"HINDRANCE EFFECTS"

IN

CELLULOSE SUBSTITUTION REACTIONS

A Thesis

by

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Ph.D. Chemistry

Raymond U. Lemieux

"HINDRANCE EFFECTS" IN CELLULOSE SUBSTITUTION REACTIONS

A method was developed for the accurate estimation of the acetyl content of trityl cellulose acetates. Monotrityl cellulose diacetate (I) was prepared and fully characterized. The nitration of I, to yield a "cellulose-6-nitrate diacetate", was found to be accompanied by considerable deacetylation. The nature of this deacetylation was studied.

The replacement by iodine of tosyloxy and nitrate groups in the cellulose molecule was studied. At least 0.52 of the nitrate groups in a "cellulose-6-nitrate" were definitely shown to occupy the primary position. Some of the results indicate that application of the "Oldham - Rutherford Rule" to cellulose may prove misleading.

The investigations made clear that hindrance effects operate in the reactions of certain cellulose derivatives. The suggestion is made that these effects are largely polar in nature.

A variety of new "selectively" substituted cellulose derivatives and the investigation of their structures is described.

Analytical methods for the semi-micro estimation of terminal methyl groups (ethoxy, acetyl, acetoxy and etnylidene), sulfur and iodine are described.

GENERAL INTRODUCTION

During the recent war confidential research programs were organized in an attempt to improve the quality and uniformity of military cellulose nitrate explosives.

Several laboratories in Britain and the United States studied the mechanism of decomposition of cellulose nitrates of the nitrogen content (N, 12.6-13.4%) usual in technical nitrations. Since the detailed structures of these substances are unknown and since their thermal or alkaline decomposition under the most closely controlled conditions always results in extremely complex molecular debris, correct interpretation of the data is a difficult matter. Three years ago, Dr. C. B. Purves and his coworkers in this laboratory undertook the preparation of various selectively substituted cellulose mono- and dinitrates. It was believed that if this were done, then experiments on the thermal and alkaline decomposition of these simpler substances should yield a less complex mixture of products, more susceptible to analysis and capable of yielding more information concerning the mechanism of the reactions.

Levi, Zuckerman and Purves (1) first undertook the preparation of a cellulose-6-nitrate. The method was based on the experimental evidence provided by Hearon, Hiatt and Fordyce (2) that trityl cellulose is largely composed (90-93%) of 6-monotrityl anhydroglucose units. The preparation consisted of the acetylation of trityl cellulose, replacement of the trityloxy group by

nitrate groups and subsequent deacetylation to cellulose-6-mononitrate. Their work suggested tnat instead of the expected monotrityl cellulose diacetate a monotrityl cellulose monoacetate was obtained which, on nitration, yielded a cellulose mononitrate monoacetate. In other words, a steric hindrance effect appeared to operate in the acetylation and nitration steps. The implications that such a steric effect would have on the preparation of cellulose derivatives was obviously sufficiently important to warrant further investigation and the present Thesis had this original objective.

A repetition of the synthesis of Levi, Zuckerman and Purves (1) gave similar, but not identical results. It was found that the standard acetyl analyses employed by them were faulty. After better analytical methods for acetyl were developed it was possible to reinterpret their results. Hearon, Hiatt and Fordyce's (2) proof, based on the "Oldham - Rutherford Rule" (21), that suitably prepared monotrityl celluloses are largely (90%) substituted at the primary position, was substantiated in a variety of ways. Hindrance effects were encountered in the substitution of certain cellulose derivatives. The results indicate that a portion of the nitrate and p-toluene sulfonyl groups in certain cellulose derivatives, which were replaceably by iodine through the action of sodium iodide in acetone, occupied secondary positions.

An attempt was made throughout tne Thesis to interpret the results, together with the relevant portions of published carbohydrate chemistry, from the standpoint of modern, electronic, chemical theory.

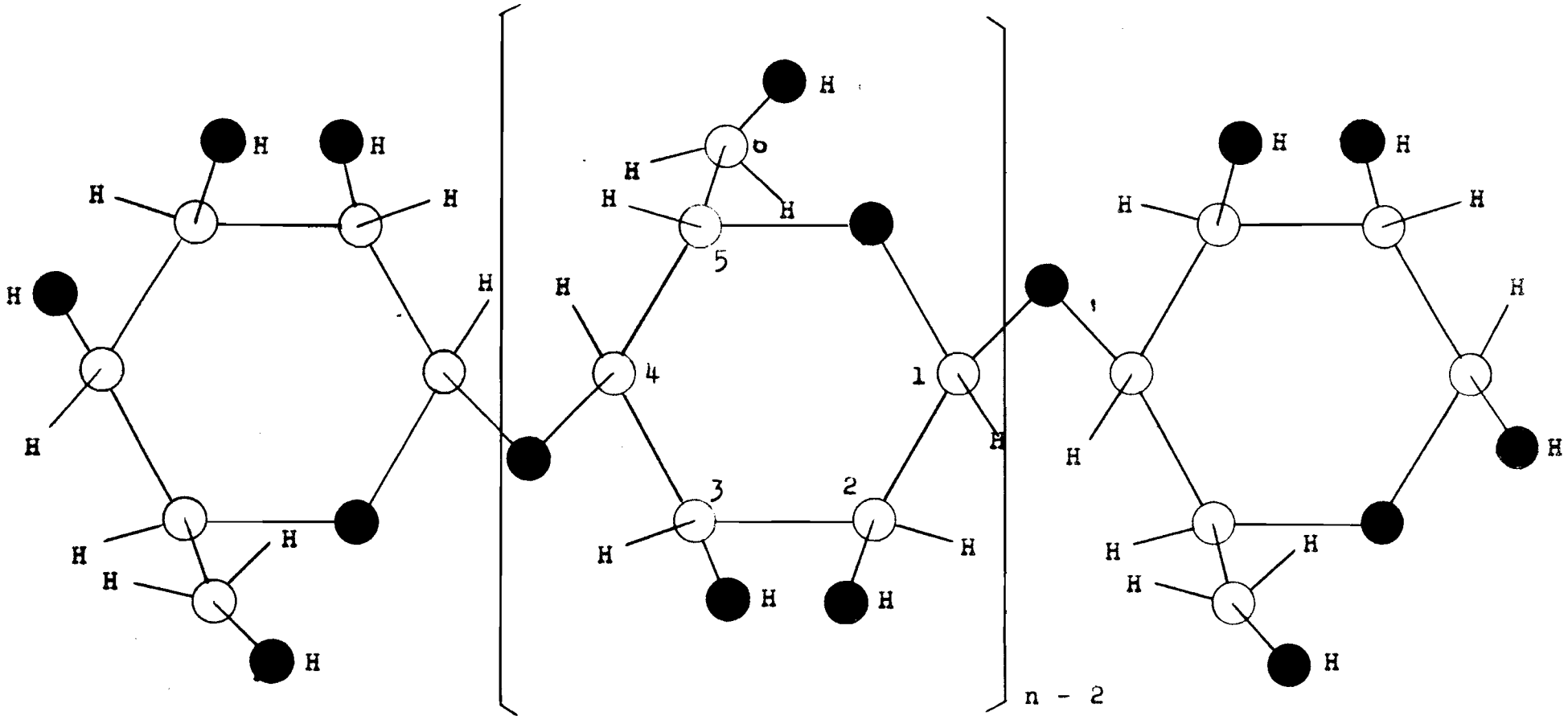
HISTORICAL INTRODUCTION

There are so many readily available reviews and text-books (4,5,6) covering the physical and chemical properties of cellulose and its derivatives that this survey need only deal with the specialized literature having a direct bearing on the present research.

A comprehensive historical survey of theories about the structure of the cellulose molecule has been made available recently by Purves (7). Cellulose has been established as a natural high polymer the building units of which are β-glucose units condensed through the 1 - 4 positions as shown in Figure I.

Since all but one (the terminating unit of the open chain) of the reducing groups of glucose are involved in the glycosidic linkages between the individual anhydroglucose units, cellulose lacks the reducing properties of sugars and all its non-degradative reactions are a result of its hydroxyl groups. Since n-2 of the anhydroglucose units possess three free hydroxyl groups and n is generally in the order of 100 to 1000, the additional pair in the terminating units can be neglected in ordinary stoichiometric considerations. Inspection of Figure I makes it clear that each anhydroglucose unit contains one primary alcohol group, one secondary alcohol unit adjacent to the glycosidic (mixed acetal) carbon atom, and another which is not adjacent. Equal amounts of these three kinds of hydroxyl group are therefore present in cellulose.

Figure I



Cellulose

○ - carbon atoms, ● - oxygen atoms

The reactions of cellulose resemble those which are observed with simple glycosides. Under suitable conditions the hydroxyl groups may form addition compounds with alkalis, alcoholates with highly electropositive metals such as the alkalis or thallium, and a wide variety of esters and ethers with esterifying and etherifying reagents. These reactions have led to many cellulose derivatives of great industrial importance.

However, the conversion of raw cellulose into uniform products entails difficulties which arise from its complex physical properties (8). X-ray examination (9) has led to the conclusion that the cellulose fiber is a sponge-like structure that is partly crystalline and partly amorphous. The crystalline localities are the result of chain segments coalescing into a three dimensional oriented arrangement, while the amorphous regions are loosely packed, unoriented chain segments which are responsible for the very large internal surface of the cellulose fiber. It is extremely probable that the crystalline regions are the result of hydrogen bonding between various hydroxyl groups (10) of one chain and hydroxyl or acetal oxygen atoms on an adjacent chain. The reactions of the cellulose fiber are therefore highly heterogeneous and take place first at the internal surface (accessible fraction). Penetration of, and further reaction in, the densely packed crystalline regions follows more slowly. The conditions required for the expansion of the crystal lattice are highly varied, the extent of reaction and uniformity of product depend on many variables such as the type of reagent used, its

concentration, the reaction medium, temperature, pretreatment of the fiber, etc. (11).

To overcome the difficulties in causing cellulose to react uniformly, it has been found advantageous to disorganize as completely as possible the crystalline regions. This object can be accomplished by the use of reagents which are able to form addition compounds with cellulose and thus swell or even dissolve the fibrous structure. These compounds, which may be formed with alkalis, ammonia, amines, cuprammonium ion, inorganic acids and quaternary ammonium salts, are rather unstable and may be readily decomposed by water or dilute acid to regenerate a more amorphous cellulose commonly termed "regenerated cellulose". This regeneration has been accomplished by the hydrolysis of cellulose esters such as the xanthate or acetate (12). Regenerated cellulose is much more readily accessible to all types of reagents (13) and its reactions, although still heterogeneous, are believed (14) to approximate those carried out in homogeneous solution. The procedure has made possible the preparation of a wide variety of fairly uniformily substituted cellulose derivatives under conditions which would otherwise merely have brought about a superficial reaction with the cellulose fibers. Often the esterification and etherification reactions are carried out on the swollen cellulose addition complexes themselves. "Alkali cellulose" the product resulting from the interaction of strong sodium hydroxide solutions and

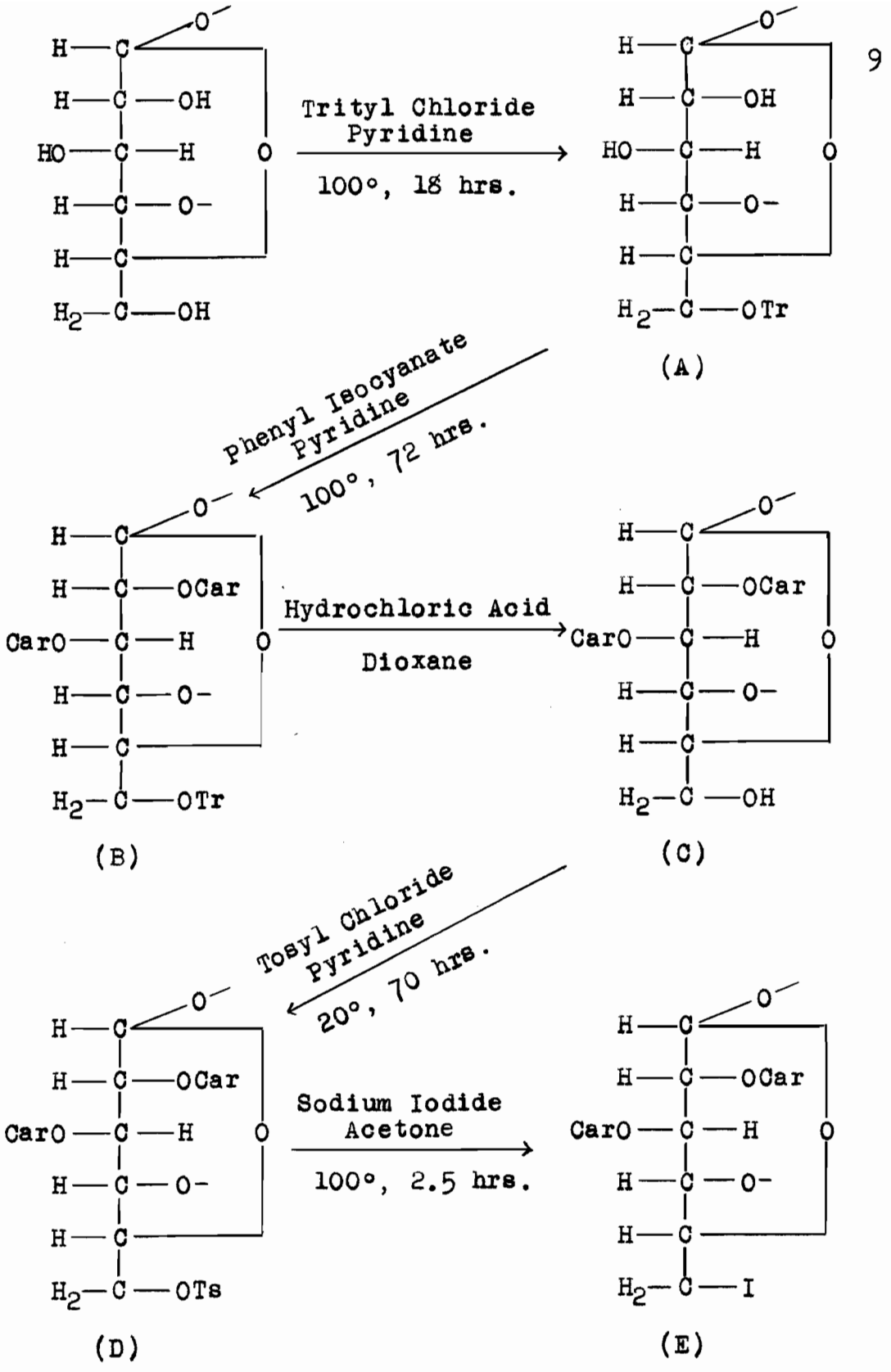
fibrous cellulose, is an intermediate in virtually all industrial preparations of cellulose derivatives.

There are limited number of reactions which may be carried out on cellulose in homogeneous solution. Some examples are, the etherification of cellulose dissolved in aqueous quaternary ammonium hydroxides, the partial hydrolysis of cellulose triesters (15), and the substitution of the free hydroxyl groups in partially substituted cellulose derivatives which are soluble in the reaction media. In such cases the cellulose would be expected to behave merely as a polyhydroxy compound and every one of the hundreds of hydroxyl groups along the macromolecules would have an equal chance to react. The products obtained should therefore be substituted in a random distribution of uniform average density along the length of the cellulose chains (14). Evidence to support this view consists of the complete and increased range of solubility shown by products prepared in homogeneous systems and the uniformity in substitution of the fractions of varying degrees of polymerization which can be separated.(16).

The different reactivities found among the hydroxyl groups of simple polyhydroxy compounds is well known (17) and would suggest that the three kinds of hydroxyl groups in cellulose would possess differences in reactivity. However, since the substitution of dissolved cellulose is a random reaction, the derivatives formed are a perfectly continuous series of products which gradually change in physical properties as the substitution increases. Until substitution is complete, the relative

amounts of reaction undergone by the three kinds of hydroxyl group would be different.

Helferich and Koester (18) have found that highly swollen cellulose and starch react with trityl chloride in pyridine solution to form monotrityl derivatives. The degree of specificity of this reagent for primary hydroxyl groups (19) suggested that the aromatic residue is situated for the most part in the 6-position of the anhydroglucose units. Although the conditions required to bring about this etherification are much more strenuous than those used to tritylate secondary alcohol positions of certain carbohydrates (19), Hearon, Hiatt and Fordyce (2) were able to contribute the following evidence that at least 90% of the trityl groups occupy the primary hydroxyl positions of the cellulose molecule. They showed (20) that phenyl isocyanate reacts readily and, in general, completely with all free hydroxyl groups in cellulose or its derivatives. Since the resulting phenyl carbanilide is extremely resistant to both alkaline and acid hydrolysis, it was chosen as a suitable substituent for blocking the free hydroxyl groups in monotrityl cellulose (A). Monotrityl cellulose dicarbanilate (B) was prepared and the trityl groups were hydrolysed in dioxane - aqueous hydrochloric acid solution to yield a cellulose dicarbanilate (C). This derivative condensed rapidly with excess p-toluene sulfonyl chloride (tosyl chloride) in pyridine and the tosyloxy group in the product (D) was readily replaceable by iodine on heating with sodium iodide and acetone at 100° for only two and one-half



Tr = $-C(C_6H_5)_3$, Car = $-CONHC_6H_5$, Ts = $-SO_2C_6H_4CH_3$

hours. Since this product (E) contained 0.90 iodine atoms per anhydroglucose unit, the same molar amount of trityl groups was allocated to the 6-position of the cellulose molecule. This allocation was made on the basis of the Oldham - Rutherford rule (21) for the selective displacement of primary, as distinct from secondary, tosyloxy groups by iodine under the conditions employed (22).

Helferich and Koester (18) first studied the acetylation of monotrityl cellulose. Their analytical results indicated that a monoacetate formed while monotrityl starch yielded a product with 1.5 acetyl groups per anhydroglucose unit. Acylation of the monotrityl cellulose with monochloroacetyl chloride yielded a product of substitution 1.5 according to the halogen content. Sakurada and Kitabatake (23) claimed the preparation of a monotrityl cellulose diacetate through the action of acetic anhydride on monotrityl cellulose in pyridine solution. Their product, however, analyzed for only 1.78 acetyl groups per anhydroglucose unit. Detritylation in chloroform solution containing dry hydrogen chloride yielded a "diacetyl cellulose" which analyzed for 1.57 acetyl groups per anhydroglucose unit. More recently, Shorigin and his collaborators (24) confirmed Helferich and Koester's earlier view that monotrityl cellulose forms an acetate of substitution 1.5. Levi, Zuckerman and Purves, on the other hand, recently described a monotrityl cellulose monoacetate (1).

Methylation of monotrityl cellulose with dimethyl sulfate or with methyl iodide and silver oxide proceeded slowly and trityl

groups began to split off after one methyl group per anhydroglucose unit was introduced. Although it must be remembered that the above observation may have originated in local acidity during the alkylation, certain trityl ethers are alkali sensitive (25).

Helferich and Koester also showed that the Chugaev - Zerevitinov method for the determination of free hydroxyl groups accounted for approximately two active hydrogen atoms per anhydroglucose unit in monotrityl cellulose. Shorigin and his collaborators (24) could not prepare the xanthate of monotrityl cellulose presumably because no complex formed with concentrated sodium hydroxide. This effect was attributed to loss of alcoholic properties owing to the presence of the heavy trityl groups. However, more recently, Rogovin, Makarova-Zemlyanskaya and Shein (26) succeeded in xanthating monotrityl cellulose by means of carbon disulfide in pyridine, pyridine-chloroform or chloroform potassium hydroxide solution, the latter medium giving the highest degree of xanthation. The product was insoluble in 4-6% aqueous sodium hydroxide but soluble in pyridine-chloroform. The degree of substitution apparently varied between half and one xanthate group per anhydroglucose unit.

On nitration of a monotrityl cellulose "monoacetate" in chloroform solution by the addition of a phosphoric anhydride-nitric acid mixture (27) Levi, Zuckerman and Purves (1) obtained a "monoacetyl" cellulose mononitrate, and not the expected monoacetate dinitrate. Controlled saponification of this product removed the acetyl group preferentially to yield a cellulose

derivative which analysed very closely for a cellulose mono-nitrate. Confirmation and extension of these results formed the basis for the present research.

Although there is much controversy over the structure of "alkali-cellulose" it has been largely agreed that cellulose forms definite addition complexes with sodium hydroxide (28). Various methods of investigation (29) all tend to indicate that in solutions containing less than 35% sodium hydroxide an alkali-cellulose compound is formed corresponding to the approximate formula, $(C_6H_{10}O_5)_2.NaOH$ (30). Evidence for the formation of another compound, $C_6H_{10}O_5.NaOH$, in concentrations above 35% is not so clear.

Studies on the structure of cellulose xanthates probably throw most light on the structure of "alkali-cellulose" since the xanthation consists merely of mixing "alkali-cellulose" with carbon disulfide at room temperature. Lieser (31) showed that xanthate groups are replaced by methyl groups when the former are subjected to the action of diazomethane. This agent was supposed to leave all free hydroxyl groups unsubstituted (32). He obtained a partially methylated cellulose having approximately one methoxyl group per anhydrocellobiose unit. On hydrolysis with sulfuric acid, the methyl cellulose yielded a mixture of monomethyl glucose and unmethylated glucose. It was later shown (33) that at least a small proportion of the methyl groups were located in the 2-position. Although x-ray evidence does not support this indication for uniform substitution throughout the cellulose fiber (34), the fractionation of the diethyl chloro-

acetamide derivative of a normally prepared cellulose xanthate, substitution about 0.5, yielded fractions which showed very little difference in degree of substitution (35). The indication accordingly was that the xanthate groups were uniformly distributed over all chains and that the cellulose xanthate could not consist of a mixture of unequally and unevenly substituted cellulose chains. For example, it was pointed out by Cramer and Purves (36) that only cellulose acetates which average 2.1 to 2.6 acetyl groups per anhydroglucose unit are soluble in acetone. Such soluble products must be prepared by the partial hydrolysis of the triacetate, rather than by the partial esterification of cellulose. These observations were taken to suggest that true acetone solubility depends not only upon the numerical ratio of acetyl to hydroxyl group but also on their relative distribution along the macromolecules.

As pointed out earlier in this review, the reactions of cellulose are very similar to those of simple polyhydroxy compounds. For this reason many of these reactions have been interpreted by drawing analogies with the behavior of monosaccharides, especially glucosides (37). Percival and his collaborators recently published the results of investigations which render doubtful the value of such analogies. Heddle and Percival (38) were able to show that addition compounds of the type $C_7H_{14}O_6.KOH$ could be isolated from the interaction of α- and β-methylglucosides and potassium hydroxide. Methylation of these compounds with dimethyl sulfate under mild conditions yielded a product

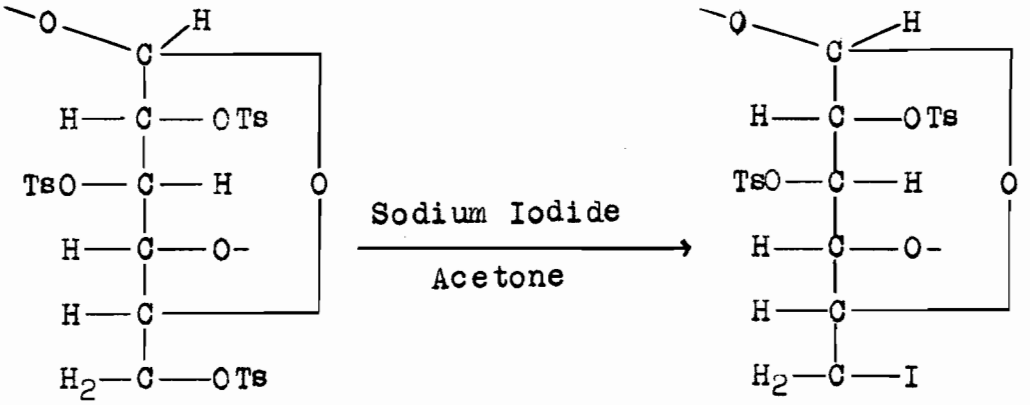
from which 6-methyl glucosazone was isolated. On the assumption that methylation took place at the point of attachment of the potassium hydroxide, it was concluded that the primary position was the most active toward potassium hydroxide complex formation. Percival and Ritchie (39) found that cellobiose formed the complex $C_{12}H_{22}O_{11}$.KOH in which it was clearly shown that the potassium hydroxide was attached to the reducing group since crystalline β-methylcellobioside heptaacetate was isolated from the product resulting from methylation of the complex and subsequent acetylation of the partially methylated product. In addition, by using more concentrated alkali the complex $C_{12}H_{22}O_{11}$.2KOH was formed and was converted to a monomethyl methylcellobioside with the methyl group occupying the primary position of the non-reducing glucose unit of cellobiose. It is remarkable that a change in configuration of the glucosidic linkage is sufficient to alter the result. Maltose appears able to form tri- as well as mono- and di-potassium hydroxide derivatives and a dimethyl methylmaltoside was isolated. On hydrolysis of the partially methylated product 2-methyl glucose and 2,6-dimethyl glucose were isolated as derivatives. Sucrose yielded a tri-potassium hydroxide derivative which, on treatment with dimethyl sulfate, yielded trimethyl sucrose with the methyl groups occupying the three primary positions. Although galactose utilized only one mole of potassium hydroxide, with the point of complex formation at the reducing position, Percival and Ritchie (39) found that lactose formed di- and tri- derivatives. The positions occupied were shown to be

the reducing position of the glucose unit and the second and fourth positions of the galactose unit. Although no explanation was given for this anomalous behavior of lactose, wherein secondary hydroxyl groups reacted preferentially to primary ones, it was inferred that the reactions of polysaccharides need not be analogous to those of their component monosaccharides. An extension of this technique to amylose and cellulose potassium hydroxide addition compounds of the type, $(C_6H_{10}O_5)(KOH)_x$, resulted in partially methylated derivatives, the hydrolysis of which, yielded glucose and partially methylated glucose derivatives (40). Most of the methyl groups were shown to occupy the 2-position in amylose and the 2- and 3-positions in cellulose. The fact that in neither case were derivatives of the expected 6-methyl glucose isolated pointed to a lack in similarity between the reactions of these polyglucosides and glucose. It is unfortunate that these enlightening results were not more firmly established by a more quantitative treatment. However, there can be little doubt that the general conclusions drawn from this work are valid.

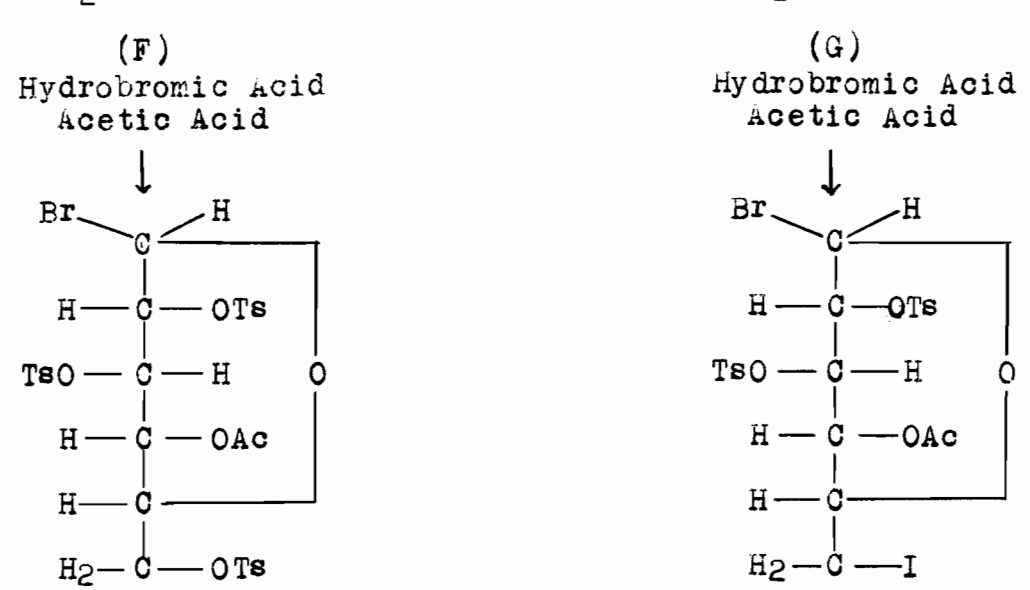
Caesar and Cushing (41) assembled molecular models of D-glucose, amylose and cellulose employing Fisher - Hirschfelder models in which relative atomic size, valence length and direction are probably not far from reality. Inspection of these molecular models led to interesting conclusions with respect to the stereorelations between the hydroxyl groups, especially those in the primary positions. The primary hydroxyl groups on the amylose model are free to rotate 360° and protrude from the outside of a

spiral chain. They appear to be equally accessible to reagents. In the cellulose molecule the primary hydroxyl groups are wedged tightly and cannot rotate (45° play is allowed in certain rotational positions). This rotational freedom in starch plus the accessibility of the primary hydroxyl groups would imply that the primary hydroxyl groups may play a relatively more important role than in cellulose. A further observation which may prove to be important is that the spacing between the hydrogen of the primary hydroxyl and the oxygen of the secondary hydroxyl in the 2-position is so close that chelation might be expected. In considering such steric relations, the effect of spacial configuration, as noted by Hatch and Adkins (42), on the replacement value of alcohols in ester alcoholysis, should probably be kept in mind.

Hess and his coworkers carried out some interesting experiments which seem to be in accord with the conclusions of Caesar and Cushing regarding the relative reactivity of starch and cellulose. They showed that starch swollen in pyridine reacts with tosyl chloride at temperatures below 20° to yield tritosyl starch (F)(43). Iodination of this derivative in sodium iodide and acetone yielded ditosyl monoiodostarch (G). These two starch derivatives, when degraded with hydrobromic acid in glacial acetic acid, gave a 78.7% yield of 1-bromo-tritosyl-acetyl-hexose (H) and 85.1% of 1-bromo-ditosyl-acetyl-iodohexose (I) respectively (44). The latter substances were converted to the methyl glucosides, which were identified as 2,3,6-tritosyl-4-acetyl-β-methyl-



(F)



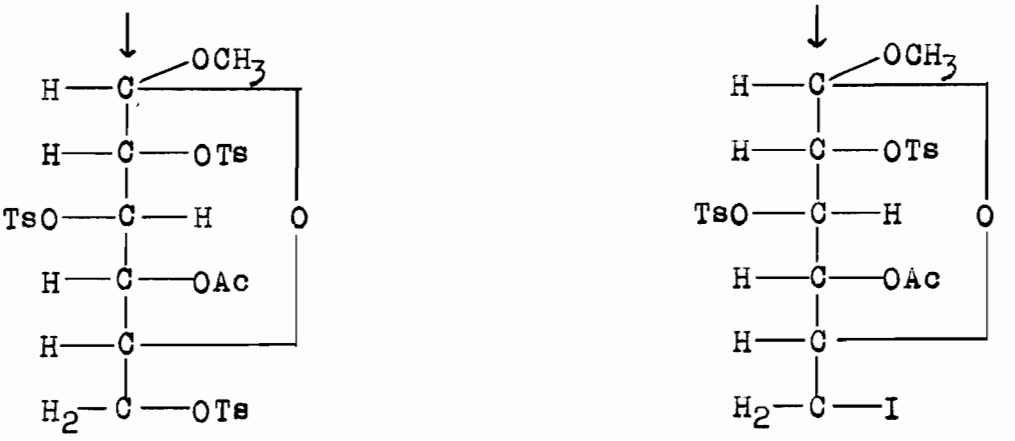
(G)

Hydrobromic Acid
Acetic Acid

(H)

(I)

Silver Oxide
Methanol



(J)

(K)

glucoside (J) and 2,3-ditosyl-4-acetyl-6-iodo-β-methylglucoside (K), respectively (45). These observations provide definite proof, that at least tritosyl starch iodinates preferentially at the primary position. At higher temperatures, the product obtained on the tosylation of starch was a ditosyl-monochloro derivative (43). The position of the chlorine atom in this derivative does not seem to have been established although analogy with the corresponding iodo derivative suggests that chlorine would enter position 6. Hess and Ljubitsch (46) studied the tosylation of cellulose swollen in pyridine. Tosylation with tosyl chloride at 15 to 20° gave products containing two tosyl groups per anhydroglucose unit with only slight amounts of chlorine (0.2%) and nitrogen (0.7%). When the temperature was raised a complex product was formed which contained large amounts of sulfur, chlorine and nitrogen. In order to prevent the introduction of chlorine, Bernoulli and Stauffer attempted the tosylation of cellulose with tosyl anhydride (47), however reaction did not take place. On the basis that 1-chloro-2,3,4,6-tetratosyl-glucose is formed by condensing glucose with tosyl chloride in pyridine solution, they have suggested that the traces of chlorine found in ditosyl cellulose are mainly situated at the reducing carbon of degraded cellulose chains (48).

Wolfrom, Sowden and Metcalf (49) condensed cellulose swollen in pyridine with methyl sulfonyl chloride (mesyl chloride). As with the tosylation, the reaction proceeded approximately to the dimesyl stage and the product contained negligible

amounts of chlorine and nitrogen. The initial part of the mesyl content versus time rate curve rose rapidly and continuously and no break could be detected at the monomesylation stage. With long periods of time, the sulfur content of the product decreased.

Differences in reactivity between the three hydroxyl group positions have been observed for reactions of cellulose or its derivatives, other than that of tritylation. These reactions represent a wide variety of types as inspection of the following list will make evident.

(1) Carré and Mauclère (50) found that the treatment of cotton with thionyl chloride in pyridine resulted in the introduction of one atom of chlorine for each anhydroglucose unit. The product was however dark in color and almost a powder.

(2) Segall (51) was able to denitrate cellulose trinitrate in pyridine-hydroxylamine solution selectively to yield a cellulose dinitrate which was stable to further action by the same reagent at room temperature. When hydroxylamine hydrochloride was substituted for the hydroxylamine, the nitrate group was removed oxidatively to produce an oxycellulose-mono-oxime dinitrate.

(3) By allowing furoyl chloride to act upon cellulose in the presence of pyridine, a cellulose trifuroate was obtained by Kobe and Montonna (52). When this triester was hydrolyzed, one furoyl group appeared to be more firmly bound than the other two. They suggested that the more resistant unit was probably the one attached to the primary hydroxyl group.

(4) Formic acid (98%) is capable of esterifying cellulose

at room temperature (53) but proceeds only to the monoformate state. This esterification would seem analogous to the corresponding formylation of starch in which the substituent has been definitely shown to occupy the primary position. The proof consisted of quantitatively accounting for the unesterified 2, 3-positions by oxidation with periodic acid (54). Although the catalytic formylation of cellulose yields the triester, there seems to be a tendency for formylation to stop at the diformate stage (55).

(5) Sodium metal dissolved in liquid ammonia reacts with cellulose to yield cellulosates. A difference was noted in the reactivity of the three hydroxyls (56) since hydrogen corresponding to one hydroxyl group per anhydroglucose unit was rapidly liberated while the other two were slow to react.

(6) Champetier and Viallard (61) have shown that after a sufficiently long time all the hydroxyl groups of cellulose exchange hydrogen with deuterium. This indicates that the reaction takes place not only in the amorphous but also in the crystalline regions. Mark and his collaborators (62) have recently substantiated the observation by King and Ouellet (63) that the exchange rates of deuterium oxide with hydroxyl groups in cellulose is a multistep reaction and that in most cases the take-up of deuterium starts rather rapidly and, after a certain time slows down to a zero-order process which continues over a long period of time. This initial rapid reaction corresponds to the substitution of one deuterium atom per anhydro-

glucose unit. However, it was pointed out that more experimental evidence is required before the assumption can be made that all the primary hydroxyl groups, whether inside or outside of the crystallized regions, exchange faster than the secondary ones.

The behavior of cellulose toward deuterium exchange (and toward alcoholate formation with sodium) may, of course, have been caused by the ratio of accessible to crystalline cellulose in the samples used.

Studies on the distribution of substituents in various cellulose derivatives have furnished interesting data regarding the reactivity of the various free hydroxyl groups in these substances.

Mahoney and Purves (57) devised an interesting method for investigating the distribution of ethoxyl groups in an ethyl cellulose whose degree of substitution was 2.48 ethoxyl groups per anhydroglucose unit. Tosylation, followed by iodine replacement of the certain tosylexy groups, indicated the presence of 0.124 free primary hydroxyl groups. Unimolecular rate relations were applied to the tosylation data, since the rate of tosylation was determined in twelve-fold excess of acyl chloride. Substraction of the tosyloxy groups replaced by iodine from the molar amount introduced after various times of tosylation left differences which were taken as corresponding to the progressive esterification of free secondary hydroxyl groups. The reaction involving the introduction of tosyloxy groups replaceable by iodine was

shown to be sharply completed after two hours. On plotting the values corresponding to the tosylation of secondary positions against time in days, a curve was obtained, the shape of which suggested that esterification of these hydroxyl groups consisted of a very slow, first order reaction superimposed on a faster one which was complete in a day. Mathematical analysis of this rate curve showed that the data agreed very closely with a unimolecular, fairly rapid tosylation of 0.151 mole of hydroxyl superimposed on a slow tosylation of 0.245 mole. Lead tetraacetate oxidation showed this ethyl cellulose to contain a negligible number of unsubstituted α-glycol units in the 2, 3-positions (58). The cellulose ether was a high grade technical material prepared in heterogeneous reactions with alkali-cellulose. Assuming a purely random distribution of ethyl groups a minimum number of 0.037 glycol groups should have been present (59). Degradation in ethanolic hydrogen chloride yielded partly substituted ethylglucopyranosides which periodate oxidation showed to contain 0.25 to 0.29 glycol unit in the 3,4-positions. Oxidation of the corresponding mixture of reducing sugars with lead tetraacetate revealed the presence of 0.13 to 0.15 mole of glycol in the 1,2-position. These data, combined with those from the tosylation experiments, made it clear that the ethyl cellulose had 0.151 mole of free hydroxul groups per anhydroglucose unit in the second position and 0.245 mole in the third. The first order rate constants of the tosylation of the free hydroxyl groups showed a relative reactivity of 1:33:215 for the

third, second and sixth positions, respectively.

Data for the rate of tosylation of an acetone-soluble cellulose acetate containing 2.44 acetyl groups per anhydroglucose unit, interpreted in a similar manner (60), led to the conclusion that 0.198 mole of the 0.56 mole of free hydroxyl group was in the sixth position, 0.223 mole in third and 0.139 mole in the second. The ralative reactivities of the three positions toward tosylation in pyridine solution were 1:20.5:223 for the third, second and sixth positions, respectively. The allocation of these reactivities to these positions in the order given was by analogy with the ethyl cellulose results. Because of different steric and other effects caused by the different substituents, there is no reason to expect the rates for the tosylation of ethyl cellulose to be exactly the same in magnitude as those for acetyl cellulose. However, these effects could hardly be large enough to obliterate or reverse a ratio of rates, one of which is twenty or thirty times the other. This reasoning was used to justify the above analogy. The samples isolated from the tosylation mixture after seven days of reaction had undergone partial chlorination, presumably caused by the action of the pyridinium chloride liberated in the course of the reaction. It was pointed out that no such replacement complicated the equally prolonged tosylation of ethyl cellulose. Since the acetone-soluble acetate used contained more free hydroxyl group (0.223 mole) in the third position than elsewhere, at first sight it appeared that this position must have deacetylated

most rapidly during the production of the acetone soluble acetate from the parent cellulose triacetate. This apparent anomaly was accounted for by assuming that the original "triacetate" contained a few unacetylated hydroxyl groups in the sluggishly reacting position three.

Earlier work, by Cramer and Purves (35), consisted of arresting tosylation after the initial rapid reaction, when 0.19 moles had been introduced. Most of this amount was presumably in the primary position because iodination, followed by reductive degradation, gave a 12% yield of isorhamnose tetraacetate. The latter substance was recovered in only 50% yield in a control preparation from 6-tosyl-α-methylglucoside.

Quinlan (64) studied the products resulting from the oxidation in homogeneous solution of the same acetone-soluble cellulose acetate used by Cramer and Purves (35). The latter showed that the acetate contained approximately 0.25 mole of free primary hydroxyl group. The oxycellulose acetates resulting from the oxidation by permanganate or chromium trioxide in acetic acid solution had undergone no loss of acetyl and their degree of polymerization (viscosity method) was always greater than half that of the original acetate. These observations made it clear that the oxidizing agents had attacked, almost exclusively, the free hydroxyl positions.

The theoretical uronic annydride content of these oxycelluloses, calculated on the assumption that all the free

primary positions were preferentially oxidized to carboxyl groups, was 17%. However, oxidation of this material, with sufficient oxidant to make two oxygen atoms available per primary hydroxyl, yielded oxycelluloses with only 8.6 to 12% uronic anhydride content. The reaction with the free primary positions seemed preferred since oxidation with only one oxygen atom available yielded an oxycellulose containing 6.3% uronic anhydride. This carboxyl group content represents 75% of the oxidant consumed.

Chromium trioxide was shown to be the more suitable oxidizing agent since it caused less degradation than permanganate. A glacial acetic acid solution of chromium trioxide has been used to prepare sugar acids; e.g., Haworth and Wiggins (65) have recently used this mixture to oxidize 2,4:3,5-dimethylene glucitol to dimethylene saccharic acid. Gladding and Purves (66) have used this reagent to oxidize highly amorphous cellulose. Their analyses for carbonyl and carboxyl groups in the resulting oxycellulose showed that the chromium trioxide used in its preparation could be nearly quantitatively accounted for.

INTERPRETATIONS, ON THE BASIS OF MODERN CHEMICAL THEORY, OF SOME PORTIONS OF CARBOHYDRATE CHEMISTRY RELEVANT TO THIS THESIS

Although this research is concerned with the reactions of the complex cellulose molecule, electronic considerations will play an important part in the interpretations suggested for the experimental results. So few attempts of this nature have been made in the field of carbohydrates that there is little to be gained from the past experience of others. Isbell (67) has recently offered electronic explanations for various reactions involving unsaturated carbohydrate linkages. With this exception, only miscellaneous special applications, such as that suggested by Dorée and Healy (68) for the action of ozone on cellulose, have been put forward. Nevertheless, most scientists consider the electronic theory generally valid (69), applicable to chemistry as a whole, and comprising one of the most powerful means for gaining satisfactory interpretations of the rate and path followed by organic reactions (70). It seems reasonable that whatever tools it provides, for the interpretation and correlation of experimental facts, should be earnestly and constantly applied in all fields of chemistry, including carbohydrates. In the long run the theory should be able to cope with the more subtle and acute problems of chemistry. As stated by Adkins and Adams (71), "Such problems as the relationship of the constitution of substances to their physiological action, or of the

processes involved in the elaboration of products in plant or animal tissue, possibly must wait for their solution upon a thorough knowledge of the relationship of structure to those factors which determine the course, extent and rate of reactions".

The molecular model which serves as a basis for the modern electronic theories of reactions is one that visualizes a space distribution of atomic nuclei around which the extra-nuclear electrons form a continuous statistical distribution of electron density of quantized states and resonance. All chemical changes are pictured as electrical transactions resulting in electronic systems of greater stability. The electrical specification of a molecule requires a knowledge of the positions and the mobility of the electron densities, that is, with the state of polarization of the system and with its polarizability. The state of polarization and the polarizability of a molecule depend on the kinds of atoms involved in its composition and in the manner in which they are linked (type of bond) in positions relative to each other. The reactions of carbohydrate molecules have revealed the existence of acetal, hemiacetal, hydroxyl and glycol groupings. The distinctive feature of the electronic configurations of these groups is the presence of two unshared electron pairs in the valence shells of the oxygen atoms.

Owing to the higher effective nuclear charge of an oxygen atom relative to carbon, a permanent inductive displacement of electron density toward the oxygen atom will take place. That is, there will be an unequal sharing of the electron pair of

the covalent bond, in favor of the oxygen atom, creating a centre of low electron density on the carbon atom. This deficit is overcome in part by secondary inductive displacements in adjacent links, and by a similar mechanism is transmitted with successive diminution to more distant atoms in the system. This characteristic increases as the effective nuclear charge (or electronegativity) of the hetero atom becomes larger; i.e., as the atom moves to the right in the Periodic Table, N < O < F, etc. It also follows that the particular degree of electronegativity displayed by an atom is dependent on the electronegativity of the other atoms attached to it. These inductive displacements, designated as I effects, represent a relatively permanent condition of the molecule and determine the positions of the electron densities in the molecule.

As a result of the inductive effects of chlorine and oxygen, alkyl halides and ethers will react with electropositive reagents more readily than the parent hydrocarbons (72) and will undergo direct substitution preferentially on the α-carbon. The introduction of an hydroxyl or alkoxyl group in an aliphatic system containing the carboxyl group results in an increase in the "strength" of the acid (73). The presence of two hetero atoms in close proximity in an organic system will lead to an enhanced reactivity of the system. The reactivity of α-halogenated ethers is well known and the hemiacetal equilibrium (74) which is common to all sugars is a result of this activity,

$$X\text{-}CHOH\text{-}OR \rightleftharpoons XCHO + HOR$$

The deformability of an hetero oxygen atom and the tendency of its unshared electron pairs to engage in electromeric effects (i.e., electron donor activity) are properties related to the mobility of the electrons in the valence shell. These characteristics have an inverse relationship to the polarization effects so that the more electronegative an hetero atom, the less polarizable will be its electrons. Electromeric displacements are dynamic and are called into being only in a manner to aid a reaction. The development of a critical electron density at the site of reaction is considered an essential feature of the development of the energy of activation.

The tautomeric mechanism for electron displacement can only operate in conjunction with unsaturated linkages since they involve a change in octet affiliations of one or more electron pairs. Since only saturated carbohydrate derivatives will be dealt with, its characteristics need not be fully discussed. However, the electromeric properties of oxygen are so well displayed when linked to unsaturated and aromatic structures that a few examples will be given in order to gain an insight into the extent of its polarizability. Furan is an example of such structures, which have been termed by Robinson (75) as heteroenoid systems. In these structures the hetero atom tends to increase its covalence with the α-carbon of the unsaturated system and as a result the electron donor activity of the hetero atom may be transmitted to the β-carbon. Pauling (76) has considered 8% of the structure of furan to be constituted of the

resonance structures thus made possible. The most stable types of oxonium compounds are the cyclic structures derived from the pyrones. This stability of pyrylium and pyroxonium salts has been attributed to an ability of the conjugated unsaturated system to dissipate the high residual charge on the oxygen atom by means of resonance effects (77). That the ability of the unsaturated system to do this is dependent on the polarizability of the oxygen atom is made clear by the fact that cyclopentadiene exhibits no resonance energy.

The inductomeric effect also depends on the polarizability of the atoms linked in a molecule and is called into play by a change in the electrostatic environment. It, however, differs from the tautomeric effect in that it does not involve change in octet affiliations of any electron pair. There seems to be some conflict as to when an inductomeric effect ceases to be such and passes into the realm of tautomeric mechanism (78).

Inductomeric effects involving covalently linked oxygen are most commonly displayed in coordination processes where it acts as an electron donor. This activity of the oxygen atom leads to the formation of oxonium compounds, which are postulated as intermediate complexes in a wide variety of reactions. The oxonium complexes derived from simple alcohols are well known to be highly active systems and their behavior involves a consideration of a variety of alternative courses of reaction. Since the proton acceptor activity (basicity) of an hetero-oxygen atom is largely associated with its polarizability, which

in turn is dependent on the state of electronegativity of that oxygen atom, it is not surprising to find that the basicity is largely determined by the electronegativity of the groups to which the oxygen atom is attached (79). This interaction between a proton donor and an oxygen atom is an example of a phenomenon termed hydrogen bonding. The factors which regulate the stability of hydrogen bonds have not yet been worked out in detail, but it is becoming evident that the more electronegative the atom to which the hydrogen is bound, the greater the coordinating tendency of the hydrogen atom. Therefore, in alcoholic hydroxyl groups, R-O-H, increasing electronegativity of the R group increases the lability of the hydrogen atom and the alcohol is said to be more "acidic" in nature. On the other hand, increasing electron release by the R group augments the mobility of the unshared electrons in the oxygen atom and there is increasing tendency for the alcohol to form the cation component of the complex.

The esterification and etherification of hydroxyl groups are in part related to the lability of the O-H bond. In dealing with a specific reaction it is essential to formulate a definite reaction mechanism and to take into account the type of displacement that will facilitate or impede the necessary electronic change. An important consideration is that an increase in the "acidity" of an alcoholic hydroxyl group is accompanied by a consequent weakening of its nucleophilic properties. It is highly probable that a nucleophilic attack by the alcohol is a major

step in virtually all the reactions of hydroxyl groups.

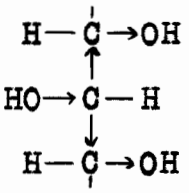
While a great variety of information has been accumulated with regard to the properties and reactions of alcoholic hydroxyl groups varying in "acidity" from tertiary aliphatic alcohols to some primary alcohols such as benzyl, the consideration for theoretical reasons of alcoholic hydroxyl groups of more highly "acid" nature has been extremely limited. For the purpose of this Thesis an alcoholic hydroxyl group is defined as, "any hydroxyl group attached to a carbon atom whose dissociation into proton and anion is not obviously enhanced to any appreciable degree by intramolecular resonance structures such as have been shown to exist for carboxylic acid and phenolic hydroxyl groups (80)". It follows that the varying "acidities" of such alcoholic groups are brought about purely by the inductive mechanism and are dependent on the electronegativities of the other groups in the molecule. The scarcity of information available on highly "acidic" alcoholic hydroxyl groups is undoubtedly connected with the limited number of stable compounds containing an hydroxyl group attached to the same carbon as one or more highly electronegative groups. The enhanced activity of the hydroxyl usually leads to a molecular decomposition,

$$X\text{-}CHOH\text{-}OR \longrightarrow XCHO + ROH$$

$$X\text{-}CClOH\text{-}R \longrightarrow X\text{-}CO\text{-}R + HCl$$

An examination of the molecular structure of polyhydroxy alcohols serves to illustrate that in all probability these substances contain hydroxyl groups attached to carbon atoms of

low electron density because of the -I effect of the electronegative oxygen atoms linked to the adjacent carbon atoms.



These groups of substances (together with the sugars and their glycosides) may therefore contain hydroxyl groups whose behavior toward a given reagent may differ to a marked degree, in both reactivity and extent of reaction, to that of aliphatic alcohols. It will be the purpose of the following section to review the reactions of simpler carbohydrates in an attempt to detect to what degree this postulation is true.

In the field of tautomerism, ease of methylation has long been regarded as a criterion of mobility of the proton. The methylation of certain phenyl alcohols under identical conditions yielded the following percentages of methyl ether (81),

$PhCH_2OH$ - 64%

$PhCH_2CH_2OH$ - 19%

$PhCH_2CH_2CH_2OH$ - 5%

$PhCH_2CH_2CH_2CH_2OH$ - 0%.

Thus it was assumed that methylation with dimethyl sulfate and alkali is rendered easier by the proximity of a phenyl group. Since there are many examples of the phenyl group having an electron attracting influence; e.g., phenyl acetic acid is stronger than acetic acid, it was concluded that proximity of

the phenyl group increased the ionic character of the O-H bond by induction.

Percival (82) pointed out that "the isolation of eighty authenticated compounds from various carbohydrates and alkalies which appear to contain the metallic hydroxide and sugar in stoichiometric proportions (83) seems to preclude the possibility that the phenomenon is due to adsorption or to a fortuitous precipitation of the metallic constituent along with the sugar residue. In particular, when both the reacting hydroxide and sugar are soluble in the reaction medium, simple mixing affording a precipitate of the compound, it would seem clearly a case of chemical reaction". He objected to the suggestion (84) that the acidity exhibited by sugars was due to enolic forms because such an explanation could only apply to reducing sugars. While similar compounds have been isolated through the action of alkali on sucrose, α- and β-methylglucosides, amylose and cellulose (85). He therefore concluded that the normal hydroxyl might be acidic.

By using the glass electrode as a reference electrode, the amounts of a base bound by glucose, fructose, sucrose and lactose at various pH values have been determined and the apparent dissociation constants calculated. This work (86) confirmed earlier observations (87), using an hydrogen electrode, and showed that each sugar had at least two dissociation constants.

There is therefore ample direct evidence for the acidic nature of sugar hydroxyls. That this acidity is due to -I effects at the carbon atom to which the hydroxyl is attached is supported

by a variety of evidence; for example, the high acidity of glyceric and gluconic acids (88). That chloral hydrate is a normal valence compound and not a complex of the type RCHO--H_2O seems to have been firmly established (89,90). The stability of the hydrate has been attributed to the strongly electrophilic nature of the carbon atom of the carbonyl caused by the high electronegativity of the attached trichloromethyl group. In this respect it is noteworthy that Wolfrom (91) has shown that aldehydo-galactose pentaacetate forms crystalline carbonyl addition compounds with alcohols and water which by their distinctive rotations were shown to be true valence compounds. Brigl and Muhlschlegel (92) obtained an aldehydo-pentabenzoate of glucose which crystallized as an alcohol addition compound. The fact that such compounds did not from with the acetate, although the mutarotation exhibited by the acetate in alcohol showed the formation of such structures in solution, indicates that the nature of the substituent groups incluences the polarity of the carbonyl group. Späth (93) has shown that compounds of the type $RCH(OAc)_2$, formed through the action of acetic anhydride on aldehydes, are most readily obtained when the group R is highly electronegative; e.g., CCl_3-, C_6H_5-, C_6H_5-CH=CH-. Micheel (94) and Wolfrom (95) have prepared fully acetylated aldose sugars in which the carbonyl group was in the diacetate form. These properties of acyclic sugars may be taken as strong evidence for the electronegative nature of the groups attached to the carbonyl group.

Meerwein and his coworkers (96) isolated $CCl_3-CH(OCH_3)_2$ from the reaction of diazomethane with chloral hydrate in ether solution. They considered this result a proof that the hydrate was a normal valence compound and that its methylation was possible because of the high "acidity" of the hydroxyl groups. Dimethyl sulfate in the presence of alkali was used by Maguene (97) for the preparation of methyl glycosides. That the compound $C_6H_{12}O_6.KOH$ can be readily isolated from an alcoholic solution of glucose and potassium hydroxide has already been mentioned, see Page 34. Percival (98) showed that by a single treatment of this potassium glucosate with pure methyl sulfate under mild conditions, apart from unchanged glucose, β-methylglucoside and its α- isomeride could be obtained as the crystalline acetates. For all the reducing sugars (maltose, cellobiose, lactose, galactose) the hemiacetal hydroxyl was found to be most readily methylated under these conditions. These results would indicate that the hemiacetal hydroxyl in sugars is the most "acidic" in character. This increased acidity is probably comparable to that of the hydroxyl groups in chloral hydrate and attributable to the ring oxygen atom attached to the same carbon atom. It is probable that an analogy exists between the formation of β,β-dichloro vinyl acetate on the reduction of chloral diacetate or chlorochloral acetate with zinc dust and acetic acid (99) and the formation of glycals on the similar reduction of acetohalogen sugars (100).

The hemiacetal hydroxyl group also possesses distinctive

basic properties in that it readily enters many reactions of the type,

$$HO\overset{-}{\underset{}{-}}\overset{+}{C}H-O^{-} + R\overset{+}{-}X \rightarrow X\overset{-}{-}\overset{+}{C}H-O^{-} + R\overset{+}{-}OH.$$

Superficially its reactions with acetyl halides resemble those of tertiary aliphatic alcohols. Acetyl chloride reacts with primary and secondary aliphatic alcohols to form acetates, hydrogen chloride being evolved, while with the tertiary aliphatic alcohols the alkyl chlorides are formed with the liberation of acetic acid (101). Wolfrom (95) showed that acyl halides interact with the hemiacetals of aldehyde sugars and 1-chloro, 1-bromo and 1-iodo derivatives could be prepared. The reaction of hexose pentaacetate with halogen acids in glacial acetic acid (102) is reminiscent of the behavior of triphenyl methyl acetate under similar conditions. Furthermore, it is notable that triphenyl carbinol reacts extremely readily with acetyl chloride to form triphenyl methyl chloride. The properties of tertiary alphatic alcohols are attributed to electron release by the electropositive alkyl groups, while the groups attached to the central carbon atom of triphenyl carbinol and to the reducing position of cyclic sugars, although in each case highly polarizable, are strongly electronegative. It would seem clear, therefore, that the electronic interpretation of these reactions must be different.

Direct evidence for the high electronegativity of the triphenyl methyl group is accumulating. Garner and Hellerman (103) attributed the reactions of certain compounds containing as a

substituent the β,β,β-triphenylethyl grouping as due to the electron attracting influence of the phenyl groups in the triphenylmethyl group; e.g., the ready formation of β,β,β-triphenylethyl chloramine.

The generally accepted explanation of the existence of free triphenylmethyl is that the affinities of the central carbon atom are exhausted by the three phenyl groups to such an extent that it is incapable of forming hexaphenyl ethane. Although Hückel (104) refuted the theory, it has been recently reinstated by Shorigin and Machinskaya (105). It is possible that steric hindrance is a factor of appreciable magnitude (106). However, it has been shown that the stability of triphenylmethyl, either as a free radical or as an ion, is due to resonance stabilization (107). The fact that this stability is increased by the substitution for the phenyl groups of napthyl or p-diphenyl groups which offer more resonance forms, is strong evidence in favor of attributing the instability of hexaphenyl ethane largely to an electronic effect. That the basicity of triphenyl carbinol is related to these electronic effects is supported by the observation (108) that the influence of substituting the methyl group in the para position is less than that of a methoxy substitution. It is probable that the methoxy group, because of its unshared electrons, increases the conjugated system. Pauling (109) pointed out that the ionic character of a bond is determined by the importance of the ionic structure ($A^+ B^-$) when the nuclei are at their equilibrium distance. The

tendency to ionize in solution is determined by the relative stability of the actual molecules in the solution and the separated ions in the solution. Therefore, the amount of ionic character of a bond should not be confused with its tendency to ionize in a polar solvent. Nevertheless, there is a certain parallelism between the ionic character of a bond and its ionizability. In view of these considerations it seems probable that the basic properties of the hemiacetal hydroxyl group of reducing sugars are connected with a high ionic character of the C-O bond. Furthermore, it would seem that the ionic character (polarity) of C-OH bonds is high for highly electropositive and for highly electronegative carbon atoms. In the former case this is readily attributable to a high reduction potential of the carbon atom. The latter is, however, more difficult to visualize. Evidence from triphenylmethyl derivatives would indicate that it is due to a higher stability of the carbonium ion. This stability arises from certain resonance possibilities, which exhaust the valence affinities of the carbon atom.

Nearly all substances containing a conjugated system which includes an oxygen atom show halochromism. Halochromism is the ability of these substances to form highly colored salt-like products with strong acids. Ohle and his coworkers (110) have pointed out that the reaction of monoacetone glucose derivatives with hydrobromic acid is not limited to the formation of ring isomeric glucosyl bromides but is complicated by a side reaction

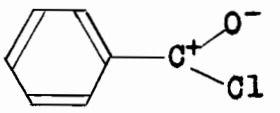
giving compounds with more firmly bound bromine. Parallel with this bromination there appears the characteristic color reaction of halochromism. This effect was shown to be dependent on the type and position of acyl group substituted at the free hydroxyl groups of the monoacetone glucose. They therefore concluded that the furanose ring structure of these glucose derivatives can be so stabilized by suitable esterification that it remains completely unaltered under conditions which normally decompose it. This effect of the nature and position of substituents on the production of halochromism suggests the existence of certain electrical properties of the sugar molecule which are not as yet understood but which undoubtedly will prove to have an important bearing on the properties of these substances.

A comparison of the alcoholysis of acyl chlorides (111) with the alcoholysis of triaryl methyl chlorides (112) in ether solution was offered by Hinshelwood, Laidler and Timm (113). These reactions were formulated as an electrophilic attack, by the highly electronegative carbon atom of the halogen compound, at the alcohol oxygen atom. Remick (114) pointed out that the activation energy for the reaction of ethanol with diphenyl methyl chloride is much greater than with triphenyl methyl chloride. He interpreted the increase as due to the greater stability of the transition state complex with the triphenyl methyl compound, relative to the diphenyl compound, because of the greater number of resonating structures made possible by the additional

phenyl group. In general, it would be expected that resonance, and hence reaction rate, would be increased by any continuation of the conjugated system of a phenyl group by unsaturated groups in the ortho or para positions, or by atoms having unshared electrons. The reaction rate would also be increased by +I groups because they would lessen the electronic constraints in the phenyl nuclei and thus aid resonance. The rates of alcoholysis of substituted triphenyl methyl chlorides are in essential agreement with these principles; they decrease in the order,

$$p\text{-OMe} > p\text{-Me} > H > p\text{-Halogens} > p\text{-}NO_2.$$

In the alcoholysis of benzoyl chloride the situation in regard to resonance is reversed, since resonance is present in the initial compound,



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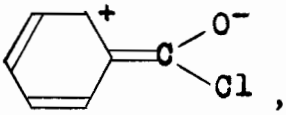


, etc.,

and presumably is destroyed when the addition complex is formed. Thus in this case, groups that augment the resonance decrease the reaction rate. The success of this interpretation was clear in that the rates of alcoholysis of substituted benzoyl chlorides increased in the order,

$$p\text{-OMe} < p\text{-Me} < H < p\text{-Halogens} < p\text{-}NO_2.$$

Since the alcoholysis of triaryl methyl chlorides and acyl chlorides is brought about by an electrophilic attack of the halogen compound at the oxygen atom of the hydroxyl group, the rate of alcoholysis is naturally also dependent on the nucleophilic properties of the oxygen atom and on its polarizability.

General experience in organic chemistry has made it evident that, as a rule, primary alcohols will undergo esterification and etherification reactions most readily, although the mobility of the unshared electrons in the secondary and tertiary aliphatic alcohols is greater. This circumstance has been related to the decreasing lability of the O-H bond on progressing from these primary to the tertiary alcohols. The observation by Freudenberg and Hess (115) that tertiary alcohols cannot be tosylated was substantiated by Gilman and Beaber (116). Helferich, Speidel and Toeldte (117) were unable to tritylate tertiary alcohols although they were able to prepare the trityl ethers of a variety of secondary aliphatic alcohols under mild conditions. Josephson (118) made similar observations.

In the field of carbohydrates it has long been recognized that as a rule the primary alcoholic groups show a definite preference towards acylation. Einhorn and Hollandt (119) described a dibenzoyl mannitol prepared by the action of a limited amount of benzoyl chloride upon mannitol. Muller (120) isolated a dibenzoyl-D-sorbitol by acylating D-sorbitol under similar conditions. Hockett and Fletcher (121) have since proved that these compounds were the 1,6-benzoyl derivatives. Lieser and Schweizer (122) found that the partial benzoylation of β-phenyl-D-glucoside led to the formation of the 6-benzoyl derivative in in high yield. Tosyl chloride has also been shown to react preferentially with the primary hydroxyl groups of polyhydroxy compounds. Compton (17) was able to isolate 6-tosyl-α-methyl-

D-glucoside triacetate in 36% yield and 6-tosyl-β-methyl-D-glucoside triacetate in 41% yield from the reaction mixture resulting from the action of a limited amount of tosyl chloride on the two isomeric glucosides. The rates of reaction of diacetone-D-glucose, diacetone-D-galactose and diacetone-L-sorbose with tosyl chloride in pyridine were studied by Hockett and Downing (123). They were able to show that for these compounds the ones containing a free primary hydroxyl group reacted much more readily. Helferich and Gnüchtel converted α-methylglucoside directly to the 6-mesyl derivative in good yields by the action of mesyl chloride in pyridine solution.

Since Helferich and his coworkers first introduced the use of trityl chloride for the preparation of trityl ether derivatives of a wide variety of alcohols (117), it has been widely experienced that the primary hydroxyl groups of polydroxy compounds generally react most readily with this reagent. This technique rapidly developed into a powerful synthetic tool in the field of carbohydrate chemistry. The preference of this reagent for primary hydroxyl groups seemed so marked that many investigators (125,126,127) made use of the reaction as an analytical method for the determination of the presence and number of primary hydroxyl groups. There developed a widespread but erroneous impression that the etherification is confined entirely to primary positions. However, Hockett and Hudson (128) demonstrated that α-methyl-D-fucopyranoside and β-methyl-D-arabinopyranoside readily tritylate at secondary hydroxyl posi-

tions and that several glycosides which contain only one primary position yielded dityrityl derivatives. Indeed, β-methyl-D-xyloside, which contains no free primary hydroxyl group, yields two isomeric monotrityl derivatives on tritylation for fourteen days at 20° and these same results are obtained with a reaction time of only one and one half hours at 100°. Zeile and Kruchenberg (129) recently reported the preparation of dityrityl derivatives of D-xylose, L-arabinose, D-ribose and the tritrityl derivatives of D-fructose and L-sorbose. It is therefore evident that trityl chloride is not a selective reagent for primary alcoholic hydroxyl groups.

Hockett and his coworkers (130) published important results on the comparative rates of tritylation and tosylation of diacetone-D-glucose, diacetone-L-sorbose and diacetone-D-galactose. When a large excess of trityl chloride was used, the tritylations conformed closely to unimolecular law with times of half change in the ratio 226:6.6:1 respectively. It was significantly noted that the galactose and sorbose derivatives showed a rather wide difference in speed of etherification although they both contain a free primary hydroxyl group. In comparing these results with those for the rates of tosylation (123) the following conclusions were drawn, (a) tosyl chloride reacts faster with all the substances than trityl chloride under the same conditions, (b) the velocity ratios are of the same order of magnitude for the three substances in the reactions with either chloride. That is, the selectivity is characteristic of the alcohol rather than of the

halide. However, it was pointed out (130) that until a large number of substances have been measured, it will be impossible to set the limits between which the primary hydroxyls will vary in reactivity or to state whether this range may ever overlap the range characteristic of secondary hydroxyls.

It is important to realize that such differences in reactivity are not limited to the distinction of primary from secondary hydroxyl groups in carbohydrate derivatives. Variations in reactivity exist among the secondary hydroxyl groups of polyhydroxy compounds which in many cases closely approach in magnitude those found between the average primary and secondary positions.

Compton (17) showed that the differences in spacial arrangement of α- and β-methylglucosides have no effect on the preferential tosylation of the 6-position but stated that among the secondary hydroxyls of aldose sugars the 2-position is usually the most reactive. In certain derivatives, the reactivity of this position may be enhanced by the nature of the other substituents to equal that of the primary hydroxyl group. Lieser and Schweizer (122) found that the partial benzoylation of both α- and β-methylglucoside in pyridine resulted in the formation of 2,6-dibenzoyl derivatives. They pointed out that the reactivity of the secondary hydroxyl group in the 2-position could be lowered by the nature of the other substituents, since the partial benzoylation of β-phenyl-D-glucoside in pyridine solution led to the formation of 6-benzoyl-β-phenyl-D-glucoside in high yield.

Robertson and Griffith (131) obtained 2-tosyl-4,6-benzylidene-α-methylglucoside in good yields through the partial tosylation of 4,6-benzylidene-α-methylglucoside. The partial benzoylation of the latter compound was more difficult to control and yields of the 2-benzoyl derivative were much lower. Bell and Synge (132) reported 6-acetyl-β-methylglucoside-2,3-dinitrate highly resistant toward tosylation at the free 4-position. Hockett and Mowery (133) showed that the tritylation of α-methyl-L-fucopyranoside in pyridine led to an 81.5% yield of the 2-trityl ether. In the case of the β-methyl-D-arabinoside, the reactivity ratio is not quite so favorable to the 2-position. They accounted for 74% of the converted glycoside as being 40% 2-trityl, 28% 3-trityl and 6% a ditrityl ether. An interesting observation was that the retritylation of 2-trityl-β-methyl-D-arabinopyranoside at 60° for ten days yielded no ditrityl ether while the retritylation of the 3-trityl derivative yielded the 2,3-ditrityl ether.

It has been largely implied that these differences in reactivity, between the various hydroxyl groups in polyhydroxy compounds, are caused by steric hindrance effects. In this review, it has so far been largely implied that the variations in reactivity are probably due to a large extent to polar factors, and the reasons for taking this view have been stressed. However, it must be acknowledged that steric hindrance is a nearly universal phenomenon and the operation of this factor must be allowed for in all considerations of reactivity. Hughes and Ingold (134)

envision steric hindrance as a repulsion caused by the interpenetration of electron clouds at very small distances.

Dostrovsky, Hughes and Ingold(135) have made it clear that the important consideration in the discussion of this phenomenon is the spacial configuration of the transition state complex, and that steric hindrance should not be associated with a particular reactant, or a particular over-all chemical reaction but rather with a particular reaction mechanism. It is for this reason that lacking the knowledge of the mechanism involved, evidence concerning the reactivity of organic compounds loses much of its significance. Data that would make it possible, even approximately, to establish the composition and structure of the transition state, together with its internal force system, is extremely limited even for the simplest and most accurately known reaction mechanisms. It is therefore evident that in the consideration of the relative reactiveness of organic compounds little can be done to evaluate the role played by steric hindrance factors. And it must therefore be stressed that any significance attached to the relative reactivity of the hydroxyl groups of a polyhydroxy compound must allow for steric hindrance effects as well as polar effects.

Although little can be done to account for the importance of steric hindrance factors in determining a specific rate, such effects are only quantitatively important; and as pointed out by Hughes and Ingold (134) they seldom seem to alter the direction of the broader distinctions. All qualitative phenomena are

determined by polar influences. Adkins and Adams (71) made it clear that the ease or speed with which a reaction takes place is partially dependent upon the ease or extent to which the electronic system of a compound can be dislocated, presumably in order to pass into the transition state, before reaction may ensue. Moreover, the ease or extent to which a given electronic system must be dislocated (from the state in which it exists in the pure compound) before it forms a new product bears no relationship whatsoever to the relative stability of the electronic systems on the two sides of the equation. However, the extent of the reaction, if reversible, is determined by the relative stability. In reversible reactions, the equilibrium point indicates the relative stability of the electronic systems and is expressed, thermodynamically, as

$$-\Delta F = RT\ln K.$$

In inorganic chemistry, the relative stability of the electronic systems of the ions involved in the reactions commonly termed "oxidation-reduction reactions" can be readily measured potentiometrically. Through the development of the generalized concept of oxidation-reduction (136), it has become recognized that all chemical reactions involve shifts of electrons from one energy level to another and it is now obvious that at one extreme there is a complete loss (or gain); e.g.,

$$Ce^{++++} + Fe^{++} \longrightarrow Fe^{+++} + Ce^{+++},$$

while at the other extreme, to use a simple picture, there is a slight shift of electrons away from (or toward) a given atom.

The particular triumph of this theory is the fact that it makes clear the path followed by many organic reactions. That is, we would not ordinarily expect one reducing agent to react with another. However, its practicability is obscured by the facts that organic reactions are often comprised of competing reactions and also many reactions that should take place; i.e., that are thermodynamically feasible, do not do so unless suitably catalyzed. It is therefore evident that even qualitative changes in the course of a reaction cannot always be reliably interpreted as caused by changes in the particular polar factors under consideration. Nevertheless, it seems reasonable that, if a qualitative change in the products of a reaction occurs, the cause of this change is at least provisionally accounted for by a change in the relative amount and kind of electron density contributed to the bond in question by the atoms which form it. As an example, the reactions employed by Freudenberg and Hess (115) to distinguish aliphatic primary and secondary alcohols from phenols may be considered. If the tosyl derivatives of the former are boiled in hydrazine, hydrazine derivatives of both the alcohol and ester are formed while phenolic tosyl esters give the free phenol and the p-toluene sulfinic acid salt of hydrazine. The reaction with ammonia is a more remarkable qualitative change. Aliphatic alcohol tosyl esters yield p-toluene sulfonic acid and amines while with phenolic tosyl esters, p-toluene sulfonamide results. The variation in products obtained by the action of acetyl chloride upon (a) tertiary aliphatic alcohols, (b) primary

and secondary aliphatic alcohols, (c) triphenyl carbinol, see Page 37, forms another example of qualitative changes brought about in the reactions of alcohols by changes in ionic character of the carbon to oxygen bond.

If the occurence of qualitative differences in the mode of reaction is detected among the various hydroxyl group positions in polyhydroxy compounds, it is believed that, at least under certain conditions, these differences can be interpreted to indicate variations in the electrical status of the carbon to oxygen bonds in those positions.

The enhanced reactivity of the secondary hydroxyl group in the 2-position of glucose has already been mentioned. That this increased reactivity is largely due to polar effects is indicated by the fact that Brigl (137) was able to prepare 2-trichloroacetyl-3,4,6-triacetyl-1-chloroglucose in high yields through the action of phosphorus pentachloride on glucose pentaacetate. It seems unlikely that all of the other three acetyl groups remain largely unaffected because of steric hindrance factors.

Fischer (138) has shown that a preferential replacement of the primary acetyl group takes place when pentaacetyl glucose is treated with liquid hydrobromic acid to yield 1,6-dibromo-2,3,4-triacetyl-glucose. Analogy to the aliphatic alcohols would suggest that the secondary positions would be more labile.

Oldham (139) discovered that the primary nitrate group situated at the 6-position of glucose is replaceable by iodine on

heating with sodium iodide and acetone. Irvine and Rutherford (140) showed that 2,3-dimethyl-6-iodo-β-methylglucoside-4-nitrate can be obtained in good yields by heating the 4,6-dinitrate in sodium iodide and acetone for six hours. This result indicated that the reaction could be used preferentially to replace primary nitrate groups in the presence of secondary ones. However, Bell and Synge (141) showed that if 4,6-ethylidene-β-methylglucoside-2,3-dinitrate is heated in sodium iodide and acetone for only one hour a high yield of the 3-mononitrate derivative is obtained. More recently, Dewar and Fort (142) found that this reaction required a period of heating of about twenty hours, preferably with cooling and release of pressure after ten hours. Thus it was shown that, under these conditions, certain secondary nitrate groups are relatively stable while others are preferentially denitrated to yield the free alcohol. Dewar, Fort and McArthur (143) examined the effect of heating β-methylglucoside-2,3,4,6-tetranitrate in sodium iodide and acetone. They claimed, that under the conditions used, the 4-nitrate group of 2,3-dimethyl-β-methylglucoside-4,6-dinitrate is removed. This fact, together with the enhanced reactivity of the 2-nitrate group in 4,6-ethylidene-β-methylglucoside-2,3-dinitrate led them to expect that the product would consist largely of the 6-iodo derivative of the 3-nitrate. Although evidence was obtained that this compound is formed, it was found that a greater proportion (nearly fourfold) of a product derived from the 6-iodo-2-nitrate resulted. These observations on the behavior of nitrate groups at various

positions of certain β-methylglucoside derivatives make it clear that the stability and type of reaction which takes place is not necessarily determined by the position occupied by the nitrate group (except for the iodination reaction which may be specific for the primary position) but by the nature and position of the other substituents in the molecule. There is also some indication that the denitration of certain secondary positions takes place more readily than the iodination of certain primary groups. It will be shown later, see Page 101, that for cellulose trinitrate, at least one nitrate group is denitrated much more rapidly than the iodination of another (presumably the 6-position). It is therefore unlikely that this difference in mode of reaction between secondary and primary nitrates toward the sodium iodide-acetone reagent can be attributed to steric hindrance influences. It is difficult to understand how the supposedly less sterically hindered primary position can be quantitatively iodinated while a more sterically hindered secondary position is simultaneously more rapidly denitrated. It therefore seems necessary to attribute these qualitative changes to differences in polarity of the nitrate groups. In this respect, it is interesting to note the marked effect the covalent form of nitric acid has in increasing its nitrating power (144,145). Benford and Ingold (146) have shown that nitric acid dissolved in acetic anhydride or nitromethane produces a stronger nitrating agent than nitric acid itself. They believe this is due to the ability of these substances to react with nitric acid to produce

mixed anhydrides, $AcONO_2$ and $CH_2=NO-ONO_2$. Remick (147) has concluded that these results could have been predicted from the knowledge that nitric acid is an electrophilic reagent and hence $X^- - {}^+NO_2$ should be a stronger nitrating agent than $HO^- - {}^+NO_2$ if X is more electronegative than HO.

Murray and Purves (148) studied the effect of solvent and cation on the displacement of the primary nitrate group in cellulose nitrates. Their conclusions were that optimum conditions are an anhydrous medium with a ketone solvent. Sodium iodide proved much superior to zinc iodide, barium iodide or calcium iodide. Since the denitration of secondary nitrates takes place without inversion and is accompanied by the liberation of iodine, the reaction undoubtedly follows a reductive mechanism. A pressure always develops, whether the gas formed is a product of the denitration or of side reactions seems unknown.

Since Freudenberg (149) showed that the tosyloxy group in the 6-position of galactose was replaceable by iodine on heating in sodium iodide and acetone, the application of this reaction in carbohydrate chemistry has become so extensive that it now forms one of the most valuable techniques in the field. On discovering that the replacement in the case of 2,3-diacetyl-4,6-ditosyl- and 2,3,4,6-tetratosyl-β-methylglucosides was restricted to the primary tosyl group and was quantitative, Oldham and Rutherford (21) proposed the reaction as a method for the identification and estimation of the 6-hydroxyl group in glucose derivatives. The reaction was subsequently named the "Oldham-

Rutherford rule". Hann, Ness and Hudson (22) applied the Rule to a large variety of carbohydrate derivatives and found it generally valid. The position of the iodine atom was firmly established in each case by replacement of the iodine by hydrogen and determining the terminal methyl group thus formed.

However, some special structural influences have been discovered which throw doubt on its general applicability. Tipson and Cretcher (150) found that all four tosyl groups of tetratosyl erythritol are removable by sodium iodide and acetone and that the erythritol undergoes extensive change to a volatile product which they identified as butadiene. In view of this observation and the fact that all the tosyl groups in tritosyl glycerol are removable (151) they concluded that the "Oldham-Rutherford rule" is not generally valid. On testing 5,6-ditosyl-1,2:3,4-dibenzylidene-D-sorbitol with sodium iodide in acetone, Hann, Ness and Hudson (22) obtained 1,2:3,4-dibenzylidene-D-sorbitoleen. They therefore concluded that tosyl groups, one of which is attached at a primary and the other at an adjacent secondary hydroxyl position, are both removed by sodium iodide and acetone with the ultimate production of a double bond. It should be pointed out that Bell, Friedman and Williamson (152) treated 6-tosyl monoacetone glucose with sodium iodide and acetone and obtained a sulfur and iodine-free material containing an unsaturated link. Although further examination was not made, it was suggested that the product was probably a 5,6-glucoseen derivative. On the other hand, 6-tosyl-3,5-benzylidene

monoacetone glucose gave a good yield of the 6-iodo compound. It therefore seems that the intermediate CH_2I—CHOTs-, suggested by Hann, Ness and Hudson (22) may not actually be required for the production of double bonds under the conditions of this reaction.

A wide variation in reaction conditions have been experienced as necessary for the iodination of primary tosyloxy groups. Freudenberg and Raschig (153) found that thirty-six hours at 125° are required to iodinate 6-tosyl-di-isopropylidene-D-galactose; 1,4-ditosyl-2,3-isopropylidene-D-xylulose and 1-tosyl-β-diacetone-D-fructose (154), and 1,6-ditosyl-2,3-isopropylidene-L-sorbose (155) all display marked resistance to iodination of the 1-tosyloxy group. For example, Morgan and Reichstein (156) showed that a reaction period of thirty-six to forty-eight hours at 125 to 130° is required for complete iodination of 1,6-ditosyl-2,3-isopropylidene-D-fructose. Levene and Raymond (154) ascribed this resistance to iodination of tosyloxy groups situated at the 1-position of ketose sugars to the influence of the keto group. Tipson and Block (157) found that sodium iodide in acetone has no effect on the tosyl ester of phenol.

Ness, Hann and Hudson (158) recently encountered interesting differences in reactivity toward iodination between the two primary tosyloxy groups of certain sugar alcohol derivatives. They showed that 1,6-ditosyl-2,4-methylene-D-sorbitol preferentially yields the 6-iodo derivative. On prolonging the time of heating the di-iodo derivative was formed, but in low yields

unless the 3,5-positions were protected by acetyl groups. An important observation was that 1,6-ditosyl-2,4:3,5-dimethylene-D-sorbitol behaved in a similar fashion, giving a quantitative yield of 1-tosyl-6-iodo-2,4:3,5-dimethylene-D-sorbitol with sodium iodide and acetone for two hours at 100°. The variation in reactivity, between the two primary positions, was therefore adduced to the influence of the D-sorbitol configuration. It is notable that Haworth and Wiggins (65) found a striking difference in the ease of formation of the 1,6-dibenzoates of mannitol and sorbitol. Whereas mannitol dibenzoate was readily obtained in 80% yield, the yield of sorbitol dibenzoate was never found to exceed 25%. They suggested that the reason for this difference, although not obvious, may be associated in some way with the cis-orientation of the hydroxyl positions in the 2- and 3-positions of mannitol and their trans-orientation in sorbitol. It seems probable that the cause of this apparent resistance toward esterification, of one of the primary hydroxyl groups of sorbitol, is related to the influence which stabilizes the tosyloxy group at the 1-position toward replacement by iodine.

Treatment of certain tosyl-carbohydrate derivatives with sodium iodide and acetone has been observed to yield anhydro derivatives. This type of detosylation has been noticed for both primary and secondary tosylated positions. Müller (159) obtained dibenzoyl-ditosyl-anhydro-mannitol on treating 1,6-dibenzoyl-2,3,4,5-tetratosyl-mannitol with sodium iodide in acetone at 100°. On treating 2,3,7-tritosyl-D-gluco-D-gulo-heptosan-

<1,5>β<1,6> in acetonyl acetone solution with sodium iodide, Montgomery, Richtmeyer and Hudson (160) obtained 2,3-ditosyl-4,7-anhydro-D-gluco-D-gulo-heptosan. Similar treatment of the 4-acetyl derivative yielded 83% of the 7-iodo derivative.

The fact that structural influences have been shown capable of bringing about qualitative differences in the product obtained on treating compounds containing the tosyloxy group at a primary position is sufficient evidence to prove the "Oldham-Rutherford rule" may not be universally applicable. Nevertheless, its general validity, when iodination takes place, would remain unchallenged unless evidence is obtained that secondary tosyloxy groups are replaceable by iodine under the conditions generally used. Dorman (161) conducted a research on the iodine replacement of tosyloxy groups in aliphatic compounds. He was able to obtain 20% yields of sec. butyl iodide on treating sec. butyl tosyl ester at room temperature with sodium iodide and acetone. He therefore pointed out that care should be exercised in drawing conclusions as to structure from experiments based on this reaction. By titrating the residual inorganic iodide following the reaction of certain tosyl derivatives of monoacetone xylose with sodium iodide and acetone, Levene and Raymond (162) found that tosyl ester groups on secondary hydroxyl groups are replaceable by iodine to a small extent, (Table I). Although the primary tosyloxy groups were preferentially replaced, it is evident that the extent of the replacement is not only dependent on the length of time in which the reaction is allowed to proceed but also on the other groups in the molecule.

TABLE I

REPLACEMENT OF TOSYLOXY GROUPS BY IODINE

Monoacetone Xylose Derivative		% Tosyl removed at 100°	
	Group	2 hours	6 hours
5-Tosyl	Primary	67	88
3-Acetyl-5-tosyl	Primary	32	59
3-Benzoyl-5-tosyl	Primary	38	62
5-Acetyl-3-tosyl	Secondary	6	4
5-Benzoyl-3-tosyl	Secondary	3	5

Hess, Littmann and Pfleger (44) found that on heating 2,3,6-tritosyl-4-acetyl-β-methylglucoside in sodium iodide and acetone at 130° for twenty-five hours, a compound analyzing approximately for a di-iodo tosyl derivative was obtained. Although this compound was not crystalline and was never fully characterized, this observation would indicate that under special structural conditions, secondary tosyloxy groups may be as readily replaced by iodine as are certain primary tosyloxy groups, see Page 55. It would therefore seem not out of the realm of possibility that certain structural influences exist that would render a secondary tosyloxy group in a carbohydrate derivative as readily replaceable by iodine as the average primary one.

There is a marked solvent role in the iodide displacement reaction of tosyloxy groups. While it has been shown (163) that for certain tosyl compounds iodo formation is cut from 90% to 40-45% on substituting acetonyl acetone for acetone, in some cases acetonyl acetone seems to be preferred (164). Ness, Hann

and Hudson (158) showed that while 1,6-ditosyl-2,4:3,5-dimethylene-D-sorbitol gives a quantitative yield of the 6-monoiodo derivative when heated at 100° in sodium iodide and acetone, this monotosyl-monoiodo derivative is converted in a 92% yield to the 1,6-di-iodo compound when refluxed with sodium iodide and acetic anhydride for two hours.

Finkelstein (165) has shown that di-iodo compounds having the iodine atoms attached at adjacent carbon atoms cannot be prepared by the action of sodium iodide and acetone on the corresponding dichloro or dibromo derivatives, since the di-iodo compound readily loses iodine to form unsaturated substances. Tipson and Cretcher (150) have pointed out that the formation of butadiene on the treatment of tetratosyl erythritol with this reagent is probably an analogous reaction. Irvine and Oldham (166) applied this method for halogen exchange to 6-bromo-trimethyl-methylglucoside and thus converted it to the corresponding 6-iodo derivative. It was subsequently shown that this reagent could be generally used for the displacement of chlorine atoms situated at primary positions of carbohydrates. However, there are notable exceptions. Littmann and Hess (167) reported 6-chloro-2,3-ditosyl-4-acetyl-α-methylglucoside to be stable. Bell and his coworkers (152) have also found a similarly stable chlorine atom in a chloro-tosyl-3-methyl-monoacetoneglucose.

Hess and his coworkers (44) found that tosyloxy groups in carbohydrate derivatives can often be replaced by chlorine through the action of pyridinium chloride in pyridine. Like the iodination

reaction, it seems to have a preference for primary tosyloxy groups. This chlorine displacement of tosyloxy groups often takes place in the tosylation reaction mixture through the action of the pyridinium chloride released by the tosyl chloride on ester formation. For example, Hess and Pfleger (43) showed that starch swollen in pyridine reacts with tosyl chloride at 18–20° in nine days to give a nearly quantitative yield of tritosyl starch. However, at higher temperatures, the product contains two tosyl groups and a chlorine atom per anhydroglucose unit. Levene and Tipson (168) found that, on tosylating uridine with tosyl chloride in pyridine, they obtained a ditosyl-chloro-uridine which yielded a ditosyl-monoiodouridine on treatment with sodium iodide and acetone.

Bernoulli and Stauffer (48) condensed glucose with tosyl chloride in pyridine for five days at room temperature and obtained 1-chloro-2,3,4,6-tetratosyl-glucose. Although the chlorine atom may have been introduced by the action of pyridinium chloride on a pentatosyl glucose derivative, there is a strong likelihood that the reaction was a direct chlorine-hydroxyl group displacement. For example, Hess and Kinze (169) obtained 2,3,6-tritosyl-4-acetyl-α-chloroglucose on treating 2,3,6-tritosyl-4-acetyl-β-glucose with trityl chloride in pyridine. The halogenation of the hemiacetal hydroxyl of sugars by acetyl halides has already been mentioned.

Hess and Stenzel (37) observed that 2,3-ditosyl-4-acetyl-β-methylglucoside reacts smoothly with tosyl chloride and pyridine

to give the 2,3,6-tritosyl derivative. The α-derivative is unchanged and on heating undergoes chlorination to 2,3-ditosyl-4-acetyl-6-chloro-α-methylglucoside. They extended the reaction to the alpha and beta glucosides themselves. A summary of their data is given in Table II.

TABLE II

"TOSYLATION" OF α- AND β-METHYLGLUCOSIDES

Temp. (°C)	Time (days)	Products isolated
	α-Methylglucoside	
20	16	100% tetratosyl (I)
35	4	25% tritosyl-chloro (II)
65	4	29% tritosyl-chloro (II)
80	4	54% ditosyl-dichloro (III)
	β-Methylglucoside	
20	16	100% tetratosyl (IV)
35	4	100% tetratosyl (IV)
65	4	44% tritosyl-chloro (V)
80	4	35% tritosyl-chloro (V)
95	4	16% ditosyl-dichloro (VI)

Since the tetratosyl and tritosyl chloro compounds react smoothly with pyridinium chloride in pyridine to form dichloro compounds while the α- and β-glucosides themselves are unchanged by such treatment, they concluded that the reaction consists in a replacement of the tosyloxy groups by chlorine. They interpreted their data as follows. The replaceable tosyloxy groups in I, see

Table II, react more readily than those in IV and, therefore, show the same difference in behavior as do the α- and β-forms of 2,3-ditosyl-4-acetyl-methylglucoside. Furthermore, III has the known structure of 2,3-ditosyl-4,6-dichloro-α-methylglucoside (170). The tritosyl-chloro compound (II) reacts with sodium iodide and acetone and a tosyloxy group is replaced by iodine. Assuming the validity of the "Oldham-Rutherford rule" they concluded this displacement to be at the 6-position. Also since III does not react with sodium iodide and acetone and since II gives III with pyridinium chloride in pyridine, they concluded that II was 2,3,6-tritosyl-4-chloro-α-methylglucoside.

The significance of these observations is obvious. There exists a reaction which normally shows some preference for primary positions becoming in a special case significantly preferential for a secondary position. It must be remembered that these conclusions are based on the crystalline derivatives obtained. However, it is evident that since 25% of II was isolated, its formation must have been one of the main reactions. Helferich and Knüchtel (124) have recently published interesting results which concern this apparent enhanced activity of the fourth position of glucose. They have shown that 1,2,3,6-tetracetyl-4-mesyl-glucose can be converted to the corresponding 4-iodo derivative by treatment in sodium iodide and acetone at 135°. The action of this reagent on 2,3,4,6-tetramesyl-α-methylglucoside gave an almost quantitative yield of the 6-iodo derivative.

Helferich, Speidel and Toeldte (117) have pointed out that trityl chloride in pyridine could be used for preparing the trityl ether derivatives of alcohols. They showed that these ethers were remarkably stable to alkali, even in boiling alcohol. However, it was later found (171) that the α- and β-tetraacetates of 6-trityl glucose were unstable in alkali. They showed that in dilute methanolic hydrochloric acid the trityl ethers investigated were converted at room temperature to trityl methyl ether. Most carbohydrate trityl ethers are extremely sensitive to acid. Solutions of halogen acid in glacial acetic acid or chloroform rapidly split the trityl to oxygen bond to yield trityl chloride and the alcohol. Because of this sensitivity to acid, it is probable that pyridine is required in tritylation reaction mixtures in order to take up the liberated halogen acid. Although the majority of trityl ethers yield trityl bromide and the alcohol on treatment with hydrobromic acid, some cases are known where the ether linkage breaks between the carbohydrate group and the ether oxygen, thus yielding triphenyl carbinol and the carbohydrate bromohydrin. For example, Wolfrom, Quinn and Christman (172) have shown that the treatment of 6-trityl glucose ethyl mercaptal tetrabenzoate with hydrobromic acid in chloroform solution always yields the 6-bromo derivative. In the removal of the trityl group from 6-trityl galactose ethyl mercaptal tetraacetate by the action of hydrobromic acid in glacial acetic acid, experiments would

occasionally produce the 6-bromo mercaptal tetraacetate and considerable deacetylation would occur. More recently, Wolfrom, Burke and Waisbrot have found (173) that the detritylation of 1-trityl-2,3,4,5-tetraacetate-L-fucitol with hydrobromic acid in glacial acetic acid solution yields the 1-bromo derivative. Oldham and Rutherford (21) have mentioned that the removal of the trityl residue from a certain secondary position of a glucose derivative is a matter of great difficulty. On the other hand, Hockett and Hudson (128) have taken the sudden decomposition of monotrityl-α-methyl-L-fucoside as possibly indicating a relatively low stability of this compound. Levene and Tipson (168) have reported the 5-trityl derivative of uridine as being extremely unstable. The variation in the relative stability of the two oxygen bonds in carbohydrate trityl ether derivatives indicates that marked differences may exist in the electrical properties of the carbon atoms in carbohydrate residues. This is also evidenced by the marked variations in stability of carbohydrate trityl ether linkages to acid fission.

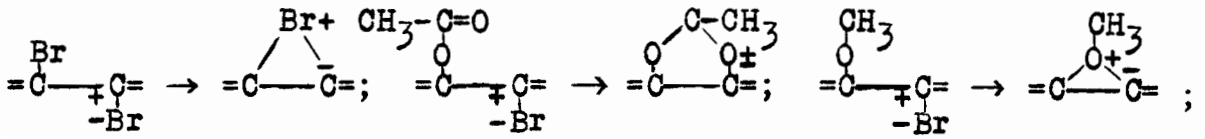
It is believed that the foregoing discussion of the reactions of carbohydrates has made clear certain properties of these substances. First of all, it seems evident that the general chemical properties of the hydroxyl groups found in sugars and polyhydroxy alcohols resemble those of hydroxyl groups found on carbon atoms under the stress of strong electronegative inductive forces. The origin of these inductive effects is undoubtedly due to the presence of the numerous oxygen atoms in these

molecules. The wide variations in properties exhibited by the large number of possible geometrical and optical isomers makes it evident that the spacial configuration of these polar groups relative to one another plays an important role in determining the particular properties of each hydroxyl group. The operation of these influences is probably accounted for by what has been termed the field effect (174). This inductive mechanism is characterized by the fact that the electrical fields of two atoms (not directly bound to each other) interact owing to the transmission of electrical influence directly through space instead of through a chain of electronic linkages. Thus, if the electronegativities of constituent atoms were the only factors involved, fumaric and maleic acids should be equally strong. The fact that they are not is generally interpreted (175) as meaning that their steric differences result in different amounts of electrical influence operating directly through space. It is evident that the magnitude of such field effects would be strongly influenced by environmental conditions, especially solvent, and the problem of disentangling field effects from normal inductive effects is indeed an extremely complex one. In practice it has so far been found impossible to do this and the term inductive effect is used to designate the combined effect of the two mechanisms (176).

An idea of the importance of inductive effects transmitted through primary valence bonds in determining the chemical properties of adjacent groups in carbohydrate derivatives may

probably be gained from the following considerations. Meerwein and coworkers (177) observed that although ethylene glycol is unreactive toward diazomethane in ether solution, the monoacetate will readily form the monomethyl ether derivative. This result was attributed to an increase in the lability of the oxygen to hydrogen bond through the influence of the acetyl group. Similarly, the acid nature of the hydroxyl groups in benzyl alcohol, ethylene chlorohydrin and trimethylene chlorohydrin is rendered sufficiently high for reaction with diazomethane through the introduction of the electronegative phenyl group and chlorine atoms into the inactive methyl, ethyl and propyl alcohols, respectively. An especially pertinent example is the ready methylation of the secondary hydroxyl group in sym. glycerol dichlorohydrin.

Winstein and his coworkers (178) have made it clear that the rates and steric results of replacement reactions of complex compounds with more than one functional group may be dependent on effects by these substituent groups other than their supply and withdrawal of electrons to the seat of reaction by induction or resonance effects. They were able to show that optically active α-acetoxy, α-dibromo or α-methoxy-bromo compounds undergo substitution of the halogen atoms with retention of configuration. This was explained as being due to the interaction of the carbonium ion with the neighboring group to form intermediates such as;



with complete inversion. The reaction of these intermediates with the substituting anion result in a second inversion, thus giving a net retention of configuration. The participation of adjacent groups in this manner seems greatly to influence the ease of the substitution, since the transconfiguration undergoes the substitution reactions more readily. Another example of the influence of configuration on the ease of reaction is the alkaline hydrolysis of tosyl esters (179). The presence of an adjacent hydroxyl in a trans-relation greatly lowers the energy of activation. In this caae interaction also takes place with the formation of an ethylene oxide ring. Both of these reactions involve the formation of an intermediate carbonium ion and since the reaction normally results in Walden inversion (180) the more important steric factors are readily understood.

However, little information is available in the influence of steric factors on the reactions of polyfunctional molecules such as carbohydrates which are not as evidently affected by such interactions. The actual positions in space of the atoms composing the molecules of polyhydroxy alcohols are unknown. however, Hann and Hudson (181) have pointed out that a relation seems to exist between the structures of various methylene and benzylidene acetals of polyhydroxy alcohols and the cis-trans configurations of the hydroxyl groups in the polyalcohol. The spacial configurations of cyclic sugars with cis or trans relationships between adjacent hydroxyls attached to rigid ring

structures have made possible the application of certain reagents which attack α-glycols for the identification of their structures. Such a reagent is lead tetraacetate which in the hands of Hockett (182) has been developed into a powerful tool for the determination of the cis and trans relationships in these substances. In open chain polyhydroxy alcohols, since there is no fixed space relation among the various hydroxyl groups, because of free rotation around carbon to carbon single bonds, configuration showed no effect upon the rate of lead tetraacetate oxidation (183). Boeseken (184) has shown that the configuration of polyhydroxy alcohols can be deduced from their influence on the conductivity of boric acid. Heidt, Gladding and Purves (185) have pointed out that the oxidative cleavage of α-glycols into dialdehyde by periodate or lead tetraacetate is probably preceeded by the formation of a reaction complex of definite spacial configuration and the action of these reagents is consequently dependent on geometrical as well as electronic factors. Drawings suggested that the space between two hydroxyl groups is about 3A° for cis glycols when the groups are coplanar and increases up to a maximum of about 5.5 A° when the groups are in the trans configuration. Thermal energy would always produce some oscillation of the groups and the average distances would be somewhat more and somewhat less, respectively, than those indicated. On these geometrical considerations it would be expected, although with little or no certainty, that substitution reactions, which do not involve inversion, would be

more sterically hindered by a substituent in cis-relation than by one in the trans.

In addition to these cis-trans influences on reaction rate, certain other evidence regarding the spacial configuration of sugar molecules is accumulating which may prove important in this respect. For example, the fact that the alkaline saponification of 6-tosyl (186), 6-nitrate (187), 6-bromo (188) and 6-sulfonyl (189) glucose derivatives yield 3,6-anhydroglucose compounds, and the fact that 2,3-anhydro-β-methylalloside rearranges to 3,6-anhydro-β-methylglucoside (190), have been interpreted as indicating that in the glucopyranose molecule the C_6 atom is situated in space in close proximity to the C_3 atom.

The general subject of the dialdehyde cleavage of α-glycols by periodate and lead tetraacetate has been recently reviewed by Heidt, Gladding and Purves (185). The fact that these two oxidants oxidize glycols in an identical, highly selective way together with the great similarity between the reaction kinetics of their oxidations led them to believe that their underlying mechanisms must depend upon certain common physical features. On the assumption that these oxidants possess residual valencies which enable the central atom to coordinate with two hydroxyl groups, they attached the more rapid oxidation of cis-glycols, in comparison to that of the trans configuration, to the closer proximity of the alcoholic oxygens. The ability of the oxidant to annex an electron from each of the two glycol oxygen atoms

was linked to the oxidant's oxidation potential and to the reduction potential (electronegatively) of the oxygen atoms of the glycol group. For example, the fact that pinacol oxidizes more readily than ethylene glycol in basic solution but more slowly in acid solution was attributed, by Price and Knell (191), to the greater basicity of pinacol (since it is a tertiary aliphatic alcohol). Criegee and Sitzber (192) have shown that although periodic acid is usually a more rapid oxidant than lead tetraacetate in its action as a glycol splitter, this superiority may be reversed with increasing number and size of the groups attached to the α-glycol group. They supposed that the effect of the polar character of the hydroxyl groups is not clearly apparent because of these screening effects. The increased stability of α-hydroxy acids, α-keto acids and oxalic acid to oxidation by these reagents (192,193) may be taken as further evidence that the relative rates of oxidation of various α-glycols are affected by what has been termed (185) the reduction potential of glycol groups. It would also seem reasonable to assume that the large variations in the nucleophilic properties of the hydroxyl groups found in carbohydrates and their derivatives, manifested by the large variations in reactivity toward numerous reagents, would in its own right and independently of steric hindrance effects contribute largely to variations in oxidizability by these reagents.

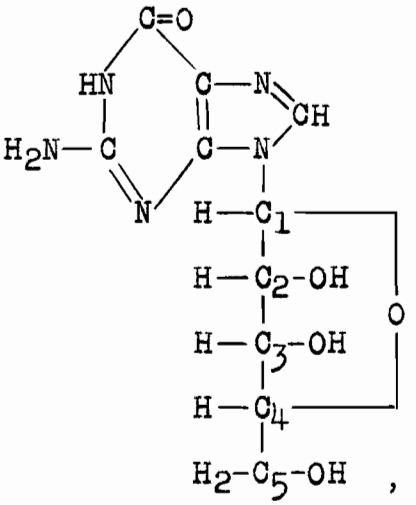
The conclusions drawn from the carefully investigated mechanism of hydrolysis of carboxylic esters have become such common knowledge that their development will not be reviewed. The alkaline hydrolysis of esters has been rather firmly established as a nucleophilic attack on the carbonyl carbon atom by the hydroxyl ion followed by the elimination of the alkoxyl cation which subsequently reacts with water. Ingold and Nathan (194), on the basis of this mechanism, came to the conclusion that an increase in the electronegativity of X or R in the ester X-CO-OR should favor the hydrolysis since the attacking reagent is nucleophilic. This prediction was shown to be generally true. An example of this in carbohydrate chemistry is the preferential saponification of 2-trichloroacetyl-3,4,6-triacetyl-methylglucoside to the 3,4,6-triacetyl derivative in high yields (137).

The sodium methylate catalyzed transesterification of alcohols is known to be a reversible reaction. Consequently, the relative amounts of alcohol found at equilibrium would be expected to depend on the relative amounts of energy in each kind of bond involved in the alcoholysis reaction. The redistribution reaction between certain, suitably catalyzed ester and alcohol mixtures has been shown to result in a random equilibrium mixture; i.e., the composition of the product can be calculated in advance from the law of probability. In other words, there are no directive effects of structure (82). However, it is evident from the results of Hatch and Adkins (42)

that these are only special cases. In the light of such considerations, some observations by Bell and Synge (141) may have important theoretical significance. They pointed out that sodium methylate in methanol will readily remove two acetyl groups from 2,6-diacetyl-β-methylglucoside-3,4-dinitrate. However, the same treatment applied to 6-acetyl-β-methylglucoside-2,3,4-trinitrate is without effect. They postulated that possibly in each case an equilibrium is reached, but in the latter the reaction does not proceed far. This view was supported by the fact that in the former experiment, on evaporation of the solution, an uncrystallizable residue was obtained. Repeated treatment of this residue with sodium methylate yielded a further crop of crystalline β-methylglucoside-3,4-dinitrate. They further pointed out that this behavior is intermediate between that of 4,6-diacetyl-β-methylglucoside-2,3-dinitrate, which is converted quantitatively into the corresponding dinitrate on treatment with sodium methylate under the same conditions, and 6-acetyl-β-methylglucoside-2,3,4-trinitrate, which is not affected. Such equilibrium measurements, being entirely free of all steric hindrance influences, would definitely decide whether or not the large variations observed in the reactions of the various hydroxyl group positions in sugars, polyhydroxy alcohols and glycosides were essentially polar in nature.

Interesting synthetic procedures have been recently introduced which undoubtedly are taking advantage of the variations in acidity among the hydroxyl groups found in carbohydrates.

For example, Gulland and Hobday (195) showed that the phosphorylation of guanosine,



with phosphorus oxychloride in pyridine yields the 5-phospho ester, but phosphorylation with phosphorus oxychloride in saturated baryta yields the 3-phospho esters. Gulland (196) probably correctly explained this variation in reactivity toward esterification by drawing an analogy to the work of Percival which was outlined in the introduction, see Page 13. Since salt formation does not always take place preferentially with primary groups, and since attempts to phosphorylate glucose with phosphorus oxychloride in presence of calcium carbonate (instead of calcium hydroxide or barium hydroxide) met with failure, he concluded that acylation in aqueous baryta is analogous to a Schotten - Baumann reaction which involves reaction between an acylating agent and an alcoholate.

Certain general conclusions regarding the properties of glucose can be drawn from this survey of its reaction,

(1) The first (glucosidic) hydroxyl position. Although less active than the hemiacetal of aliphatic aldehydes, it is very active. Its stability is probably due to the high electronegativity of the rest of the carbohydrate molecule. Removal of the hydroxyl at the 2-position greatly enhances this activity (197) and introduction of highly electronegative groups stabilizes it (198).

(2) The sixth (primary) hydroxyl position. It usually undergoes all the reactions which are ordinarily thought of as preferential for primary hydroxyl groups. However, this activity can be strongly impaired by the introduction of certain types of groups at other positions in the molecule (199).

(3) The second (secondary) hydroxyl position. It has been shown to rival and sometimes surpass the sixth position in certain reactions of particular glucose derivatives (122). The reactivity of this position is definitely influenced by the nature of the other substituents in the molecule (17). In the glucose series it has never been shown to display greater preference than the primary position toward tritylation, iodine replacement of tosyloxy groups and other such reactions which have become largely recognized as specific for primary positions. However, experience with other aldose sugar derivatives indicate that this position may, under favorable circumstances, acquire properties which closely resemble those of what may be termed the average primary hydroxyl position (19). Of the secondary hydroxyl groups in glucose this position is most active in alcoholate formation with thallium metal (199).

(4) The fourth (secondary) hydroxyl position. For certain derivatives, this position has been shown to rival the primary position in reactivity toward certain reagents such as the chlorine displacement of tosyloxy groups (37) and the iodine displacement of mesyloxy groups (124). It may, however, be rendered highly resistant toward tosylation (132).

(5) The third (secondary) hydroxyl position. The only property characteristic of this position is that it remains inconspicuous under the constantly increasing number of reactions which are found and applied for the purpose of characterizing the positions of carbohydrates. Nitrate groups situated in this position have been shown to be largely resistant to denitration by sodium iodide and acetone (142) but this has been shown to be dependent on the nature of the other groups in the molecule (143). It is usually considered the most resistant position toward esterification in the glucose molecule.

Cellulose is a high polymer of glucose linked through the 1-4 positions. From the conclusions which have been drawn regarding the dependency of the reactivity of carbohydrates on factors such as spacial configuration, type and location of substituents, etc., it is reasonable to expect that the reactions of the free hydroxyl positions in cellulose need not be, and most probably are not, analogous to the corresponding positions in free glucose. The glucose unit in cellulose has a highly electronegative, and possibly highly polarizable, group substituted at its fourth position. This substituent must affect its

chemical nature through the inductive mechanism; similarly for the 4-glucose residue substituted at its glucosyl position. Field effects and steric hindrance remain unknown quantities in determining the properties of cellulose. However, the known differences in properties between cellulose and starch, see Page 15, indicate that these effects may well be very important. On the basis of experiments carried out on α-methyl-glucoside-6-nitrate (187), Levi, Zuckerman and Purves (1) expected the alkaline saponification of their "cellulose-6-mononitrate" to yield 3,6-anhydroglucose derivatives. However, no indication for the formation of such an anhydro ring could be found. It is therefore believed that, if any detailed knowledge of the reactions of cellulose is to be obtained, studies on cellulose itself are required.

EXPERIMENTAL

ANALYTICAL PROCEDURES

Standard Solutions and Sampling.

1. Sodium hydroxide solutions were prepared, carbonate free, by the method outlined by Niederl and Niederl (200). All alkali solutions were standardized against dry potassium acid phthalate using phenolphthalein indicator.

2. Sodium thiosulfate solutions, stabilized by sodium carbonate (1 g. per litre), were standardized frequently against dry potassium iodate samples.

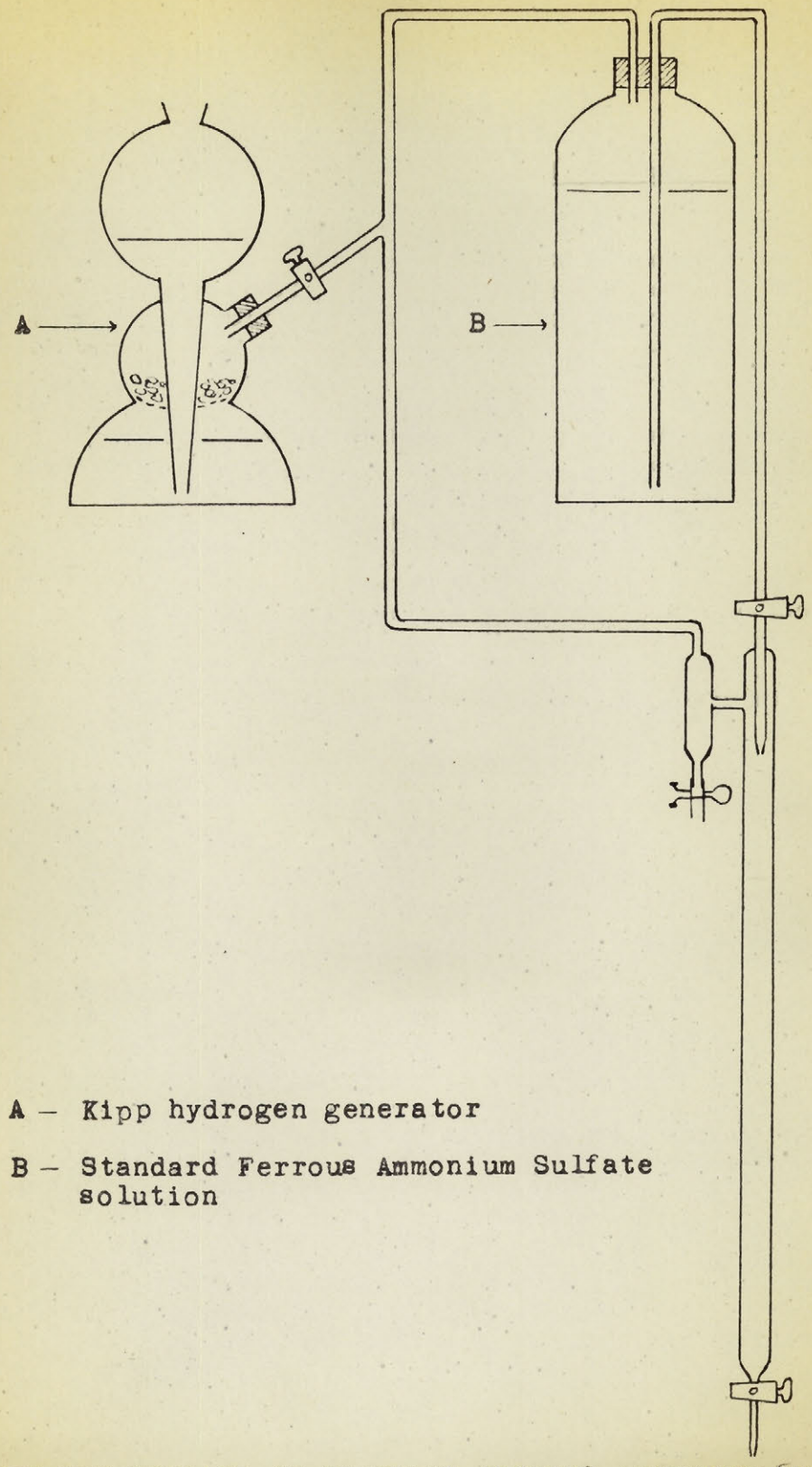
3. All acid solutions were standardized against freshly standardized sodium hydroxide solutions.

4. Ferrous ammonium sulfate, 24 g., was dissolved in 40 ml. of concentrated sulfuric acid and diluted to 2 litres. This solution was stored in an hydrogen atmosphere in an apparatus, see Fig. IA, which was a modification of the method described by Zintl and Reinacher (201).

Ceric ammonium sulfate solution (0.01 N) was prepared in 1 N sulfuric acid solution.

The ferrous ion solution was standardized against standard permanganate and the ceric ion solution against standard sodium thiosulfate solution. Titration of the ferrous ion solution with the ceric ion solution, or vice versa, showed that methyl red was a good dependable reversible redox indicator for these solutions (202). Methyl red indicator solution was prepared

FIG. IA



A – Kipp hydrogen generator

B – Standard Ferrous Ammonium Sulfate solution

APPARATUS FOR STORAGE OF STANDARD FERROUS AMMONIUM SULFATE SOLUTION

by treating 0.2 g. of "Analar" methyl red with 50 ml. of 6 N sulfuric acid solution and diluting to 200 ml.

5. In order to prevent sampling errors, all the cellulose derivatives were reprecipitated from homogeneous solution before analysis. This precaution enabled minute micro-samples accurately to represent the composition of the whole product. Unless otherwise stated, the samples were dried *in vacuo* at 65° just previous to weighing to five decimal points in grams by means of an accurate semi-micro air-damped balance.

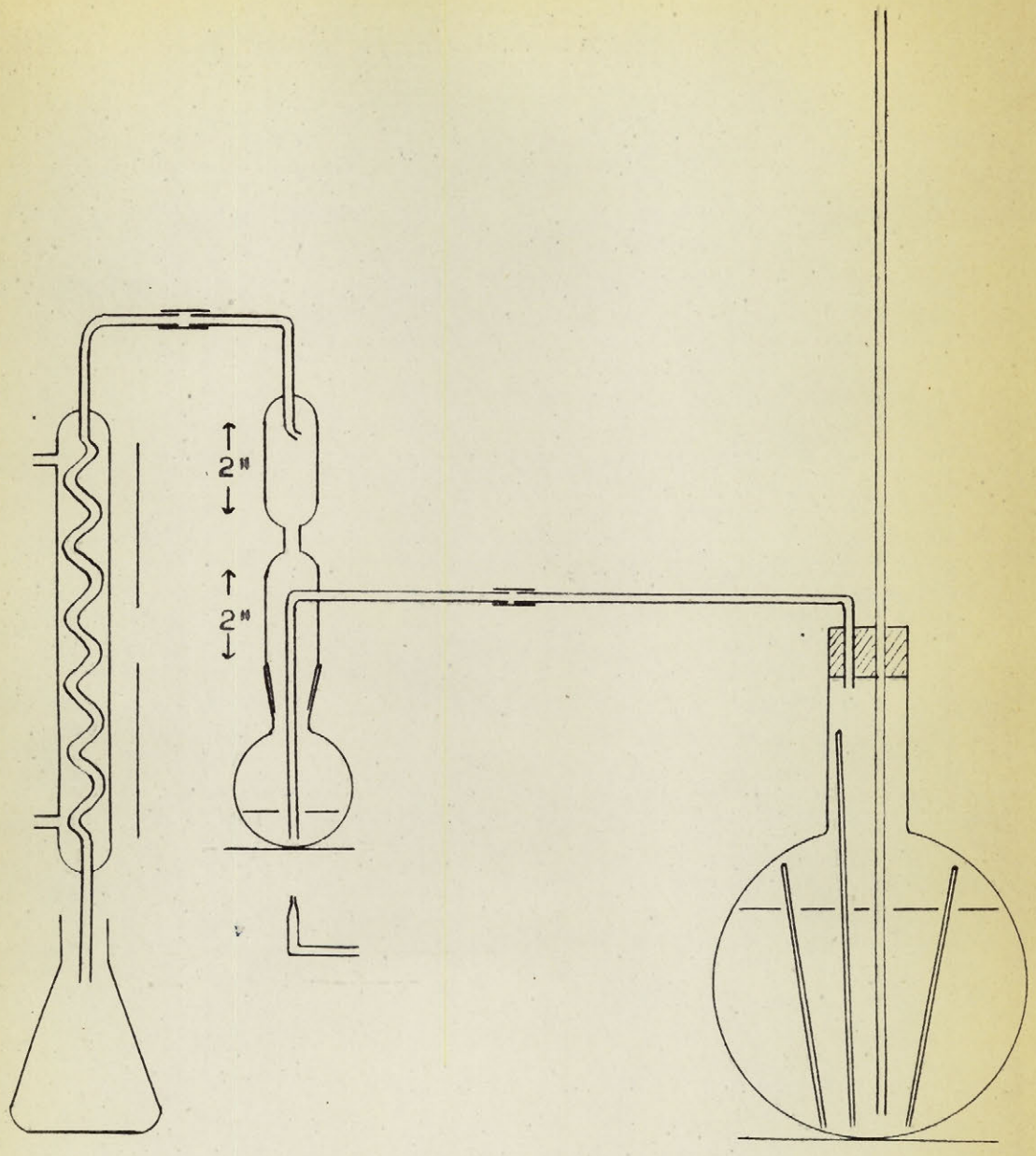
Analytical Methods

Acetyl determinations.- The following three methods were used.

1. Carefully shredded samples were heated in alcoholic sodium methylate before acidification with p-toluene sulfonic acid. The acetyl group was recovered in the form of methyl acetate by distillation in the identical manner and apparatus described by Cramer, Gardner and Purves (203). This method was used in the beginning of the research but later was abandoned for most purposes. Although reagents of the highest purity were used, and the directions followed explicitly, high and variable blanks were always obtained and the accuracy of the results were therefore always uncertain. Furthermore, this technique was definitely shown not generally valid for all cellulose acetate derivatives. Although, of the methods used, it yielded the best results for cellulose nitrate acetates, it has been claimed to yield somewhat high results for these substances (203).

2. Ost distillation method. (a) Analysis of macro-samples was accomplished in an identical manner as that described by Genung and Mallatt (207). The apparatus employed was built to the specifications recommended. (b) Since it became desirable to apply this general method of acetyl analysis to materials which were not sufficiently abundant for macro-scale analysis, a semi-micro adaptation was made. A sample of sufficient size to yield a 15-20 ml. titration with 0.02 N sodium hydroxide solution was accurately weighed into a 100 ml. round-bottom ground glass flask. The sample was covered with 2 ml. of 72% sulfuric acid, tightly stoppered, and allowed to stand at room temperature with occasional shaking until solution was complete. After standing at least six hours, 10 ml. of carbon dioxide-free water was added, the flask was attached to the apparatus described in Fig. II, and steam distillation was conducted at such a rate that 250 ml. were collected in thirty minutes. The distillate was immediately titrated with 0.020 N sodium hydroxide solution until the first permanent pink coloration to phenolphthalein was observed. Blank determinations were conducted and showed a constant value of 0.50 ± 0.04 ml. The accuracy of the method was fully established to be well within one part in a hundred by analysis of a variety of cellulose acetates of known constitution. For acetyl determinations in the presence of halogen, approximately 50 mg. of pure silver oxide was added to the sample before the addition of sulfuric acid.

FIG. II

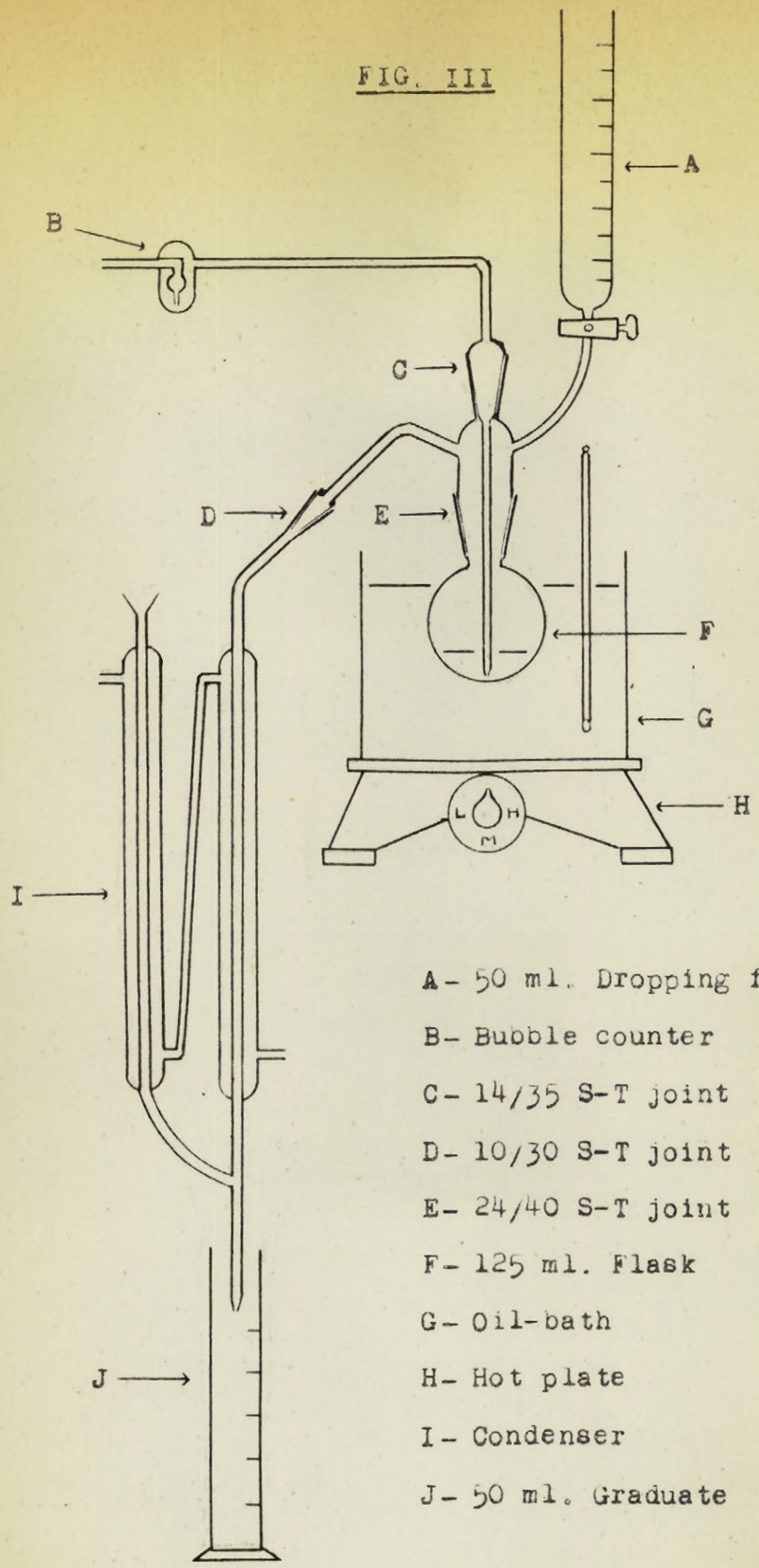


APPARATUS FOR SEMI-MICRO ACETOXY GROUP ESTIMATION (OST)

3. A semi-micro adaptation of the terminal methyl group determination described by MacGregor, Evans and Hibbert (204) was refined to yield accurate acetyl and terminal methyl group contents for many substances.

PROCEDURE: A 15-50 mg. sample (depending on the acetyl content) was weighed into the 100 ml. round bottom flask, Fig. III. The sample was covered with 10 ml. of a 30% chromium trioxide solution. The hot plate under the oil-bath was turned to "High" and the apparatus assembled. Nitrogen gas was passed through at a rate of 1-2 bubbles per second. After fifteen minutes the temperature of the oil-bath was 100-110° and the hot plate was turned to "Medium" at which setting it liberated sufficient heat to raise the temperature of the bath to 155° within half an hour. This temperature was maintained until the end of the determination. Too rapid an initial rise in temperature resulted in high blanks. Distillation began at 135-140°. After 5 ml. of distillate had collected in the 50 ml. graduate, 5 ml. of distilled water was added from the 50 ml. graduated dropping funnel. After 5 ml. more of distillate had collected, 5 ml. more of water was added. This procedure was continued until 50 ml. of water was added and 55 ml. of a very faintly yellow distillate was collected. The condenser was then detached from the still-head and both arms were washed into a 250 ml. Erlenmeyer flask. The contents of the graduate were then quantitatively transferred to the same flask. This solution was titrated with standard carbon dioxide-free 0.020 N sodium hydroxide solution until the end-point just began

FIG. III



A- 50 ml. Dropping funnel

B- Bubble counter

C- 14/35 S-T joint

D- 10/30 S-T joint

E- 24/40 S-T joint

F- 125 ml. Flask

G- Oil-bath

H- Hot plate

I- Condenser

J- 50 ml. Graduate

APPARATUS FOR THE DETERMINATION OF ACETYL GROUPS BY DISTILLATION FROM AQUEOUS CHROMIUM TRIOXIDE SOLUTION

to fade (phenolphthalein indicator). The liquor was then brought to a boil to remove carbon dioxide, cooled to room temperature under the cold water tap, and the titration continued until the pink coloration remained stable for ten seconds. Approximately 0.5 g. of sodium bicarbonate was then added, followed by 10 ml. of 10% sulfuric acid and after carbon dioxide evolution had ceased, 1 g. of potassium iodide was added. The solution was stoppered, shaken and allowed to stand in the dark for five minutes. The liberated iodine was titrated with 0.020 N sodium thiosulfate. The blank was taken as four-thirds of this volume. This ratio was fixed experimentally.

DISCUSSION: Slight variations in operating conditions caused large variations in the blank determination, a feature which seems inherent to this general method. On titrating the chromic acid in the distillate, iodometrically, it was found that the acidity of the blank was equivalent to four-thirds the oxidative equivalent. Thus a blank determination could be carried out directly on the distillate of each run. This refinement rendered the technique highly useful as a rapid method of acetyl determination. Although the blanks varied in magnitude between 0.50 and 1.00 ml., the reproducibility and accuracy of the results of determinations carried out on a wide variety of substances left little doubt that this method yielded acetyl values within a maximum error of 0.2 per cent.

From Table III, it is seen that the oxidation quantitatively

TABLE III

ACETYL DETERMINATION BY CHROMIUM TRIOXIDE-DISTILLATION

No.	Compound	% Acetyl Found	% Acetyl Theory
1	Rhamnose hydrate	23.1	23.6
2	Isorhamnose tetraacetate	64.5	64.8
3	Glucose pentaacetate	55.0	55.0
4	α-Methylglucoside tetraacetate	47.5	47.5
5	6-Trityl-α-methylglucoside triacetate (a)	23.4	23.0
6	Acetone-sol. cellulose acetate	38.8	38.6
7	Monoethylidene methylglucoside	12.7	12.7
8	Ethyl cellulose (b)	27.4	27.6
9	Monotrityl cellulose	-0.04	00.0

(a) M.P. (uncorr.) 145-7°. This sample, prepared by Gladding and Purves (27), was reported by them to melt at 142-5° contrary to the previously reported M.P. 137°. The material was therefore probably impure.

(b) Hercules Powder Co. sample X2167-12.

recovered the terminal methyl groups in the first two substances as acetic acid. This method for primary desoxy group analysis in carbohydrates should prove more widely applicable and convenient than that described by Nicolet and Shinn (205).

Determinations of the ethylidene content of a monoethylidene methylglucoside (206) and of the ethyl groups in an ethyl cellulose were also successful. The method should therefore find application for group analysis in ethylidene derivatives of various polyhydroxy substances. The determination of ethoxy in the presence of methoxy groups has always been a difficult matter. The selective estimation of the former in this manner would seem readily possible for numerous types of compounds. It should be kept in mind that the method is limited in its application to compounds which either contain no terminal methyl groups or to the very restricted number of compounds with terminal methyl groups which oxidize quantitatively to acetic acid (204). It seems that the carbon atom adjacent to the methyl group in the compound must be linked to at least one oxygen atom; e.g., butyrates or propionates cannot be quantitatively determined.

The most important feature of the determination is that the acetyl content of a sample can be estimated in two and half hours. For this reason it should find extensive application for control purposes in the cellulose acetate industry, especially since samples require no pretreatment and the moisture content can be determined independently.

Sulfur determinations.- Since the semi-micro gravimetric determination of sulfur was believed to be too tedious for routine work, it was decided to combine the wet Carius combustion method (209) with the volumetric sulfate determination described by Hallett and Kuipers (210).

PROCEDURE: A sample, containing between 0.5 and 3 mg. of sulfur was weighed into a 15 to 30 cm. Pyrex tube with 1 mm. walls and 1 cm. in diameter. The addition of 20 to 25 mg. of sodium chloride was followed by the addition of 0.3 to 0.5 ml. of pure fuming nitric acid. (If the substance reacted violently with the nitric acid, the acid was added in a thin-walled tube which was later washed out with the contents and crushed with a stirring rod.) The tube was sealed and digested at 280-300° for four to six hours (211). After cooling, the tube was opened and the contents washed into a 250 ml. Erlenmeyer flask. The solution was evaporated to dryness on an asbestos covered hot plate, 5 ml. of concentrated hydrochloric acid was added and the mixture evaporated to dryness. Another similar acid treatment usually showed the residue free of nitrate. The sides of the flask were then washed down with 5-10 ml. of water and the resulting solution evaporated to dryness. Fifty ml. of 50% ethanol-water was added, a measured scoopful (approximately 0.15 g.) of the tetrahydroquinone indicator (212) and the resulting bright yellow solution was titrated to a stable pink end-point with standard 0.0180 N barium chloride solution.

A calibration curve was established by the analysis of

various amounts of pure N,N' diphenyl thiourea in the manner described by Hallett and Kuipers (210). The plot, Fig. IV, ml. of barium chloride solution versus mg. of sulfur in the sample, shows that these values check with the curve drawn from the values obtained by the titration of various volumes of standard potassium sulfate solution. The blank thus obtained is shown to be approximately 0.20 ml. of 0.0180 N barium chloride solution.

DISCUSSION: The semi-micro sulfur analysis described by Mahoney and Michell (213) proved to be unreliable in the hands of this operator. The leaching effect on the indicator of the large amounts of sodium chloride, the presence of carbon residue and the difficulties involved in removing the last traces of peroxide (210) rendered the end-point of the titration extremely difficult to observe. Hallett and Kuipers have firmly established a rapid and reliable volumetric semi-micro sulfur determination. It, however, involves the use of expensive special combustion apparatus which is not available in this laboratory. They studied the use of tetrahydroquinone indicator for the estimation of sulfate. Their conclusions were:

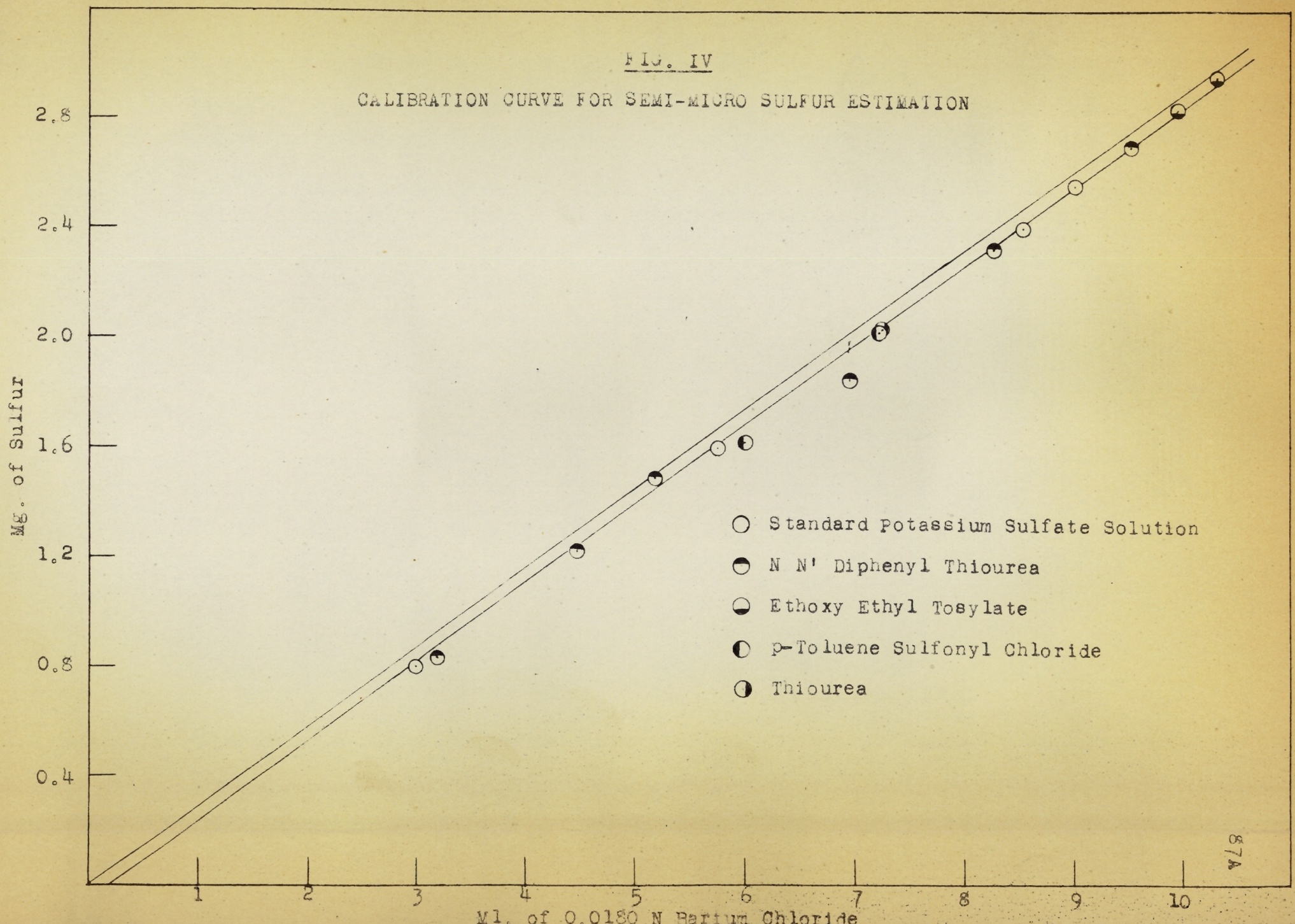
(1) A color standard should be used.

(2) The end-point does not coincide with the stoichiometric amount of barium chloride solution required for sulfate present in the solution, and blank corrections must be applied.

(3) The titration should be carried out between 15 and

FIG. IV

CALIBRATION CURVE FOR SEMI-MICRO SULFUR ESTIMATION



87A

20° at a pH between 6.5 and 7.0.

(4) The volume of the solution being titrated should be 50 ml. ± 1 ml. at the beginning and 60 ml. ± 4 ml. after the titration.

(5) When the sulfur content of the solution is below 0.5 mg. the end-point is not reproducible.

(6) Titration of standard sulfate solutions prepared from sulfuric acid gave different end-points depending upon the base, ammonium or potassium hydroxide, used to bring the solution to neutrality.

(7) The most satisfactory amount of sulfur for routine work is 1 to 2 mg.

If the hydrochloric acid treatment was omitted, the addition of the tetrahydroquinone indicator did not produce the normal bright yellow coloration but only a faded pale yellow which failed to yield a sharp end-point. This effect was probably analogous to that observed by Hallett and Kuipers when they found hydrogen peroxide an unsuitable oxidizing agent to convert sulfite to sulfate, since its complete removal proved a matter of great difficulty and its presence resulted in bleaching of the indicator.

The Carius method for combustion is very practical in that it requires little attention and is applicable to all types of sulfur compounds, whether solid or liquid.

This method for sulfur determination requires little working time and the results obtained indicate that its precision,

see Table IV, compares very favorably with that of standard methods described in the literature (200). Its most commendable feature is the directness and simplicity of the techniques involved.

TABLE IV

DETERMINATION OF THE SULFUR CONTENT OF VARIOUS COMPOUNDS

No.	Compound	% Sulfur Found	% Sulfur Theory
1	Ethoxy ethyl tosylate	12.9 13.0	13.1
2	Tosyl chloride	16.8	16.8
3	Thiourea	42.2	42.1

Nitrogen Determinations.-

1. Aminoid nitrogen was determined by a standard semi-micro Kjeldahl method (214).

2. Nitrate nitrogen was determined by an unpublished semi-micro adaptation of the Gunning method (215) which was established by Zuckerman in this laboratory. A sample, 7 to 40 mg., was weighed into an appropriate Kjeldahl flask, together with 100 mg. of pure salicylic acid. Two ml. of concentrated sulfuric acid was added and after standing at room temperature for thirty minutes, with occasional shaking, the

sample completely dissolved. Sodium thiosulfate, 300 mg., was then added and the mixture was heated gently for five minutes. After cooling, 600 mg. of potassium sulfate was added and the digestion was completed in the usual way. The ammonia was distilled into 5 ml. of 2% boric acid and titrated with standard 0.01 N sulfuric acid solution as described by Ma and Zuazaga (216) using methyl red-bromcresol green mixed indicator. A reagent blank of 0.10 ml. was subtracted from the volume of standard sulfuric acid required to turn the blue solution to pink. The following results, obtained in the analysis of potassium nitrate, give a good indication of the degree of accuracy obtained. Calcd. for KNO_3: N,13.9. Found: N,13.9, 13,9, 14.0%.

Iodine Determinations.- Iodine was estimated by weighing a 20 to 30 mg. sample into a 250 ml. Erlenmeyer flask. The sample was covered with 25 ml. of water and 1 g. of potassium hydroxide pellets was added. The mixture was boiled for five to ten minutes until solution was complete, water being occasionally added to keep the volume constant. Certain samples which did not readily go into solution under these conditions were covered with 10 ml. of dioxane and allowed to dissolve, the potassium hydroxide pellets were added, followed by a slow addition of water to the heated mixture. When solution was complete, the dioxane was readily removed by continued boiling and addition of water. The resulting cooled solution was diluted to 100 ml.

with distilled water, neutralized to phenolphthalein with 2 N sulfuric acid and 2 ml. of the acid was added in excess. Five to eight drops of bromine were then added. Any cellulose material that had precipitated during acidification was thereby usually oxidized and redissolved. The excess of bromine was then destroyed by the addition of eight drops of formic acid, with shaking. Six more drops were added after the color of bromine had disappeared. The estimation of iodine, now present as iodate, was by adding excess potassium iodide and titrating the liberated iodine with standard 0.02 N sodium thiosulfate solution (217). This method constantly yielded accurate results of high reproducibility, as illustrated by analysis of pure 6-iodo-α-methylglucoside triacetate. Calcd. for $C_{13}H_{19}O_8I$: I, 29.5. Found: I, 29.4, 29.5%.

Trityl Determinations.- The method described by Hearon, Hiatt and Fordyce (2) was used. A sample, 0.5 to 1 g. was dried at 100° for one hour and weighed into a 250 ml. Erlenmeyer flask. Concentrated sulfuric acid, 10 ml., was added and the sample dissolved with occasional stirring. The flask containing the digested sample was swirled continually while a stream of distilled water from a wash-bottle was directed into it. The solution darkened and as the carbinol precipitated the color changed to a dark green, yellow and finally grey. At this point, the stream from the wash-bottle was discontinued and the mixture was diluted with 90 ml. of distilled water. The granular precipitate was transferred into a previously dried and weighed sintered

glass filter funnel where it was washed with water until the underside of the funnel was acid free (litmus paper). The material was dried at 100° for one hour, cooled in a desiccator and weighed.

PREPARATIVE PROCEDURES

Freshly distilled, anhydrous solvents, pure reagents and distilled water were used throughout this work. Levi, Zuckerman and Purves (1) have shown that if these precautions were not observed the cellulose products accumulated large amounts of ash which was too strongly held to be removed by the methods tried. Ground glass fittings were employed throughout and any possible contamination from rubber or cork stoppers were therefore eliminated.

A. Preparation of "Cellulose-6-mononitrate"

Regeneration of Cellulose.- High grade technical cellulose acetate (218), 120 g., previously dried in vacuo over phosphorus pentoxide, was heated under reflux on the steam bath for two hours with 3100 ml. of 0.024 N sodium methylate (219). The liquor should remain alkaline to aqueous phenolphthalein. After recovery, the insoluble residue of regenerated cellulose was washed with 500 ml. of hot methanol, extracted with dilute acetic acid, rewashed with much water, and preserved as a white, highly

swollen mass under distilled water. A small sample dried at 105° had negligible amounts of ash and acetyl.

(I) Monotrityl Cellulose (2). - The highly swollen, regenerated cellulose (dry weight 62.5 g.) was heated on the steam bath for one hour with 900 ml. of 50% aqueous pyridine and, after recovery, the removal of water was completed by three similar treatments with dry pyridine. Between these treatments as much solvent as possible was expressed by means of a rubber dam, but the cellulose was never allowed to become dry. The pyridine-wet mass was then heated on the steam bath for eighteen hours with one litre of dry pyridine and 245 g. of trityl chloride. A standard method (220) was used to synthesize the trityl chloride. All glass equipment was used and stirring was continuous through a mercury seal. The resulting dark red solution was filtered through cotton into 10 litres of methanol and the crude monotrityl cellulose precipitated. A reprecipitation from pyridine solution into methanol left a white, fibrous product which was washed with methanol, then extracted with warm water to remove any absorbed pyridine, rewashed with methanol to remove the water and dried in vacuo over potassium hydroxide. The yield was 139 g. or 89% of theory.

Anal. Calcd. for 0.99 trityl groups per anhydroglucose unit: Trityl, 59.8; C, 74.0; H, 5.95. Found: Trityl, 59.5, 59.5; C, 73.5, 73.2; H, 6.04, 5.87%.

(II) Monotrityl Cellulose Acetate (1). - The trityl cellulose, 115 g., was dissolved in 1500 ml. of anhydrous pyridine and the clear, yellow solution was cooled to -15°. Acetic anhydride, 750 ml., also cooled to -15°, was added and after one hour the temperature of the mixture was allowed to rise to that of the room. At the end of the first day, the mixture had become a gel and after five days at room temperature the gel was incorporated into 7 litres of ice-water to precipitate the insoluble monotrityl cellulose acetate which was freed from the pyridine-acetic anhydride mixture by repeated trituration in a large mortar. The crude product, a pale yellow, friable powder, was washed with distilled water, then methanol, and was dried in air. Purification was by solution in chloroform and precipitation into 14 litres of diethyl ether. After drying in vacuo at room temperature, a sample was found to lose 7.5% by weight after subsequent drying for one hour at 100°, whereas the calculated loss for 0.5 mole of ether was 7.66%. This tenacious retention of ether could also be overcome by reprecipitation of trityl cellulose acetate from chloroform into low boiling petroleum ether. The yield of ether-free product was nearly quantitative. The preparation had a yellow color, was readily soluble in chloroform, swelled in pyridine and benzene and was insoluble in other common organic solvents.

Anal. Calcd. for 0.98 trityl, 1.67 acetyl groups per anhydroglucose unit: Trityl, 50.8; Acetyl, 15.3; C, 71.3; H, 5.74.

Found: Trityl, 51.0, 50.8, 50.5, 50.5; Acetyl (Method 3), 15.4, 15.5,(see Table XV , Page 138); C, 71.2, 70.3; H, 5.53, 5.74%.

(III) "Cellulose Acetate Mononitrate" (1). - The monotrityl cellulose acetate, 58 g., was dissolved in 1 litre of anhydrous chloroform, the solution was cooled to -10°. Phosphoric anhydride, 26 g., dissolved in 360 ml. of 98% nitric acid (miscible in chloroform without turbidity) was added at -10° and after fifteen minutes the temperature of the mixture was allowed to rise to that of the room. Thirty minutes later the mixture of precipitated cellulose product and nitrating solution was poured with vigorous stirring into 7 litres of distilled water and chopped ice made from distilled water. The triphenylmethyl carbinol remained dissolved in the chloroform and the cellulose acetate nitrate was recovered as large, yellow lumps. The latter were washed with distilled water and were triturated in a large porcelain dish with cold, saturated sodium bicarbonate solution until all acidity had been removed. The water repellency of the lumps, caused by absorbed chloroform, rendered this procedure extremely tedious and it is not recommended for further use. After a final wash with distilled water, the yellow product was dried in air. Purification was by solution in 850 ml. of dioxane, filtration, and precipitation into 9 litres of distilled water, followed by three extractions at room temperature with 600 ml. volumes of methanol. The final

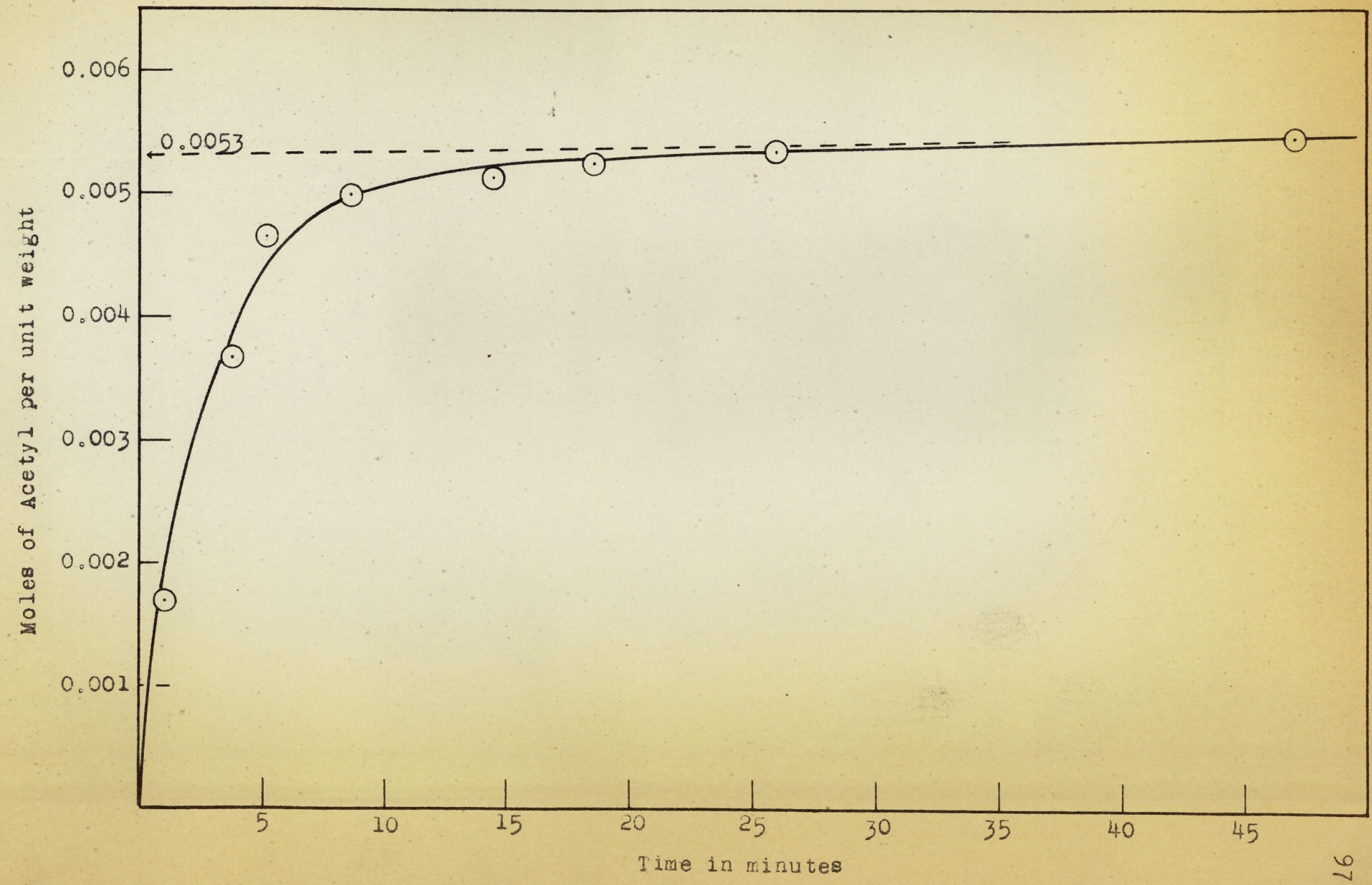
drying was in vacuo at 45°. This purified product was a trityl and ash free, white, fibrous substance that was insoluble in water, ether and chloroform but was readily soluble in dioxane, acetone, acetonyl acetone and pyridine. The yield was 33 g. or 98% of theory, according to its analysis. When slowly heated, the acetate-nitrate suddenly burst into flame and burned violently.

Anal. Calcd. for 1.43 acetyl and 1.10 nitrate groups per anhydroglucose unit: Acetyl, 22.6; N, 5.68; C, 39.1; H, 4.35 Found: Acetyl (Method 1) 22.5, 22.6; N, 5.62, 5.70, 5.67; C, 38.0, 38.4; H, 4.63, 4.15%.

Deacetylation of "Cellulose Acetate Mononitrate (III)". - A sample of the acetate-nitrate, 0.5031 g. was dissolved in 250 ml. of peroxide-free dioxane and 25 ml. aliquots were pipetted into 125 ml. flasks. These aliquots were mixed with 5.00 ml. amounts of 0.197 N sodium hydroxide solution and allowed to stand for various lengths of time, after which, 10 ml. volumes of 0.107 N sulfuric acid solution were added. The resulting mixtures were immediately back titrated to phenolphthalein indicator with the 0.197 N alkali. The plot shown in Fig. V is a composite of two runs. Other runs carried out with minor variations in conditions, all gave identical results. The plot shows that 0.53×10^{-2} moles of apparent acetyl were rapidly saponified per gram of the nitrate-acetate. Since

FIG. V

RATE OF DEACETYLATION OF CELLULOSE-6-NITRATE ACETATE (III)



analysis of this latter substance showed it to have a unit molecular weight of 271.5, this amount corresponded to the removal of 1.44 apparent acetyl groups per anhydroglucose unit (theory is 1.43). Diphenylamine tests of the neutral solutions showed that nitrite was formed, probably, however, in negligible amounts.

(IV) "Cellulose-6-mononitrate" (1). - The nitrate-acetate (III), 5.39 g. (0.0285 mole acetyl), was dissolved in 800 ml. of dioxane and 110 ml. of 0.197 N aqueous caustic sode (0.0217 mole) was added, dropwise and with efficient stirring, at room temperature. The mixture sometimes became cloudy owing to the separation of solids but the addition of small amounts of water caused the precipitated material to redissolve at once. After forty-five minutes the solution, no longer alkaline to phenolphthalein, was poured into 5 litres of distilled water and the resulting white, very fine precipitate of cellulose nitrate was filtered with some difficulty. The crude product was repeatedly washed with distilled water and dried, in vacuo, at 65°. The yield was 4.2 g. or 89% of theory. The dried product was a yellow powder which could be highly swollen in a variety of organic solvents but no solvent or mixture of solvents was found to dissolve it completely.

Anal. Calcd. for 1.10 nitrate and 0.42 acetyl groups per anhydroglucose unit: N, 6.42; C, 35.8; H, 4.25. Found: N, 6.67, 6.71; C, 35.0, 35.2; H, 4.26, 4.28%.

Degradation during Synthesis of "Cellulose-6-mononitrate". - The sample, 7.5 mg. or less, was accurately weighed and dissolved in 25 ml. of suitable pure solvent. The viscosity, η_{sp}, was then determined at 25.0°, on a 5 ml. aliquot, using Ostwald viscometers with times of flow for pure water of 118.1 and 98.4 seconds. A fixed proportion (15 ml.) of the original 25 ml. of solution was weighed to determine its volume, diluted to 25 ml. with pure solvent, and used to redetermine the specific viscosity at the lower concentration calculated from the dilution ratio. This process was repeated until the quotient η_{sp}/c (c expressed as a percentage) attained the nearly constant value known as the intrinsic viscosity $[\eta]$ and noted in Table XVI , Page 142.

B. Studies on the Iodination of "Cellulose-6-mononitrate Acetate(III)"

(V)"6-Desoxy-6-iodocellulose Acetate (Nitrate)" (139,148). - Two grams of the acetate-nitrate (III) and 5 g. of oven dried, but not fused, sodium iodide were dissolved in 100 ml. of acetone, and the solution was heated in a sealed tube at 100° for sixteen hours. A brown colored liquid, giving a positive test for free iodine and containing crystals identified as sodium nitrate, resulted. The iodine was recombined by adding decinormal sodium thiosulfate solution and the liquid was concentrated to a volume of 15 ml. Dilution of the concentrate with water caused the precipitation of cream colored fibers which were recovered by

filtration, washed free of salts by water and were dried in air. The yield was 2.30 g., or 98% of the theoretical amount calculated from the analytical data. The product was recovered as pure white fibers by precipitation from dioxane solution into methanol, but this purification did not alter the iodine content. Re-iodination, with sodium iodide in acetone at 100° for twelve hours, caused a slight decrease (1.3%) in iodine content, with further denitration. This product represented the maximum iodine content obtained on the iodination of this acetate-nitrate under a variety of conditions.

Anal. Calcd. for 1.43 acetyl, 0.18 nitrate and 0.80 iodine atoms per anhydroglucose unit: N, 0.80; I, 31.9. Found: N, 0.80, 0.82; I, 31.6, 31.5%.

Iodination of α-Methyl-2,3,4-triacetyl-glucopyranoside-6-nitrate (139).- The material, 2 g., was iodinated simultaneously and exactly as described in the preparation of the iodocellulose acetate (V). No discoloration occurred. When the solution was evaporated to dryness, a white, water insoluble, crystalline product was recovered, whose weight of 2.28 g. was 96% of theory.

Anal. Calcd. for a mixture containing 0.85 iodine atom and 0.15 nitrate group per α-methyl-2,3,4-triacetyl-glucoside unit: I, 25.7; N, 0.50. Found: I, 25.5, 25.7; N, 0.66, 0.60%.

Iodination of "Cellulose Trinitrate". - Some preliminary experiments were also carried out on the rate of iodination and denitration of cellulose trinitrate in acetone and sodium iodide at 100°. The widespread degradation which usually accompanies this reaction (148) was largely prevented by the addition of 5% allyl alcohol in order to absorb the liberated iodine. The results obtained are summarized in Table V. These date show that after eight hours' reaction at 100°, only 1.47 positions remained substituted. Since there were 2.92 nitrate groups in the original cellulose nitrate, 1.45 nitrate groups were lost in the time required for the replacement of 0.48 nitrate groups by iodine.

TABLE V

IODINATION OF CELLULOSE TRINITRATE

Hours	N %	I %	Substitution	
			Nitrate grps. per g. u.	Iodine atoms per g. u.
0	13.9	-	2.92	-
8	5.45	23.3	0.99	0.48
18	2.96	29.8	0.58	0.66
34	0.67	37.6	0.12	0.73

C. Preparation of "6-Desoxycellulose Acetate"

(VI) "6-Desoxy-6-iodocellulose Acetate (Nitrate)". - A large scale preparation was carried out by dissolving 7.1 g. of the nitrate-acetate (III) in 200 ml. of dry acetone and 25 g. of sodium iodide. This solution was heated in a stainless steel bomb at 100° for twenty-two hours. The product was isolated as before. Purification was by reprecipitation from a filtered acetone solution into water. The yield was 8.4 g. of cream colored fibrous material.

Anal. Calcd. for 0.74 iodine atoms, 0.05 nitrate and 1.43 acetyl groups per anhydroglucose unit: I, 30.4; N, 0.23; Acetyl, 20.2. Found: I, 30.3, 30.2; N, 0.24, 0.25; Acetyl (Method 2), 20.9%.

(VII) "6-Desoxycellulose Acetate". - The iodo compound (VI), 4 g., was dissolved in 50 ml. of acetic anhydride and 50 ml. of glacial acetic acid was added. Zinc dust, 25 g., was added, in 5 g. lots, to the steam heated solution over a period of half an hour, together with about 0.1 g. amounts of copper acetate. Stirring was vigorous and continuous. After a total time of heating of two and a half hours, the mixture was cooled and poured with stirring into a litre of iced water. The zinc-fiber mixture was recovered by filtration, washed with water and air-dried. Three extractions with acetone, 100 ml., were combined, filtered and

concentrated to 50 ml. Precipitation into water yielded 2.6. g. of a fibrous material which dried to a powder. Purification was by solution in 20 ml. of dioxane, filtration through a very fine sintered glass funnel and precipitation into water. The pure white powder, free both from iodine and nitrate, slowly dissolved in 72% sulfuric acid, but was immediately and greatly discolored by the acid.

Anal. Calcd. for cellulose with 0.52 isorhamnose units and 2.00 acetyl groups: Acetyl, 36.1; Apparent Acetyl (Acetyl plus terminal methyl groups as acetyl), 45.5. Found: Acetyl (Method 2), 34.8, 35.8, 35.9; Apparent Acetyl (Method 3), 45.2, 45.4%. The calculation of the number of isorhamnose units from this data will be further considered on Page 160.

Attempted Preparation of a "6-Desoxycellulose (VIII)". - The desoxycellulose acetate (VII), 0.4 g., was suspended in 30 ml. of 0.15 N sodium methylate in absolute methanol and allowed to stand with occasional stirring for twenty-four hours at room temperature. A very fine precipitate was left after that time. It was recovered and washed with dry methanol. The yield, 0.040 g., of a dark colored, water soluble product was approximately 15% of theory. This precipitate probably represented the methanol insoluble fraction. Solubility difficulties rendered it impossible to separate the soluble portion from the sodium salts.

Anal. Calcd. for cellulose with 0.52 mole isorhamnose units: Apparent acetyl (Method 3), 14.6. Found: 14.6%.

Partial Nitration of Desoxy-iodocellulose Acetate (VI). - The iodo-compound, 1 g., was dissolved in 40 ml. of acetonitrile and 1 g. of silver nitrate was added, (140). After heating under reflux for two hours, the solution was freed of silver iodide by filtration through a Büchner funnel lined with dry asbestos. The resulting clear solution was concentrated to 30 ml. and poured, with stirring, into water. The cream colored precipitate (IX) was recovered, washed with water and air dried. Purification was by solution in acetone, filtration and precipitation into water.

Anal. Calcd. for 1.43 acetyl, 0.39 nitrate and 0.34 iodine atoms per anhydroglucose unit (IX): N, 1.97; I, 15.6. Found: N, 1.89, 1.91; I, 15.2, 15.4%.

Reduction of Iodocellulose Acetate Nitrate (IX). - The iodo-compound (IX), 0.6 g., was treated with 20 ml. of 50% acetic anhydride-acetic acid and 5 g. of zinc dust with copper acetate in an identical manner to that used to prepare the desoxycellulose acetate (VII). The yield was 0.313 g. of a pure white powder (X) which was both iodine and nitrate free.

Anal. Calcd. for cellulose with 0.20 isorhamnose units and 2.43 acetyl groups (X): Acetyl, 40.0; Apparent Acetyl (Acetyl plus terminal methyl groups as acetyl), 43.3. Found: Acetyl (Method 2), 40.3, 39.8; Apparent Acetyl, (Method 3), 43.7. A more detailed consideration of the structure of this material is given on Page 160.

D. Attempted Estimation of the Free 2,3-Glycol Groups in Monotrityl Cellulose (I).

With Periodate. - The trityl cellulose, 0.195 g., was highly swollen by solution in 5 ml. of pyridine and precipitation into 25 ml. of 15% aqueous acetic acid. The precipitate plus supernatant mother liquor was mixed, at 20° and zero time, with 25 ml. of 0.2 M periodic acid (5 moles of periodic acid per anhydroglucose unit). Reagent blanks were also made up. Malaprade's arsenite-iodine titration (221) was used to follow the disappearance of periodate from the trityl cellulose mixture. After three, eighteen and ninety-three hours, the consumption of periodate (corrected for the blank) corresponded to 1.25, 1.25 and 1.25 ml. of 0.047 N iodine solution, or to 0.061 moles per anhydroglucose unit in the trityl cellulose. The final pH of the mixture was 4.8.

The calculated amount of periodate was very rapidly utilized in a parallel oxidation of ethylene glycol.

With Lead Tetraacetate. - An 0.021 g. sample of the trityl cellulose was highly swollen in 15 ml. of chloroform, and 5 ml. of 0.1 N lead tetraacetate (5 moles) in glacial acetic acid was added to the mixture at 20°. Reagent blanks were prepared. Aliquots of the liquids were subsequently estimated for unused tetraacetate by adding excess of aqueous potassium iodide solution, highly buffered with sodium acetate, and by titrating the

liberated iodine with 0.0202 N sodium thiosulfate (222). The blanks proved rather stable. After one and two days, the trityl cellulose had consumed lead tetraacetate equivalent to 0.01 and 0.39 ml., respectively, of the thiosulfate, or equivalent to 0.076 moles per anhydroglucose unit.

E. Studies on the Acetylation of Trityl Cellulose (1,18,23,24)

The cellulose acetate (218) was regenerated and tritylated in the manner previously described, see Pages 92,93. Tritylation was however carried out at 95 to 100° for a period of forty hours. The yield was 92% of theory. The dry, soft fibrous product (XI) was nearly white.

Anal. Calcd. for 1.04 trityl groups per anhydroglucose unit (XI): Trityl, 61.0. Found: Trityl, 61.2, 61.1%.

Acetylation with Acetyl Chloride (223). - Pyridine, 50 ml., was added dropwise with vigorous mechanical stirring to a solution of 17 g. of acetyl chloride and 300 ml. of dry toluene cooled in an ice-salt bath. To this cooled slurry of pure white acetyl pyridinium chloride, 11 g. of the trityl cellulose (XI), dried at 80° for ten hours and dissolved in 100 ml. of pyridine, was added. The stirring was continued for one hour then the mixture was allowed to stand at 8-10° for three days. At higher temperatures the solution discolored. When chloroform was used

instead of the toluene, the reddish material which formed (224) adhered to the cellulose derivative so tenaciously that it could not be removed; in fact it gave every indication of being chemically bound. The weight of the adhering substance was approximately 80 g. per anhydroglucose unit. Dry ethanol, 50 ml., was added; the gel was broken up and allowed to stand overnight. During this time all crystalline material disappeared to leave a yellow gel and an orange supernatant liquid. The mixture was transferred into 400 ml. of dry methanol and the precipitate ground in a mortar with methanol before being washed with methanol. The finely divided material was then shaken in 500 ml. of water containing 25 g. of sodium bicarbonate. The product (XII) assumed a white color. After recovery it was washed with much water, then with methanol and air dried. Purification was by solution in chloroform, filtration and precipitation into methanol, washing with methanol and drying in vacuo over calcium chloride.

Anal. Calcd. for 1.02 trityl and 1.60 acetyl groups per anhydroglucose unit (XII); Trityl, 51.9; Acetyl, 14.5. Found: Trityl, 51.8, 51.7; Acetyl (Method 3), 14.4, 14.6%.

Acetylation with Acetic Anhydride. - Dried trityl cellulose (XI), 20.0 g., was dissolved in 200 ml. of pyridine. To this solution, cooled to -15°, 130 ml. of acetic anhydride dissolved in 100 ml. of pyridine was added. After standing at 0° for five hours, the mixture was kept at 20° for five days. Dry

ethanol, 50 ml., was then added and after intimate admixture, the gel was allowed to stand overnight at 0°. It was then transferred to water, ground in a mortar with water, washed with water followed by methanol and air dried. Purification was by solution in chloroform, filtration and precipitation into methanol. Yield, dried *in vacuo* at 60°, was 22.4 g. of a pure white fibrous material.

Anal. Calcd. for 0.99 trityl and 1.49 acetyl groups per anhydroglucose unit (XIII): Trityl, 51.7; Acetyl, 13.8. Found: Trityl, 51.7, 51.5; Acetyl, 13.9%.

Carbanilation of Trityl Cellulose Acetate (XIII) (20). - Dry pyridine, 200 ml., was added to 12.0 g. of the very finely divided trityl-acetate (XIII) (dried *in vacuo* at 80° for six hours). Phenyl isocyanate, 20 g., was then added and the mixture, stirred until solution was complete, was maintained at 100° for seventy hours. The dark red solution was poured into methanol, the precipitate washed with methanol and air dried. Purification was by solution in chloroform, filtration and re-precipitation into methanol. Yield was 15.4 g. of a fibrous tan colored material.

Anal. Calcd. for 0.96 trityl, 0.52 phenyl urethyl and 1.47 acetyl groups per anhydroglucose unit (XIV): Trityl, 44.6; N, 1.52. Found: Trityl, 44.3, 44.2; N, 1.52, 1.52%; see Table VI.

TABLE VI

TRISUBSTITUTION OF TRITYL CELLULOSE ACETATE (XIII) BY REACTION WITH PHENYL ISOCYANATE

	Moles Trityl per g.u.	% Trityl Calcd.	% Trityl Found	Moles Acetyl per g.u.	% Acetyl Calcd.	% Acetyl Found	Free Hydroxyls per g.u.	Moles Carbanyl per g.u.	% N Calcd.	% N Found
Trityl Cellulose Acetate (XIII)	0.99	51.7	51.7 51.5	1.49	13.8	13.9	0.52	-	-	-
Trityl Cellulose Acetate Carbanilate (XIV)	0.96	44.3	44.3 44.2	(1.47)	(12.0)	-	0.00	0.57	1.52	1.52 1.52

Rate of Acetylation of Trityl Cellulose. - An 8% solution of the trityl cellulose in dry pyridene was prepared. Aliquots, 25 ml., of this solution were contained in ground glass stoppered Erlenmeyer flasks. At zero time, 10 ml. of pure acetic anhydride was added to each bottle. Some of these bottles were kept at +45°, others at +5° and -15°, for various lengths of time. Isolation was by adding the gel to iced distilled water in a large mortar where it was thoroughly ground, recovered, washed with water, then methanol and dried in vacuo over potassium hydroxide. The samples were dried at 100° for one hour before being analyzed for acetyl content by the chromium trioxide distillation method. Some of the samples which retained an odor of pyridine were dissolved in pure chloroform and precipitated into methanol. The degree of acetyl substitution was calculated, assuming the trityl substitution as 1.00 per anhydroglucose unit (mol. wt. 404), from the relation,

$$\frac{4300x}{404 + 42x} = \% \text{ Acetyl.}$$

The choice of 1.00 trityl group was made since the results in Table XV , see Page 138, seem to indicate that approximately 0.04 trityl group was lost in these preparations.

The trityl analyses of the samples isolated after one and three days reaction at 45° substantiate the formation of monotrityl cellulose diacetate. The gradual loss in trityl groups is noteworthy.

(a) Acetylation at 45° for one day.

Anal. Calcd. for trityl cellulose acetate substitution 1.98 acetyl and 1.02 trityl groups: Acetyl, 17.1; Trityl, 49.7. Found: Acetyl, 17.2, 17.5; Trityl, 50.2%.

(b) Acetylation at 45° for three days.

Anal. Calcd. for trityl cellulose acetate substitution 2.01 acetyl and 0.99 trityl groups: Acetyl, 17.8; Trityl, 49.4. Found: Acetyl, 18.0; Trityl, 49.5%.

The results, obtained for the rate of acetylation of trityl cellulose, are tabulated in Table VII and their plot is shown in Fig. VI.

F. The Nature of the Detritylation of Monotrityl Cellulose Diacetate

(XV) Monotrityl Cellulose Diacetate. - The trityl cellulose (XI), 15.3 g., dried at 100° for eight hours, was dissolved in 200 ml. of pyridine. The solution was cooled to 0° and 80 ml. of pure acetic anhydride, also cooled to 0°, was added. The mixture was shaken until homogeneous, then put into a bath at 45° for two days. The gel was broken up by grinding in a mortar with ice water, washed with water then methanol and dried *in vacuo* over potassium hydroxide. The tan colored fibers were dissolved in chloroform, filtered free of insoluble impurities and precipitated into methanol. The yield was 18.3 g. or 99% of theory.

TABLE VII

RATES OF ACETYLATION OF MONOTRITYL CELLULOSE

Time (days)	% Acetyl	Acetyl grps. per g.u.
	45°	
0.96	17.2 17.5	1.99
3.0	18.0(a)	2.04
5.0	17.5	2.00
	5°	
0.28	9.53(b)	0.99
0.55	11.4(c) 11.5	1.19
2.0	13.9	1.49
7.0	14.9	1.63
60.0	14.2	1.55
	-15°	
2.5	12.2	1.30
6.0	12.8	1.39
11.0	13.3	1.44

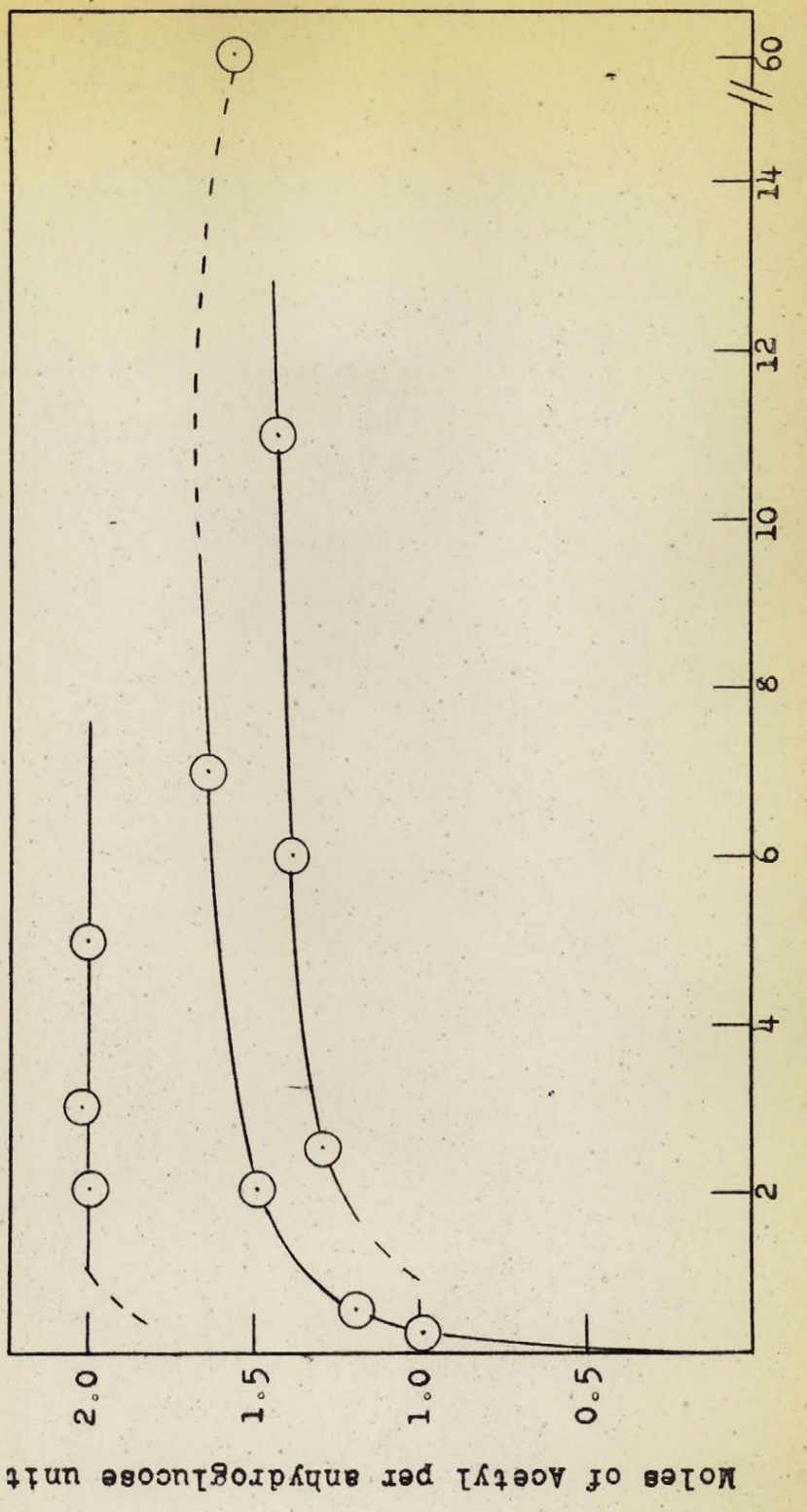
(a) Reprecipitated from chloroform.

(b) Soluble in pyridine and dioxane.

(c) Acetylating mixture had just begun to gel.

FIG. VI

RATE OF ACETYLATION OF MONOTRITYL CELLULOSE (XI)



Anal. Calcd. for 1.04 trityl and 1.96 acetyl groups per anhydroglucose unit: Acetyl, 17.0. Found: Acetyl (Method 3), 16.9, 16.9%.

Detritylation of Monotrityl Cellulose Diacetate (XV) (23).- (a) The diacetate, 1 g., was dissolved in 50 ml. of chloroform. Dry hydrogen chloride was passed through the solution, which immediately gelled, with shaking until the resulting mixture was saturated with hydrogen chloride. After standing overnight the mixture was added to 250 ml. of methanol containing 10 ml. of pyridine. The highly swollen mass was recovered by filtration, washed with methanol, pressed free of excess methanol, dissolved in pyridine, filtered and reprecipitated into methanol. The fibers were washed with methanol, then with water and finally with hot water to remove the adsorbed pyridine. Drying was in vacuo over calcium chloride. The yield was 0.5 g. of trityl and chloride free, white strong fibers (XVI). Of the common organic solvents tried, pyridine alone dissolved this material.

Anal. Calcd. for 1.58 acetyl groups per anhydroglucose unit(XVI):Acetyl, 29.7. Found: Acetyl (Method 3), 29.7, 29.7%.

(b) In a large scale preparation, 10.0 g. of the diacetate (XV) was dissolved in 100 ml. of pure chloroform. At 0°, 200 ml. of chloroform, saturated with dry hydrogen chloride, was added. The flask was tightly stoppered and the mixture shaken for six

hours at room temperature. The mixture was then transferred to 2 litres of 50% methanol-petroleum ether (b.p. 30-60°) containing 100 ml. of pyridine. The swollen mass was collected and washed with methanol, redissolved in pyridine, the solution filtered and poured with stirring into water. The white fibers were washed with water, then dried in vacuo over calcium chloride. The yield was 3.5 g. of white brittle fibers (XVII). Since the yield was 78% of tneory, the methanol-petroleum ether mixture was evaporated to 500 ml. volume and 1 litre of petroleum ether was added. This step made possible the recovery of an additional 0.8 g. of the cellulose acetate, raising the yield to over 90%. The chloroform used in this preparation was later shown to contain traces of water. This is undoubtedly the reason for the degradation which took place in this preparation.

Anal. Calcd. for 1.45 acetyl groups per anhydroglucose unit: Acetyl 27.8. Found: Acetyl, 1st fraction (XVII), 27.8; 2nd fraction, 27.6%.

Periodic Acid Oxidation of Cellulose Acetate (XVII). - Samples, 0.045 g., of the acetate were dissolved in 2 ml. volumes of pyridine. The addition of 10 ml. of 15% aqueous acetic acid caused the precipitation of a highly swollen, nearly colloidal, solid phase. At zero time, 10 ml. volumes of 0.5 N periodic acid were added. Reagent blanks were prepared. At various times thereafter, the amount of periodic

acid present was determined by the Malaprade arsenite-iodine titration method (221). Sufficient 20% potassium hydroxide solution was added, with stirring, to nearly neutralize all the acetic acid; 2 g. of sodium bicarbonate was then added, followed by 25.00 ml. of 0.22 N arsenite solution. The excess arsenite was subsequently back titrated with 0.0207 N iodine solution. The results are listed in Table VIII, and the plot for the rate of oxidation is shown in Fig. VII.

TABLE VIII

PERIODIC ACID OXIDATION OF CELLULOSE ACETATE (XVII)

Weight of Sample	Time (hrs.)	Ml.0.0207N Iodine Solution (A)	(B)	(A - B)	Moles of Periodate consumed per unit mol. wt.
-	0	-	23.00	-	-
0.0424	48	30.70	26.42	4.28	0.233
0.0428	73.5	33.58	27.00	6.58	0.354
0.0419	96	34.63	27.91	6.72	0.371
0.0431	120	36.00	28.55	7.55	0.400

A and B are the volumes of standard iodine solution required for the back titrations in the analyses of the reaction mixtures and blanks, respectively.

A - B corresponds to the amount of periodate consumed by the sample of cellulose acetate.

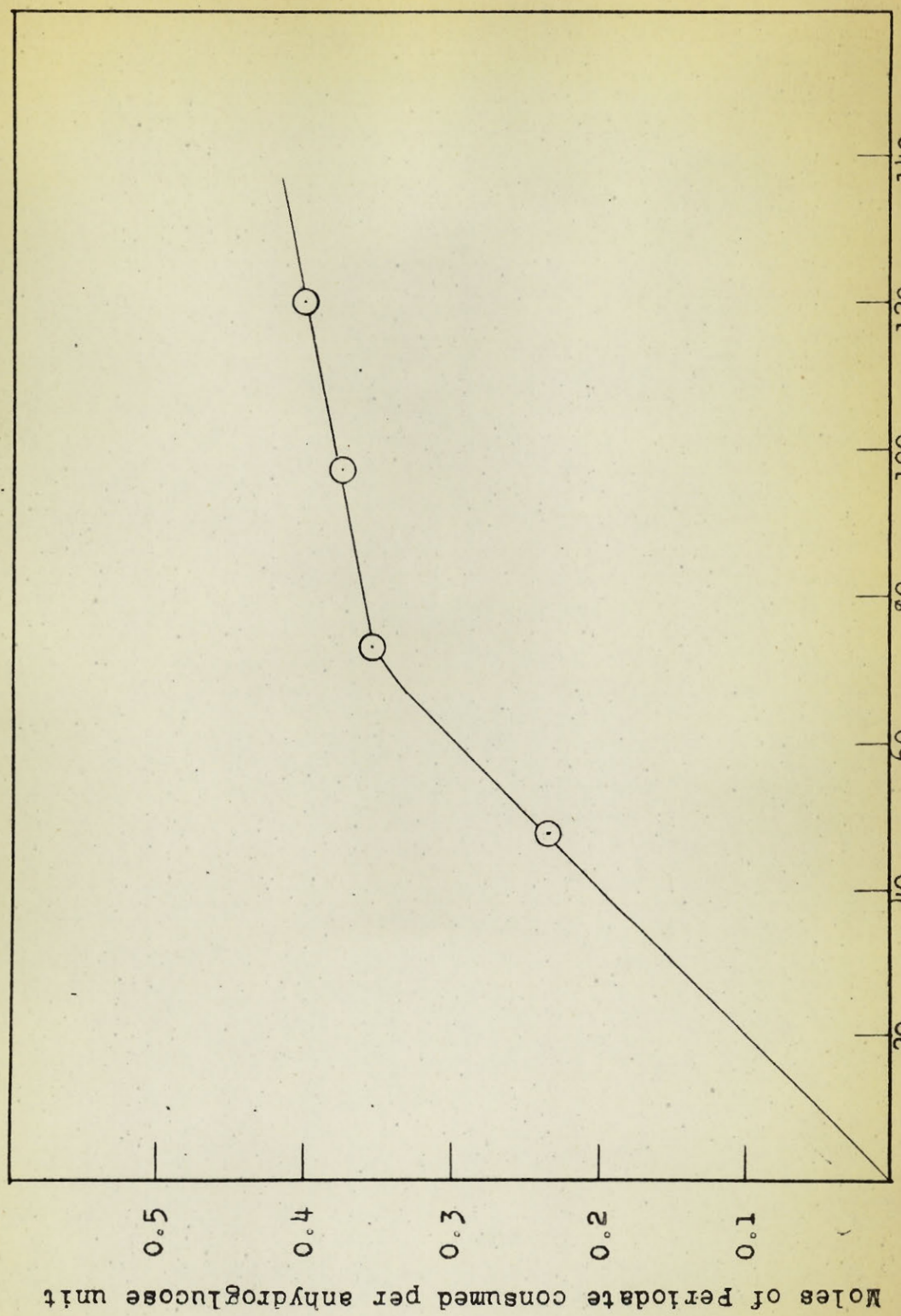


FIG. VII

PERIODATE OXIDATION OF CELLULOSE ACETATE (XVII)

Rate of Tosylation of Cellulose Acetate (XVII). - A 0.25 g. sample of the acetate was dissolved in 3 ml. of pyridine. At zero time and at 20°, 3.5 g. of tosyl chloride dissolved in 7 ml. of pyridine was added. At various time intervals, 2 ml. samples were withdrawn and the tosyl-acetates isolated by first decomposing the excess tosyl chloride in 2 ml. of 5:1 acetone-water, then precipitation into water. The results are given in Table IX and their plot is shown in Fig. VIII.

TABLE IX

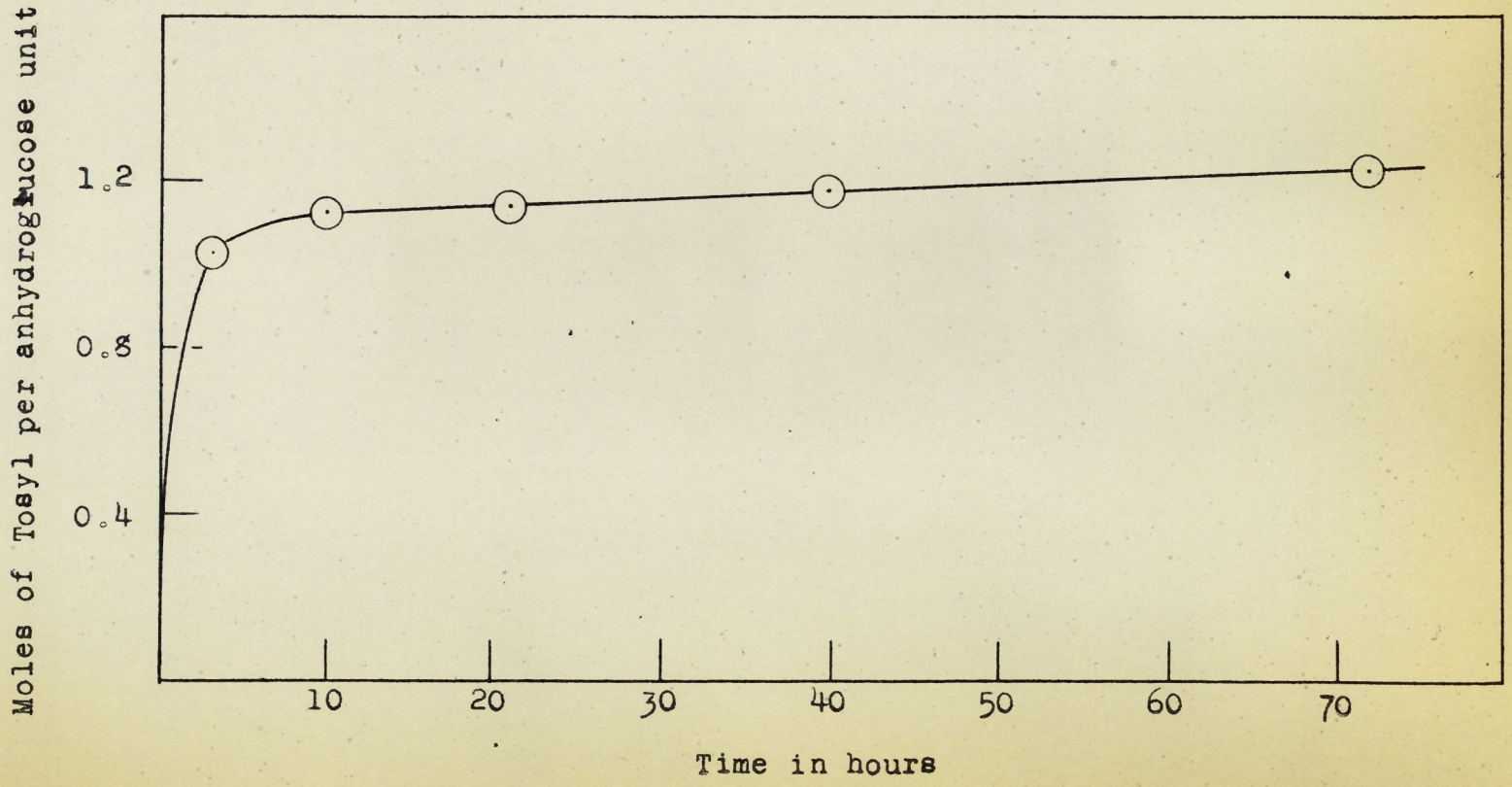
RATE OF TOSYLATION OF CELLULOSE ACETATE (XVII)

Time (hours)	% Sulfur	Moles of Tosyl per unit mol. wt.
3.0	8.66	1.03
10.0	9.10	1.13
21.0	9.15	1.14
40.0	9.35	1.18
72.0	9.55	1.23

A Tosyl Cellulose Acetate (XVIII). - The cellulose acetate (XVII), 1.39 g., was dissolved in 10 ml. of pyridine and 20 g. of tosyl chloride, dissolved in 40 ml. of pyridine, was added. The resulting solution was kept at 20° for seventy-two

FIG. VIII

RATE OF TOSYLATION OF CELLULOSE ACETATE (XVII)



hours. Isolation of the product was accomplished by a slow addition of the solution to 40 ml. of acetone containing 10 ml. of water. Stirring was continuous and the mixture was cooled in an ice salt bath. The resulting solution was poured with stirring into 1.5 litres of water. The yield was 2.44 g., or 86% of theory, of a pure white, fibrous product. This product was extremely resistant to acid hydrolysis. Solution in 72% sulfuric acid was incomplete after four days.

Anal. Calcd. for 1.45 acetyl, 1.50 tosyl groups per anhydroglucose unit: Acetyl, 13.7; S, 10.6. Found: Acetyl (Method 2), 13.8, 13.9; S, 10.7%.

Iodination of Tosyl Cellulose Acetate (XVIII). - The tosyl acetate, 1.05 g., was dissolved in 25 ml. of dry acetone and 10 g. of sodium iodide was added. The solution was heated at 100° for two and one-half hours. A considerable amount of iodine was liberated. The solution was poured with stirring into water. The precipitate was washed free of iodide, then dried in air. Purification was by a reprecipitation from acetone into water. The yield, air dried, was 0.91 g. of bright yellow, brittle fibers (XIX). The analyses show that 0.35 moles of tosyl group were lost.

Anal. Calcd. for 0.82 iodine atoms, 0.33 tosyl groups and 1.45 acetyl groups per anhydroglucose unit (XIX): I, 28.6; S, 2.90; Acetyl, 16.7. Found: I, 28.7, 28.3; S, 3.06, 2.86, 2.92; Acetyl (Method 2), 16.7, 16.5%.

G. Further Characterization of the Monotrityl Cellulose (XI)

A Monotrityl Cellulose Tosylate (XX). - The trityl cellulose (XI), 11.0 g., was dissolved in 100 ml. of pyridine. To this solution, 100 mg. of tosyl chloride in 100 ml. of pyridine was added, and the mixture was allowed to stand at 20° for six days. Sodium bicarbonate, 90 g., was dissolved in 1.5 litres of 50% aqueous acetone and the solution was cooled to -18°. To this cooled mixture kept in an ice-salt bath, the tosylating mixture was slowly added with rapid mechanical stirring. Much carbon dioxide was evolved. The white fibrous precipitate was washed with water, extracted with acetone, washed with much water and air dried. Purification was by solution in dioxane, precipitation into water, steeping in warm water to remove pyridine and washing with water. The dry cream colored product weighed 14.4 g. This material was soluble in dioxane, pyridine and chloroform.

Anal. Calcd. for 0.91 tosyl and 1.04 trityl groups per anhydroglucose unit (XX): S, 5.30; Trityl, 46.0. Found: S, 5.34; Trityl, 46.5, 46.2, 46.0%.

(XXI) Monotosyl Cellulose. - The trityl cellulose tosylate (XX), 5 g., was dissolved in 50 ml. of dry chloroform. Chloroform, 100 ml., saturated with dry hydrogen chloride and cooled to 0° was added. After standing for one hour, the mixture was transferred to 1 litre of 30-60° petroleum ether

containing 10 ml. of pyridine. The white fibers were recovered, washed with methanol and dried in the atmosphere. Purification was by dissolving in pyridine, filtration and precipitation into methanol. After washing with methanol, the trityl-free, pure white fibers were dried in vacuo over calcium chloride. The yield was 2.7 g. Pyridine alone, of the solvents tried, dissolved this substance.

Anal. Calcd. for 0.91 tosyl group per anhydroglucose unit: S, 9.64. Found: S, 9.56, 9.64%.

(XXII) Monotosyl Cellulose Diacetate. - The monotosyl derivative (XXI), 1.5 g., dried in vacuo at 60°, was dissolved in 25 ml. of dry pyridine and 10 ml. of acetic anhydride was added. After standing at 20° for five days the solution was poured with stirring into ice water. After washing with water, the white fibers were air dried. The yield was 1.9 g. This substance, like the tosyl-acetate (XVIII), proved highly resistant to acid degradation.

Anal. Calcd. for 0.91 tosyl and 2.00 acetyl groups per anhydroglucose unit: S, 7.54; Acetyl, 22.0. Found: S, 7.50, 7.49; Acetyl (Method 2), 21.9, 22.3%.

Iodination of Monotosyl Cellulose Diacetate (XXII). - The tosyl-acetate, 1 g., was dissolved in 25 ml. of acetone. This solution was heated with 10 g. of sodium iodide at 100°

for two and one-half hours. The cooled solution was precipitated into water, the fibers collected and washed with water until iodide free. After drying in air, the material was dissolved in acetone, the solution filtered and poured into water. The washed fibers were dried in vacuo over calcium chloride. The yield was 0.9 g. of tan colored fibrous material (XXIII).

Anal. Calcd. for 0.11 Iodine atoms, 0.80 tosyl and 2.00 acetyl groups per anhydroglucose unit (XXIII): Acetyl, 22.6; I, 3.67. Found: Acetyl (Method 2), 22.4, 22.9; I, 3.60, 3.61%.

(XXIV) "6-Iodocellulose Dicarbanilate" (2). - A sample of this material was desired in order to attempt its reduction by catalytic hydrogenation. This technique could not be used for the reduction of iodocellulose acetates since the latter deacetylated and precipitated under the alkaline conditions required for the hydrogenation.

The conditions described by Hearon, Hiatt and Fordyce (2), see Page 9, were used. The iodocellulose derivative did not analyze as expected. The iodine content was slightly low and the nitrogen content high. The sulfur content was too low to be accurately determined on the amount of material available. Nevertheless, the results are believed to be in sufficiently good agreement with those published to assume that the iodocellulose dicarbanilate contained close to 0.90 atoms per anhydroglucose unit. The trityl cellulose (XI) was therefore

probably nearly identical in structure to the preparation reported by Hearon, Hiatt and Fordyce (2). The "6-iodocellulose dicarbanilate" proved to be only partially soluble in dioxane. This derivative was not re-iodinated. The results of this preparation are presented in Table X.

H. Studies on the Nitration of Trityl Cellulose Acetates

Nitration of Various Cellulose Acetate Derivatives. - The nitration mixture (225) was prepared by an addition, under anhydrous conditions, of 100 g. of phosphoric anhydride to 400 g. of pure freshly distilled anhydrous nitric acid. Stirring was continuous and the mixture was cooled in an ice-salt bath.

Volumes of 25 ml. each were added at 0° to 50 mg. samples and the resulting mixtures allowed to stand various lengths of time. In each case the cellulose product was recovered in a sintered glass filter funnel where it was washed with 50% ethanol-water cooled to -15° (225). After boiling in ethanol for five minutes, the fibers were recovered and this treatment repeated two more times. After expressing the excess ethanol, the fibers were dissolved in acetone, the solution filtered free of insoluble impurities and poured with stirring into distilled water. The precipitated product was washed with water, air dried, then dried *in vacuo* at 65° previous to analysis. The results obtained for a variety of cellulose acetates and the cellulose acetate-nitrates (III) and (IV) are tabulated in

TABLE X

PREPARATION OF IODOCELLULOSE DICARBANILATE

		Trityl Cellulose (XI)	Trityl Cellulose Dicarbanilate	Cellulose Dicarbanilate	Tosyl Cellulose Dicarbanilate	Iodocellulose Dicarbanilate (XXIV)
Trityl Groups per g.u.		1.04	1.04	-	-	-
% Trityl	Calcd.	61.0	-	-	-	-
	Found	61.2,61.1	-	-	-	-
Carbanyl Grps.		-	1.96	1.92	1.92	1.92
% N	Calcd.	-	4.24	6.87	4.90	5.28
	Found	-	4.29,4.28	6.85,6.88	4.96,4.98	5.55,5.62
Tosyl Groups		-	-	-	0.98	(0.08)
% S	Calcd.	-	-	-	5.70	0.50
	Found	-	-	-	5.72	0.4
Iodine Atoms		-	-	-	-	(0.90)
% I	Calcd.	-	-	-	-	22.4
	Found	-	-	-	-	20.9,21.0

Table XI. The data show that the substitution of cellulose acetates can be completed to trisubstitution by nitration under these conditions. Furthermore, this nitration is accompanied by little, if any, deacetylation.

Nitration of Various Trityl Cellulose Acetates. - Some of the products derived from the rate of acetylation studies, see Page 112, were nitrated with a 25% phosphorus pentoxide in pure nitric acid mixture. The nitrating mixture, 25 ml., was added to 1.5 g. of the trityl-acetate at -15°. The mixture was kept at 0° for the times indicated in Table XII. The fibres were then recovered on a sintered glass funnel, washed with ice cold 50% acetic acid, then added to 50% ethanol. After washing three times with ethanol, they were boiled in ethanol for five minutes. Pressed free of ethanol, the fibers were dissolved in acetone, filtered and the solution poured into water. The fibers were colored a slight pink. This coloration was removed by a precipitation from acetone solution into methanol. The pure white fibers were dried in air, then in vacuo at 60° for six hours before analysis. The results for trityl cellulose acetates, varying in acetyl content, are given in Table XII.

TABLE XI

NITRATION OF VARIOUS CELLULOSE ACETATES

Run No.	Substance	Composition of Substance					Time (hours)	Composition of Nitrate-Acetate		
		% Acetyl	Moles Acetyl per g.u.	% N	Moles Nitrate per g.u.	Free Hydroxyls per g.u.		% N(a) Calcd.	% N Found	Moles Nitrate introduced
1.	Unswollen linters	-	-	-	-	3.0	1.0	14.14	14.1	2.98
2.	Acetate-Nitrate (III)	22.6	1.43	5.68	1.10	0.47	3.0	7.50	7.10	-
3.	"	"	"	"	"	"	5.75	7.50	7.15	-
4.	"	"	"	"	"	"	8.0	7.50	7.30	-
5.	(b) Homogeneous Nitration (c)	-	-	-	-	-	1.0	7.50	7.35) 7.45	0.44
6.		22.6	1.43	5.68	1.10	0.47	6.5	7.50	7.45) 7.55	0.47
7.	Acetate-Nitrate (IV)	-	0.42	6.68	1.10	1.48	1.0	12.20	12.20	1.48
8.	Acetone-soluble Cellulose Acetate	38.6	2.33	-	-	0.67	0.5	3.06	3.04 2.97)	0.67
9.	Cellulose Acetate	43.6	2.86	-	-	0.14	1.0	0.70	0.70 0.70)	0.14

(a) For nitration to complete substitution of 3.00, assuming no loss of acetyl.
(b) Product from run No. 4 after reprecipitation to create a new surface.
(c) By solution in nitric acid-acetic acid-acetic anhydride (1:1:1) mixture (226).

TABLE XII

NITRATION OF VARIOUS TRITYL CELLULOSE ACETATES

Run No.	Composition of Trityl-Acetate		Time (mins.)	Composition of Acetate-Nitrate			Moles Acetyl lost (x - z)
	% Acetyl	Moles Acetyl per g.u. (x)		% N	Moles Nitrate per g.u. (y)	Moles Acetyl per g.u. (z)	
1	11.5	1.19	90	9.94 9.95	2.09	0.91	0.28
2	13.9	1.49	30	8.60 8.65	1.81	1.19	0.30
3	17.5	2.00	30	6.61 6.58	1.38	1.62	0.38

I. Further Characterization of the "Cellulose-6-nitrate Acetate (III)"

Methylation with Diazomethane. - An anhydrous solution of diazomethane (227) in dioxane-diethyl ether (6:1 by volume) was prepared. To 50 ml. of the deeply yellow solution, 1 g. of the acetate-nitrate (III) was added. The resulting solution was allowed to stand at 5-10° for three days. On pouring into water, after destruction of the excess diazomethane with acetic acid, a white fibrous precipitate was obtained which tended to powder on drying.

Anal. Calcd. for 1.43 acetyl, 1.10 nitrate, 0.23 methoxyl groups per anhydroglucose unit: Methoxyl, 2.60. Found: Methoxyl, 2.53, 2.60%.

Free Hydroxyl Determination. - The procedure and calculation was exactly as described by Wolfrom, Dickey, Hoffman and Olin (228) except that before decomposing the acetylating mixture with water, 25 ml. of pure dioxane was added. This addition made possible a more uniform precipitation of the acetate-nitrate. When this procedure was omitted, highly erratic results were obtained.

Samples, 0.3 to 0.4 g., were accurately weighed into 30 ml. ground glass stoppered tubes. Two ml. amounts of the pyridine-acetic anhydride reagent (1:7 by volume) were then weighed into the tubes. The resulting solutions were allowed to stand one day at room temperature. Dioxane, 25 ml., was added to each tube

before the contents were drowned in 150 ml. volumes of water, contained in 600 ml. beakers, with vigorous manual agitation. After the contents of the tube had been quantitatively transferred to the beaker, the mixture was allowed to stand for three hours and the excess acetic acid was titrated with 0.1945 N sodium hydroxide solution until the phenolphthalein end-point persisted for ten seconds on vigorous agitation with a glass rod. For the purpose of blank determinations, 2 ml. samples of the acetylating reagent were weighed in glass stoppered 5 ml. weighing bottles. At the time of the determination the stoppers of the bottles were loosened and the bottles placed in 600 ml. beakers containing 150 ml. of water. One hour was allowed for hydrolysis, then a solution of 0.3-0.4 g. of the nitrate-acetate (III) in 25 ml. of dioxane was rapidly added with manual agitation. The resulting suspension of finely divided fibers was allowed to stand three hours before titration as in the determination. The volumes of standard alkali required were plotted against the weight of acetylating mixture used. Blanks, for the various weights of acetylating mixture used, were read from this plot.

The number of free hydroxyl groups found per unit molecular weight (271.5) of the acetate-nitrate (III) were 0.23, 0.25. The product from the acetylation was recovered and its nitrogen content was determined.

Anal. Calcd. for 1.10 nitrate and 1.43 + 0.24 acetyl groups per anhydroglucose unit: N, 5.46. Found: 5.39, 5.41%.

J. Unesterified Primary Hydroxyl Groups in Acetone-Soluble Cellulose Acetate

A 6-Desoxycellulose (XXVIII). - The acetone-soluble cellulose acetate (218), which was the source of the cellulose used throughout the research, was tosylated under conditions (36) which guaranteed reaction of all free primary hydroxyl groups. The product (XXV) was iodinated to yield an iodocellulose acetate tosylate (XXVI) which was found to contain 0.203 iodine atoms per anhydroglucose unit. The iodo-compound was reduced under the conditions described by Cramer and Purves (36) to yield a desoxycellulose acetate tosylate (XXVII). The analyses of these substances are tabulated in Table XIII.

The desoxycellulose acetate tosylate (XXVII), 0.5. g., was suspended in 25 ml. of dry methanol and 20 ml. of 0.15 N sodium methylate in methanol was added. The mixture was heated under reflux for two hours. The highly colored yellow supernatant liquid was removed and the brown powder (XXVIII) was repeatedly washed with water, then dried in vacuo. Drying for analysis was at 100° for one-half hour. The yield, 0.08 g., was approximately 25% of theory.

Anal. Calcd. for cellulose with 0.128 isorhamnose units (XXVIII): Apparent Acetyl, 3.46. Found: Apparent Acetyl (Method 3), 3.44%.

TABLE XIII

UNESTERIFIED PRIMARY HYDROXYL GROUPS IN ACETONE-SOLUBLE CELLULOSE ACETATE

		Acetone-Soluble Cellulose Acetate	Tosyl Cellulose Acetate (XXV)	Iodocellulose Tosyl Acetate (XXVI)
Moles Acetyl per g.u.		2.33	2.33	2.33
% Acetyl	Calcd.	-	32.6	-
	Found	38.6	31.6,31.6(a)	-
Moles Tosyl per g.u.		-	0.299	0.096
% S	Calcd.	-	3.14	1.03
	Found	-	3.13,3.34	1.03,0.95
Iodine Atoms per g.u.		-	-	0.203
% I	Calcd.	-	-	8.70
	Found	-	-	8.69,8.70

(a) This analysis may be 1% low. On the basis of the analysis of the iodo-compound (XXVI), the acetyl substitution was accepted as 2.33.

(XXIX) "Cellulose Triacetate". - The acetone-soluble cellulose acetate, 5 g., was dissolved in 75 ml. of pyridine. The solution was cooled to -15° and 30 ml. of similarly cooled acetic anhydride was added. After standing at 0° for seven days the solution had gelled. The gel was triturated with iced water and the white product air dried. Purification was by solution in chloroform and precipitation of the filtered solution into methanol. After washing with methanol, the pure white fibers were dried in vacuo. The yield, 5.4 g., was quantitative.

Anal. Calcd. for 2.86 acetyl groups per anhydroglucose unit: Acetyl, 43.6. Found: Acetyl, (Method 2) 43.5, 43.7, (Method 3) 43.7%.

Attempts to complete the trisubstitution by acetylation at higher temperatures always resulted in slightly colored products which were consequently impure.

Rates of Oxidation of Cellulose Derivatives by Chromium Trioxide in Glacial Acetic Acid (64). - The cellulose compound, accurately weighed, was dissolved in pure glacial acetic acid (distilled from chromium trioxide) and the total weight of the solution was determined. Aliquots were pipetted into weighed 125 ml. flasks and the weight of cellulose derivative in each flask could be accurately determined from the weight of the aliquot. The flasks were placed in a thermostat at 20.0°. At zero time, 25 ml. of a chromium trioxide-glacial acetic acid solution,

also at 20.0°, was added to each flask and at various times thereafter the oxidation was stopped by the addition of excess ferrous ion solution. The excess ferrous ion was then back titrated with ceric ion solution using methyl red as redox indicator. Reagent blanks were run. The results were expressed as atoms of oxygen consumed per anhydroglucose unit. The rates, at which the acetone-soluble cellulose acetate, the tosyl cellulose acetate (XXV) and the "cellulose triacetate (XXIX)" consumed oxygen, are shown in Fig. IX. The experimental data are tabulated in Table XIV.

TABLE XIV

RATE OF OXIDATION OF CELLULOSE DERIVATIVES BY CHROMIUM TRIOXIDE IN GLACIAL ACETIC ACID

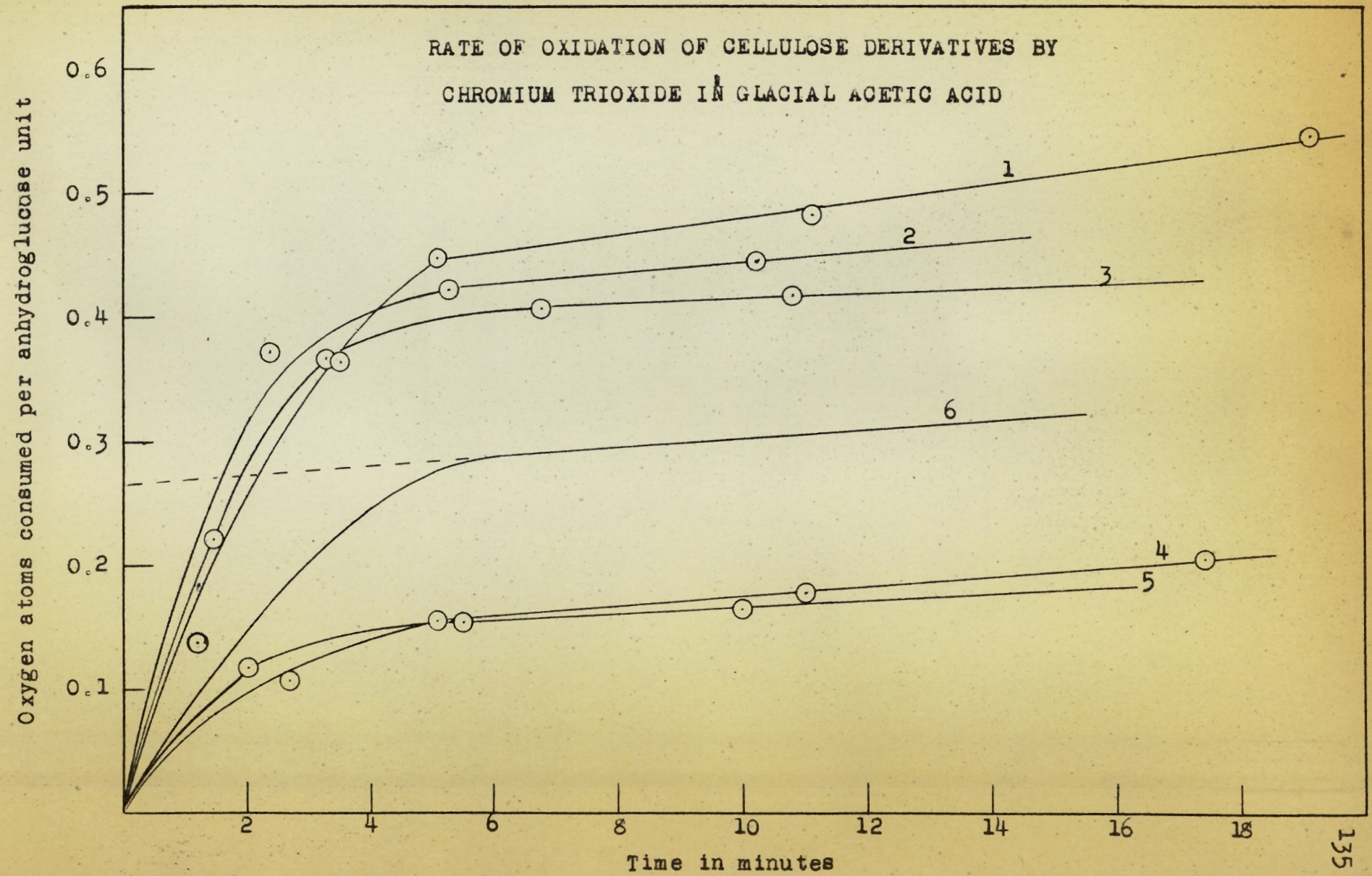
Run No.	Wt. Sample (g.)	Time (mins.)	Ml. Fe^{++} Sol'n. equiv. to CrO_3 consumed	Oxygen atoms consumed per g.u.
Acetone-Soluble Cellulose Acetate (Unit mol. wt. 260)				
1,260 Oxygen atoms available per unit mol. wt.				
			(0.0314 N)	
1	0.159	3.5	14.25	0.364
2	0.159	5.1	17.59	0.450
3	0.159	11.1	18.85	0.483
4	0.159	19.1	21.36	0.546
0.710 Oxygen atoms available per g.u.				
			(0.0370 N)	
1	0.211	1.20	5.99	0.137
2	0.211	2.33	16.12	0.368
3	0.211	5.30	18.57	0.424
4	0.211	10.2	19.56	0.446
5	0.211	22.5	20.88	0.476
0.645 Oxygen atoms available per g.u.				
			(0.0370 N)	
1	0.204	1.38	9.40	0.222
2	0.204	3.30	15.53	0.366
3	0.204	6.75	17.22	0.406
4	0.204	10.8	17.72	0.418
5	0.204	103	21.22	0.500

Cont'd.

TABLE XIV (Cont'd)

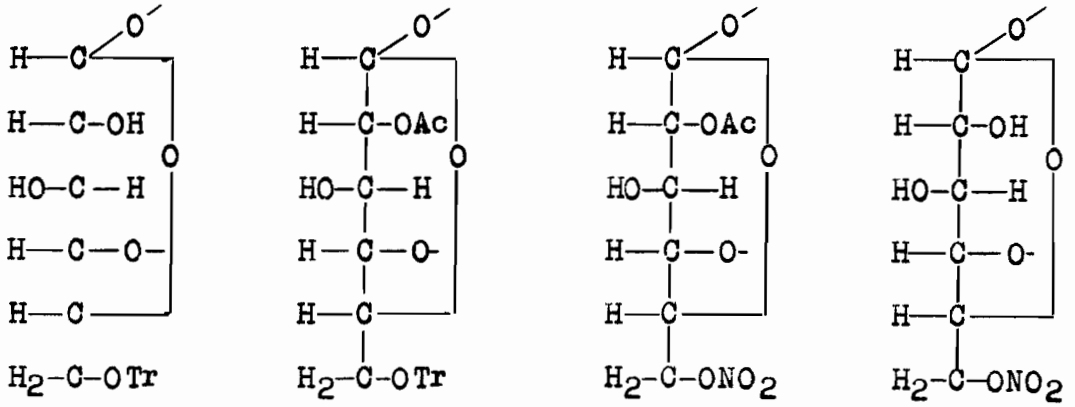
Run No.	Wt. Sample (g.)	Time (mins.)	Ml. Fe^{++} Sol'n. equiv. to CrO_3 consumed	Oxygen atoms consumed per g.u.
Tosyl Cellulose Acetate (XXV) (Unit mol. wt. 306)				
0.885 Oxygen atoms available per g.u.				
			(0.0314 N)	
1	0.196	2.70	4.40	0.108
2	0.196	5.10	6.50	0.159
3	0.196	11.0	7.35	0.180
4	0.196	17.4	8.50	0.208
5	0.196	30.0	9.70	0.238
"Cellulose Triacetate (XXIX)" (Unit mol. wt. 282)				
0.825 Oxygen atoms available per g.u.				
			(0.0314 N)	
1	0.190	2.00	5.40	0.120
2	0.190	5.50	7.10	0.158
3	0.190	10.0	7.50	0.167
4	0.190	21.0	7.90	0.176

FIG. IX


RATE OF OXIDATION OF CELLULOSE DERIVATIVES BY
CHROMIUM TRIOXIDE IN GLACIAL ACETIC ACID
Oxygen atoms consumed per anhydroglucose unit
0.6
0.5
0.4
0.3
0.2
0.1
1
2
3
4
5
6
2
4
6
8
10
12
14
16
18
Time in minutes

DISCUSSION OF RESULTS

As mentioned in the Introduction, the original object of the research was to confirm and extend the work of Levi, Zuckerman and Purves (1) on the synthesis of a "cellulose-6-nitrate". This synthesis involved the acetylation of Hearon, Hiatt and Fordyce's "6-trityl cellulose" (L) to a "monoacetate" (M) in which the location of the acetyl group in the second and third positions was unknown. The group is assumed to occupy the 2-position for structural representation only. The displacement of trityl group in the trityl-acetate (M) was subsequently effected by nitration. The product, a "mononitrate-monoacetate" (M) was selectively deacetylated to the "6-nitrate" (O).



(L) (M) (N) (O)

In repeating this synthesis and in related research, it was realized that the standard acetyl analysis (203) used by the earlier workers, although reproducible, was giving consistently

low results. This unaccounted-for acetyl was found responsible for the interpretation placed by them on the deacetylation curve for the monoacetate-mononitrate (N). The alkali consumption corresponded to the presence of one acetyl group per anhydroglucose unit because the results were calculated on the basis of too small a unit molecular weight.

Much time was accordingly spent in comparing various methods of standard acetyl analysis. Although the Ost (207) and saponification (208) methods yielded higher results, the values obtained were also unsatisfactory. Levi, Zuckerman and Purves (1) attributed an apparent loss in trityl groups in the acetylation of trityl cellulose (L) to an absorption of diethyl ether. Repetition of the synthesis, without the use of diethyl ether as a precipitation medium, yielded substantially the same results. In the isolation of the trityl-acetate (XIII, Experimental Section), the procedure was improved so that, instead of the usual tan colored product, a pure white derivative was obtained. Acetyl analyses by standard methods failed to yield values which corresponded to that expected from the trityl content. Consequently the standard, published methods were abandoned. A highly satisfactory method, based on the oxidation of the sample in aqueous chromic acid and recovery of the acetic acid by distillation, was developed.(Experimental Section, Method 3). The applicability of the technique for the estimation of acetyl in a variety of pure standard substances was described on

Page 83.

TABLE XV

ACETYL ESTIMATION OF VARIOUS TRITYL CELLULOSE ACETATES

Trityl Cellulose	Composition of Trityl Cellulose		Trityl Cellulose Acetate	Composition of Trityl Cellulose Acetate as calculated from the Acetyl content (Method 3) and the Trityl content				
	% Trityl (1)	Moles Trityl per g.u. (2)	(3)	% Trityl (4)	% Acetyl (Method 3) (5)	Moles Trityl per g.u. (6)	Moles Acetyl per g.u. (7)	% Acetyl (other methods) (8)
I	59.5	0.98	II	50.5	15.3	0.98	1.67	10.7 (a)
XI	61.1	1.04	XIII	51.7	13.9	0.99	1.49	9.28, 12.2 (b)
XI	61.1	1.04	XII	51.7	14.5	1.00	1.55	-
XI	61.1	1.04	(d)	49.5	18.0	0.99	2.01	-
XI	61.1	1.04	(e)	50.2	17.2, 17.5	1.02	1.98	14.0, 14.6 (c)
(f)	61.1	1.04	(f)	52.3	13.8	1.01	1.51	9.60, 9.15 (a)

(a) Volatile ester method (203).

(b) Saponification in pyridine solution (208).

(c) Ost distillation method (207).

(d) and (e) Products from acetylation with acetic anhydride and pyridine at 45° for three and one days, respectively.

(f) Preparation and trityl analyses by V. Grassie of this laboratory.

Comparison of columns 2 and 6 in Table XV shows that the amount of trityl substitution present in six different preparations of trityl cellulose acetates, as calculated from their acetyl and trityl contents, (columns 4 and 5), is in good agreement with the trityl substitution of the original trityl cellulose. The use of the earlier, erroneous acetyl values (column 8) in the calculations led to an apparent slight decrease in trityl substitution as a result of the acetylation. Such a decrease is not to be expected from the conditions used.

In order more firmly to establish the validity of the new method of acetyl analysis for trityl cellulose acetates, the composition of the trityl-acetate (XIII) was checked by an independent method. Hearon, Hiatt and Fordyce (20) have shown that phenyl isocyanate in pyridine solution reacts readily and, when properly used, completely with all free hydroxyl groups in cellulose or its derivatives. Their observation, that the trisubstitution of trityl cellulose can be completed in this manner, was confirmed with the trityl cellulose (XI) used in this work, see Table X. Consequently, a sample of the trityl cellulose acetate (XIII) was carbanilated under the conditions used for completing the substitution of trityl cellulose itself. The results, listed in Table VI, show that this method accounted for the expected number of free hydroxyl groups, calculated from the assumption that the acetyl as well as the trityl determinations, were correct. The new method for acetyl analysis was accordingly used throughout the research.

The reason why the Ost method for acetyl estimation failed accurately to determine the acetyl content of trityl cellulose acetate is not known. The acetyl content of 6-trityl-α-methylglucoside triacetate, 23.0%, was correctly recorded by the Ost method as 22.6, 22.6%. There is therefore little possibility that the missing acetic acid in the trityl cellulose acetate work condensed with the trityl residue in the presence of the sulfuric acid. This conclusion is also borne out by the fact that the trityl contents of the trityl cellulose acetates either checked very well with theory or were somewhat lower. Since trityl was estimated with strong sulfuric acid, any condensation with acetyl would have tended to give high values. It may prove significant that the amount of acetyl which was not determined by the Ost technique corresponds roughly to the loss in acetyl which accompanies the detritylation of monotrityl cellulose diacetate (see below).

The "cellulose-6-nitrate monoacetate(III)", obtained by the nitration of the trityl-acetate (II), was fully characterized and shown to contain 1.43 moles of acetyl and 1.10 moles of nitrate. At the time of its preparation, faulty acetyl analyses had indicated that this substance contained one mole of acetyl and one nitrate group per anhydroglucose unit. Consequently, in the preparation of the "cellulose-6-nitrate" (IV) insufficient alkali was added completely to remove all acetyl groups. That the preferential deacetylation of "cellulose-6-nitrate acetate" can in fact be carried out was shown by measurements summarized in

Fig. V. Acetyl groups were quantitatively removed by the alkali in a short period of time, but the nitrate groups proved rather stable to the conditions used. In this manner, V. Grassie, of this laboratory was able to prepare a "cellulose-6-nitrate" which was nearly acetyl-free. The mode of thermal decomposition of this substance was investigated by him (3) .

The trityl cellulose acetate (II) contained 1.67 moles of acetyl group, whereas only 1.43 moles remained in the acetate-nitrate (III) obtained through the nitration of the former by a nitric acid-chloroform mixture. It is noteworthy that this nitration not only removed 0.24 moles of acetyl but left 0.37 free hydroxyl groups in the acetate-nitrate (III). These hydroxyl groups were subsequently nitrated under conditions which are known to yield trisubstitution for cellulose derivatives (225),(see Table XI).

An attempt was made to assess the amount of degradation accompanying the synthesis of the "cellulose-6-nitrate" (IV) by the Kraemer and Lansing (229) modification of Staudinger's viscosity method. Since no solvent common to all derivatives was found, it was necessary to determine their intrinsic viscosities $[\eta]$, in a variety of solvents. These viscosities (Table XVI) are by Staudinger's earlier theory proportional to the average degree of polymerization (D.P.), but inspection of the data for cellulose acetate or cellulose acetate-nitrate (III) shows that variations caused by change in solvent amount to at least ±10% Ignoring variations of this or lesser magnitude, the data suggest

that the intrinsic viscosity or the D.P. was reduced by one-third to one-half during the tritylation of the cellulose. This result is contrary to Hearon, Hiatt and Fordyce's (2) conclusion that the cellulose undergoes scarcely any degradation during this etherification. Heuser (230) has remarked that absence of degradation in such a reaction would appear rather improbable. Degradation in all subsequent steps was apparently inconsequential. Since the nitrated derivatives were slowly degraded by pyridine, the corresponding viscosities in Table XVI are probably slightly low.

TABLE XVI

INTRINSIC VISCOSITIES(a) OF VARIOUS CELLULOSE DERIVATIVES

Substance	Base M.W.	Intrinsic Viscosities $[\eta]$ in Acetone	Dioxane	Pyridine	Acetic Acid
Cellulose Acetate(b)	260	1.70	2.16	1.65	2.20
Cellulose	284(c)	2.20		1.80(e)	
Trityl-Cellulose(I)	399			0.95	
Trityl-Acetate(II)	469				Chloroform 1.20
Acetate-Nitrate(III)	272	0.99	1.19	0.79(e)	
"6-Nitrate" (IV)	(d)	1.23			

(a) Quotient of η_{sp} (relative viscosity minus unity) by percentage concentration as concentration tends to zero.
(b) Starting material.
(c) Regenerated and after nitration (H_3PO_4-HNO_3) to N = 13.4%.
(d) After nitration to N = 11.2%.
(e) Unstable and therefore probably low.

A variety of conditions were used for the nitration of trityl cellulose acetates. All of the methods used brought about some deacetylation. In similar fashion, some loss in acetyl occurred during the detritylation of the monotrityl cellulose diacetate (XV) to the acetates (XVI) and (XVII). As a consequence of this loss the trityloxy groups in a trityl cellulose acetate cannot be selectively replaced by nitrate. Of the nitrating conditions used, the method employed for the preparation of the "cellulose-6-nitrate acetate" (III) yielded nitrates of lowest degree of nitration. Murray and Purves (148) have shown that cellulose nitrates of low degree of substitution have nearly 50% of the nitrate groups situated at the primary position. This indication for the preferential nitration of the primary position made it likely that, although only 1.43 of the hydroxyl positions in the "cellulose-6-nitrate acetate" (III) were blocked by acetyl, the 1.10 moles of nitrate group introduced largely occupied the positions which were originally occupied by the trityl groups.

Two methods were available for the proof of this assumption. The first was the estimation of the number of completely unsubstituted 2,3-glycol groups in the "cellulose-6-nitrate" by oxidation with periodate or lead tetraacetate. No oxygen consumption was detected when the "cellulose-6-nitrate" (IV) was exposed to either of these reagents. The "6-nitrate" (IV) was later shown to contain 0.42 acetyl as well as 1.10 nitrate groups. Since iodination located 0.80 of these 1.52 groups at the primary

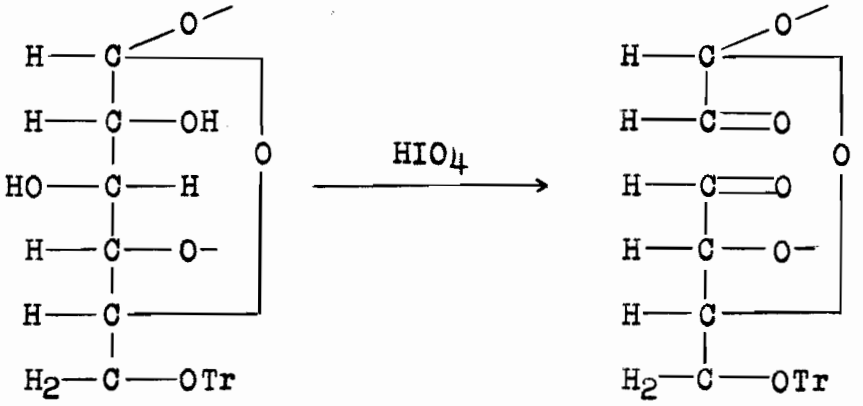
position (see below), the derivative should have contained at least 0.28 (1.00 - (1.52 - 0.80)) free glycol groups. The method was therefore abandoned. The second attempt to check the above assumption was by selective replacement of the primary nitrate groups in the "6-nitrate" by iodine through the action of sodium iodide in acetone (148), a variety of conditions being employed. The maximum replacement obtained indicated that of the 1.10 nitrate groups in the acetate-nitrate (III), 0.80 were replaceable by iodine and therefore situated in the primary position. A parallel experiment with α-methylglucoside-6-nitrate-triacetate showed that, at least for this substance, the conditions used caused only an 85% replacement. In this case primary nitrate groups were certainly displaced by iodine and no oxidative denitration took place since no free iodine was liberated. The experiments with cellulose trinitrate showed that cellulose nitrates may contain highly active secondary nitrate groups which are readily removed under the conditions of iodination. Since the cellulose trinitrate must have contained very close to one mole of primary nitrate, and only 0.73 iodine atoms were introduced, it is evident that the replacement of primary nitrate groups by iodine may not be altogether quantitative. The side reactions which are involved are probably analogous to the double bond and anhydro-ring formation which has been observed to take place on the iodine displacement of some tosyloxy groups (see Page 54). These considerations make it probable that the acetate-nitrate (III) contained as a minimum 0.80 moles of primary nitrate.

Although no exception is known to the rule that only primary nitrate groups are replaceable by iodine, the general trends of these so-called "selective reactions", as traced in an earlier section of this Dissertation, have made it evident that absolute certainty can never be attacned to their significance. It was therefore realized tnat structure of the "cellulose-6-nitrate acetate" (III) should be confirmed by an independent method. Such confirmation could be most readily accomplished by the replacement of the iodine atoms in the iodocellulose by hydrogen and by determining the terminal methyl groups thus formed.

Since the catalytic hydrogenation of halogen compounds requires alkaline conditions the iodocellulose acetate (VI) could not be reduced in this manner. Hearon, Hiatt and Fordyce (20) have shown that the carbanyl group (phenyl urethyl) is very stable to both alkaline and acid hydrolysis. It was therefore believed that the "6-iodocellulose dicarbanilate" (XXIV) would be an ideal derivative for attempting a catalytic hydrogenation of the iodine atom. However, it proved stable to a twenty-four hour exposure to Raney nickel in the presence of diethylamine (242). Recourse was therefore made to the reduction of iodine by a zinc-copper couple and acetic acid (36). This technique made possible the preparation of a 6-desoxycellulose acetate (VII) whose analysis revealed the presence of 0.52 terminal methyl groups. This isorhamnose content was confirmed by the terminal methyl content of the 6-desoxycellulose

(VIII) obtained by deacetylation of VII.

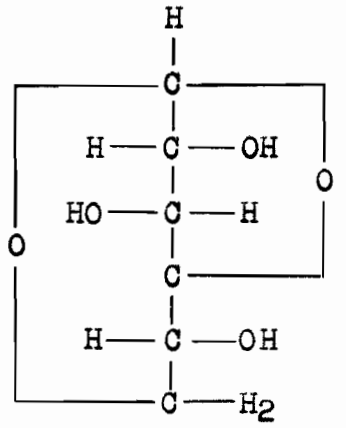
The quantitative estimation of the α-glycol groups in the 2,3-positions of pure cellulose by periodate oxidation has been firmly established (231,232). Gladding and Purves (233) have shown that the reaction proceeds best in the pH range 2 to 4.2. It seemed reasonable to expect that, if monotrityl cellulose is largely composed of 6-trityl anhydroglucose units (P), it should consume periodate and be converted to the dialdehyde structure (Q). This result would provide a proof of its



(P) (Q)

structure independent of that offered by Hearon, Hiatt and Fordyce (2). Mahoney and Purves (59) have used this technique to determine the free α-glycol groups in a variety of ethyl and methyl ethers of cellulose. Application of this method to the monotrityl cellulose (I) showed that it consumed only 0.06 moles periodate per unit molecular weight. Since it is likely that the nitrate groups in the "cellulose-6-nitrate acetate" (III) largely occupied the positions at which the trityl groups were

situated and at the very least 0.52 moles of these positions were shown to be primary, it may be concluded that the trityl cellulose contained free 2,3-glycol groups which proved resistant to both periodate and lead tetraacetate oxidation. This result, however, need not be taken as proof against the accepted (2) structure for trityl cellulose. Steric and polar effects (see Page 70) have already been noted which prevented the ready dialdehyde cleavage of some α-glycols by periodate. Probably the most outstanding resistance of an α-glycol to periodate and lead tetraacetate is that reported by Dimler, Davis and Hilbert (234). They isolated and characterized a new anhydro form of glucose and established its structure as D-glucosan ⟨1,4⟩β⟨1,6⟩ (R). This compound was shown to be completely resistant to



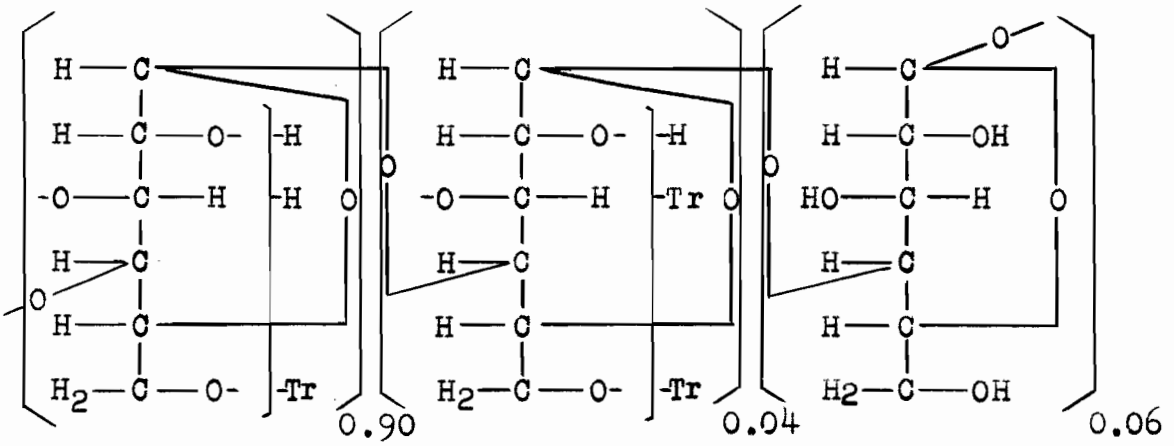
(R)

oxidation over a prolonged period by either periodic acid, sodium periodate or lead tetraacetate. They suggested that the resistance of this glycol group to oxidation is a combined effect of the trans-glycol configuration and the rigidity conferred upon

the spacial arrangement of the hydroxyl groups by the double lactol ring structure. Another consideration is the possibility that the state of polarization or polarizability of the alcoholic oxygen atoms of the glycol group may be such as either to render coordination difficult or to render the decomposition of the coordination complex to the dialdehyde and iodate difficult.

From the past experience with pure cellulose, it would be expected that periodate would attack any free anhydroglucose units in monotrityl cellulose. The rapid consumption of 0.06 mole of periodate per unit molecular weight is therefore possibly attributable to the presence of 0.06 completely unsubstituted anhydroglucose units. On this supposition the structure of the monotrityl cellulose (I) can be represented as in Fig. X.

MONOTRITYL CELLULOSE (I)



Total 0.98 moles trityl

FIG. X

This extremely homogeneous substitution is well supported by the uniform solubility properties of the substance. The structure is strong support for the theory that regenerated cellulose, swollen in pyridine, reacts much like cellulose in homogeneous solution (8). The high solubility in pyridine of the cellulose acetates (XVI) and (XVII) and the monotosyl cellulose (XXI), which are probably nearly fully substituted in secondary positions, may indicate that pyridine is able to swell starch or cellulose because of its ability to solvate those hydroxyl groups (the primary) which are held largely responsible for the hydrogen bonding between adjacent cellulose chains (13).

Since 0.08 of the trityl groups are situated in ditrityl units, and at least 0.52 moles were assumed in the 6-position, at least 0.48 6-monotrityl anhydroglucose units were present in the monotrityl cellulose (I).

The seemingly anomalous (23) observation that trityl cellulose (I) containing 2.02 moles of free hydroxyl only acetylated to an acetyl content of 1.67 moles, after five days at room temperature, is supported by the curves for rate of acetylation (see Fig. VII). Independent confirmation of the conclusion that trityl cellulose acetylates beyond the monoacetate stage and only very slowly beyond a substitution of 1.5 to 1.7 at ordinary temperatures, is provided by an apparent hydroxyl determination conducted on a sample of the trityl cellulose (XI) by L. Wolfrom (235). Acetylation in pyridine-acetic anhydride

and determination of the excess acetic acid indicated that only 1.44 hydroxyl groups had reacted after one day at room temperature, whereas 1.96 were present.

Verley and Bolsing (236) have pointed out that the pyridine used in conjunction with acetic anhydride, for the acetylation of alcohols, neutralizes the acetic acid formed in the substitution reaction. Esterification with pyridinium acetyl chloride also failed to acetylate trityl cellulose completely. It has been suggested (237) that ketene is the active acetylating agent in this mixture. Under similar conditions of concentration and temperature acetyl chloride in pyridine is considerably more reactive than acetic anhydride in pyridine (223). The reaction between trityl cellulose and acetyl chloride may not have gone to completion because of an insufficient supply of the slightly soluble pyridinium acetyl chloride diffusing into the acetylating mixture.

The mechanism of the acetylation of trityl cellulose at temperatures below 25° is difficult to explain. No information seems to be available as to whether this reaction is reversible or irreversible. The fact that both acetic anhydride and acetyl chloride liberate an acid on reaction with alcohols and that these reactions were carried out in the presence of the basic pyridine makes it probable that the reaction is irreversible. The fact that both acetylations did not go to completion may therefore be attributable to a steric hindrance effect. This effect may have been overcome by the increased thermal agitation

at 45° under which conditions the completely substituted monotrityl cellulose diacetate was formed.

In the absence of detailed knowledge regarding the reversibility or otherwise of the pyridine-acetic anhydride acetylation of alcohols, it would seem legitimate to consider the possibility that it may be reversible. The assumption that it is reversible would yield a more ready explanation for the observed drop in the degree of esterification from the value of 1.63 moles of acetyl after a reaction time of seven days at 5° to 1.55 moles on extending the reaction for a period of two months. The observation that the degree of substitution did not slowly rise to completion, but instead decreased, would indicate that the introduction of some acetyl groups into the cellulose molecule enhanced the resistance of the other free positions toward acetylation. That is, at the beginning of the acetylation the more resistant hydroxyl groups acetylated more completely than after they were regenerated and the other hydroxyl positions were largely substituted. The above results are reminiscent of those obtained by Meiszner (238) on the nitration of pure absorbent cotton. A sulfuric-nitric acid-water nitrating mixture which gave 12.21% nitrogen in two hours at 20°, gave 11.91% in six hours and 10.08% after eight days' immersion. The nitration reaction has definitely been established as reversible (239).

The fact that the tosylation of trityl cellulose resulted in a monotosyl monotrityl (XX), instead of a ditosyl monotrityl

derivative, parallels the formation of a ditosyl rather than a tritosyl derivative from cellulose itself. The detritylation of the former material yielded a monotosyl cellulose (XXI) which was acetylated readily enough to the expected monotosyl cellulose diacetate (XXII). Since the tosylation of the trityl cellulose would be expected to cover all free hydroxyl groups remaining in the primary positions, iodination of the monotosyl cellulose diacetate (XXII) should provide an independent check for the structure of trityl cellulose. The fact that only 0.11 tosyl groups were replaceable by iodine is in good agreement with the earlier conclusion that about 0.9 moles reacted in the monotosylate-dicarbanilate (see Table X). The combined results suggest that the trityl groups in the trityl cellulose (XI) occupy approximately 0.9 moles of hydroxyl position, presumably the sixth, whose tosyl ester is replaceable by iodine. Monotosyl cellulose (XXI), with its substituent mostly (0.8 moles) in a secondary position, should prove an interesting starting material to study the tritosylation of cellulose or the identification (245) of the position (or positions) occupied by the hydroxyl groups in trityl cellulose which proved resistant to tosylation.

Since the nitration of monotrityl cellulose diacetate was invariably accompanied by considerable deacetylation, another approach to the synthesis of "cellulose-6-nitrate" was investigated. It seemed likely that if the trityl diacetate could be detritylated without acetyl wandering, then the primary hydroxyl groups thus formed could be preferentially tosylated. Purves and

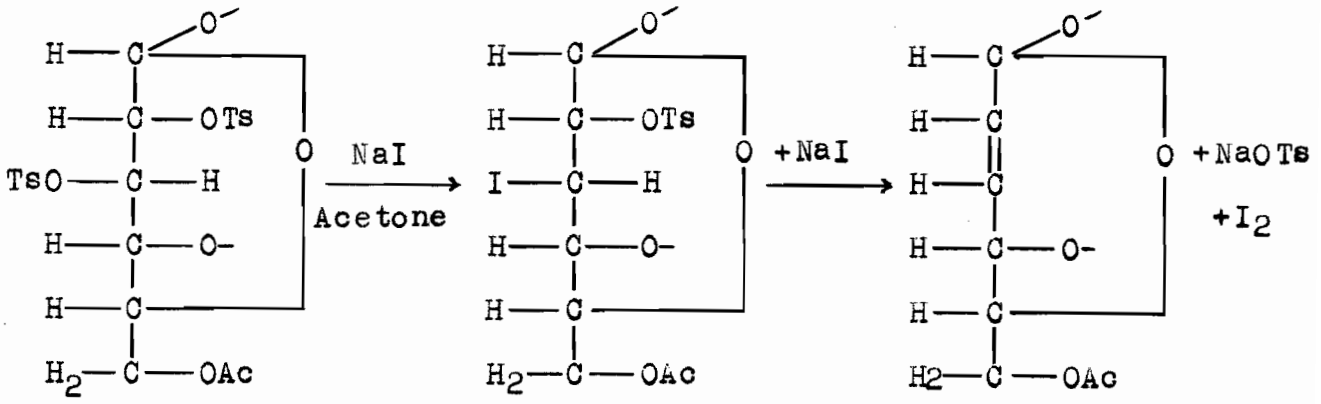
his coworkers (36,60) have shown that the primary hydroxyl group in technical cellulose esters and ethers is considerably more rapidly esterified than either of the secondary ones. The cellulose acetate (XVII) was therefore prepared, 0.54 moles of acetyl being lost. Sakurada and Kitabatake (23) have had a similar experience in the preparation of "diacetyl cellulose" from the same source.

A study of the rate of tosylation of the cellulose acetate (XVII) showed that the 1.55 free hydroxyl groups in this compound readily consumed 1.12 moles of tosyl chloride (see Fig. VIII). The rate of tosylation, though much slower, was appreciable thereafter. In the preparation of the tosyl cellulose acetate (XVIII), with a higher concentration of tosyl chloride than previously, no less than 1.50 of the available 1.55 hydroxyl groups reacted in the short period of seventy-two hours. On the basis of Gardner and Purves' (60) relative rates for the tosylation of the free hydroxyl groups in cellulose acetates, the cellulose acetate (XVII) contained approximately 0.4 free hydroxyl groups at the 2-position and 0.9 to 1.0 free primary hydroxyl groups.

In order to prove the above structure for the cellulose acetate (XVII), the compound was tested for free 2,3-glycol groups by periodic acid. Figure VII shows that 0.3 to 0.4 moles of periodate were consumed per unit molecular weight. Although the reagent blanks were rather unstable for a reaction which was extended over such a long period of time (five days), the amounts of periodate consumed are believed large enough to indicate that

dialdehyde cleavage was the main reaction.

Iodination of the tosyl-acetate (XVIII) showed that 0.82 moles of the tosyl groups were replaceable by iodine. However, the iodination reaction caused a loss of 0.35 moles of tosyl with the liberation of a substantial amount of free iodine. The liberation of free iodine has only been observed to take place when a secondary tosyl group is adjacent to one in a primary position that is undergoing replacement by the halogen.(22). This reaction leads to the formation of a double bond and has been likened to the decomposition of α-di-iodo compounds to olefins and iodine (see Page 59). Since only one α-glycol group exists in the cellulose molecule; i.e., at the 2,3-positions, these results indicate that the tosyl cellulose acetate (XVIII) contained glucose units of the structure (S) which underwent detosylation to form the compound (T). This explanation, of



(S) (T)

course, involves the assumption that the ditosylate of a secondary group might behave like the similar ester of one containing a primary alcohol.

The structure for the tosyl cellulose acetate (XVIII) can have the following explanations.

(a) Although the rate of tosylation of the cellulose acetate (XVII) is not in agreement with the following assumption, it may be supposed that the detritylation of the monotrityl cellulose diacetate (XV) was accompanied by acetyl wandering from secondary to primary positions. The detritylation of α-monotrityl glycerol diacetate has been shown to yield the α, γ-glycerol diacetate (240). This assumption would yield a ready explanation for the presence of 0.3 to 0.4 moles of 2,3-glycol groups in the cellulose acetate (XVII).

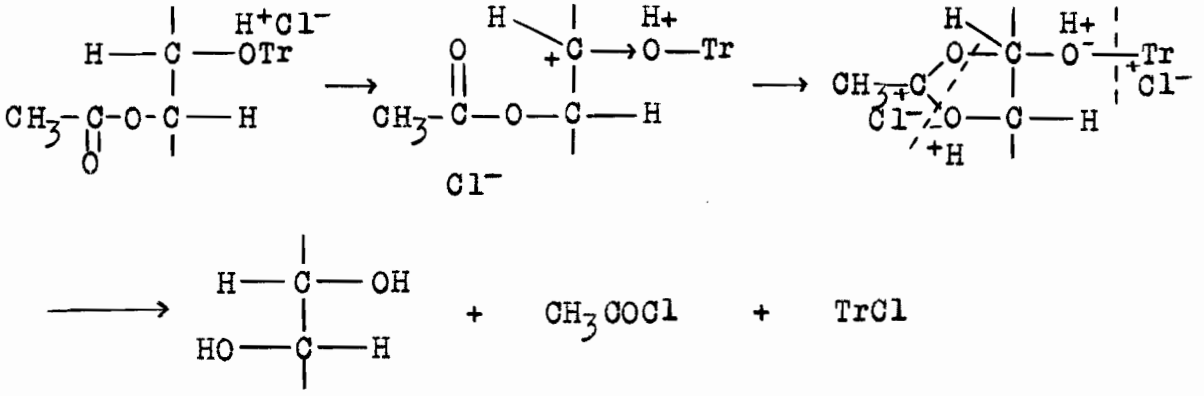
(b) An alternative explanation may be based on the assumption that negligible acetyl wandering took place and that considerably more than 0.10 trityl groups in the trityl cellulose (XI) were situated at secondary positions. This assumption finds some support through the possibilities it offers for the explanation of some of the results.

The loss in acetyl on the detritylation of trityl cellulose acetates seems anomalous for a variety of reasons. Cellulose acetates are unaffected under conditions in which trityl cellulose acetates undergo substantial deacetylation (compare Table XI and Table XII). The utilization of 25% phosphoric anhydride in pure nitric was shown (Table XI) to bring about the trisubstitution of a variety of cellulose acetates without loss of acetyl. The results confirm the total substitution of the "cellulose-6-nitrate acetate" (III) and the "cellulose-6-nitrate" (IV) arrived at by

elementary and group analysis. These nitrating conditions were applied to a variety of trityl cellulose acetates (Table XII). The date show that the acetyl loss accompanying the nitration was at a maximum after the trityl acetates had reached an acetyl substitution of 1.5, which is the point where the low temperature acetylation of trityl cellulose stopped. Consequently, the 0.38 acetyl groups which were labile to nitration were readily introduced into the trityl cellulose at low temperatures and do not occupy the positions which are more highly resistant to acetylation. This conclusion would mean that the trityl cellulose had approximately 0.5±0.15 moles of free hydroxyl which were different in nature to another 0.5±0.15 moles. It is noteworthy that the cellulose acetate (XVI) which was prepared by the detritylation of trityl cellulose diacetate with hydrogen chloride in chloroform solution under carefully anhydrous conditions involved an acetyl loss (0.41 moles) which closely parallels the loss involved in the nitration of trityl-diacetates.

The rate of tosylation of the cellulose acetate (XVII) indicates that at least one mole of highly active hydroxyl group was present. On the assumption that 0.90 moles of free primary hydroxyl group were present, since the acetate (XVII) contained 1.55 free hydroxyl groups, there would be 0.65 free secondary hydroxyl positions. On this basis, the maximum number of free 2,3-glycol groups would be 0.65/2 or 0.325 which corresponds to the amount found. It is therefore unlikely that the detrityla-

tion was largely (90%) restricted to the primary position and accompanied by a random loss of acetyl at secondary positions. The results point more toward the freeing of a considerable number of secondary hydroxyl groups through detritylation. Winstein and his coworkers (178) were able to show that displacement reactions at a carbon atom, which is adjacent to an acetoxy group, may be affected by the neighboring group. These groups can prevent the usual Walden inversion, which accompanies the type of reaction they studied (see Page 66) by the formation of cyclic intermediates whose eventual decomposition lead to products of the same configuration as the initial reactant. Because of the steric relationship involved in this mechanism it is restricted to trans configurations. The rate controlling step in the acid hydrolysis of esters is considered to be the nucleophilic attack at the carbonyl carbon atom by hydroxyl ion (243). The deacetylation which accompanied the detritylation of trityl cellulose acetates, on this basis, might be caused by the acid cleavage of a secondary trityl ether bond producing a transient cyclic structure as pictured below.



The increased positive charge at the carbonyl carbon atom might enhance the ability of the acetyl group to add a chloride (or nitrate) ion from the environment and to split off as acetyl chloride (or acetyl nitrate). Although the mechanism would apply for any trityl and acetoxy groups appropriately located in space, such an interaction would not be expected to yield the high content of free glycol observed. Wolfrom (172) has reported that the detritylation of 6-trityl galactose ethyl mercaptal tetraacetate is accompanied by some deacetylation of the carbohydrate residue. This trityl derivative underwent an anomalous detritylation in that, instead of leading to the alcohol and triphenylmethyl bromide, the bromohydrin was sometimes formed (see Page 64).

Since the trityl groups have been shown to occupy highly active positions, the measurements of the rate of tosylation of the acetate (XVII) do not contradict this suggestion (for the structure of trityl cellulose). The liberation of free iodine with a substantial loss of tosyl, which accompanied the iodination of the tosyl-acetate (XVIII), is further indication that active tosyl groups were situated at other positions than the primary.

Whatever the explanation of these results may prove to be, the data showed that a "6-tosyl cellulose acetate" could not be prepared and iodinated to a "6-iodo-cellulose acetate" as selectively as was anticipated. The iodo-compound obtained should be convertible to "cellulose-6-nitrate acetate" through

the action of silver nitrate in acetonitrile solution. However, the original procedure proposed by Levi, Zuckerman and Purves (1) seems to remain the better method for the preparation of the substance.

A reinvestigation of the properties of the "cellulose-6-nitrate acetate" (III) made possible speculations regarding the structure of the "6-desoxycellulose acetate" (VII). Methylation of the acetate-nitrate (III) with diazomethane showed that only 0.23 moles of methoxyl were introduced. This amount agrees with the 0.23 moles which the free hydroxyl determination (see Page 127) failed to find and both reactions may be concerned with the identical positions in the molecule. The nature of these positions is unknown. They may have originated in an oxidative degradation of the cellulose chain under the conditions used for the nitration. Nitrogen dioxide has a strong preference for oxidizing the primary positions in cellulose to carboxyl groups (241). Moreover, the method by which the acetate-nitrate (III) was isolated from the nitrating mixture was very tedious and some oxidative acid hydrolysis of nitrate groups may have taken place. If carboxylic hydroxyl units were in fact present, they would be methylated by diazomethane but probably would not be registered by the acetylation procedure for alcoholic groups. Whatever their nature, these positions were apparently nitratable with 25% phosphoric anhydride in nitric acid (Table XI).

If the "different" 0.23 hydroxyl group positions are assumed to be retained by the "6-iodocellulose" (III) and by its reduction

TABLE XVII

SUMMARY OF THE ANALYTICAL RESULTS OBTAINED FOR VARIOUS PRODUCTS WHICH WERE PREPARED IN ORDER TO GAIN AN INSIGHT INTO THE STRUCTURE OF MONOTRITYL CELLULOSE

Cellulose Derivative	Acetate-nitrate (III)	Iodo-acetate-nitrate (VI)	Desoxy-acetate (VII)	Iodo-acetate-nitrate (IX)	Desoxy-acetate (X)
Unit molecular weight	162+42x+45y =271.5	162+42x+45y+110z =307	162-16z+42x =235.5	162+42x+45y+110z =277	162-16z+42x =259
Free hydroxyl group positions					
Total	0.47	0.78	0.46	0.84	0.37
No. esterifiable/g.u.	0.24	0.55	0.00	0.61	0.00
No. non-esterif./g.u.	0.23	0.23	0.23	0.23	0.23
Acetyl groups					
No. per g.u. (x)	1.43	1.43	2.03	1.43	2.43
% Acetyl (calcd.)	22.6	20.1	36.7	-	40.4
% Acetyl (found)	22.5,22.6	20.9	35.8	-	40.3,39.8
Nitrate groups					
No. per g.u. (y)	1.10	0.05	-	0.39	-
% N (calcd.)	5.68	0.23	-	1.97	-
% N (found)	5.70,5.67	0.24,0.25	-	1.91,1.89	-

Cont'd.

TABLE XVII (Cont'd)

Cellulose Derivative	Acetate-nitrate (III)	Iodo-acetate-nitrate (VI)	Desoxy-acetate (VII)	Iodo-acetate-nitrate (IX)	Desoxy-acetate (X)
Iodine atoms (or desoxy positions)					
No. per g.u. (z)	-	0.74	(0.74)	0.34	(0.34)
% I (calcd.)	-	30.6	-	15.6	-
% I (found)	-	30.3,30.2	-	15.4,15.2	-
"Secondary desoxy positions"					
No. per g.u.	-	-	0.23	-	0.14
Primary desoxy positions					
No. per g.u.	-	-	0.51	-	0.20
% Apparent acetyl (calcd.)	-	-	45.9	-	43.6
% Apparent acetyl (found)	-	-	45.4,45.2	-	43.7
Hydroxyl positions accounted for	3.00	3.00	3.00	3.00	3.00

product, "6-desoxycellulose acetate" (VII), the structure of the latter might have the following interpretation. The structure of "cellulose-6-nitrate acetate" (III) is listed in Table XVII as 0.24 moles of esterifiable hydroxyl group, 0.23 moles of hydroxyl group which are non-esterifiable, 1.43 moles of acetyl and 1.10 moles of nitrate group. Its iodination resulted in the removal of 1.05 moles of nitrate group, 0.31 of which were not replaced by iodine. The three positions in the "6-iodocellulose acetate" (VI) were therefore accounted for as 0.55 moles of esterifiable hydroxyl groups, 1.43 moles of acetyl, 0.05 moles of nitrate and the 0.23 moles of hydroxyl which were non-esterifiable. The assumption that any non-esterifiable positions in the iodo-compound had origin in the "cellulose-6-nitrate acetate" (III) is not fully justified. Although the denitration of secondary positions by the action of sodium iodide in acetone has been used for the regeneration of the carbohydrate residue (143), this reaction involves much degradation (148) and the yields are low (143). Moreover, in the iodination of cellulose nitrate, a maximum iodine content is reached after which the iodine content drops, the products of the latter change being unknown. These observations make it probable that the constitution of the cellulose residue was somewhat altered by the iodination reaction. Whatever the cause of the failure of certain hydroxyl positions to respond to the reductive acetylation used to prepare the "6-desoxycellulose acetate" (VII), it is seen

from Table XVII that their number was 0.46 moles per glucose unit. Since the iodocellulose (VI) contained 0.74 iodine atoms, the desoxycellulose acetate (VII) should not contain more than 0.74 desoxy positions. Calculation of the number of terminal methyl groups in the acetate (VII) on the assumption that all the iodine atoms were quantitatively reduced (i.e., the unit molecular weight was calculated on the basis of 0.74 desoxy positions or was 162 - 0.74x16) leads to the presence of 0.51 primary desoxy positions. The composition of this compound as represented in Table XVII is therefore 0.23 free hydroxyl positions which are not esterifiable, 2.03 acetyl groups, 0.23 "secondary" and 0.51 primary desoxy positions. This structure therefore leaves 0.46 positions unaccounted for, one-half of which has been attributed to non-esterifiable positions of unknown nature and the other half to secondary positions. In order to test whether there was any connection between these halves, the desoxycellulose acetate (X) was prepared. If the reductive acetylation was accompanied by side reactions such as anhydro-ring formation, the product would reveal two unesterifiable positions for every iodine atom not reduced to terminal methyl. On this basis, the product (X) should have contained only 0.14x2= 0.28 unesterified positions. However, 0.37 hydroxyl group positions were unaccounted for. That is, more hydroxyl group positions were found unesterified than could be accounted for through anhydro-ring formation in the displacement of iodine atoms. Consequently, some

of the non-esterified positions must have originated from a different source than through iodine displacement. The fact that the analyses of X (see Table XVII) check very well for 0.23 moles of non-esterifiable position (wnich may have originated in the acetate-nitrate (III)) and 0.14 "secondary desoxy groups" is evidence that the 0.46 non-esterifiable positions in the desoxycellulose acetate (VII) were of the origin already implied. These interpretations therefore indicate that the iodine replacement of nitrate groups in the "cellulose-6-nitrate acetate" (III) was not restricted to primary positions. However, the interpretations have many serious objections. Possibly one of the most prominent is the fact that, since the desoxy-cellulose acetates were highly degraded, the amount of chain endings present in the substances may well have a noticeable effect on the analytical data. However, it was thought worthwhile to present the interpretation in the light of the anomalous results obtained for the rate of acetylation of trityl cellulose, the nature and degree of acetyl loss on the detritylation of trityl cellulose acetates, the anomalous tosylation rates and anomalous iodination of the tosyl-acetate (XVIII). All these results suggest that cellulose displays some highly anomalous reactions. Applications of the so-called selective reactions, as aids in determining its properties and the structure of its derivatives, may therefore prove to be misleading.

All the desoxy cellulose acetates prepared were highly sensitive to alkali and attempts to deacetylate them failed to give

desoxycelluloses capable of being isolated in good yields. Although Bergmann, Schotte and Lechinsky have reported that the marked sensitivity of 2-desoxyglucose to alkali may be increased by substituents in the molecule (197), the alkali sensitivity of desoxycelluloses cannot safely be attributed to secondary desoxy groups because of the strong possibility that oxycellulose is present in the material. The rapid dark coloration assumed by desoxycelluloses when treated with strong acids is another property characteristic of 2-desoxyglucose but also of methyl pentosans.

In searching for an independent method for either proving or disproving the validity of the "Oldham - Rutherford Rule" in the cellulose series, Miss Quinlan's (64) oxidations of acetone-soluble cellulose acetate in homogeneous solution seemed promising. Her qualitative results showed that either chromium trioxide or potassium permanganate in glacial acetic acid solution tended to yield oxycellulose acetates of high uronic acid content. It was believed that studies of the rate of oxygen consumption by suitable partially substituted cellulose acetates might be interpreted to yield the content of free primary hydroxyl groups. Success would depend on a highly preferential oxidation of the primary alcohol units to carboxylic acid.

Preference was given to chromium trioxide because permanganate tends to precipitate manganese oxides which complicate the quantitative estimation. Permanganate caused greater chain degradation than chromic oxide (64).

Preliminary experiments showed that the usual iodometric titrations were unsstisfactory for following the chromium trioxide consumption. A tendency for the liberated iodine to adsorb tenaciously to the precipitated cellulose acetate caused variable errors in estimation in the order of 5 to 10% of theory. The ferrous ion-ceric ion titration was finally chosen because all the ions involved are positively charged; i.e., Fe^{++}, Fe^{+++}, Ce^{+++}, Ce^{++++}, Cr^{+++}. This circumstance was believed to reduce adsorption errors. Also, ceric ion is known to be only a very mild oxidant for most organic material, at lower temperatures, unless suitably catalyzed. Errors caused by further oxidation of the carbohydrate residue during the titration would therefore be expected to be negligible, especially if stirring was efficient. Back titration of ferrous ion in the presence of precipitated cellulose acetate by ceric ion solution, using methyl red indicator, definitely showed that quantitative estimations could be made.

Oxidation rate measurements were carried out on the sample of acetone-soluble cellulose acetate which formed the starting material for the trityl cellulose preparations described in this research. The rate curves obtained are shown in Fig. IX. The plots, 1, 2 and 3, refer to initial chromium trioxide concentrations which made 1.26, 0.710 and 0.645 atoms of oxygen available per anhydroglucose unit. All show that the oxidation consists of a rapid initial stage which is complete in two to four minutes and which is followed by a much slower secondary oxidation, even

at high concentrations of oxidant. From Miss Quinlan's results(64) it is clear that the initial rapid oxidation could not be concerned, to any considerable degree, with chain degradation or to attack at positions blocked by acetyl. These side reactions may become important in the slower secondary phase.

The cellulose acetate, with 2.33 moles of acetyl per anhydroglucose unit, averaged 0.67 moles of free hydroxyl of which 0.203 (Table XIII) were shown to be primary by the method of Cramer and Purves (36). Assuming that all exposed hydroxyl positions were readily oxidized, the material could consume 0.67 atoms of oxygen if secondary positions were oxidized to ketone and the primary positions to aldehyde, or 0.87 atoms if the primary were converted to carboxyl. The fact that only 0.4±0.02 atoms of oxygen were rapidly consumed shows that some of the alcohol groups were more resistant to oxidation than others. It remained to be seen whether the oxidation was restricted to primary positions. In order to gain this information, the cellulose acetate was tosylated under conditions known to esterify completely the free primary positions (36). The oxidation of the tosyl cellulose acetate (XXV) showed that it also consumed oxygen at a rapid initial rate, but to a much lesser extent than the original cellulose acetate. Whether this decrease corresponds to the presence of fewer secondary as well as primary hydroxyl groups is unknown. The fact that some oxidation of the tosylated product did occur indicates the presence of oxidizable groups in the cellulose acetate molecule which were present both before and

after tosylation. It was hoped that more information could be gained by preparing a cellulose triacetate and using it for a blank. Acetylation of the cellulose acetate did not, however, yield a triacetate but instead a degree of substitution of 2.86 moles. The fact that this compound (XXIX) had the same initial rapid oxygen consumption (0.14 moles) as the tosyl acetate (XXV) (Fig. IX) may be coincidental but it is likely that there was a relation between this amount and the 0.14 free hydroxyl positions which remained in the "cellulose triacetate". Furthermore, there may be a relation between these positions and the 0.14 oxygen atoms which were rapidly consumed by the tosyl cellulose acetate. More detailed experiments on the structure of the resulting oxycelluloses will have to be carried out before this point is clarified. Nevertheless, it is interesting to note that if plots 4 and 5 in Fig. IX are subtracted from plot 1, plot 6 is obtained and may provisionally be attributed to primary alcohol group oxidation. Its extrapolation shows that 0.26 to 0.27 atoms of oxygen were consumed. Since two atoms of oxygen are necessary to convert a primary alcohol group to carboxyl, the result suggests that 0.13 to 0.14 primary groups were present in the acetone-soluble cellulose acetate. Oddly enough, this value checks very well with that obtained by determination of the terminal methyl groups in the "6-desoxycellulose" (XXVIII). Whether this agreement is fortuitous or not will have to be proven by more detailed investigation.

SUMMARY

The preparation of selectively substituted cellulose derivatives is greatly complicated by the fact that, although reagents may show some preference for certain types of hydroxyl groups, there is no clean-cut guarantee that their action was quite specific. The derivatives obtained may consequently never be free of the products resulting from unexpected side-reactions. Moreover, these by-products can never be separated since they form part of the same molecule. The structure of these derivatives is very complex and the interpretation of analytical results and other kinds of information leading to the solution of structure can never be complete. Nevertheless, the synthesis of cellulose derivatives whose constitutions are largely known can yield a variety of useful information. Since the products of a reaction can, at any time, be quantitatively isolated and purified, much useful information regarding the reactivity of the various positions can be obtained. When dealing with non-fibrous, low molecular weight compounds, the separation of the products is often limited by the number of crystalline derivatives which can be isolated, but when separated, their constitutions can usually be determined in an unambiguous fashion. This is the great difference between such studies in the low and high molecular fields.

A section of this Thesis was devoted to a general review

of certain portions of carbohydrate chemistry which are relevant to the work. An attempt was made to interpret the data through the application of modern chemical theory.

The attempt was made in order to gain an idea of the relative importance of steric and electronic factors in determining the wide variations which have been observed in the properties of hydroxyl groups or substituents at hydroxyl group positions. It was realized that carbohydrates, in general, have highly labile electronic systems. Consequently, the chemical properties exhibited by these substances are largely dependent on polar effects. That the introduction of substituents in carbohydrate molecules can have marked effects on the properties of other groups in the molecule, was substantiated by a large number of examples.

Since steric effects were shown very probably to be of only secondary importance, it became clear that the so-called specific reagents which are used for the purpose of distinguishing secondary from primary positions should not be expected to find universal application. That is, it is actually in order to expect that exceptions to the general rules should be found. The survey of the literature showed that this expectation is generally true and few, if any, of the selective reagents have stood the test of time. There is little doubt that the use of selective reagents, and the discovery of new ones, will continue to contribute invaluably toward the synthesis and investigation of

molecular structures. However, it is important to realize that care should constantly be applied in drawing conclusions from information gathered in this manner.

It is probable that the large accumulation of "anomalous" results in this work was because of the fact that all the products of reactions with the anhydroglucose unit of cellulose were constantly recovered quantitatively. The ability correctly to interpret such experimental results obviously depends entirely on the scope and the accuracy of the analytical methods.

The reactions of the cellulose molecule were found to be highly variable. Although free cellulose reacts quantitatively with periodate, the introduction of the trityl group (and possibly the nitrate) at the primary position rendered the free 2,3-glycol position stable to the reagent. While the tosylation of trityl cellulose resulted in a monotosyl derivative, the results indicated that in certain suitably substituted cellulose acetates all three positions reacted rapidly. However, in acetone-soluble cellulose acetates the tosylation of many of the free hydroxyl groups proceeds very sluggishly (60). Cellulose itself, swollen in pyridine, reacts with tosyl chloride to produce a ditosyl derivative (46). Under the same conditions, starch is trisubstituted (43). Cellulose itself in suitable physical condition can be nearly trisubstituted through the action of acetic anhydride in pyridine. However, trityl cellulose contains certain hydroxyl groups which have a marked

resistance toward the esterification.

Although cellulose derivatives have not been prepared in which more than one mole of tosyl or nitrate group was found replaceable by iodine, there can be no certainty, on the basis of the present experimental data, that the replacement obtained was restricted to one position (presumably the sixth). It can be expected that substituents in one unit of the cellulose molecule may affect the properties of positions in adjacent as well as the same unit. Consequently, it may well be that partially substituted celluloses contain a good variety of hydroxyl and substituent groups which differ substantially in their states of polarity and polarizability. The observation by Gardner and Purves (60) that partially substituted cellulose acetates undergo partial chlorination on tosylation of the free hydroxyl groups while the tosylation of a partially substituted ethyl cellulose, under identical conditions, had no such effect, may be evidence that the tosyl-acetates contained tosyloxy groups of greater reactivity than did the tosyl-ethyl compound.

Although the proof for the structure of monotrityl cellulose, on the basis of the "Oldham - Rutherford Rule", as provided by Hearon, Hiatt and Fordyce (2), was evidently substantiated in this work in a variety of ways, certain results were obtained which pointed toward the existence in cellulose of secondary positions which may behave much like primary positions toward selective reagents. These results, however, were obtained by

studies of very complex materials and they are not considered sufficiently clean-cut to warrant definite conclusions in that respect. The experiments must be considered of a preliminary nature and they must therefore be repeated under a wider variety of conditions. It may well be that the structure of trityl celluloses varies considerably from one preparation to another.

The importance of finding the correct interpretation of these anomalous observations is obvious. The diversity of applications of cellulose and its derivatives can only increase with the enlargement of detailed knowledge regarding its chemical properties. An appreciation of the limits of the uses to which cellulosic materials can be put will necessarily be largely derived from studies on the effects of substituents on such properties as stability toward degradation, oxidation, solubility, further substitution, etc. It seems reasonable to expect that much of this information can be derived from studies on selectively substituted cellulose derivatives of known constitution. Since it is probable that many of the reactions of cellulose derivatives are dependent on transmissional effects in the molecule, the preparation of selectively substituted cellulose derivatives with groups of varying electronegativity should prove interesting from the stand-point of enzyme hydrolysis of polysaccharides. It may be that the ability of enzymes to hydrolyse these substances under extremely mild conditions is a result of their ability to contribute (or withdraw) electron density at specific positions in polysaccharides and thereby to provide electron

displacements which render the glycosidic bonds more labile and therefore more susceptible to hydrolysis. As stated by Irvine and Robertson (244), "To have a halting stage in purely constitutional studies will in no sense react to the disadvantage of sugar chemistry, and will afford an opportunity for interpreting biological changes in terms of structure and for testing accepted structures through their capacity to afford a rational explanation of biological reactions. The smooth syntheses by which the complex saccharides are built up in Nature from simpler units; the equally astonishing natural processes whereby, with the minimum of energy change, sugars are oxidized, reduced, or degraded; the facility with which through configuration changes one sugar is transformed into another - these are all problems of immense scope and of special importance to the biochemist.

Fortunately signs are not lacking that the attention of chemists is being attracted to these problems and to the mechanism of the fundamental reactions of which sugars are capable. We may therefore look forward to a period when dramatic discoveries will be few in number, when more attention will be paid to the specific properties of the individual hydroxyl groups in sugars, and when the biochemical distinction between one sugar and another will be studied in terms of the configuration of the asymmetric systems which form the carbohydrate chain".

CLAIMS TO ORIGINAL RESEARCH

1. A standard method for terminal methyl group estimation was refined and adapted for the accurate determination of the acetyl content of trityl cellulose acetates.

2. The analytical method made possible the study of the nature and rate of acetylation of trityl cellulose.

3. Trityl cellulose diacetate was prepared and its nitration to "cellulose-6-nitrate diacetate" was studied. The nitration was shown to be accompanied by considerable deacetylation under the methods used.

4. Iodination of a "cellulose-6-nitrate acetate" showed that 0.80 of the nitrate groups were replaceable by iodine. At least 0.52 of the iodine atoms were shown to occupy primary positions.

5. The introduction of the trityl group into the cellulose molecule was shown to cause a marked hindrance to the acetylation or tosylation of the remaining free hydroxyl groups. Periodate was shown incapable of cleaving free 2,3-glycol groups in trityl cellulose.

6. The structure of the cellulose acetate derived from the detritylation of monotrityl cellulose diacetate was investigated.

7. Some twelve new "selectively" substituted cellulose derivatives were prepared and fully analyzed.

8. A new method, based on following the rate of oxidation by chromium trioxide in acetic acid, for determining the constitution

of partially substituted cellulose acetates was investigated.

9. Each intermediate in the preparation of "cellulose-6-nitrate" by the procedure first studied by Levi, Zuckerman and Purves (I), was fully and accurately analyzed. The extent of degradation in each step was followed. Every stage in the synthesis was studied in detail. At least 0.80 of the nitrate groups in the product were shown to be replaceable by iodine when treated with sodium iodide and acetone.

10. Evidence was obtained that the cellulose molecule displays highly anomalous properties and that the application of selective reagents, such as the iodine replacement of tosyloxy or nitrate groups, for the estimation of primary hydroxyl groups may prove misleading.

11. A procedure for the volumetric estimation of sulfur was established.

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