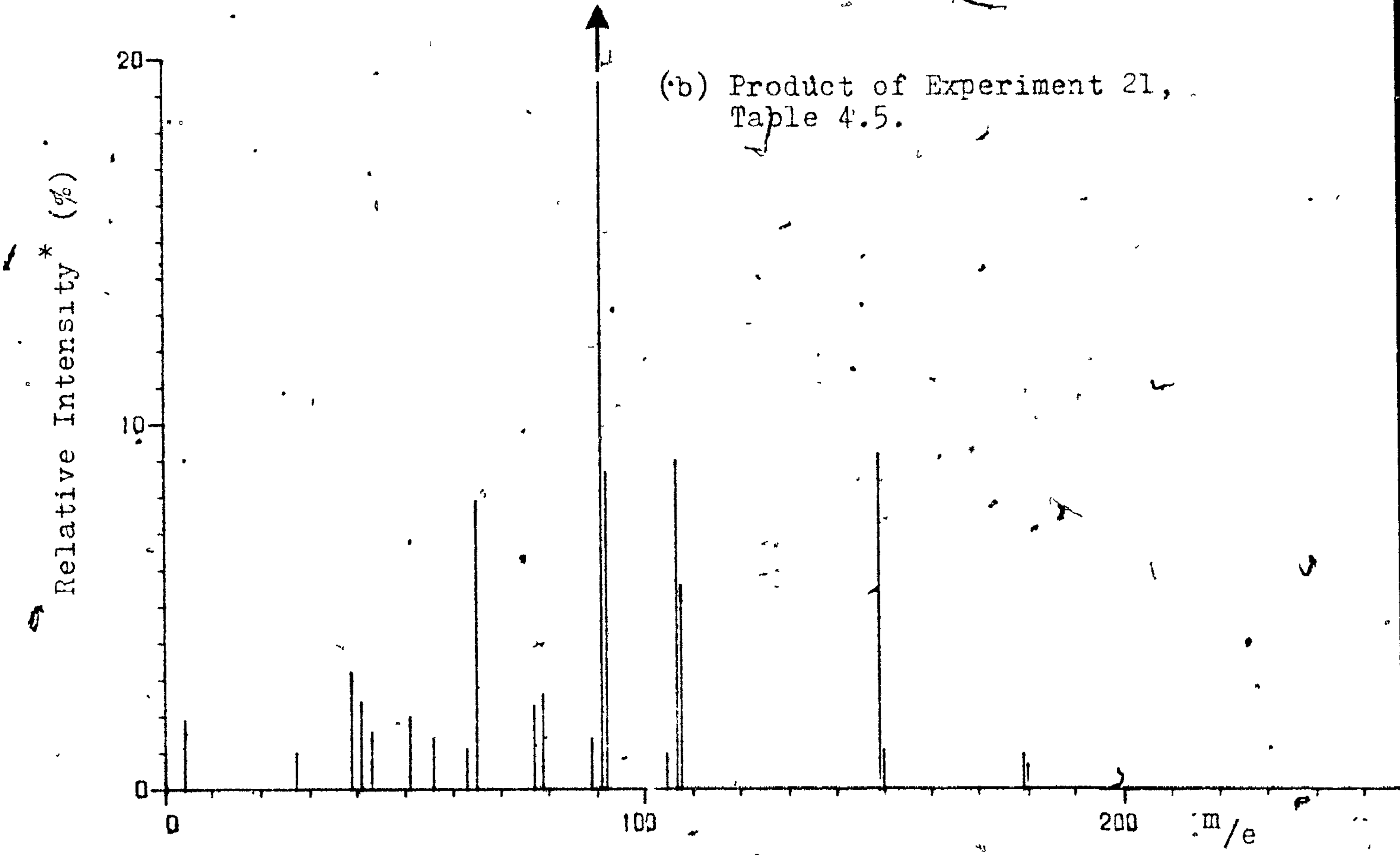
The molecular ion (m/e 270) does not survive, presumably because the presence of two benzyl groups greatly promotes its decomposition to very stable fragments (see discussion in ref.225).

The peak at m/e 149 may correspond to the fragment $PhCH_2O\overset{+}{C}(Me)_2$. The nature of the peak at m/e 107 obtained from certain benzyl ethers is still unsettled, but $\text{ØCH=}\overset{+}{O}\text{-H}$ has recently been proposed (226).

Fig.8.1



(a) Authentic 1,2-dibenzyloxy-2-methylpropane



(b) Product of Experiment 21, Table 4.5.

* relative to the base peak at m/e 91

p-Chlorobenzyl alcohol was obtained from Aldrich Chemical Co.

p-Chlorobenzyl benzyl ether was prepared by Williamson synthesis as described in ref.227. Yield 70%, b.p. 113° at 0.1 mm, n_D^{20} 1.5692. Lit. (227) b.p. 114° at 0.1 mm; n_D^{20} 1.5698.

p-Methoxybenzyl benzyl ether was made similarly (227). Yield 51%, b.p. 125° at 0.1 mm, n_D^{20} 1.5636. Lit. (227) b.p. 146-147° at 0.4 mm; n_D^{22} 1.5625.

8.5 Stoichiometric Reductions of Acetals with $HCo(CO)_4$

8.5.1 Preparation of $HCo(CO)_4$ Solutions

First, a stock solution of $[Co(B)_6]^{++}$ $[Co(CO)_4]_2^-$ — where B is N,N-dimethylformamide (DMF) — was prepared by dissolving dicobalt octacarbonyl (Ventron Corp.) 13.7 g, 40 mmol) in 40 ml of hexane and adding 35 ml of N,N-dimethylformamide. The mixture was allowed to react overnight, with the evolved carbon monoxide escaping from the serum-capped 100 ml flask via a syringe needle. After 12 hours the reaction had terminated and the mixture had separated into a clear upper layer (hexane) and a pink lower layer (the complex dissolved in DMF). The needle was removed and the solution was stored at 5°C until required.

A batch of $HCo(CO)_4$ solution was prepared from the $Co(CO)_4^-$ stock solution as follows: the apparatus in Fig.8.2 was set up, flask B was filled with anhydrous sodium sulphate (~ 10 g), and the side arm of flask A was closed with a serum cap. The gas burette was filled with carbon monoxide and then flasks A and B were evacuated* and filled with carbon monoxide. The operation was repeated, each time filling the gas burette from the carbon monoxide manifold, and filling the flasks A and B from the gas burette. (The burette was used as a low-pressure reservoir of carbon monoxide).

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* By means of a syringe needle connected to a water aspirator.

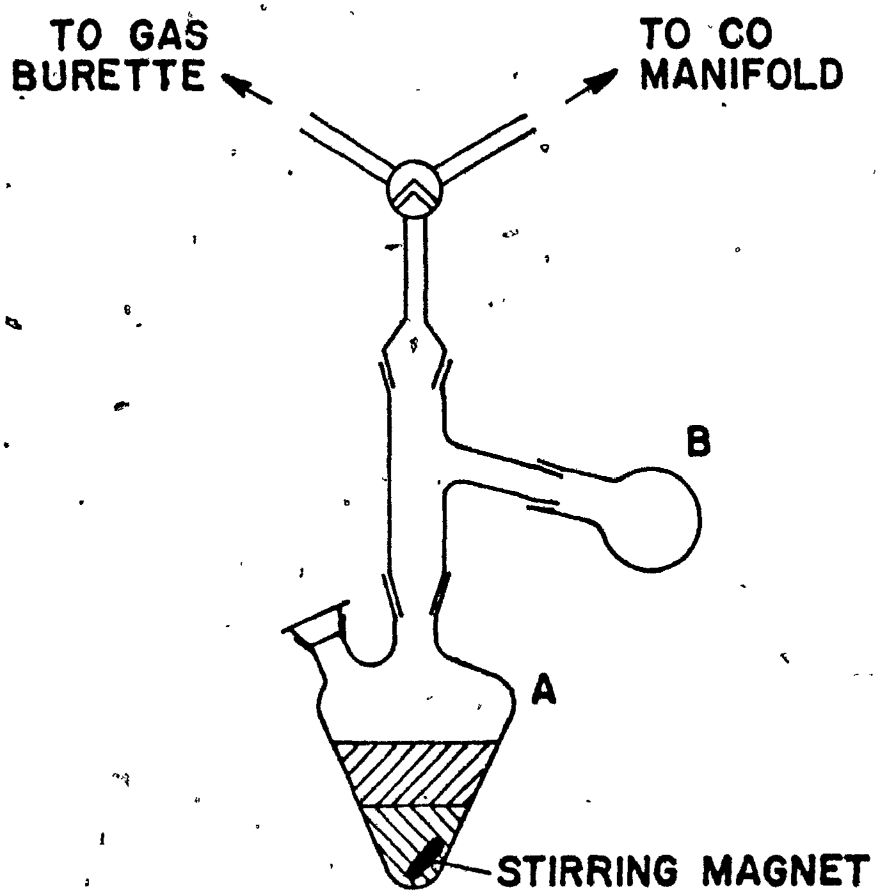

Fig.8.2 Apparatus for the Preparation of $HCo(CO)_4$

Next, hexane (25 ml) and cobalt complex-DMF solution (10 ml) were added to flask A by syringe, and a final carbon monoxide purge was made. Flask A was cooled to 0^o in an ice-bath and 10 ml of concentrated hydrochloric acid was added with rapid stirring. Five minutes later the lower blue layer was removed, and the pale yellow solution of $HCo(CO)_4$ in hexane was washed three times with 3 ml amounts of air-free water. When most of the wash water had been removed by syringe, the apparatus was tilted so that the sodium sulphate in B entered flask A. After stirring for an hour, samples of $HCo(CO)_4$ solution were withdrawn for use — but were generally found to be still too damp for acetal reductions. Further drying was achieved by transferring the solution by syringe to a serum-capped Erlenmeyer flask containing 5g of molecular sieve (Linde 5A). The hexane solution showed the following carbonyl stretching frequencies (cm^{-1}); 2115 (w), 2070 (m), 2053 (s), 2030 (s), 1992 (w) in agreement with the published spectra (151).

8.5.2 General Reduction Procedure

From this point on, Experiment 1, Table 5.1 will be described; it is typical of the general procedure. The pale yellow solution of $HCo(CO)_4$ was analysed gasometrically (according to Eq.5.3) as follows: a 1 ml sample of solution was injected into excess aqueous potassium iodide/iodine solution* in a flask connected to a second carbon monoxide-filled gas burette. A 51.5 ml volume of carbon monoxide saturated with water and hexane at 23°C was produced. This gas (36.6 ml, dry at NTP) is equivalent to 0.41 mmol of $HCo(CO)_4$.

A 6 ml amount of the $HCo(CO)_4$ solution (2.46 mmol $HCo(CO)_4$) was added to an Erlenmeyer flask containing 1 mmol of benzaldehyde dibenzylacetal in 20 ml of hexane under a CO atmosphere. The mixture, standing at room temperature, darkened

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* The flask also contained a little hexane to maintain saturation of the gas in the burette.

very slowly. The progress of the reaction was followed by removing 2 μl samples by syringe for gas chromatography. $HCo(CO)_4$ was detectable in these aliquots by its odour up to 212 hours after mixing. After 260 hours the mixture composition as determined by g.l.c. remained constant at 43% dibenzyl ether, 25% starting material, 29% benzaldehyde (by hydrolysis) and an unquantified amount of benzyl alcohol.

The almost black solution was next cooled in a dry ice-acetone mixture, whereupon small orange crystals of dicobalt octacarbonyl separated, m.p. 50-52°. Lit. (228) m.p. 51-52°. The crystals were filtered and roasted at 750° in a weighed porcelain crucible*. Yield of Co_3O_4 = 108 mg, equivalent to 1.35 mmol of cobalt (55% recovery).

8.6 The Reductive Cleavage of p-Methoxybenzyl Alcohol and its Ethers

8.6.1 Procedure

Reductions with catalytic $HCo(CO)_4$ were accomplished according to the description given in 8.4.1. Reductions with stoichiometric quantities of $HCo(CO)_4$ were as reported in 8.5 , while the borane reductions near ambient resembled those described in 8.2.1.

The isolation and identification of the products of Experiment 1, Table 6.1 are described here in detail as an illustration of the methods used.

The products of the reaction of anisyl alcohol (6.0 g) with $HCo(CO)_4$ were removed from the autoclave and made up to 50.0 ml in benzene for later quantitative analysis by g.l.c. A portion of this solution (40 ml) was allowed to stand open to the air for 24 hours to oxidise the catalyst to an insoluble

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[*] The ignition of cobalt complexes to Co_3O_4 at 750° is discussed in ref.229.

residue, and then most of the benzene was removed by evaporation at 30°C on a rotary evaporator. Silica gel chromatography of the residue (eluent: benzene with increasing amounts of ether) yielded the following fractions (in order of elution):

(i) p-methyl anisole (34), 2.80 g (66%), n_D^{22} 1.5118. Lit. (230) n_D^{20} 1.5117. G.l.c. retention time and i.r. spectrum identical to authentic sample.

(ii) A mixture of dianisyl ether (37) and 3-methyl-6,4'-dimethoxydiphenylmethane (38), 0.11 g (2%). Gas chromatography showed two incompletely separated peaks of equal height. P.m.r.; δ 6.8 (m, aromatic protons); 3.77 (s, Ar-CH_2-Ar of diarylmethane and Ar-CH_2-O of dianisyl ether); 3.70 (s, one-OCH_3 of diarylmethane); 3.66 (s, one-OCH_3 of diarylmethane and -OCH_3 of dianisylether); 2.18 (s, CH_3 of diarylmethane). These chemical shifts and coincidences were later confirmed by synthesis of the pure compounds.

(iii) p-methoxyphenethyl formate (36), 0.093 g (1.3%). P.m.r. spectrum identical with synthesised sample; i.r. shows λ_{max} 1732, 1116 cm^{-1} (5.77, 8.57μ), ester carbonyl. This compound was warmed with aqueous sodium hydroxide, and the p.m.r. spectrum of the product so formed was that of p-methoxyphenethyl alcohol (35).

(iv) bis-2-(p-methoxyphenyl)ethyl ether (39) 0.156 g (2.5%), $n_D^{22.6}$ 1.5504. Synthesised sample $n_D^{22.7}$ 1.5508. P.m.r. spectrum identical with synthesised sample.

(v) p-methoxyphenethyl alcohol (35), 1.13 g (17%) $n_D^{24.5}$ 1.5345. P.m.r. and i.r. spectra identical to pure material (Aldrich, $n_D^{24.5}$ 1.5362).

After all the product compounds had been identified and synthesised, a quantitative g.l.c. analysis of the original mixture was made with calibration standards of pure product compounds dissolved in benzene.

8.6.2 Source of Starting Materials

p-Methoxybenzyl alcohol (or p-Anisyl alcohol) (31) was purchased (Eastman).

p-Methoxybenzyl methyl ether (32) was prepared both by methylation of anisyl alcohol (31) with methyl iodide and silver oxide, and by addition of anisyl chloride (173) to sodium methoxide in methanol (48), the product had b.p. 87-89° at 6 mm. Lit. (49), b.p. 85° at 5 mm.

2-(p-Methoxybenzyloxy)anisole (or, p-Anisyl guaiacyl ether) (45) was prepared by a 2-step synthesis as follows: anisyl alcohol was converted into anisyl chloride (173). From the latter 45 was prepared according to ref.233. After recrystallisation from ethanol, material of m.p. 95-95.5°, Lit. (233) m.p. 94-96° (234), 97° was obtained in 28% overall yield.

Compound 45 was later prepared more easily as follows: guaiacol (12.4 g), p-anisyl alcohol (31) (16.6 g), and dicyclohexylcarbodiimide (DCC, Aldrich, 22 g) were mixed and heated for 16 hours at 150±10°. After cooling, the congealed mass was stirred with 500 ml of ether and filtered. The ether extract was evaporated to small bulk; then a little ethanol was added, causing the product to crystallise. Recrystallisation from ethanol yielded 9.7 g (40%) of material m.p. 94-96°, m.m.p. 94-96° (with previously prepared material).

p-Methoxyphenacetaldehyde (40) was prepared by ozonolysis of chavicol methyl ether (K. and K. Laboratories) according to ref.220; b.p. 89-90° at 3 mm; λ_{max} 1725 cm^{-1}; semicarbazone m.p. 172°. Lit. (220) b.p. 78-79° at 1.4-1.5 mm semicarbazone m.p. 175-176°; (221) 173°.

8.6.3 Source of Authentic Samples of the Reduction Products Described in Chapter 6.

p-Methoxyphenethyl formate (36) - The compound has not previously been described. p-Methoxyphenethyl alcohol (35, 3.0 g) and DCC

(5.0 g) were heated to 100°, and excess formic acid (2.0 g) was cautiously added dropwise. The mixture was heated for 8 hours at 85°, and the solid mass was then extracted with ether. G.l.c. analysis of the extract showed the crude product to contain 15% of unchanged alcohol (35). The latter was readily separated on a short (25 cm) silica gel column, with 90% benzene, 10% ether as eluent. Yield 2.3 g (65%) of colourless liquid; b.p. 100-101° at 0.1 mm; $n_D^{24.3}$ 1.5147; λ_{max} 1730, 1167 cm^{-1}; p.m.r.; δ 7.87 (1 H, s, -O-CHO), 6.9 (4 H, m, aromatic), 4.23 (2 H, t, J=7 Hz, $-CH_2-OCO-$), 3.69 (3 H, s, -OMe), 2.81 (2 H, t, J=7 Hz, $Ar-CH_2-$).

Anal. Calc. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.71

Found : C, 66.6; H, 6.75

Dianisyl ether (37) - This compound was prepared according to ref.173; b.p. 162-172° at 0.2 mm, recrystallised from ethanol/petroleum ether, m.p. 48-49°; p.m.r.; δ 6.9 (4 H, m, aromatic), 3.77 (2 H, s, $Ar-CH_2-O-$), 3.66 (3 H, s, -OMe). Lit. m.p. values (173, 235) range from 39° to 49°.

3-Methyl-6,4'-dimethoxydiphenylmethane (38) was previously prepared (236) by Friedel-Crafts addition of p-methoxybenzoyl chloride to p-methylanisole (34); followed by a reduction step.

In this work, 38 was prepared in a single rapid step from p-methoxybenzyl methyl ether (32) and p-methylanisole (34); the latter was used in a large excess to prevent unwanted additional coupling reactions. Concentrated sulphuric acid (0.5 g) was added dropwise with stirring to a mixture of 34 (15.0 g) and 32 (1.1 g). A slight permanent pink colour was produced. After 10 minutes, the lower layer was separated and the upper layer was washed with sodium carbonate solution and then with water. p-Methylanisole was evaporated on a rotary evaporator at 70° and the residue was distilled *in vacuo*. Yield 1.35 g (77%) of a colorless oil; b.p. 160-162° at 0.1 mm; which crystallised after refrigeration for several days; m.p. 71.5-72.5°C. Lit. (53, 54) b.p. 178-180° at 3 mm; m.p. 74°.

P.m.r.; δ 6.7 (7 H, m, aromatic), 3.79 (2 H, s, Ar-CH_2-Ar), 3.66 (3 H, s, -OMe), 3.70 (3 H, s, -OMe), 2.18 (3 H, s, Ar-Me).

Anal. Calc. for $C_{16}H_{18}O_2$: C, 79.3; H, 7.49

Found : C, 79.1; H, 7.56

Bis-2-(p-methoxyphenyl)ethyl ether (39) - This compound has not been previously reported. It was prepared as follows: p-methoxyphenethyl alcohol (35) (5 g) and $H_2SO_4 \cdot 3H_2O$ (178, 179) (0.25 g) were mixed and heated with stirring at 140±5° for 6 hours. After cooling, benzene (10 ml) was added and the product was washed with potassium carbonate solution, followed by water, and dried over anhydrous sodium sulphate. The benzene extract was passed through a short (15 cm) silica gel column (benzene eluent) to remove unreacted alcohol (~10% by g.l.c.).

The product so obtained (4 g, 85%), 99% pure by g.l.c., was distilled in vacuo, b.p. 193-195° at 0.06 mm; n_D^{23} 1.5508; p.m.r.; δ 6.8 (8 H, m, aromatic), 3.65 (6 H, s, -OMe), 3.49 (4 H, t, J=7 Hz, -CH_2-O-), 2.71 (4 H, t, J=7 Hz, Ar-CH_2-).

Anal. Calc. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.74

Found : C, 75.4; H, 7.76

All attempts at crystallisation were unsuccessful.

p-Methoxyphenethyl methyl ether (41) - was prepared by methylation of p-methoxyphenethyl alcohol (35). A small amount of 35 (2.0 g) was shaken with excess methyl iodide (15 g) along with silver oxide (5g) and some molecular sieve (Linde 3A) for 24 hours. The small quantity of unmethylated alcohol was removed from the product by passing it through a short silica gel column, and the sweet-smelling product was distilled in vacuo, b.p. 65-67° at 0.025 mm, n_D^{21} 1.5099. Lit. (237) b.p. 119-121° at 12 mm.

Anal. Calc. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.49

Found : C, 72.2; H, 8.35

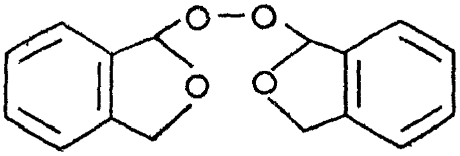
8.7 Reductive Cleavage of 1,3-Dimethoxyphthalan

8.7.1 Reduction with Borane in THF

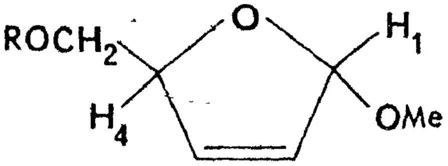
The compound 1,3-dimethoxyphthalan (50, mixed isomers; 60% *c*, 40% *t*, 1.74 g, 9.7 mmol) was treated with borane in THF (25 ml, 1M) at 22°C. After 90 hours, g.l.c. analysis of a small sample showed 40% of the starting material remaining. Warming the mixture at 35-40° for 6 hours completed the reaction. The products were worked up as described in 8.2.1 and the mixture was distilled.

The first fraction obtained was phthalan (57), 0.7 g (60%), b.p. 83-85° at 15 mm; n_D^{25} 1.5428, m.p. 4-5°. P.m.r.; δ7.02 (4 H, m, aromatic), 5.92 (4 H, s, Ar-CH_2-O). Lit. (238) b.p. 192°; n_D^{25} 1.5440; m.p. 6°.

Exposure of the sample to air for several weeks resulted in its conversion into a white crystalline solid — the peroxide 67 (238, 190) m.p. 136-138° (recryst. ether). Lit. (238, 190) m.p. 137.5-139.5°, 139°.



67



54

The protons on the five-membered rings of 67 exhibited an ABX type p.m.r. spectrum ($CDCl_3$ soln.) which was analysed as follows: AB part (methylene protons) δ_A 5.02, δ_B 5.19, J_{AB}=-13 Hz, J_{AX}= 0 Hz; X part (methine proton) δ6.73, J_{BX}= 2 Hz*. Long-range coupling appears to be normal in this type of

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* This value is taken directly from the line spacing. Although the X doublet was sharp, giving no evidence of virtual coupling, such an effect must be anticipated in this system. Virtual coupling if operative, would render the observed line spacing

structure, being evident also in the spectra of 56 (Fig.7.3) and 61 (p.157). The value of the coupling constant for 56, 61 and 67 was 2 Hz[*]. This is reasonable, since Lemieux et al. found ^5J(H1, H4) to be 4.4 Hz for the α-D-furanoside 54 in which the five-membered ring contains a discreet double bond (192).

The second distillate fraction obtained was α-methoxy, 2-hydroxymethyl toluene (58), 0.235 g (16%), b.p. 130-140° at 18 mm, n_D^{22} 1.5301; p.m.r. identical to that of the synthesised material.

The preparation of g.l.c. calibration standards from the distillate fractions permitted quantitative analysis of the initial chromatogram: 72% of 57 and 28% of 58. A very small peak, about 0.4% of the total area, was present at a retention time of 3.9 minutes, between 57 (1.5 mins) and 58 (4.7 mins); this peak had retention times identical to those of 1,2-bismethoxymethylbenzene (59) on both SE-30 (non-polar) and Carbowax 20M (polar) g.l.c. columns.

8.7.2 Reduction with $HCo(CO)_4$

Dicobalt octacarbonyl (98%, Ventron, 0.4 g, 1.15 mmol) dissolved in benzene (4 ml) was placed inside the glass liner of an autoclave, and 1,3-dimethoxyphthalan (mixed isomers; 60% c, 40% t, 2.7 g, 15 mmol) was placed in an open ampoule suspended above the solution. The autoclave was pressurised to 2400 psig with 2:1 H_2/CO mixture. After heating to 145°, it was tilted to mix the contents, and heating was continued at 160±5° for 90 minutes. The autoclave was cooled and vented, and the products were made up to 50 ml with benzene prior to g.l.c. analysis. Compounds 57 and 59 were indicated from the g.l.c. analysis, plus two unknown compounds and a broad composite peak at the same retention time as the starting material.

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[*] Assumed to be positive as in ref.192.

A small portion of the benzene solution was silylated by treatment with pyridine and trimethylsilyl chloride (Eastman) and the g.l.c. analysis was repeated. The chromatogram was similar, but one peak had shifted from the composite and appeared at longer retention time. This peak had the same retention time as the trimethylsilyl ether of <u>58</u>.

A 40 ml portion of the benzene solution was evaporated; the catalyst was allowed to oxidise*, and the mixture was chromatographed on silica gel, with benzene containing 1 to 10% ether (b.v.) as eluent. The following fractions (in elution order) were obtained:

(i) phthalan (<u>57</u>), 15 mg (1%), identified by its p.m.r. spectrum; the recovery is poor because this compound co-distils with the benzene eluent;

(ii) 1-methoxyphthalan (<u>61</u>), 75 mg (4%); the aliphatic portion of the p.m.r. spectrum of this compound was of the ABX type, which was analysed as follows: AB part (methylene protons); δ_A 4.92, δ_B 5.07, J_{AB}=-13 Hz, J_{AX}=0 Hz; X part (methine proton); sharp doublet, δ 6.02, J_{BX}=2 Hz**; by analogy with the work of Lemieux <u>et</u> <u>al</u>. (192) the methine proton will be coupled to the methylene proton which is <u>trans</u> to it (see Section 7.3); from its <u>cis</u> relationship to the methoxyl group this latter proton would also be expected to give the downfield methylene signal — as is the case; the p.m.r. spectrum also showed a methoxyl, δ 3.35 (3 H, s) and aromatic protons, δ 7.26 (4 H, m); the material suffered oxidation and/or polymerisation before it could be further characterised;

(iii) 2-methoxymethylbenzaldehyde (<u>63</u>), 0.344 g (19%), n_D^{22} 1.5324; λ_{max} 1699 cm^{-1}; p.m.r.; δ10.14 (1 H, s, CHO), 7.5 (4 H, m, aromatic), 4.80 (2 H, s, Ar-CH$_2$-O), 3.41 (3 H, s, -OMe);

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* If this oxidation step is omitted, Co$_2$(CO)$_8$ decomposes on the silica gel liberating CO gas and destroying the continuity of the column.

** See footnote p. 155.

this compound does not appear to have been reported previously; its structure was confirmed by chemical methods:

(a) a small quantity of <u>63</u> in methanol solution was reduced with excess borohydride. After isolation from the inorganic materials, the product was silylated and examined by g.l.c. — it gave a peak at the same retention time as the trimethylsilyl ether of <u>58</u>.

(b) <u>63</u> formed a semicarbazone, m.p. 190-191° (recryst. EtOH).

Anal. Calc. for $C_{10}H_{13}N_2O_3$: C, 58.0; H, 6.32; N, 20.3
Found : C, 57.5; H, 6.24; N, 22.7

(c) a thin film of <u>63</u> left open to air for 5 hours fully oxidised to 2-methoxymethylbenzoic acid, m.p. 96-97° (recryst. from water); Lit. (240) m.p. 96-97°;

Anal. Calc. for $C_9H_{10}O_3$: C, 65.1; H, 6.02
Found : C, 65.0; H, 6.16

(iv) phthalide (<u>62</u>), 54 mg; m.p. 67-70° (not recryst.); p.m.r., g.l.c., identical to authentic sample (m.p. 72-74°, Aldrich);

(v) 1,3-dimethoxyphthalan (<u>50</u>) (starting material), 0.45 g. (21%); n_D^{23} 1.5100; some of this material had undergone hydrolysis during chromatography, and appeared as <u>o</u>-phthalaldehyde (<u>51</u>, 0.145 g) largely in fraction (ii) (from which it was separated by means of aqueous hydroxylamine); traces of <u>51</u> were evident as contaminants in fractions (iii), (iv) and (v);

(vi) 1,2-bis-methoxymethylbenzene (<u>59</u>), 0.346 g (17%); n_D^{23} 1.5060; p.m.r., g.l.c. identical to those of the authentic sample.

8.7,3 Preparation of 1,3-Dimethoxyphthalan (<u>50</u>)

The method of Schmitz (185) was followed exactly, and <u>50</u> was obtained in 76% yield, b.p. 114-115° at 11 mm; n_D^{25} 1.5094. Lit. (185) b.p. 113.5-114.5° at 11 mm; (191)

116-118° at 11 mm, n_D^{20} 1.5110. The repeated distillations found necessary by Aso and Tagami (191) to rid the product of phthalaldehyde tetramethyl acetal were not required. In several preparations the distillate was found (g.l.c.) to be 99.1-99.7% pure, the single impurity having slightly longer retention time than (50). The product was a mixture of stereoisomers (60% cis and 40% trans) as determined by p.m.r.; (5% b.w. in CCl_4) δ 7.31* (4 H, s, aromatic), 6.17 (0.4 H, s, trans-methine), 5.94 (0.6 H, s, cis-methine), 3.370 and 3.365** (6 H, two singlets, methoxyl). Lit. (191) p.m.r. (CCl_4) δ 7.17 (aromatic), 6.05 and 5.81 (methine) and 3.25 (methoxyl protons). There is an apparent downfield shift of 0.12-0.14 ppm for the measurements given here relative to the published values (191). The reason for the difference is not clear; spectra were run at a wide range of concentrations (3%-50%) but shift values varied by only 0.02 ppm throughout the range. Aso and Tagami, however, do state that their original shift values "were corrected with TMS standard" — this correction may be the source of the discrepancy.

The isomers of 50 were separated as follows: silica gel (80 g, 0.08 mm particle size) was carefully dried and then packed as a slurry with benzene containing 3% of ether by volume (both solvents anhydrous) to form a column 65 x 2 cm. Traces of water were removed from the silica by a preliminary elution of a gram of 50 — it was largely converted into o-phthaldialdehyde (51) during elution. Then three 1.5 g samples of 50 were successively eluted as quickly as possible, the first 10%, and last 10% of eluted product being combined.

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* The chemical shifts were accurately determined (±0.005 ppm) relative to TMS using the frequency sweep mode and a precision frequency counter. An upfield sweep of 0.4 Hz/sec was employed.

** The two methoxyls are not resolved at a sweep rate of 1 Hz/sec (Fig.7.4). The upfield signal is the stronger of the two methoxyls and is presumably, therefore, due to the cis-isomer. In benzene solution, the cis-isomer gives the downfield signal (191).

In this way a 90% t: 10% c mixture (~ 0.4 g) and a 14% t:86% c mixture (~ 0.4 g) were obtained. Repeating the procedure with these mixtures yielded 31 mg of the pure trans compound (p.m.r., Fig. 7.5) and 26 mg of a 6% t:94% c product (p.m.r., Fig.7.6). Slow elution gave worse separations than fast elution, presumably the silica gel slowly equilibrated the isomers.

8.7.4 Source of Authentic Samples of the Reduction Products

Phthalide (62) was purchased (Aldrich).

1,2-Bis-methoxymethylbenzene (59) and α-methoxy, 2-hydroxymethyltoluene (58) were prepared by methylation of phthalyl alcohol. Phthalyl alcohol was prepared according to ref.238 by reduction of phthaloyl chloride with lithium aluminum hydride*; b.p. 146-147° at 1.7-2.0 mm, $n_D^{21.5}$ 1.5625 (supercooled), m.p. (recryst. benzene) 63.5-64°. Lit. (238) m.p. 63-64°.

Phthalyl alcohol (2 g), silver oxide (4 g), methyl iodide (20 g), benzene (8 g) and molecular sieve (Linde 3A, 10 g) were shaken together for 2 days. G.l.c. showed two product peaks, both less polar (peak shape) and both more volatile (retention time) than the starting material (some of which remained). After filtration and solvent removal, the product was applied to a 25 cm silica gel column and was eluted with benzene containing 5% of ether. The first fraction yielded 0.55 g of 59, n_D^{24} 1.5051, p.m.r.; δ 7.20 (4 H, m, aromatic), 4.40 (4 H, s, Ar-CH_2-O), 3.27 (6 H, s, -OMe). Although previously prepared, only the b.p. of this compound was reported (241).

The second fraction yielded 1.3 g of 58; b.p. 121° at 7 mm, $n_D^{23.5}$ 1.5309. Lit. (240) b.p. 132° at 13 mm.

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* Phthalyl alcohol was also obtained as the only product in an attempted reduction of phthalide to 1-phthalanol by $LiAlH_4$ at 35°C — this is contrary to the indications given in ref.239.

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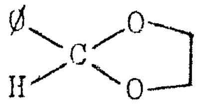
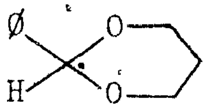
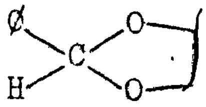
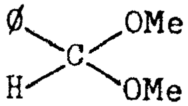
APPENDIX 1

THE EFFECT OF RING SIZE UPON THE RATE OF ACETAL REDUCTION BY BORANE (BH$_3$)

During the studies of acetal cleavage by borane, some competitive reductions of acyclic, five- and six-membered acetals of benzaldehyde were conducted. The results of the first experiment presented in Table A.1 indicate that the five-membered ring is cleaved about nine times faster than its six-membered counterpart.

TABLE A.1

Competitive Reduction of Pairs of Acetals*
by Borane in THF

Substrate	Product Formed, mmol	Reaction Time, min.
	0.12	31
and		
	0.013	
	0.14	40
and		
	0.30	

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* The acetal mixture (1.25 mmol of each) was treated with excess borane (0.95M) in THF at 0°C. Analysis by g.l.c.

This rate difference reflects the greater stability of the six-membered ring when C_2 bears a phenyl substituent. It is well known, for example, that the acid-catalysed equilibration reaction of benzaldehyde with polyhydric alcohols affords derivatives of 2-phenyl-1,3-dioxane rather than 2-phenyl-1,3-dioxolane (242, 243); glycerol, however, is exceptional in having the opposite preference (244). There is no substantiated example of diastereomeric forms of a substituted 2-phenyl-1,3-dioxane resulting from such an equilibration reaction (201), and it has been predicted (245) and verified experimentally (246, 247) that the preferred 2-phenyl-1,3-dioxane derivatives have the phenyl group equatorial in a chair form of the 1,3-dioxane ring.

Solvolysis exhibits the same rate difference as does reductive cleavage, five-membered cyclic acetals of benzaldehyde cleaving about ten times faster than six-membered acetals (199).

The picture is quite different, of course, with two substituents at C_2 : acetone, for example, exhibits a strong preference for forming five-membered isopropylidene rings. Presumably the axial methyl group required by the dioxane ring is responsible for this difference (245). One would consequently predict faster reductive cleavage of 2,2-dialkyl-dioxanes than 2,2-dialkyl-dioxolanes.

The second experiment in Table A.1 shows that benzaldehyde dimethylacetal cleaved faster than its five-membered cyclic counterpart. This result is most likely due to the favourable entropy term in the cleavage of acyclic acetals.

APPENDIX 2

A COMPARISON OF RATES OF ACETAL REDUCTION BY $LiAlH_4$-$AlCl_3$ AND BH_3

Published data on the rates of $LiAlH_4$-$AlCl_3$ reductions of acetals in diethyl ether solution (27) indicate that the mixed hydride reacts faster than borane in THF. However, since the solvent undoubtedly plays a major rôle by solvating the active species, the two reagents should be compared in the same solvent. In order to do this the rates of reduction of 2-phenyl-1,3-dioxolane (4) by both borane and mixed hydride reagents was measured in THF solution.

Borane in THF (20 ml, 1M solution) was diluted to 0.42M with additional THF (28 ml) and 4 (10 mmol) was added, making the solution 0.21M in acetal. Simultaneously a THF solution (48 ml) of $LiAlH_4$ (20 mmol) and $AlCl_3$ (20 mmol) — theoretically 0.83M in "AlH_2Cl" (Eq.A.1) — was also mixed with 4 (10 mmol) yielding the same acetal concentration as above.

$$LiAlH_4 + AlCl_3 \longrightarrow 2\ AlH_2Cl + LiCl \qquad A.1$$

At fixed time intervals aliquots were removed from each solution and quenched in aqueous sodium carbonate. The organic material, after extraction with benzene, was analysed by g.l.c. As the results in Table A.2 show, the rates of reduction are almost identical, although, according to Eq.A.1, the mixed hydride is more concentrated. Thus at concentrations of about 0.4M in THF, borane appears to be a somewhat faster reducing agent than mixed hydride.

TABLE A.2

Reduction of 2-Phenyl-1,3-dioxolane* by Borane and by $LiAlH_4$-$AlCl_3$ in THF at 0°

Time Elapsed, min.	Borane Reduction, mmol of product formed	Mixed Hydride Reduction, mmol of product formed
6	0.10	0.07
14	0.18	0.15
30	0.35	0.29
62	0.64	0.57
126	0.99	1.2
255	1.9	1.9
460	2.8	3.1

---

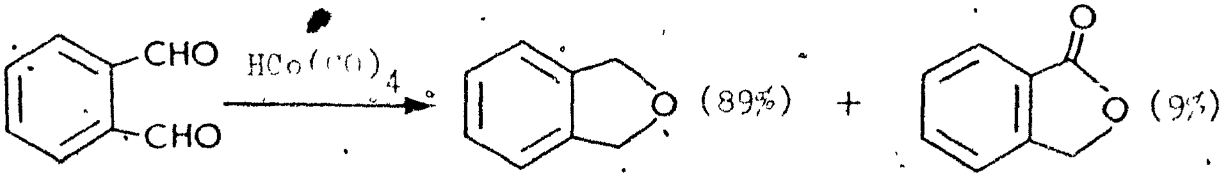
* 10 mmol acetal reacted with (i) 20 mmol BH_3 (ii) 20 mmol $LiAlH_4$ + 20 mmol $AlCl_3$. Total solution volume in each case equals 48 ml. Therefore, concentrations were, acetal: 0.21M, BH_3: 0.42M, AlH_2Cl: 0.83M.

APPENDIX 3

REDUCTION OF PHTHALALDEHYDE (51)

(a) Reduction with $HCo(CO)_4$

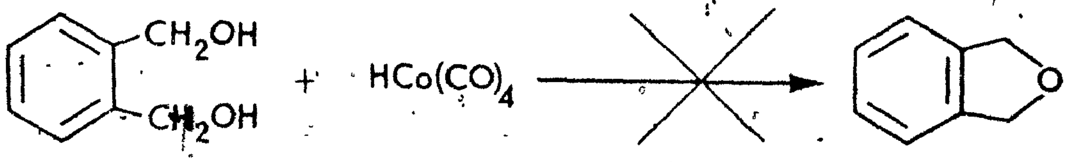
In an attempt to unravel the complex mixture of products obtained from the reduction of 1,3-dimethoxyphthalan (Section 7.5) the reduction of phthalaldehyde by $HCo(CO)_4$ was examined. The product was not the expected phthalyl alcohol (68) but was chiefly phthalan (57) with a trace of phthalide (62) (Eq.A.2).



51 57 62

A.2

The most likely mechanism for phthalan formation appeared to be *via* dehydration of first-formed phthalyl alcohol (68). Accordingly phthalyl alcohol was treated with $HCo(CO)_4$ in the same manner as phthalaldehyde — but only a trace of phthalan (< 2%) was formed and much of the alcohol was recovered unchanged. Consequently phthalyl alcohol cannot be an intermediate in the reduction of phthalaldehyde to phthalan (Eq.A.3),



68 57

A.3

and a different mechanism must be sought. Scheme A.1, which is purely speculative, illustrates one possible route to the observed products. In keeping with current theories of aldehyde reduction (121, 122) hydrocobalt tricarbonyl is indicated as the active species involved in coordination to the carbonyl oxygen.

Phthalide (62), which is isomeric with the starting material, can be obtained from it by the Cannizzaro reaction (248) — a hydride transfer catalysed by OH^-. Scheme A.1 indicates how $HCo(CO)_3$ may operate as a hydride transfer catalyst in this case.

(b) Reduction with Borane in THF

A THF solution of phthalaldehyde became hot when the borane solution was added. G.l.c. analysis of a silylated sample of product revealed an 80% yield of phthalyl alcohol and 10% of phthalan. The usual work-up procedure resulted in 52% recovery of phthalyl alcohol (68) m.p. 63-64° (recryst. benzene). Lit. (238) m.p. 63-64°.

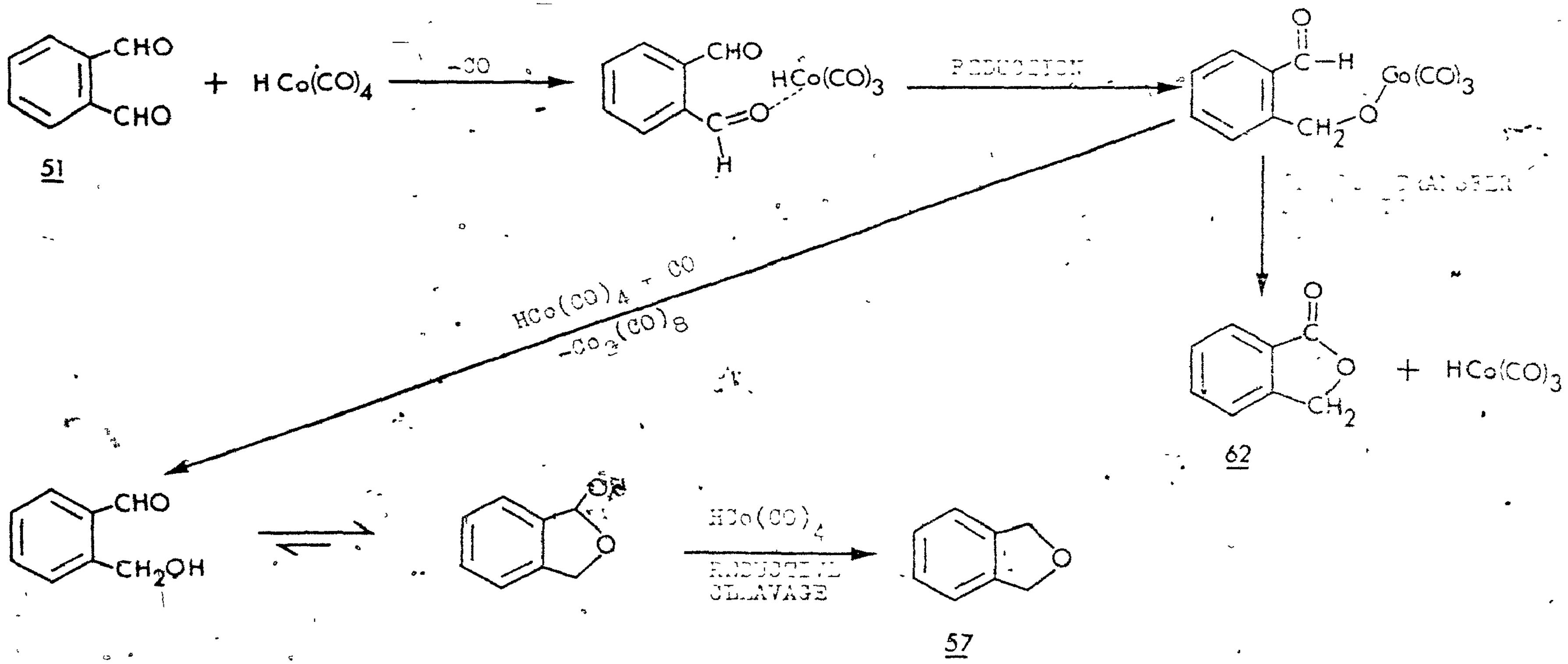
(c) Experimental Details of the Reduction of Phthalaldehyde with $HCo(CO)_4$

Phthalaldehyde (2.3 g) dissolved in 20 ml. of ether* was heated for 3 hours at 160° with $Co_2(CO)_8$ (0.4 g) under 2500 psig of a 2:1 H_2/CO gas mixture. G.l.c. analysis revealed only two major products; phthalan (57), 89% yield, and phthalide (62), 9% yield. The dark brown solution was evaporated on a rotary evaporator at 0°, and the residual liquid was distilled under reduced pressure. The first fraction obtained was water, 0.12 g (n_D^{21} 1.3400, $CuSO_4$ test), followed by phthalan, 1.48 g (72%); b.p. 86-87° at 20 mm; m.p. 6-7°C; n_D^{21} 1.5459. Lit. (238, 190) b.p. 106° at 36 mm, 85° at 20 mm, m.p. 6°, n_D^{25} 1.5440.

---

* Benzene was used in a preliminary experiment, but the phthalan product co-distilled with this solvent and thus was not isolable.

The viscous black distillation residue was extracted with warm CCl_4 (4 x 5 ml), and the combined filtered extracts were evaporated to dryness. The residue so obtained was dissolved in a little benzene and applied to a silica gel column, eluent: benzene with increasing amounts of ether. Phthalide, 0.147 g (6.4%) was eluted by 4% ether in benzene; m.p. (crude) 60-64°, (recryst. CCl_4) 72°; m.m.p. with authentic material 73-74°. The i.r. spectra (CCl_4) of the recrystallised product and authentic phthalide were identical.

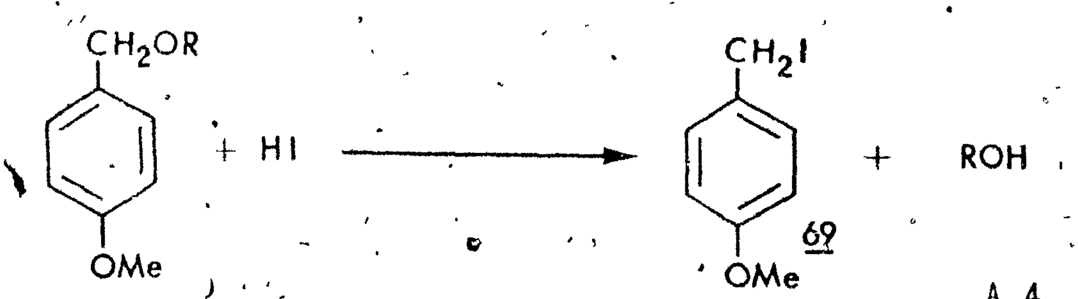

CHO
CHO
51
+ HCo(CO)4
-CO
HCo(CO)3
REDUCTION
C—H
Co(CO)3
CH2
TRANSFER
62
+ HCo(CO)3
HCo(CO)4 + CO
-Co2(CO)8
CH2OH
HCo(CO)4
REDUCTIVE CLEAVAGE
57

SCHEME A.1

APPENDIX 4

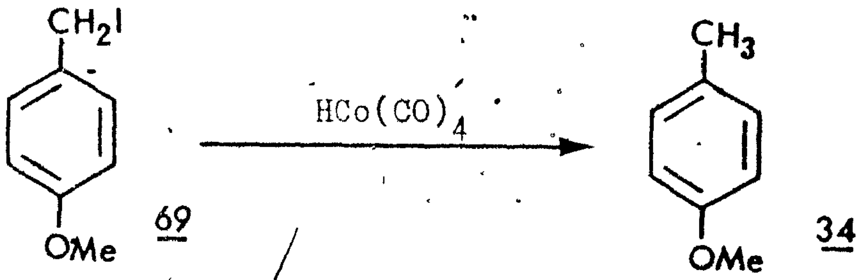
THE REDUCTION OF BENZYL HALIDES BY STOICHIOMETRIC AMOUNTS OF $HCo(CO)_4$

During preliminary investigations of the reduction of p-methoxybenzyl ethers by stoichiometric amounts of $HCo(CO)_4$, addition of a catalytic amount of iodine to the reaction mixture was found to cause rapid and complete reductive cleavage of the substrate. In considering the mechanism of the reaction it seemed reasonable to suppose that iodine would be rapidly reduced by $HCo(CO)_4$. The hydrogen iodide so formed would then be expected to cause cleavage of the ether according to Equation A.4.



A.4

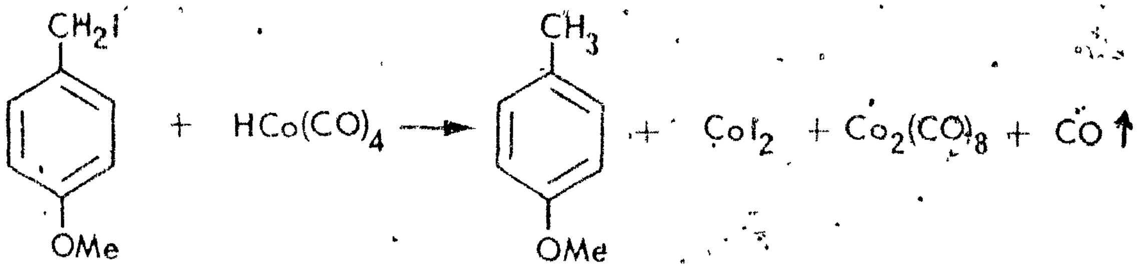
The aromatic product obtained, however, was p-methyl anisole (34), not p-methoxybenzyl iodide (69). Thus the indication was that $HCo(CO)_4$ reduces 69 to 34 (Eq.A.5).



A.5

p-Methoxybenzyl Iodide Reduction

Accordingly 69 was prepared and treated with a slight excess of $HCo(CO)_4$ solution in benzene at 7°C. The mixture darkened rapidly and gas (CO) evolved. p-Methylanisole (34) was formed in good yield and the cobalt appeared both as CoI_2 (water-soluble) and $Co_2(CO)_8$ (benzene soluble). Equation A.6 illustrates the reaction along with the analytical results obtained for each compound.



mmol: 1.0 1.6* 0.93 0.41 0.43 1.7**

A.6

The analytical results can be approximated by a suitable combination*** of Equations A.7 and A.8

$$ArCH_2I + HCo(CO)_4 \rightleftharpoons ArCH_3 + \tfrac{1}{2}CoI_2 + \tfrac{1}{2}Co_2(CO)_8 + 2CO \qquad A.7$$

$$ArCH_2I + 2\,HCo(CO)_4 = ArCH_3 + HI + Co_2(CO)_8 \qquad A.8$$

It proved rather difficult to decide unequivocally in the presence of moisture and CoI_2 whether or not small amounts of hydrogen iodide were produced.

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* This figure represents the $HCo(CO)_4$ consumed — 2.3 mmol being present initially, and 0.7 mmol remaining after the reaction.

** The CO may contain a little hydrogen from decomposition of $HCo(CO)_4$.

*** Roughly (3 x A.7) + (1 x A.8).

Benzyl Iodide Reduction

Benzyl iodide reacted in the same way as 69, but the reaction was slow even at 20°. When the temperature was raised to 40°, brisk reduction and gas evolution began; the analytical results are shown underneath Equation A.9.

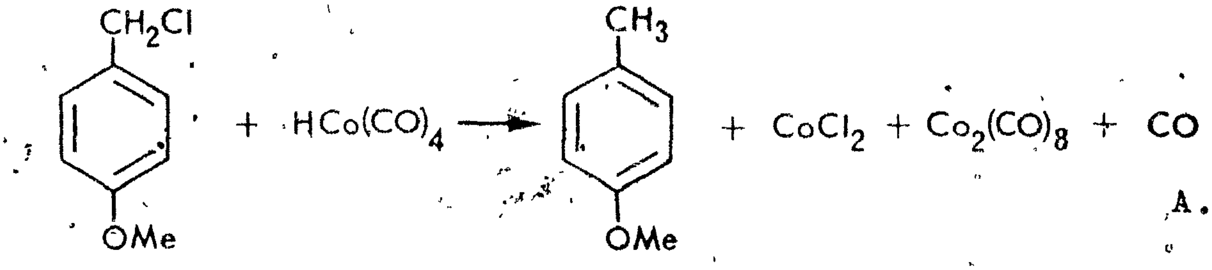
$$PhCH_2I + HCo(CO)_4 \longrightarrow PhCH_3 + CoI_2 + Co_2(CO)_8 + CO \qquad A.9$$

mmol: 2.0 4.3^* 2.0 1.0 1.5

p-Methoxybenzyl Chloride Reduction

A temperature of 50° was required to effect the reductive cleavage of p-methoxybenzyl chloride. In this case the yield of reduction product was only 40%; no starting material remained. Judging from the waxy solid (insoluble in water and in benzene) adhering to the flask, polymerisation had occurred.

Analytical results for this reduction are shown underneath Equation A.10.



A.10

mmol: 1.6 3.5^{**} 0.65 0.71 1.3 3.0

Experimental Details

p-Methoxybenzyl iodide (69) was prepared in 62% yield by adding an acetone solution of sodium iodide to p-anisyl chloride according to ref. 249; m.p. (recryst. ether) 30-31°.

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[*] 4.5 mmol initially present, 0.2 mmol remained after the reaction.

[**] 3.7 mmol initially present, 0.2 mmol remained after the reaction.

Lit. (249) m.p. 32.5°.

Benzyl iodide was purchased from K. and K. Laboratories Inc.

p-Methoxybenzyl chloride was prepared according to ref. 173, b.p. 78-81° at 0.35 mm. Lit. (173) b.p. 113-114° at 15 mm.

The reduction of 69 exemplifies the general procedure: a solution of 69 (0.248 g, 1 mmol) in benzene (5 ml) was added by syringe to a stirred solution of $HCo(CO)_4$ (2.3 mmol) in 10 ml of benzene* cooled to 7°C. Carbon monoxide (45 ml; 39 ml at NTP, 1.7 mmol) was evolved over a period of 1 hour. When gas evolution had ceased, the benzene solution was washed twice with water to remove the cobalt iodide product as a pale pink solution. (This solution became an intense blue colour upon addition of concentrated hydrochloric acid due to formation of the tetrachlorocobalt anion, and also yielded a yellow curdy precipitate with silver nitrate solution.) The cobalt iodide solution was evaporated to dryness (dark green solid) in a weighed crucible, and the crucible was roasted at 750°C. Purple iodine fumes evolved. The yield of Co_3O_4 obtained was 33.2 mg (229), equivalent to 0.41 mmol of cobalt.

Next, the "total cobalt carbonyl" remaining in a 7 ml portion of the benzene solution was estimated by decomposing the cobalt carbonyls with iodine and measuring the volume of gas evolved (Section 8.5.2). The volume of gas collected was 64.9 ml at NTP, equivalent to 6.2 mmol of CO for the total 15 ml of benzene solution, indicating the presence of 1.55 mmol of $Co(CO)_4$.

To estimate the fraction of unchanged $HCo(CO)_4$ in the "total cobalt carbonyl" a further 5 ml of the benzene solution was shaken with nickel o-phenanthroline chloride (163). The precipitated nickel o-phenanthroline salt of $HCo(CO)_4$ was washed free of $Co_2(CO)_8$, dissolved in pyridine, and decomposed with iodine solution. The CO yield was 20.6 ml (corrected to NTP),

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* The solution was prepared and analysed as described in 8.5.1 and 8.5.2.

indicating 0.69 mmol $HCo(CO)_4$ remaining in the full 15 ml of final solution.

Consequently 1.6 mmol $HCo(CO)_4$ had been consumed and, by difference, the remaining "cobalt carbonyl" corresponds to 0.43 mmol $Co_2(CO)_8$.

Finally, g.l.c. analysis for p-methylanisole (34) by interpolation between "bracketing" standards indicated the concentration of 34 to be 0.75 g/100 ml, equivalent to 0.11 g/15 ml — a yield of 93%.

APPENDIX 5

THE TREATMENT OF LIGNIN AND CELLULOSE WITH $HCo(CO)_4$ AND RELATED CATALYSTS, AND WITH BORANE

Introduction

Freudenberg has represented the average structure of lignin by a model consisting of 18 mono-, di-, and trifunctionally linked phenylpropane units (250), with ether linkages predominating. Bolker and Brenner (251) pointed out that most of the trifunctionally linked units in the model are bearers of benzyl ether links, and that scission of these bonds would yield only linear lignin fragments (or fragments bearing short branches). This is the type of process which would convert a cross-linked polymer into a soluble, linear form. Other results in the literature suggest that reactions at the benzyl position are important in delignification processes operating under acidic conditions (252, 253).

The lignin-carbohydrate bond in wood may also be a benzyl ether link (254).

Heterogeneous catalytic hydrogenolysis of lignin is extremely useful as a tool for the elucidation of lignin structure. Investigations in this field up to 1965 have been reviewed by Schweers (255) and much important work continues to appear (256-258). Although patents have been granted for pulping processes employing heterogeneous catalysis (e.g. ref. 259), such systems suffer from the often conflicting requirements of having good catalyst penetration into the wood during reduction, and facile catalyst removal from the pulp afterwards.

A homogeneous reducing agent would not suffer these drawbacks. A search for such a compound undertaken in this laboratory soon proved $HCo(CO)_4$ in benzene or water solution to be capable of cleaving benzyl ethers especially when the latter had a p-methoxy substituent (1). The same catalyst also rendered 90% of a periodate lignin sample soluble in dioxane-water solvent after treatment at 180-200° for 8 hours. However, under the same conditions for 1-2 hours, cellulose (cotton linters) was severely depolymerised (1).

By making use of the solvent effect for benzyl ether cleavage by $HCo(CO)_4$ (Chapter 6), the author was able to achieve good solubilisation of lignin in acetone solvent under much milder conditions than previously employed (Table A.3).

TABLE A.3

Solubilisation of Spruce Periodate Lignin by $HCo(CO)_4$ in Acetone Solution[a]

Temperature, °C	Time, h.	Insoluble Lignin[b] Recovered, %
120-130	13	10
115-125	2.5	31

(a) Lignin (0.55 g) and $Co_2(CO)_8$ (0.22 g) in 10 ml acetone were heated under 2000 psig of synthesis gas ($2H_2$:1CO). (b) The acetone solution was filtered, and the filtered solid was washed with acetone, 10% aqueous acetic acid (to remove catalyst traces), ethanol, dioxane-water (9:1) and finally ethanol again.

However, when cellulose (degree of polymerisation of approx. 500) was treated similarly in acetone solution, it was reduced to a weight average degree of polymerisation of approximately* 150, as determined by gel permeation chromatography.

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* The values are approximate because of the lack of a suitable standard to calibrate the g.p.c. apparatus. The relative values are, of course, still useful.

In other words, even under mild temperature conditions cellulose is so degraded by $HCo(CO)_4$ as to be useless for paper-making.

Modified $HCo(CO)_4$ Catalysts

The acidity of $HCo(CO)_4$ appears to be the cause of the cellulose depolymerisation; consequently, attempts were made to reduce the acidity of the catalyst. The easiest way to do this is to replace one of the CO ligands by a phosphine ligand, yielding $HCo(CO)_3PR_3$*. This is the well-known catalyst of the "Shell oxo process" (when R is an alkyl group) — a lower pressure version of the original Ruhrchemie process (see ref. 100, pp.22, 73 and references cited therein). Phosphine-modified cobalt hydrocarbonyls are much weaker acids than $HCo(CO)_4$; incorporation of a single triphenyl phosphine ligand, for example, reduces the acidity by about 7 pK_a units to pK_a 2.7. Substitution by a single trialkyl phosphine (R = n-butyl or cyclohexyl) yields compounds of pK_a 8 to 10 (ref.107, p.181).

The modified catalysts, while less active than $HCo(CO)_4$ in hydroformylation (260), remain good reducing agents for olefins and aldehydes (107). Indeed the major disadvantage of the Shell oxo process is its rather high yield (10-15%) of paraffins formed by reduction of the olefin feedstock.

The major differences in behaviour between phosphine-modified cobalt hydrocarbonyls and $HCo(CO)_4$ are fairly easily explained: the phosphorus ligands are better σ-donors than CO, but are poorer π-acceptors. As a consequence, the remaining CO-ligands are more strongly bonded because the cobalt atom has the tendency to transfer the increased negative charge obtained from phosphorus to the remaining CO-ligands by π-donation. Some of the increased negative charge is also donated to the hydrogen atom, making it more hydridic. The increased strength of the CO-metal bond in modified cobalt carbonyls accounts for

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* The chemical properties of these compounds are reviewed in refs.107 and 169.

both the higher thermal stability of these catalysts and their lower activity in hydroformylation.

The Reaction of Phosphine-modified $HCo(CO)_4$ with p-Methoxybenzyl Methyl Ether, with Lignin and with Cellulose.

Table A.4 shows the results obtained for the treatment of p-methoxybenzyl methyl ether; lignin, and cellulose with tributyl phosphine-modified cobalt hydrocarbonyl. Entry #1, added for comparison purposes, comprises data taken from ref.1. It is clear that addition of tributyl phosphine (Entries 2 and 3) reduces the reactivity of the catalyst towards all three substances examined. Unfortunately there appears to be no P/Co ratio which would yield a catalyst capable of solubilising lignin without causing excessive damage to cellulose.

Besides the obvious practical objectives of this work with regard to wood pulping, it was also our intention to test the theory of Bolker and Brenner (251) that benzyl ether cleavage is the key step in delignification. Experiment 2, Table A.4 shows a divergence of behaviour between the model compound p-methoxybenzyl methyl ether and lignin — thus failing to confirm the theory (which predicts, for example, 25-30% solubilisation of lignin if 65% of the benzyl ether bonds are broken).

The Treatment of Lignin with Borane in THF

At the end of Chapter 6 mention was made of the reductive cleavage of a p-methoxybenzyl ether in 75% yield by borane in THF at 135°. This observation encouraged us to treat spruce periodate lignin with borane under the same conditions. After extraction of the solid product with dioxane-water (9:1), followed by careful drying, only a 5% weight loss was observed.

Similarly, refluxing a lignin sample with $LiAlH_4$-$AlCl_3$* mixture in THF, followed by extraction and drying afforded only 10% weight loss.

These results lead us to one of three conclusions; either

(i) the apparent low reactivity is due to poor penetration of the reagents into the lignin matrix,

(ii) the p-methoxybenzyl ether model compounds are not structurally complex enough to be of value in predicting the chemistry of lignin, or,

(iii) benzyl ether bond cleavage is not the key to cross-link scission in lignin.

There are indications that both conclusions (ii) and (iii) may be true. For example, in the reaction of $HCo(CO)_4$ with a β-guaiacyl veratryl glycerol, a good yield of guaiacol was obtained (1); this signified β-cleavage.

Having amassed some evidence that α-ether cleavage does not correlate well with lignin solubilisation, it might now be fruitful to examine β-cleavage in the same way..

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* This system is also known to reductively cleave p-methoxybenzyl ethers (230). It was checked by the author on the lignin model compound p-anisyl guaiacyl ether (45) and was found to give a 74% yield of reduction product 34.

TABLE A.4

The Treatment of p-Methoxybenzyl Methyl Ether, Lignin and Cellulose with Phosphine-Modified Cobalt Hydrocarbonyl[a]

Entry #	P/Co Ratio[b]	p-Methoxybenzyl Methyl Ether Cleavage[c], %	Spruce Periodate Lignin Solubilisation, %	Viscosity of Treated Cellulose[d], centipoise
1	0[e]	100[f]	66[f]	2.0[g]
2	1.1	65.	2.5	3.4[h]
3	1.37	1	–	4.8[h]

(a) For 1.8 hours at 180±5°, under 2500 psig (initial) synthesis gas ($2H_2$:1CO).
(b) Tributyl phosphine added to 1 mmol $Co_2(CO)_8$ dissolved in 5 ml of benzene.
(c) Measured as % yield of p-methylanisole (34) obtained. (d) At 0.5% C.E.D. The author is indebted to Mr. V. Berzins, PPRIC, for these measurements. (e) The data for this example is taken from ref.1. (f) Reaction time, 8 hours. (g) Initial value 14.8 centipoise. (h) Initial value 26.3 centipoise.

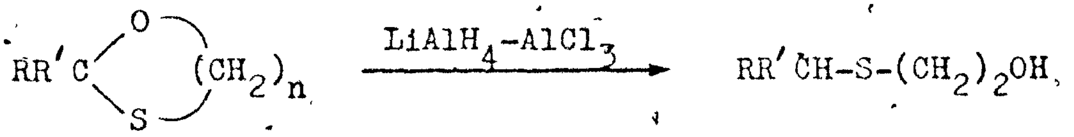
APPENDIX 6

SOME SUGGESTIONS FOR FUTURE WORK

As a scientific investigation proceeds, new items of knowledge often suggest to the experimenter interesting areas of research which are not within the scope of the study in progress. Four such items are listed below.

(i) The temperature dependence of the rate of acetal cleavage by borane would be worth examining. From such measurements, both the activation energy and the entropy of the reaction would be available. A large negative value for ΔS would support the proposed mechanism (Eq.2.14)*.

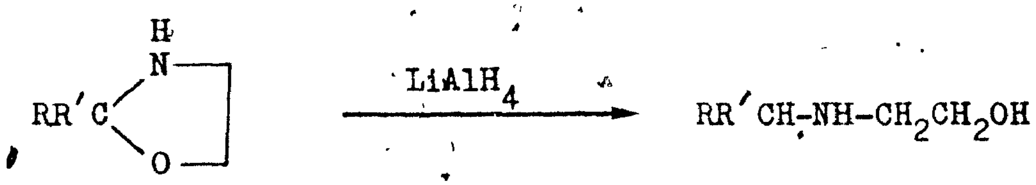
(ii) Eliel et al. (206) have shown that an $LiAlH_4$-$AlCl_3$ mixture reduces hemithioacetals, cleaving the C-O bond (Eq.A.11).



A.11

The behaviour of borane in THF in this regard may be worth examining.

(iii) Oxazolidines are reduced to amino alcohols by $LiAlH_4$ (261) (Eq.A.12),



A.12

and amino ethers are cleaved by Grignard reagents (262) (Eq.A.13).

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* The author is indebted to Dr. I.S. Butler for this observation.

$$R_2N\text{-}CH_2\text{-}OR' \xrightarrow{R''MgX} R_2N\text{-}CH_2\text{-}R'' + R'OMgX \qquad \text{A.13}$$

Reductive cleavage of both types of compound by borane in THF appears to the author to be very likely.

(iv) As mentioned in Section 7.3, the preparations of 1,3-dimethylphthalan and 1,3-diphenylphthalan* previously described (190) were, in all likelihood, mixtures of *cis*- and *trans*-isomers. This would be easy to ascertain from the p.m.r. spectra, and if the assumption proved to be correct, separation of the isomers would probably not be too difficult.

In the same way the 6-bromo-1,3-dimethoxyphthalan of Weygand *et al*. (270) was also perhaps a mixture of isomers. After two recrystallisations the product still had a wide melting range (65-69°), although the microanalysis was very close to the calculated value.

Doubtless many other 1,3-disubstituted phthalans have been prepared but the isomers not separated. The author has not made a thorough examination of the literature on this point.

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* Two m.p.s were recorded for this material (190); 84-87° (recryst. ethanol), and 87-90.5° (recryst. acetic acid). This may represent two crystalline structures, or alternatively the separated *cis*- and *trans*-isomers.

APPENDIX 7

A LIST OF POTENTIAL HOMOGENEOUS HYDROGENATION AGENTS WHICH, USED FOR TREATING p-ANISYL GUAIACYL ETHER, FAILED TO PRODUCE A SIGNIFICANT AMOUNT OF REDUCTIVE CLEAVAGE

As the title suggests, Table A.5 is a list of failures. It is given here only to prevent unnecessary duplication of effort in the future.

TABLE A.5

Reagent	Ref.	Conditions Employed	Remarks
$K_3^+ [HCo(CN)_5]^{\equiv}$	(263)	Ambient to 40°	No reduction
π-$C_5H_5Fe(CO)_2H$	(264)	2-6° benzene/water solv.	No reduction
$K^+ [HFe(CO)_4]^-$	(265)	Ambient ethanol/water solv.	Trace of Reduction only
$H_2Fe_3(CO)_{11} \cdot NR_3$ [a]	(266)	170°, 15h. benzene/water solv.	2% reductive cleavage
$H_2Fe_3(CO)_{11} \cdot NR_3$	(266)	240°, 1h. benzene/water solv.	8% reductive cleavage

(a) This catalyst is prepared from $Fe(CO)_5$ and an amine by heating under hydrogen pressure. The amine used was N-(2-hydroxyethyl)-pyrrolidine.

CLAIMS TO ORIGINAL RESEARCH

(1) The reductive cleavage of acetals by borane in THF has been discovered. A carbonium ion mechanism is proposed for this reaction on the basis of product distribution, and reaction rate studies. The reaction was found to be fourth-order; first-order in acetal and approximately third-order in borane. A mechanism accounting for the high order in borane is put forward, together with supporting evidence gathered from the literature.

(2) The rates of acetal reduction by $LiAlH_4$-$AlCl_3$ and by BH_3 were compared in THF solvent, and reduction by borane was found to be slightly faster than by "AlH_2Cl".

(3) Solutions of trimethylamine-borane in acetic acid were also found to effect the reductive cleavage of acetals.

(4) Aromatic acetals, unlike their aliphatic counterparts, give the relatively simple products of reductive cleavage when heated with catalytic amounts of $HCo(CO)_4$. A mechanism for this reduction is presented along with supporting experimental evidence. Stoichiometric amounts of $HCo(CO)_4$ at conditions near ambient were also found to reduce acetals to ethers.

(5) Diethers were always found among the products obtained when cyclic acetals of benzaldehyde reacted with catalytic amounts of $HCo(CO)_4$. A mechanism for diether formation is presented and supporting experimental evidence is provided. The formation of dibenzyl ether during benzaldehyde reduction by $HCo(CO)_4$ — a reaction hitherto unexplained — is now accounted for.

(6) The reductive cleavage of p-methoxybenzyl alcohol (31) by catalytic amounts of $HCo(CO)_4$ has been examined in greater

detail than before, and all new products detected have been explained in terms of current knowledge of the chemistry of the catalyst. The anomalous behaviour of 31 observed by earlier investigators is attributed to the ability of this substrate to react with the catalyst at low temperatures.

(7) The reductive cleavage of p-methoxybenzyl methyl ether (32) was shown to differ by only a small detail from that of 31. An explanation for this difference, the formation of p-methoxyphenethyl methyl ether (41), is offered.

(8) Stoichiometric amounts of $HCo(CO)_4$ under conditions near ambient also reduced p-methoxybenzyl ethers, but the yields were low. The same was true when borane in THF was the reducing agent; good yields were, however, obtainable at 135°.

(9) The cis- and trans- isomers of 1,3-dimethoxyphthalan (50) were separated by repeated chromatography on silica gel.

(10) The products resulting from the reaction of 50 with $HCo(CO)_4$ and with borane in THF have been isolated and characterised. $HCo(CO)_4$ preferentially attacks the ring oxygen, whereas borane prefers to attack the exocyclic oxygen.

(11) The reaction of phthalaldehyde with $HCo(CO)_4$ was found to give phthalan as major product. Phthalyl alcohol, which is unreactive to the catalyst, cannot be an intermediate in this reaction.

(12) The reduction of benzyl halides by stoichiometric amounts of $HCo(CO)_4$ has been observed.

EPILOGUE

Whether or not it is clear to you, doubtless the Universe is unfolding as it should.

Desiderata