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CONFORMATIONAL ANALYSIS OF THE EQUILIBRIA AND RATES FOR THE ANOMERIZATION OF ACETYLATED ALDOPYRANOSES (PART ONE)

THE CHARACTERIZATION OF 1,2:5,6-DIISOPROPYLIDENE-3-DEOXY-3-AMINO-α-D-ALLOFURANOSE (PART TWO)

by

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A thesis submitted as a partial
requirement for the degree of

DOCTOR OF PHILOSOPHY

in the

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OTTAWA

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February 1959.

"格物致知"

—大學五章—

"The perfecting of knowledge
depends on the investigation of matters"
— The Great Learning, Chap. V.—

"The Great Learning" was a text
of Confucius (551-479 B. C.)
The Author.

PREFACE

Steric effects in the course of chemical reactions have received much attention in the past two decades. These considerations deal with the exact shapes (conformations) of molecules and have resulted in the development of a field in organic chemistry known as conformational analysis. This development has greatly deepened our understanding of the properties of organic molecules.

The acetylated sugars and related acetylated glycosyl halides play an important rôle in synthetic carbohydrate chemistry. The numerous studies based on these compounds have shown them to possess a number of puzzling properties. The present investigation was particularly intended to determine why, for many of these compounds, the anomer with the 1-substituent in axial orientation appeared to be thermodynamically more stable than its equatorial equivalent. The study of this anomalous property was approached through an investigation of the anomerization of the acetylated aldopyranoses. A variety of non-bonded interaction energies in the ground states were obtained from the equilibrium data and a satisfactory rationalization of the relative stabilities of the anomers was made. Moreover, a mechanism of the anomerization reaction was deduced through a conformational analysis of the possible transition states.

During the course of this research, it became apparent that the interaction energies derived from the anomerization data may be useful to determine the absolute configuration of new sugars. Application of this idea to a hexosamine derived from the new antibiotic kanamycin led to conclusion that the substance was, in all probability, 6-D-glucosamine or 6-D-galactosamine. It was found that the substance was in fact the 6-D-glucosamine. However, the method was not applicable to 2- or 3-hexosamines. Another hexosamine derived from kanamycin was shown to be 3-D-glucosamine by synthetic methods.

I wish to express my sincere gratitude to Prof. R.U.Lemieux for his constant assistance and inspiring suggestions through the course of this study and his support through the National Research Council of Canada for grant in aid of research.

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ABSTRACT

A quantitative conformational analysis was made of the anomerization equilibria of the acetylated aldopyranoses. The following non-bonded interaction energies were obtained, based on the assumption that the difference in free energy between the anomeric pairs can be taken as equal to the difference in non-bonded interactions.

(1) The anomeric effect, 1290 cals./mole.

(2) An acetoxymethyl group on carbon 5 enhances the anomeric effect by 220 cals./mole.

(3) The skew interaction between two acetoxy groups, O/O-H/H, is 540 cals./mole.

(4) The diaxial interaction between an acetoxy group and a hydrogen atom, H:O-H:H, is 180 cals./mole.

(5) The diaxial interaction between two acetoxy groups, O:O-H:H, is 2020 cals./mole.

These interaction energies are all related to the interaction term H/O-H/H, that is the skew interaction between an acetoxy group and a hydrogen atom relative to the same interaction between two hydrogen atoms. The above values for the interaction energies are based on the assumption that the value of H/O-H/H is negligibly small. This type of assumption has been made by all previous workers in the field of conformational analysis and is required for a comparison of the values presently

obtained with those values of similar interactions reported in the literature.

The acetylated amono-sugars with an acetamido group on carbon 2 or 3 were found to undergo anomalous anomerization reactions. These results could be due to the formation of stable oxazolinium or oxazinium ions in the anomerization media.

The relative stabilities of the transition states in the anomerization of the acetylated aldopyranoses were examined in a number of different ways. It was concluded that the results would best be rationalized on the basis of a bimolecular mechanism. Conformational analyses of the transition states indicated that the activated complexes of the aldopentopyranose tetraacetates may assume a half-chair form. However, a deformed chair seemed more plausible for the transition states of the aldohexopyranose pentaacetates. The reason for this difference between the pentoses and hexoses is discussed.

The reaction of the base-catalyzed anomerization of the D-glucopyranose pentaacetates was investigated.

The amino-sugar moieties from the hydrolysis of the new antibiotic kanamycin were identified as 3-D-glucosamine and 6-D-glucosamine. The configuration of 1,2;5,6-diisopropylidene-3-deoxy-3-amino-α-D-allofuranose was established. This proves that inversion occurs in the replacement of a tosyloxy group on secondary carbon atoms with ammonia or hydrazine and provided unequivocal identification of 3-D-glucosamine.

CONFORMATIONAL ANALYSIS OF THE EQUILIBRIA AND RATES FOR THE ANOMERIZATION OF ACETYLATED ALDOPYRANOSES

(PART ONE)

I. INTRODUCTION

A. Conformational Analysis

The purpose of this research was mainly to obtain information pertaining to the conformational effects on the properties of sugars and their derivatives. For this reason, it is appropriate to begin this thesis with a survey of the pertinent aspects of conformational analysis.

1. Introductory Survey

The development of the electronic theory, mainly in the 1930's, provided a greatly deepened understanding of the properties and reactions of organic compounds (1-4). However, it was clearly apparent that other factors were involved, and which appeared more difficult to assess. The effect of size and relative positions of groups in molecules irrespective of their electrical properties, known as the steric effect, has received much attention in the past two decades. This approach has proven especially fruitful in the past ten years and was mainly responsible for the establishment of a field in organic chemistry known as conformational analysis.

Conformational analysis is concerned with the determination of the relative stabilities of the various conformations (shapes) for an organic molecule. Only intramolecular effects usually

are considered which arise from interactions between non-bonded atoms. Originally, only steric (5) and resonance (6) effects were considered but more recently electrostatic interactions (7) have been found to be important too. Conformational analysis of transition states as well as molecules in the ground state have proven of great value in the understanding of rates of reaction.

Until very recently, most of the work in the field of conformational analysis consisted of qualitative applications of a number of general rules to the chemical problems, and there were few results which could be used to give quantitative data. Hence it was considered worthwhile to review the recent work which deals with quantitative aspects of conformational analysis, and to emphasize some of the more fundamental aspects of this subject.

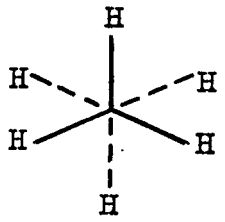
The term "conformation", first proposed by Haworth (8), was used to designate a particular shape or arrangement in space of the atoms in a molecule in which more than one arrangement can be brought about by simple rotations about single bonds. German researchers use the word "constellation" as synonymous to "conformation". In the literature of chemical physics the term "rotational isomer" is used in a similar sense.

2. Restricted Rotation of Acyclic Hydrocarbons

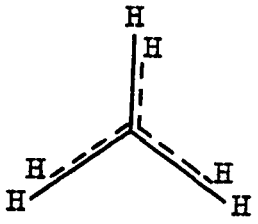
According to the theory of covalent bonding (9), a single bond has full circular symmetry about its internuclear axis. It follows that rotation about single bonds should be completely free. Although optical isomers of symmetrical ortho-substituted diphenyl derivatives had been known since the early 1920's (10), and correct explanation was given almost simultaneously by Turner and Le Févre (11), by Bell and Kenyon (12), and by Mills (13) as a result of steric repulsion between the ortho-groups which inhibits planar forms and prevents the free rotation about the interannular bond. However, the existence of such restricted rotation about the single bonds was not realized universally until the statistical mechanical treatment failed to give agreement between calculated and experimental thermodynamic data of simple hydrocarbons.

In 1936, Kemp and Pitzer (14) showed that the deviation of the calculated from the experimental values was due to the assumption of free rotation about a single bond. These authors postulated a sinusoidal potential barrier restriction to such internal rotation. For example, in ethane two distinct conformations are possible. One is the staggered form (I) in which all the hydrogen atoms are equidistant from each other. The other one is the eclipsed form (II) in which all the hydrogen atoms are opposite one another. Owing to the repulsive inter-

action at the close distance, the eclipsed form possesses higher energy than the staggered form.



I



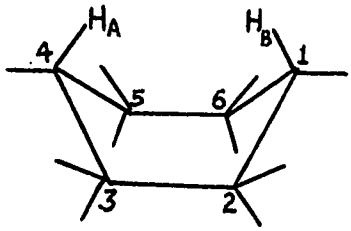
II

In going from one staggered form to another by rotating one methyl group about the carbon-carbon bond, ethane must pass through the eclipsed higher-energy species. Thus a potential-energy barrier to free rotation exists.

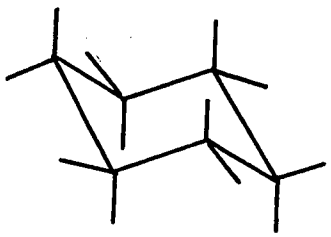
Although no quantitative theory has yet been advanced to account for these barriers to internal rotation, it is assumed that they arise from the repulsion of the electron pairs forming the carbon-hydrogen bonds. The basic cause is presumably the same as that responsible for the repulsive van der Waals forces between separate molecules.

3. Non-bonded Interaction in Alicyclic Compounds

Sachse and Mohr (15,16) pointed out that cyclohexane, a six-membered ring compound, could exist in two non-planar, strainless forms, namely the boat (III) and the chair (IV).



III



IV

In the chair form, all the carbon-hydrogen bonds are equivalent to the staggered form of ethane; whereas in the boat form, there is total eclipsing of the bonds on carbon atoms 2 and 3, 5 and 6. In addition, there is a strong repulsive interaction due to proximity of the two hydrogen atoms H_A and H_B in the so-called "flagpole positions". It follows that the chair form should be more stable than the boat form, and it has been estimated that the energy difference between these two forms is about 7.2 - 10.6 kcal./mole (17). Experimental evidence supporting the chair form for cyclohexane was obtained from Raman (18,19) and infrared (20) spectra and electron diffraction data (21).

Owing to the abundance of six-membered ring compounds in nature, the growing interest in regard to the conformational analysis of these alicyclic compounds is evident from a number of reviews in the literature (22-25). Attention is focused on steric interactions, that is those caused by interpenetration of electron shells when the interatomic distance between two non-bonded atoms is less than the sum of their atomic radii.

As seen in the formula in Table I, the cyclohexane molecule in the chair form has two distinctly different orientations for the twelve substituents on the ring atoms. Six (a) are perpendicular to the mean plane of the ring and are referred to as the axial substituents (26), and the other six (e) which lie approximately in the plane of the ring, are known as the equatorial substituents.

Table I shows the interatomic distances in the cyclohexane ring as calculated by Angyal and Mills (27), and Corey and Sneen (28). The values given by Pauling (29) for the van der Waals radii of atoms are listed in Table II.

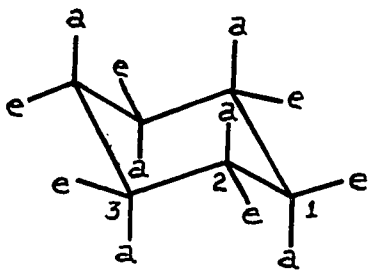
Table II

van der Waals Radii of Atoms

		H	1.2 Å		
N	1.5 Å	O	1.40	F	1.35 Å
P	1.9	S	1.85	Cl	1.80
		CH_3	2.0		

Table I

Interatomic Distances in the Chair Form of Cyclohexane Ring



Position	Interatomic Distances			
	H - H	O - O	C -C	H - C
1e -v2e	2.49 Å	2.83 Å	2.96 Å	
1e - 2a	2.49	2.83	2.96	
1a - 2a	3.06	3.66	3.88	
1a - 3a	2.54	2.54	2.54	2.57 Å

The data in Tables I and II show clearly that any axial substituent other than a hydrogen atom on the cyclohexane ring would cause steric interactions. Therefore, an equatorial substituent should be more stable than an axial substituent. This is one of the fundamental principles of conformational analysis. Quantitative evaluation of such interaction energies has received much attention since the early 1940's.

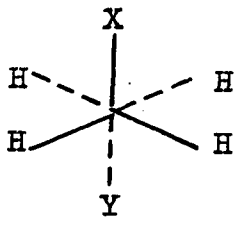
4. Quantitative Aspects of Conformational Analysis

Conformation and Spectrum: The energy barriers between the conformations of organic compounds are usually too low to allow the separation of conformationally pure liquid or gaseous compounds. Nevertheless, any rapid physical method of analysis can, in principle, yield a measure of the concentration of a given conformation. The methods which have been used most extensively are based on Raman and the infrared spectroscopy.

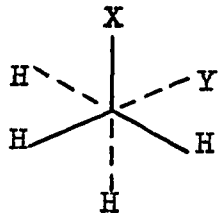
It was shown (30) that, for many 1,2-disubstituted ethanes, the spectrum of the liquid contained bands for two conformations while in the solid the bands of only one conformation remained. Thus the bands associated with each conformation may be selected unequivocally. Although it is difficult to obtain the absolute intensities of Raman bands, the relative intensity of a trans band and a skew band yields a measure of the ralative concentration of the two conformations. Thus for the equilibrium

trans $CH_2X - CH_2Y$ (V) $\rightleftharpoons$ skew $CH_2X - CH_2Y$ (VI)

$$K = (\text{constant})\ I_s/I_t \qquad (1)$$



V



VI

where K is the usual equilibrium constant and I is the appropriate measure of intensity of the given Raman band.

If these measurements are made as functions of temperature (31), the heat of reaction may be obtained from the following equation

$$\Delta H = R\left[\frac{d\ln K}{d(1/T)}\right] = R\left[\frac{d\ln(I_s/I_t)}{d(1/T)}\right] \qquad (2).$$

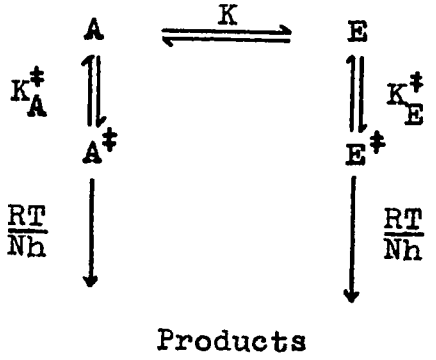
Conformational energies obtained by methods equivalent to the one just described, together with the potential-energy barrier of some simple compounds calculated from thermodynamic data have been reviewed by Dauben and Pitzer (32).

Recently, Pickering and Price (33) obtained the conformational energy between an axial and an equatorial hydroxyl group in cyclohexanol from infrared spectrum. The axial hydroxyl group in the conformationally homogeneous cis-4-t-butylcyclohexanol (cf.page 13) has an absorption peak at 955 cm^{-1}, and that of the equatorial

hydroxyl group in the trans isomer at 1070 cm^{-1}. From the relative intensity of these two peaks in the spectrum of cyclohexanol, it was calculated that an equatorial hydroxyl is favored by 0.3 - 0.4 kcal./mole over an axial hydroxyl.

Conformation and Reactivity: In order to appreciate the relationship between conformation and reactivity, one must recognize that both ground and transition states may exist in more than one conformation. The energy barrier for conformational changes usually being small as compared to those for reaction, the rate-determining steps in typical reactions are usually much slower than the rates of equilibration among conformational isomers and, consequently, the relative concentrations of the various conformations is assumed to remain constant.

It is possible for certain types of compounds in certain reactions to form the same transition state. However, usually different conformations in the ground state must be expected to yield different transition states. In view of the short life of the transition states, equilibration of transition states is assumed to never occur. Hence, the rate of a reaction of a compound which can react in either of two conformations, such as E (when the substituent is equatorial) and A (when the substituent is axial) can be expressed as follows where the transition state $A^{\ddagger}$ and $E^{\ddagger}$ may or may not be identical.



K is the equilibrium constant for the ground-state conformations and $K_A^{\ddagger}$ and $K_E^{\ddagger}$ are related to the free energies of activation from the axial and equatorial conformations, respectively. For a unimolecular reaction, the rate of formation of products, dP/dt, is given by the expression,

$$\frac{dP}{dt} = \frac{RT}{Nh} \cdot K_A^{\ddagger} [A] + \frac{RT}{Nh} \cdot K_E^{\ddagger} [E] \qquad (3),$$

where [A] and [E] are the concentrations of the ground-state conformations. Dividing by [A + E], the total concentration of reacting species, gives

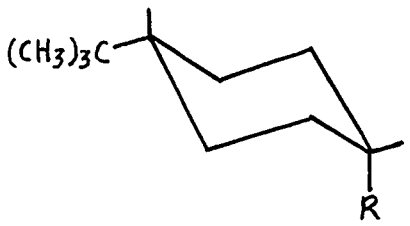
$$\frac{dP/dt}{[A+E]} = \frac{RT}{Nh} \cdot \frac{[A]}{[A+E]} K_A^{\ddagger} + \frac{RT}{Nh} \cdot \frac{[E]}{[A+E]} K_E^{\ddagger} \qquad (4)$$

or, $$k = N_A k_A + N_E k_E \qquad (5),$$

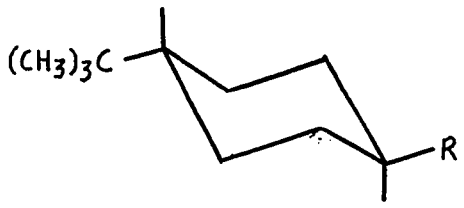
where k is the first order rate constant and k_A, k_E are rate constants corresponding to pure A or E type reactions. N_A and N_E

are the mole fractions of A and E, respectively. Thus the observed rate constant k is a weighted average of the rate constants characteristic of the conformational isomer A and E.

Winstein and Holness (34) derived this equation, and applied it to reactions of 4-t-butylcyclohexyl derivatives. Using the parameters of interaction energy obtained from acyclic compounds (35,36), they estimated that an axial t-butyl group was less stable than the equatorial isomer by at least 5.8 kcal./mole. Thus the tertiary butyl group serves as a compelling but remote handle, effective in controlling the conformational position of a 1-substituent. That is, a cis-4-t-butylcyclohexyl derivative (VII) must have the 1-substituent in the axial position,



VII



VIII

unless the difference in energy between the axial and equatorial positions of the 1-substituent (R) is greater than 5.8 kcal./mole, which, in general, will be unlikely. Thus, a cis-4-t-butylcyclohexyl derivative (VII) would have N_A equal to unity. Similarly, the trans-4-t-butylcyclohexyl derivative

(VIII) will have N_E equal to unity. The measured rate constants for the diastereomeric 4-t-butylcyclohexyl derivatives would therefore be k_A in one case and k_E in the other. It is assumed that the tertiary butyl group is sufficiently distant from the reaction center that polar and steric effects due to the t-butyl group tend to be small or negligible.

Winstein and Holness (34) studied the rates of chromic acid oxidation of the 4-t-butylcyclohexanols, the rates of saponification of the acid phthalate esters, and the rates of solvolysis of the tosyl derivatives under a variety of conditions. The same reactions were studied with the cyclohexyl compounds. The cyclohexyl compounds gave rates of oxidation and solvolysis intermediate between those of the equatorial and axial 4-t-butylcyclohexyl derivatives, and hence the values of N_A and N_E for cyclohexanol and cyclohexyl toluenesulfonate could be calculated from equation (5).

In Table III are listed the conformational energies obtained from reaction rates based on this method.

Table III

ΔF (Axial-Equatorial) for the given Substituent on a Cyclohexane Ring (37)

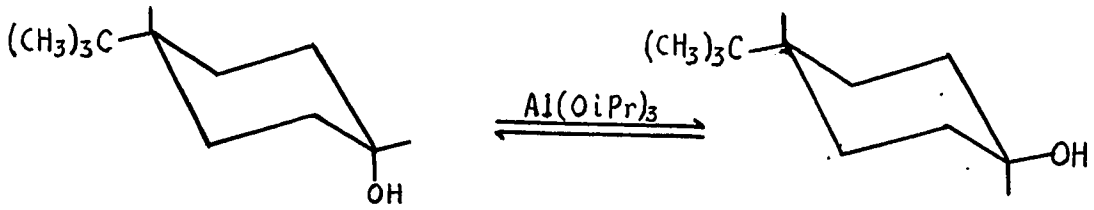
(Data for the given solvent at 25-50°C)

Group	Solvent	ΔF (a-e) kcal./mole
$t\text{-}C_4H_9$	-	5.4
$i\text{-}C_3H_7$	H_2O	3.3
$n\text{-}C_4H_9$	H_2O	2.1
$n\text{-}C_3H_7$	H_2O	2.1
C_2H_5	H_2O	2.1
CH_3	-	1.8
OTs	EtOH	1.7
$OCOC_6H_4COO^-$	H_2O	1.2
OH	75% HOAc	0.8

Although this is a clever method to determine the conformational energies from kinetic data, the accuracy of the results obtained must be accepted with reservation. The difference in reactivity between equatorially and axially oriented functional groups in diastereomeric 4-t-butylcyclohexyl derivatives is not sufficiently large (34) to be measured with accuracy. For example, the rate of acetylation of an equatorial

hydroxyl group is less than four times that of an axial hydroxyl group (38). Thus, a small error in measuring the reaction rates would introduce a relatively large error in the conformational energies derived therefrom. Eliel (38) has pointed out that the conformational energies determined by the kinetic method was correct only in the order of magnitude.

Conformation and Equilibrium: A more direct method for determining the difference in the interaction energies for the two chair forms of cyclohexanol is by the equilibration of the cis- and trans-4-t-butylcyclohexanols by means of aluminum isopropoxide. Since the t-butylcyclohexanols are conformationally homogeneous, the equilibrium between the configurational isomers must, then, correspond to the conformational equilibrium between axial and equatorial hydroxyl.



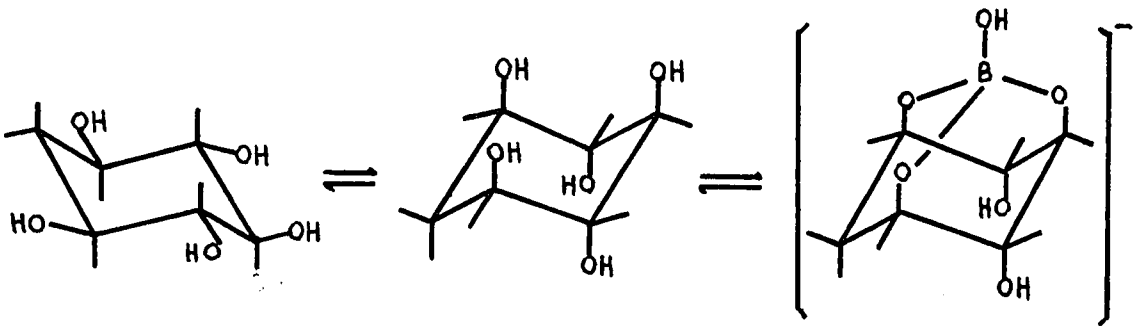
IX X

The equilibrium concentration of the two isomers as well as some alkylcyclohexanols has been determined by Eliel and Ro (39). They found a free energy difference of -0.96 kcal./mole for reaction (IX) to (X).

An ingenious method of conformational analysis was developed by Angyal and McHugh (40) who found that cyclitols which possess cis hydroxyl groups in the 1,3 and 5 positions give complexes with sodium borate in aqueous solution with the components in 1:1 ratio. Since complex formation reduces the pH of a borate solution, the complexes must be anions of acids stronger than boric acid. From the changes of pH caused by the addition of varying amounts of cyclitols, the equilibrium constant

$$K = \frac{[\text{complex}^-]}{[\text{borate}^{-3}][\text{cyclitol}]} \qquad (6)$$

was determined. A tridentate structure (XIII) was assigned to the complex of scylloquercitol (XI) which must react by way of the conformation XII.



XI XII XIII

Table IV shows the equilibrium constants obtained by these authors.

Table IV

Reaction of Borate Ion with Cyclitols at 22°

Compound	K	F kcal./mole
Scylloquercitol	5.0	-0.95
Epiquercitol	310	-3.36
cis-Quercitol	7.9×10^3	-5.26
Myoinositol	25	-1.90
Epiinositol	7.0×10^3	-5.20
cis-Inositol	1.1×10^6	-8.15

From these equilibrium constants, the free energy changes in the reactions were determined. The authors assumed that the free energy differences between two cyclitols were due to the different non-bonded interactions in the complexes and in the parent cyclitols. The following terms were considered: the energy of interaction between two axial oxygen atoms, (O:O)*; between an axial oxygen and an axial hydrogen atom, (O:H); and between two oxygen atoms on adjacent carbon atoms, both being

* In this thesis, the notations "X:X" and "X/X" are used to denote the diaxial and skew interactions, respectively, between the two relevant atoms when the ring is in the chair form.

equatorial or one axial and one equatorial, (0/0). Other non-bonded interactions were neglected.

In each case, on formation of the complex, the more stable chair (XI) is converted into the (XII) conformation and then esterified with borate ion. The free-energy change for the esterification was called ΔF_B. Thus for scylloquercitol, the relevant energy terms are:

in the cyclitol, $4(0/0)$;

in the complex, $\Delta F_B + 2(0:H) + (0:0)$.

The difference between these values is the free-energy change of complex formation and can be equated with the experimentally determined value; that is, for scylloquercitol,

$$-0.95 = \Delta F_B + 2(0:H) + (0:0) - 4(0/0) \qquad (7).$$

Each of the cyclitols gave a similar equation, with the result that six equations in four unknowns were obtained. The best values to satisfy these equations were found by the method of least squares and shown in Table V.

Table V

Interaction Energies of Cyclitols on Borate Ester Formation

ΔF_B	-2.5 ± 0.2 kcal./mole
(O/O)	0.35 ± 0.07
(O:H)	0.45 ± 0.05
(O:O)	1.9 ± 0.1

B. Principles of the Effect of Structure on Rates

1. Application of the Transition State Theory in Rate Problems

The great power of the transition state theory of reaction rates results from the fact that the rate processes can be treated as a special type of chemical equilibrium. Since chemical equilibrium is a thermodynamic function, it depends only upon the initial and final states of the process under consideration. In no way is an equilibrium dependent upon the manner in which the change from the fixed initial to the fixed final state is carried out (41). Thus the transition state theory makes rate problems independent of the variable time factor.

According to the transition state theory, the rate of a reaction is governed by the concentration of activated complexes, $X^{\ddagger}$, which give rise to the products with a universal rate constant RT/Nh. The concentration of activated complexes is determined by an "equilibrium" with the reactant molecules. The "equilibrium constant" of this process is represented by the symbol $K^{\ddagger}$. The activated complexes are molecules sufficiently energized and properly oriented to possess free energy in excess of a critical amount which specifies the transition state for a given reaction (42,43).

k = Rate at unit concentration of reactants

$$= \frac{RT}{Nh} \cdot K^{\ddagger} = \frac{RT}{Nh} e^{-\Delta F^{\ddagger}/RT} \qquad (8).$$

Other than temperature, the important variable which determines reaction rate is the free energy of activation, $\Delta F^{\ddagger}$. This free energy term, as a true thermodynamic quantity, depends only upon the nature of two fixed states. In this case the fixed states are the reactant and transition states. The manner in which the reaction proceeds from a given reactant to a given transition state in no way affects the rate (44).

Organic chemists have frequently been interested in the relative reactivities of a series of structurally similar compounds. This can be conveniently expressed in terms of structural effect

on the free energy of activation. Thus, from equation (8), the difference in free energy of activation for two different reactions is,

$$\Delta\Delta F^{\ddagger} = -RT\ln \frac{k}{k_o} \qquad (9);$$

where k and k_o are the rate constants.

According to the basic relation of statistical thermodynamics, the relative free-energy of activation, $\Delta\Delta F^{\ddagger}$, comprises of a potential-energy term, $\Delta\Delta E_p^{\ddagger}$, and a kinetic-energy term $-RT\ln(\pi Q^{\ddagger})$ (45,46). Thus,

$$\Delta\Delta F^{\ddagger} = \Delta\Delta E_p^{\ddagger} - RT\ln(\pi Q^{\ddagger}) \qquad (10),$$

where $(\pi Q^{\ddagger})$ involves temperature-dependent kinetic energies of motion.

2. Polar, Resonance and Steric Effects

The qualitative theories of reactivity that have been developed through the years, indicate that three basic factors may contribute to the potential-energy term, $\Delta\Delta E_p^{\ddagger}$: (a) polar, (b) resonance, and (c) steric (47,48). A change in polar, resonance and steric interactions from reactant to transition state leads to polar, resonance and steric effects, respectively.

$$\Delta\Delta E_p^{\ddagger} = \Delta\Delta E_{\sigma}^{\ddagger} + \Delta\Delta E_{\psi}^{\ddagger} + \Delta\Delta E_R^{\ddagger} \qquad (11)$$

and $$\Delta\Delta F^{\ddagger} = \Delta\Delta E_{\sigma}^{\ddagger} + \Delta\Delta E_{\psi}^{\ddagger} + \Delta\Delta E_{R}^{\ddagger} - RT\ln(\pi Q^{\ddagger}) \qquad (12)$$

where $\Delta\Delta E_{\sigma}^{\ddagger}$, $\Delta\Delta E_{\psi}^{\ddagger}$ and $\Delta\Delta E_{R}^{\ddagger}$ are factors contributed from polar, resonance and steric effects, respectively.

3. Entropy Effect

The kinetic-energy term, $-RT\ln(\pi Q^{\ddagger})$, was assumed to be small. However, in certain reaction series (49-51), this term becomes a dominant factor in rate process.

Since there is no way to evaluate the partition function ($\pi Q^{\ddagger}$), one must resort to the measurable term $\Delta\Delta S^{\ddagger}$.

$$\Delta\Delta S^{\ddagger} = R\ln(\pi Q^{\ddagger}) + RT\,\frac{d\ln(\pi Q^{\ddagger})}{dt} \qquad (13).$$

If the term $RT\,\frac{d\ln(\pi Q^{\ddagger})}{dt}$ is small as compared with $R\ln(\pi Q^{\ddagger})$ and, as a first approximation, can be taken as negligible (this is justified from the fact that the enthalpy of activation, $\Delta H^{\ddagger}$, is usually constant within the experimental intervals of temperature), then,

$$\Delta\Delta S^{\ddagger} = R\ln(\pi Q^{\ddagger}) \qquad (14),$$

and,
$$\Delta\Delta F = \Delta\Delta E_{p}^{\ddagger} - RT\ln(\pi Q^{\ddagger})$$
$$= \Delta\Delta E_{p}^{\ddagger} - T\Delta\Delta S^{\ddagger}$$

$$= \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger} \qquad (15),$$

or,
$$\Delta\Delta E_p^{\ddagger} = \Delta\Delta H^{\ddagger} \qquad (16).$$

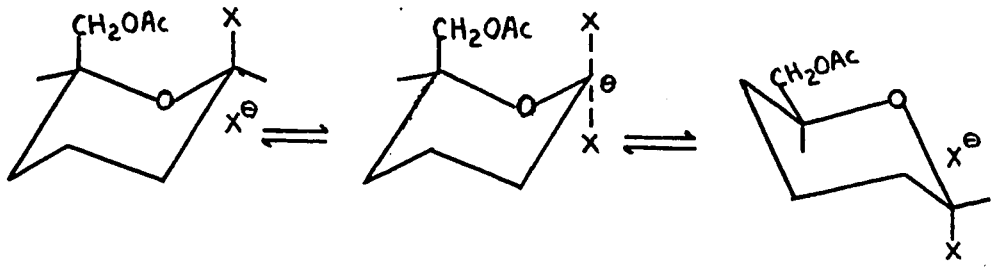
Therefore, the entropy effect can be estimated from the measured ~~xxxx xf~~ enthalpy of activation.

C. Scope of the Work

1. General Introduction

The acetylated sugars, along with the acetylated glycosyl halides and acetylated glycosides, play a central rôle in synthetic carbohydrate chemistry. There is a growing interest in their reactions for both theoretical and practical reasons. The successful synthesis of sucrose (52) is an example of an application of theoretical development in this field. In this section, a review is made of the theoretical studies which appear to have provided a better understanding of the properties and reactions of these compounds.

Hassel and Ottar (5), in 1947, attempted to rationalize the fact that the thermodynamically stable forms for the O-acetylated halides of the hexoses and heptoses could be expected in several cases to have the 1,5-trans configurations. A theory was advanced, based on the effect of steric interactions in the transition state (XV) on the relative rates for its decomposition to the 1,5-cis (XIV) and 1,5-trans forms (XVI).



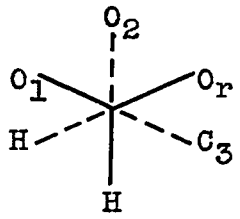
XIV XV XVI

It was suggested that the transition state should decompose more rapidly to the 1,5-trans isomer because of the steric interaction between the axial substituents at 1- and 5-positions. It was felt that the conformation of the initial form of the product should have the halogen in axial orientation in order to leave space for the departing group. In the pentose series, there is no large 5-substituent, therefore, according to these authors, the 3-acetoxy group plays the dominant rôle.

Obviously, steric interactions in the transition states cannot influence the relative stabilities in the ground states. Therefore, although intelligent, this rationalization is without any theoretical background.

Reeves (53,54) made an extensive study on the shape of pyranoside rings through the investigation of the complexing of cuprammonium ion with the free glycol groups in these compounds. His studies led to the conclusion that the glycosides, in most cases, have the pyranose ring in the chair form in preference to any boat form whenever both are structurally possible. This would be expected on the basis of conformational theory.

Reeves derived the following so-called "conformational instability factors": (a) any axial substituent (other than hydrogen) introduces an element of instability into the conformation — especially important is an axial oxygen atom on carbon 2 when its carbon-oxygen valence bisects the two carbon-oxygen valences of carbon 1, which was termed the Δ2-effect.

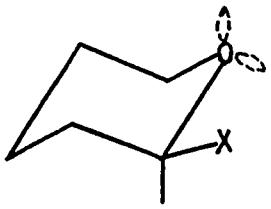


XVII

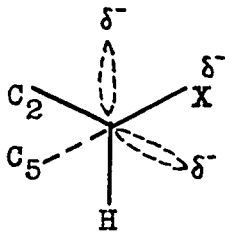
Reeves' conclusion together with the principle of conformational analysis as applied by Hassel and Ottar, clearly suggested that, at least in may cases, the stable anomer for acetylglycosyl halides is the anomer that possesses the halogen atom in axial orientation.

Edward (55) suggested that this situation may arise from a dipole-dipole interaction between the ring-oxygen atom and an equatorial substituent on carbon 1. No theoretical reason has yet been proposed to account for the dipole-dipole interaction other than the suggestion that a skew interaction of the polar equatorial bond with both p-orbitals of the ring-oxygen atom may lead to the instability. Clearly the preference for an axial orientation by a large halogen atom could not arise from steric

reasons.



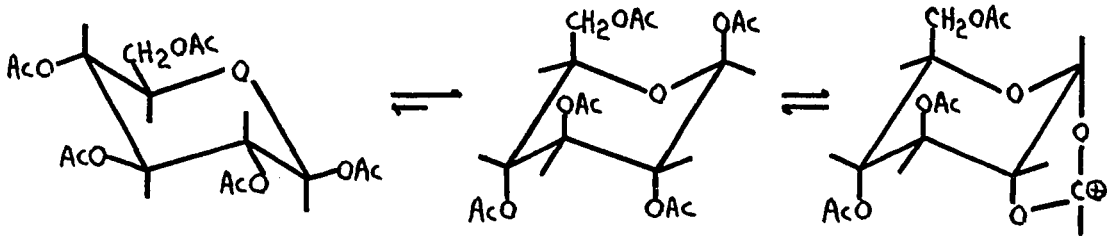
XVIII



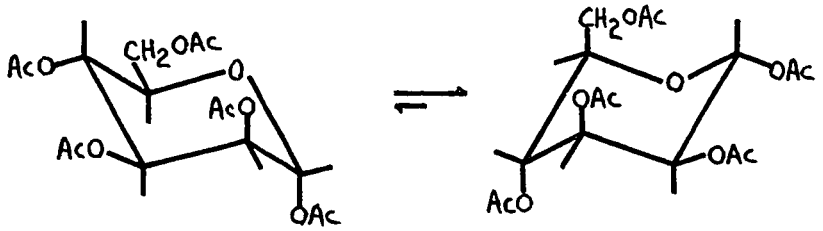
It is to be noted, however, that until recently there was no definite information on the actual conformations of the acetylated sugars, glycosyl halides and glycosides. Lemieux and coworkers (56) had, in fact, obtained data through a study of the rates for the dissociation of the 1-acetoxy group of certain sugar acetates which could be rationalized in two ways depending on the conformation of the sugar acetate in the ground state. In this respect, it must be noted that the principles of conformational analysis are mainly derived from studies of hydrocarbons. An extrapolated application of these principles to the case of acetylated sugars may be made, but certainly not without some reservation and further justification. An unambiguous decision on these matters could therefore not be made until direct evidence for the conformation of the sugar derivatives became available.

For example, Lemieux and Brice (56) have studied the relative rates of exchange of the 1-acetoxy group in sugar acetates with carbon-14 labelled $SnCl_3OAc^*$. The high reactivity found for β-D-glucopyranose pentaacetate (XIX) as compared with α-D-mannopyranose pentaacetate (XXII) could be attributed to the more

favorable orientations of the 1- and 2-acetoxy groups in the gluco-configuration if these compounds are existing in the conformations XX and XXIII.



XIX XX XXI



XXII XXIII

The above studies and notions were interesting, not because they shed light on the reasons for the rather puzzling properties of these sugar derivatives, but because they clearly indicated that the compounds possess abnormal properties which could not be accounted for on the basis of the established parameters for conformational analysis.

2. Purpose of this Work

One of the most effective approaches to the problem of gaining quantitative information on conformational effects is a study of the equilibria between isomeric compounds (cf. p. 16). Consequently, it was felt desirable to undertake a study of the

anomerization equilibria for acetylated sugars and glycosyl halides. Initial experiments with the acetylated glycosyl halides proved unrewarding, and attention was therefore directed entirely towards the sugar acetates. The acetylated aldopyranoses were chosen as the experimental means because of their accessibility, i.e., they can be prepared in pure state.

These compounds undergo a reversible reaction between the alpha and beta anomers under general acid-catalyzed conditions. The equilibrium nature of this reaction has been reported by several authors (57-61), and it has been shown that the reaction is specific to the anomeric center and no change other than anomerization takes place (59). Evidence showed that, with sulfuric or perchloric acid as catalyst, a true equilibrium was established between the alpha and beta anomers (59-61). Therefore, a quantitative conformational analysis can be made from the equilibrium data.

The mechanism of the anomerization of acetylated aldopyranoses has been subject to extensive studies. Different interpretations of kinetic data resulted in proposal of different mechanisms. There seems to be no unequivocal evidence for the mechanism of the reaction. Actually, to date, only studies of the anomerization of the D-glucopyranose pentaacetate have been reported and there is no basis for assuming that all acetylated aldopyranoses will anomerize with the same mechanism.

As will be seen later on, the conformations of acetylated

aldopyranoses in the ground states are now known and consequently, conformational analyses of the rates of anomerization may allow conclusions as to the structure of the transition states and thus shed light on the mechanisms of reaction.

D. Configuration of the Sugars

A positive establishment of the configurations of the compounds used in this study is a requirement for any quantitative analysis of the experimental data. The configurations of the isomeric sugars have been established beyond doubt (62). However, the ring structure of the sugars and their derivatives had, for a time, been subject to great confusion. Also, direct evidence regarding to the absolute configuration of the anomeric carbon atom came only in recent years.

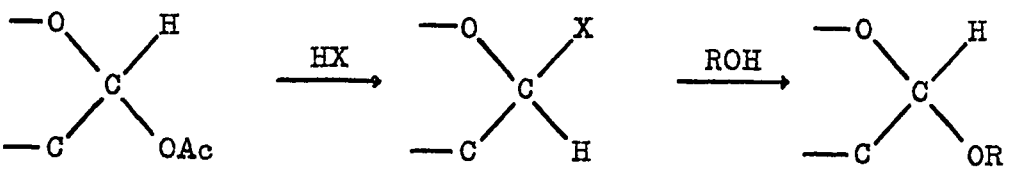
1. Ring Structure of the Sugars

Fischer (63) adopted the ring structure formula to explain the formation of isomeric methyl D-glucosides from D-glucose. He placed the ring closure on the fourth carbon, by analogy with the γ-lactones. This was an arbitrary assumption which later proved to be incorrect.

Hirst (64), in 1926, established the pyranose ring structure of the methyl D-glucosides by the classical methylation technique. An easier and more direct method to establish the

ring size involves the oxidation of the glycosides with the glycol-splitting reagent sodium periodate (65,66).

Armstrong (67) had related the ring structure of α-D-glucose to methyl α-D-glucoside. Hudson (68), from the enzymatic hydrolysis of sucrose, showed that the glucose unit liberated is α-D-glucopyranose. Bertrand and Roth (69) noted that low temperature acetylation of D-glucose with acetic anhydride in pyridine does not involve structural change of the parent sugar, i.e., α-D-glucose gave the alpha pentaacetate and β-D-glucose gave the beta pentaacetate. However, it is to be noted that the structure of the sugar acetate produced depends on the condition of acetylation. For example, high temperature acetylation of galactose yields appreciable amount of the furanose isomers. Therefore, it was felt necessary to establish the ring size of the sugar acetates. Unfortunately, for most of the sugar acetates, a pyranose ring structure was assigned on the basis that a pyranose ring is more stable than a furanose ring of the sugars. Only in few cases (70,71), has the ring size been established through the transformation of the acetate (XXIV) to halide (XXV) and then to glycoside (XXVI).



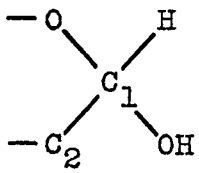
XXIV XXV XXVI

It has been shown that these reactions do not involve the change of ring structure (71).

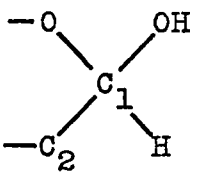
Lemieux et.al. (72), who introduced proton magnetic resonance spectroscopy into the field of carbohydrate chemistry, obtained the conclusive evidence that the acetylated sugars are, in fact, the derivatives of pyranoses. The compounds used in this study with the physical constants and references of preparation are tabulated in Experimental (Table VI , page 46).

2. Configuration of the Anomeric Carbon Atom

Cyclization of a sugar molecule into the hemiacetal ring structure creates a new asymmetric carbon atom. Consequently, two stereoisomers, designated as alpha and beta anomers, are formed with the difference in configuration on carbon 1,(XXVII) and XXVIII).



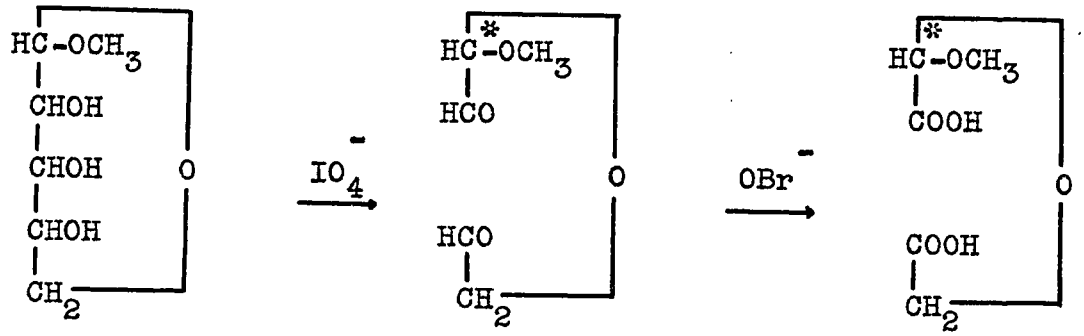
XXVII



XXVIII

Classification of the alpha and beta anomers was first attempted by Hudson (68). His "Rule of Isorotation" was based on van't Hoff's principle of optical superposition. Hudson arbitrarily assigned the anomers with higher specific rotation as

the alpha. The validity of Hudson's classification was confirmed by periodate oxidation followed by hypobromite oxidation of glycopyranosides (65), which removes carbon 3 as formic acid and destroys the asymmetry of carbon atoms 2 and 4, and yields a dibasic acid. Thus, when an aldopentopyranoside (XXIX) is subject to a periodate and hypobromite oxidation, the only asymmetric center left in the product (XXXI) is that of carbon 1.



XXIX XXX XXXI

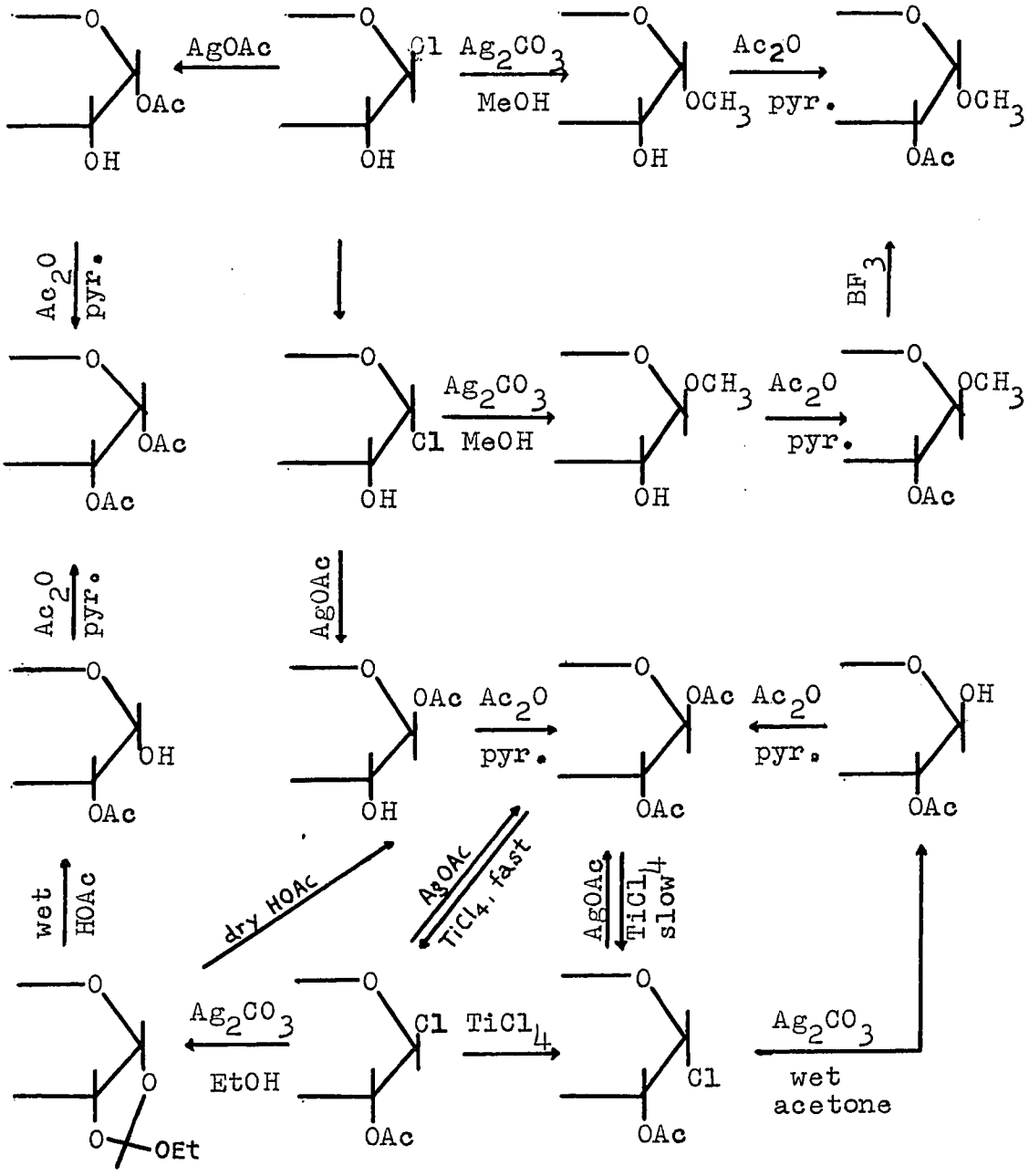
Therefore, all the alpha anomers give the same final oxidation product; whereas the beta anomers give the enantiomorph.

The method of alpha-, beta-designation, initiated by Hudson, is empirical and bears no necessary relation to the absolute configuration of the anomeric carbon atom.

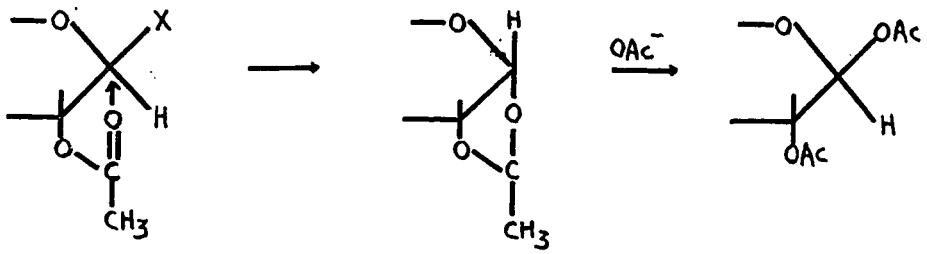
Böeseken (73,74) made an attempt to show the relative configuration of the anomeric carbon atom of D-glucose. This was based on his observation of the conductivity of the sugar freshly dissolved in a boric acid solution. The cis-glycols form a complex with boric acid, which, being a stronger acid than boric

acid itself, increases the conductivity of the solution. The conductivity of α-D-glucose in the presence of boric acid decreases during mutarotation as it is converted in part into β-D-glucose; the reverse is true for β-D-glucose. The velocity of this change parallels that of the mutarotation. On this basis, the hydroxyl groups on carbon atoms 1 and 2 of α-D-glucose were assigned the cis relationship. This view has been confirmed by x-ray diffraction (75).

Recently, a convincing proof for the configuration of the anomeric carbon atom came from the following reaction sequences (76-86).


AgOAc
Cl
Ag_2CO_3
MeOH
Ac_2O
pyr.
OAc
OH
OCH_3
Ac_2O
pyr.
BF_3
Ag_2CO_3
MeOH
AgOAc
$TiCl_4$, fast
AgOAc
$TiCl_4$
slow
dry HOAc
wet
HOAc
Ag_2CO_3
EtOH
$TiCl_4$
Ag_2CO_3
wet
acetone
OEt

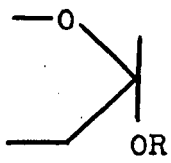
Direct displacement of a halogen atom involves inversion of configuration. In the presence of a 2-acetoxy group, the difference in reaction route between the 1,2-cis and 1,2-trans anomers is due to the participation of the neighboring acetoxy group (56, 87) in the case of 1,2-trans anomers to form the intermediate acetoxonium ion (XXXIII) which reacts with the environment to give a product (XXXIV) with a net result of retention of configuration.



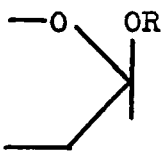
XXXII XXXIII XXXIV

Lemieux and coworkers (72) found, from proton magnetic resonance spectra, that the spin-spin coupling constant for 1,2-diaxial hydrogen atoms on a six-membered ring is 2-3 times larger than when the hydrogen atoms are skewed. This conclusion was mainly derived from the results of the conformationally pure cis- and trans-4-t-butylcyclohexanols and their acetate. Applied to the acetylated pyranoses, the generally accepted configuration of the anomeric carbon atom conforms with the above rule. This is another convincing proof to show the absolute configuration of carbon 1 from the physical method.

From all the evidence cited above, the configuration of the anomeric carbon atom shown below can be safely considered as absolute and definite.



XXXV (α-D-anomer or β-L-anomer)



XXXVI (β-D-anomer or α-L-anomer)

E. Conformation of a Pyranose Ring

Much of the chemistry of the pyranose sugars was placed on a rational basis by the work of Reeves (53,54). It has been mentioned in the previous section (cf. page 25) that Reeves investigated the conformations of sugar molecules by examining their capacity of complex formation with cuprammonium ion. He concluded that pyranose rings assume a chair form in preference to any boat form. However, it should be noted that Reeves' work was entirely based on an empirical approach. Even the structures of the complexes are unknown and, consequently, his conclusions are merely rationalizations and not proofs. X-ray diffraction revealed that a chair form for a pyranose ring is preferred in the crystal lattice (88-92). Proton magnetic

resonance spectra of acetylated aldopyranoses substantiated the chair form for the pyranose rings. Since there is no evidence ever observed to the contrary, it seems reasonably safe to conclude that the chair form of a pyranose ring is energetically favored over a boat form.

F. Proposed Mechanisms for the Acid-Catalyzed Anomerization of the Acetylated Aldopyranoses

The anomerization process, an interconversion between the alpha and beta anomers, is a general acid-catalyzed reaction. The anomerizing action of Lewis acids on acetylated sugar is well known and has found frequent application in the preparation of the more stable anomers. The catalysts usually used are anhydrous zinc chloride (57,93-96), stannic chloride (97), sulfuric acid (58,59,98) and perchloric acid (60).

The rate of anomerization is of first order with respect to the concentration of sugar acetate. The reversible reaction

$$\alpha\text{-anomer} \underset{k_\beta}{\overset{k_\alpha}{\rightleftharpoons}} \beta\text{-anomer}$$

is analogous to the mutarotation of the free sugars. Solution of the rate equation is obtained in the following manner:

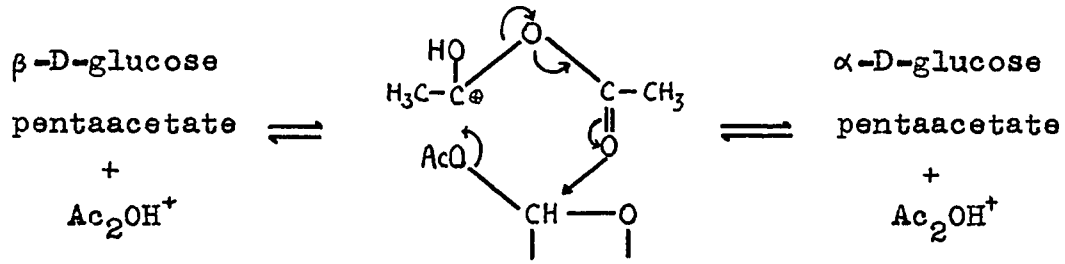
$$\frac{-d[\alpha]}{dt} = \frac{d[\beta]}{dt} = k_\alpha[\alpha] - k_\beta[\beta] \qquad (20).$$

Expressing the concentration factors in terms of rotation, and integration yields the equation,

$$k_\alpha + k_\beta = \frac{2.303}{t} \log \frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty} \qquad (21),$$

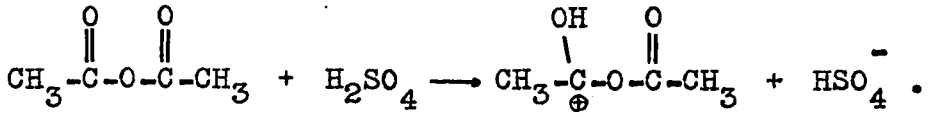
which was first applied by Hudson (99).

A mechanistic study of the anomerization of the D-glucopyranose pentaacetates was first made by Bonner (59), who used a mixture of acetic acid and acetic anhydride as solvent and sulfuric acid as catalyst. He found that the rate of anomerization was increased by increasing the concentration of acetic anhydride. The reaction was free from salt effect, i.e., the addition of lithium bisulfate had no effect on the rate. On the other hand, the addition of inert basic solvent, such as ethers, retarded the reaction. On the basis of these experimental facts, Bonner proposed the following mechanism:



XXXVII

The sulfuric acid is considered essentially completely ionized as follows,



The rate-determining stage in the reaction was considered to involve the attack of the conjugate acid on the anomeric acetoxy group of the sugar acetate to give the transition state (XXXVII) which then decomposes either to the reactants or, through inversion, to the products.

Bonner's reasoning was based on the ease of formation of a six-membered ring in nature (the transition state involves a six-membered ring). There was no decisive kinetic evidence to substantiate this mechanism. Moreover, the mechanism ~~xtxts~~ as Bonner suggested is against the principle of microscopic reversibility (99a).

Much of the credit in the kinetic study on the anomerization of D-glucopyranose pentaacetates was due to Painter (100), who used dry acetic acid as solvent and perchloric acid as catalyst. This author found that the first order rate constant was increased with increasing concentration of sugar acetate or by replacing part of the acetic acid with non-basic inert solvent. Since these experimental facts were not predicted from Bonner's mechanism, Painter suggested the conjugated acid of sugar acetate, $SOAcH^+$, instead of the conjugated acid of solvent, as the reacting species. The first order rate depends on the concentration of the conjugated acid of sugar acetate.

$$r = k[SOAcH^+] \qquad (22).$$

Moreover, there is a competition of the proton between the solvent and the acetylated sugar molecules.

$$AcOH + H^+ \overset{K_1}{\rightleftharpoons} AcOH_2^+ \qquad (23).$$

$$SOAc + H^+ \overset{K_2}{\rightleftharpoons} SOAcH^+ \qquad (24).$$

An equilibrium is established between the conjugated acids.

$$AcOH_2^+ + SOAc \overset{K_3}{\rightleftharpoons} SOAcH^+ + AcOH \qquad (25).$$

$$[SOAcH^+] = \frac{K_3[SOAc]\ [AcOH_2^+]}{[AcOH]} \qquad (26).$$

Since, $r = k[SOAcH^+]$

$= (k_\alpha + k_\beta)\ [SOAc]$,

therefore, $(k_\alpha + k_\beta)\ [SOAc] = \frac{kK_3[SOAc][AcOH_2^+]}{[AcOH]} \qquad (27).$

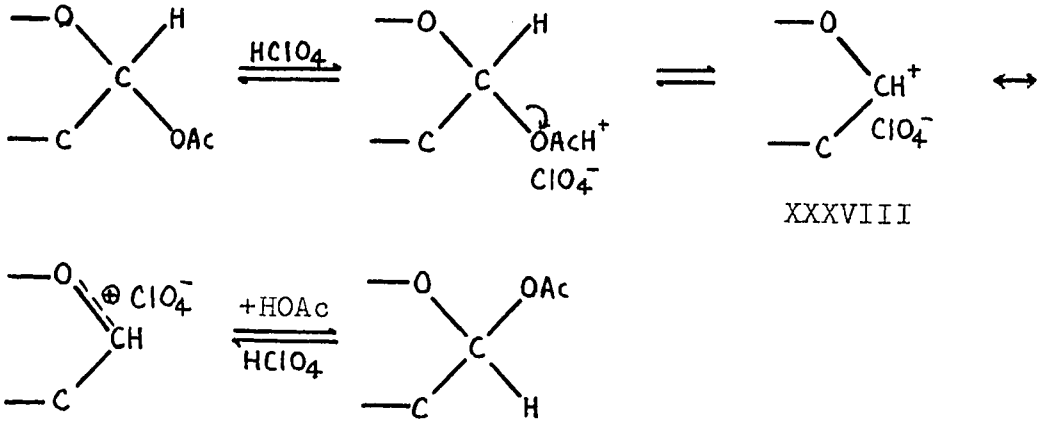
Perchloric acid, being a strong acid, can be assumed to be completely dissociated and acetic acid is a much stronger base than the sugar acetate. Thus the concentration of the conjugated acid of acetic acid, $AcOH_2^+$, can be taken as equal

to the concentration of perchloric acid. Therefore,

$$(k_\alpha + k_\beta)\,[\mathrm{SOAc}] = \frac{kK_3[HClO_4][\mathrm{SOAc}]}{[\mathrm{AcOH}]} \qquad (28).$$

From this equation, the rate should be first order with respect to the concentration of perchloric acid, and any change of the ratio between the sugar acetate and acetic acid will affect the first order rate constant. These facts were all verified experimentally.

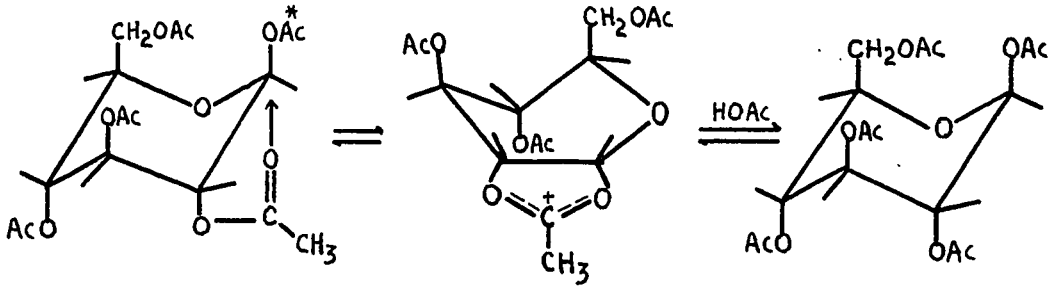
Furthermore, the reaction rate increased faster when the non-basic solvent added had a low dielectric constant. From these experimental facts, Painter suggested an ion-pair mechanism based on an acetal model, and postulated the formation of the carbonium ion (XXXVIII) or the carboxonium ion (XXXIX) as the rate-determining step.



XXXVIII

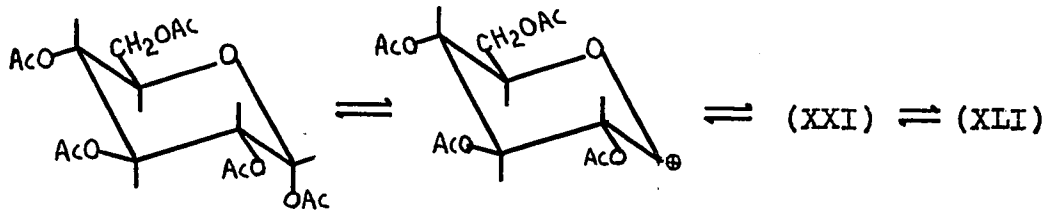
XXXIX

Lemieux and coworkers (56) studied the rate of isotopic exchange of D-glucopyranose pentaacetates labelled in the 1-acetoxy group with carbon-14, under anomerizing conditions. They found that the rate of exchange for the β-anomer is about seventeen times faster than the rate of anomerization. This result demonstrated clearly the participation of a trans 2-acetoxy group (87) to form the resonance stabilized acetoxonium ion (XXI) which is expected to give back the β-anomer (XLI) on reaction with the solvent acetic acid.



XL XXI XLI

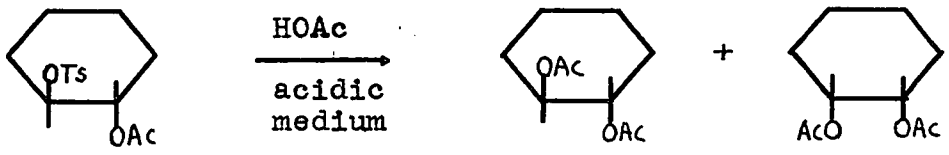
For the α-anomer, the rate of exchange is, within experimental error, equal to the rate of anomerization. This result meets the stereochemical requirement for a bimolecular reaction. However, it does not exclude a carbonium ion mechanism because the acetoxonium ion (XXI) would be expected to be more stable than the carbonium ion (XLIII) formed from the dissociation of 1-acetoxy group. It is conceivable that the carbonium ion (XLIII) would be rearranged instantaneously to the acetoxonium ion (XXI) which reacts with the solvent to give rise the β-anomer.



XLII XLIII

Hurd and Holysz (101) discovered that the 1,2-cyclic ketal is formed on the reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide with dialkyl cadmium; which, in fact, shows the formation of the 1,2-α-cyclic carbonium ion from other carbonium ions. The reverse must be expected. In view of the fact that the acetoxonium ion is undoubtedly present in the anomerization system, these authors pointed out that anomerization may take place through the transformation of carbonium ions.

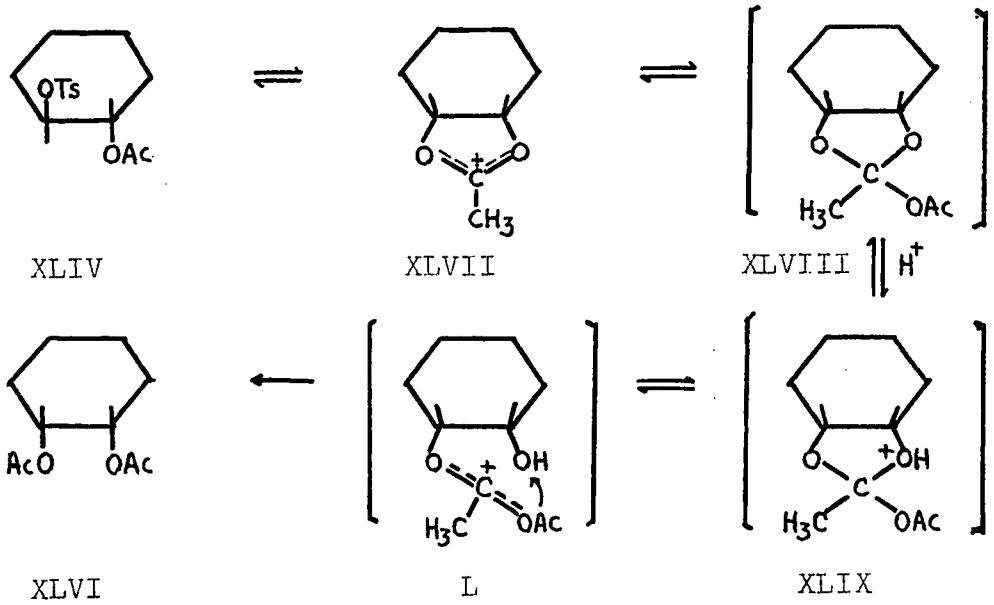
Recently, Winstein et.al. (102) found that, in acidic medium, the acetolysis of trans 1-tosyloxy-2-acetoxy-cyclohexane (XLIV) yielded a substantial amount of cis 1,2-diacetoxy-cyclohexane (XLVI).



XLIV XLV XLVI

They postulated the following mechanism to account for the

formation of the cis isomer from the intermediate acetoxonium ion (XLVII).



XLIV XLVII XLVIII

XLVI L XLIX

This result indicated that an ionic mechanism for the anomerization of sugar acetates as conceived by Lemieux is highly probable.

II EXPERIMENTAL

Melting points were determined with the Leitz hot stage apparatus, and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer single beam double pass instrument. Proton magnetic resonance spectra were measured in the National Research Council of Canada with a Varian V-4300 spectrometer at a fixed frequency of 40 Mc./sec.

The chemicals used are listed below:

Perchloric acid: "Baker Analyzed" Reagent; assay ($HClO_4$) 70.8%.

Acetic acid: Reagent grade, assay (HOAc) minimum 99.7%.

Acetic anhydride: Fischer Certified Reagent; assay (Ac_2O) 97.8%.

Most of the compounds used in this study were prepared by published method. The physical constants and references of preparation are listed in Table VI.

Table VI

Physical Constants of the Sugar Derivatives

Compound	M.P.	$[\alpha]_D$	Reference
α-D-Xylopyranose Tetraacetate	56 - 57	89.3	(93)
β-D-Xylopyranose Tetraacetate	127 -127.5	-24.7	(93)
α-L-Arabopyranose Tetraacetate	95 - 96.5	42.5	(103)
β-L-Arabopyranose Tetraacetate	85 - 85.5	147.2	(103)
α-D-Lyxopyranose Tetraacetate	95 - 96	25	(104)
α-D-Ribopyranose Tetraacetate	75 - 78	54.0	(105, this thesis, p.63)
β-D-Ribopyranose Tetraacetate	110 -111	-52.0	(106)
α-D-Glucopyranose Pentaacetate	113.5-114	101.6	(107)
β-D-Glucopyranose Pentaacetate	132.3-133	3.8	(68)
α-D-Mannopyranose Pentaacetate	73 - 74	55.0	(94)
β-D-Mannopyranose Pentaacetate	115 -116.2	-25.2	(108)
α-D-Galactopyranose Pentaacetate	95 - 98	106.7	(95)
β-D-Galactopyranose Pentaacetate	144.5-147	25	(109)

Table VI. (continued)

Compound	M. P.	$[\alpha]_D$	Reference
β-D-Allopyranose Pentaacetate	97 -100	-14.6	(56, this thesis, p.64)
α-D-Altropyranose Pentaacetate	119.5-121	63	(70)
α-D-Talopyranose Pentaacetate	106 -107	70.2	(110)
α-D-Gulopyranose Pentaacetate	113	86.2	(111)
6-Deoxy-α-D-Glucopyranose Tetraacetate	119.5	123.8	(112)
6-Deoxy-β-D-Glucopyranose Tetraacetate	147	18.9	(112a)
6-Deoxy-6-Chloro-α-D-Glucopyranose Tetraacetate	162 -164	111.6	(113)
6-Dexoy-6-Chloro-β-D-Glucopyranose Tetraacetate	114 -115	17.6	(114)
6-Deoxy-6-Iodo-α-D-Glucopyranose Tetraacetate	182	102.0	(115)
6-Deoxy-6-Iodo-β-D-Glucopyranose Tetraacetate	152	9.1	(115)
6-Tosyl-α-D-Glucopyranose Tetraacetate	184 -185	97.0	(116)
6-Tosyl-β-D-Glucopyranose Tetraacetate	203 -205	23.9	(116)
3-Tosyl-α-D-Glucopyranose Tetraacetate	72 -75	84.4	(This thesis p.64)
3-Tosyl-β-D-Glucopyranose Tetraacetate	170 -171	13.7	

Table VI (continued)

Compound	M.P.	$[\alpha]_D$	Reference
2-Deoxy-2-Acetamido-α-D-Glucopyranose Tetraacetate	139-140	93.5	(118)
2-Deoxy-2-Acetamido-β-D-Glucopyranose Tetraacetate	188-189	1.2	(118)
3-Deoxy-3-Acetamido-β-D-Glucopyranose Tetraacetate	206-209	8.1	(This thesis, p.66)
6-Deoxy-6-Acetamido-α-D-Glucopyranose Tetraacetate	141-142	110	(This thesis, p.68)
6-Deoxy-6-Acetamido-β-D-Glucopyranose Tetraacetate	115-120	9.9	(This thesis, p.67)

Preparation of the Catalyst Solution:

An approximately 1:1 mixture of acetic acid - acetic anhydride, 0.1M in perchloric acid, was made as follows.

A 1:1 mixture by volume of acetic acid - acetic anhydride, ca. 95 ml., was added to 1.420 g. of 70.8% perchloric acid contained in a 100 ml. volumetric flask cooled in ice-water, as the reaction of the acetic anhydride with the water in the perchloric acid librates large amounts of heat. The flask was then placed in a constant temperature bath and after the solution reached the bath temperature, the volume was finally adjusted with the solvent at the same temperature.

A previous investigator (60) has shown that the rate of anomerization varies with the concentration of acetic anhydride. Since the results were used for comparative purposes, the exact concentration of acetic anhydride was not calculated. However, in order for the kinetic data to be valid for comparison, the perchloric acid used was from the same reagent bottle and the same grade of acetic acid and acetic anhydride was used through all the experiments.

Anomerization of the Acetylated Aldopyranoses:

Unless otherwise mentioned, all the experiments of anomerization of the acetylated aldopyranoses were carried out in

the following manner.

Ten ml. of the thermostatted catalyst solution were added to a solution of two millimoles of the sugar acetate in 10 ml. of the 1:1 acetic acid - acetic anhydride contained in a 50 ml. Erlenmeyer flask kept at the desired temperature. The contents were quickly mixed by swirling, poured into a jacketed polarimeter tube through which fluid was pumped from the thermostat to maintain the reaction temperature. The temperature was controlled within ± 0.1°C using Lo-Temp bath manufactured by Wilken Anderson Co. with ethylene glycol-water as circulating medium. The reaction was followed in a Schmidt-Haensch polarimeter which could be read to 0.02 degrees of arc. It was necessary to wipe the condensation away from the outside of the cover glasses before a reading could be taken at the low temperatures.

The initial readings were obtained by extrapolation to zero time of the plot of log $(\alpha_t - \alpha_\infty)$ against time. In all cases, these rotations were, within experimental error, the same as those obtained from a solution of the sugar acetate in the solvent without catalyst.

The concentration of perchloric acid was slightly different for different batches of catalyst solution due to slight differences in the weight of perchloric acid used. Painter (60,100) has shown that the rate of anomerization is first order with respect to the concentration of perchloric acid. This experimental fact was used to reduce all the kinetic data to exactly 0.05 M

perchloric acid in order to establish relative rates of reaction.

The observed first order rate constants are listed in Table VII (page 78) and experimental plots are shown in Figs. 1 and 2.

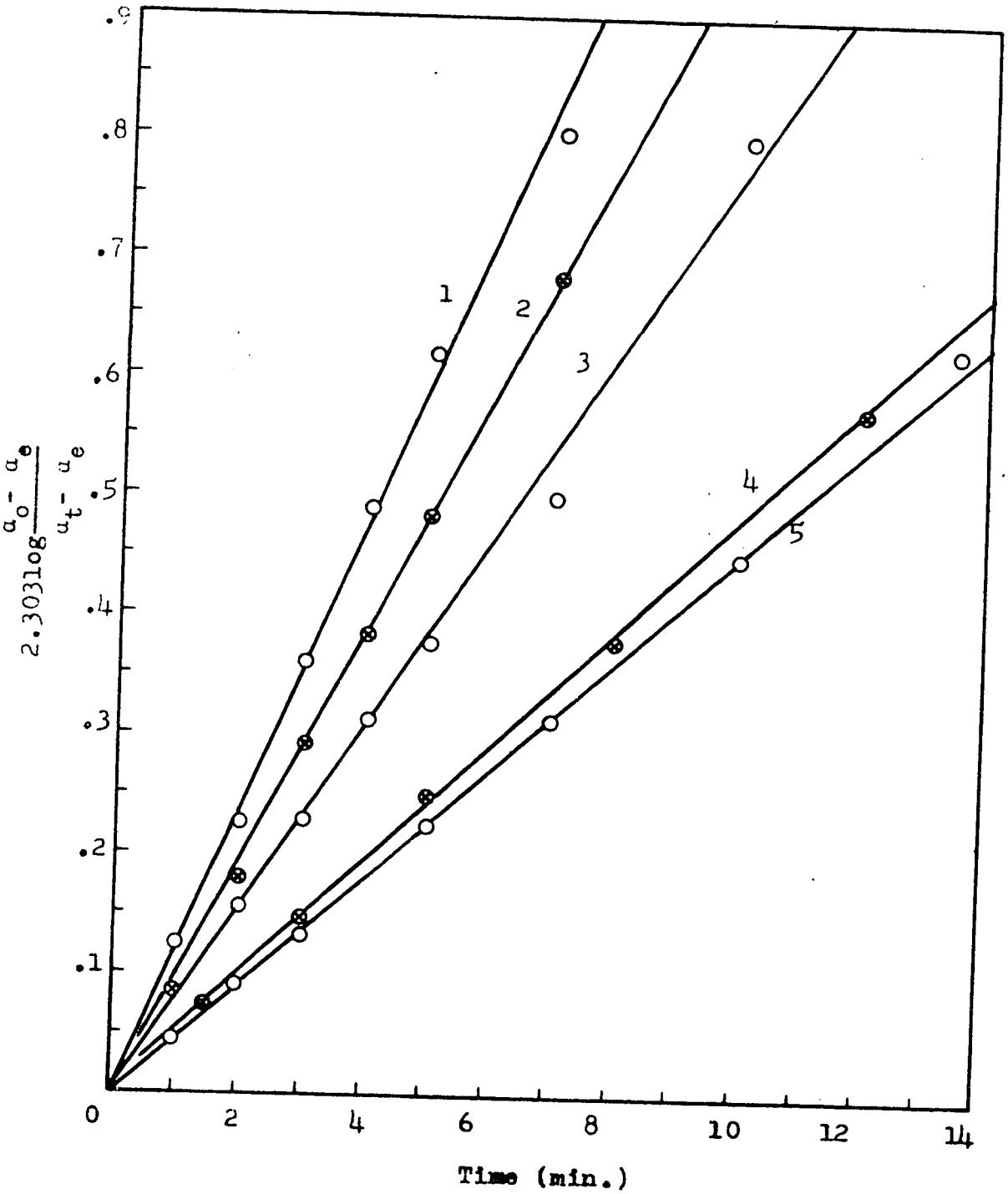


Fig. 1. Rates of Anomerization of Acetylated Aldopyranoses in 1:1 HOAc - Ac_2O containing 0.05 M $HClO_4$ at 25°C.

1. β-D-Xylo, 2. α-L-Arabo, 3. α-D-Lyxo,
5. β-D-Ribo, 4. 6-Deoxy-D-Gluco.

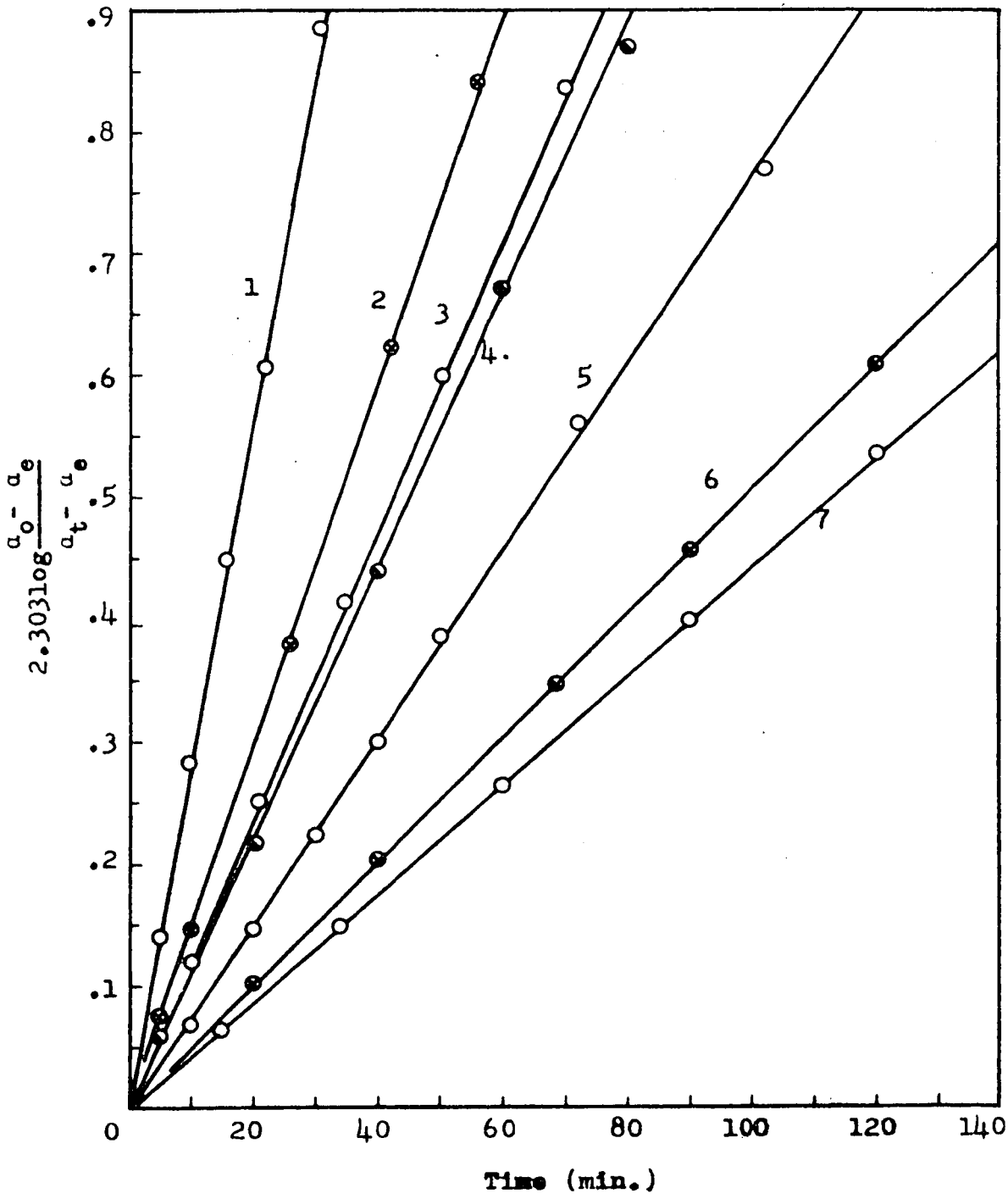


Fig. 2. Rates of Anomerization of Aldohexopyranoses Penta-acetates in 1:1 HOAc-Ac_2O containing 0.05M $HClO_4$ at 25°C.

1. α-D-Altro, 2. α-D-Gulo, 3, β-D-Galacto, 4. α-D-Talo, 5. β-D-Allo, 6. β-D-Manno, 7. β-D-Gluco.

Infrared Spectra of the Acetylated Aldopyranoses.

The potassium bromide pressed disc technique, invented independently by Schiedt and Reinwein (119) and by Stimson and O'Donnell (120) in 1952, and which has been demonstrated suitable for quantitative determinations (121-125), was used in a comparison of the spectra of the equilibrium and synthetic mixtures of the acetylated aldopyranoses.

The equilibrium mixture was recovered from the reaction solution by pouring the solution into ice-water (ca. 100 ml.). The perchloric acid was neutralized with sodium bicarbonate and the solution was extensively extracted with chloroform. The extract was washed once with water, then with sodium bicarbonate solution until no more carbon dioxide was evolved, and finally washed once again with water. After drying over anhydrous sodium sulfate, the chloroform solution was evaporated under reduced pressure to a small volume, then transferred into a weighing bottle. The remaining solvent was evaporated under an infrared lamp with a slow current of compressed air. Finally, the syrup was dried in a vacuum desiccator for a day.

A 10 ml. solution of the equilibrium mixture in purified dioxane was prepared with a concentration approximately of one mg. of sample per ml. A solution of a synthetic mixture composed of the alpha and beta anomers as calculated from the equilibrium rotation, was also prepared with the same concentration

as the solution of equilibrium mixture. One ml. aliquots of each solution were added separately into three ml. volumes of a 10% aqueous solution of potassium bromide (reagent grade). The solution was mixed with a microspatura, and then freeze-dried.

The dried, fine powder was pressed into a disc in a rectangular Bairddie by applying a hydraulic pressure of 10,000 lbs. per sq. in.

It was found that the transparency of the potassium bromide disc, thus prepared, in infrared was highly dependent upon the manner that the hydraulic pressure was applied. In order to get a satisfactory result, the pressure was gradually increased to 10,000 pounds over a period of two minutes and the disc of the two samples (equilibrium and synthetic mixtures) was prepared under the same conditions as much as possible.

The characteristic absorption peaks of the acetylated aldopyranoses are in the region 1200-800 cm^{-1}.

The spectra of the equilibrium and synthetic mixtures together with the spectra of the alpha and beta anomers of the acetylated aldopyranoses are shown in Figs. 3-8.

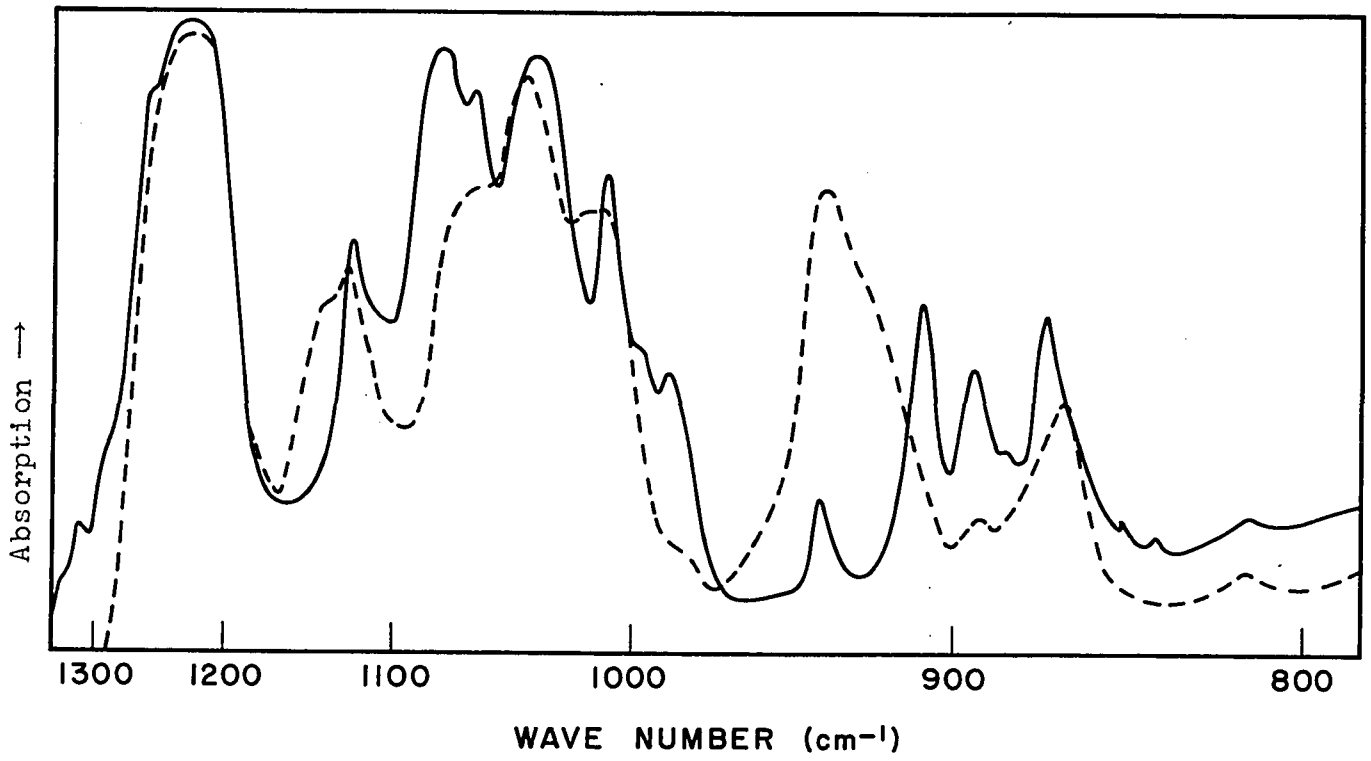


Fig. 3a. Infrared Spectra of D-Xylopyranose Tetraacetates

—— β-anomer ---- α-anomer

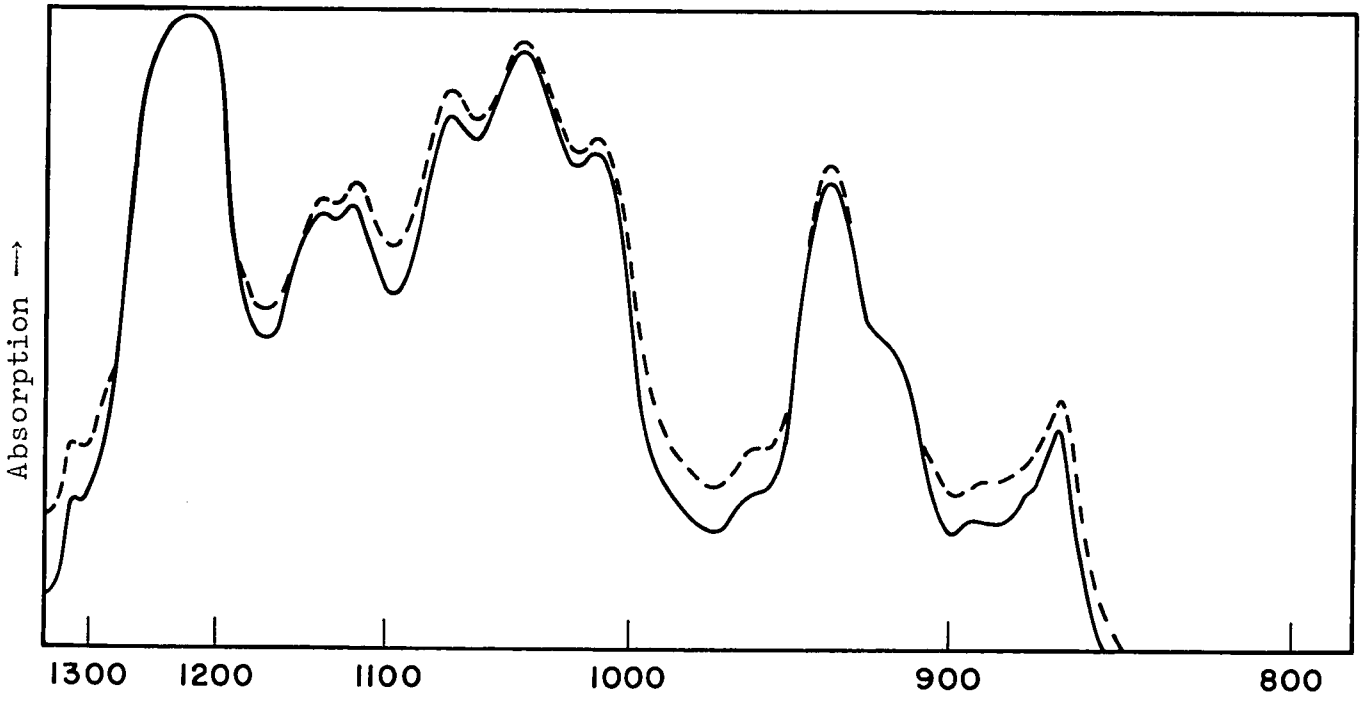


Fig. 3b. Infrared Spectra of D-Xylopyranose Tetraacetates

—— synthetic mixture ---- equilibrium mixture

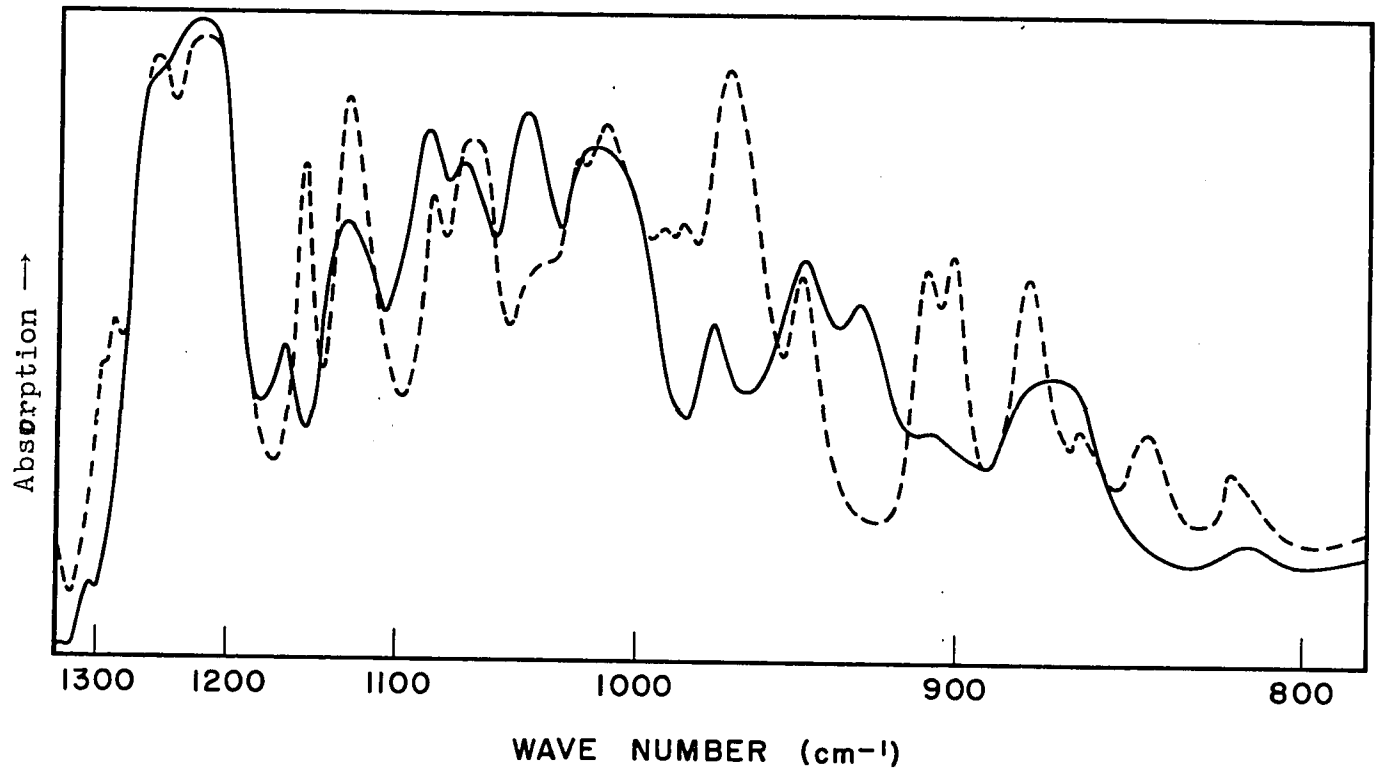


Fig. 4a. Infrared Spectra of D-Ribopyranose Tetraacetates
—— α-anomer ---- β-anomer

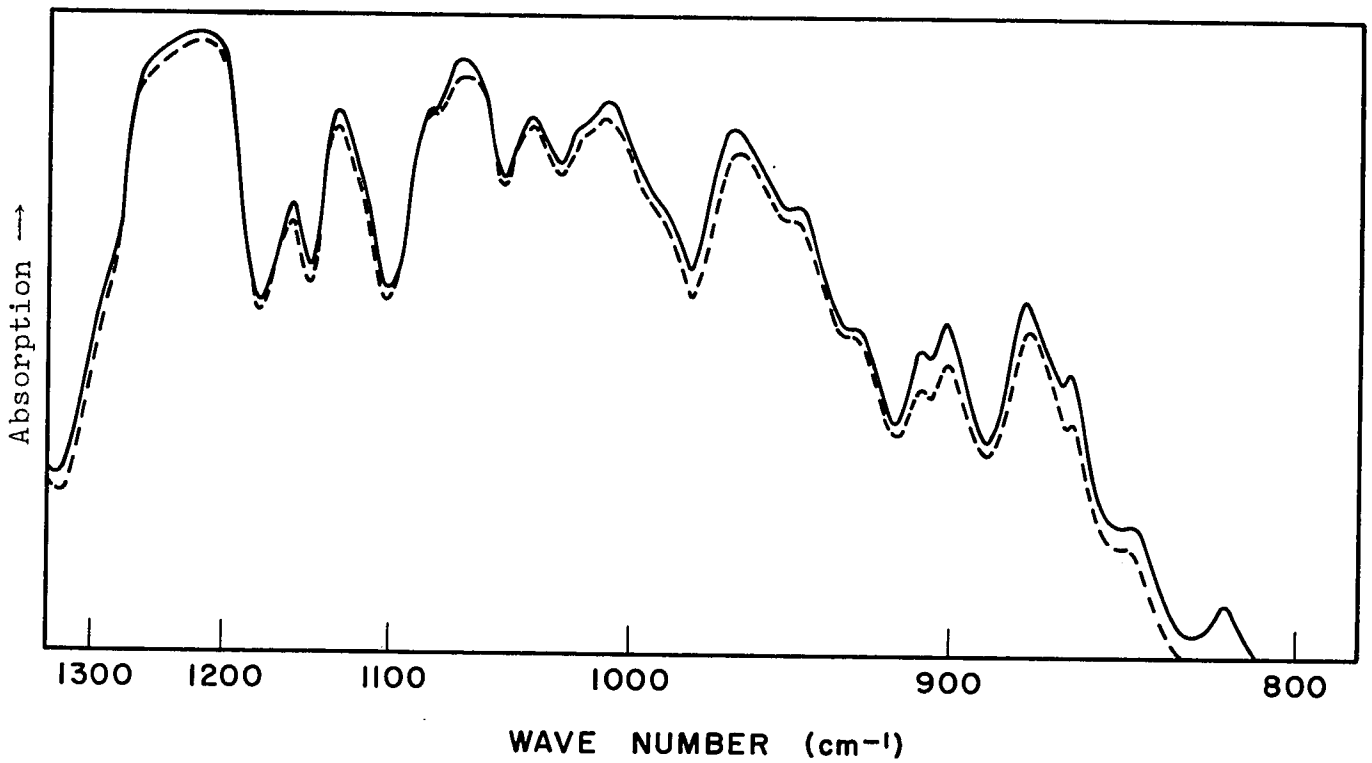


Fig. 4b. Infrared Spectra of D-Ribopyranose Tetraacetates
—— synthetic mixture ---- equilibrium mixture

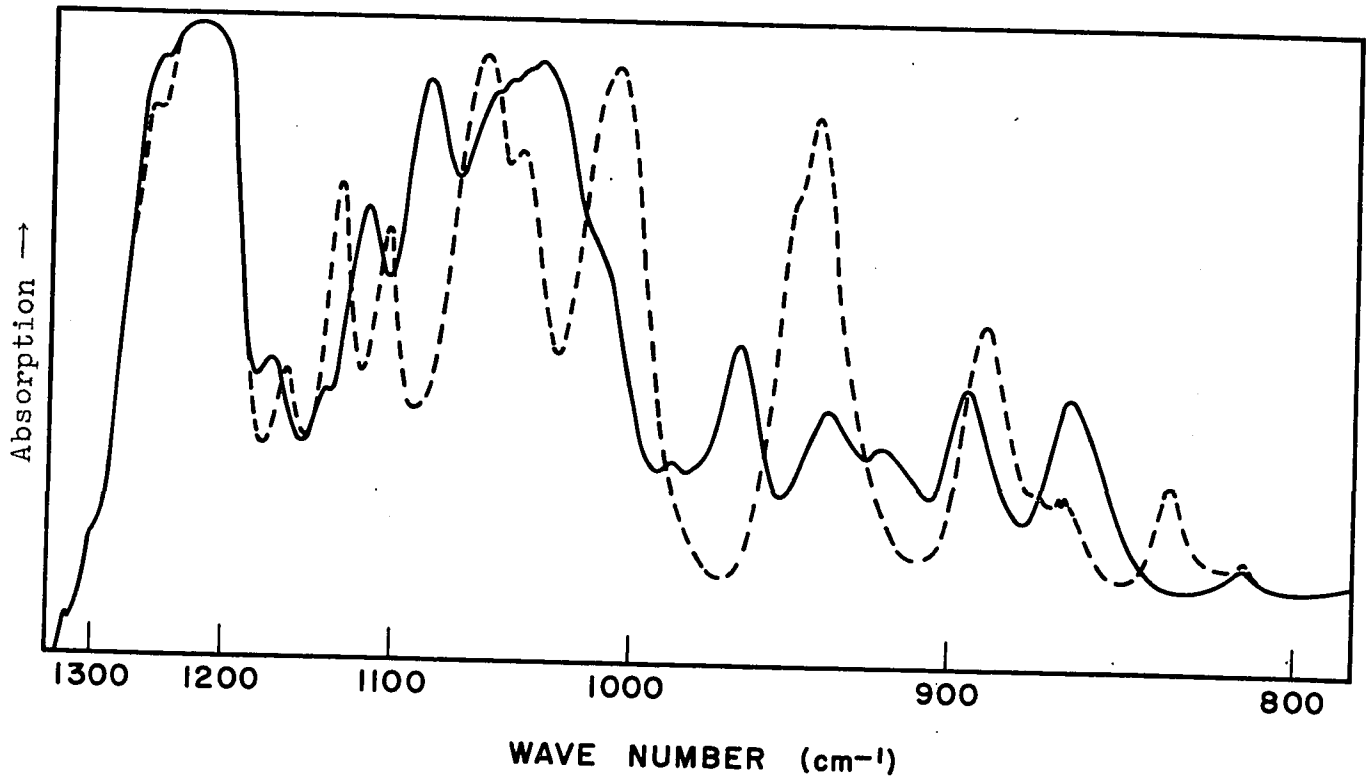


Fig. 5a. Infrared Spectra of L-Arabopyranose Tetraacetates
—— α-anomer ---- β-anomer

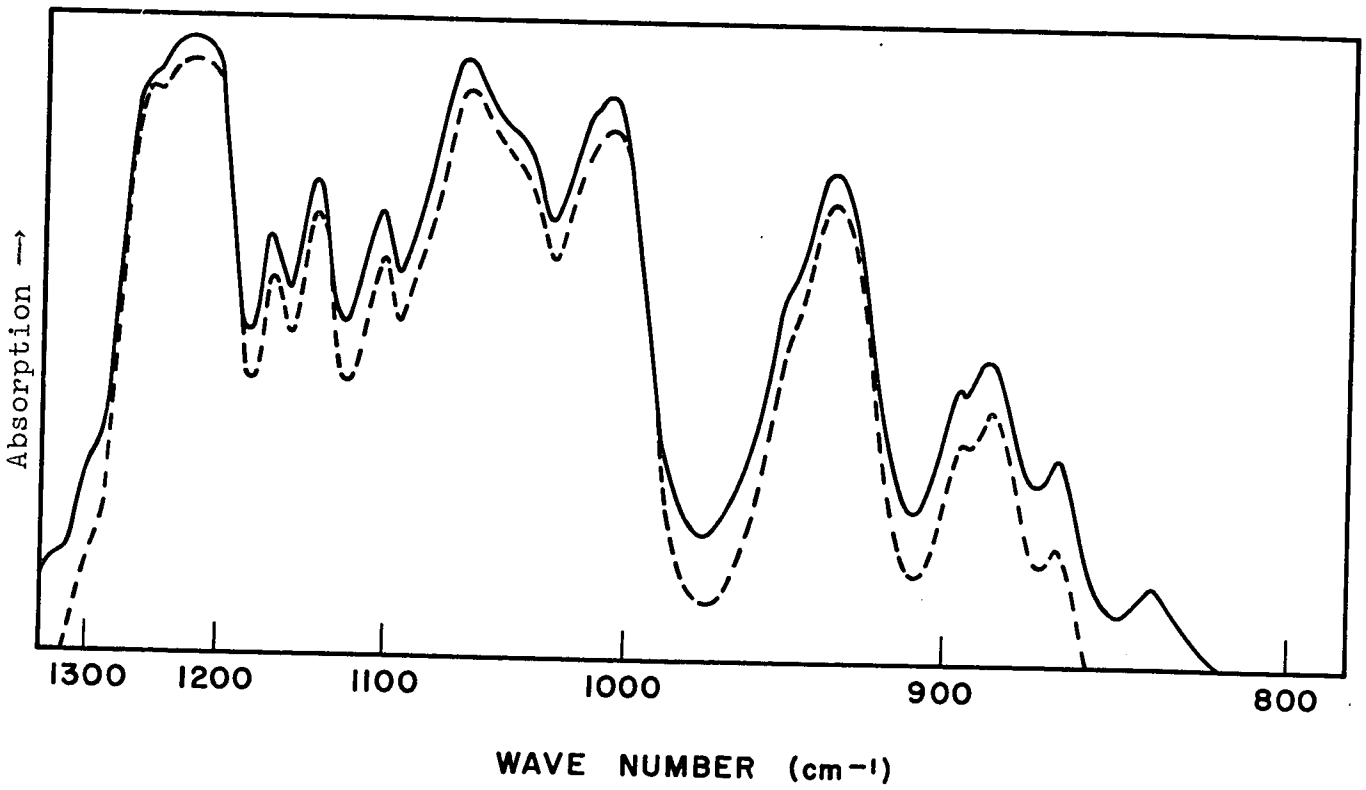


Fig. 5b. Infrared Spectra of L-Arabopyranose Tetraacetates
—— equilibrium mixture ---- synthetic mixture

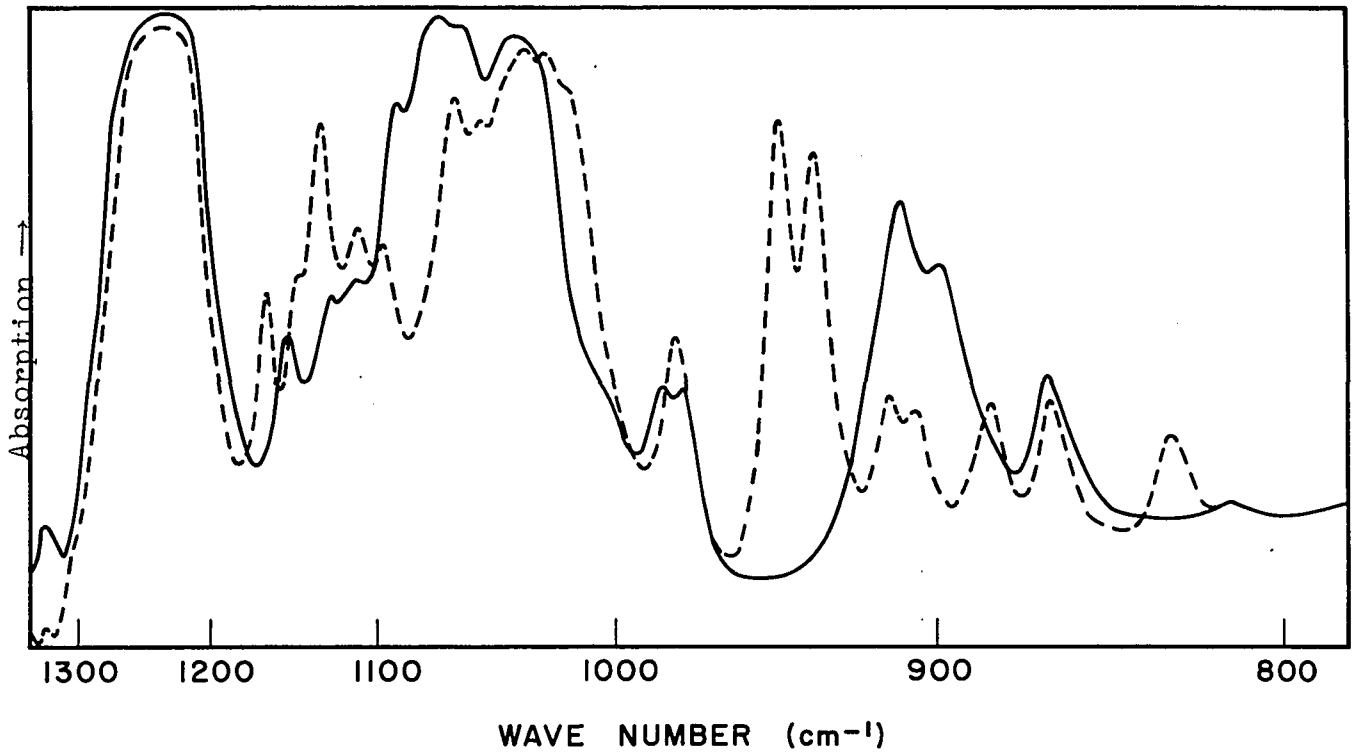


Fig. 6a. Infrared Spectra of D-Glucopyranose Pentaacetates
—— β-anomer ---- α-anomer

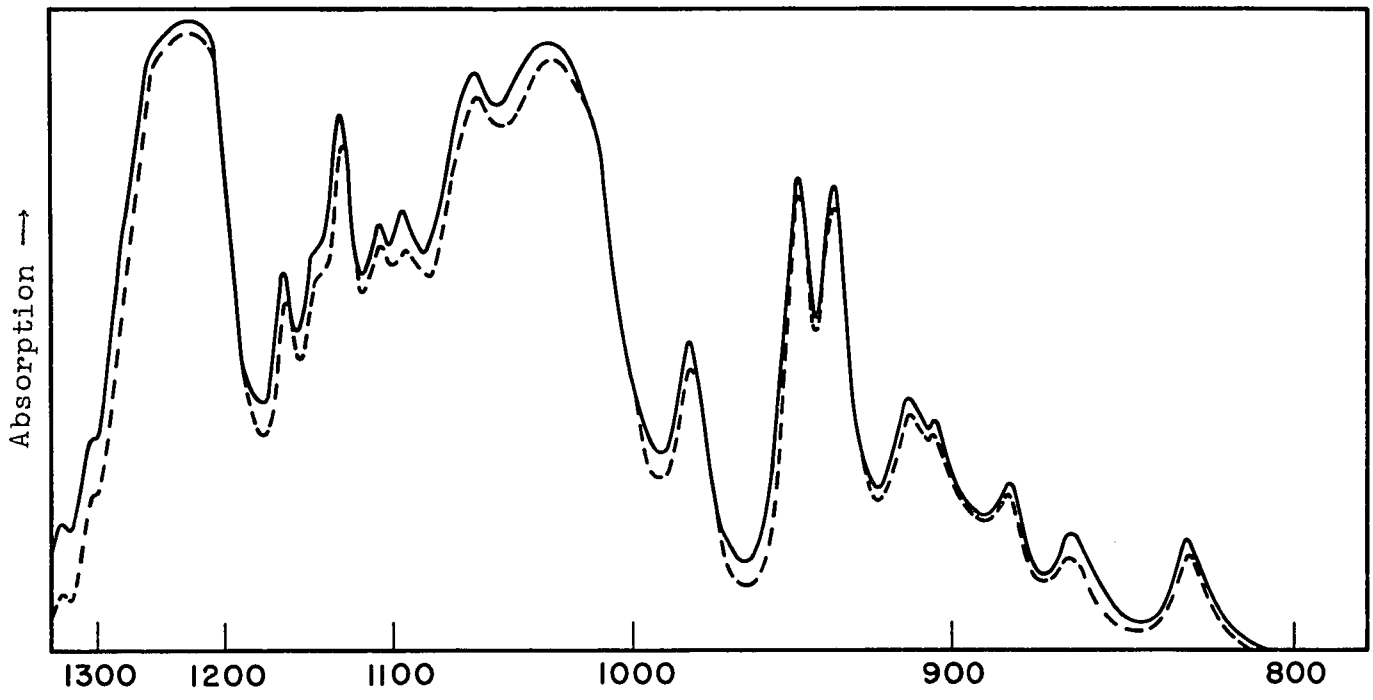


Fig. 6b. Infrared Spectra of D-Glucopyranose Pentaacetates
—— synthetic mixture ---- equilibrium mixture

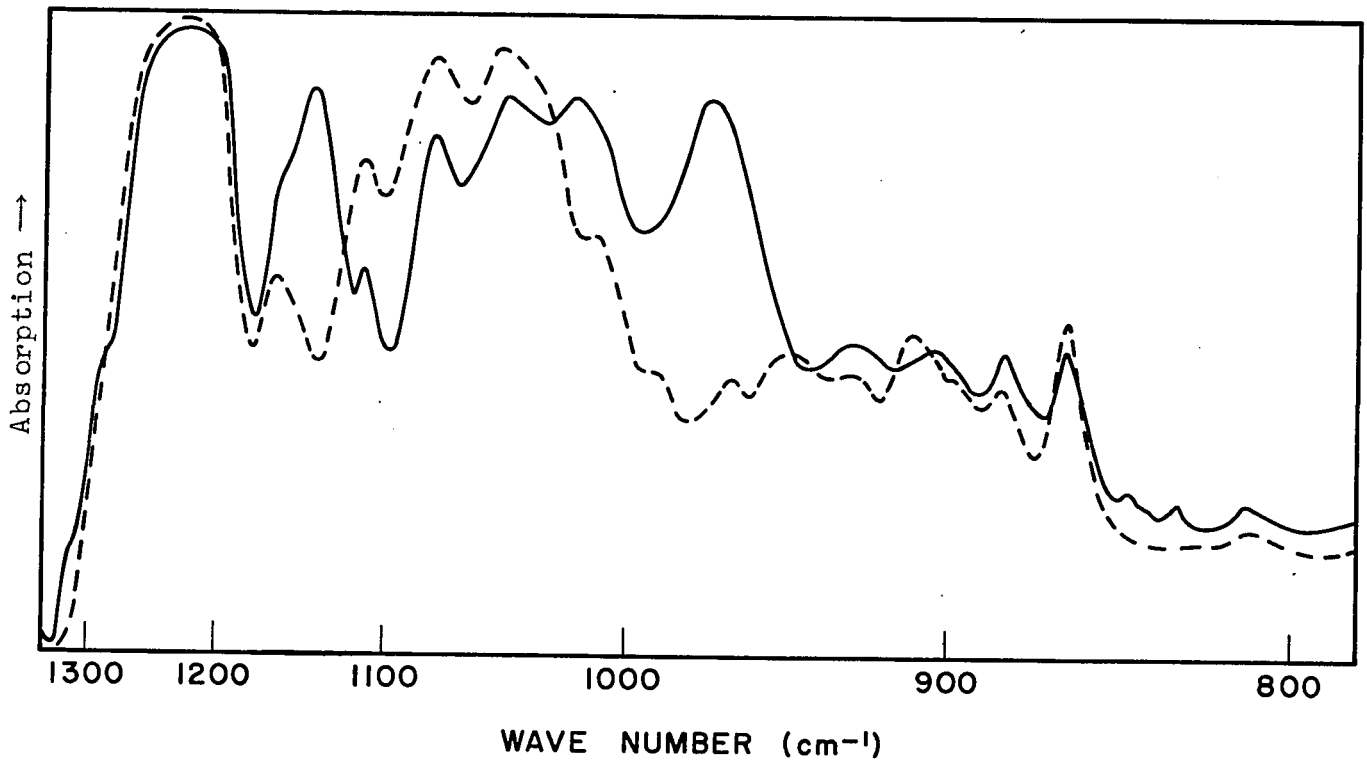


Fig. 7a. Infrared Spectra of D-Mannopyranose Pentaacetates
—— α-anomer ---- β-anomer

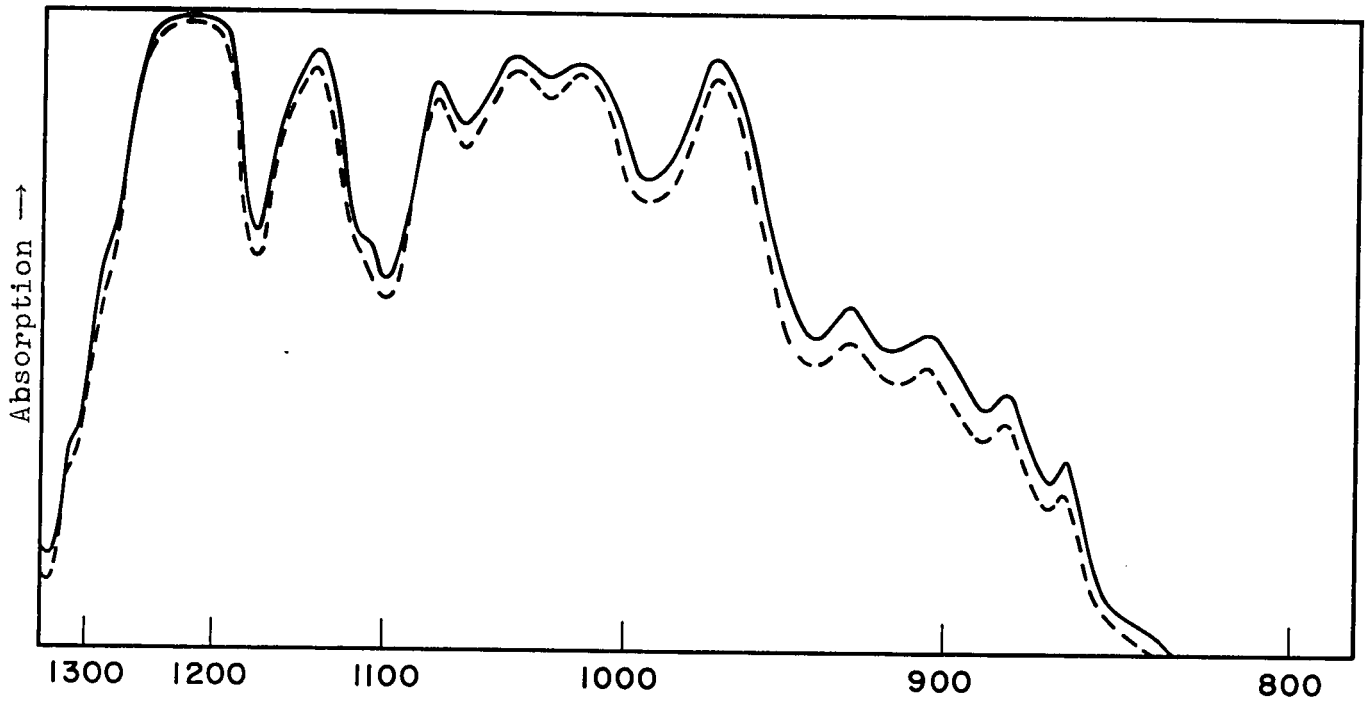


Fig. 7b. Infrared Spectra of D-Mannopyranose Pentaacetates
—— synthetic mixture ---- equilibrium mixture

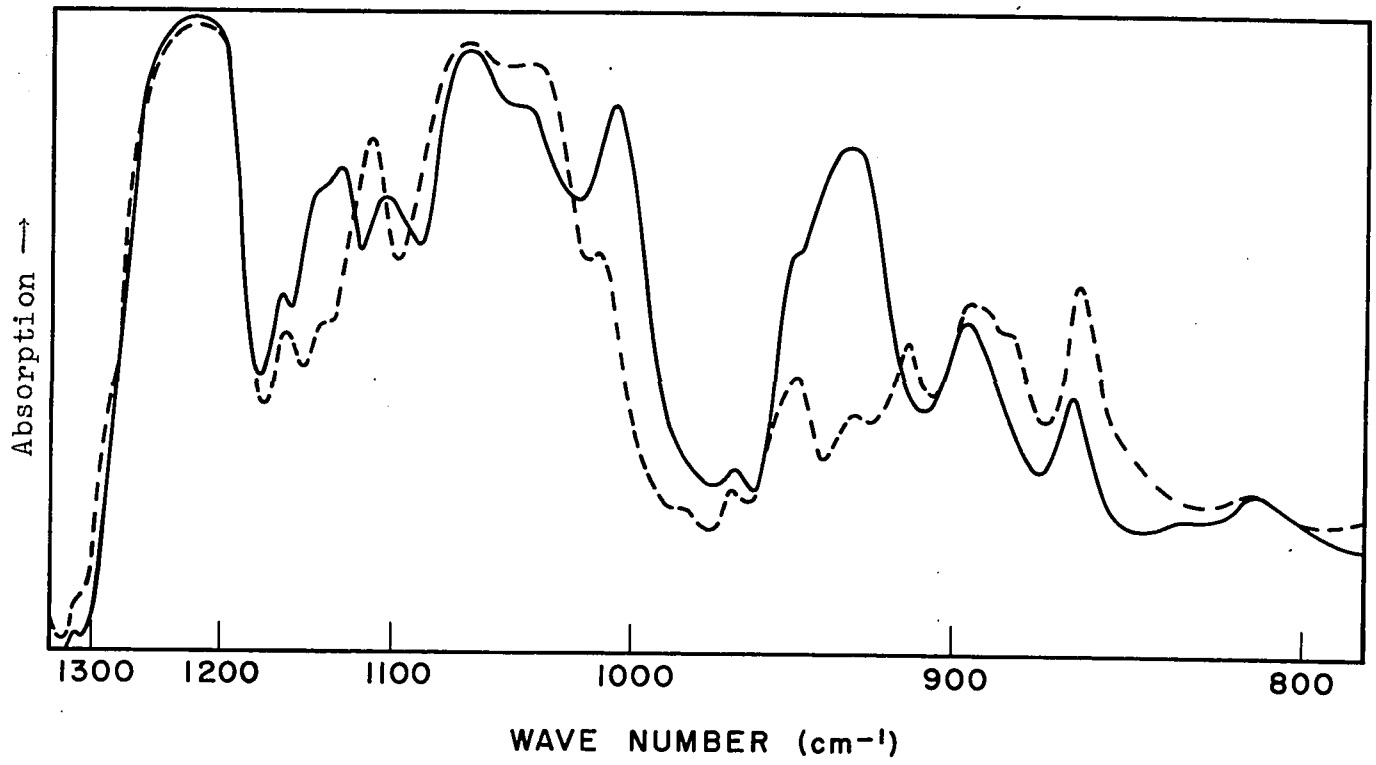


Fig. 8a. Infrared Spectra of D-Galactopyranose Pentaacetates
—— α-anomer ---- β-anomer

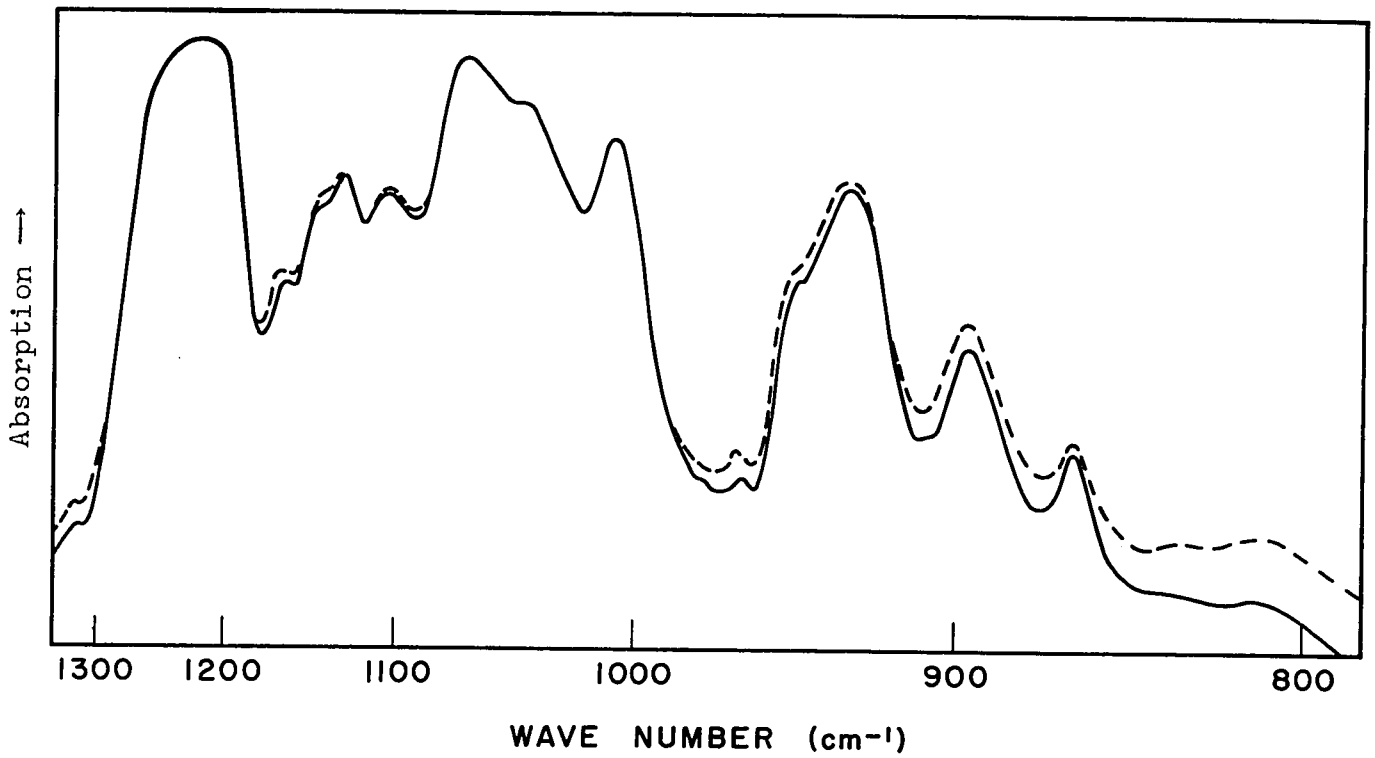


Fig. 8b. Infrared Spectra of D-Galactopyranose Pentaacetates
—— synthetic mixture ---- equilibrium mixture

α-D-Ribopyranose Tetraacetate:

β-D-Ribopyranose tetraacetate, eight grams, was anomerized in 1:1 acetic acid - acetic anhydride with perchloric acid as catalyst. After equilibrium had been reached, the solution was poured into ice-water and the equilibrium mixture was isolated in the usual way as described before. The β-anomer which crystallized from a thick ethanol solution, was removed by centrifugation. The ethanol solution was concentrated in order to remove further amount of crystallizable β-anomer. After this procedure was repeated a few times, the remaining syrup had a specific rotation 48°. The syrup was dissolved in a small amount of ethanol, and seeded with α-D-ribopyranose tetraacetate which had been obtained by chromatographic separation of a portion of the syrup on a Magnesol-Celite (5:1, acetone washed) column. The elution was with benzene containing 0.2% ethanol. The crude product was repeatedly recrystallized from ethanol until constant rotation.

Yield, 0.8 g. (10%); m.p. 75-78°C;

$[\alpha]_D$ 54.0 (c, 2 in chloroform).

Anal. calc'd for $C_{13}H_{18}O_9$: C, 49.0 ; H, 5.70.

Found: C, 49.1 ; H, 5.76.

This compound was found convertible to the β-anomer by anomerization.

β-D-Allopyranose Pentaacetate:

Lemieux and Brice (56) acetylated D-allose with acetic anhydride and sodium acetate at 100° to obtain β-D-allopyranose pentaacetate in 28% yield. The following method was found to give a better yield.

D-Allose, one gram, was reacted with a 1:1 mixture of acetic anhydride and pyridine. The mixture was left overnight at 4°C. A 1.8 g. yield of crystalline product was isolated in the usual way after seeding an alcoholic solution.

Two recrystallizations from ethanol gave a 1.5 g., 62% yield, m.p. 97.5-99.5°C, $[\alpha]_D$ -14.8 (c, 2 in chloroform). Lit., m.p. 97-100°C, $[\alpha]_D$ -14.6 (c, 1.5 in chloroform).

3-Tosyl-α-D-Glucopyranose Tetraacetate:

This compound was prepared in 56% yield from the β-anomer by anomerization. The β-anomer which crystallized from the equilibrium mixture was removed by centrifugation. The α-anomer began to crystallize from the remaining syrup after standing at room temperature for several days. The product was recrystallized from ethanol to constant rotation. $[\alpha]_D$ 84.4 (c, 2 in chloroform); m.p. 72-75°C.

Anal. Calc'd for $C_{21}H_{26}O_{12}S$: C, 50.2 ; H, 5.22

Found: C, 50.2 ; H, 5.19.

1-Deutero-acetoxy β-L-Arabopyranose Triacetate:

α-L-Arabopyranose tetraacetate, two grams, was refluxed on steam bath with 1.5 g. of titanium tetrachloride in 30 ml. of dry chloroform for two hours. The solution, after cooling under tap water, was shaken with ca. 60 ml. of ice-water in a separatory funnel. The separated chloroform layer was washed with water, dried over anhydrous potassium carbonate, and evaporated to dryness. The residue, triacetyl β-L-arabopyranosyl chloride, was recrystallized from chloroform-ether.

Yield, 1.25 g. (67%); m.p. 150-151°C.

One gram of the triacetyl β-L-arabopyranosyl chloride was heated on steam bath with 0.6 g. of deuterated silver acetate* in 10 ml. of acetonitrile for three hours. After the removal of silver chloride, the α-L-arabopyranose tetraacetate was isolated and purified in the usual way.

Yield, 0.75 g. (70%); m.p. 92-94°C.

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* The deuterated acetic acid of high purity was kindly supplied by the National Research Council of Canada. The acetic acid was converted to silver acetate by reacting with a solution of silver nitrate neutralized with sodium hydroxide. The precipitated silver acetate was filtered, washed with water, alcohol and ether, and dried under vacuum.

The 1-deutero-acetoxy α-L-arabopyranose triacetate, 0.75 g., was anomerized to the β-anomer with perchloric acid as catalyst in four ml. of deuterated acetic acid* which was previously distilled over phosphorus pentoxide. After equilibrium had been reached, the perchloric acid was neutralized with anhydrous sodium carbonate and the solvent was recovered by evaporation under reduced pressure. The residue was worked up in the usual way to yield a syrup which was chromatographed on a Magnesol-Celite column (53 x 170 mm). by eluting with one liter of benzene containing 0.2% of t-butyl alcohol. The column was extruded and developed with 1% alkaline potassium permanganate solution (126). A crystalline β-L-arabopyranose tetraacetate, 100 mg., was obtained from the zone between 54 to 97 mm from the top of the Magnesol-Celite column. The crude product was recrystallized from isopropyl alcohol. m.p. 84-85°C.

3-Deoxy-3-Acetamido-β-D-Glucopyranose Tetraacetate:

3-Deoxy-3-acetamido-tri-O-acetyl methyl α-D-glucopyranoside, 200 mg, prepared by the method of Peat and Wiggins (127), was heated on steam bath in five ml. of 4N hydrochloric acid for two hours. The solution was evaporated under reduced pressure to a dry syrup with frequent addition of benzene to remove the hydrogen chloride. The syrup was acetylated with acetic anhydride and sodium acetate catalyst and the product was isolated

in the usual way. The resulting syrup was treated overnight with five ml. of glacial acetic acid previously saturated with hydrogen bromide at 0°. The solution was poured into ice-water (ca. 20 ml.) and extracted immediately with three times of ten ml. portions of chloroform. The chloroform extract was washed with sodium bicarbonate solution, water, dried over anhydrous sodium sulfate, then evaporated to a syrup which was taken up in five ml. acetic acid - acetic anhydride. Silver acetate, 0.1 g., was added and the mixture was shaken for three hours. The product was worked up in the usual way and recrystallized from methyl isobutyl ketone.

Yield, 70 mg. (34%), m. p. 206-209°;

$[\alpha]_D$ 8.4 (c, 0.8 in chloroform).

This compound was found to be identical with kanosamine pentaacetate, an acetylated derivative of a component of the new antibiotic kanamycin (128). The identity was established by mixture melting point and infrared spectrum.

6-Deoxy-6-Acetamido-β-D-Glucopyranose Tetraacetate:

To a solution of five grams of 1,2-isopropylidene-α-D-glucofuranose in 30 ml. of dry pyridine was added with cooling 4.3 g. of p-toluenesulfonyl chloride (129). The solution was left overnight at room temperature. Evaporation of the solvent under reduced pressure left a syrup which was extracted

with five times with 30 ml. portions of ether. The ether extract was washed with ice-cold dilute hydrochloric acid, water and sodium bicarbonate solution, dried over anhydrous sodium sulfate, evaporated to dryness. The dry syrup was dissolved in 30 ml. of anhydrous methanol previously saturated with ammonia at 0°. The solution was left overnight at room temperature. After the removal of solvent by evaporation, the remaining syrup was heated in 30 ml. of N hydrochloric acid on the steam bath for three hours. The solution was evaporated to dryness under reduced pressure. Acetylation of the syrup in acetic anhydride with sodium acetate catalyst and isolation of the product in the usual way gave 6-deoxy-6-acetamido-β-D-glucopyranose tetra-acetate which was recrystallized from methyl isobutyl ketone.

Yield, 0.1 g. (1% overall); m.p. 115-120°;

$[\alpha]_D$ 9.9 (c, 0.8 in chloroform).

The spectrum (infrared) of this compound was identical with that of an acetylated derivative of one of the amino-sugar moieties from the antibiotic kanamycin (130), and the mixture melting point was not depressed.

6-Deoxy-6-Acetamido-α-D-Glucopyranose Tetraacetate:

The alpha anomer was isolated in 46% yield from the equilibrium mixture of the beta anomer and recrystallized from methyl isobutyl ketone.

$[\alpha]_D$ 110° (c, 1 in chloroform); m.p. 141-142°C.

Anal. calc'd for $C_{16}H_{23}O_{10}N$: C, 49.4 ; H, 5.95; N, 3.60.
Found: C, 49.2 ; H, 5.98 ; N, 3.70.

Anomerization of 3-Deoxy-3-Acetamido-β-D-Glucopyranose Tetraacetate:

The anomerization of 3-deoxy-3-acetamido-β-D-glucopyranose tetraacetate was, at first, carried out by dissolving 39.0 mg. of the sample in two ml. of 1:1 acetic acid - acetic anhydride containing 0.05 M in perchloric acid. No change in rotation was observed. Then, a 1.0 M perchloric acid solution in the same solvent was tested. A plot of polarimetric reading against time is shown in Fig. 9. No crystalline product could be isolated from the equilibrium mixture.

Anomerization of 2-Deoxy-2-Acetamido-D-Glucopyranose Tetraacetate:

2-Deoxy-2-acetamido-α-D-glucopyranose tetraacetate, 778 mg., was dissolved in 20 ml. of 1:1 acetic acid - acetic anhydride containing 1.0 M in perchloric acid. The first order rate constant is shown in Fig. 10.

2-Deoxy-2-acetamido-β-D-glucopyranose tetraacetate, 77.8 mg., was dissolved in two ml. of the same catalyst solution as above. The polarimetric reading was plotted against time as shown in Fig. 11.

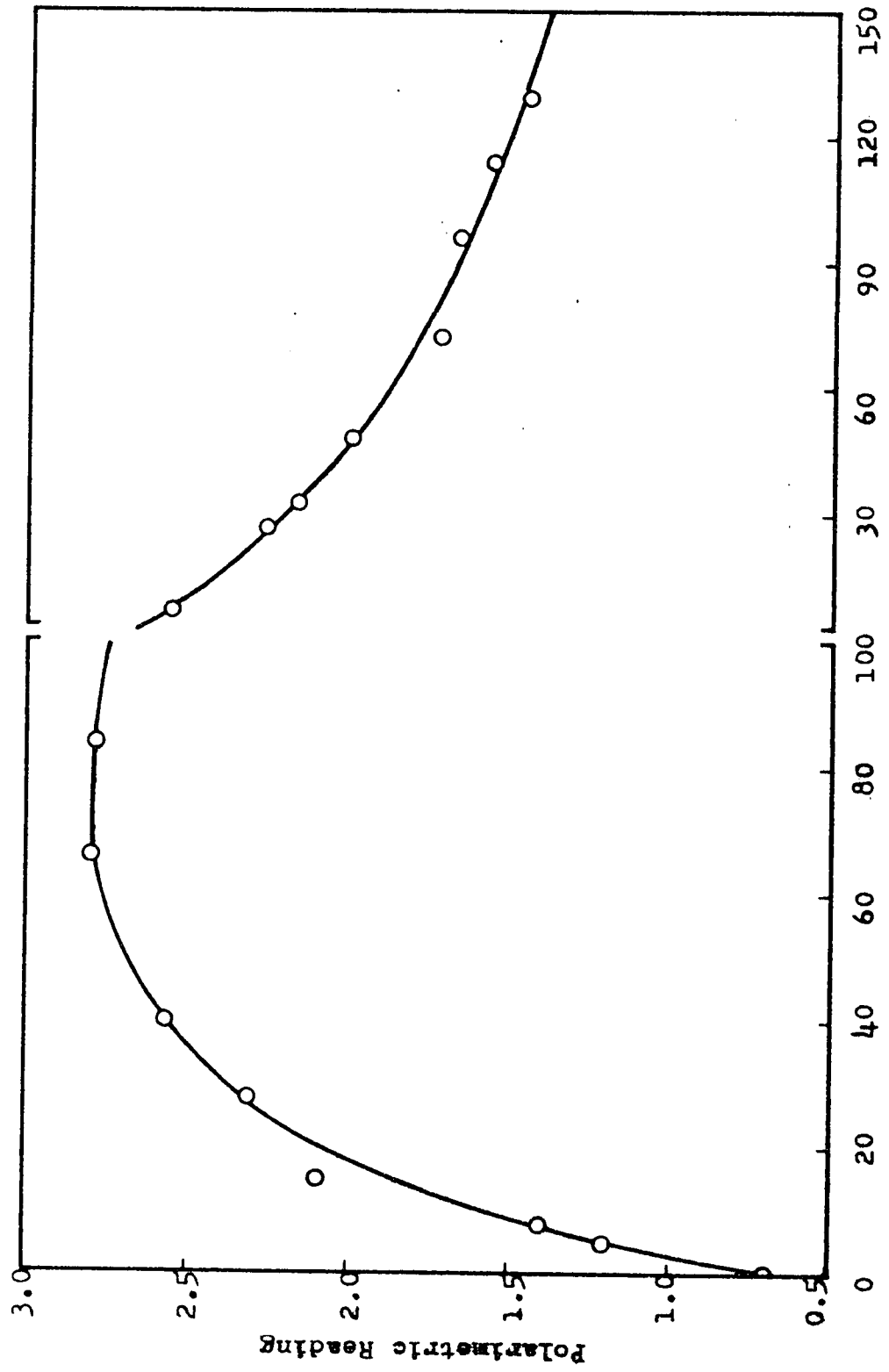

Fig. 9. Rotational Change of 3-Deoxy-3-Acetamido-β-D-Glucopyranose Tetraacetate under Anomerization Conditions.

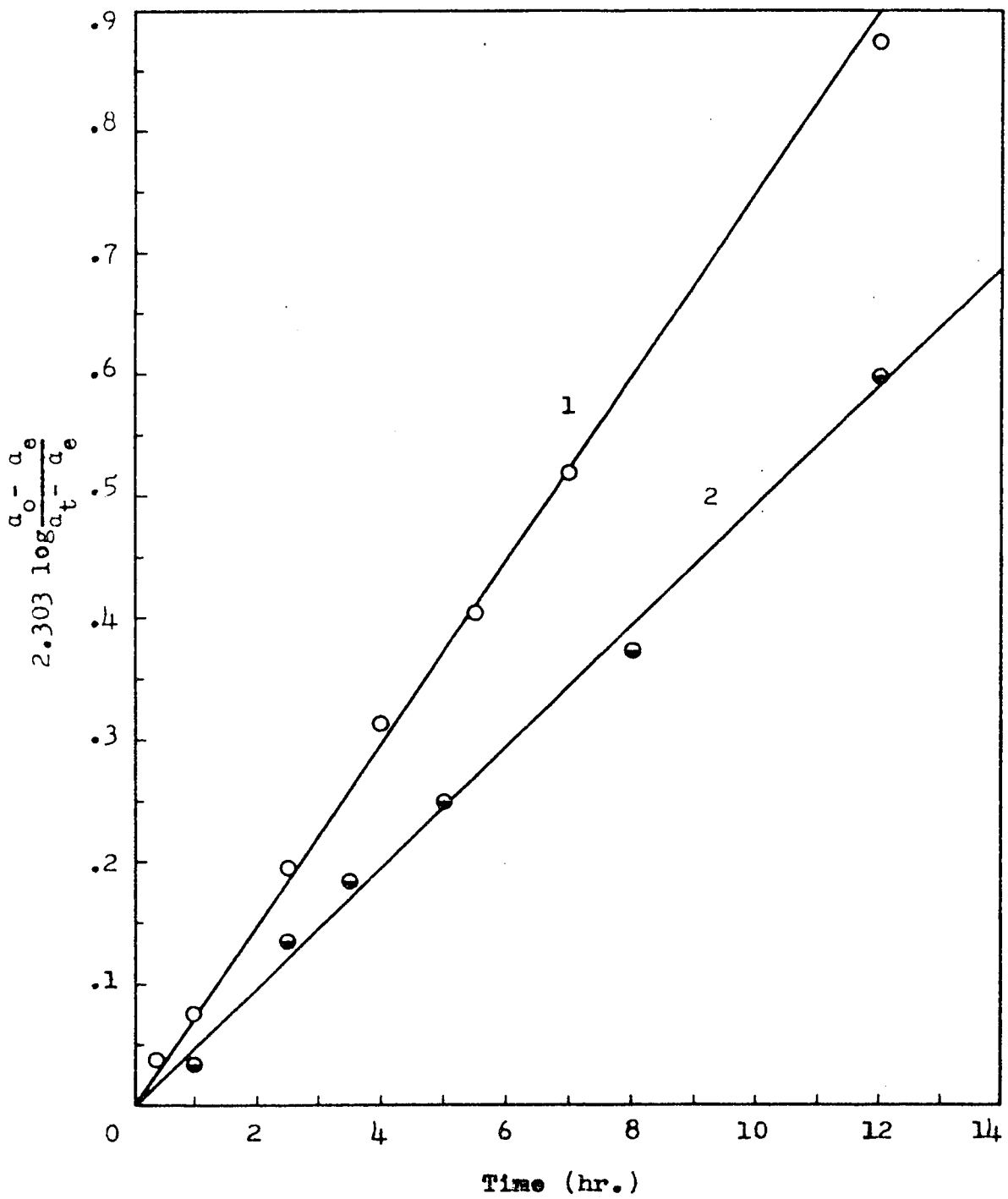

Fig. 10. First-order Rates in the Anomerization of the Acetylated Amino-sugars.

1. 6-Deoxy-6-Acetamido-β-D-Glucopyranose Tetraacetate.
2. 2-Deoxy-2-Acetamido-β-D-Glucopyranose Tetraacetate.

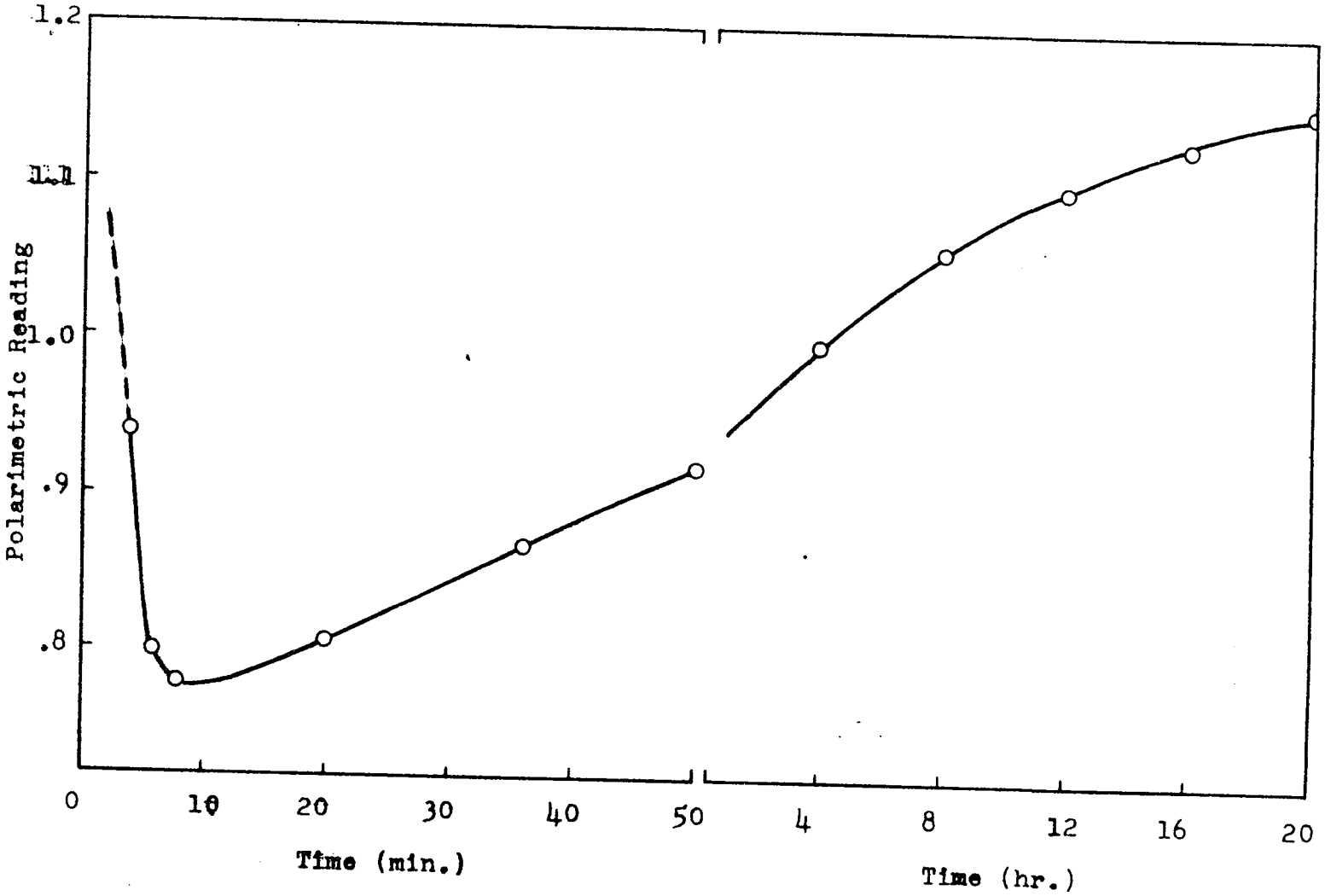

Fig. 11. Rotational Change of 2-Deoxy-2-Acetamido-β-D-Glucopyranose Tetraacetate under Anomerization Conditions.

β-D-Glucopyranose-1-d Pentaacetate:

D-Gluconolactone*, three grams, was gently heated in 1.5 ml. of deuterium oxide** until the solution was complete. The deuterium oxide was reclaimed by freeze-drying technique. This procedure was repeated three times in order to replace the hydrogen atoms of the hydroxyl groups by deuterium. Lactonization of any free carboxylic acid was accomplished by heating the solid residue to melt under reduced pressure. The resulting syrup, in 20 ml. of deuterium oxide in a 50 ml. beaker with a magnetic stirrer, was reduced with a total amount of 30 g. of 5% sodium amalgam added in small portions during a period of two hours. The temperature was controlled below 10°C., and the pH was maintained between 3.0 to 3.5 by the addition of deuterated sulfuric acid. At the end of reduction, the solution was neutralized with anhydrous sodium carbonate to pH 6.5. After the recovery of deuterium oxide, the residue was extracted with 15 ml. of 50% aqueous methanol. The insoluble salt was removed by filtration and the filtrate was evaporated to dryness. Acetylation of the syrup in acetic anhydride with sodium acetate catalyst yielded 21 g. (29% overall) of β-D-glucopyranose-1-d pentaacetate, m.p. 132-133.5°C.

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* The D-gluconolactone was kindly supplied by Mr. A.J. Liston.

** The deuterium oxide was purchased from the Atomic Energy Ltd. of Canada with a purity of 99.57%.

Anomerization of β-D-Glucopyranose-1-d Pentaacetate with Base-Catalyst:

β-D-Glucopyranose-1-d pentaacetate, 0.5 g., was anomerized by the method of Wolfrom (131) with crushed solid sodium hydroxide as catalyst. This yielded 0.2 g. (40%) of the α-anomer after recrystallized from ethanol. m.p. 109-110°C.

1-Deutero-acetoxy β-D-Glucopyranose Tetraacetate:

Tetraacetyl β-D-glucopyranosyl chloride, one gram, was refluxed with 0.45 g. of deuterated silver acetate in 10 ml. of acetonitrile for three hours. The product was isolated and purified in the usual way.

Yield, 0.8 g. (75%); m.p. 132-134°C.

Anomerization of 1-Deutero-acetoxy β-D-Glucopyranose Tetraacetate with Base Catalyst:

Anomerization of the beta pentaacetate, 0.8 g., by the method of Wolfrom yielded 0.3 g. (38%) of the alpha pentaacetate. m.p. 110-111°C.

III. DISCUSSION OF RESULTS

A. Configurational Effect on Chemical Equilibria

The literature reports the anomerization of sugar acetates under a variety of conditions. It has long been known that the behavior of the anomerization of the D-glucopyranose pentaacetates in acetic anhydride containing a mineral acid is that expected for an equilibrium reaction. In 1951, Bonner (59) obtained evidence in support of this expectation by an infrared analysis of the equilibrium mixture. Lemieux, Huber and Brice (61) confirmed Bonner's conclusion by an isotopic dilution analysis. Thus, the D-glucopyranose pentaacetates undergo, beyond doubt, reversible anomerization in an equilibrium process under the conditions used by Bonner (59), Painter (60, 100) and Lemieux et. al. (61). However, no investigation in this regard has been made of the anomerization of other aldopyranose acetates. In view of the fact that only a few of the free sugars show simple mutarotation phenomena, it seemed desirable to establish whether or not all of the sugar acetates studied in the present research like the D-glucopyranose pentaacetates enter into an equilibrium process with their anomer under conditions used which employ 1:1 acetic acid-acetic anhydride containing 0.05M perchloric acid. For this reason, whenever both the alpha and beta anomers were available in crystalline forms, the infrared spectra of the equilibrium mixture and a synthetic mixture of the composition

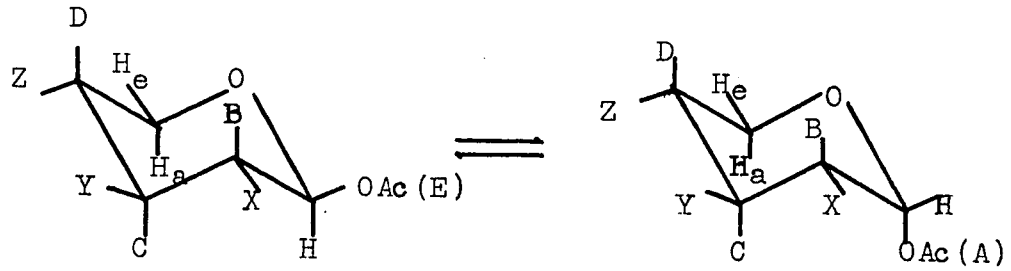
as indicated from the equilibrium rotation were compared quantitatively using the potassium bromide pressed disc technique. In no case was any difference found except for a slight vertical displacement which can be attributed to a slight difference in transparency of the potassium bromide disc in infrared (see Figs. 3-8, pp. 57-62). Since Kuhn (132) has shown the marked dependence of the infrared spectra of carbohydrates on structure, it seems reasonably certain that there cannot be any appreciable quantity of other carbohydrate substances in the anomerized product and , consequently, it is apparent that true equilibrium was established between the alpha and beta anomers in each of the anomerization reactions. This is the experimental basis for the validity of conformational analysis made in this thesis.

As has been pointed out on page 37, there can be little doubt about the conformations of the rings of the aldopyranose acetates. Moreover, as will be seen later on, the results of the present work can only be rationalized on the basis of these chair forms and, consequently, provide corroborative evidence.

1. The Acetylated Aldopyranoses

a. The Aldopentopyranose Tetraacetates

The anomerization reaction is specified by the following general formulation.



LI LII

The equilibrium and kinetic data obtained for the anomerization of aldopentopyranose tetraacetates are listed in Table VII. The non-bonded interactions which are present in each anomer are listed in Table VIII. The differences in the non-bonded interactions between the anomeric pairs are given in Table IX.

All previous investigations concerned with the conformational analysis of chemical equilibria are based on the assumption that the difference in free energy between two isomers in equilibrium is equal to the difference in non-bonded interactions. This assumption can only be justified if the entropy change and solvent effect accompanying the anomerization reaction are small or negligible. In the anomerization of sugar acetates, the equilibrium constant does not change appreciably in a variety of solvents (57-61). Therefore, solvent effects can be neglected. No reliable information exists regarding the entropy change in the anomerization of the sugar acetates available. Attempts to

Table VII

Equilibrium and Kinetic Data for the Anomerization of the Aldopentopyranose Tetraacetates

Acetylated Aldopyranose	Temp. (±0.1°)	Observed Optical Rotation α_o (β-anomer)	α_o (α-anomer)	α_e	Equilibrium Constant[1]	ΔF° cals./mole Found	ΔF° cals./mole Calc.	Rate Constant x10^5 sec.$^{-1}$ $k_\beta+k_\alpha$	k_β	k_α
D-Xylose	25.0°	-1.50°	6.25°	4.92°	4.8±0.2	-940	-930	456	378	78
	15.2	-1.46	6.20	4.96	5.2±0.2			142		
	3.0	-1.35	6.27	4.92	5.6±0.2			31.1		
D-Lyxose	25.0	-5.96[2]	1.58	1.00	12.0	-1480	-1470	309	285	24
	15.2		1.62	1.02				98		
	4.6		1.60	0.98				25		
D-Ribose	25.0	-3.83	3.93	-2.20	0.27±.01	780	730	168	36	132
	15.2	-3.85	3.97	-2.24	0.26±.01			51.3		
	4.6	-3.93	4.02	-2.32	0.25±.01			13.0		
L-Arabinose	25.0	9.62	2.72	8.50	5.0±0.2	-960	-930	362	60	302
	15.2	9.70	2.78	8.60	5.0±0.2			115		
	3.0	9.95	3.04	8.94	5.8±0.2			25.1		

1. The anomerization in each case is taken as proceeding from the anomer with the 1-acetoxy group in equatorial orientation (see the general formulation, p. 77).

2. The average value for 2A (133) under the conditions for anomerization was found to be 37,620 for the sugar acetates where both anomers are known. This rotation was calculated using this value for 2A and the rotation of the anomer (see Table XVII, p. 96a).

3. See the text on p. 96 for the calculated values of ΔF.

Table VIII

Non-bonded Interactions for the Aldopentopyranose Tetracetates

Aldopyranose Tetraacetate	Positions of Acetoxy Groups[1]	Non-bonded Interactions (2)									
		H:H	H:O	O:O	H:p	O:p	O/p	H/p	H/H	H/O	O/O
1. β-D-Xylo	E X,Y,Z	4	-	-	2	-	2	1	1	8	3
2. α-D-Xylo	A	2	2	-	2	-	1	2	2	7	3
3. β-D-Lyxo	E B,Y,Z	3	1	-	1	1	2	1	3	6	3
4. α-D-Lyxo	A	1	3	-	1	1	1	2	3	7	2
5. β-D-Ribo	E X,C,Z	2	2	-	2	-	2	1	3	6	3
6. α-D-Ribo	A	1	2	1	2	-	1	2	4	5	3
7. α-L-Arabo	E X,Y,D	3	1	-	1	1	2	1	3	6	3
8a. β-L-Arabo	A	1	3	-	1	1	1	2	4	5	3
8b. β-D-Arabo[3]	E,B,C,Z	1	3	-	1	1	2	1	4	6	2

1. The notations used to indicate the positions of the acetoxy groups are given in the general formulation on page 77.

2. The notations "X:X" and "X/X" are used in the sense as on page 18. "p" represents p-orbitals of the lone-pair electrons on the ring oxygen. The skew interactions involving the p and H_a, H_e which are present in each anomer, are not counted in this Table.

3. Taken as energetically equivalent to the chair conformation for β-L-arabopyranose tetraacetate which has the 1-acetoxy group in equatorial orientation.

Table IX

Differences in Non-bonded Interactions between

Anomeric Aldopentopyranose Tetraacetates

Compounds[1]	Configuration	Differences in Non-bonded Interactions
(1 - 2)	xylo	$2(H{:}O\text{-}H{:}H) - (O/p\text{-}H/p) - (H/O\text{-}H/H)$
		$= 2[(H{:}O\text{-}H{:}H) - (H/O\text{-}H/H)] - [(O/p\text{-}H/p) - (H/O\text{-}H/H)]$
(3 - 4)	lyxo	$2(H{:}O\text{-}H{:}H) - (O/p\text{-}H/p) - (O/O\text{-}H/H) + (H/O\text{-}H/H)$
		$= 2[(H{:}O\text{-}H{:}H) - (H/O\text{-}H/H)] - [(O/p\text{-}H/p) - (H/O\text{-}H/H)]$
		$- [(O/O\text{-}H/H) - 2(H/O\text{-}H/H)]$
(5 - 6)	ribo	$(O{:}O\text{-}H{:}H) - (O/p\text{-}H/p) - (H/O\text{-}H/H)$
		$= [(O{:}O\text{-}H{:}H) - 2(H/O\text{-}H/H)] - [(O/p\text{-}H/p) - (H/O\text{-}H/H)]$
(7 - 8a)	arabo	$2(H{:}O\text{-}H{:}H) - (O/p\text{-}H/p) - (H/O\text{-}H/H)$[2]
(8b- 8a)	arabo	$- (O/p\text{-}H/p) + (O/O\text{-}H/H) - (H/O\text{-}H/H)$
		$= [(O/O\text{-}H/H) - 2(H/O\text{-}H/H)] - [(O/p\text{-}H/p) - (H/O\text{-}H/H)]$

1. Numbers for compounds correspond to those in Table VIII.

2. Same as for the xylo-configuration.

Table X

Calculation of Non-bonded Interaction Energies in the Aldopentopyranose Tetraacetates

(a) Definition of non-bonded interaction terms

$$M = (H{:}O - H{:}H) - (H/O - H/H)$$
$$N = (O{:}O - H{:}H) - 2(H/O - H/H)$$
$$Q = (O/O - H/H) - 2(H/O - H/H)$$
$$P = (O/p - H/p) - (H/O - H/H)$$

(b) Equations for non-bonded interaction energies from the equilibrium data of the pentose acetates (Table VII)

i.	xylo	$2M - P =$	-940 cals/mole
ii.	lyxo	$2M-P-Q =$	-1480
iii.	ribo	$N - P =$	780
iv.	arabo	$2M - P =$	-960
v.	β-arabo	$Q - P =$	-750

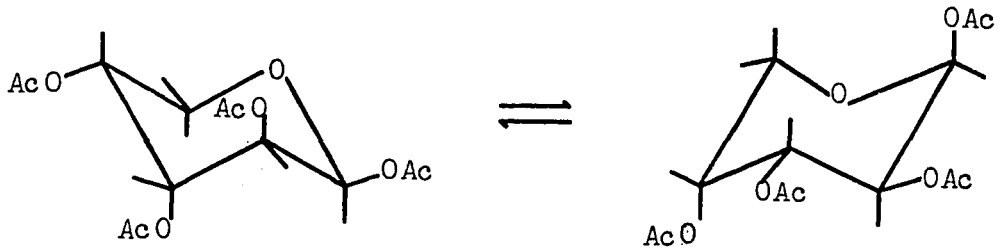
(c) Calculated values for non-bonded interaction energies in the aldopentopyranose tetraacetates

$$M = 175 \text{ cals./mole}$$
$$N = 2070$$
$$Q = 540$$
$$P = 1290$$

measure the heat of anomerization reaction in microcalorimeter were not acceptable because of the difficulties in reproducing the experimental data. This result was probably due to the fact that the solvent system yields a highly exothermic reaction with moisture. It was also not possible to obtain an accurate measure of the entropy change from the temperature coefficient of the equilibrium constant since the change in equilibrium constant was too small (relative to the error involved in its measurement) in the temperature range allowable for the experiments. These studies did, however, indicate that the $T\Delta S$ term in the anomerization reactions is probably in no case greater than about 20% of the enthalpy change. It is concluded, on this basis, that a consideration of the changes in free energy from the point of view of non-bonded interactions should be a useful procedure as a first approximation.

Defining non-bonded interactions as given in Table X, section a, it follows that the anomerization data allow the setting up of the first four equations in Table X, section b. It is seen that equations (i) and (iv) are the same within experimental error as was anticipated from the conformational analysis. Thus, the anomerization data could yield only three equations involving four unknowns. A fourth equation could be obtained by measuring the difference in free energy between the two chair forms (LIII and LIV) for β-L-arabopyranose tetraacetate. For this compound, two acetoxy groups are in equatorial orientation

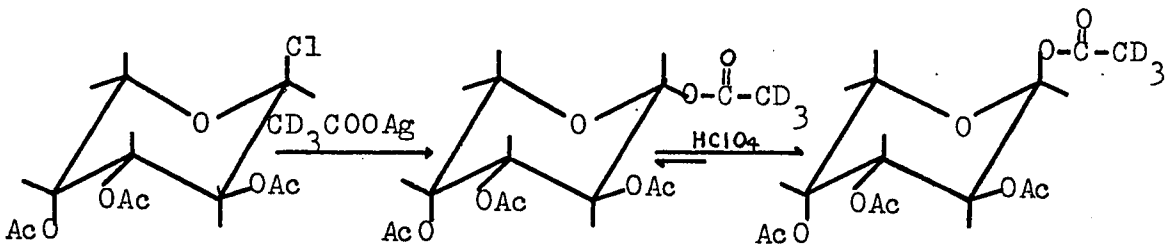
and two are in axial orientation regardless of which chair conformation the compound possesses.



LIII LIV

Lemieux, Kullnig, Bernstein and Schneider (72) have shown that the proton magnetic resonance spectrum for β-L-arabopyranose tetraacetate has the signals of the hydrogen atoms in the acetoxy groups split into two peaks of equal intensity. Moreover, evidence was presented that the signal from the axial acetoxy groups occurs at lower field than those for equatorial acetoxy groups. This has now been confirmed from the observation that the spectrum of 1-deuteroacetoxy-α-D-glucopyranose tetraacetate lacks the low field signal for the axial 1-acetoxy group which is present in the undeuterated compound.

A 1-deuteroacetoxy β-L-arabopyranose triacetate was prepared by the reaction of triacetyl β-L-arabopyranosyl chloride (LV) with deuterated silver acetate. Since direct replacement of a halogen atom involves inversion of configuration, this reaction gave the alpha anomer which was anomerized with perchloric acid in deuterated acetic acid to yield the beta anomer.



LV LVI LVII

A proton magnetic resonance spectrum was taken for (LVII) in chloroform solution at room temperature. Should this compound exist essentially in one conformation, either (LIII) or (LIV), the intensity of one of the two signals from the acetoxy groups would be reduced to one-half as compared with the other upon the introduction of a deuteroacetoxy group. The relative intensity of OAc_e/OAc_a measured from the spectrum was found to be 1.46. This can only be expected as a result of an equilibrium between the chair forms (LIII) and (LIV).

The completeness of deuteration of the 1-acetoxy group was indicated from the relative intensity of the three secondary hydrogen atoms on the ring (signal I, Fig. 12) to the hydrogen atoms of the acetoxy groups (signal II, Fig. 12). The ratio for the undeuterated compound is one to four, whereas in the deuterated compound, it is one to three.

Thus the relative concentration of the two chair forms can be calculated as follows.

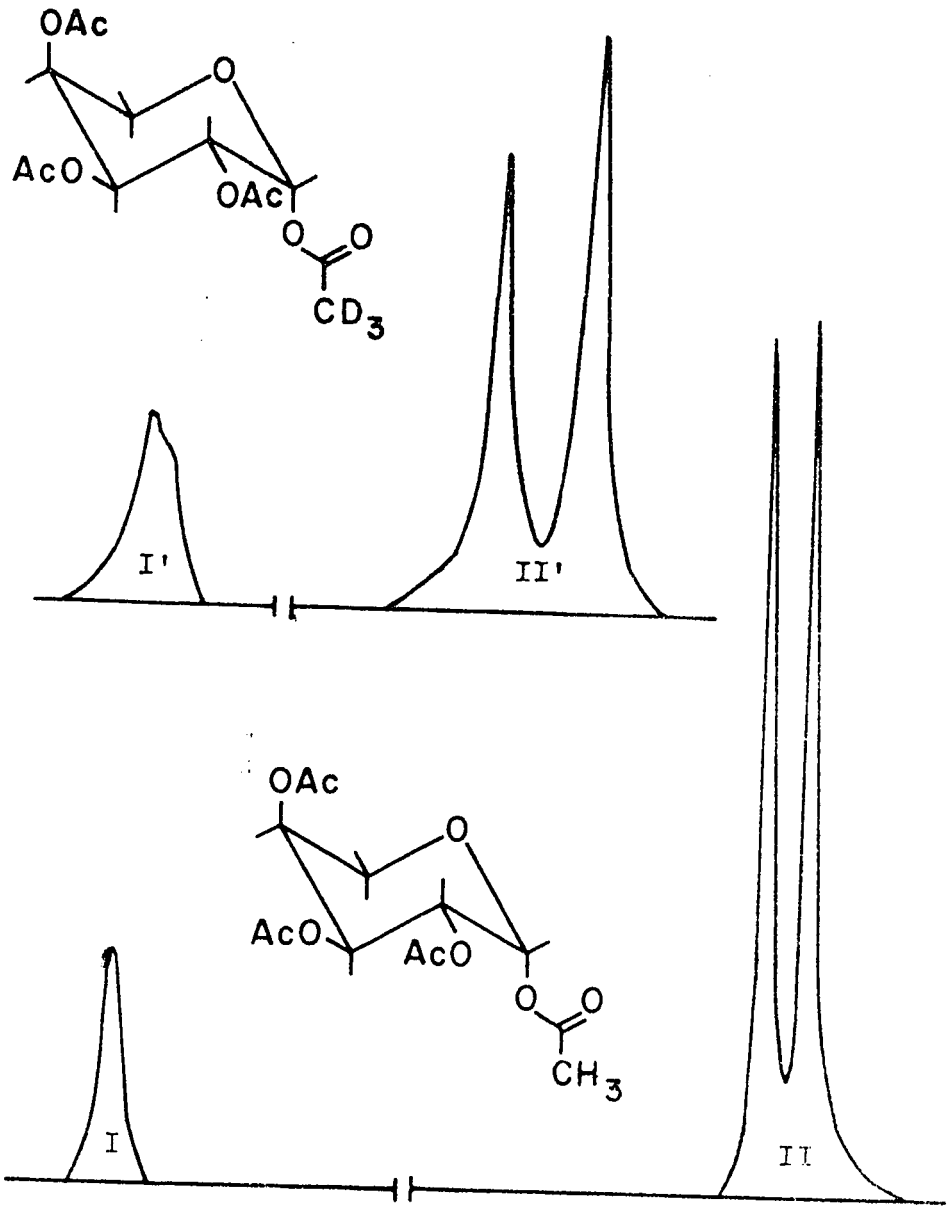


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Fig. 12. Proton Magnetic Resonance Spectra of the Acetoxy Groups in β-L-Arabopyranose Tetraacetate (II), and 1-Deuteroacetoxy β-L-Arabopyranose Triacetate (II')

$$OAc_e/OAc_a = (2[LIV] + [LIII])/([LIV] + 2[LIII]) = 1.46.$$

Since [LIII] = 1-[LIV],

therefore, [LIV] = 0.78, [LIII] = 0.22,

and, K = [LIV]/[LIII] = 3.54

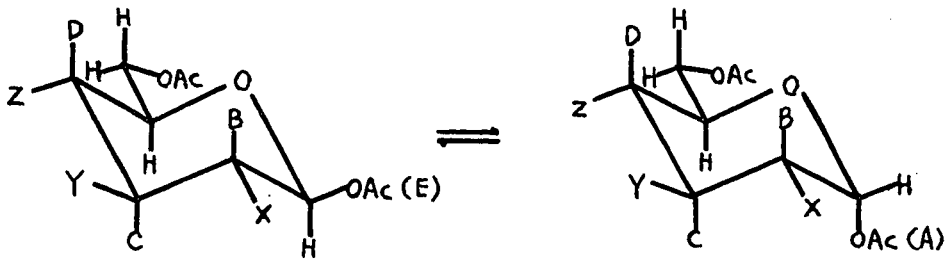
where K is the equilibrium constant between the two chair forms. The difference in free energy is

$$\Delta F^{\circ} = -RT\ln K = -750 \text{ cals./mole,}$$

Equation (v) in Table X, section b, is the result of the conformational analysis for the chair-chair transformation of the β-L-arabopyranose tetraacetate, which is equated with the difference in free energy between the two chair forms. Thus, from the four equations, the four non-bonded interactions were obtained. The values derived from these equations are given in Table X, section c.

b. The Aldohexopyranose Pentaacetates

A general formulation for the anomerization of the aldohexopyranose pentaacetates is as follows.



LVIII LIX

The equilibrium and kinetic data are given in Table XI. Table XII listed the non-bonded interactions which are present in the isomeric sugar acetates. The differences in non-bonded interactions between the anomeric pairs are given in Table XIII. They are expressed in terms of M, N, Q and P' (cf. Table X, page 81) in Table XIV, section a.

The anomeric effect, P', is believed different to that, P, obtained from the aldopentopyranose tetraacetates for the following reason.

A comparison of the free energy change in the anomerization process between a hexose and a pentose which involves the same interaction terms reveals, as seen in Table XIV, section b, that there is a consistent difference between these two series. Since P' is the interaction term in common in each anomeric pair, the variation of free energy change from a pentose to a hexose is, therefore, likely due to a change in magnitude of P' from P. From the mean value of the variation, the value of P' is taken as 1510 (P+220) cals./mole for the hexose series. From the value of P', the average values of the other interaction energies were calculated using the equations in Table XIV, section a, and are reported in section c of the same Table. The averaged non-bonded interaction energies for the pentose and hexose acetates are given in the first part of Table XV. These values all involve the interaction term H/O-H/H. The present work does not allow an estimation of the magnitude of

Table XI

Equilibrium and Kinetic Data for the Anomerization of the Aldohexopyranose Pentaacetates

Acetylated Aldopyranose	Temp. (±0.1°)	Observed Optical Rotation α_o (β-anomer)	Observed Optical Rotation α_o (α-anomer)	α_e	Equilibrium Constant	ΔF° cals./mole Found	ΔF° cals./mole Calc.	Rate$_5$ Constant x 10^5 sec.$^{-1}$ $k_\beta + k_\alpha$	k_β	k_α
D-Glucose	25.0°	0.49°	8.76°	7.64°	6.4±0.3	-1100	-1150	16.6	14.4	2.2
	15.2	0.50	8.79	7.70	6.6±0.3			4.2		
	4.6	0.47	8.80	7.79	7.3±0.3			0.92		
D-Mannose	25.0	-2.05	4.25	3.90	17±2	-1690	-1690	19.0	17.9	1.1
	15.2	-2.06	4.24	3.96	18±2			5.0		
	4.6	-2.08	4.20	3.95	20±3			1.04		
D-Allose	25.0	-0.97	6.55	1.44	0.47	450	510	26.5	8.5	18.0
	15.2	-0.97		1.41				7.02		
	5.7	-0.98		1.43				1.74		
D-Galactose	25.0	2.12	8.99	8.12	6.9±0.4	-1150	-1150	44.8	39.1	5.7
	15.2	2.15	9.03	8.20	7.3±0.4			12.2		
	4.6	2.20	9.11	8.34	8.0±0.4			2.57		
D-Altrose	25.0	-2.99	5.66	2.46	1.7	-310	-30	107	68.1	38.9
	15.2		5.61	2.48				32.0		
	5.7		5.70	2.54				8.9		
D-Talose	25.0	-2.14	5.31	4.85	15	-1620	-1690	43.6	40.9	2.7
D-Gulose	25.0	-1.41	6.11	1.00	0.47	450	510	55.2	17.6	37.6
	15.2		6.09	0.96				14.8		
	5.7		6.10	0.98				3.8		

Table XII

Non-bonded Interactions for the Aldohexopyranose Pentaacetates

Aldopyranose Pentaacetate	Positions of Acetoxy Groups		Non-bonded Interactions									
			H:H	H:O	O:O	H:p	O:p	O/p	H/p	H/H	H/O	O/O
9. β-D-Gluco	E	X,Y,Z	5	1	-	2	-	2	1	0	7	3
10. α-D-Gluco	A		3	3	-	2	-	1	2	1	6	3
11. β-D-Manno	E	B,Y,Z	4	2	-	1	1	2	1	2	5	3
12. α-D-Manno	A		2	4	-	1	1	1	2	2	6	2
13. β-D-Allo	E	X,C,Z	3	3	-	2	-	2	1	2	5	3
14. α-D-Allo	A		2	3	1	2	-	1	2	3	4	3
15. β-D-Galacto	E	X,Y,D	4	2	-	1	1	2	1	2	5	3
16. α-D-Galacto	A		2	4	-	1	1	1	2	3	4	3
17. β-D-Altro	E	B,C,Z	2	4	-	1	1	2	1	3	5	2
18. α-D-Altro	A		1	4	1	1	1	1	2	3	6	1
19. β-D-Talo	E	B,Y,D	4	1	1	-	2	2	1	4	3	3
20. α-D-Talo	A		2	3	1	-	2	1	2	4	4	2
21. β-D-Gulo	E	X,C,D	2	4	-	1	1	2	1	3	5	2
22. α-D-Gulo	A		1	4	1	1	1	1	2	4	4	2

Table XIII

Differences in Non-bonded Interactions between

Anomeric Aldohexopyranose Pentaacetates

Compounds[4]	Configuration	Differences in Non-bonded Interactions
(9 - 10)	Gluco[1]	2(H:O-H:H) - (O/p-H/p) - (H/O-H/H)
(11 - 12)	Manno[2]	2(H:O-H:H) - (O/p-H/p) - (O/O-H/H) + (H/O-H/H)
(13 - 14)	Allo[3]	(O:O-H:H) - (O/p-H/p) - (H/O-H/H)
(15 - 16)	Galacto[1]	2(H:O-H:H) - (O/p-H/p) - (H/O-H/H)
(17-- 18)	Altro	(O:O-H:H) - (O/p-H/p) - (O/O-H/H) + (H/O-H/H)
		= [(O:O-H:H) -2(H/O-H/H)]-[(O/p-H/p) -(H/O-H/H)]
		-[(O/O-H/H) -2(H/O-H/H)]
(19 - 20)	Talo[2]	2(H:O-H:H) - (O/p-H/p) - (O/O-H/H) + (H/O-H/H)
(21 - 22)	Gulo[3]	(O:O-H:H) - (O/p-H/p) - (H/O-H/H)

1. The same expression as the xylo-configuration (see Table IX).
2. The same expression as the lyxo-configuration.
3. The same expression as the ribo-configuration.
4. Numbers for compounds correspond to those in Table XII.

Table XIV

Calculation of the Non-bonded Interaction Energies in the Aldohexopyranose Pentaacetates

(a). Equations for the non-bonded interaction energies from the equilibrium data of the hexose acetates (Table XI).

Gluco	2M - P' =	-1100 cals./mole
Manno	2M-P'-Q =	-1690
Allo	N - P' =	450
Galacto	2M - P' =	-1150
Altro	N-P'-Q =	-310
Talo	2M-P'-Q =	-1620
Gulo	N - P' =	450

(b). Average increase in the anomeric effect (P) for the hexose acetates over that for the pentose acetates[1].

$\Delta F^{\circ}_{1,2}-\Delta F^{\circ}_{9,10}$	=	-160 cals./mole
$\Delta F^{\circ}_{1,2}-\Delta F^{\circ}_{15,16}$	=	-210
$\Delta F^{\circ}_{3,4}-\Delta F^{\circ}_{11,12}$	=	-210
$\Delta F^{\circ}_{3,4}-\Delta F^{\circ}_{19,20}$	=	-140
$\Delta F^{\circ}_{5,6}-\Delta F^{\circ}_{13,14}$	=	-330
$\Delta F^{\circ}_{5,6}-\Delta F^{\circ}_{21,22}$	=	-330
Average		-220

(c). Average values for the non-bonded interaction energies in the aldohexopyranose pentaacetates(2).

P'	=	P + 220 =	1510 cals./mole
M	=	190	
N	=	1960	
Q	=	530	

---

1. The subscripts refer to the numbers for the compounds in Table XII.

2. Equation for the altrose derivatives was not used.

Table XV

Averaged Non-bonded Interaction Energies for the Pentose and Hexose Acetates and the Effect of the Magnitude of the H/O-H/H Interaction on the Magnitude of the other Interactions

M = 180 cals./mole

N = 2020

Q = 540

P = 1290 (pentoses)

P' = 1510 (hexoses)

H/O - H/H	H:O - H:H	O:O - H:H	O/O - H/H	O/p - H/p
-100	80	1820	340	1190
0	180	2020	540	1290
100	280	2220	740	1390
200	380	2420	940	1490
300	480	2620	1140	1590

this interaction. The effect of varying the value for this interaction between -100 and 300 cals./mole is given in the same Table. It is felt that this procedure most clearly points out the fact that the absolute values for the variety interaction energies were not obtained in this or any other study of these molecular properties.

Previous investigators have simply assumed that the H/O-H/H interaction is negligibly small. Thus, the interaction energies reported in Table XV should be compared to those of previous workers when H/O-H/H has a value of zero. It is to be noted at this point that, under this condition, the values presently obtained for the H:O-H:H, O:O-H:H and O/O-H/H interactions are in remarkably good agreement with the results of previous workers.

As seen in Table XVI, the reported values of a diaxial interaction between an oxygen and a hydrogen atom range from 150 to 450 cals./mole. The higher values were obtained from experiments in aqueous media. The high interaction energy thus obtained may result in part from the difference in solvation of equatorial and axial hydroxyl groups. An equatorial hydroxyl group, being sterically less hindered, can be expected to be solvated with the water molecules through hydrogen bonding more readily than an axial hydroxyl. Consequently, the difference in free energy between an equatorial and an axial

Table XVI

A Comparison of the Interaction Energies

Obtained from Different Methods

Method	Interaction Energy cals./mole	t°	Solvent	Reference
(a). O:H - H:H				
Anomerization Equilibrium	180	25	1:1 HOAc-Ac_2O	This thesis
Infrared Analysis	150-200	20	CS_2	(33)
Acetylation of Cyclohexanol	260	25	Pyridine	(38)
Acetylation of 4,4-dimethyl Cyclohexanol	280	25	Pyridine	(38)
Chromic Acid Oxidation of Cyclohexanol	400	40	75% HOAc	(34)
Calc'n of Interaction from Cyclitols	450	22	Water	(40)
Epimerization of 4-t-butyl Cyclohexanol	480	89	Isopropanol	(39)
(b). O:O - H:H				
Anomerization Equilibrium	2020	25	1:1 HOAc-Ac_2O	This thesis
Calc'n of Interaction from Cyclitols	1900	22	Water	(40)
(c). O/O - H/H				
Anomerization Equilibrium	540	25	1:1 HOAc-Ac_2O	This thesis
Calc'n of Interaction from Cyclitols	350	22	Water	(40)

hydroxyl as determined in aqueous solution probably is not equal to the difference in the intramolecular non-bonded interactions. This is clearly shown in the mutarotation of free sugars, e.g., the equilibrium mixture of D-glucose contains 62% of beta anomer and 38% of alpha anomer (135) in aqueous solution. If the interaction terms have the same values as those in the acetylated sugars, then, this represents a solvent effect of 1.4 kcal./mole which must be related to the hydrogen bondings. A detailed discussion in regarding the hydrogen bondings of the sugar molecules was given in a paper by Patterson and Kabayama (136). The value of 180 cals./mole for H:O-H:H from the present work is in excellent agreement with Price's value of 150-200 cals./mole, both in non-aqueous solutions.

The diaxial and skew interactions between two oxygen atoms are in good agreement with the values reported by Angyal and McHugh.

The existence of such agreement in interaction energies not only indicates that a pyranose ring is geometrically similar to a cyclohexane ring but also justifies the application of the proton magnetic resonance spectroscopy to determine the free energy difference in the chair-chair transformation of β-L-arabopyranose tetraacetate.

From these agreements, one can draw the following rather remarkable conclusion that the relative stabilities of the

sugar acetates are solely determined by the non-bonded interactions involving those oxygen atoms bonded to the ring carbon atoms inspite of the fact that the acetylated sugars are highly complex molecules containing numerous polar carbon-oxygen single and double bonds.

The calculated values of the free energy difference between anomeric sugars given in Tables VII and XI are based on the average non-bonded interaction energies in Table XV. It is seen that with a fair degree of accuracy, the difference in free energy is a statistical difference in the non-bonded interactions in the anomeric compounds.

Since the beta anomers for the D-lyxo-, D-gulo- and D-talopyranose acetates and the alpha anomer of D-allopyranose pentaacetate could not be crystallized, it was not possible to measure their specific rotations. Resort had therefore to be made calculation of the specific rotations using Hudson's "Rule of Isorotation" (133). The procedure was to take the average value of the contributions, $A=\frac{([M]_\alpha - [M]_\beta)}{2}$, to rotation by the anomeric center for the known crystalline aldopyranose acetates and to apply this mean value to each of the known crystalline anomers of the above sugars using Hudson's rule to calculate the contribution to rotation by the basal or B-portion of the molecule (133). The resultant B-values and the mean A-value could then be used to estimate the molar rotations of the unknown anomers. The results of these

Table XVII

Molar Rotation of the Acetylated Aldopyranoses in 1:1 Acetic Acid-Acetic Anhydride

Acetylated Aldopyranoses	$[M]_\alpha$	$[M]_\beta$	$\frac{[M]_\alpha - [M]_\beta}{2}$
D-Glucose	43,800	2,450	20,675
D-Mannose	21,250	-10,250	15,750
D-Galactose	44,950	10,600	17,175
D-Altrose	28,300	-14,750	22,025
D-Xylose	31,250	-7,500	19,375
D-Ribose	19,650	-19,150	19,400
L-Arabinose	13,600	48,100	17,250
		Average	18,810
D-Lyxose	7,800	[-29,820]*	
D-Allose	[32,770]*	-4,850	
D-Gulose	30,550	[-7,070]*	
D-Talose	26,550	[-10,700]*	

* Figures shown in brackets were calculated by Hudson's "Rule of Isorotation".

calculations are shown in Table XVII.

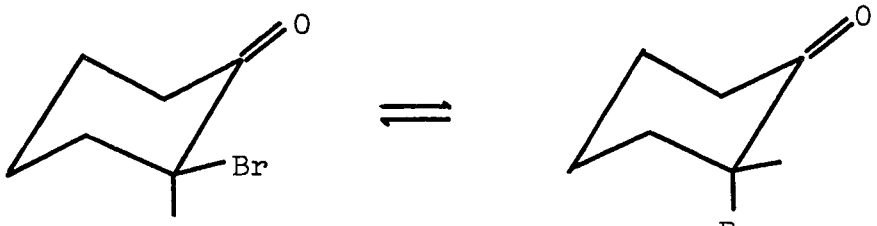
2. The Anomeric Effect

The interaction term O/p-H/p, referred to as the anomeric effect in this thesis, comprises a force which destabilizes the equatorial orientation for a 1-acetoxy group relative to the axial orientation.

According to the principles of conformational analysis (137), an equatorial substituent on a cyclohexane ring is energetically favored over an axial substituent (cf. page 9). The main difference between a pyranose ring and a cyclohexane ring is the presence of an oxygen atom in the ring in replacing of one of the carbon atoms. One would, therefore, conclude that the abnormal behavior exhibited is probably due to the effect of the ring-oxygen atom. Edward (55) has suggested that the effect arises from dipole-dipole interaction between the ring-oxygen atom and the equatorial substituent on carbon 1 (cf. page 26). According to Edward's suggestion, the origin of the dipole at the ring oxygen may be the p-orbitals. There is, however, no clear-cut theoretical basis for this assumption and, as will be seen later on, it is most likely that the anomeric effect arises from electrostatic interactions between carbon 1 to acetoxy group and carbon 5 to ring-oxygen bonds. Nevertheless, it is useful as an aid in conformational analysis

to identify the anomeric effect in terms of the orientation of the 1-substituent relative to the assumed p-orbitals of the ring-oxygen as was done in Tables VIII and XII.

A non-bonded interaction due to a dipole-dipole interaction has been suggested in the case of α-bromocyclohexanone. Corey (7), from infrared spectroscopy, showed that the bromine atom of α-bromocyclohexanone is in the axial orientation, and calculated the energy difference between the two chair forms, (LX) and (LXI), through a consideration of the dipole-dipole interaction between C-Br and C=O bonds. On this basis, he concluded that the conformation with the bromine in axial orientation (LXI) should be more stable by about 2.7 kcal./mole.



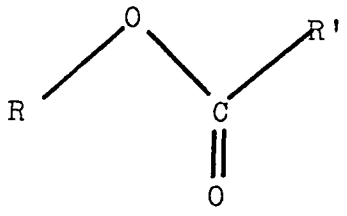
LX ⇌ LXI

However, more recently, Allinger and Allinger (138) have shown through a study of the equilibration of diastereomeric 2-bromo-4-t-butylcyclohexanones that the bromine atom favors the axial orientation by only 0.32 to 0.75 kcal./mole.

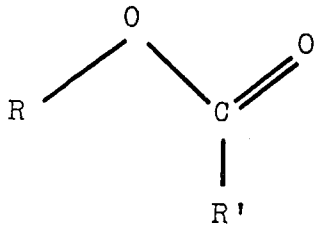
A situation similar to the anomeric effect is present in the molecule of methylal. Since an anomeric effect has an

interaction energy of about 1.3 kcal./mole, one would predict that the two methyl groups in methylal would tend to orient themselves in such a way as to avoid skew interactions of the carbon-oxygen bonds with the p-orbitals of the other oxygen atom. The four conformations which are possible for methylal with neighboring atoms in skewed orientation, are shown in Fig. 13. Among these four possible conformations, only two, (I) and (III), are free of the anomeric effect as identified above. However, the two methyl groups in (III) are in a similar situation as two axial methyl groups on a six-membered ring. Thus, conformation (I) would be expected to be the most stable one. In this respect, it is of decided interest that (I) is in fact the conformation for methylal as established by dipole measurements (139) and confirmed by electron diffraction (140).

Nash (141) pointed out that the lone-pair electrons in a conjugated system, such as in the esters of carboxylic acids, tend to assume a trans configuration. It has been shown from



LXII



LXIII

dipole moments that esters exist in the form (LXII). This conformation would also be expected to be the stable one from

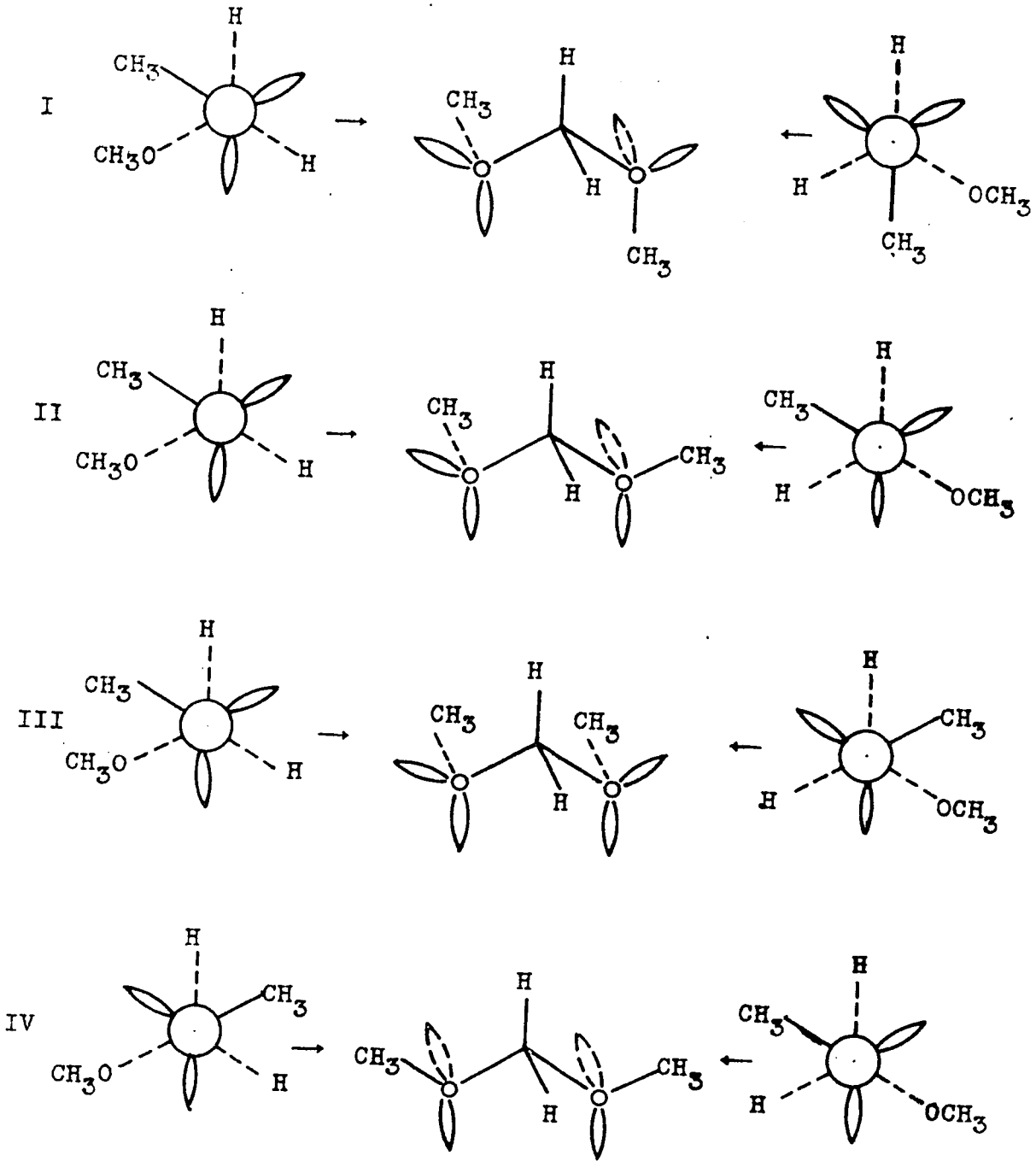


Fig. 13. The Conformations of Methylal

the foregoing reasonings.

A calculation of the dipole-dipole interactions for the anomeric effect was based on bond dipole moments which were treated as point charges located at the center of each atom in view of the fact that the derived formulas are not applicable to intramolecular interactions of close distance.

The interatomic distances between O_1 and C_1 (see Fig. 14) and between O_1 and O_r remain the same whether O_1 is in equatorial or in axial orientation. Therefore, when O_1 changes orientation from equatorial to axial, the only variable is the electrostatic interaction between O_1 and C_5 as shown in Fig. 14.

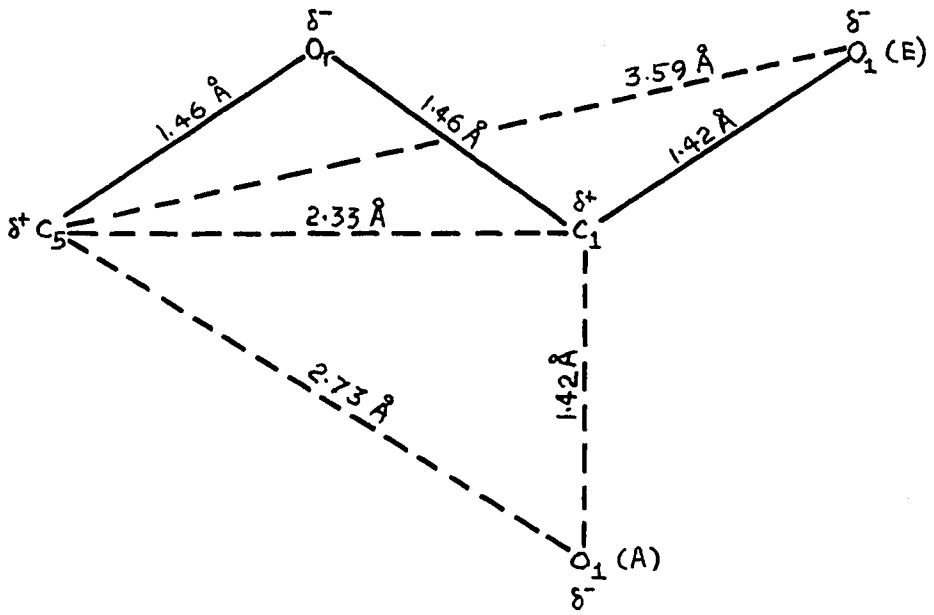


Fig. 14. Geometry of an Equatorial and an Axial 1-Substituent in relation to Carbon 5.

From x-ray diffraction analyses of D-glucose and sucrose (142), the valence angle for the ring-oxygen atom was calculated to be 111.5° and 104.5°, respectively. Consequently, the valence angle for the ring-oxygen atom was taken as that for the regular tetrahedral, 109.5°. The average value of the carbon to ring-oxygen bond distance of 1.46 A (142) and a dipole moment of 1.6 Debye units (143) were used. The difference in interaction energy between an equatorially and axially oriented C_1-O_1 bond calculated on this basis, was 1.55 kcal./mole. Thus, the anomeric effect can be accounted for on the basis of these electrostatic interactions. In his speculations on the assumed anomeric effect, Edward stressed the idea that the origin of the dipoles at the ring-oxygen were the lone-pair electron orbitals. However, since the lengths of these atomic dipoles are much shorter than the lengths of bond dipoles, the polarization of the carbon 5 to ring-oxygen bond is probably the main contributing factor to the anomeric effect. This conclusion is supported by the data presented in the next section which is related to the effect of the electronegativity of the 5-substituent on the anomeric effect.

3. Effect of 5-Substituent on Anomerization Equilibria

The variation of free energy change from a pentose to a hexose was assumed (see page 87) to be due to a change in

magnitude of the anomeric effect. Since the difference between a pentose and a hexose is in the substituent on carbon 5, and the anomeric effect is polar in origin, it is likely that the effect brought on by the substituent is related to the difference in the polarities of the groups. In order to test this postulation, a series of compounds with different substituents on carbon 6 of D-glucose were prepared and their anomerization properties were determined. The results are summarized in Table XVIII.

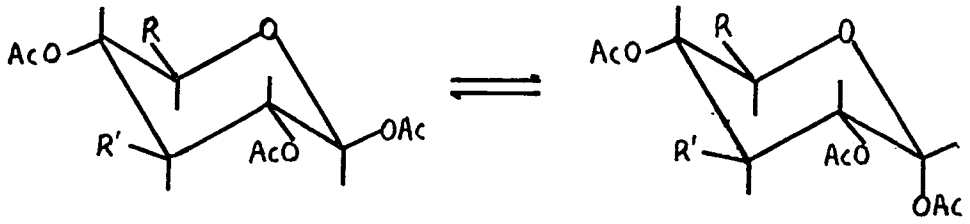
A methyl group is sterically comparable to an acetoxymethyl group. On the other hand, the polarity of a methyl group is similar to that of a hydrogen atom. The difference in free energy between the 6-deoxy-D-glucopyranose tetraacetates ($R=CH_3$, $R'=OAc$) is practically the same as the D-xylopyranose tetraacetates ($R=H$, $R'=OAc$). This result clearly suggests that, as would be expected, the difference between the anomeric effects P and P' (see Table XV) does not arise for steric reasons.

As seen from the equilibrium data shown in Table XVII, the equilibrium shifts to favor the alpha anomer with increasing electronegativity of the 6-substituent. On the other hand, Lemieux and Huber have shown that a change in the polarity of the 2-substituent has little effect on the anomerization equilibrium (61).

There is a fundamental difference in conformation of the

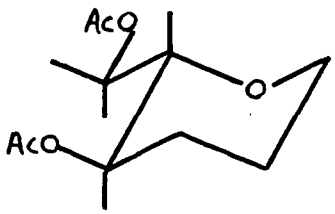
Table XVIII

Effect of the 5-Substituent on Anomerization Equilibrium

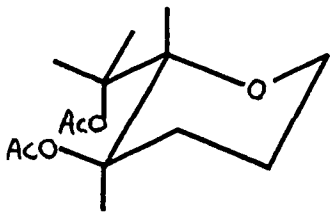


Substituents		Observed Optical Rotation			Equilibrium	ΔF°
R	R'	α_o (β-anomer)	α_o (α-anomer)	α_e	Constant	cals./mole
$-CH_2OTs$	OAc	2.20	10.01	9.32	10.3 ± 0.5	-1390 ± 30
$-CH_2OAc$	OTs	1.19	8.47	7.51	6.6 ± 0.3	-1120 ± 30
$-CH_2OAc$	OAc	0.49	8.76	7.64	6.4 ± 0.3	-1100 ± 30
$-CH_2Cl$	OAc	0.51	8.80	7.62	6.0 ± 0.3	-1070 ± 30
$-CH_2I$	OAc	0.78	9.05	7.75	5.4 ± 0.2	-1000 ± 20
$-CH_3$	OAc	1.50	8.51	7.83	4.9 ± 0.2	-950 ± 20
$-H$	OAc	-1.50	6.25	4.92	4.8 ± 0.2	-940 ± 20
$-CH_2NHAc$	OAc	0.27	8.57	6.22	2.5 ± 0.1	-550 ± 20

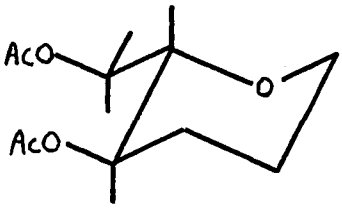
6-substituent in relation to the configuration on carbon 4. These are shown in LXIV to LXVI and LXVII to LXIX with the relative interaction energies shown in the brackets.



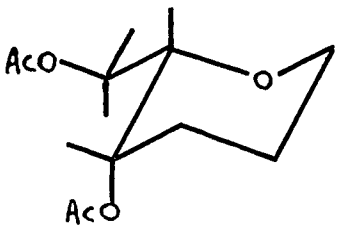
LXIV (0)



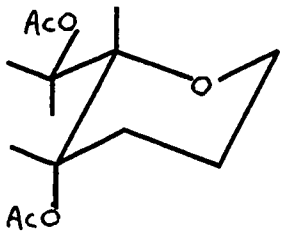
LXV (180)



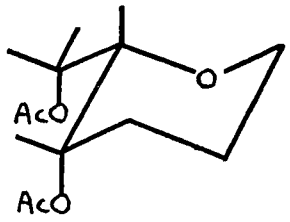
LXVI (1280)



LXVII (C)



LXVIII (360)



LXIX (2180)

For the gluco-configuration, the electrostatic interactions between 1- and 6-acetoxy groups were calculated in LXIV and LXV. The average value is 320 cals./mole lower for an alpha anomer than for a beta anomer.

From the fact that the effect of the 6-acetoxy group is about the same in either gluco- or galacto-configuration, the actual orientation of the 6-substituent does not make any significant difference to the magnitude of this effect. There-

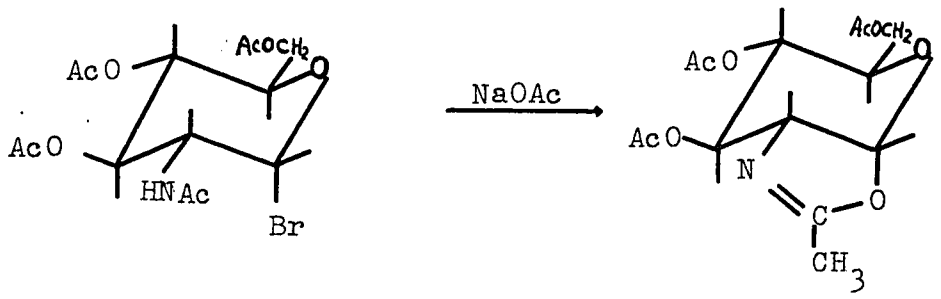
fore, it can be simply looked at as an increase in strength of the positive charge on carbon 5 because of the inductive effect of the electronegative 6-substituent.

4. Anomaly of the Acetylated Amino-Sugars

The results from the acetylated aldopyranoses were self-consistent. However, when this work was extended to the acetylated amino-sugars, certain anomalies were observed. Thus, when α-D-glucosamine pentaacetate was treated under the anomerization conditions, the specific rotation changed from 107° to 31.2°. The same equilibrium rotation was reached starting with beta anomer. Thus, had a true equilibrium been established between the alpha and beta anomers, the equilibrium rotation would require that the equilibrium mixture contains 87% of the beta anomer. However, the alpha anomer can be isolated from the equilibrium mixture in 35% yield. Moreover, the anomerization of the β-D-glucosamine pentaacetate is not first order in kinetics. As seen in Fig. 11, the rotation rapidly decreased to a minimum, then rose slowly to the equilibrium rotation. Evidently, the reaction was not a simple equilibration of the alpha and beta anomers. It is of interest to note that the specific rotation of the beta anomer is 1.2° in chloroform solution, 10° in 1:1 acetic acid - acetic anhydride mixture and

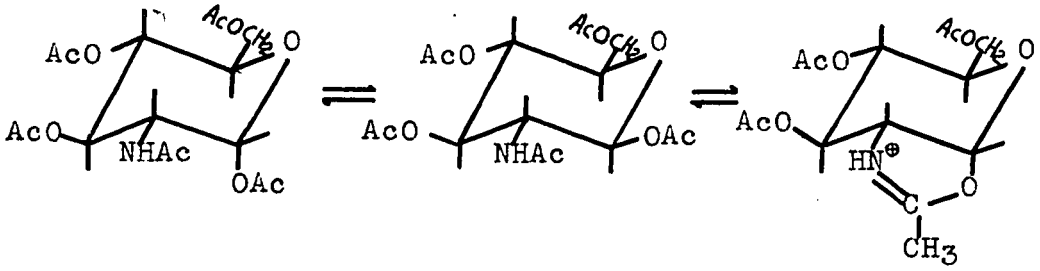
near 20° in the same mixture of solvents but containing an excess of perchloric acid. Apparently, protonation of the acetamido group can markedly change the specific rotation of the compound.

White (144), in 1940, reported that when tetraacetyl α-D-glucosaminyl bromide (LXX) was treated with sodium acetate in aqueous solution, the specific rotation changed from an initial value 115° to a constant final value 23°. From the solution, a crystalline product with an analysis corresponding to (LXXI) and a specific rotation of 54.0° was obtained.



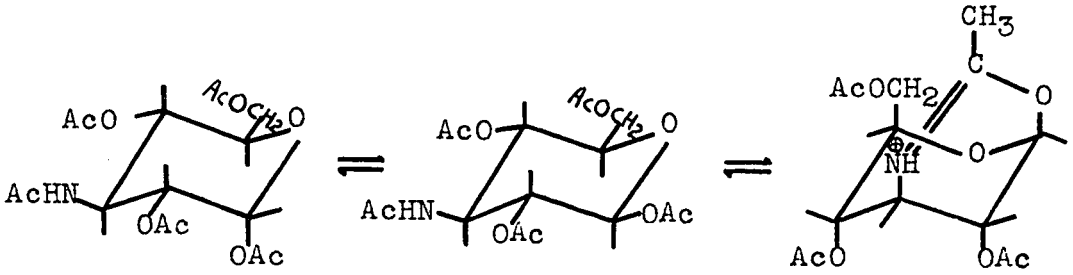
LXX LXXI

This observation together with the evidence that β-D-glucopyranose pentaacetate rapidly forms the 1,2-acetoxonium ion under anomerization conditions, clearly suggested that the oxazolinium ion (LXXIV) is perhaps the most stable product formed in the attempted anomerization of the D-glucosamine pentaacetates. The rapid initial reaction of the beta anomer supports this contention.



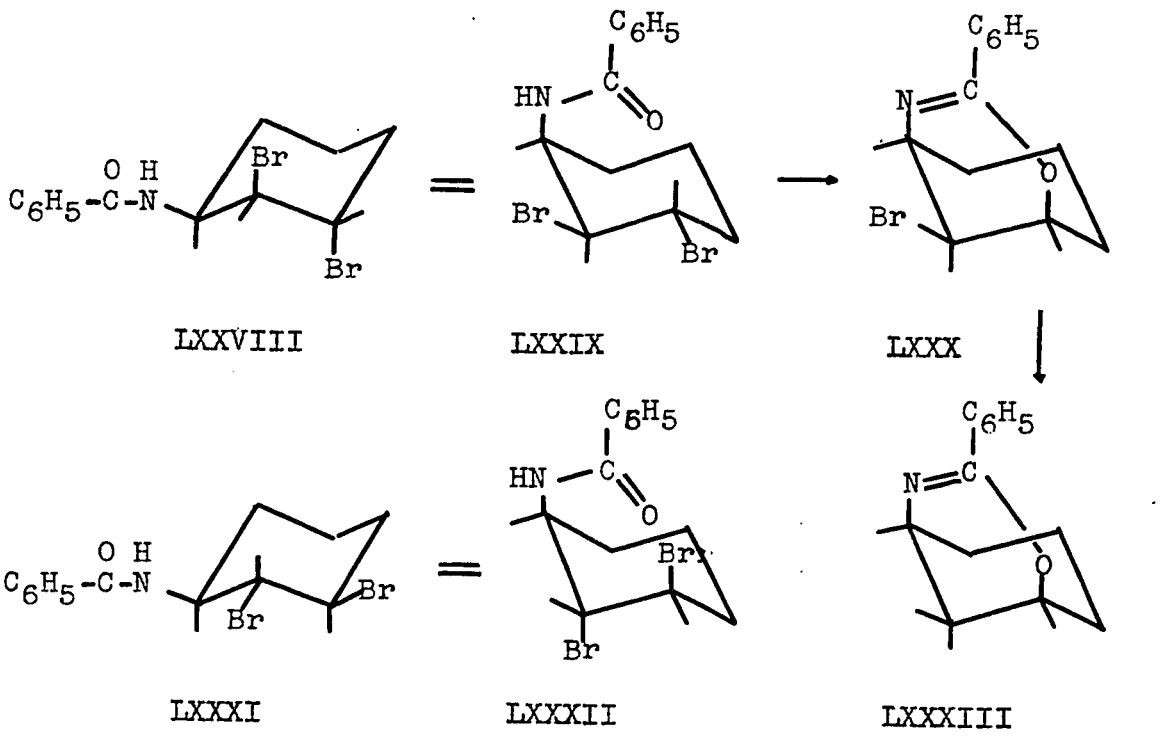
LXXII LXXIII LXXIV

Not only the D-glucosamine pentaacetates which have an acetamido group on carbon 2, exhibited the abnormal behavior under anomerization conditions. Treatment of 3-deoxy-3-acetamido-β-D-glucopyranose tetraacetate in the anomerization medium resulted in a rise in rotation to a maximum as shown in Fig. 9, which was followed by a slow decrease to the specific equilibrium rotation of 35.1°. This result could be due to the formation of an oxazine ring.



LXXV LXXVI LXXVII

Indeed, Winstein and coworkers (145) recently published their results on the study of solvolytic behavior of the isomeric 2,3-dibromo-1-benzamidocyclohexanes (LXXVIII) and (LXXXI) in glacial acetic acid in the presence of silver acetate.



LXXVIII LXXIX LXXX

LXXXI LXXXII LXXXIII

Under these conditions, (LXXVIII) appears to react substantially more rapidly than did (LXXXI). Hydrogenation of (LXXX) over a palladium catalyst to remove the bromine atom gave rise to a bromine-free compound whose melting point was identical with the oxazine (LXXXIII) reported by Burford, Hewgill and Jefferies (146). This result indicated that an oxazine ring was formed in preference to an oxazoline ring.

With an acetamido group on carbon 6, no complication was observed. Thus, 6-deoxy-6-acetamido-β-D-glucopyranose tetraacetate followed the first-order kinetics in anomerization as shown in Fig. 10, and the alpha anomer can be isolated in fair yield from the equilibrium mixture.

B. Configurational Effect on Chemical Reactivities

According to the transition state theory, reaction rates depend only upon the nature of the reactant and the activated complex (transition state) (cf. p. 21).

In the anomerization of a sugar acetate, the geometry of carbon 1 will be changed in going from the reactant to the transition state regardless of the reaction mechanism. A solvolytic mechanism would lead to a trigonal carbonium or carboxonium ion, whereas a bimolecular mechanism would lead to a pentavalent carbon atom in the transition state. Thus, either mechanism must cause distortions of the chair conformation of the pyranose ring. Since such changes must bring about changes in some of the non-bonded interactions in the ground state, the free energy of activation is, therefore, expected to vary with the configuration of the sugar acetates.

Since the diastereoisomeric acetylated sugars are structurally the same, polar effects due to inductions through sigma bonds can be neglected. Also, there is no reason to expect any appreciable differences in resonance energy. Consequently, it was anticipated that a conformational analysis of the non-bonded interactions in the ground and transition states for the anomerization reaction would allow a rationalization of the relative rates of reaction.

On this basis, since $\Delta\Delta E_{\sigma}^{\ddagger}$ and $\Delta\Delta E_{\varphi}^{\ddagger}$ in equation (11) (see p. 22) are taken as zero, then

$$\Delta\Delta E_{p}^{\ddagger} = \Delta\Delta E_{R}^{\ddagger} \qquad (29),$$

and

$$\Delta\Delta F^{\ddagger} = \Delta\Delta E_{R}^{\ddagger} - RT\ln(\pi Q^{\ddagger}) \qquad (30).$$

As a first approximation, $RTd(\ln \pi Q^{\ddagger})/dt$ in equation (13) (see p. 23) can be taken as negligible, consequently,

$$\Delta\Delta F^{\ddagger} = \Delta\Delta E_{R}^{\ddagger} - T\Delta\Delta S^{\ddagger} \qquad (31),$$

and

$$\Delta\Delta E_{R}^{\ddagger} = \Delta\Delta H^{\ddagger} \qquad (32).$$

For reactions in solution, the difference between the enthalpy of activation and the experimental heat of activation is RT.

$$E_{exp.} = \Delta H^{\ddagger} + RT \qquad (33).$$

However, the RT term cancels out for the relative enthalpy of activation, $\Delta\Delta H^{\ddagger}$. Thus, a measure of $\Delta\Delta H^{\ddagger}$ can be expected to provide a measure of the changes in non-bonded interactions (strain energy) which take place in the change from the reactant to transition state.

The heat of activation for the anomerization reactions were determined from the temperature coefficients of the reaction rates. The values are given in Tables XIX and XX.

Since the anomerization is a reversible process, the measured rate constant is the sum of k_{α}, the rate constant from α-anomer to β-anomer, and k_{β}, the rate constant from β-anomer to α-anomer. A plot of $\ln(k_{\alpha} + k_{\beta})$ against $1/T$ gives $E_{\alpha+\beta}$,

Table XIX

Thermodynamic Data for the Anomerization of Aldopentopyranose Tetraacetates

Configuration	Thermodynamic Constants, cals./mole at 25°					
	$E_{exp.}$	$\Delta\Delta F^{\ddagger}$	$\Delta\Delta H^{\ddagger}$	$T\Delta\Delta S^{\ddagger}$	$H_r - H_s$ *	$H_r^{\ddagger} - H_s^{\ddagger}$
1. β-D-Xylo	19,800	0	0	0	0	0
2. α-D-Xylo	20,800	-940	-1,000			
3. β-D-Lyxo	20,400	-170	-600	-500	-M-R = -180-R	-780-R
4. α-D-Lyxo	21,900	-1,640	-2,100			
5. β-D-Ribo	21,600	-1,400	-1,800	-400	-2M = -360	-2,160
6. α-D-Ribo	20,800	-630	-1,000			
7. α-L-Arabo	19,900	-140	-200	-100	-M-R = -180-R	-380-R
8. β-L-Arabo	20,900	-1,100	-1,200			

* Calculated from the differences in non-bonded interactions from Table IX and the interaction energies listed in Table XV. The value for R = (O:p-H:p) - (H/O-H/H) is probably of the same magnitude as Q = 540.

Table XX

Thermodynamic Data for the Anomerization of Aldohexopyranose Pentaacetates

Configuration	Thermodynamic Constants, cals./mole at 25°					
	$E_{exp.}$	$\Delta\Delta F^{\ddagger}$	$\Delta\Delta H^{\ddagger}$	$T\Delta\Delta S^{\ddagger}$	$H_r - H_s$	$H_r^{\ddagger} - H_s^{\ddagger}$
9. β-D-Gluco	23,300	0	0	0	0	0
10. α-D-Gluco	24,400	-1100	-1100			
11. β-D-Manno	23,500	130	-200	-300	-M-R =-180-R	-380-R
12. α-D-Manno	25,200	-1540	-1900			
13. β-D-Allo	24,000	-310	-700	-400	-2M=-360	-1060
14. α-D-Allo	23,600	140	-300			
15. β-D-Galacto	22,700	600	600	0	-M-R =-180-R	420-R
16. α-D-Galacto	23,900	-550	-600			
17. β-D-Altro	21,100	930	2200	1300	Q-3M-R = -R	2200-R
18. α-D-Altro	21,400	590	1900			
19. β-D-Talo		620				
20. α-D-Talo		1000				
21. β-D-Gulo	23,300	120	0	-100	Q-3M-R = -R	-R

which is the weighted average value of E_α and E_β, the individual heat of activation for the anomerization reaction from α-anomer to β-anomer and from β-anomer to α-anomer, respectively. The measured rate constant can be separated into k_α and k_β using the equilibrium constant, and the individual heats of activation, E_α and E_β, can be calculated from the values of the individual rate constants, k_α and k_β, at different temperatures. However, this procedure introduces the experimental error of the equilibrium constant which, in many cases, is rather large. Therefore, it was decided to obtain E_α and E_β from $E_{\alpha+\beta}$ based on the equilibrium constant at 25° and calculated as follows.

As discussed in previous section (see p.82), the entropy change in the anomerization reaction is small. Therefore, the heat of reaction, ΔH, can be taken as equal to the free energy change, ΔF°. Since,

$$k_\alpha = \frac{1}{(1+K)}(k_\alpha + k_\beta) \qquad (34),$$

where K is the equilibrium constant, and

$$E_{\alpha+\beta} = \frac{-R\ln (k_\alpha + k_\beta)_2/(k_\alpha + k_\beta)_1}{(1/T_2 - 1/T_1)} \qquad (35).$$

From equations (34) and (35),

$$E_\alpha = E_{\alpha+\beta} + \frac{R\ln (1+K_2)/(1+K_1)}{(1/T_2 - 1/T_1)} \qquad (36),$$

and

$$E_\beta = E_\alpha + \Delta H = E_\alpha + \Delta F^\circ \qquad (37).$$

The equilibrium constant at another temperature can be calculated from the following equation based on the equilibrium constant at 25°.

$$\Delta H = \frac{-R\ln(K_2/K_{25^\circ})}{(1/T_2 - 1/298)} = \Delta F^\circ \qquad (38).$$

The relative free energies of activation, $\Delta\Delta F^\ddagger$, and the relative enthalpy of activation, $\Delta\Delta H^\ddagger$, in Tables XIX and XX were based on β-D-xylopyranose tetraacetate as the reference compound in the case of the pentoses and β-D-glucopyranose pentaacetate for the hexoses. These values were calculated using the following expressions.

$$\Delta\Delta F^\ddagger = \Delta F_r^\ddagger - \Delta F_s^\ddagger = -RT\ln(k_s/k_r) \qquad (39),$$

and

$$\Delta\Delta H^\ddagger = \Delta H_r^\ddagger - \Delta H_s^\ddagger = E_{exp.(r)} - E_{exp.(s)} \qquad (40),$$

wherein the subscript "r" refers to the reference compound and subscript "s" refers to the other sugar acetate. Thus, from the well known expression,

$$\Delta\Delta F^\ddagger = \Delta\Delta H^\ddagger - T\Delta\Delta S^\ddagger \qquad (41),$$

the values of $T\Delta\Delta S^\ddagger$ were obtained.

The experimental error in obtaining these results is estimated to be approximately 500 cals./mole. Therefore, the degree of uncertainty is of the same magnitude as the measured values of $T\Delta\Delta S^\ddagger$ except for the D-altropyranose pentaacetates. This indicates that the entropy effect is not the important factor in determining the relative rates of the sugar acetates in

the anomerization reaction.

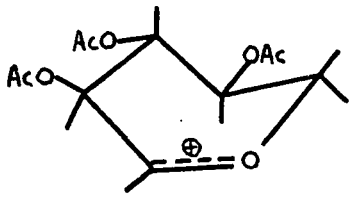
The relative stabilities of the sugar acetates in the ground state can be estimated from the non-bonded interaction energies as determined in the previous section. The values are listed in the column $(H_r - H_s)$ in Tables XIX and XX. The term R in these values is related to the skew interaction between an axial acetoxy group on carbon atom 2 or 4 with the ring-oxygen atom. It was not possible to estimate the magnitude of this interaction. However, it seems reasonable to assume that it will be no greater than the skew interaction between two neighboring acetoxy groups. Although this interaction will be somewhat altered by any distortion of the pyranose ring, it must also be present in the transition state. Consequently, the term R can be expected to have no significant effect on the relative rates of reaction and will be neglected in the subsquent conformational analysis for the transition states. Since,

$$\Delta\Delta H^{\ddagger} = \Delta H_r^{\ddagger} - \Delta H_s^{\ddagger} = (H_r^{\ddagger} - H_r) - (H_s^{\ddagger} - H_s)$$
$$= (H_r^{\ddagger} - H_s^{\ddagger}) - (H_r - H_s), \qquad (42),$$

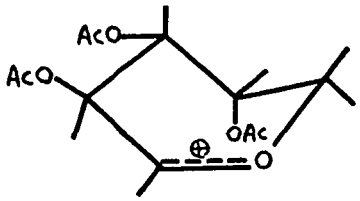
the values of $(H_r^{\ddagger} - H_s^{\ddagger})$ can be calculated, which is related to the relative stabilities or the differences in non-bonded interactions of the isomeric sugars in the transition state.

A consideration of the $(H_r^{\ddagger} - H_s^{\ddagger})$ values in Table XIX shows that the non-bonded interactions in the transition state for the ribo-configuration is about 2160 cals./mole more than that for the xylo-configuration. It is inconceivable that such a

large difference in stabilities for the ions (LXXXIV) and (LXXXV). In fact, an axial 3-acetoxy group as in (LXXXIV) could be expected to stabilize the ion relative to an equatorial 3-acetoxy group as

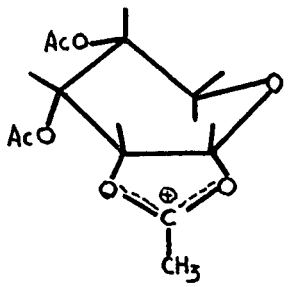


LXXXIV

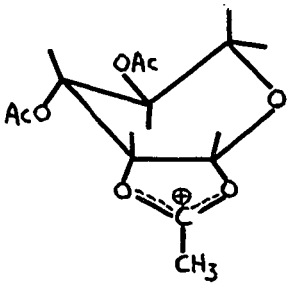


LXXXV

in (LXXXIV), since the negative end of the C_3-OAc bond will be closer to the positive ion center in (LXXXV) than in (LXXXIV). Therefore, the solvolytic process is, in all probability, not the mechanism for the anomerization of sugar acetates. Likewise, the large difference (1380 cals./mole) in stabilities between lyxo- and ribo-configuration in the transition states makes the mechanism similar to Winstein's (see p. 45) improbable, since conformational analysis of the acetoxonium ions (LXXXVI) and (LXXXVII) derived from these compounds would require the ions to have about the same stabilities. Although these acetoxonium ions are the intermediates and not the transition states, it can



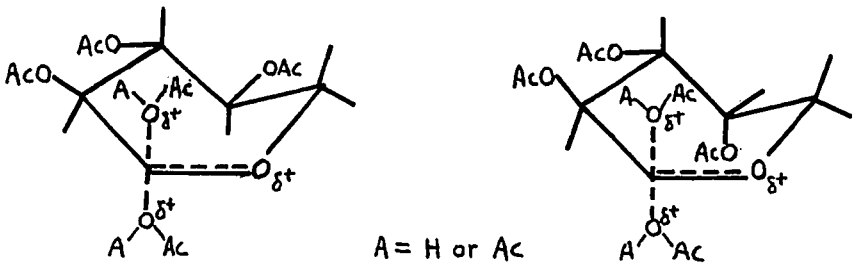
LXXXVI



LXXXVII

be expected that the actual transition states would be geometrically similar to these acetoxonium ions.

On the other hand, the large difference in stabilities between the two transition states of xylo- and ribo-configuration can be satisfactorily explained on the basis of a bimolecular mechanism, as shown in (LXXXVIII) and (LXXXIX), since a strong



LXXXVIII LXXXIX

interaction between the axial 3-acetoxy group and the acetoxy group at the reaction center can be expected for (LXXXIX), which is not the case for the transition state (LXXXVIII). The same argument applies to the difference in stabilities of the transition states for the gluco- and allo-compounds.

It is therefore concluded that the anomerization process is an S_N2 type reaction.

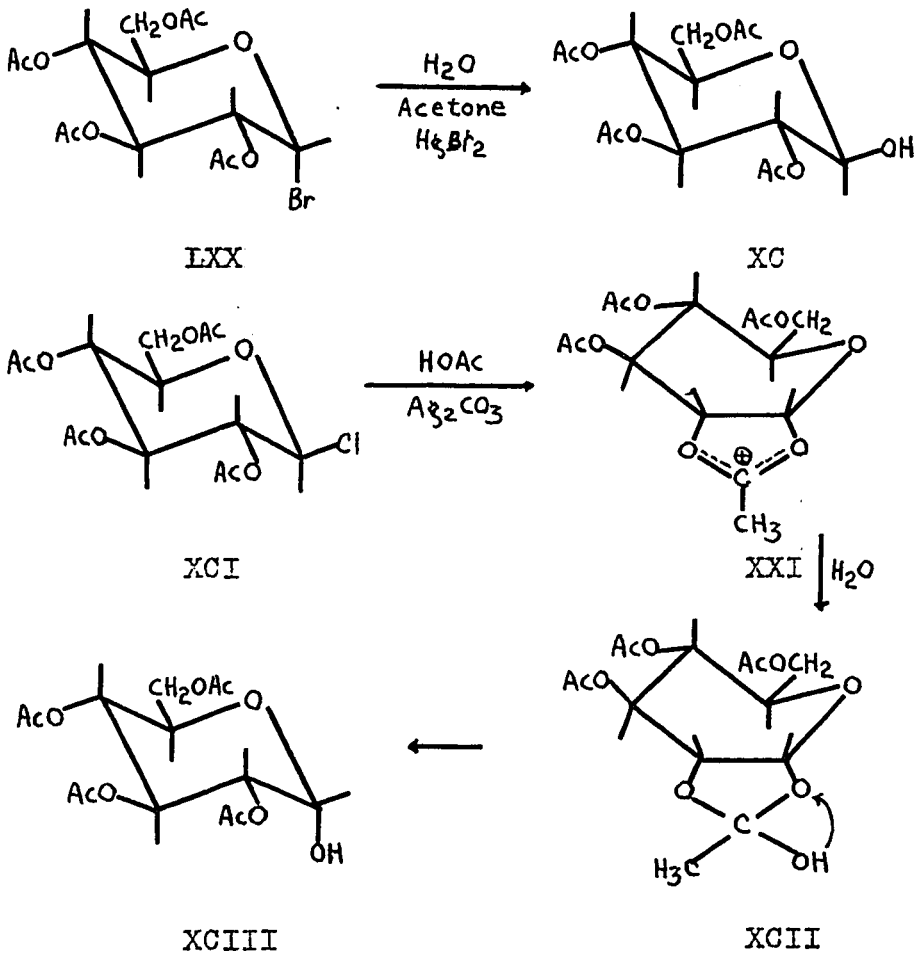
The high reactivity of the 1-acetoxy group as compared with the other acetoxy groups in these compounds must be related to the presence of the ring oxygen. The activation of the 1-substituent of sugar derivatives by the ring oxygen in solvolytic processes is undoubtedly due to resonance stabilization in the

transition state (147). As pointed out by Streitwieser (148), similar resonance stabilization can be present for a bimolecular process. Certainly, the high reactivity of the anomeric center cannot be due to the electronegativity of the ring oxygen which, in fact, can be expected to deactivate this position regardless of whether the mechanism is S_N1 (149) or S_N2 (150), although the effect should not be so great in the case of S_N2 reactions.

Thus, the anomerization reaction may possess S_N1 character to certain extent, i.e., the C_1-OAc bond could be stretched considerably due to the resonance effect of the ring oxygen before a covalent bond is formed between the reaction center and the solvent molecule to achieve a bimolecular transition state. In other words, bond breaking may lead bond formation.

In this respect, it seems worthwhile to cite experimental data reported in the literature, which were interpreted as S_N1 reactions but for which the stereochemical results meet the requirements of the S_N2 mechanism.

Lindberg (151), in 1947, treated tetraacetyl α-D-glucopyranosyl bromide (LXX) in acetone in the presence of water and mercuric bromide and isolated the 2,3,4,6-tetraacetyl β-D-glucopyranose (XC) as the product. From the rotation of the reaction solution, it was concluded that (XC) was produced in high purity. If a free carbonium ion has ever been achieved from an S_N1 mechanism, it would be expected to rearrange to



the 1,2-acetoxonium ion (XXI) which is undoubtedly more stable than a free carbonium ion due to the resonance stabilization. Then, the alpha anomer (XCIII) instead of the beta anomer (XC) would be the product as in the case of the tetraacetyl β-D-glucopyranosyl chloride (XCI) (152).

A similar situation was the reaction of LXX in methanol, which led to a quantitative yield of methyl tetraacetyl β-D-glucopyranoside (153), whereas the reaction of XCI in methanol yielded orthoester (154).

Lemieux and Huber (155) studied the solvolysis of the 3,4,6-triacetyl D-glucopyranosyl chlorides in acetic acid. In both cases, inversion occurred at the anomeric carbon atom.

Moreover, from isotopic exchange studies under the anomerization conditions, it was found that the rate of exchange for the 1,2-cis sugar acetates is, within experimental error, equal to the rate of anomerization (56, 157).

As seen in Table XXI, the rate of anomerization of the glucopyranose pentaacetates decreases with increasing concentration of acetic acid at constant concentration of the perchloric acid except when the concentration of the acetic acid is of the same order of magnitude or less than that of the sugar acetates ; that is 0.1-0.007 M. At the low concentration of acetic acid, the rate of reaction becomes substantially independent of the concentration of acetic acid. Painter (100) has suggested that, in the anomerization media, the sugar acetate and acetic acid behave as bases and compete for the protons from the perchloric acid as shown in equation (25) (see p. 41). On this basis, since the anomerization must be initiated from a protonated sugar acetate, the rate of the anomerization should decrease, as was observed, with increasing concentration of acetic acid regardless of whether the mechanism is S_N1 or S_N2 if the concentration of acetic acid is high as compared to that of the sugar acetate. However, when the concentration of acetic acid is near that of the sugar acetate, a decrease in concentration

Table XXI

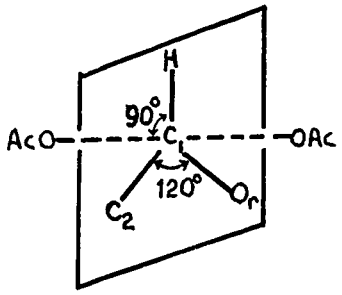
Anomerization of 0.051 M D-Glucopyranose Pentaacetate in Acetic Acid and Methylene Dichloride (100)

$(AcOH)_2$ M	$HClO_4$ M	$k_\alpha + k_\beta$, $min.^{-1}$ Found	Calc'd to 0.1M $HClO_4$
8.6	0.045	0.0032	0.0070
7.05	0.045	0.0035	0.0078
6.14	0.053	0.0059	0.0111
4.38	0.053	0.0092	0.0174
2.63	0.053	0.0194	0.037
1.41	0.0106	0.0095	0.090
0.895	0.0106	0.0153	0.144
0.361	0.0106	0.0423	0.400
0.103	0.0036	0.0321	0.890
0.093	0.00088	0.0086	0.971
0.0585	0.00088	0.0093	1.06
0.0516	0.0021	0.023	1.10
0.0069	0.00088	0.0085	0.97
0.0231	0.00088	0.0101	1.15
0.0034	0.00044	0.0019	0.43

should tend to decrease the rate of reaction if the mechanism is bimolecular while tending to increase the rate because of the increasing concentration of protonated sugar acetate. That is, at low concentration of acetic acid, the two effects would tend to cancel each other if the mechanism is S_N2 and results auch as those presented in Table XXI would be anticipated. Therefore, Painter's kinetic data support our contention that the mechanism of the anomerization is a bimolecular mechanism and involves a molecule of acetic acid in the transition state.

In view of the fact that the anomerizations in all probability proceed by way of an S_N2 mechanism, it was felt of interest to attempt a detailed conformational analysis of the kinetic data.

The configuration of a carbon center in the transition state of a bimolecular nucleophilic substitution is that of a doubly complexed carbonium ion as shown in XCIV.



XCIV

In the case of an S_N2 reaction at the anomeric center of a sugar acetate, the ring oxygen must be expected to participate

in the stabilization of the transition state. Otherwise, as seen on page 118, the uniquely high reactivity of the 1-acetoxy group of a sugar acetate could not be rationalized. Thus, the carbon 1 to ring-oxygen bond must be expected to possess double bond character in the transition state. Therefore, the geometry of the pyranose ring in the transition state can be expected to be similar to that of cyclohexene which is known to exist in the so-called half-chair conformation (156).

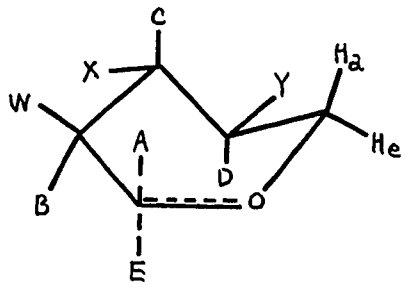
Consequently, the method of vector analysis described by Corey and Sneen (28) was used to calculate the interatomic distances in the transition state with the pyranose ring in the half-chair conformation. The results of these calculations are given in Table XXII.

Conformational analyses of the transition states based on the half-chair are complicated by the fact that this conformation possesses four different orientations; namely, axial (C and D), equatorial (X and Y), quasi-axial (B and H_a), and quasi-equatorial (W and H_e) (see Table XXII). For this reason, interactions in the chair form are not strictly identical to any of the interactions in the half-chair form. This is especially the case for steric interactions which are an exponential function of interatomic distances. However, electrostatic interactions are not nearly so sensitive to interatomic distances since these interactions vary inversely with distance.

As a first approximation, it seems reasonable to assume

Table XXII

The Interatomic Distances in a Half-chair Conformation of a Bimolecular Transition State for the Anomerization of Acetylated Aldopyranoses



Positions	Atoms (O-O)	Positions	Atoms (O-O)
E/B	2.06 Å	B/X = W/C	
A/W	2.33	= D/H_e	
E/W	3.21	= X/Y	2.80 Å
A/B	3.50	W/X Y/H_e	2.94
A/C	2.48	B/D C/H_a	2.70
A/H_a	2.89	C/Y X/D	2.71

that all interactions between an acetoxy group and a hydrogen atom, and between two hydrogen atoms are negligible, except when the interaction involves an acetoxy group at the anomeric center (A and E) with a quasi-axial or quasi-equatorial hydrogen at the 2-position. The remaining interactions in the transition states for the aldopentopyranose tetraacetates are listed in Table XXIII. Table XXIV shows the differences in these non-bonded interactions together with the differences in stabilities of the transition states with the transition state for the xylose tetraacetates as the reference compound.

First of all, the difference in the stabilities of the transition states for the xylo and arabo configurations is reasonable since, as seen from Table XXII, the D substituent is 0.09 A closer to the X substituent than is the Y substituent. If it is assumed that the skew interaction X_0/Y_0 has the same value, 540 cals./mole, as found for a skew interaction between two acetoxy groups in the ground state, then the interaction X_0/D_0 would have a value of 540 + 380 = 920 cals./mole. The interaction C_0/Y_0 is identical to X_0/D_0 and would have the same value.

Secondly, in the expression (Table XXIV) for the relative stabilities of the transition states for the xylo and ribo configurations, the difference in the interactions $(X_0/Y_0) - (C_0/Y_0)$ can be taken as -380 cals./mole. The skew interaction W_0/X_0 should be smaller than the W_0/C_0 skew interaction in view of

Table XXIII

The Non-bonded Interactions in the Transition State of the Aldopentopyranose Tetraacetates

Configuration	Position of Acetoxy Groups	Non-bonded Interactions[1]
Xylo	W,X,Y	$A_O/W_O + E_O/B_H + W_O/X_O + X_O/Y_O + A_O/C_H$
Lyxo	B,X,Y	$A_O/W_H + E_O/B_O + B_O/X_O + X_O/Y_O + A_O/C_H$
Ribo	W,C,Y	$A_O/W_O + E_O/B_H + W_O/C_O + C_O/Y_O + A_O/C_O$
Arabo	W,X,D	$A_O/W_O + E_O/B_H + W_O/X_O + X_O/D_O + A_O/C_H$

1. The subscripts "O" and "H" denote an acetoxy group and a hydrogen atom, respectively.

Table XXIV

Differences in Non-bonded Interactions between the Isomeric Aldopentopyranose Tetraacetates in the Transition States

Transition States Compared	Differences in Non-bonded Interactions	Relative Stabilities $H_r^{\ddagger} - H_s^{\ddagger}$
1. Xylo - lyxo	$A_O/W_O - E_O/B_O + E_O/B_H$	
	$- A_O/W_H + W_O/X_O - B_O/X_O$	-780
2. Xylo - ribo	$W_O/X_O - W_O/C_O + X_O/Y_O$	
	$- C_O/Y_O + A_O/C_H - A_O/C_O$	-2160
3. Xylo - arabo	$X_O/Y_O - X_O/D_O$	-380

the interatomic distances shown in Table XXII. This difference should not be great, however, since these skew interactions between acetoxy groups are largely electrostatic repulsions. Consequently, it can be concluded that the main reason for the difference in the stabilities of these transition states is the $A_O/C_O - A_O/C_H$ interaction which probably has a value greater than 1500 cals./mole. This, of course, is precisely the conclusion which had to be expected on the basis of an S_N2 mechanism for the anomerization.

Thirdly, a consideration of the interactions for the transition states of the xylo and lyxo configurations would lead to the expectation that the interaction $E_O/B_O - E_O/B_H$ should be considerably greater than $A_O/W_O - A_O/W_H$. This follows from the fact that the substituents E and B are considerably closer together than the substituents A and W (see Table XXII). The experimentally determined difference in stabilities reported in Table XXIV is in agreement with this expectation since $B_O/X_O - W_O/X_O$ is undoubtedly much less than 780 cals./mole.

Therefore, it is concluded that, in all probability, the aldopentopyranose tetraacetates undergo anomerization by way of a bimolecular nucleophilic substitution reaction with the pyranose ring in the half-chair conformation as required by the resonance theory.

It was not possible, however, to rationalize satisfactorily the kinetic data for the aldohexopyranose pentaacetates with

the pyranose ring in the half-chair conformation. Instead, a slightly deformed chair form seems best to fit the experimental results. As will be seen later on, this situation may arise from the introduction of an acetoxymethyl group on carbon 5, which can be expected to resist the pyranose ring assuming the half-chair donformation.

First of all, as seen from the kinetic data presented in Table XI, for epimeric compounds with the difference in configuration on carbon 4, the compound with the acetoxy group in axial orientation reacts more rapidly. Thus,

$$\Delta F_{9}^{\ddagger} - \Delta F_{15}^{\ddagger} = 590 \text{ cals./mole},$$

$$\Delta F_{11}^{\ddagger} - \Delta F_{19}^{\ddagger} = 490,$$

$$\Delta F_{13}^{\ddagger} - \Delta F_{21}^{\ddagger} = 430,$$

where the subscripts refer to the numbers of the compounds given in Table XX.

From a Fisher, Hirshfelder and Taylor molecular model, the internal motions of the substituents in an acetylated sugar molecule are highly restricted. This is especially true for the hexoses, wherein an additional steric strain exists between the substituents on carbon atoms 4 and 5. This strain, although remote from the reaction center, may cause steric effects in the rate process, and the effect of the orientation of the 4-acetoxy group may be related to the strain.

Moreover, the kinetic data suggested that the axial orientation for the 3-acetoxy group is the more favorable for reaction. Thus,

$$\Delta F^{\ddagger}_{10} - \Delta F^{\ddagger}_{14} = 1240 \text{ cals./mole},$$

$$\Delta F^{\ddagger}_{16} - \Delta F^{\ddagger}_{22} = 1120.$$

These results cannot be anticipated on the basis of a half-chair model for the transition state.

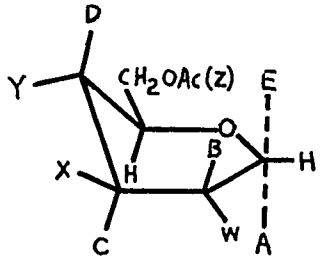
Furthermore, the rate of anomerization of β-D-talopyranose pentaacetate is nearly the same as that of β-D-galactopyranose pentaacetate (see Table XI). According to the data given in Table XXII, the interatomic distance between the positions B and D is increased from 2.54 Å in a chair form to 2.70 Å in a half-chair form. This would greatly reduce the steric strain between the acetoxy groups at these positions in talo-configuration. Therefore, had the anomerization reaction taken place by way of a half-chair conformation in the transition state, one would expect that β-D-talopyranose pentaacetate should react much faster than did β-D-galactopyranose pentaacetate.

The replacement of the equatorial hydrogen atom on carbon 5 by an acetoxymethyl group to transform D-xylopyranose tetraacetate to D-glucopyranose pentaacetate increases the enthalpy of activation by 3.5 kcal./mole (see Tables XIX and XX). This large difference in energy of activation cannot be accounted for on the basis of the difference in non-bonded interactions.

It is, therefore, more likely attributed to the difference in resonance stabilization by the ring oxygen of the transition states. From the fact that the 6-deoxy-D-glucopyranose tetraacetates anomerize eleven times faster than the D-glucopyranose pentaacetates, it clearly suggested that the polar 6-acetoxy group reduces the resonance stabilization of the transition state through participation of the ring oxygen. Resonance stabilization can be expected to be at maximum with the pyranose ring in the half-chair conformation.

Moreover, in changing from a chair to a half-chair form, the major shift in orientations are the substituents on carbon atoms 2 and 5, which change from axial to quasi-axial and from equatorial to quasi-equatorial. Therefore, it is conceivable that it should be less favored for the pyranose ring of an hexose acetate to assume a half-chair conformation in the transition state as compared with a pentose acetate since the large equatorial acetoxymethyl group is undoubtedly solvated in the anomerization media. Thus, the acetoxymethyl group may have an anchoring effect which tends to prevent the pyranose ring of an hexose acetate from assuming a half-chair conformation in the transition state. Consequently, other alternative conformations may require less energy. The foregoing conformation analysis suggests that a deformed chair (XCV) is a plausible model.

The model contemplated is one which would have the ring oxygen and carbon atoms 1,2,3 and 5 in one plane. Examination of such a model shows that the distance between the ring-oxygen and carbon 2 is increased over that for the chair form and that the substituents on carbon atom 4 are more strongly eclipsed with trans-substituents and less eclipsed with cis-substituents on carbon atoms 3 and 5.



XCV

Thus, on the basis of this model, a cis-relationship between the acetoxy group on carbon 4 and the acetoxy group on carbon 3 and between the acetoxy group on carbon 4 and the acetoxymethyl group on carbon 5 would be more favorable than when the relationship is trans. Obviously, then, this would rationalize the above mentioned experimental facts regarding the effects on reactivity brought on changes in configuration at carbon atoms 3 and 4. It must be kept in mind that the acetoxymethyl group in all likelihood remains in a near equatorial orientation.

Another consequence of this model is that axial substituents on carbon atoms 3 and 5 are further removed from the substituents complexed to the anomeric center than is the case in the half-chair conformation. Therefore, an axial 3-acetoxy group should

not destabilize the transition state for an hexose acetate as greatly as for a pentose acetate.

The non-bonded interactions in the transition states of the aldohexopyranose pentaacetates are listed in Table XXV, based on the same assumptions as made for the pentoses; i.e., the interactions between the hydrogen atoms and the skew interactions between an acetoxy group and a hydrogen atom are negligible. Table XXVI shows the differences in these non-bonded interactions together with the relative stabilities of the transition states with the transition state of the D-glucopyranose pentaacetates as the reference compound.

It is necessary to make two simplifying assumptions in order to deal with these expressions as shown in Table XXVI. First of all, it seems reasonable to assume that the following differences in skew interactions between two acetoxy groups can be taken as zero:

$$A_O/W_O - E_O/B_O,$$
$$W_O/X_O - B_O/X_O,$$
$$W_O/X_O - W_O/C_O,$$
$$X_O/Y_O - C_O/Y_O,$$
$$X_O/Y_O - X_O/D_O;$$

also, the $E_O/B_H - A_O/W_H$ is assumed to be zero. Secondly, it is assumed that there is no substantial change in the magnitude of the diaxial interactions B_O/D_H and D_H/B_H on going from the ground to the transition states. That is, these interactions

Table XXV

The Non-bonded Interactions in the Transition States of the Aldohexopyranose Pentaacetates

Configuration	Position of Acetoxy Groups	Non-bonded Interactions
Gluco	W,X,Y	$A_O/W_O + E_O/B_H + W_O/X_O + X_O/Y_O + Y_O/Z$
Manno	B,X,Y	$A_O/W_H + E_O/B_O + B_O/X_O + X_O/Y_O + Y_O/Z + B_O/D_H$
Allo	W,C,Y	$A_O/W_O + E_O/B_H + W_O/C_O + C_O/Y_O + Y_O/Z + A_O/C_O$
Galacto	W,X,D	$A_O/W_O + E_O/B_H + W_O/X_O + X_O/D_O + D_O/Z + B_H/D_O$
Altro	B,C,Y	$A_O/W_H + E_O/B_O + C_O/Y_O + Y_O/Z + A_O/C_O + B_O/D_H$
Gulo	W,C,D	$A_O/W_O + E_O/B_H + W_O/C_O + D_O/Z + A_O/C_O + B_H/D_O$

Table XXVI

Differences in Non-bonded Interactions between the Isomeric Aldohexopyranose Pentaacetates in the Transition States

Transition States Compared	Differences in Non-bonded Interactions	Relative Stabilities $H_r^{\ddagger} - H_s^{\ddagger}$
4. Gluco - manno	$A_O/W_O - A_O/W_H + E_O/B_H - E_O/B_O$ + $W_O/X_O - B_O/X_O - B_O/D_H$	-380
5. Gluco - allo	$W_O/X_O - W_O/C_O + X_O/Y_O - C_O/Y_O$ - A_O/C_O	-1060
6. Gluco - galacto	$X_O/Y_O - X_O/D_O + Y_O/Z - D_O/Z$ - B_H/D_O	420
7. Gluco - altro	$A_O/W_O - A_O/W_H - E_O/B_O + E_O/B_H$ + $W_O/X_O + X_O/Y_O - C_O/Y_O$ - $A_O/C_O - B_O/D_H$	2200
8. Gluco - gulo	$W_O/X_O - W_O/C_O + X_O/Y_O + Y_O/Z$ - $D_O/Z - A_O/C_O - B_H/D_O$	0

have values of 180 cals./mole in the transition states. This assumption is supported by the facts that β-D-talopyranose pentaacetate anomerizes at about the same rate as β-D-galactopyranose pentaacetate and β-D-glucopyranose pentaacetate at about the same rate as β-D-mannopyranose pentaacetate. Thus, it is apparent that the 2,4-diaxial interaction between acetoxy groups in the talose derivative plays no rôle in determining its reactivity. This suggests that the interatomic distance between these two substituents remains unchanged on the compound passing from the ground state to the transition state.

Application of these assumptions and the differences in the stabilities of the transition states given in Table XXVI, to the expressions for the differences in non-bonded interactions yields the following results.

In the case of the transition states for the glucose and mannose derivatives, a difference in stability of -180 cals. per mole would be expected as compared with a difference of -380 cals./mole determined experimentally.

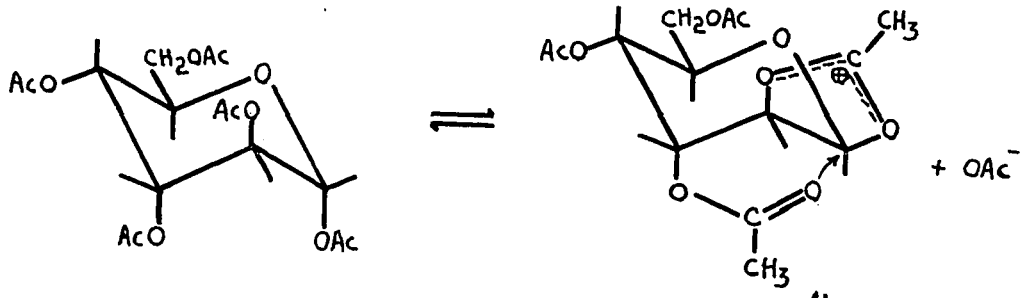
From the difference in the stabilities of the transition states for the glucose and allose derivatives, A_0/C_0 is expected to have a value of 1060 cals./mole. This interaction for 1,3-diaxial acetoxy groups is considerably less than that for the corresponding interaction in the ground state. On the basis of the model for the transition state, this result is not unexpected since the distance between these groups is increased substan-

tially on going from the ground state to the transition state.

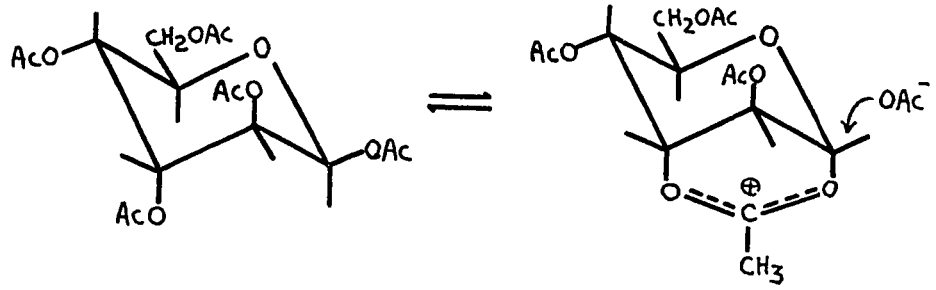
Proceeding to the galactose data, $Y_0/Z - D_0/Z$ is expected to be about 600 cals./mole. If these values for A_0/C_0 and $Y_0/Z - D_0/Z$ are now applied for an estimation of the difference in stability between the transition states of the glucose and gulose derivatives, a value of 640 cals./mole is calculated for the skew unteraction X_0/Y_0 which is in good agreement with the value, 540 cals./mole, found for the interaction between skewed acetoxy groups in the ground state.

Now, if the skew interaction W_0/X_0 is assumed to have a value equal to that $X_0/Y_0 = 640$ cals./mole, a difference in stability between the transition states for the glucose and altrose compounds of -600 cals./mole would be expected. As a matter of fact, the transition state for the altrose derivative was found to be 2200 cals./mole more stable than that for the glucose pentaacetate. This clearly either discredits this attempt to rationalize the relative rates of reaction or the altrose derivatives undergo anomerization by way of a different mechanism. A change in mechanism is, in fact, not unlikely in view of the unique configuration for this compound which has both the acetoxy groups at positions 2 and 3 in axial orientation. In view of this configuration and the established facts that 1,2-trans sugar acetates are known to undergo rapid dissociation of the 1-acetoxy group with the participation of the 2-acetoxy group and that an axial 3-acetoxy group can be expected to behave similarly, it

is probable that the anomerization of the altrose derivatives proceeds by way of the intermediate 1,2- and 1,3-bridge ions, (XCVII)and(XCVIII), respectively.



XCVI XCVII



XCIX XCVIII

In this respect, it is noteworthy that the formation of oxazoline and oxazine rings from 2-acylamido and 3-acylamido compounds, respectively, is well established (145). Also, as shown earlier, evidence was presented on page 108 that 3-β-D-glucosamine pentaacetate undergoes dissociation of the 1-acetoxy group with the participation of the 3-acetamido group. Thus, there can be little doubt that the participation of an axial 3-acetoxy group is feasible.

C. The Reaction of Base-catalyzed Anomerization of the D-Glucopyranose Pentaacetates

Although Lewis acids are generally used as the catalyst in the anomerization of the acetylated sugars, Wolfrom (158) has noted a variant of this reaction wherein the beta anomer of the mannose, galactose and lactose acetates were anomerized by the action of dry sodium hydroxide in dioxane. Lindberg (159) used ascarite in pyridine to convert the β-D-glucopyranose pentaacetate into the alpha anomer.

Our interest in studying this reaction was to explore the possibility, although unlikely, that the base might have abstracted the proton from the anomeric center. If this were the case, then the disaccharides could be anomerized with base catalyst. In order to test this possibility, β-D-glucopyranose-1-d pentaacetate was prepared and anomerized by the action of crushed sodium hydroxide. Had the deuterium atom been abstracted by the base from carbon 1, then there would be an exchange of the deuterium from the sugar molecule and the proton from the base catalyst. The proton on the carbon 1 has a unique signal in the proton magnetic resonance spectrum, which is completely absent in the spectrum for the β-D-glucopyranose-1-d pentaacetate. Therefore, any deuterium-proton exchange can be recognized easily from the spectrum of the product. However, the experimental result demonstrated that there was no deuterium-

proton exchange. Consequently, the base did not abstract the proton from carbon 1 in the anomerization process.

A 1-deuteroacetoxy-β-D-glucopyranose tetraacetate was prepared and, likewise, anomerized by the action of the base. From the proton magnetic resonance spectrum as shown in Fig. 15, it was estimated that about one-third to one-half of the deuteroacetoxy group had been exchanged during the course of anomerization. This result, although interesting, does not allow any conclusion regarding to the mechanism of the reaction. Attempts to anomerize the β-D-glucopyranose pentaacetate with base catalyst in the presence of 2,3,4,6-tetraacetyl α-D-glucopyranose which was labelled with carbon-14 in the glucose unit in order to test the possibility of trans-esterification were unsuccessful due to the difficulties encountered in the isolation of a pure product. This reaction was not further investigated.

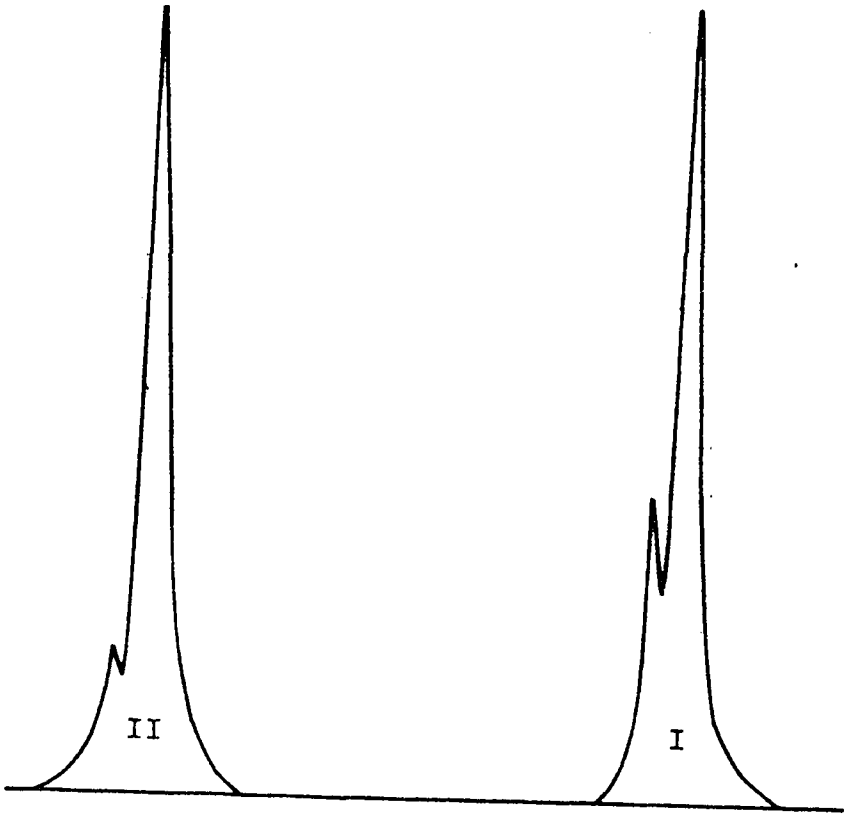


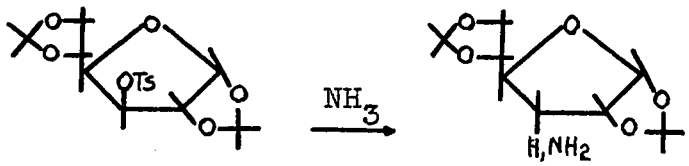
Fig. 15. Proton Magnetic Resonance Spectra of the Acetoxy Groups in α-D-Glucopyranose Pentaacetate (I), and the α-anomer Obtained from the Base-catalyzed Anomerization of 1-Deuteroacetoxy β-D-Glucopyranose Tetraacetate (II).

THE CHARACTERIZATION OF 1,2:5,6-DIISOPROPYLIDENE-3-DEOXY-3-AMINO-α-D-ALLOFURANOSE (PART TWO)

I. INTRODUCTION

The discovery of 3-D-glucosamine (3-deoxy-3-amino-D-glucose) as a component of the new antibiotic kanamycin (128) renewed ~~the~~ interest in this compound. Several preparations of the amino-sugar had been reported but its configuration has not been rigorously established.

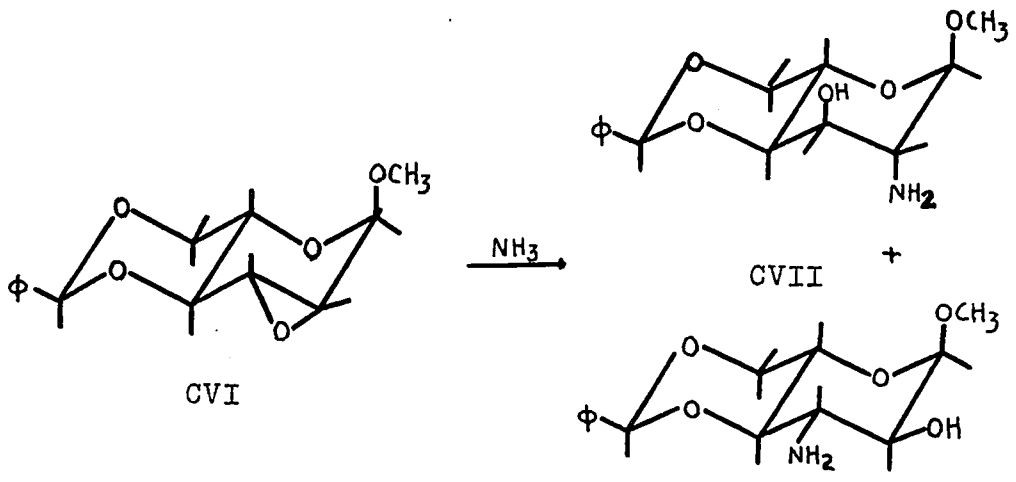
Freudenberg et. al. (160), in 1926, found that ammonolysis of 1,2:5,6-diisopropylidene-3-tosyl-α-D-glucofuranose (CIV) replaced the tosyloxy group by the amino group.



CIV CV

Hydrolysis of the isopropylidene groups gave a syrupy 3-D-hexosamine sulfate. These authors were unable to ascertain whether or not inversion of configuration on carbon 3 occurred during the replacement reaction.

Peat and Wiggins (127), in 1938, treated methyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside (CVI) with ammonia to obtain two amino-sugar derivatives, one (CVII) with the altro-configuration in 90% yield and the other (CVIII) with the gluco-configuration. These authors reported that the physical constants of some derivatives of the latter compound were identical with those reported by Freudenberg et. al. for



CVI

CVII + CVIII

their syrupy hexosamine. Thus, the ammonolysis product of Freudenberg was characterized as 1,2:5,6-diisopropylidene-3-α-D-glucosamine and reported as such in all handbooks of carbohydrate chemistry. With proper modification of Freudenberg's method, this amino-sugar can be prepared in fair yield and it seems to provided an attractive route to synthesize the 3-D-glucosamine.

However, Cope and Shen (161) pointed out that Walden inversion should occur in the direct replacement of a tosyloxy group by ammonia and, consequently, the product obtained by Freudenberg should have D-allose configuration.

The object of this work was to establish the configuration of the 3-hexosamine prepared by Freudenberg.

II. EXPERIMENTAL

1,2:5,6-Diisopropylidene-3-Deoxy-3-Hydrazino-α-D-Allofuranose (CIX):

The 1,2:5,6-diisopropylidene-3-deoxy-3-hydrazino-α-D-allofuranose was prepared in 60% yield using Freudenberg's procedure (162) which involves refluxing 1,2:5,6-diisopropylidene-3-tosyl-α-D-glucofuranose with anhydrous hydrazine.

1,2:5,6-Diisopropylidene-3-deoxy-3-Amino-α-D-Allofuranose (CX):

A solution of 3.0 g. of (CIX) in 60 ml. of 95% ethanol was hydrogenated overnight with Raney nickel catalyst at a temperature of 80° and a pressure of 40 lbs. per sq. in. After the removal of catalyst, the solution was evaporated to dryness under reduced pressure. This left a crystalline crude product which was recrystallized from chloroform-ether.

Yield, 2.36 g. (83%); m. p. 92-93°;

$[\alpha]_D^{32}$ 37.1 (c, 2.5 in chloroform).

Reported m. p. 92-93°; $[\alpha]_D^{18}$ 40.5 (in $C_2H_4Cl_4$) (160).

1,2:5,6-Diisopropylidene-3-Deoxy-3-Acetamido-α-D-Allofuranose (CXI):

One gram of (CX) was acetylated with acetic anhydride in pyridine. The product was isolated in the usual way and re-

crystallized from ether.

Yield, 1.0 g. (86%); m. p. 127-128°;

$[\alpha]_D$ 71.3 (c, 2 in chloroform).

Anal. Calc'd for $C_{14}H_{23}O_6N$: C, 55.80; H, 7.69; N, 4.65.

Found: C, 55.87; H, 7.73; N, 4.85.

1,2-Isopropylidene-3-Deoxy-3-Acetamido-α-D-Allofuranose (CXII):

Two hundred mg. of (CXI) was heated in two ml. of 0.2 N hydrochloric acid on the steam bath for two hours. The solution was cooled and neutralized with dilute sodium hydroxide. N-acetylation was accomplished by addition of 0.5 ml. of acetic anhydride. The solution was left at room temperature for four hours and, then, deionized by passing through a column containing mixed ionic exchange resin (15 x 160 mm., Dowex 4 and Amberite IR-120H). The column was eluted with one liter of water. Evaporation of the solvent under reduced pressure left a colorless syrup which crystallized after storage in the refrigerator, ca. 4°, for three days.

Yield, 50 mg. (29%); m. p. 145-150°.

Two recrystallizations from ethanol raised the m. p. to 154-156°.

Anal. Calc'd for $C_{11}H_{19}O_6N$: C, 50.56; H, 7.33; N, 5.36.

Found: C, 50.25; H, 7.44; N, 5.29.

Periodate Oxidation of 1,2-Isopropylidene-3-Deoxy-3-Acetamido-α-D-Allofuranose:

Preliminary periodate oxidation study of (CXII) was carried out using Beckman DK-2 recording spectrophotometer to determine the concentration of the periodate ion which has an absorption peak at 222 mμ (163) and a molar extinction coefficient ε, 13,500.

Two mg. of (CXII) was dissolved in 5.0 ml. of 0.01 M sodium metaperiodate solution. After certain period of time, a 1.0 ml. aliquot of the solution was diluted to 100 ml. with water and the concentration of the periodate ion was determined with the UV spectrophotometer.

It was found, in this way, that compound (CXII) consumed one mole equivalent of sodium metaperiodate and the reaction was complete within few minutes.

1,2-Isopropylidene-3-Deoxy-3-Acetamido-α-D-Ribofuranose Acetate (CXV):

To a solution of twelve mg. of (CXII) in two ml. of water was added eleven mg. (one mole equivalent) of sodium metaperiodate. After ten minutes, an excess of sodium borohydride (ca. 10 mg.) was added and the solution was left overnight at 4°. The excess sodium borohydride was destroyed with a drop of glacial acetic acid. The residue from the evaporation of the solution under reduced pressure was acetylated with acetic anhydride in pyridine. The product was isolated in the usual way and recrystallized from ethanol.

Yield, 5 mg. (40%); m. p. 158-160°.

3-D-Ribosamine Hydrochloride (CXVI):

The crystalline product (CXV), five mg., was hydrolyzed by heating with N hydrochloric acid at 80° for three hours. The solution was, then, evaporated to a dry syrup to which two drops of concentrated hydrochloric acid was added. The resulting solution was seeded with 3-D-ribosamine hydrochloride*. Two mg. (60% yield) of a crystalline product was obtained. The infrared spectrum (KBr disc) and x-ray diffraction pattern were identical with that of an authentic sample.

This compound has no melting point. Under polarized light, the crystals lost their birefringence at around 160°. However, it did not melt up to 270°. The same behavior was observed with the authentic sample.

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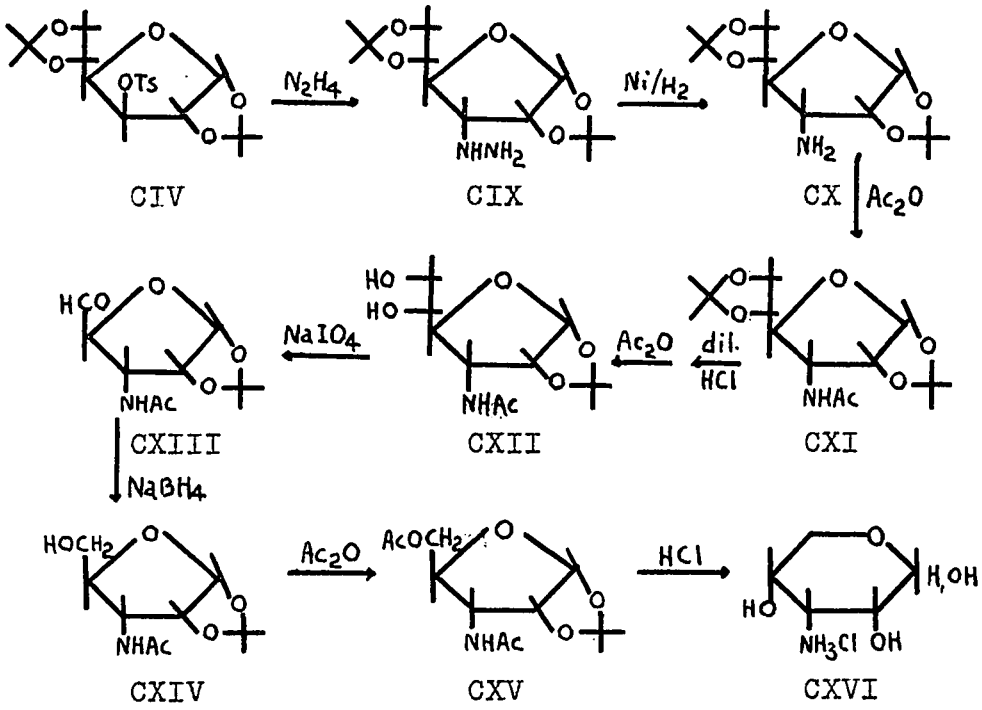
* The authentic sample was obtained from the Bristol Research Laboratories Inc., Syracuse, N. Y.

III. DISCUSSION OF RESULTS

Direct ammonolysis of 1,2:5,6-diisopropylidene-3-tosyl-α-D-glucofuranose (CIV) resulted in extensive degradation of the compound and, consequently, gave a low yield (16%) of the amino-sugar. On the other hand, hydrazinolysis of (CIV) in boiling anhydrous hydrazine took place smoothly with 60% yield. The conversion of the hydrazino-sugar to the corresponding amino-sugar was accomplished by hydrogenation with Raney nickel catalyst to give an 83% yield of a pure product with the same melting point and rotation reported for the compound obtained by the direct ammonolysis.

The configuration of the amino-sugar thus prepared, was established by degradation to the known 3-D-ribosamine hydrochloride (CXVI). This was accomplished by taking advantage of the fact that the 5,6-isopropylidene group is more susceptible to hydrolysis in dilute acid than the 1,2-isopropylidene group. Periodate oxidation of the partially hydrolyzed product (CXII) cleaved the 5,6-glycol and yielded an aldehydo-compound (CXIII) which was reduced to the pentose derivative (CXIV) with sodium borohydride. The reduced product was acetylated in order to get a crystalline intermediate (CXV) which was hydrolyzed with hydrochloric acid to the known 3-D-ribosamine hydrochloride. 3-D-ribosamine is a constituent of the antibiotic puromycin and has been synthesized by Baker (164). Their identity was characterized by infrared spectrum and x-ray diffraction pattern.

This established unequivocally that compound (CX) has the D-allose configuration and direct replacement of a tosyloxy group on a secondary carbon atom by hydrazine or ammonia involves Walden inversion.



These results establish beyond doubt not only the identity of 3-D-allosamine but also that of the epimeric 3-D-glucosamine. The 6-deoxy-6-amino-D-glucose and 3-deoxy-3-amino-D-glucose samples prepared in Part I of this work were the reference samples for the identification of these compounds as the products of the hydrolysis of the new antibiotic kanamycin.

APPENDIX

The anomeric effect has been interpreted on the basis of dipole-dipole interactions (cf. p. 101). Such interactions would result in reduced dipole moment for the stable anomer. The dipole moment of a few anomeric pairs have been determined. In all cases, the thermodynamically stable anomer has a higher dipole moment than its anomer (see Table XXV). Since the polyacetates contain so many polar groups within the molecule, it is not surprising that the molecular dipole moment has no correlation with the anomeric effect. Owing to the partial free rotation of each acetoxy group, a theoretical calculation of the molecular dipole moment is rather difficult. An estimation can be made. However, such a treatment does not afford any useful conclusion to the experimental results.

For the purpose of keeping a permanent record, the dipole moments measured are listed in Table XXVII.

Table XXVII

Dipole Moment of Acetylated Aldopyranoses

Aldopyranose Pentaacetate	Total Polarization	Electronic Polarization	Dipole Moment Debye units
β-D-Gluco	233.8	83.3	2.69
α-D-Gluco	392.9	83.3	3.86
β-D-Manno	230.5	83.3	2.66
α-D-Manno	299.3	83.3	3.22
β-D-Galacto	303.7	83.3	3.25
α-D-Galacto	316.3	83.3	3.34

Note: The dielectric constants of the samples were measured in benzene solution.

CLAIMS OF ORIGINAL RESEARCH

1. A quantitative conformational analysis of the acetylated aldopyranoses was made and the following interaction energies were obtained.
   (a) The anomeric effect.
   (b) The skew interaction between two acetoxy groups.
   (c) The diaxial interaction between an acetoxy group and a hydrogen atom.
   (d) The diaxial interaction between two acetoxy groups.
2. The anomeric effect was interpreted on the basis of dipole-dipole interaction between the carbon 1 to 1-substituent bond and the carbon 5 to ring-oxygen bond.
3. The polar effect of the 5-substituent on anomerization equilibrium was investigated.
4. Evidence was obtained that the 2-deoxy-2-acetamido- amd 3-deoxy-3-acetamido-D-glucopyranose tetraacetates form oxazolinium and oxazinium ions, respectively, under the anomerization conditions.
5. Proton magnetic resonance spectroscopy was found to be applicable in the determination of equilibrium between conformational isomers.
6. It was concluded from the relative stabilities of the transition states that anomerization of the acetylated

aldopyranoses is a bimolecular reaction.

7. A half-chair conformation was suggested for the transition states of the aldopentopyranose tetraacetates and a deformed chair conformation was proposed for the transition states of the aldohexopyranose pentaacetates.

8. Evidence was obtained from the rates of D-altropyranose pentaacetates that an axial 3-acetoxy group participates in the anomerization areaction.

9. A reaction mechanism was proposed for the acid-catalyzed anomerization of the acetylated aldopyranoses.

10. The amino-sugar moieties from the hydrolysis of the new antibiotic kanamycin were identified.

11. The configuration of 1,2;5,6-diisopropylidene-3-deoxy-3-amino-α-D-allofuranose was established.

12. The following sugar derivatives have been prepared for the first time.

    (a) α-D-ribopyranose tetraacetate,

    (b) 3-tosyl-α-D-glucopyranose tetraacetate,

    (c) 1-deuteroacetoxy-α- and β-L-arabopyranose triacetate,

    (d) 1-deuteroacetoxy-α- and β-D-glucopyranose tetraacetates,

    (e) α- and β-D-glucopyranose-1-d pentaacetates,

    (f) 3-deoxy-3-acetamido-β-D-glucopyranose tetraacetate,

    (g) 6-deoxy-6-acetamido-α- and β-D-glucopyranose tetraacetates.

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