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CONFORMATIONAL PREFERENCES FOR SOLVATED HYDROXYMETHYL GROUPS IN HEXOPYRANOSE STRUCTURES

BY

© JOHN T. BREWER

A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled,

CONFORMATIONAL PREFERENCES FOR SOLVATED HYDROXYMETHYL GROUPS IN HEXOPYRANOSE STRUCTURES

submitted by John T. Brewer, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

The effects that solvent and temperature have on the conformational preference of the hydroxymethyl function at C5 of hexopyranose structures were investigated. The molecular rotations of model compounds, 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol and 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol, were compared to those of the carbocyclic analogs, optically active *trans*- and *cis*-2-hydroxymethylcyclohexanol. Where possible, infrared spectroscopy and nuclear magnetic resonance spectroscopy supplemented the investigations.

In the case of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol, intramolecular hydrogen bonding of the C6 hydroxyl function to the ring oxygen predominates in the aprotic solvent, 1,2-dichloroethane. However, intramolecular hydrogen bond formation between the C6 and C4 hydroxyl functions is promoted by the addition of small amounts of dimethyl sulphoxide. In water, or in pure 1,2-dimethyl sulphoxide, the conformation in which the C6 and C4 hydroxyl functions oppose each other appears to be of minimal importance. The conformation of 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol that has the C6 hydroxyl function *syn*-axial-like to the C4 hydroxyl function appears to be favoured in 1,2-dichloroethane and possibly even in water.

The effects that solvent and temperature have on the $^{1}\underline{C}_{4} \rightleftarrows {}^{4}\underline{C}_{1}$ conformational equilibrium of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose were also studied. It was found that a small amount of a *para*-substituted pyridine base in a 1,2-dichloroethane solution of this diol is able to promote the formation of an intramolecular hydrogen bond between the opposing hydroxyl functions of the $^{1}\underline{C}_{4}$ conformation. This ability increases with increases in the basicity of the substituted pyridine.

ACKNOWLEDGEMENTS

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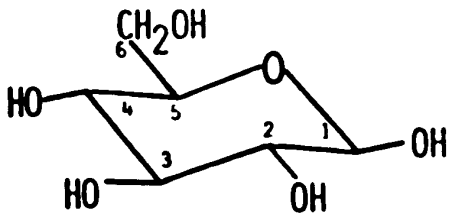
INTRODUCTION

1. Objectives of this study

Conformation: "The non-identical arrangement of the atoms in a molecule, obtainable by rotation about one or more single bonds." (1)

One of the milestones of modern chemistry has been the correlation of the physical and chemical properties of simple organic molecules with their preferred conformations (2, 3, 4). Texts are available that are devoted entirely to conformational analysis and which provide a comprehensive treatment of the subject (1, 5). The conformation and composition of monosaccharides in solution has been reviewed recently by Angyal (6). Other saturated heterocyclic compounds have been surveyed and reviewed by Eliel (7) and Riddell (8).



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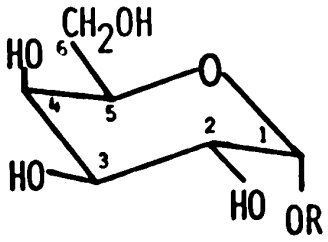

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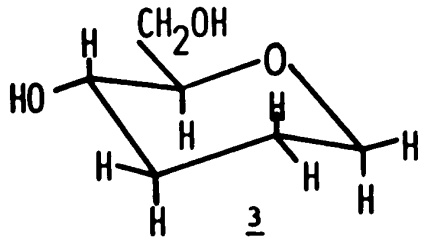
Hexopyranoses - e.g., β-D-glucopyranose (1), and hexopyranosides - e.g., α-D-galactopyranosides (2), are compounds which are of fundamental importance in carbohydrate chemistry. Their exocyclic C6-O6 bond has three

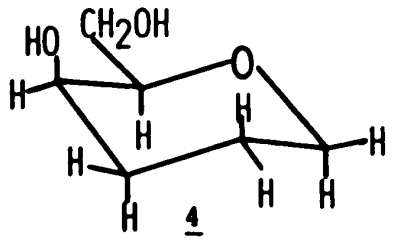
orientations in which it defines the ideal minimum-energy dihedral angles of +60°, -60° or 180° with the bonds between neighbouring atoms. Considering only *vicinal* effects on the relative populations of these so-called staggered conformations, two situations are encountered; the one existing for compounds that have a 4,5-*erythro* configuration and the other for compounds with a 4,5-*threo* configuration. These are illustrated in Figure 1.

A major portion of this discussion will deal with the orientations of the exocyclic C-O bonds of compounds 3, 4, 5 and 6 in different solvent systems. The molecular rotations, $[M]_D^t$, and where possible, the infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra of these compounds, supplied the data that will be discussed.



3

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol



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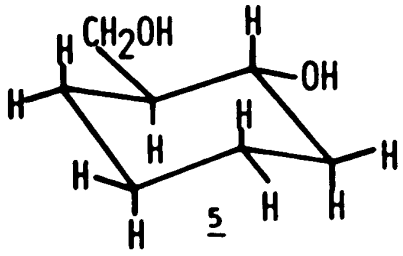
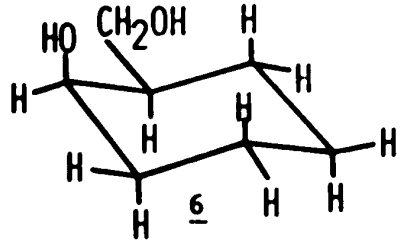
1,5-Anhydro-2,3-dideoxy-D-*threo*-hexitol



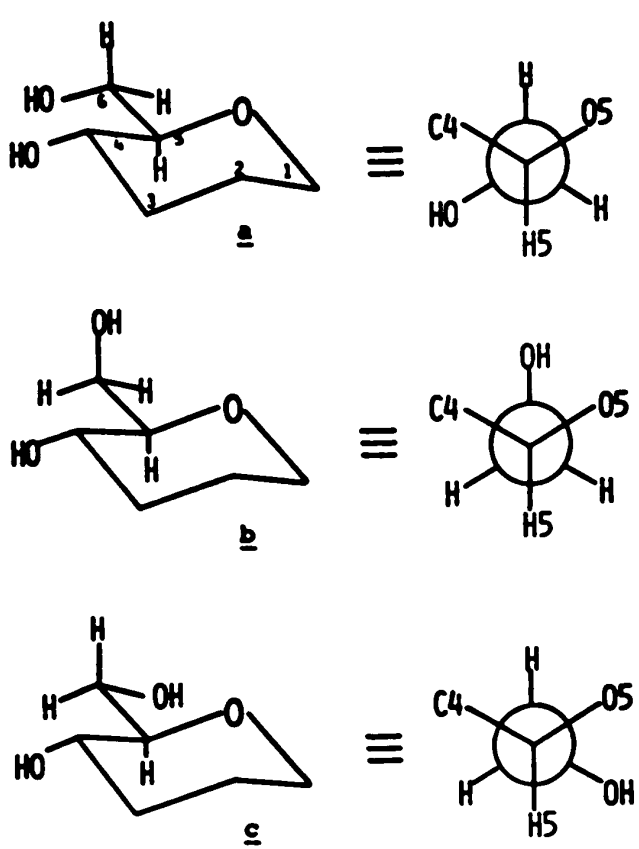
5

(1R,2S)-(-)-*trans*-2-Hydroxymethylcyclohexanol



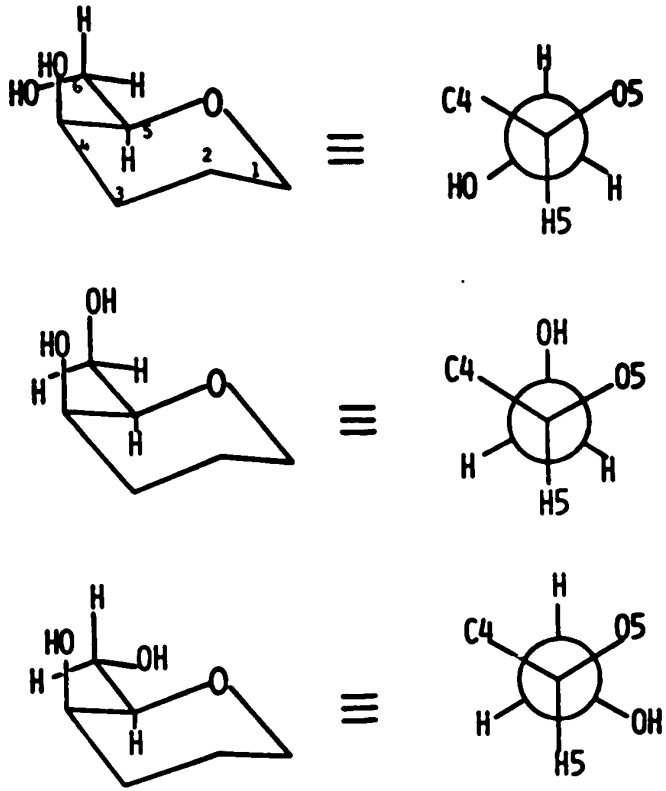
6

(1R,2R)-(-)-*cis*-2-Hydroxymethylcyclohexanol



a b c

The a, b and c rotamers of compounds with 4,5-D-*erythro* configurations.



The a, b and c rotamers of compounds with 4,5-D-*threo*-configurations.

Fig. 1: Staggered orientations of the hydroxymethyl functions of pyranose and pyranoside structures.

In order to achieve a deeper understanding of the role that hydrogen bonding plays in determining the conformational distributions of these four compounds, the first portion of the discussion will deal with the effects of changes in temperature and solvent on the chair-chair equilibrium position of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose, (7). The molecular rotations of 7, in different solvent systems and at different temperatures, supplied the data used in the analysis.

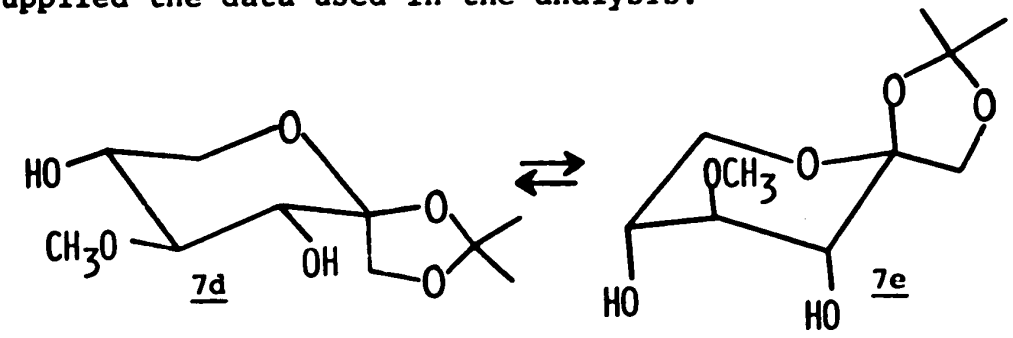


Fig. 2: The chair conformations of 1,2-*O*-isopropylidene -4-*O*-methyl-β-D-sorbopyranose (7)

Conformational analysis that is based on measurements of the average of the individual conformational values of a specific physical property requires a measurement or an accurate prediction of the magnitude of that property for each of the contributing conformers. Therefore, if optical rotation is to be a useful tool for the conformational analysis of a molecule in solution, values are required for the optical rotation of each of the individual conformations.

The structures of compounds 3 to 6 are sufficiently simple that the molecular rotations of their important conformations can be predicted. A variation of the rules (9 - 19) that have been developed for the *a priori* calculation of the molecular rotations of simple pyranoses, pyranosides, and substituted cyclohexanes or tetrahydropyrans, can be used for this purpose.

The molecular rotations of the chair conformers of compound 7 can not be predicted in this way because of the uncertain contributions of the dioxolane ring. Fortunately, there are only these two conformers that need to be considered for solutions of 7, and it will be shown how their molecular rotations can be experimentally determined.

At this point, it is appropriate to discuss the current concepts of the relationship between the optical rotations and the molecular structures of simple saturated compounds that contain only carbon, hydrogen and oxygen atoms.

2. Optical activity and molecular structure

a) Atomic asymmetry

The asymmetric carbon atom in Fig. 3 is substituted by four different substituent atoms or groups of atoms whose capacities for polarization decrease in the order

A > B > D > E

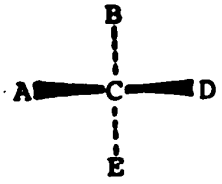


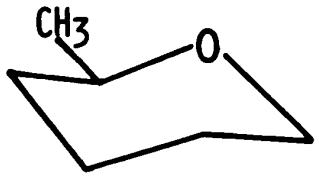
Fig. 3: A single asymmetric carbon centre

Theoretically, these substituent atoms, in the configuration shown, can be described as forming a left-handed screw of polarizability and should produce a dextrorotatory contribution to molecular rotation (11).

Each asymmetric carbon atom in a fully saturated compound containing only carbon, hydrogen and oxygen must be connected either to two carbon or to two oxygen atoms. Contributions to the total molecular rotation from such individual centres of atomic asymmetry, acting independently of one another, are considered to be small. Referring to such compounds Whiffen states that "contributions, referring to asymmetric centres are negligible, i.e., contribute less than 20 to the molecular rotation." (10). Brewster says, "We are in no position to evaluate the atomic asymmetry but could now suggest that it be neglected until it can be shown to be large enough to require attention." (14).

R-(+)-2-Methyltetrahydropyran (8) is a molecule whose rotation may be caused entirely by pure atomic asymmetry. Lemieux and Martin (9) have reported that its

molecular rotations, in a variety of solvents, are less than 5°.



R-(+)-2-Methyltetrahydropyran

8

To summarize, the individual asymmetric carbon centres in compounds considered in this thesis will make a small but not necessarily negligible contribution to their molecular rotations. These contributions are independent of conformational geometry and will therefore be independent of conformational distributions.

b) Conformational asymmetry

The molecular rotations of saturated and conformationally restricted molecules are often much larger than are expected from consideration of the individual centres of optical activity alone. In fact, the rotations of saturated cyclic compounds are for the most part a result of conformational asymmetry.

The three-bond (4 atom) chains in Fig. 4 are examples of asymmetric conformational units. It can be shown

that such units can give rise to optical activity and that the magnitude of the optical activity is a function of the sine of the dihedral angle (14). The units that are considered in this thesis originate in staggered conformations where ϕ is ideally 60°, -60°, or 180°. The value of a unit for ϕ = 60° is of course equal but opposite to its value when ϕ = -60°. The units are symmetrical when ϕ = 180° and make no contribution to optical activity. The four atoms comprising a unit may be any of C, H, or O, subject to the bonding restrictions of organic molecules.

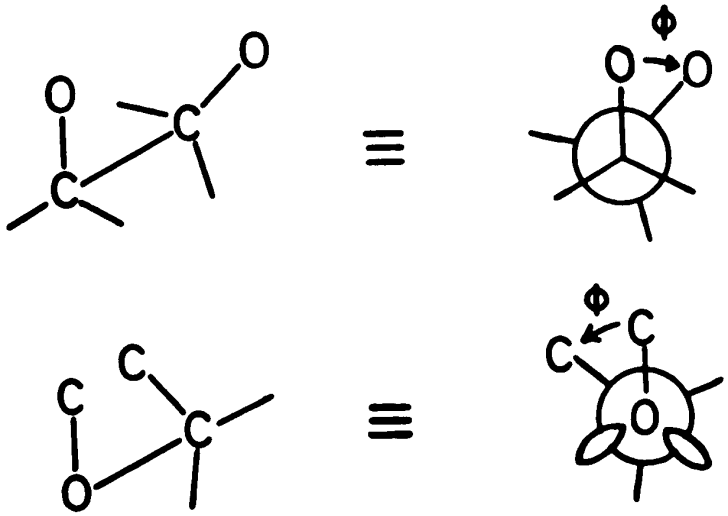
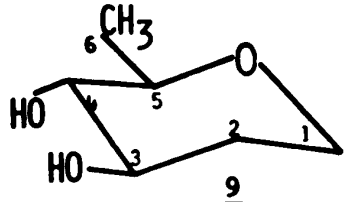


Fig. 4: Examples of three-bond units of conformational asymmetry, defining torsional angles of ϕ°

c) Whiffen's empirical rules

In 1956 Whiffen (10) showed empirically that the observed rotations of cyclitols and pyranoid carbohydrates

can be expressed solely in terms of the sum of all of their contiguous three-bond asymmetric units, exclusive of those that terminate in O-H (i.e. C-C-O-H). This latter type may be neglected if, in his words "all three potential minima which arise from rotation about the C-OH bond are of equal depth, or if terms involving hydrogen atoms are small." Then he states that "both conditions are approximately met". An example of how a molecule is broken down into these units is presented in Fig. 5, for 1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol (9).



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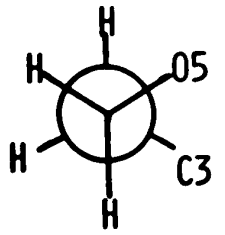
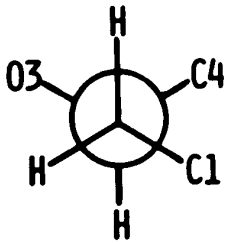
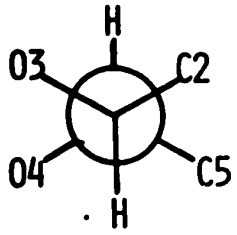


$[M_1]$: along C1-C2 $-O|H+C_r|O-C_r|H+H|H-H|H+H|H$

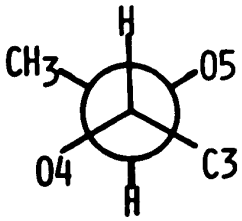


$[M_2]$: along C2-C3 $+C_r|H-C_r|C_r+C_r|H-H|H+O|H-O|H$

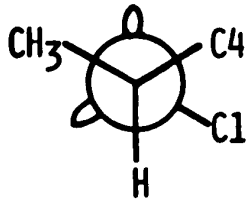
continued.....

$[M_3]$: along C3-C4 

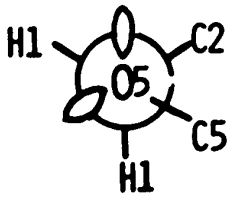
$-C_r|H+C_r|C_r-C_r|H+O|H-O|O+O|H$

$[M_4]$: along C4-C5 

$+O_r|H-C_r|O_r+C_r|H-O|H+O|C-C|H$

$[M_5]$: along C5-O5 

$+C_r|\bar{C}_r-\bar{C}_r|H$

$[M_6]$: along O5-C1 

$-\bar{C}_r|C_r+\bar{C}_r|H$

The expected molecular rotation of compound 9 equals $\sum_{i=1}^{6}[M_i]$, or (O|C-C|H-O|H+H|H)-(O|O-2O|H+H|H). This difference is defined as H-F and equals -11°. (see Table 1). The observed rotation of 9, in water and at 25°C, is -14.5° (see p. 89).

Fig. 5: The breakdown of the conformational asymmetry of 1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol (9)

TABLE 1

Structural contributors to the molecular rotations of pyranoid carbohydrates and polyhydroxycyclohexanes; a comparison of Whiffen's and Brewster's parameters

Whiffen's Parameters			Brewster's Parameters	
Notations	Symbol	Empirical value, in units of $[M]_D$	Notation	Empirical value, in units of $[M]_D$
O|O-2O|H+H|H	F	+ 45°	k(O-H)(O-H)	+ 45°
O_g|O-O_g|H-O|H+H|H	G	+ 32°	k(O-H)(O-H)	+ 45°
O|C-C|H-O|H+H|H	H	+ 34°	k(C-H)(O-H)	+ 50°
O_r|O-C_r|O-O_r|H+C_r|H	I	+ 43°	Permolecular asymmetry	+ 60°
$\bar{C}_r$|O_g-$\bar{C}_r$|H+C_r|H_r -C_r|O_g+O_g|H-H|H	J	+113°	Permolecular asymmetry	+100°
$\bar{C}_r$|C-$\bar{C}_r$|H+C_r|H-C_r|C +C|H-H|H	K	*ca.* -29°	-	-
		-	k(C-H)(C-H)	+ 60°

O_g ≡ a glycosidic oxygen

O_r ≡ a ring oxygen

C_r ≡ a ring carbon

These tabulated units could be arranged in terms of the six parametric groupings listed in Table 1. These parameters make a distinction between ring oxygens, glycosidic oxygens and hydroxylic oxygens. They also distinguish a unit that contains a central C-C bond; i.e. O/C ≡ C-C-C-O, from one that contains a central C-O bond; i.e. C_o/O ≡ C-O-C-O.*

The numerical values that Whiffen assigned to these six parameters are empirical and gave the best fit to experimental values for molecular rotations at the sodium D line, 5893A°, of solutions of polyhydroxycyclohexanes and pyranoid carbohydrates.

He assigned a fixed value of 30° to the contribution from the hydroxymethyl functions of D sugars. This allowance was reversed in sign for the corresponding L series.

Methyl α-D-glycopyranosides were, on the average, 100° more positive, and methyl-β-D-glycopyranosides 100° more negative than the corresponding free sugar. These values were reversed for the "L" series.

---

* Whiffen used the symbol $\bar{C}|O$ for C_o/O, and $\bar{C}|C$ for C_o/C.

d) Brewster's interpretation of optical activity

In 1959 Brewster published an analysis of the optical rotation of organic molecules (11, 12, 13) that applied to a wide range of cyclic and acyclic compounds.

Once again, combinations of asymmetric three-bond units were considered to be basic structural contributors to optical rotatory power. Brewster, like Whiffen, did not distinguish between the three rotameric positions of O-H bonds; both considered hydroxyl functions as a single unit. In contrast to Whiffen, Brewster did not differentiate hydroxylic oxygen atoms from glycosidic and ring oxygen atoms, and consequently required only three parameters to define the conformational asymmetry that originates in asymmetric four-atom chains. These, with the structural features that give rise to each of them, are:

k(O-H)(O-H), generated by two *gauche* oxygen atoms

k(O-H)(C-H), generated by *gauche* oxygen and carbon atoms

k(C-H)(C-H), generated by two *gauche* carbon atoms

The first of these, k(O-H)(O-H), which is related to the F and G parameters of Whiffen, was assigned to the empirically derived value of 45°. The second term, k(C-H)(O-H), was given a value of 50°, using data from hydroxysteroids and terpenols. This compares favourably with the observed rotation of *trans*-2-methylcyclohexanol, now known

to be 49° (in methanol) (20). He assigned an empirical value of 60° to k(C-H)(C-H), using data obtained from saturated optically active alkanes.

The exocyclic C6-O6 bond of D-hexopyranoses was assigned the empirically determined contribution of +25°. He considered the geometries of two of the rotameric orientations of this bond and noted that "the positive sign of this value is consistent with the smaller size of the ether oxygen as compared to C4 *and its substituents*." (12).

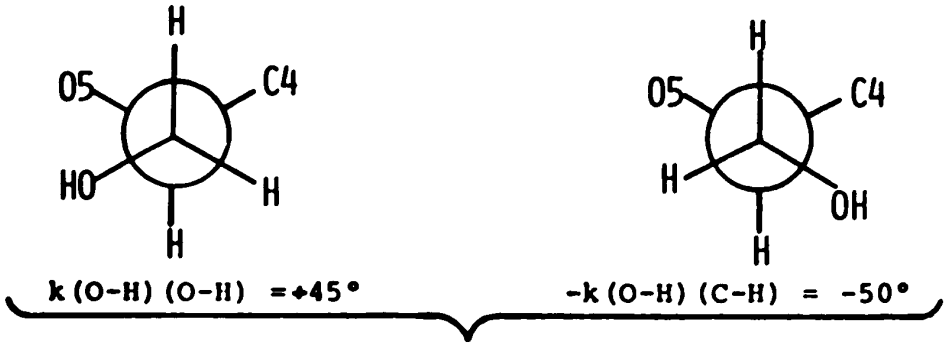


Fig. 6: The "allowed" orientations of the C6-O6 bond of D-hexopyranoses, according to Brewster (12)

Brewster pointed out that the presence of axial hydroxyl groups at C1, C2 and C4 of a pyranoid ring gave rise to additional rotatory power. This was taken to be the result of the asymmetric positioning of C3, the ring oxygen, the axial OH function and the axial H atom that opposes it. Brewster referred to this as a permolecular

pattern, and he assigned values of ±60°, and ±100° to the partial structures that are illustrated in Fig. 7. These terms replaced Whiffen's I and J parameters.

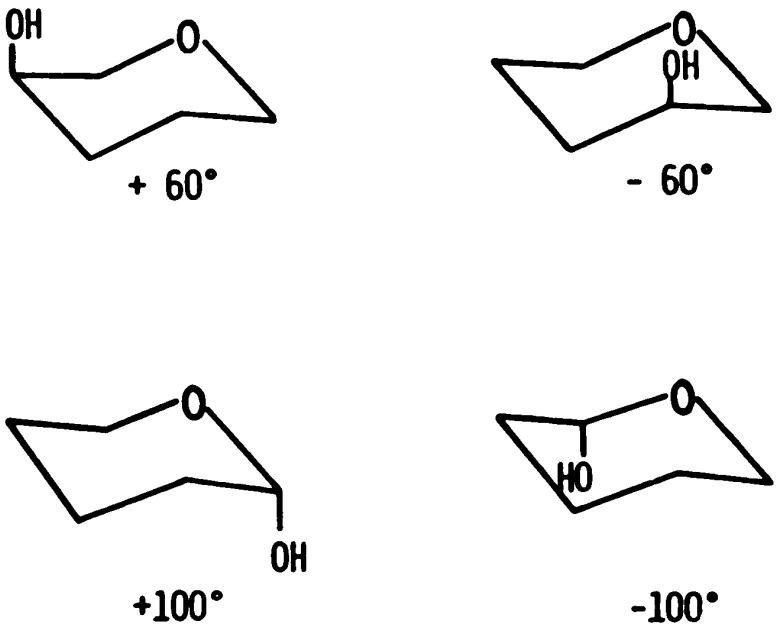


Fig. 7: Partial structures exhibiting permolecular asymmetry, with empirical rotatory powers that were assigned to them by Brewster (12).

e) Yamana's proposals

Yamana (15, 16, 17) has developed a set of rules for the analysis of the optical activity of molecules. His treatment is theoretically based on Kirkwood's quantum mechanical study of the optical activity generated by the pairwise interaction of terminal atoms of asymmetric bond chains (21). He has calculated theoretical values for

rotatory powers of these interactions. These values do not in themselves give good estimates of observed rotation, but must be multiplied by empirically obtained correction factors (16).

Yamana's treatment of this subject is extensive and detailed, but is not easy to simplify for routine predictions of molecular rotation.

f) The empirical rules of Lemieux and Martin

Lemieux and Martin (9) recently proposed what appeared to be a convenient set of simplified rules for the estimation of the rotatory power of aldopyranoses, methyl aldopyranosides, and polyhydroxycyclohexanes. Molecular rotations were assumed, to a first approximation, to be due to the asymmetry of *gauche*, contiguous three-bond units, the approach that had been taken previously by Whiffen and then partially adopted by Brewster. However, only units having terminal carbon or oxygen atoms were included in the tabulation. Units that terminated in hydrogen or hydrogens were considered to be of negligible importance. In contrast to the procedure of Whiffen, their analysis made no distinction between ring, glycosidic and hydroxylic oxygen atoms. They required only three parameters, which were defined as O/O, O/C and C_o/O. A fourth unit, C_o/C, was required for estimates of the rotations

of methyl ethers of pyranoid compounds. Each of these parameters, which involves only one three-bond unit of conformational asymmetry, is shown in Fig. 8.

They assigned the O/O unit a value of 45°, the same value that Whiffen had used for his F parameter (see Table 1), which defines the same structural feature, although in a more complex manner.

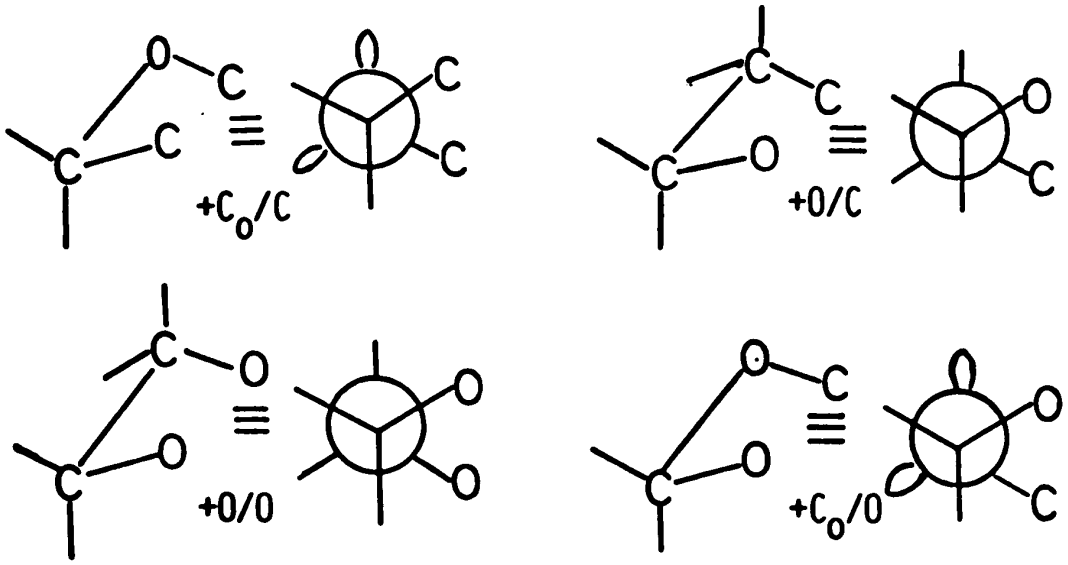


Fig. 8: The rotational parameters of Lemieux and Martin

The dominant rotamer expected for the aglycone function of methyl-α-D-glycopyranosides has the CH_3 group *gauche* to the ring oxygen and *trans* to the C1-C2 bond (22 - 25), an arrangement which defines a C_o/O unit. A C_o/O unit is also defined by the C5-O5 and the C1-O1 bonds in both α-D-pyranoses and α-D-pyranosides, a structural feature which was included in Whiffen's J parameter. The

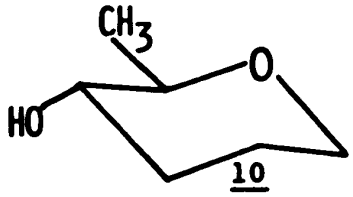
empirical value of 115° that Lemieux and Martin used for these C_o/O units was essentially the same as that value of 113° that Whiffen gave to his J parameter.

The value of 10° that they gave to their O/C unit was much smaller than either the value of 50° that Brewster gave to his corresponding k(C-H)(O-H) parameter, or the value of 34° that Whiffen used for his H parameter. However, this value of 10°, together with the values assigned to the other two units, led to a close correspondence between the observed and predicted rotations of pyranoid carbohydrates, without the necessity for extra "adjusting factors" such as permolecular terms (12) or a distinction between different types of oxygen atoms (10). This value for O/C seemed particularly appropriate in the light of the molecular rotations observed for 1,5-anhydro-2,3,6-trideoxy-D-*erythro*-hexitol (10) and 1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol (9), model compounds with a fixed conformation in water. The rotation that Lemieux and Martin reported for compound 3; +53° in water, also required a small O/C value in order to indicate its expected preference for the 3c conformation.

Unfortunately the purities of compounds 9, 10 and 3, and therefore their rotations, became suspect. These compounds had only been characterized as syrups and may have contained small amounts of optically active impurities, which could have led to completely misleading

rotations. In addition, residual solvents, if present, would have resulted in numerically low rotations.

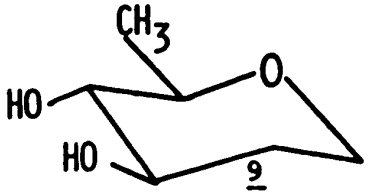
For this project, a correct estimate of the value of the C/O and the O/O rotational parameters was necessary in order that the rotations of conformers of compounds with an exocyclic hydroxymethyl function could be analyzed. Therefore, it was decided to resynthesize compounds 3, 9 and 10, using techniques that would ensure their optical purities. This has been done as a part of this project and it is now apparent that the +O/C unit that is contained in these compounds has a value of +45°; a result which requires modifications to the general set of parameters proposed by Lemieux and Martin. These adjustments have been incorporated into the procedure for evaluation of molecular rotations that will be used in this thesis (see p. 150).



10

$[M]_D$ predicted: +C/O

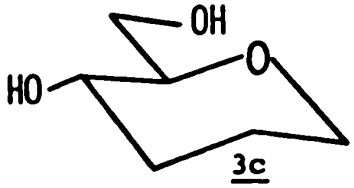
$[M]_D$ observed: +14° in water (9)



9

$[M]_D$ predicted: +C/O-O/O

$[M]_D$ observed: -32° in water (9)



3c

$[M]_D$ predicted: +C/O+O/O

$[M]_D$ observed: +53° in water (9)

3. Intramolecular hydrogen bonds involving hydroxyl functions

a) General considerations

The strong and specific interaction known as the hydrogen bond can have a profound influence on the conformation adopted by hydroxylated compounds.

The structure of a general hydrogen bond can be represented by the notation A-H···B. For hydrogen bonds discussed in this thesis, A-H is a hydroxylic O-H function. If this O-H is intramolecularly bonded, B will be either a hydroxyl-type or else an ether-type oxygen. When O-H is intermolecularly hydrogen-bonded to a solvent molecule, B will be either the sulphoxide oxygen of dimethyl sulphoxide (DMSO), or the nitrogen atom of a pyridine ring.

The electronic nature of hydrogen bonds has been the topic of considerable discussion (26 - 34). Pimentel has compared strong hydrogen bonding in symmetrical species such as $(FHF)^-$ to the three centre covalent hydrogen bridge bond in diboranes (29). The controversy over the electronic structure of weak hydrogen bonds - that is, types that will be studied in this thesis - concerns the amount and the nature of covalent bonding between A-H and B.

The simplest electrostatic model considers only the interactions of the point charge dipole moments of the

A-H and the B functions. The dipoles themselves are not considered to be altered as a result of hydrogen bond formation. More sophisticated electrostatic models take account of the distribution of electron densities of the σ bond orbital linking A and H, and the non-bonded lone-pair electrons of B. A realistic extension of the simple electrostatic approach considers that polarization of electronic densities results because of the proximity of the A-H and B dipoles. This additional, and induced electrostatic energy has been considered as an important contributor to hydrogen bond formation (33).

The valence bond concepts of the hydrogen bond replace or supplement the idea of induced, or polarization energy, with delocalization energy that is introduced *via* contributions that are made to the wave function by canonical forms iv and v (Fig. 9) (30). Bratoz has applied a charge transfer theory to O'··H-O systems which allows a degree of dative covalent bonding between the lone-electron-pair of O' and the antibonding O-H orbital (28).

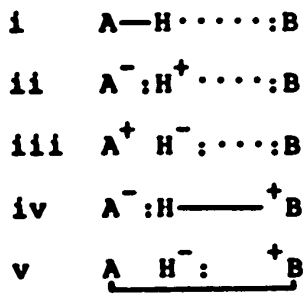
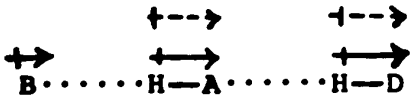


Fig. 9: Valence bond structures for the A-H...B hydrogen bond

It is generally concluded that simple fixed-dipole interactions do not adequately explain the properties of hydrogen bonds (28 - 34). Some degree of electrostatic polarization and/or charge transfer is necessary. The physical result of either of these concepts will be a shift of electron density along the B···H-A system, towards A.



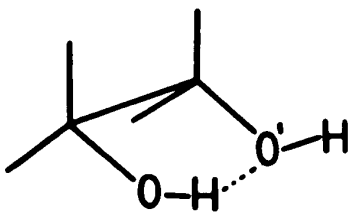
permanent dipoles: ⟷

dipoles that result from transferred electron densities: ⇢

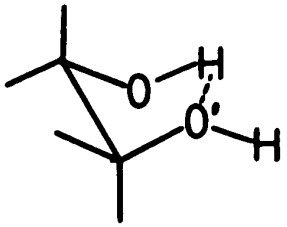
Now consider the situation in which A is involved as the lone-electron-pair donor in the hydrogen bond system H-A···H-D. The transferred charge (or induced dipole) in the vicinity of H-A that is set up on formation of a hydrogen bond with B results in an additional electrostatic stabilization of the A····H-D bond. Lemieux and Pavia (35) have noted that "*such hydrogen-bond conjugation* can conceivably be of importance as a force which originates in an anionic centre for the organization of macromolecules into specific conformations as are known to exist for proteins and nucleic acids. Certainly, the results require the proton-accepting power of a solute in aqueous solution to be extended by this *hydrogen-bond conjugation* to influence the structure of the water beyond its immediate environment."

b) Infrared spectroscopy and intramolecular hydrogen bonding

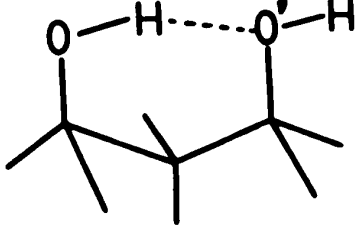
Intramolecular hydrogen bonding of hydroxyl functions of saturated *vicinal* diols and hydroxyethers will be termed 1,2-type hydrogen bonding in this thesis. Unless structurally incapable of doing so, such compounds form 1,2-type bonds only in staggered conformations, so that the two C-O bonds are *gauche* to each other. (Fig. 10, ii). The energy required to overcome the torsional strain of the eclipsing conformation (Fig. 10, i) would be greater than the stability gained by hydrogen bond formation. Exceptions to the *gauche* geometry of 1,2-type hydrogen bonds occur for compounds in which the two C-O bonds are structurally restricted to, or forced towards the eclipsed geometry (36, 37).



i. eclipsed 1,2-type hydrogen bonding



ii. *gauche* 1,2-type hydrogen bonding



iii. 1,3-type hydrogen bonding

Fig. 10: The geometries of intramolecular hydrogen bonds.

Two 1,3-substituted hydroxyl functions can form an intramolecular hydrogen bond in which the two C-O bonds are coplanar, without introducing any torsional strain.* This, as well as bonding between 1,3-substituted OH and OR functions, will be referred to as 1,3-type hydrogen bonding. A simplified electrostatic approach to calculations of the O-H···O' bond strength predicts that this strength will increase as the O-H bond becomes colinear with one of the electron-lone-pair orbitals of O' (34), an arrangement that is more closely approached with 1,3-type bonds than it is with 1,2-type bonds that have the *gauche* geometry.

Infrared spectroscopy has been extensively used to study these types of intramolecularly hydrogen-bonded hydroxyl functions (38). Using concentrations of diols in carbon tetrachloride that were low enough to suppress intermolecular hydrogen bonding, Kuhn (39, 40) reported that the infrared (i.r.) spectra of many diols contained two OH absorption bands in the 3500-3650 cm^{-1} region. The stretching frequencies of the hydrogen-bonded O-H (A-H) bonds occurred at lower wavenumbers than those of the remaining free O-H (B) bonds. The differences in the two frequencies were reported as frequency shifts, $\Delta\nu_{OH}$, in cm^{-1}.

---

* There is, of course, non-bonded steric interaction energy between the two opposing oxygen atoms.

Other workers (41) obtained frequency shifts by subtracting the O-H bonded frequency from that of a free OH group in a structurally equivalent position in a suitable reference compound. The qualitative interpretation of the size of $\Delta\nu_{OH}$ is not affected by the method of calculation that is chosen.

It is generally accepted that the strength of the general hydrogen bond, A-H····B, is related to the size of the frequency shift of the A-H bond from that of a free A-H bond. (29, 42, 43). Kuhn (39, 40) noted that the $\Delta\nu_{OH}$ of an intramolecularly bonded hydroxyl group was related to the separation, L, in A°, of the proton of O-H from the centre of the second oxygen atom, O', by the empirical formula:

$$\Delta\nu_{OH} = (\frac{250}{L} - 74)\,cm^{-1}$$

For L greater than 3.3A°, the Kuhn equation predicts that intramolecular hydrogen bonds do not form.

Normal values for $\Delta\nu_{OH}$ of 1,3-type hydrogen bonds, in carbon tetrachloride, vary somewhat according to the nature of the compound, but in general lie between 70 and 130 cm^{-1}. The values for $\Delta\nu_{OH}$ that are observed for 1,2-type hydrogen bonds are smaller. They usually do not exceed 50 cm^{-1} unless structural factors can hold the two hydrogen bonded functions in a semi-eclipsed or eclipsed conformation

(see *endo-* and *exo-cis*-2,3-bicyclo [2.2.1] heptanediol, Table 2).

Most of the i.r. studies that have been done on intramolecular hydrogen bonding have been conducted in carbon tetrachloride (40). This so-called inert solvent is not expected to form a complex with hydroxyl functions and therefore should not effect their hydrogen bonding patterns. Frequency shift values, $\Delta\nu_{OH}$, measured in carbon tetrachloride do not necessarily apply to other solvents. Allerhand and von R. Schleyer (44) have done an extensive study of this solvent effect and report that the free hydroxyl stretching frequencies, the bonded hydroxyl stretching frequencies, and therefore $\Delta\nu_{OH}$ are solvent dependent. They believe, however, that 1,2-dichloroethane and carbon tetrachloride may be used interchangeably as solvents with little effect on the values of $\Delta\nu_{OH}$. Data, to follow in the next chapter, will show that this appears to be true for 1,3-type hydrogen bonds, but not for 1,2-type bonds.

Foster and his co-workers (45, 46) have used i.r. spectroscopy to study intramolecular hydrogen bonds in a wide range of tetrahydropyran, tetrahydrofuran and dioxane structures. They have also studied the relative intensities of the hydroxyl stretching absorptions of acyclic diols and hydroxyethers and report that the formation of conformations

TABLE 2

The hydroxyl group stretching frequencies

(ν_{OH}, in cm^{-1}) in the infrared spectra of certain diols

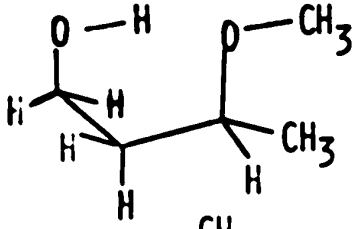
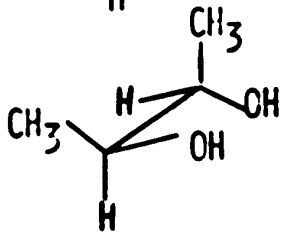
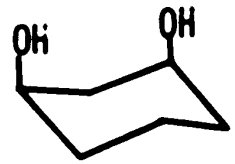
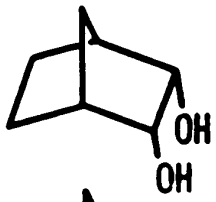
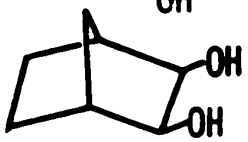
Compound	ν_{OH} "free"	ν_{OH} bonded	$\Delta\nu_{OH}$	L, in A°	Solvent	Ref.
	3634	3602	32	2.34	CCl_4	40
	3626	3587	39	2.34	CCl_4	40
	3640	3536	104	1.62	CCl_4	44
	3608	3508	100	1.62	$ClCH_2CH_2Cl$	44
	3633	3591	42	2.34	CCl_4	36

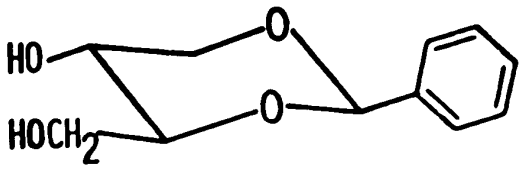
TABLE 2 (Continued)

Compound	ν_{OH} "free"	ν_{OH} bonded	$\Delta\nu_{OH}$	L, in A°	Solvent	Ref.
	3619	3544	75	1.62	CCl_4	40
	3633	3531	102	1.4	CCl_4	37
	3633	3529	103	1.4	CCl_4	37

that contain a 1,2-type hydrogen bond is preferred to the formation of conformations that contain a 1,3-type hydrogen bond (47).

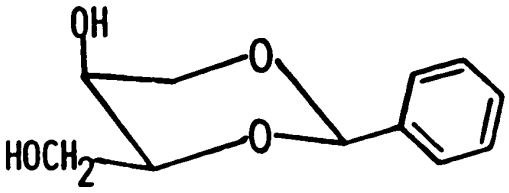
This preference, also reported by Kuhn (48), is partially statistical in the case of compounds that are able to form 1,2-type bonds in either of two energetically similar *gauche* conformations. In addition, the steric interaction energies of the hydrogen-bonded conformations must be considered along with the actual hydrogen bond strengths in any analysis of conformational preference. Whereas hydrogen bond strengths are probably greater for 1,3-type than for 1,2-type bonds (as their larger values of $\Delta\nu_{OH}$ indicate), conformations that contain a 1,3-type hydrogen bond are in part destabilized by steric interactions between the opposing C-O bonds (Fig. 10,iii). In terms of free energy, therefore, it is not surprising that a conformation that is intramolecularly hydrogen-bonded by *gauche* hydroxyl functions should be preferred to one that is stabilized by a hydrogen bond between opposing 1,3-substituted hydroxyl groups.

Foster extended his studies to include compounds 11, 12, 13 and 14, in which both 1,2-type and 1,3-type hydrogen bonding was possible (49, 50).



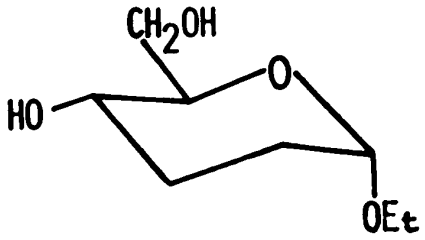
1,3-*O*-Benzylidene-L-erythritol

11



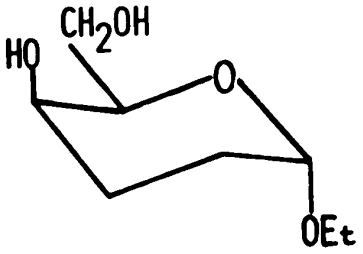
1,3-*O*-Benzylidene-L-threitol

12



Ethyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside

13



Ethyl 2,3-dideoxy-α-D-*threo*-hexopyranoside

14

The orientations that the hydroxymethyl functions of 1,3-*O*-benzylidene-L-erythritol (11) and 1,3-*O*-benzylidene-L-threitol (12) adopt in carbon tetrachloride were apparent from the hydrogen bond absorptions of their i.r. spectra. Foster reported that compound 11 had a strong absorption at 3644 cm^{-1}, which he assigned to a free hydroxyl group. The moderate absorption at 3614 cm^{-1}, shifted by 30 wavenumbers, was assigned to a 1,2-type hydrogen bond between the primary hydroxyl group and O3. The third, weaker absorption, at 3565, with a $\Delta\nu_{OH}$ of 79 cm^{-1},

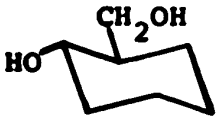
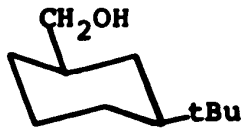
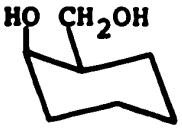
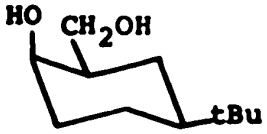
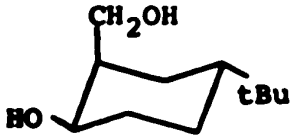
was assigned to a 1,3-type bond between the hydrogen of the primary hydroxyl function and the oxygen atom of the secondary hydroxyl group at C2.

The *threo* isomer, 1,3-benzylidene-L-threitol (12), also had a free hydroxyl absorption at 3644 cm^{-1}, but of much lower intensity than that of 11, the *erythro* compound. There were two stronger bonds that corresponded to 1,2-type hydrogen bonds. The one with $\Delta\nu_{OH}$ of 21 was assigned to a hydrogen bond between the primary hydroxyl group and O3, and the one with $\Delta\nu_{OH}$ of 54 to a hydrogen bond between the secondary hydroxyl group and one or both of the ring oxygens. There was a weak absorption at 3565 cm^{-1} ($\Delta\nu$ = 99) that was assigned to a 1,3-type hydrogen bond between the two hydroxyl functions. The authors note that "the large $\Delta\nu$ value associated with the last absorption may arise because the secondary hydroxyl group is bonded to the ring-oxygen atoms which would make its oxygen atom more basic and hence a better proton acceptor ..." (49). Certainly, the low intensity of the free hydroxyl absorption in the spectrum of 12 is evidence that cumulation of the intramolecular hydrogen bonds occurs when compound 12 adopts the conformation shown below in Fig. 11. However, by comparison with the more recent observations of frequency shifts of the bonded hydroxyl functions of 2-hydroxymethylcyclohexanols, listed in Table 3, there does not now appear to be anything unusual about the shift of 99 cm^{-1} that Foster reported for 12.

TABLE 3

Infrared spectral data for

2-hydroxymethylcyclohexanols, in carbon tetrachloride

Compound	ν_{OH} max (cm^{-1})			Ref.
	Free Primary OH	Free Secondary OH	Bonded OH	
	3638 (sh)*	3623	3525	51
	3631	3622	3537	38**
	3642 (sh)*	3628	3538	51
		3631	3541	38**
		3625	3548	38**

* shoulder: the greater part of the primary OH function is assumed to be hydrogen-bonded to the oxygen atom of the secondary OH function

** listed only as "unpublished observations by Sicher" in Ref. 38

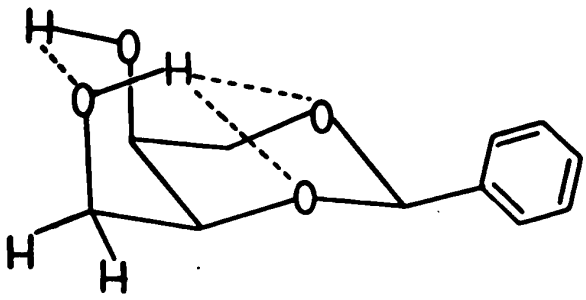


Fig. 11: Cumulation of intramolecular hydrogen bonds in 1,3-*O*-benzylidene-L-threitol (12).

The intensities of the hydroxyl stretching frequencies of ethyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside in carbon tetrachloride allowed Foster to make deductions on the preferred orientation of its hydroxymethyl function (50). There was an absorption for the free secondary hydroxyl group and absorptions for the primary hydroxyl group, hydrogen-bonded principally to the ring oxygen atom (cf. conformations 13b and 13c in Fig. 12), and, to a smaller extent, to the oxygen atom of the secondary hydroxyl group (conformer 13a in Fig. 12).

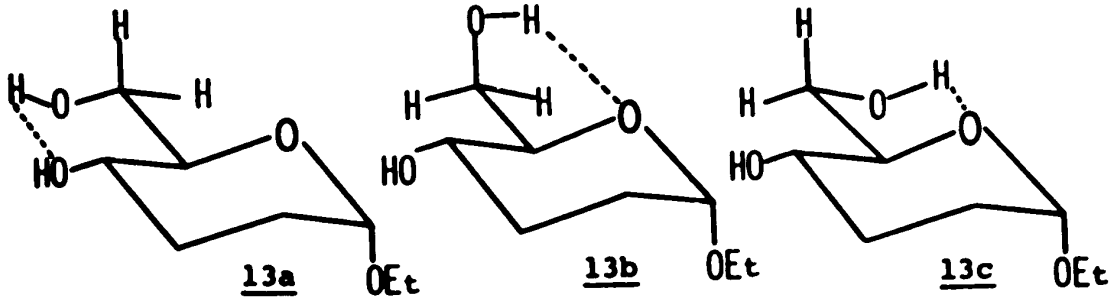


Fig. 12: The three principal conformations of ethyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside in carbon tetrachloride.

The *threo* isomer, ethyl 2,3-dideoxy-α-D-*threo*-hexopyranoside(14)had strong absorptions at 3596 cm^{-1} and 3527 cm^{-1} that were respectively assigned to 1,2-type and 1,3-type hydrogen-bonded hydroxyl functions. The amount of free hydroxyl absorption, at 3630 cm^{-1}, was less than that of the *erythro* isomer and is referred to by Foster as "weak". The anomeric effect of the axial aglycone function in carbon tetrachloride (22, 23, 24) and the preference of the CH_2OH function for the equatorial conformation restrict 14 to the $^4C_1$ conformation. The small free hydroxyl absorption can be accounted for by proposing cumulated hydrogen bond arrangements, such as in 14b and 14b', or a conformation such as 14b" in which both hydroxyl functions are simultaneously bonded to the ring-oxygen atom.

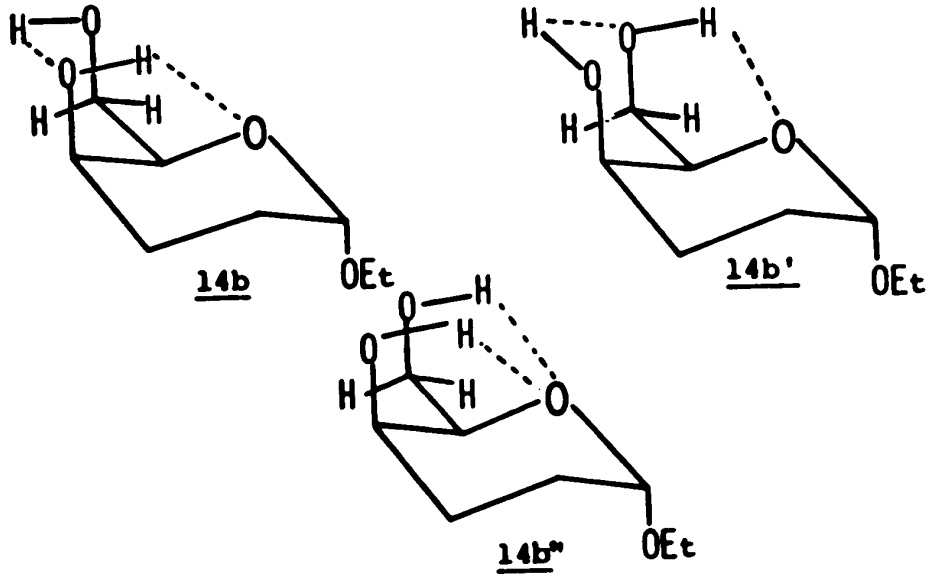


Fig. 13: Possible cumulated intramolecular hydrogen bonds in ethyl 2,3-dideoxy-α-D-*threo*-hexopyranoside (14)

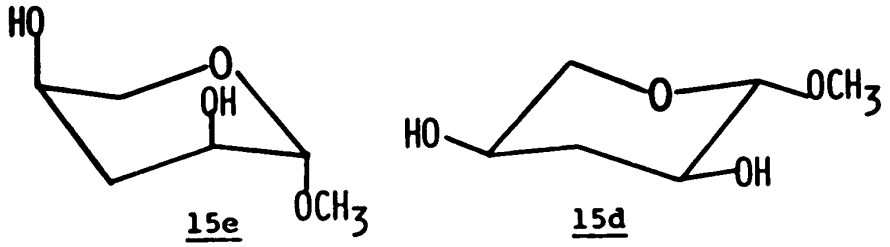
Values of $\Delta\nu_{OH}$, which are a measure of hydrogen bond strength, should increase if the strengths of individual hydrogen bonds are increased because of cumulation, i.e. if hydrogen bond conjugation occurs. It is, however, difficult to predict the magnitude of such an increase. The frequency and the frequency shift of the 1,3-hydrogen-bonded hydroxyl group of compound 14 (3527 cm^{-1}, $\Delta\nu_{OH}$ 103) are not substantially different from the corresponding values of *cis*-2-hydroxymethylcyclohexanols (cf. Table 3). Therefore, if the 1,3-type hydrogen bond energy of 14 has been increased because of the cumulated hydrogen bond arrangement made possible by the ring oxygen, the effect that this has had on the frequency and frequency shift is not significant. The absence of such an effect was cited earlier, in the discussion of compound 12. One can only say, with reference to the i.r. spectra and the structures of these two compounds, 12 and 14, that cumulation, but not necessarily conjugation, of intramolecular hydrogen bonds occurs.

4. Applications of molecular rotation to conformational analysis

Analyses of conformational equilibria that are based on the observed rotation of simple saturated compounds of carbon, oxygen and hydrogen have not, until recently, been very common. The chair-chair equilibrium positions of

optically active *cis*-2-methylcyclohexanol (12,16), 1,2/3,5 and 1,2,5/3-cyclohexanetetrol (52), and 1,2/3,4-cyclohexanetetrol (53) have been interpreted from their observed rotations in solution and the predicted rotations of their chair conformers. Foster (49) used Whiffen's rules in order to study the chair-chair equilibrium positions of the ethyl hexopyranosides discussed on page 29. More recently, Tocanne used optical rotation to study the conformational equilibria of 1,3-dioxanes (54).

Lemieux and co-workers have discussed the relationship of the optical rotations of certain pyranosides and tetrahydropyran derivatives to the nature of the solvent (9,22,35,55,56). For example, they demonstrated that the different optical rotations that were observed for solutions of methyl 3-deoxy-β-L-*erythro*-pentopyranoside (15) in different solvents resulted "almost exclusively" from changes in its chair-chair equilibrium position (35,56). Using Brewster's rules, they calculated the molecular rotation for each of the chair conformers of 15. They were then able to use the observed rotations of this compound to calculate the percentages of its two conformations in the different solvents. These percentages were in accordance with percentages that they calculated using values of $J_{1,2}$ that were taken from corresponding n.m.r. spectra in the various solvents.



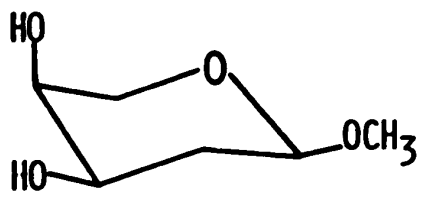
15e 15d

Fig. 14: The chair conformations of methyl 3-deoxy-β-L-*erythro*-pentopyranoside (15)

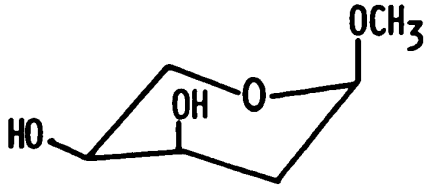
The 15e conformation predominated in chloroform, stabilized by both the anomeric effect (22, 23, 24) and by intramolecular hydrogen bonding between the two hydroxyl functions. When they used pure solvents, that formed intermolecular hydrogen bonds with the hydrogens of the two hydroxyl groups (such as water, DMSO, and pyridine), the n.m.r. and optical rotation data showed that compound 15 preferred the 15d conformation. Lemieux proposed that "hydrogen-bonding of both hydroxyls with the solvent (ROH ··· S) increases the negative charge on the oxygen atoms through polarization of the O-H bond (RO←H←S) to such an extent that the repulsion of the C-O bond dipoles in opposing axial orientation becomes adequately large to force the compound from the 1-C (15e) to the C-1 (15d) conformation." (35).

Methyl 2-deoxy-α-L-*erythro*-pentopyranoside (16) also preferred the intramolecularly bonded conformation,

(16e), in chloroform, and the other chair conformer, (16d), in water (56).

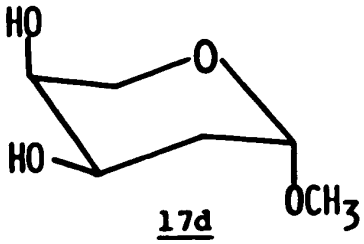


16d

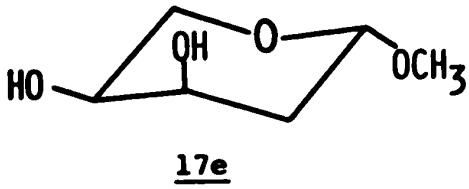


16e

Fig. 15: The chair conformations of methyl 2-deoxy-α-L-*erythro*-pentopyranoside (16)



17d



17e

Fig. 16: The chair conformations of methyl 2-deoxy-β-L-*erythro*-pentopyranoside (17)

The anomeric effect is certainly partially responsible for the stabilization of conformations 15e and 16e in chloroform. There is, however, a weakening of the anomeric effect in water (22) and one might ask to what extent this is responsible for the shift to the 15d or 16d conformations in aqueous solution. That this cannot be the dominant factor was shown by a study of the n.m.r. spectra and optical rotations of methyl 2-deoxy-β-L-*erythro*-

pentopyranoside (17) in water, DMSO and chloroform (56). In all three solvents, the data indicate preference for the 17d conformation. Compound 17 does not, however, have opposing OH and OR functions in either conformation and so the electrostatic repulsion that intermolecular hydrogen bonding with water or DMSO sets up in conformers 16e or 15e cannot occur in this case.

Having established the relationship between the optical activities and the conformational preferences of 15 and 16, Lemieux was able to interpret the changes in the optical activities of these and other intramolecularly bonded compounds that resulted on the addition of dimethyl sulphoxide to their solutions in 1,2-dichloroethane.

The molecular rotation of methyl 4-*O*-methyl-3-deoxy-β-L-*erythro*-pentopyranoside (18) in pure 1,2-dichloroethane indicated that it preferred conformation 18e, which can be stabilized by an intramolecular hydrogen bond between the hydroxyl function at C2 and the methoxyl oxygen atom at C4. As the percentage of dimethyl sulphoxide was increased and, as a result, the percentage of the C2 hydroxyl that was intermolecularly hydrogen-bonded increased, the rotation of 18 decreased smoothly, until in pure DMSO it corresponded to a high percentage of conformer 18d. Lemieux concludes that "repulsion between the C4-OCH_3 group in axial orientation with the C2-hydroxyl hydrogen hydrogen bonded to

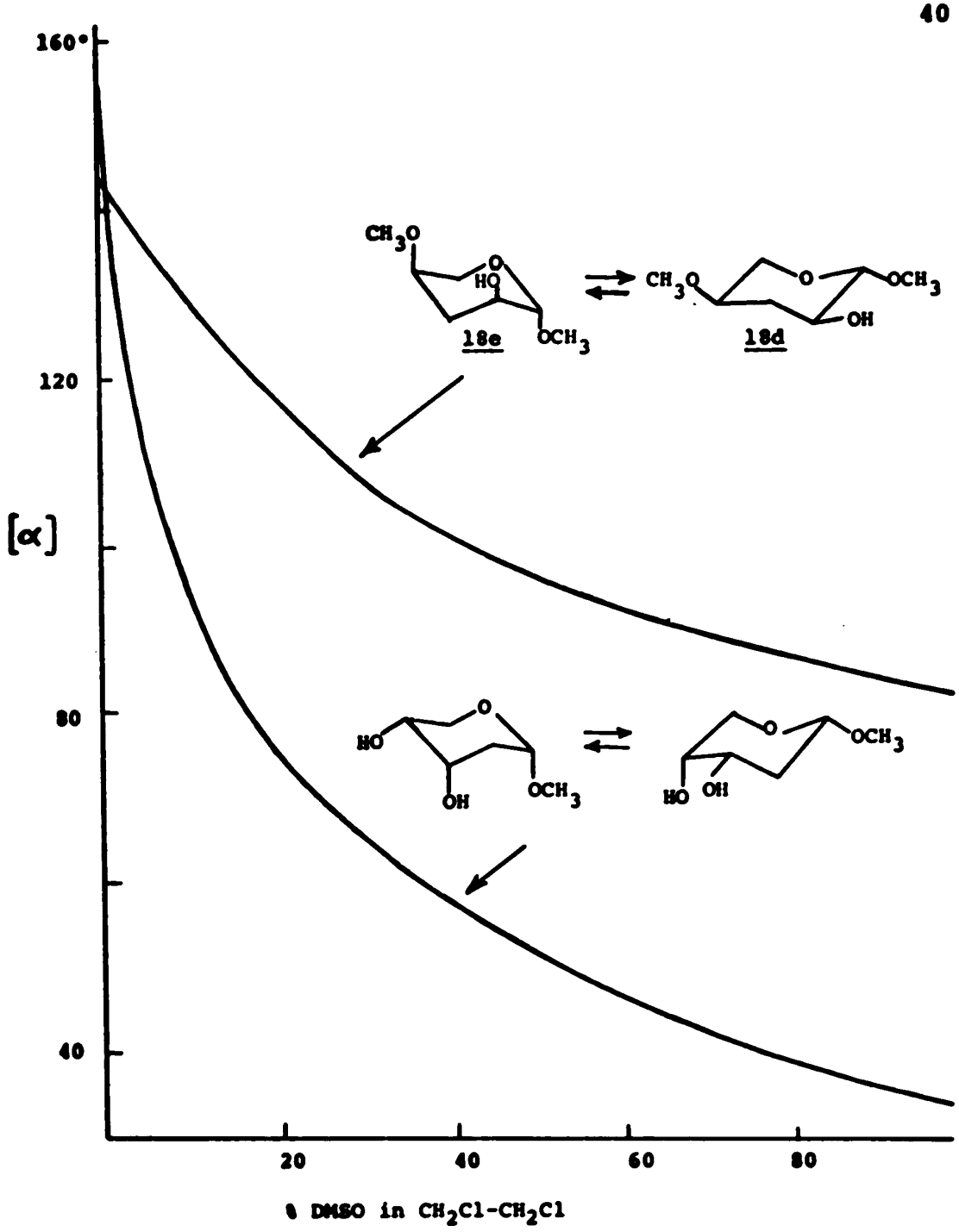
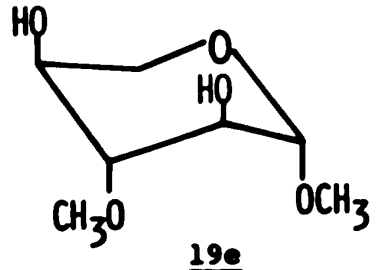


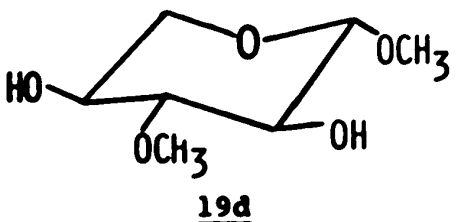
Fig. 17: Plots of the change in specific rotation which occurs with increasing amounts of dimethylsulfoxide for solutions of methyl 4-*O*-methyl-3-deoxy-β-L-*erythro*-pentopyranoside and methyl 2-deoxy-α-D-*erythro*-pentopyranoside in ethylene chloride (35)

dimethylsulphoxide was sufficiently strong to require the 1-C (18d) conformation" (35). This conclusion was supported with n.m.r. data. The plot of the optical rotation of 18 vs the percentage of DMSO in the solvent, referred to in this thesis as a *rotation curve*, is presented in Fig. 17. The rotation curve for methyl 2-deoxy-α-D-*erythro*-pentopyranoside, also presented in Fig. 17, showed that it behaved in a similar manner to 18 in binary solutions of DMSO and 1,2-dichloroethane (35).

The rotation curves for the *cis*-1,3-diols, 15, 7 and 19, required a slightly different interpretation (35, 55). At low concentrations of DMSO (0 to 0.5 molar), their rotations were shifted towards values that were expected for the conformations that permitted a 1,3-type hydrogen bond; i.e. 7e, 15e and 19e. Then, as the DMSO concentrations were further increased, their rotations shifted in the other direction, towards values expected for the conformations in which the two hydroxyl groups were equatorial to the ring.



19e



19d

Fig. 18: The chair conformations of methyl 3-*O*-methyl-β-L-xylopyranoside (19)

Lemieux has proposed the following explanation for these inflected rotation curves. The general hydrogen bonding forms for these 1,3-diols, which can only exist in two conformations, are shown in Fig. 19. In pure 1,2-dichloroethane, the e conformation is stabilized by an intramolecular hydrogen bond between the two hydroxyl functions. At low concentrations of dimethyl sulphoxide, the remaining free hydroxylic proton, H', can enter into an intermolecular hydrogen bond with the oxygen of the sulphoxide function, designated as B. If the optical rotation of the monosolvated e' conformation has the same value as e, then the shift towards this rotation at low concentrations of dimethyl sulphoxide means that $K_2 < K_1$. This in turn means that the intramolecular hydrogen bond that stabilizes this e' conformation has been strengthened by the existence of the intermolecular hydrogen bond between O'-H' and the solvent,B. The probable reason for this "hydrogen bond conjugation" (35), discussed in general terms on pg. 22, is the polarization of the O'-H' bond by the dimethyl sulphoxide.

At higher concentrations, the dimethyl sulphoxide begins to saturate both of the hydroxyl functions with intermolecular hydrogen bonds, and the equilibrium designated by K_3 becomes important. Because of the electrostatic and steric repulsions that occur in structure e", d" is heavily favoured. The optical rotations of such solutions reflect

this increased percentage of the d" conformation.

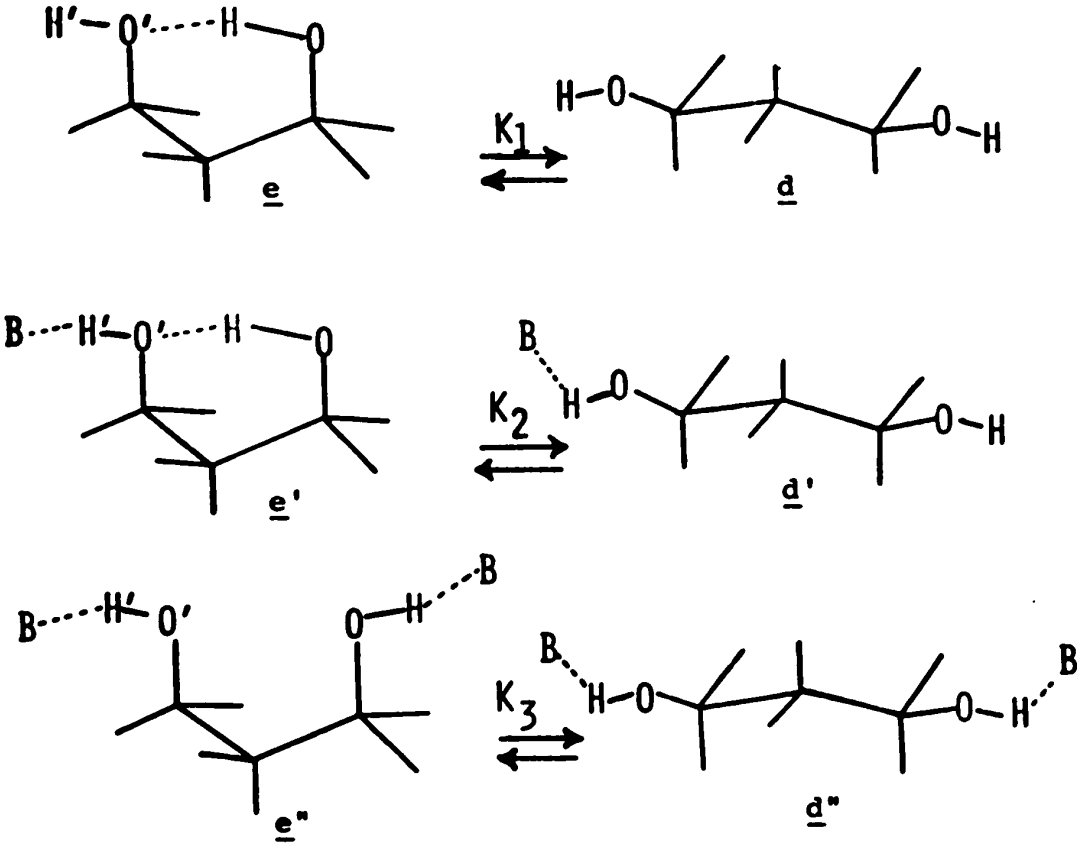


Fig. 19: The intramolecular hydrogen bond patterns of 1,3-diols.

One objective of the present study of compound 7 was to prepare and discuss its rotation curves in 1,2-dichloroethane, using various *para*-substituted pyridines as the hydrogen-bond-accepting base, B . This study shows that the ability of these pyridines to stabilize the intramolecularly hydrogen-bonded conformation of 7 increases with their basicities.

The second objective of the work with 7 was to obtain a deeper understanding of the hydrogen-bonding behaviour of 1,3-diols in binary solutions of 1,2-dichloroethane and a "base" such as DMSO, or pyridine. For this purpose, the rotation curves of 7 were prepared at more than one temperature, using molar concentrations rather than "percentages" (35) of the hydrogen-bond-accepting base. Quantitative thermodynamic values will be assigned to the equilibrium between the mono-solvated 7e' conformation and the di-solvated 7d" conformation.

Lemieux and Martin have also reported an inflected rotation curve for 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) in binary DMSO/1,2-dichloroethane solutions (9). They discussed how this should occur through changes in the orientation of the hydroxymethyl group as the amount of DMSO in the solvent was increased. The three rotameric conformers of 3 are shown below in Fig. 20 along with the molecular rotations that Lemieux and Martin assigned to them using their values for the O/O and C/O parameters, namely, 45° and 10° respectively.

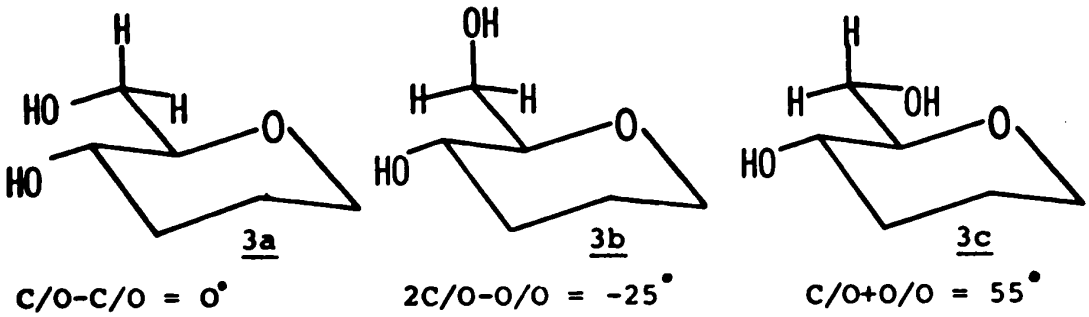


Fig. 20: The three principal conformations of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3), with rotations that were assigned to them by Lemieux and Martin

Compound 3, as they had prepared it, had a rotation of +20° in pure 1,2-dichloroethane which, ignoring the 3b rotamer, corresponded to about equal preference for 3a and 3c. The additions of small amounts of dimethyl sulphoxide to solutions of 3 in dichloroethane decreased this rotation, indicating that the 1,3-type intramolecular hydrogen bond, which is only possible in the 3a conformation, had once again been strengthened. At higher concentrations of dimethyl sulphoxide the rotations of the solutions of 3 became more positive than the original rotation of +20°. In pure DMSO, the rotation had risen to +42°, which was taken as evidence for a high population of conformation 3c.

This rotation work has been repeated, using pure compound 3, as part of this project. Rotation curves for this compound, in binary solutions of 1,2-dichloroethane and DMSO, have been prepared at 15, 25 and 35°C, and will be

discussed, along with similar rotation work with compounds 4, 5 and 6. The effects that the ring oxygen and C4 hydroxyl functions of compounds 3 and 4 have on the orientation of their hydroxymethyl functions can be determined by comparison of the molecular rotations of these compounds with the rotations of their carbocyclic analogs, 5 and 6.

Rotation curves will also be presented for the monomethyl ethers of 3, 1,5-anhydro-2,3-dideoxy-6-*O*-methyl-D-*erythro*-hexitol (20) and 1,5-anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol (21), as well as for the dimethyl ether of 3, 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol (22). These curves illustrate the effect that blockage of one or both of the hydroxyl groups of 3 has on the orientation of its exocyclic C6-O6 bond.

EXPERIMENTAL

1. Methods

a) Spectroscopic

Routine nuclear magnetic resonance (n.m.r.) spectra were recorded with 60 and 100 MHz spectrometers operated by this Department. Chemical shifts are reported in *tau* (τ) values, relative to tetramethylsilane (TMS). The 220 MHz spectra on pages 177 and 187 were purchased from

The Canadian 220 MHz NMR Centre
Ontario Research Foundation
Sheridan Park, Ontario.

Infrared (i.r.) spectra were recorded with a Perkin-Elmer Grating Spectrophotometer (Model 421), at ambient temperature, using matched 1 mm or 5 mm sodium chloride cells.

The solvents used for the n.m.r. and i.r. analyses will be specified with descriptions of individual spectra.

b) Chromatography

Thin layer chromatography (t.l.c.) was done on Silica Gel G. Solvent systems used to develop the plates will be specified for individual compounds in section 3 of this chapter. Unless otherwise specified, compounds were detected with a spray of 3-5% sulphuric acid in ethanol

followed by heating on a hot plate.

Preparative column chromatography was done with silicic acid (100-200 mesh). Experimental detail for individual compounds will be supplied in section 3 of this chapter.

An F and M Scientific 776 Prepmaster Jr. was used for all of the gas-liquid partition chromatography (g.l.p.c.). Operational data are supplied for specific compounds in section 3.

c) Distillation

The routine removal of organic solvents was carried out *in vacuo* (water aspiration, 10-20 mm) at 30-40° using a rotary evaporator except where otherwise noted. When necessary, chloroform, methylene chloride, benzene or ether solutions were pre-dried with anhydrous sodium sulphate before concentration.

Fractional distillations were done on a spinning band or Vigreux column. Molecular-type distillation was used to separate certain of the liquid compounds from materials of much higher boiling point, e.g. inorganic salts. The apparatus that was used is shown in Fig. 21.

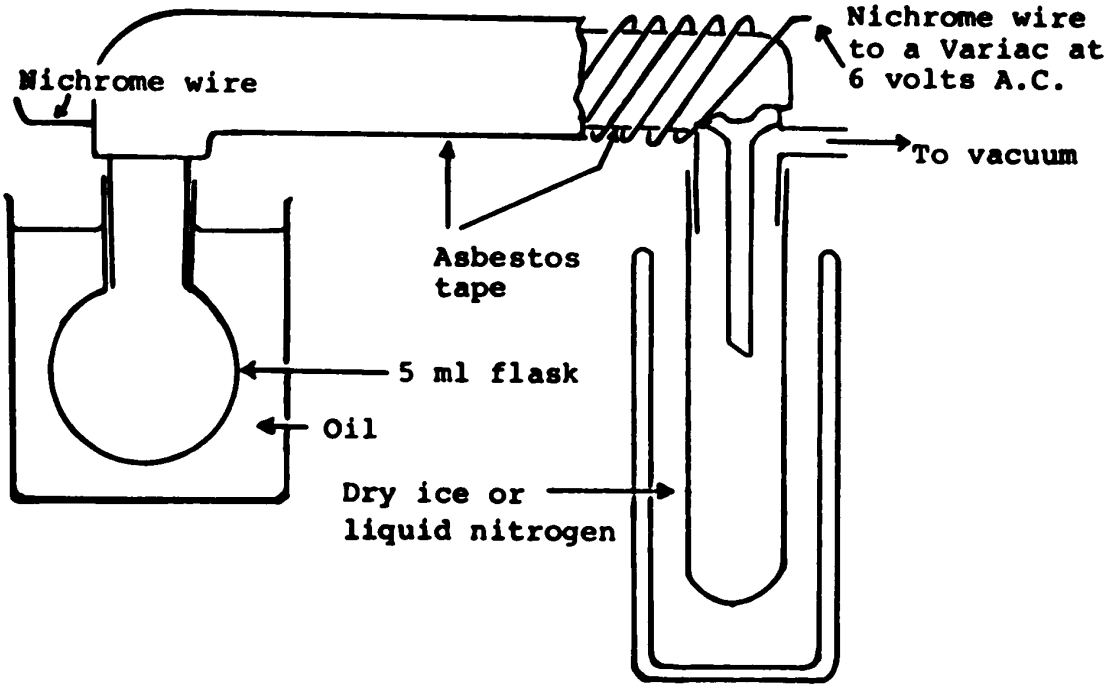


Fig. 21: Distillation apparatus

d) Melting points

Melting points were determined on a Leitz Microscope Heating Stage (Model 350), and like boiling points are uncorrected.

e) Elemental analysis

Elemental analyses were performed in this department by Mrs. D. Mahlow and Mrs. A. Dunn.

f) Optical rotations

i) Polarimeter

All optical rotations were measured with a Perkin-Elmer polarimeter (Model 141), at the D line (5892A°) of sodium vapour. The instrument was periodically checked for accuracy with a standard solution of sucrose (c, 1.0 in water) and/or by comparison with the rotation of a solution that was registered by an identical polarimeter in another laboratory.

Solution temperatures were adjusted by the circulation of thermostatted water through the glass jacket of a 10.0 cm polarimeter tube. The same tube, with a sample chamber of approximately 6 ml , was used throughout the investigations.

The manufacturer of the instrument claims a zero-point of ±0.002°. However, for most of the solutions studied, successive measurements of direct angular rotation were reproducible to ±0.001°. Polarimetric measurement error is calculated as $\frac{0.001^{\circ} \times M.W.}{c}$, where c is the concentration of a compound in g per 100 ml and M.W. is its molecular weight.

ii) Purification of optically active compounds

This section and the one that follows are concerned with the purification and preparation of solutions of optically active compounds whose molecular rotations were required as part of the study of the effects of conformational and configurational structure on optical activity.

Chloroform, containing 0.75% ethanol as a preservative, was usually used as a solvent for those compounds whose optical rotations were measured for characterization purposes only.

The purity of solid compounds could be ensured by recrystallization, followed by removal of residual traces of solvent *in vacuo* (∿ 0.1 mm). This was repeated until the melting points and the optical rotations were constant.

The solid compounds could be weighed directly into tared and calibrated volumetric flasks of approximately 7 and 10 ml. The flasks were dried in an oven (120°C) and cooled to room temperature under anhydrous conditions, prior to the addition of the compounds.

Liquid compounds were prepared in an optically pure state according to the following procedure. A crystalline derivative, or a precursor, of a compound was recrystallized to constant rotation and melting point. Preparations of these specific derivatives are detailed in section 3 of this chapter. The liquid compounds were then generated from the purified solids by direct and chemically unequivocable procedures.

All such liquids, except for compound 3, were then distilled, using the apparatus in Fig. 21, in sufficient quantities for all necessary rotation work. The distillate

was dried over a few Linde 4A type molecular sieves. A g.l.p.c. analysis was done to confirm the purity of the distillate, in particular the lack of organic solvents. Micro analyses and/or infrared spectra were taken to provide a proof of the absence of moisture.

Aliquots of these pure, anhydrous liquid compounds were transferred to the volumetric flasks with clean dry syringes (Hamilton 100 ul) and then their weights were recorded.

Compound 3 was too viscous to be transferred conveniently by micro-syringe. Sufficient material for the rotation work was prepared from its crystalline di-*O*-acetate. The material was then dissolved in anhydrous 1,2-dichloroethane and any water that it contained removed as an azeotrope by distillation, at normal pressure, of the major portion of the solvent (57). A portion of the remaining solution, containing enough compound for a single rotation, was concentrated at 14 mm pressure and 50°C. Then, the remaining anhydrous compound 3 was distilled directly into the tared volumetric flask (0.2 mm at a bath temperature of 90° to 100°C). The amount of compound that actually distilled was determined from the increase in the weight of the flask. The infrared spectrum of the solution of 3 made up for rotation study in pure 1,2-dichloroethane showed no absorption that was due to the presence of water.

iii) Solutions of the optically active compounds

There is an estimated absolute error of ±0.1 mg in the measurements of the weights of optically active compounds that were introduced into the volumetric flasks. This results in relative errors in the molecular rotation of solutions (weighing errors) that range from maxima of ±0.4% in the case of compound 5 (*ca.* 25 mg in 7 ml of solution) to ±0.1% for compound 7 (*ca.* 100 mg in 10 ml of solution).

For solutions that were to generate a point on a rotation curve, the dimethyl sulphoxide or the pyridine base was added to the flask, and its weight recorded, after the addition and the weighing of the optically active compound.* The flask was then filled to the volumetric calibration line with 1,2-dichloroethane, at 25°C. This filling temperature was maintained with a water bath, thermostatted at 25°C. "Filling errors" are estimated at 0.1% of the observed rotations.

Optical rotations for the individual solutions were measured at several temperatures. The appropriate volumes of the solutions relative to their values at 25°

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* The only variation in this procedure was with 4-chloropyridine. Because of its instability in concentrated form, it was kept as a solution of known concentration in 1,2-dichloroethane. Its weight would be calculated from the amount of this solution (in gm) that was added to the flask.

have been incorporated into the calculations of the molecular rotations.

$$[M]_D^t = \frac{[\alpha]_D^t \times M.W.}{100} = \frac{\alpha_D^t \times M.W.}{c_{25} \times \frac{d_t}{d_{25}}}$$

$[M]_D^t \equiv$ molecular rotation of the optically active compound at t°C, recorded at a wavelength of 5892A°

$[\alpha]_D^t \equiv$ specific rotation of the compound, at t°C

$\alpha_D^t \equiv$ direct angular rotation of the solution of optically active compound, at t°C

$c_{25} \equiv$ concentration of optically active compound in g per 100 ml of solution, at 25°C

$d_t \equiv$ density of the solution ± density of the solvent, at t°C

$d_{25} \equiv$ density of the solution ± density of the solvent, at 25°C

Anhydrous solvents were *not* as a rule stored over molecular sieves because of turbidity that resulted, but were kept in special solvent dispensing bottles (Fig. 22). Anhydrous solvents and solutions were transferred with oven-dried (120° C) syringes. The polarimeter cell was pre-dried in a stream of dried, filtered air.

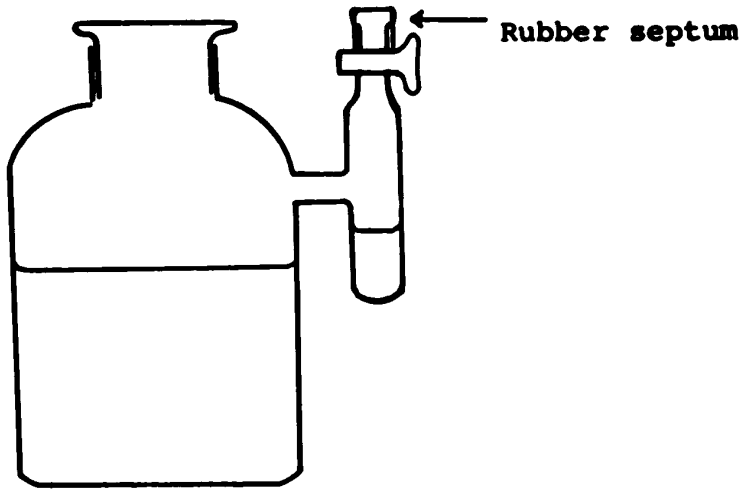

Fig. 22: Solvent dispensing bottle

2. Materials

a) Starting materials

A solution of 2-ethoxycarbonylcyclohexanone (60%) and 2-methoxycarbonylcyclohexanone (40%) was purchased from the Aldrich Chemical Co., Inc., Milwaukee, Wis. The two esters were not separated, as both were suitable starting materials for the synthesis of (±)-*cis*-2-hydroxycyclohexanecarboxylic acid (23).

Tri-*O*-acetyl-1,5-anhydro-2-D-*arabino*-hex-1-enitol (D-glucal triacetate or tri-*O*-acetyl-D-glucal) was obtained in pure crystalline form from Raylo Chemicals Ltd., Edmonton, Alberta.

Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (D-galactal triacetate or tri-*O*-acetyl-D-galactal

was purchased from Raylo Chemicals Ltd. as a 70% solution in benzene. The benzene was removed *in vacuo* before use.

Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (L-fucal diacetate or di-*O*-acetyl-L-fucal) was supplied by Mr. Werner Merlo of this laboratory.

b) General materials

i) Silica gel G

Silica gel G employed for thin layer chromatography and containing about 13% calcium sulphate as binder was purchased from E. Merck A.G., Damstadt, W. Germany.

ii) Silicic acid for column chromatography

"Silicar" cc-7, 100-200 mesh, was purchased from Mallinckrodt Chemical Works, St. Louis, Mo.

iii) Ion-exchange resin (H^+ type)

"Amberlite"-IR-120H CP resin was obtained from Mallinckrodt Chemical Works, St. Louis, Mo. It was rinsed repeatedly with methanol prior to use.

iv) Molecular sieves

Type 4A and 3A molecular sieves, manufactured by Linde Air Products Co., were obtained from British Drug Houses Ltd., Poole, England.

v) Hydrogenation catalysts

Palladium-on-charcoal (5%) was manufactured by Matheson Coleman and Bell, Norwood, Ohio. The 5% platinum-on-charcoal and 10% palladium-on-charcoal catalysts were manufactured by Engelhard Industries Ltd. of Newark, N.J.

vi) Lithium aluminium hydride (LAH)

The LAH was purchased from Metal Hydrides Inc., Beverly, Mass. It was ground into a fine powder before use.

vii) Sodium hydride

Sodium hydride, manufactured by Alfa Inorganics, Beverly, Mass., was received as a 57% suspension in oil. Prior to use, the material was mixed, under nitrogen, with anhydrous ether or Skelly B, and the solvents then carefully decanted. This procedure was repeated three times.

c) Solvents and their purification

i) 1,2-Dichloroethane

1,2-Dichloroethane was obtained from both the Fisher Scientific Co., Fair Lawn, N.J. and Eastman Organic Chemicals, Rochester, New York.

It was purified by fractional distillation over a 50 cm Vigreux column, taking advantage of the low boiling

water azeotrope (57). The initial 20% of the distillate was discarded. The anhydrous dichloroethane boiled between 80.0 and 80.5° at normal pressure.

ii) Dimethyl sulphoxide

Dimethyl sulphoxide (DMSO) was purchased from the J.T. Baker Chemical Co., Phillipsburg, N.J. It was pre-dried for 24 hours over barium oxide powder. The barium oxide was then filtered off and the DMSO distilled from the Linde type 4A molecular sieves over a 20 cm Vigreux column at a nitrogen pressure of 17 mm of Hg. The boiling point at this pressure was 79.0-79.5°.

iii) Pyridine

Pyridine was obtained from Eastman Organic Chemicals, Rochester, N.Y., or from Raylo Chemicals Ltd., Edmonton, Alberta. It was allowed to stand over barium oxide for several days before distillation at normal pressure. (B.p. 112.0-112.5°)

iv) 4-Methylpyridine (γ-picoline)

This compound was obtained from the Aldrich Chemical Co., Inc., Milwaukee, Wis. It was dried over barium oxide for several days before it was distilled at normal pressure. B.p. 140.0-140.5°.

v) 4-Chloropyridine

4-Chloropyridinium hydrochloride was purchased from the Aldrich Chemical Co., of Milwaukee, Wis. This salt (10.0 g, 0.07 mole) was dissolved in 70 ml water. Ether was added (100 ml) and the mixture was rapidly stirred and cooled to about -10°. A solution of sodium hydroxide (4.0 g, 0.10 moles) in 40 ml. of water was slowly added over a 20 minute period. The ether layer was then decanted and combined with three subsequent 150 ml ether extractions of the aqueous phase. These were dried over sodium sulphate at 0° and then concentrated at room temperature. The remaining colourless oil was treated with Linde 3A type molecular sieves and then distilled under high vacuum, at less than 45°, into a tared receiving trap that was maintained at about -80°. The 4-chloropyridine (4.3 g, 58%) was a colourless solid at -80°.

3. Synthetic investigations

a) 1,2-*O*-Isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7)

The preparation of 7 was similar to that of Ohle and Just (58). 3,4-Anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose (11.4 g, 5.6 mmole) was dissolved in a refluxing solution of sodium methoxide (11.5 g) in methanol (90 ml). After 75 minutes at reflux, the reaction was

cooled to room temperature and saturated aqueous sodium bicarbonate (5 ml) was added. The mixture was carefully adjusted to a pH of 8-9 by the addition of 6M sulphuric acid, and then concentrated to dryness *in vacuo*. Anhydrous sodium sulphate was added and the solid residues then extracted with three 150 ml portions of hot toluene.

These extracts, after concentration, yielded 12.0 g of yellow solids. Successive recrystallizations from 120 ml and then 85 ml of toluene yielded 8.5 g of chromatographically pure 7 (as shown by t.l.c., with a developing solvent of 6 parts benzene and 1 part ethanol). The crystals were decolourized with charcoal and recrystallized twice more from toluene to give colourless needles of 7, m.p. 119.5-120°, $[\alpha]_D^{20}$ - 74.8° (c, 1.0 in 1,2-dichloroethane), -29.6° (c, 1.0 in pyridine). [Lit. (58) m.p. 112-113°; (59) m.p. 118-119°, $[\alpha]_D^{20}$ - 74° (c, 0.93 in 1,2-dichloroethane) and -29.3 (c, 1.0 in pyridine)]

b) (±)-*cis*-2-Hydroxycyclohexanecarboxylic acid (23)

A mixture of 2-ethoxycarbonylcyclohexanone and 2-methoxycarbonylcyclohexanone (100 g of a 60/40 mixture - 0.61 mole of reducible ketone) was used as starting material for the synthesis of 23. Using the procedure described in the literature (60, 61, 62), 27.3 g of 23 (31%) were obtained. It was a crystalline compound with m.p. 74-76.5°.

[Lit. (60) m.p. 81°; (61) m.p. 76-78°; (62) m.p. 79-80°]

N.m.r. data, in D_2O: τ 5.73 (1 proton, a rough doublet with spacing of 2.5 Hz and a base width of 13 Hz - assigned to H2).

c) (1S,2R)-(-)-*cis*-2-Hydroxycyclohexanecarboxylic acid (24)

Compound 24 was obtained from the racemic *cis*-2-hydroxycyclohexanecarboxylic acid *via* preparation, and subsequent resolution by fractional crystallization from acetone, of its diastereomeric brucine salt, according to the procedure of Torne (61). It was a syrupy material with $[\alpha]_D^{25}$ - 31.5° (c, 1.56 in ether). [Lit. (61) - 34.7° (c, 1.74 in ether); (63) - 34.7 (in chloroform).]

d) (1R,2R)-(-)-*trans*-2-Hydroxycyclohexanecarboxylic acid (25)

This compound was prepared by base-catalyzed isomerization of the (1S,2R)-(-)-*cis*-2-hydroxycyclohexanecarboxylic acid (24) (5.0 g, 34.8 mmoles) according to the procedure of Torne (61). Optically pure 25 (1.6 g, 32%) was obtained after three recrystallizations of the product from ethyl acetate. The melting point, 107-109°, and rotation were the same as those quoted in the literature.

$[M]_D^{25}$ - 77.0° (c, 0.75 in chloroform) [Lit. (64 m.p. 110-111°, $[M]_D$ - 77.3° (chloroform); (61) m.p. 110-112°, $[M]_D^{21.5}$ - 75°(c, 3.5 in chloroform).]

N.m.r. data, in D_2O: τ 6.38 (1 proton, a multiplet with a base width of 26 Hz - assigned to H2).

e) (1R,2R)-(-)-*cis*-2-Hydroxymethylcyclohexanol (6)

1S,2R-Hydroxycyclohexanecarboxylic acid (24) (2.15 g, 14.9 mmoles) was esterified with ethereal diazomethane in the usual manner (65). The methyl ester was dissolved in 20 ml of anhydrous ether and added dropwise over 20 min. to a well-stirred mixture of lithium aluminum hydride (LAH) (0.5 g, 13 mmole) in ice-cold anhydrous ether (75 ml). The mixture was stirred at room temperature for 1 hr and then for an additional hour at reflux temperature. Then it was cooled to 5°, and excess LAH destroyed by the cautious addition of ethyl acetate (10 ml). The mixture was poured into 70 ml of 20% sulphuric acid and extracted with a 300 ml portion and then three successive 125 ml portions of chloroform. The combined chloroform extracts were dried and concentrated to 1.5 g of colourless syrup. Crystallization from ether (7 ml) at -20° afforded 0.94 g of 6. This product was then recrystallized three times from ether to constant rotation, $[M]_D^{25}$ - 46.8° (c, 0.42 in water), and a m.p. of 49-50°. Additional rotation data are

presented in Tables 13 and 17.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84.

Found: C, 64.44; H, 10.83.

Portions of the n.m.r. spectra of 6, taken in D_2O at 5°, 40° and 80° are reproduced in Fig. 41 on page 176. Coupling constants appear in Table 32, on page 177.

f) (1R,2S)-(-)-*trans*-2-hydroxymethylcyclohexanol (5)

Compound 25 (1.6 g, 11 mmoles) was esterified with ethereal diazomethane in the usual manner (65). The methyl ester was dissolved in 200 ml of ether and slowly added to a well-stirred mixture of LAH (0.85 g, 23 mmole) in 100 ml of ice-cold anhydrous ether. After the addition had been completed, the reaction was stirred for an additional 24 hrs at room temperature. At this time excess reagent was destroyed by the cautious addition of ethyl acetate (10 ml), followed after 30 min by 5 ml of water. The mixture was partitioned between 50 ml of 20% aqueous sulphuric acid and 300 ml of chloroform. The aqueous layer was extracted four times more with 125 ml portions of chloroform and the combined chloroform extracts were then dried and concentrated. The residual syrup (1.6 g) was chromatographed on a 5 x 70 cm column of silica gel, using a 7 to 3 ratio of chloroform and acetone as the eluting agent.

Chromatographically pure 5 (1.07 g, 74.5%) was isolated and then recrystallized three times from ether to constant optical activity, $[M]_D^{25}$ - 71.5° (c, 0.34 in water) and a m.p. of approximately 23-24°. [Lit. (66), $[M]_D$ 27° (in ether)]. Complete rotation data for 5 are presented in Tables 13 and 15.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84.

Found: C, 64.30; H, 10.70.

Portions of the n.m.r. spectra of 5 in D_2O are reproduced in Fig. 40. Coupling constants are listed in Table 32 on page 177.

g) The hydrogenation of tri-*O*-acetyl-D-galactal

i) The preparation of (S)-(+)-2-acetoxymethyl-tetrahydropyran (26) and tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hexitol (28).

Tri-*O*-acetyl-D-galactal (40.0 g, 147 mmoles) was hydrogenated in a solution of ethyl acetate (200 ml) and diethylamine (12 g, 16.5 mmoles) over 4.4 g of 5% palladium-on-charcoal at atmospheric pressure (see ref. 4). It was necessary to change the catalyst after 5, 16, and then 24 hours of reaction time. After a total hydrogenation time of 40 hours, the uptake of hydrogen ceased at 6 litres.

The catalyst was removed by filtration and the filtrate concentrated to about 100 ml. This solution was diluted to 500 ml with chloroform and then washed successively with 1 N hydrochloric acid (300 ml), water (500 ml), saturated sodium bicarbonate (300 ml) and finally with water (100 ml). It was dried over sodium sulphate and concentrated *in vacuo* (water aspiration at less than 35°) to 24 g of red-brown syrup. A g.l.p.c. analysis using a 6 ft, 1/4 in copper column packed with 10% Carbowax M on 60-80 mesh Ultraport and a carrier gas flow of 60 ml of nitrogen per min revealed only three components, plus residual solvent.

Component	Retention time	Percentage (by area)
1.	2.0 min at 175°	45
2.	8.2 min at 175° 4.7 min at 200°	4
3.	13.0 min at 200°	50

The first component (5.3 g) distilled from the mixture between 80° and 85° at a pressure of 13 ± 1 mm. An n.m.r. spectrum, in chloroform-d, showed that it was mainly (S)-(+)-2-acetoxymethyltetrahydropyran (26). The spectrum also contained absorbances that were due to the presence of a small amount of an additional compound or compounds, most probably ethyl acetate or N,N-diethylacetamide. This semi-pure 26, which had $[\alpha]_D^{25}$ + 12.0° (c, 0.54 in chloroform), was not further purified. [Lit. (9), b.p.

60-62° at 2 mm, $[\alpha]_D^{25}$ + 13.3° (c, 4.5 in chloroform)].

N.m.r. data for 26, in chloroform-d, τ 5.95 (2 protons, a "doublet" with a spacing of 5 Hz; assigned to the exocyclic methylene protons), 5.8-6.2 (a one proton multiplet assigned to the equatorial hydrogen of the carbon adjacent to the ring oxygen), 8.28 (a singlet corresponding in intensity to the acetate group).

A second fraction (2.1 g) distilled between 75° and 90° at a pressure of 0.08 mm. A g.l.p.c. investigation showed about a 2 to 3 ratio of the second to the third component. A small amount of the second component was separated from this mixture by preparative gas-liquid chromatography on an 80 in, 20% silicone gum rubber 10-60 w column. The n.m.r. spectrum, in chloroform-d, was consistent with spectral data reported for 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (27) in ref. 9.

N.m.r. data for compound 27, in chloroform-d: τ 5.07 (1 proton - rough singlet with a half band width of 6 Hz; assigned to H4), 5.92 (a two proton "doublet" with spacing of 5 Hz; assigned to H6 and H6') 7.9, 7.95 (three proton singlets; assigned to the acetate protons).

Finally, 6.6 g of the third compound was distilled, between 90° and 95° and at a pressure of 0.08 mm. A g.l.p.c. and n.m.r. analysis showed that the viscous oil, with

$[\alpha]_D^{25}$ + 51.3° (c, 0.69 in chloroform) was pure tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hexitol, (28). [Lit. (9) b.p. 141-144° at 2 mm; $[\alpha]_D^{25}$ + 43.7° (c, 0.75 in chloroform)].

N.m.r. data for 28, in chloroform-d: τ 7.88, 7.97, 8.03 (singlet acetate signals), 4.74 (one proton, a rough doublet with spacing of 3 Hz; H4), 5.00 (one proton, a broad multiplet with base width of 20 Hz; H3), 5.65-6.65 (5 protons) 7.5-8.6 (11 protons, including the acetate signals).

ii) The preparation of semi-pure di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (27)

When a solution of 11.0 g of tri-*O*-acetyl-D-galactal in 100 ml of ethyl acetate was hydrogenated at 2 atm, over 0.7 g of 5% palladium-on-carbon, and in the presence of 0.28 g of diethylamine, g.p.l.c. investigations showed that there was 9% of compound 27 in the reaction mixture. The catalyst was removed by filtration and the filtrate combined with several similar hydrogenation products. These products had been obtained using lower pressures and different ratios of materials to those just listed, and as a result contained somewhat lower yields of 27. This combined solution, which represented 100 g of hydrogenated galactal triacetate, was concentrated and the residual syrup was then distilled on a spinning band column.

The first fraction, 20.0 g boiling at and below 80° at 13 mm, was shown by g.p.l.c. to contain compound 26 as the major component. There was no signal corresponding to compound 27.

The second fraction that was isolated (5.7 g) distilled between 90° and 100° as the pressure was gradually lowered from 0.6 to 0.09 mm. A g.l.p.c. analysis showed that this distillate was about 75% compound 27. The rest of this fraction was composed of approximately equal amounts of 26 and 28. Nevertheless, compound 27 was sufficiently pure to permit the preparation and subsequent purification of the diol, 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (4).

h) (S)-(+)-2-hydroxymethyltetrahydropyran, (1,5-anhydro-2,3,4-trideoxy-D-*glycero*-hexitol) (29)

i) Deacetylation of (S)-(+)-2-acetoxymethyl-tetrahydropyran (26)

Compound 26, prepared as described in section g-i, (4.75 g, 30 mmoles) was deacetylated in anhydrous methanol (50 ml) containing enough sodium methoxide to give the solution a pH of 11 (determined with Hydrion pH paper). The solution was allowed to stand for twenty hours at room temperature and then was neutralized with Amberlite IR 120 (H^+) resin. The solvent was removed at 30° and then the

residual oil was distilled (molecular distillation at 0.07 mm pressure and 25°). The distillate (3.0 g), which had $[\alpha]_D^{25}$ + 19.2° (c, 0.67 in water), was examined for purity by n.m.r. and g.l.p.c.

Its n.m.r. spectrum, in chloroform-d, showed impurity peaks centred at 7.9 and 8.8 τ along with the absorptions expected for pure 29 (see p. 192). The g.l.p.c. analysis, carried out on a 6 foot, 1/4 inch copper column packed with 10% Carbowax M on 60-80 mesh Ultraport, with a nitrogen flow of 60 ml per min , showed one major peak (95% of the total area), with a retention time of 12.3 min at 110°. At this temperature the only significant impurity had a retention time of 1.3 min.

ii) Preparation of 1,5-anhydro-2,3,4-trideoxy-6-*O*-triphenylmethyl-D-*glycero*-hexitol (30)

Compound 29, as prepared in section h-i above, (2.75 g, 23.7 mmoles) was dissolved in 50 ml of ice-cold anhydrous pyridine. Triphenylmethylchloride (6.7 g, 24.3 mmoles) was added and the solution then allowed to warm to room temperature. After forty-eight hours the products were poured into a well-stirred mixture of ice and water (1 l). One hour later the solid products were isolated by filtration and recrystallized from 20 ml of methanol. Pure 30 (4.9 g, 48.5%) was obtained after two further

recrystallizations (at +15°C), first from 50 and then from 25 ml of 98% ethanol. Its melting point and optical rotation were unchanged after a further recrystallization.

M.P. 107-108°; $[\alpha]_D^{25}$ - 20.7° (c, 0.56 in chloroform)

Anal. Calcd. for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31.

Found: C, 83.56; H, 7.25.

iii) The regeneration of pure compound 29 from 1,5-anhydro-2,3,4-trideoxy-6-*O*-triphenylmethyl-D-*glycero*-hexitol (30)

The pure 1,5-anhydro-2,3,4-trideoxy-6-*O*-triphenylmethyl-D-*glycero*-hexitol (30) (4.0 g, 11.2 mmoles) was dissolved in chloroform (75 ml) at 0°. A slow stream of anhydrous hydrogen bromide gas was bubbled through the solution, with stirring, until t.l.c., using 4 parts benzene to 1 part of ethyl acetate as solvent system, indicated the complete conversion of 30 to the much less mobile 29, plus triphenylmethyl bromide. The triphenylmethyl bromide was detected as a transient yellow spot when the plates were sprayed with 3% ethanolic sulphuric acid. Compound 30 initially formed such a yellow spot, but on heating it quickly charred to black. The reaction product was concentrated at 30° and 13 ± 1 mm pressure until all but

a trace of the solvent and excess HBr had been removed. Compound 29 was then distilled from the semi-solid mass (molecular distillation at 0.08 mm with bath temperature of 30°). A small amount of trimethylamine was added to the distillate (enough to give a basic response to Hydrion (pH 1-14) paper. Excess amine was removed *in vacuo*. Then, compound 29 was re-distilled at 0.1 mm pressure, with a bath temperature of 30°, into a clean, dry receiving flask that was cooled in liquid nitrogen (Fig. 21). The product (620 mg, 47%) was stored over a few Linde 4A type molecular sieves. A g.l.p.c. investigation (as detailed in section h-i) revealed only pure 29 with a b.p. (0.8 mm) of about 30° and $[M]_D^{25}$ + 26.1° (c, 0.5 in water) [Lit. (9) b.p. 90-91° at 20 mm, $[M]_D^{25}$ + 22.1° (c, 1.0 in water)].

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.41.
$C_6H_{12}O_2 \cdot H_2O$: C, 53.70; H, 10.52.

Found: C, 61.52; H, 10.57.

N.m.r. data for 29, in chloroform-d: τ 5.93-6.12 (1 proton, a rough doublet centred at 6.01, with spacing of 11 Hz; assigned to the equatorial proton on the carbon adjacent to the ring oxygen), 6.3-6.8 (4 protons; a prominent "doublet" centred at 6.47 with spacing of 2 Hz is assigned to the exocyclic methylene protons) 8.0-9.0 (6 protons - an unresolved multiplet). Also see Fig. 46, page 192.

i) 1,5-Anhydro-2,3-dideoxy-D-*threo*-hexitol (4)

i) Preparation of 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-p-nitrobenzoyl-D-*threo*-hexitol (31)

Crude 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (27) (5.7 g), prepared as detailed in section g-ii, was dissolved in about 200 ml of anhydrous methanol. Enough sodium methoxide was added to this solution to give it a pH of 11 on Hydrion pH paper. The mixture was left overnight and then neutralized with Amberlite IR 120 (H^+) resin. A t.l.c. investigation, using 4 parts ethyl acetate to 1 part of ethanol as a solvent system, showed a major product with an approximate R_f of 0.6, and minor products with approximate R_f values of 0.3 and 0.8 respectively.

The solution was concentrated and the syrupy product triturated with about 50 ml of ether. Approximately 2.4 g of the product dissolved in ether, and it was subsequently shown by t.l.c. (same solvent as above) that this ether-soluble fraction contained the material with R_f of 0.6 as well as the minor component whose R_f was about 0.8. The least mobile of the original products was almost quantitatively insoluble in the ether. A t.l.c. of this crystalline ether-insoluble fraction showed that it had the same R_f as 1,5-anhydro-2-deoxy-D-*lyxo*-hexitol (32).

The ether-soluble syrup (2.3 g) was dissolved in 30 ml of anhydrous pyridine. Then, p-nitrobenzoyl chloride (7.6 g, 41 mmole) was added and the mixture warmed, with stirring, until it became homogeneous. The reaction was heated on a steam bath for one hour, and then the semi-solid product mixture was stirred into 150 ml of an ice-cold 5% sodium bicarbonate solution. One hour later the solids were isolated, by filtration, washed with 5% sodium bicarbonate and then with water. The light brown product, after drying, weighed 6.85 g. This afforded 5.35 g of 31 with $[\alpha]_D^{25}$ - 89.7° (c, 0.61 in chloroform) after one recrystallization from 200 ml of ethanol.* A t.l.c., using a solvent of 4 parts benzene to one part ethyl acetate, showed only the presence of one component, with an R_f of approximately 0.7. A t.l.c. of the mother liquors revealed this same material, and also substantial amounts of a faster moving substance.

The product was recrystallized once more from 150 ml of ethanol. The almost colourless crystals of 31 had $[\alpha]_D^{25}$ - 89.3° (c, 0.82 in chloroform) and melted at 150-151°

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* Enough dichloromethane was added to make the product soluble in the ethanol. Then it was distilled out, taking advantage of its low boiling azeotrope with ethanol (67). The total volume was maintained at about 200 ml by the periodic addition of hot ethanol, and the solution allowed to cool when the solvent vapours reached a temperature of 70°.

Anal. Calcd. for $C_{20}H_{18}O_9N_2$: C, 55.81; H, 4.22; N, 6.51.

Found: C, 55.73; H, 4.32; N, 6.48.

N.m.r. data for 31, in chloroform-d: τ, 1.71-1.77 (8 protons - a "doublet" centred at 1.75 with a spacing of 4 Hz; assigned to the p-nitrobenzoyl protons), 4.62 (1 proton, a rough singlet with a half band width of 5 Hz; assigned to H4), 5.44-5.57 (2 protons; assigned to H6 and H6'), 5.66-6.62 (3 protons; H1, H1' and H5), 7.5-8.6 (4 protons; H2, H2', H3 and H3').

ii) Regeneration of pure 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (4) from 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-p-nitrobenzoyl-D-*threo*-hexitol (31)

Compound 31 (4.8 g, 11.1 mmoles) was dissolved in a solution of dichloromethane (60 ml) and anhydrous methanol (100 ml) that contained 10 mg of sodium methoxide. After 2 hours, the solvent was removed and the semi-solid products extracted twice with 40 ml portions of water. A t.l.c. investigation was done, using as mobile phase a mixture of four parts of benzene to one part of ethyl acetate. A developed plate that had been spotted with the water-insoluble material (methyl p-nitrobenzoate) did not contain any components that could be charred by heating after spraying with 3% ethanolic sulphuric acid.

The combined aqueous extracts were made alkaline with 3 g of sodium hydroxide pellets and left to stand for 24 hours, in order to saponify any residual esters of p-nitrobenzoic acid. Then this basic solution was continuously extracted with ether for a period of 48 hours. The ether extracts, on concentration, yielded 1.39 g of colourless oil. A t.l.c. investigation using 4 parts of ethyl acetate to 1 part of ethanol as the mobile phase, showed only 1 detectable compound, with an R_f of about 0.6.

The syrup was dissolved in 25 ml of anhydrous methanol, and the solution dried over Linde 4A type molecular sieves. After separation of the sieves, the bulk of the methanol was distilled out at normal pressure, under anhydrous conditions. Remaining methanol was removed at room temperature using a pressure of 0.2 mm. The residual anhydrous 4 was distilled using the apparatus shown in figure 21. (0.2 mm and a bath temperature of 95°). The distillate, 1.19 g, which was shown by n.m.r. spectroscopy and by t.l.c. investigation to contain only compound 4, solidified on standing at room temperature and had $[M]_D^{25}$ + 7.0° (c, 0.5 in water). It was recrystallized at a temperature of 5° from 20 ml of anhydrous ether. This recrystallized 4 (870 mg) melted at 51-53.5° and had $[M]_D^{25}$ + 6.8° (c, 0.5 in water). Additional rotational data are listed in Tables 13 and 18.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15.

Found: C, 54.84; H, 9.20.

The n.m.r. spectrum of 4, in D_2O, is reproduced in Fig. 44, on page 192.

j) 1,5-Anhydro-2-deoxy-D-*lyxo*-hexitol (32)

A sample of this compound that had been recrystallized to constant rotation was obtained from Dr. T.L. Nagabhushan of this laboratory. It melted at 121° and had $[M]_D^{25}$ + 70.8° (c, 0.46 in water).

k) 1,5-Anhydro-2,6-dideoxy-L-*lyxo*-hexitol, (33)

Di-*O*-acetyl-L-fucal (0.5 g, 2.3 mmoles), dissolved in 5 ml of ethyl acetate, was hydrogenated at atmospheric pressure over 60 mg of 5% platinum-on-carbon. After 5 hrs of hydrogenation time, the catalyst was removed by filtration and the filtrate concentrated to a colourless oil. A t.l.c. investigation of this product, using as eluent a mixture of 3 parts benzene to 1 part of ethyl acetate, showed that the starting material had been quantitatively converted to a single, less mobile compound with an R_f of about 0.5.

About 0.4 g of this oil was dissolved in 50 ml of anhydrous methanol that contained a catalytic amount of sodium methoxide (15 mg). After 10 hrs the solution was neutralized

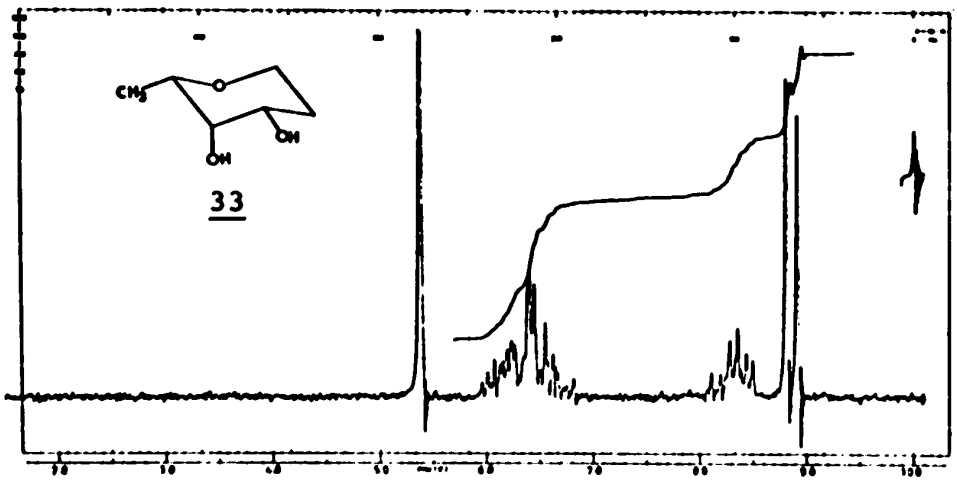


Fig. 23: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2,6-dideoxy-L-*lyxo*-hexitol (33) in (D_2O).

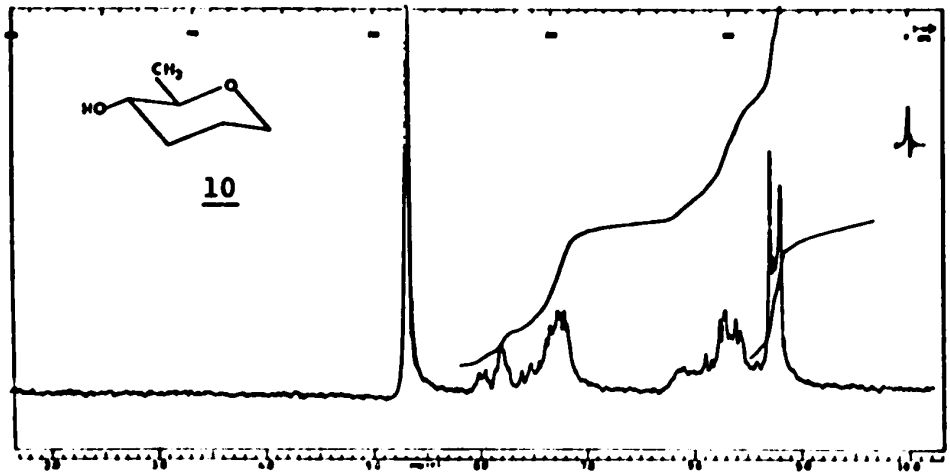


Fig. 24: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2,3,6-trideoxy-D-*erythro*-hexitol (10) (D_2O).

Fig. 25: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol (9) in (D_2O).

with Amberlite IR 120 (H^+) resin and concentrated to 160 mg of a crystalline solid. A t.l.c. investigation, using as solvent a solution of 3 parts ethyl acetate to 1 part of ethanol, revealed only one compound in this product.

This material was recrystallized three times from small amounts of ether and afforded 80 mg of compound 33, with m.p. 60-61.5° and $[M]_D^{25}$ - 54.9° (c, 0.33 in water). The molecular rotations (in water) after the second and third recrystallizations were the same.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15.

Found: C, 54.23; H, 9.27.

The n.m.r. spectrum, taken in D_2O, is reproduced in Fig. 23.

1) The hydrogenation of tri-*O*-acetyl-D-glucal — preparation of 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (34)

Tri-*O*-acetyl-D-glucal (49 g, 180 mmole) was hydrogenated at atmospheric pressure over 5% palladium on charcoal (5 g) in a solution of ethyl acetate (200 ml) and diethylamine (15 ml). It had been previously reported that this base promoted the formation of compound 34. (22, 68). The hydrogen uptake stopped, at 7.7 l. (290 mmoles), after 24 hrs.

The catalyst was removed by filtration and then the filtrate was diluted with 200 ml of benzene. This solution was washed successively with 2N hydrochloric acid (250 ml), water (250 ml), saturated sodium bicarbonate solution (250 ml), and finally with water (200 ml). Then it was concentrated to 34.5 g of residual oil. A t.l.c. investigation of this oil, using as the mobile phase a mixture of 2 parts benzene to 1 part of ethyl acetate, revealed only two components. The major product was subsequently identified as compound 34. The minor, less mobile product had the same R_f as 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (35).

A t.l.c. investigation during the course of the hydrogenation revealed the formation of an intermediate product with a larger R_f value than that of 34 or 35. As the hydrogen uptake proceeded, t.l.c. showed that this product was converted to 34.

The crude reaction product was combined with the crude product from an identical hydrogenation of 51.9 g of D-glucal triacetate, and the total product (66.5 g) fractionated on a spinning band column.

Compound 34 (56 g; 70%, based on the total hydrogenated glucal triacetate) distilled at 70-73° at a pressure of 0.07 mm. It solidified on standing at room

temperature. No 35 could be detected in the distillate by t.l.c., although there was a trace of substance with a larger R_f value than that of 34.

After two recrystallizations from toluene (25 ml) at -20°, there remained 40 g of pure 34 with m.p. 35-36° and $[\alpha]_D^{25}$ + 41.9° (c, 0.62 in chloroform), + 39.9° (c, 0.65 in ethanol). [Lit. (22) b.p. (0.7 mm) 89-90°; (69) $[\alpha]_D^{25}$ + 35° (c, 1 in ethanol)].

N.m.r. data, in benzene-d_6, for compound 34: τ 5.25 (1 proton, a multiplet with large spacings; assigned to H4), 5.7-5.8 (2 protons; H6 and H6'), 6.15 to 7.25 (H1, H1' and H5), 7.75-9.0 (10 protons, including two acetate singlets at 8.24 and 8.28). These spectral data compare favourably with those values reported for this compound in ref. 22.

m) 1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol (3)

Compound 34, (1.0 g), m.p. 35-36° and $[\alpha]_D^{25}$ + 42.0° (c, 0.79 in chloroform), was added to a solution of 50 ml of methanol containing a trace of sodium methoxide. After 12 hrs, t.l.c. showed only the diol, 3. The solution was neutralized with Amberlite IR 120 (H^+) resin, filtered and concentrated to about 0.65 g. This material was dissolved in 25 ml of 1,2-dichloroethane and solutions containing 3

prepared for rotation study as described on page 52. The material had $[M]_D^{25}$ + 70.9° (c, 0.39 in water).

Portions of the n.m.r. spectra of 3, taken at 5°, 40° and 80°C are reproduced in Fig. 43 on page 187. Coupling constants appear in Table 32 on page 176.

n) 4-*O*-Acetyl-1,5-anhydro-2,3-dideoxy-6-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (36)

i) Tosylation of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3)

A solution of 3 (8.0 g, 60.5 mmole) in pyridine (40 ml) was maintained at 0° for 2 hrs while a solution of p-toluenesulphonyl chloride (11.6 g, 61.5 mmole) in 50 ml of pyridine was slowly added. The reaction was kept at 8° for 72 hrs, and then poured into 800 ml of ice-water. The mixture was stirred for 2 hrs and then the crude product, plus pyridine, was extracted with chloroform (3 x 250 ml). The combined chloroform extracts were then washed with water (100 ml), dried, and concentrated to 14.0 g of syrupy residue.

ii) Acetylation

The syrup (14.0 g) was dissolved in 30 ml of ice-cold pyridine and treated with 10 ml of acetic anhydride. After it had stood for 4 hrs at room temperature, the reaction

mixture was poured into a vigorously stirred mixture of ice and water (600 ml). Thirty minutes later, 13.8 g (69%) of crude 36 was filtered off and then recrystallized from methanol/water (95 parts of methanol to 5 parts of water). After two such recrystallizations, 10.7 g of pure 36 was obtained.

M.p. 66-67°; $[\alpha]_D^{25}$ + 52.2° (c, 0.7 in chloroform).

Anal. Calcd. for $C_{15}H_{20}O_6S$: C, 54.86; H, 6.14; S, 9.77.

Found: C, 54.61; H, 5.99; S, 9.98.

N.m.r. data for 36, in chloroform-d: τ 2.16-2.74 (4 aromatic protons as an AA'BB' quartet, centred at 2.45); 7.55 (a three proton singlet; assigned to the CH_3 of the p-toluenesulphonyl function); 8.02 (a three proton singlet; assigned to the acetyl protons).

o) 1,5-Anhydro-2,3,6-trideoxy-6-iodo-D-*erythro*-hexitol (37)

Compound 36 (10.0 g, 30 mmole) was added to a refluxing mixture of sodium iodide (10.0 g, 66.6 mmole) in acetic anhydride (200 ml). After 90 minutes at reflux temperature, the reaction mixture was cooled and then poured into 700 ml of ice water. Solid sodium bicarbonate was added slowly and with constant stirring, until the lower of

the two liquid phases solidified. This crude product was filtered off and later combined with four 100 ml chloroform extracts of the filtrate. This chloroform solution was then washed with water (100 ml) and concentrated to dryness. The solid residue (8.5 g) was twice recrystallized from Skelly B and afforded 5.9 g of pure 37 (31%). Its melting point (66-66.5°) and rotation ($[\alpha]_D^{25}$ + 47.8° (c, 0.44 in chloroform) were unchanged after a further recrystallization.

Anal. Calcd. for $C_8H_{13}O_3I$: C, 33.82; H, 4.63; I, 44.67.

Found: C, 33.90; H, 4.36; I, 44.53.

p) 1,5-Anhydro-2,3,6-trideoxy-D-*erythro*-hexitol (10)

Compound 37 (5.5 g, 19.4 mmole) was hydrogenated at atmospheric pressure in a solution of ethyl acetate (50 ml) and triethylamine (2.0 g). The catalyst was 1.0 g of 5% palladium-on-charcoal. Twelve hours after the hydrogen uptake had ceased (20 hrs total) the mixture was filtered and the filtrate concentrated *in vacuo* (15-20 mm) to 4.0 g of syrup. This syrup was then diluted with 100 ml of dichloromethane and the solution washed successively with 0.5 N hydrochloric acid (100 ml) and saturated sodium bicarbonate solution (100 ml). Then it was dried and concentrated to yield the acetate of 10.

This oil was directly deacetylated in 50 ml of methanol that contained a trace of sodium methoxide. After 15 hrs, the solution was neutralized with Amberlite IR 120 (H^+) resin, molecular sieves were added, and the bulk of methanol distilled out at normal pressure. The residual methanol was removed at 30° and a pressure of 1.5 mm of Hg. A g.l.p.c. investigation of the residue, using a 6 ft, 1/4 in. copper column packed with 10% Carbowax M on Ultraport, 60-80 mesh, and a carrier gas flow of 60 ml of nitrogen per minute showed only chromatographically pure compound 10, with a retention time of 4.3 min at 130°.

This material was dried once again over Linde 4A type molecular sieves and was then distilled into a dry receiving flask using the apparatus depicted in Fig. 21. (0.2 mm and a bath temperature of 50°). The yield of 10 was 1.8 g (80%). A t.l.c. analysis, using as mobile phase a mixture of 3 parts benzene to 2 parts ethyl acetate, as well as a g.l.p.c. investigation, confirmed the purity of this material.

Compound 10 boiled at approximately 35° at 0.5 mm, and had $[M]_D^{25}$ + 39.0 (c, 0.44 in water). Additional rotation data are reported in Table 14.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.41.

Found: C, 61.69; H, 10.15.

The n.m.r. spectrum of 10, taken in D_2O, is reproduced in Fig. 24 on page 77.

q) 1,5-Anhydro-2-deoxy-D-*arabino*-hexitol (38)

Crude 1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol that was suitable for the preparation of 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-6-*O*-p-toluenesulphonyl-D-*arabino*-hexitol was prepared in the following manner.

Tri-*O*-acetyl-D-glucal (31 g, 114 mmoles) was hydrogenated in ethyl acetate (50 ml) over 5% palladium-on-carbon (2 g) in the absence of diethylamine (22, 68), using a Parr hydrogenation apparatus. The pressure dropped from 52.5 to 43 psi in the space of 15 minutes and then remained constant. The catalyst was removed by filtration and the filtrate concentrated to 32.5 g of syrup. This syrup was dissolved in anhydrous methanol and then deacetylated using a catalytic amount of sodium methoxide, in the same manner as was described for compound 3, on pg. 80. The product was a colourless viscous syrup. A t.l.c. study, using a solvent system of 4 parts benzene to 1 part ethanol, showed that the product contained only one component. This component had the same R_f as authentic 1,5-anhydro-2-deoxy-D-*arabino*-hexitol (38).

r) 3,4-Di-*O*-acetyl-1,5-anhydro-2-deoxy-6-*O*-p-toluenesulphonyl-D-*arabino*-hexitol (39)

i) Tosylation of 1,5-anhydro-2-deoxy-D-*arabino*-hexitol

A solution of p-toluenesulphonyl chloride (13.9 g, 73 mmoles) in 50 ml of anhydrous pyridine was added, over a period of 2 hrs, to a stirred, ice-cold solution of compound 38, prepared as described above, (10.7 g, 73.4 mmoles) in 75 ml of anhydrous pyridine. After the reaction mixture had remained for 12 hrs at 0° and then for a further 24 hrs at 8°, it was poured into 1 litre of ice-water. After 30 min of vigorous stirring, solid materials (probably ditosylates) were filtered off and discarded.

The filtrate was extracted with a 500 and then three 250 ml portions of chloroform and the combined chloroform extracts were then concentrated to 13.5 g (61.5%) of crude 1,5-anhydro-2-deoxy-6-*O*-p-toluenesulphonyl-D-*arabino*-hexitol.

ii) Acetylation

Acetic anhydride (20 ml) was added to an ice-cold solution of this crude tosylated material in 80 ml of anhydrous pyridine. After 20 hrs at room temperature, the solution was poured into a well-stirred mixture of ice and

water (600 ml). Thirty minutes later, crude 39 was filtered off, rinsed with water, and dissolved in 100 ml of hot 95% ethanol. On cooling, the solution deposited 12.4 g of 39. An analytical sample melted at 127.5-128.5° and had $[\alpha]_D^{25}$ + 49.2° (c, 0.49 in chloroform).

Anal. Calcd. for $C_{17}H_{22}O_8S$: C, 52.84; H, 5.74; S, 8.30.

Found: C, 53.05; H, 5.57; S, 8.27.

N.m.r. data, in chloroform-d: τ 2.14-2.72 (4 aromatic protons as an AA'BB' quartet, centred at 2.44); 7.54 (a 3 proton singlet; assigned to the CH_3 group of the p-toluenesulphonyl function) 8.00 (6 acetate protons); 4.82-5.34 (a 2 proton multiplet for H3 and H4).

s) 3,4-Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-6-iodo-D-*arabino*-hexitol (40)

Compound 39 (6.0 g, 20 mmoles) was dissolved in a solution of sodium iodide (6.0 g, 40 mmole) and acetone (50 ml). The solution was sealed in a pressure bottle and heated at 100° for 1 hr. After the bottle had cooled to room temperature, the liquid phase of its contents was examined by t.l.c., using 4 parts benzene to 1 part ethyl acetate as the developing agent. The t.l.c. plate showed complete and exclusive conversion of 39 to the faster moving

6-iodo derivative, (40).

The entire reaction mixture was concentrated to dryness, and then partitioned between 200 ml of chloroform and 100 ml of water. The chloroform layer was extracted with an additional 100 ml of water, dried, and then concentrated to 5.0 g (97%) of chromatographically pure 40. Recrystallization from 95% ethanol afforded 4.5 g of needle-shaped crystals with $[\alpha]_D^{25}$ + 33.8° (c, 0.51 in chloroform). They began extensive sublimation about 5° below their apparent melting point of 130-131°.

Anal. Calcd. for $C_{10}H_{15}O_5I$: C, 35.09; H, 4.42; I, 37.09.

Found: C, 35.13; H, 4.52; I, 37.03.

t) 3,4-Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-D-*arabino*-hexitol (41)

Compound 40 (3.5 g, 9.9 mmoles) was hydrogenolyzed at atmospheric pressure in a solution of ethyl acetate (50 ml) and triethylamine (1.5 g). The catalyst was 300 mg of 10% palladium-on-carbon. Six hrs after the uptake of hydrogen had ceased (12 hrs total) the mixture was filtered and concentrated to a semi-solid residue. This material was partitioned between chloroform (100 ml) and 5% aqueous sodium bicarbonate (100 ml). The aqueous layer was extracted

with a further 100 ml of chloroform and then the combined chloroform extracts were dried and concentrated to 2.1 g of chromatographically pure 41, m.p. 41-43°. The appropriate t.l.c. conditions are described on page 79. A sample recrystallized twice from Skelly B at -15° had a m.p. of 41.5-43° and $[\alpha]_D^{25}$ + 41.6° (c, 0.43 in ethanol) and $[\alpha]_D^{25}$ + 33.4 (c, 0.40 in chloroform). [Lit (70) m.p. 39-40, $[\alpha]_D$ + 45.5° (c, 1 in ethanol)].

u) 1,5-Anhydro-2,6-dideoxy-D-*arabino*-hexitol (9)

Compound 41, (1.85 g, 8.6 mmoles) was deacetylated in 50 ml of anhydrous methanol that contained about 50 mg of sodium methoxide. After the usual work-up (p. 76) the product was recrystallized from ether to a constant m.p. of 58-59.5° and $[M]_D^{25}$ - 14.5° (c, 0.22 in water).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15.

Found: C, 54.58; H, 9.14.

The n.m.r. spectrum of 9, in D_2O, is reproduced in Fig. 25, on page 77.

v) 1,5-Anhydro-2,3-dideoxy-6-*O*-triphenylmethyl-D-*erythro*-hexitol (42) as a 1:1 complex with pyridine

1,5-Anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) (8.0 g, 61 mmoles) was dissolved in 35 ml of ice-cold pyridine.

Triphenylmethyl chloride (18.0 g, 65 mmoles) was dissolved in another 50 ml of ice-cold pyridine and added to the first solution. The reaction was allowed to warm to room temperature and then stand for forty-eight hours. Then it was poured into a well stirred mixture of ice and water (300 ml) that contained 10 ml of saturated sodium bicarbonate solution. After about 1 hr the solids were isolated by filtration and then recrystallized from ether (100 ml).

The n.m.r. spectrum of the crystals that precipitated (20.0 g) indicated a 1:1 complex of 42 and pyridine. A further recrystallization from ether did not remove the pyridine signals in the n.m.r. spectrum; nor did it change the optical activity or decrease the melting point range.

M.p. 60°-100°; $[\alpha]_D^{25}$ - 32.9° (c, 0.5 in chloroform).

A t.l.c. investigation using various ratios of ethyl acetate to benzene as a developing agent failed to reveal more than one component (spray; 3% ethanolic sulphuric acid, followed by heating: test; a yellow spot that charred black).

N.m.r. spectral data, for a chloroform-d solution: τ 1.42 (a rough doublet with a spacing of 4 Hz, that is assigned to H2 and H6 of a pyridine molecule); 2.35 to 2.95 (a complex signal pattern corresponding in intensity to the 15 protons of the triphenylmethyl function and the H3, H4

and H5 protons of a pyridine molecule); 6.13 (a one proton multiplet with a total width of 25 Hz and one apparent spacing of 11 Hz that is assigned to H1 equatorial); 6.32-6.9 (6 protons, including a singlet peak for O-H); 7.7-8.85 (unresolved multiplets corresponding in intensity to four protons. The product failed to crystallize after the pyridine had been azeotropically removed with toluene.

w) 1,5-Anhydro-2,3-dideoxy-4-*O*-methyl-6-*O*-triphenylmethyl-D-*erythro*-hexitol (43)

Compound 42, as a pyridine complex (17.7 g), was dissolved in anhydrous dimethylformamide (DMF) and added to a suspension of sodium hydride (1.5 g, 63 mmole) in 50 ml of ice-cold anhydrous DMF. The mixture was stirred for 1 hr at 0°, then methyl iodide was added (20 ml) and the reaction stirred at ambient temperature for 6 hrs more. After residual sodium hydride had been destroyed by the cautious addition of methanol, the product was poured into a mixture of water (600 ml) and chloroform (250 ml). This mixture was stirred briskly for 10 minutes. Insoluble sludge was removed by filtration, rinsed with an additional 250 ml of chloroform, and then discarded.

The combined chloroform extracts were rinsed with water (100 ml) and then concentrated. The syrupy residue was triturated twice with water (500 ml) and the insoluble

43 recrystallized from methanol/ether to constant melting point and rotation. The yield of pure 43 after five such recrystallizations was 6.3 g.

M.p. 76-77°, $[\alpha]_D^{25}$ + 41.0° (c, 0.7 in chloroform).

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.24.

Found: C, 80.19; H, 7.15.

N.m.r. data, in chloroform-d: τ 2.35-3.0 (the 15 protons of the triphenylmethyl function), 6.02 (1 proton - a rough doublet with spacing of 11 Hz and a total width of 22 Hz; assigned to H1 equatorial); 6.35-7.0 (absorptions that correspond in intensity to 8 protons; the single OCH_3 peak is at 6.8).

x) 1,5-Anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol (21)

Pure 1,5-anhydro-2,3-dideoxy-4-*O*-methyl-6-*O*-triphenylmethyl-D-*erythro*-hexitol (43) (6.0 g, 15.4 mmoles) was dissolved in 50 ml of ice-cold dichloromethane. A slow stream of anhydrous hydrogen bromide was bubbled into the solution until t.l.c. (solvent system of 4 parts benzene to 1 part ethyl acetate) showed the complete conversion of 43 to triphenylmethyl bromide and the much less mobile 21.

Most of the solvent was then removed by distillation at atmospheric pressure. The remaining material was concentrated at 30° *in vacuo* (2 mm) to a semi-solid mass. The pressure was then further reduced to 0.3 mm, and 1.8 g of product was distilled using the apparatus shown in Fig. 21, with a bath temperature of 65°.

This distillate was treated with enough diethylamine to effect a basic response to pH paper (pH 1 to 14 type), and was then dried over a few Linde type 4A molecular sieves. Any excess amine was subsequently removed at a reduced pressure of 2 mm. Then, at a pressure of 0.1 mm and a bath temperature of 65°, compound 21 (1.5 g, 75%) was re-distilled into a clean, dry receiving flask. A t.l.c. using as solvent 6 parts benzene to 4 of ethyl acetate) showed that this product was chromatographically pure. A g.p.l.c. analysis, on a 6 ft, 1/4 in copper column, packed with 10% Carbowax M on 60-80 mesh Ultraport, also demonstrated the chromatographic purity of 21. It boiled at about 65° at 1 mm and had $[M]_D^{25}$ + 136.0° (c, 0.57 in water). Additional rotational data are presented in Table 20.

Anal. Calcd. for $C_6H_{14}O_3$: C, 57.51; H, 9.65.

Found: C, 57.74; H, 9.63.

N.m.r. data, in chloroform-d: τ 6.64 (the three proton singlet of the methoxyl function).

y) 1,5-Anhydro-2,3-dideoxy-6-*O*-triphenylmethyl-4-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (44)

Triphenylmethyl chloride (11.5 g, 41 mmoles) was added to a solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) (5.0 g, 38 mmoles) and pyridine (100 ml). The reaction was left undisturbed for 48 hrs at room temperature and then p-toluenesulphonyl chloride (18.0 g, 96 mmoles) was added to it. After having stood for an additional 48 hrs at room temperature, the mixture was poured into 500 ml of ice-water and after 30 minutes of vigorous stirring the syrupy, water-insoluble product was extracted into chloroform. The chloroform solution was washed with water, then with 5% sodium bicarbonate solution, and dried over sodium sulphate. After concentration to about 100 ml, the remaining pyridine was co-distilled out *in vacuo* as an azeotropic mixture with toluene.

The syrupy residue was dissolved in ether (40 ml). At 0°, the solution precipitated 10.0 g of 44 on the addition of 60 ml of hexane. A t.l.c. investigation, using 9 parts of benzene to 1 part of ethyl acetate as the mobile phase, showed that this product was chromatographically pure. The mother liquors were concentrated to 10 g of a syrup that was subsequently chromatographed on a column of silicic acid. The eluting agent was a 95 to 5 mixture of benzene and ethyl acetate. An additional 5.0 g of chromatographically

pure 44 was obtained in this manner, bringing the total yield to 75%.

A sample that had been recrystallized from ethyl acetate had a m.p. of 145-147.5° and $[\alpha]_D^{25}$ + 37.6° (c, 0.7 in chloroform).

N.m.r. spectral data, for a chloroform-d solution: τ 2.4-2.96 (a complex pattern that corresponds in intensity to the 15 protons of the trityl function and the four aromatic protons of the p-toluenesulphonyl group); 5.66 (a one proton multiplet, with a width of 22 Hz and spacing of 11 Hz); 6.38-7.26 (3 protons); 7.5-8.5 (7 protons, including the methyl singlet of the p-toluenesulphonyl function at 7.63).

z) 6-*O*-Acetyl-1,5-anhydro-2,3-dideoxy-4-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (45)

Compound 44 (2.0 g, 3.5 mmoles) was dissolved in a solution of acetic acid (10 ml) and chloroform (10 ml). A solution of 32% hydrogen bromide in acetic acid (8 ml) was added, and after stirring the mixture for 5 minutes at room temperature, the solids were filtered off. The filtrate was concentrated to about 2 ml and then partitioned between chloroform and saturated sodium bicarbonate solution. The chloroform extract was dried over anhydrous sodium

sulphate and concentrated *in vacuo*. The syrupy product was recrystallized at -15° from methanol (5 ml) and yielded 0.4 g of crystalline 45. M.p. 85.5-87.0°, $[\alpha]_D^{25}$ + 57.3° (c, 0.49 in chloroform). The mother liquors were concentrated and the residue treated with acetic anhydride and pyridine. After the usual work-up, an additional 0.35 g of 45 was obtained.

N.m.r. spectral data for 45, in chloroform-d: τ 2.1-2.7 (an AA'BB' quartet, corresponding in intensity to the four aromatic protons of the p-toluenesulphonyl function); 7.54 (a three proton singlet; assigned to the CH_3 protons of the p-toluenesulphonyl function); 8.02 (the three proton singlet of the acetate function.

aa) 1,5-Anhydro-2,3-dideoxy-4-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (46)

Compound 44 (15.0 g, 28.4 mmole) was dissolved in chloroform and the solution brought to 0°. A saturated solution of anhydrous hydrogen bromide in chloroform (50 ml) was added and the mixture left to stand at 0° for 3 hrs. Thin layer chromatography indicated the complete transfer of 44 to 46 plus triphenylmethyl bromide. The solution was concentrated and the semi-solid residue chromatographed on a 1.7 x 24 inch column of silicic acid, using a solution of 4 parts benzene to 1 part ethyl acetate as the eluting

agent. Fractions of 25 ml were collected. It was found that some acetate exchange with the solvent had occurred during this process, probably catalyzed by residual HBr.

Fraction No.	Eluted Material
1-15	NIL
10-18	trityl residues
19-25	compound 45 (1.2 g)
30-55	compound 46 (5.2 g)

The acetate, (45) was dissolved in 50 ml of anhydrous methanol and reconverted to 46, using a catalytic amount of sodium methoxide. This brought the total yield of chromatographically pure 46 to 6.2 g (75%).

N.m.r. data for 46, in chloroform-d: τ 2.12-2.72 (4 aromatic protons - an AA'BB' quartet centered at 2.42); 5.54 (1 proton - a multiplet with a total width of 30 Hz; assigned to H4); 5.8-6.9 (5 protons - the rough doublet centered at 6.06 with a spacing of 11 Hz is assigned to H1 equatorial); 7.4-8.7 (8 protons, with the O-H at 7.92 and the CH_3 of the p-toluenesulphonyl function at 7.53).

bb) 1,5-Anhydro-2,3-dideoxy-6-*O*-methyl-4-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (47)

Compound 46 (4.4 g, 15.4 mmoles) was dissolved in

50 ml of anhydrous, redistilled DMF. Barium oxide (5.0 g) and methyl iodide (10 ml) were added and the mixture gently refluxed for 60 minutes. At this point, however, a t.l.c. investigation, using as solvent a one to one mixture of benzene and ethyl acetate, showed that almost no methylation of 46 had taken place. The mixture was cooled to 0° and a slurry of sodium hydride (600 mg, 25 mmoles) in hexane was carefully added. There was immediate evolution of hydrogen, and after stirring the mixture for 4 hrs, t.l.c. showed a near quantitative conversion of 46 to a single and more mobile compound that was later identified as 47. Excess sodium hydride was destroyed with methanol and then the mixture was poured into water (200 ml) and the product extracted into chloroform (2 x 200 ml).

The combined chloroform extracts were washed with water (100 ml), dried, and then concentrated to a syrupy product (4.4 g). This product was chromatographed on a 1.75 x 30.0 inch column of silicic acid using a one to one mixture of benzene to ethyl acetate as the eluting agent. Fractions of 15 ml were collected.

Chromatographically pure 47 (3.8 g, 83%) eluted in fractions 25 to 32. It had m.p. 47.5 to 49.5° and $[\alpha]_D^{25}$ + 48.8° (c, 0.59 in chloroform). It was recrystallized from methanol to yield 2.4 g of 47 with m.p. 48-50° and $[\alpha]_D^{25}$ + 49.3° (c, 0.49 in chloroform).

Anal. Calcd. for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71; S, 10.67%.

Found: C, 56.06; H, 6.44; S, 10.54.

N.m.r. data for 47, in chloroform-d: τ 2.06-2.68 (4 aromatic protons, as an AA'BB' quartet centered at 2.39); 7.54 (a 3 proton singlet, assigned to the CH_3 of the p-toluenesulphonyl function); 6.82 (a 3 proton singlet assigned to the three methoxy protons); 5.5 (a single proton multiplet assigned to H4, with a width of about 30 Hz); 6.04 (a rough doublet with spacing of 11 Hz, assigned to H1 equatorial).

cc) 1,5-Anhydro-2,3-dideoxy-6-*O*-methyl-D-*erythro*-hexitol (20)

1,5-Anhydro-2,3-dideoxy-6-*O*-methyl-4-*O*-p-toluenesulphonyl-D-*erythro*-hexitol (47). (2.25 g, 7.5 mmole) was dissolved in 75 ml of methanol. Portions of 2% sodium amalgam were added at 30 minute intervals until starting material could no longer be detected by t.l.c. analysis, using as the mobile phase a one to one mixture of benzene and ethyl acetate. The methanolic solution was then decanted from the mercury and neutralized with carbon dioxide. It was then concentrated to a syrup that was subsequently partitioned between chloroform (200 ml) and 5% sodium carbonate solution (200 ml). The aqueous layer

was extracted again with chloroform (2 x 200 ml). The combined chloroform extracts were dried and concentrated to 1.3 g of a light oil. This oil was then purified on a column of silicic acid, using a solution of 4 parts of chloroform to 1 part of acetone as the eluting agent. A t.l.c. investigation, using this same solvent system, showed that the eluted compound 20 was chromatographically pure.

This chromatographed product was then dissolved in 3 ml of ether. Pentane (3 ml) was added and the solution left at -25° for 24 hrs. The mother liquors were then decanted (at -25°) and the recrystallized 20 (0.6 g) brought to room temperature. It melted at some point between 0° and 10°. Residual solvents were removed *in vacuo*, and solutions prepared for rotation studies in DMSO/1,2-dichloroethane. Compound 20 had b.p. (0.5 mm) about 60°, and $[M]_D^{25}$ + 84.4° (c, 0.53 in water). Additional rotational data are presented in Table 19.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65.

Found: C, 57.40; H, 9.39.

N.m.r. data, in chloroform-d: τ 6.03 (1 proton - two multiplets with a spacing of 12 Hz; assigned to H1 equatorial); 6.33-6.4 (2 protons - a "doublet" centred at 6.37; assigned to H6 and H6'); 6.6 (a singlet, corresponding in intensity to the three protons of the methoxyl function).

dd) 1,5-Anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol (22)

A solution of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) (3.9 g, 29 mmoles) in anhydrous tetrahydrofuran (THF) was slowly added to a well-stirred suspension of sodium hydride (2.4 g, 100 mmole) in anhydrous THF (75 ml). After 30 minutes, the material was cooled to 5°, and methyl iodide (15 ml) was introduced. The reaction mixture was stirred at 5° for 30 minutes and then at room temperature for an additional 60 minutes. At this point, t.l.c. investigation, using 3 parts benzene to 2 parts ethyl acetate as mobile phase, showed complete conversion of 3 to the much more mobile dimethyl derivative, 22.

Remaining sodium hydride was then destroyed by the cautious addition of methanol. The mixture was filtered, the filtrate concentrated at room temperature and 15 mm pressure, and the semi-solid residue extracted with ether (3 x 50 ml). The ether solution was then concentrated at room temperature to about 10 ml.

This 10 ml residue was subjected to distillation at 70° and a pressure of 0.1 mm. The *distillate* thus obtained was concentrated *in vacuo* (6 mm) at 45°, and then was dried over Linde type 4A molecular sieves. A t.l.c. of this oily material (3.5 g), using as a solvent system a

mixture of 3 parts benzene to 2 parts ethyl acetate, revealed only one compound, subsequently identified as compound 22. Similarly, only one component could be detected by g.p.l.c., using a 6 ft, 1/4 in copper column packed with 10% Carbowax M, on Ultraport, and a carrier gas flow of 60 ml of N_2 per minute.

Column temperature	Retention time of 22
125°C	6.4 min
135°C	3.7 min.

Compound 22, which distilled at 70° and 3 mm pressure, had $[M]_D^{25}$ + 147.0° (c, 0.53 in water). Complete optical rotation data are presented in Table 21. The infrared spectrum of a solution of 22 in carbon tetrachloride did not contain any absorptions in the region where fundamental O-H stretching occurs.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07.

Found: C, 60.06; H, 10.04.

N.m.r. data for 22, in $CDCl_3$: τ 6.0 (a one proton multiplet with a large spacing of 11 Hz; assigned to H1 equatorial); 6.54, 6.62 (two 3 proton singlets; assigned to the OCH_3 groups); 6.3-6.45 (absorptions that are assigned to H6 and H6').

4. Tables of molecular rotations

TABLE 4

Experimentally determined densities of binary solutions of 1,2-dichloroethane and dimethyl sulphoxide (DMSO)

Concentration of DMSO, in moles per litre	Solution density (d_t) in g per ml at t°C					
	d_{10}	d_{15}	d_{20}	d_{25}	d_{30}	d_{35}
0	1.268	1.261	1.253	1.246	1.239	1.232
1.3	-	1.246	1.238	1.231	1.225	1.219
4.6	-	1.208	1.202	1.196	1.190	1.184
11.7	-	1.131	1.126	1.121	1.116	1.111
Concentration of DMSO, in moles per litre	$\frac{d_{10}}{d_{25}}$	$\frac{d_{15}}{d_{25}}$	$\frac{d_{20}}{d_{25}}$	$\frac{d_{25}}{d_{25}}$	$\frac{d_{30}}{d_{25}}$	$\frac{d_{35}}{d_{25}}$
0	1.018	1.012	1.006	1.000	0.994	0.989
1.3	-	1.012	1.006	1.000	0.995	0.990
4.6	-	1.011	1.005	1.000	0.995	0.989
11.7	-	1.009	1.004	1.000	0.996	0.991

TABLE 5

Molecular rotations (°) at 20°C,

of compound $\underline{7}^{+}$ in binary 1,2-dichloroethane

and dimethyl sulphoxide (DMSO) solutions

Concentrations (moles per litre at 20°C)		
DMSO	DMSO-0.04*	$[M]_D^{20}$
0.03	-	-190.7
0.06	-	-199.6
0.12	-	-206.8
0.13	-	-209.1
0.42	-	-213.5
0.94	-	-197.1
1.31	1.27	-185.6
2.01	1.97	-164.2
2.59	2.55	-148.9
3.39	3.35	-131.6
4.28	4.24	-115.2
5.43	5.39	- 98.2
7.00	6.96	- 79.7
8.41	8.37	- 66.7
10.00	9.96	- 54.1
11.23	11.19	- 46.2
12.35	12.31	- 39.3
13.95	13.91	- 31.1

+ The concentrations of $\underline{7}$ in these solutions range from 0.0422 to 0.0434 moles per litre - at 25°C.

* The K_5 equilibrium (Fig. 31) involves the association of a second molecule of base (DMSO) with compound $\underline{7}$. The concentrations in this column include an adjustment (equal to the concentration of $\underline{7}$) for the molecule of base (DMSO) that is already hydrogen-bonded to $\underline{7}$ as a result of the K_2 equilibrium (Fig. 31).

TABLE 6

Molecular rotations (°) at 30°C, of compound 7+, in binary 1,2-dichloroethane and dimethyl sulphoxide (DMSO) solutions

Concentration (moles per litre at 30°C)		
DMSO	DMSO-0.04*	$[M]_D^{30}$
0.03	-	-186.4
0.06	-	-194.8
0.12	-	-201.5
0.13	-	-203.9
0.41	-	-211.5
0.93	-	-199.7
1.29	1.25	-189.7
5.38	5.34	-108.5
8.33	8.29	- 76.6
11.12	11.08	- 55.9
13.81	13.77	- 40.3

+ The concentrations of 7 in these solutions ranged from 0.0434 to 0.0422 moles per litre - at 25°C.

* See footnote to Table 5.

TABLE 7

Molecular rotations (°) at 20°C,

of compound $\underline{7}^{+}$ in binary

1,2-dichloroethane and 4-methylpyridine solutions

Concentrations (moles per litre at 20°C)		
4-methylpyridine	4-methylpyridine-0.04*	$[M]_D^{20}$
0.02	-	-181.8
0.06	-	-191.0
0.09	-	-197.0
0.20	-	-203.1
0.44	-	-203.7
0.90	-	-191.7
1.10	-	-184.4
1.35	-	-177.5
1.70	-	-167.7
2.21	2.17	-155.1
2.69	2.65[x]	-143.7[x]
3.13	3.09[x]	-134.4[x]
3.94	3.90[x]	-119.7[x]
4.75	4.71[x]	-107.8[x]
5.12	5.08[x]	-104.3[x]
6.70	6.66	- 89.9
7.56	7.52	- 83.8
10.24	10.20	- 75.9

+ The concentrations of $\underline{7}$ in these solutions range from 0.0423 to 0.0436 moles per litre - at 25°C.

* See footnote to Table 5.

x These data were used to obtain the average K_5 (at 20°C) for 1,2-dichloroethane/4-methylpyridine solutions (Table 27).

TABLE 8

Molecular rotations (°) at 30°C, of compound $\underline{7}^{+}$ in binary 1,2-dichloroethane and 4-methylpyridine solutions

Concentrations (moles per litre at 30°C)		
4-methylpyridine	4-methylpyridine-0.04*	$[M]_D^{30}$
0.02	-	-178.9
0.06	-	-187.3
0.09	-	-192.3
0.20	-	-198.6
0.44	-	-201.9
0.89	-	-193.3
1.09	-	-188.4
1.33	-	-182.8
1.68	-	-175.2
2.19	2.15	-164.4
2.66	2.62[x]	-154.3
3.10	3.06[x]	-146.9
3.89	3.85[x]	-132.4
4.71	4.67[x]	-121.4
5.07	5.03[x]	-118.5
6.64	6.60	-109.5
7.49	7.45	- 98.2
10.04	10.00	- 89.3

+ The concentrations of $\underline{7}$ range from 0.0423 to 0.0436 moles per litre - at 25°C.

* See footnote to Table 5.

x These data were used to obtain an average K_5 (at 30°C) for 1,2-dichloroethane/4-methylpyridine solutions (Table 27).

TABLE 9

Molecular rotations (°) at 20°C,

of compound $\underline{7}^{+}$ in binary 1,2-dichloroethane

and pyridine solutions

Concentrations (moles per litre at 20°C)		
pyridine	pyridine-0.04*	$[M]_D^{20}$
0.04	-	-183.4
0.09	-	-190.6
0.17	-	-195.7
0.50	-	-195.5
0.86	-	-188.8
1.23	-	-179.2
2.01	1.97	-160.9
2.46	2.42[x]	-150.1[x]
2.99	2.95[x]	-140.0[x]
3.54	3.50[x]	-130.2[x]
4.21	4.17[x]	-119.0[x]
4.80	4.76[x]	-114.0[x]
6.07	6.03[x]	- 97.5[x]
8.50	8.46	- 79.9
10.42	10.38	- 72.2
11.05	11.01	- 70.7
12.47	12.43	- 69.1

+ The concentrations of $\underline{7}$ in these solutions range from 0.0425 to 0.0432 moles per litre at 25°C.

* See footnote to Table 5.

x These data were used to obtain an average K_c (at 20°) for 1,2-dichloroethane/pyridine solutions (Table 27).

TABLE 10

Molecular rotations (°), at 30°C, of compound 7[+] in binary 1,2-dichloroethane and pyridine solutions

Concentrations, (moles per litre at 30°C)		
pyridine	pyridine-0.04*	$[M]_D^{30}$
0.04	-	-180.6
0.09	-	-186.6
0.17	-	-192.1
0.50	-	-194.2
0.86	-	-190.7
1.22	-	-182.8
1.99	1.95	-168.4
2.44	2.40[x]	-159.3[x]
2.96	2.92[x]	-150.5[x]
3.51	3.47[x]	-141.8[x]
4.17	4.13[x]	-131.3[x]
4.75	4.71[x]	-124.0[x]
6.01	5.97[x]	-110.5[x]
8.42	8.38	- 93.8
10.32	10.28	- 85.5
10.94	10.90	- 84.1
12.35	12.31	- 82.4

[+] The concentrations of 7 in these solutions range from 0.0425 to 0.0432 moles per litre at 25°C.

[*] See footnote to Table 5.

[x] These data were used to obtain an average K_5 (at 30°) for 1,2-dichloroethane/pyridine solutions (Table 27).

TABLE 11

Molecular rotations (°) at 20°C,

of compound 7[+] in binary 1,2-dichloroethane

and 4-chloropyridine solutions

Concentrations of 4-chloropyridine (moles per litre at 20°C)	$[M]_D^{20}$
0.05	-179.0
0.19	-187.0
0.29	-188.6
0.93	-184.8
1.39	-177.4
1.82	-168.8
3.55	-145.4

[+] The concentrations of 7 in these solutions range from 0.0426 to 0.0432 moles per litre at 25°C.

TABLE 12

Molecular rotations (°) of four solutions of compound 7+

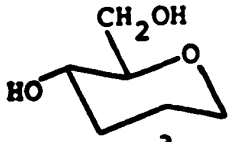
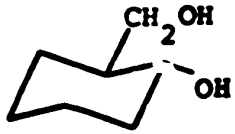
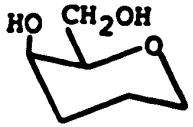
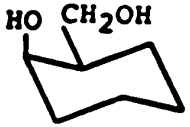
in pure 1,2-dichloroethane

Temperature (°C)	$[M]_D^t$ of individual solutions				average $[M]_D^t$
10	-176.3	-176.0	-177.0	-176.5	-176.5 ± 0.3
15	-175.7	-175.4	-176.6	-175.9	-175.9 ± 0.4
20	-174.9	-174.9	-176.0	-175.3	-175.3 ± 0.4
25	-174.3	-174.7	-175.6	-174.8	-174.9 ± 0.4
30	-173.6	-174.4	-174.8	-174.4	-174.3 ± 0.3
35	-173.1	-173.7	-174.4	-173.7	-173.7 ± 0.3

+ Concentrations of 7 range from 0.0425 to 0.0430 moles per litre at 25°C.

TABLE 13

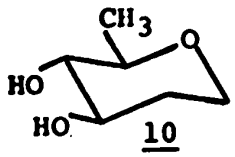
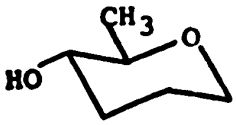
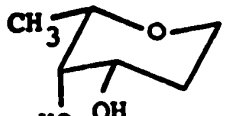
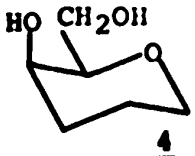
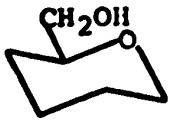
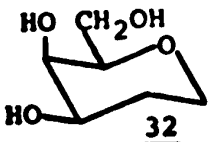
Molecular rotations (°) of related diols* recorded at several temperatures (°C) in water

Compound	$[M]_D^5$	$[M]_D^{15}$	$[M]_D^{25}$	$[M]_D^{35}$	$[M]_D^{40}$	$[M]_D^{60}$	$[M]_D^{80}$
 3	+72.3	+72.4	+70.9	+69.0	+68.5	+67.5	+65.8
 5	-75.2	-73.0	-71.5	-69.6	-69.0	-66.2	-63.0
 4	+ 9.7	+ 8.1	+ 6.8	+ 5.5	+ 5.0	+ 3.2	+ 1.4
 6	-48.7	-47.7	-46.8	-45.6	-45.1	-43.3	-41.3

* Synthesized as part of this research

TABLE 14

Molecular rotations (°) of related 1,5-anhydro-deoxyhexitols*, recorded at different temperatures in water

Compound	$[M]_D^5$	$[M]_D^{25}$	$[M]_D^{40}$	$[M]_D^{80}$
 10	-15.2	-14.5	-13.9	-13.1
 9	+39.1	+39.0	+38.9	+39.0
 33	-55.7	-54.9	-54.6	-54.7
 4	+ 9.7	+ 6.8	+ 5.0	+ 1.5
 29	+29.7	+26.2	+23.8	+19.0
 32	+74.6	+70.8	+68.5	+60.2

* Synthesized in the course of this research.

TABLE 15

Molecular rotations (°) of 1R,2S-hydroxymethylcyclohexanol[+] (5) in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide (DMSO)

Solution	Temperature, 15°C		Temperature, 25°C		Temperature, 35°C	
	Concentration of the DMSO in moles per litre	$[M]_D^{15}$	Concentration of the DMSO in moles per litre	$[M]_D^{25}$	Concentration of the DMSO in moles per litre	$[M]_D^{35}$
1	0.00	-10.5	0.00	-13.3	0.00	-15.7
2	0.20	- 5.0	0.20	- 8.6	0.20	-10.7
3	0.38	- 3.7	0.38	- 7.2	0.37	- 9.2
4	0.96	- 6.1	0.95	- 8.5	0.94	- 9.8
5	2.04	-14.1	2.02	-14.3	1.99	-14.8
6	4.59	-30.6	4.54	-30.2	4.49	-30.2
7	6.82	-42.6	6.74	-41.4	6.67	-40.7
8	10.00	-55.0	9.90	-54.1	9.80	-52.7
9	14.16	-67.3	14.00	-66.7	13.85	-65.5

[+] The concentrations of 5 range from 0.0252 to 0.0264 moles per litre at 25°C.

TABLE 16

Molecular rotations (°) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol[+] (3) in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide (DMSO)

	Temperature, 15°C		Temperature, 25°C		Temperature 35°C	
Solution	Concentration of the DMSO in moles per litre	$[M]_D^{15}$	Concentration of the DMSO in moles per litre	$[M]_D^{25}$	Concentration of the DMSO in moles per litre	$[M]_D^{35}$
1	0.00	+42.8	0.00	+42.4	0.00	+42.5
2	0.10	+32.2	0.10	+34.0	0.10	+35.8
3	0.20	+28.6	0.20	+31.1	0.19	+32.9
4	0.57	+26.0	0.56	+27.5	0.55	+29.2
5	0.98	+29.0	0.97	+29.3	0.96	+29.3
6	2.01	+36.6	1.99	+36.6	1.97	+35.9
7	4.04	+46.4	3.99	+45.3	3.95	+43.9
8	6.07	+52.2	6.00	+51.3	5.93	+49.8
9	8.38	+58.7	8.28	+57.3	8.19	+56.0
10	9.94	+60.8	9.85	+59.4	9.76	+58.0
11	14.17	+64.4	14.00	+63.9	13.85	+62.9

[+] The concentrations of 3 in solutions 2 to 11 range from 0.0268 to 0.0278 moles per litre at 25°C. The concentration of 3 in solution 1 is 0.035 moles per litre.

TABLE 17

Molecular rotations (°) at 25°C, of 1R,2R-hydroxymethy-cyclohexanol (6)[+] in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide

Concentration of the dimethyl sulphoxide in moles per litre	$[M]_D^{25}$
0.00	-46.7
0.07	-43.0
0.16	-39.5
0.44	-36.4
1.19	-37.2
1.99	-38.1
4.08	-42.0
5.92	-44.8
7.84	-46.1
9.15	-47.4
11.40	-48.3
14.00	-49.8

[+] The concentrations of 6 range from 0.0294 to 0.0299 moles per litre in these solutions

TABLE 18

Molecular rotations (°) at 25°C, of 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol[+] (4) in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide

Concentration of the dimethyl sulphoxide, in moles per litre	$[M]_D^{25}$
0.00	+ 5.5
0.16	+ 4.8
0.35	+ 4.1
0.99	+ 2.6
2.06	+ 0.4
3.88	- 2.7
7.55	- 7.4
9.84	- 8.9
14.00	-11.0

[+] The concentrations of 4 range from 0.0256 to 0.0271 moles per litre

TABLE 19

Molecular rotations (°) at 25°C, of 1,5-anhydro-2,3-dideoxy-6-*O*-methyl-D-*erythro*-hexitol (20) in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide

Concentration of the dimethyl sulphoxide, in moles per litre	$[M]_D^{25}$
0.00	- 0.8
0.13	+13.2
0.34	+25.4
0.71	+39.6
1.94	+59.0
2.55	+63.4
5.14	+68.6
6.55	+69.9
9.24	+71.3
10.65	+71.6
14.00	+69.6

+ The concentrations of 20 range from 0.0235 to 0.0246 moles per litre

TABLE 20

Molecular rotations (°) at 25°C, of

1,5-anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol[+] (21)

in binary solutions of 1,2-dichloroethane

and dimethyl sulphoxide

Concentration of the dimethyl sulphoxide, in moles per litre	$[M]_D^{25}$
0.00	+138.0
0.50	+137.3
3.98	+138.0
14.00	+137.6

[+] The concentrations of 21 range from 0.0270 to 0.0286 moles per litre.

TABLE 21

Molecular rotations (°) at 25°C, of 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol[+] (22) in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide

Concentration of the dimethyl sulphoxide, in moles per litre	$[M]_D^{25}$
0.00	133.7
0.39	133.8
1.15	135.4
5.95	136.4
14.00	136.7

[+] The concentrations of 22 range from 0.0214 to 0.0251 moles per litre.

DISCUSSION

1. The effect of solvent and temperature changes on the molecular rotation of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7)

The object of this research was to gain an improved understanding of how the nature of the solvent can effect the relative rotameric populations of the hydroxymethyl function of compounds that are simple analogs of hexopyranoses and hexopyranosides. In an "inert" solvent such as 1,2-dichloroethane intramolecular hydrogen bond formation was expected to be important in determining the relative stabilities of individual conformations of this function. For example, the primary hydroxyl function of all three rotamers of 3 and two of the rotamers of 4 can engage in such bonding (Fig. 26).

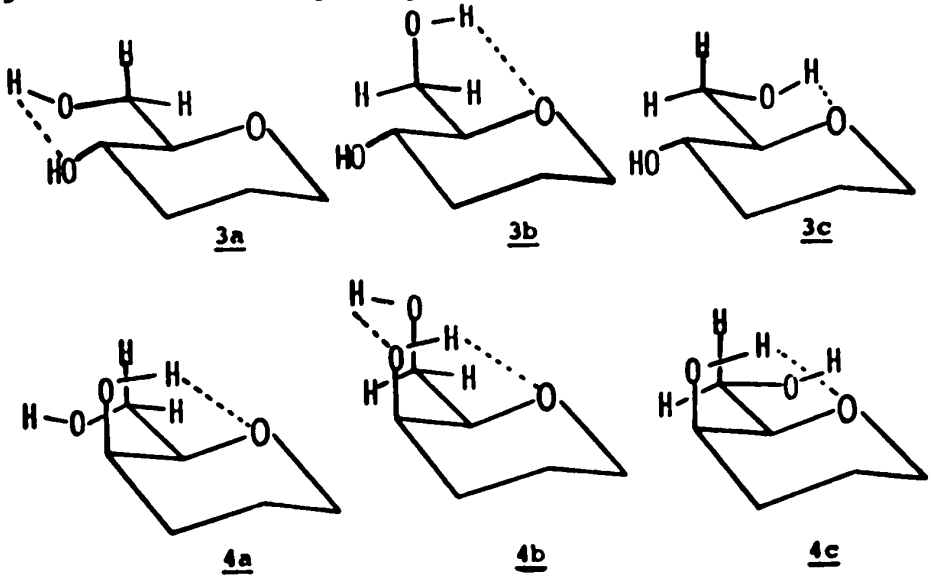
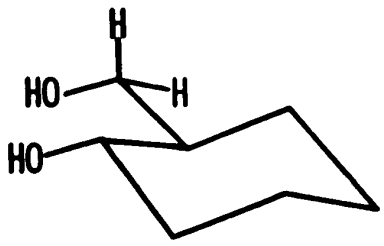


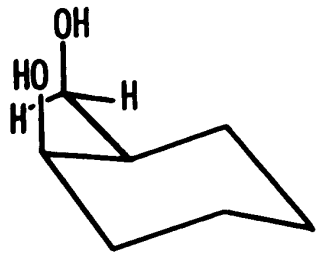
Fig. 26: Rotameric conformations of compounds 3 and 4.

Lemieux and Martin (9) have recently demonstrated that when 3 is dissolved in 1,2-dichloroethane, small amounts of DMSO can increase the stability of 3a relative to 3b and 3c. This apparent increase in the strength of the 1,3-intramolecular hydrogen bond in 3a is in accordance with the earlier observations of Lemieux and Pavia (35), who have explained such effects in terms of "hydrogen-bond conjugation" (see pp. 22 and 42). One aspect of the present project was to provide evidence for this phenomenon in the 5a conformation of compound 5, which is the carbocyclic analog of 3a.

The investigation was to be extended to include 4b and 6b, whose hydroxyl groups also have the arrangement necessary for hydrogen-bond conjugation to occur.



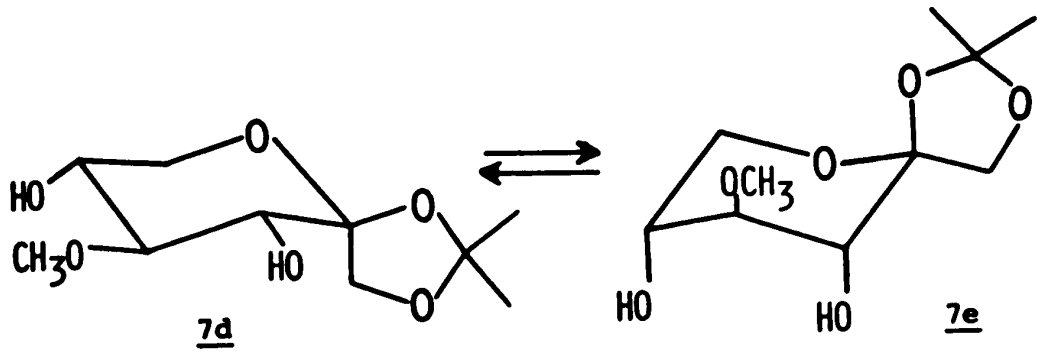
5a



6b

Previous investigations of hydrogen-bond conjugation had been carried out at only one temperature and with only one solvent system, namely 1,2-dichloroethane and DMSO (9,35). For example, Lemieux and Pavia had used

this solvent system to prepare the rotation curve[+] of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) at 25° and had reported a very pronounced inflection point. Compound 7 is readily available in quantity and in a highly pure state. It was considered that an important first step in the present research would be to carry out a more detailed investigation of its rotational behaviour, once again using 1,2-dichloroethane as an "inert" solvent, but varying the nature of the hydrogen-bond-accepting base in this solvent as well as the temperature of the solutions. Although it is structurally a more complex molecule than the above-mentioned diols, it is considered on the basis of conformational analysis that the changes in conformation that significantly affect the rotation of 7 should be restricted to the changes in equilibrium between the two solvated chair conformations that are shown below.



7d ⇌ 7e

+ A plot the $[M]_D^{25}$ of 7 in binary DMSO/1,2-dichloroethane solutions vs the percentage of DMSO in the solutions

The rotation curves that were obtained from the molecular rotations of 7 in 1,2-dichloroethane/DMSO solutions at temperatures of 20°C and 30°C are presented in Fig. 27. The individual solutions of 7 that comprise these curves were prepared at 25° and then their rotations recorded at these two temperatures. These rotational data appear in Tables 5 and 6 (pp. 105 and 106). These rotations, as well as the DMSO concentrations that accompany them, were corrected for the approximate changes in solution volumes relative to their values at 25°. Average values of 1.005 and 0.995 were used for $(\frac{d_{20}}{d_{25}})$ and $(\frac{d_{30}}{d_{25}})$ respectively, in the general calculations on p. 54. These average density ratios were obtained from the experimentally determined data that are listed in Table 4 (p. 104).

The effects that increasing concentrations of 4-methylpyridine, pyridine and 4-chloropyridine have on the molecular rotations of solutions of 7 in 1,2-dichloroethane are compared in Fig. 28, 29 and 30. The rotational data that were used to plot these curves are listed in Tables 7 to 11 (pp. 107 to 111). The individual solutions were all made up at 25°C and then their rotations were recorded at 20°C and 30°C.[+] Corrections for volume

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[+] Because of the unstable nature of 4-chloropyridine, (71,72) a complete rotation curve was not prepared for this base. The rotations of solutions containing it were only recorded at 20°C, as soon as possible after preparation.

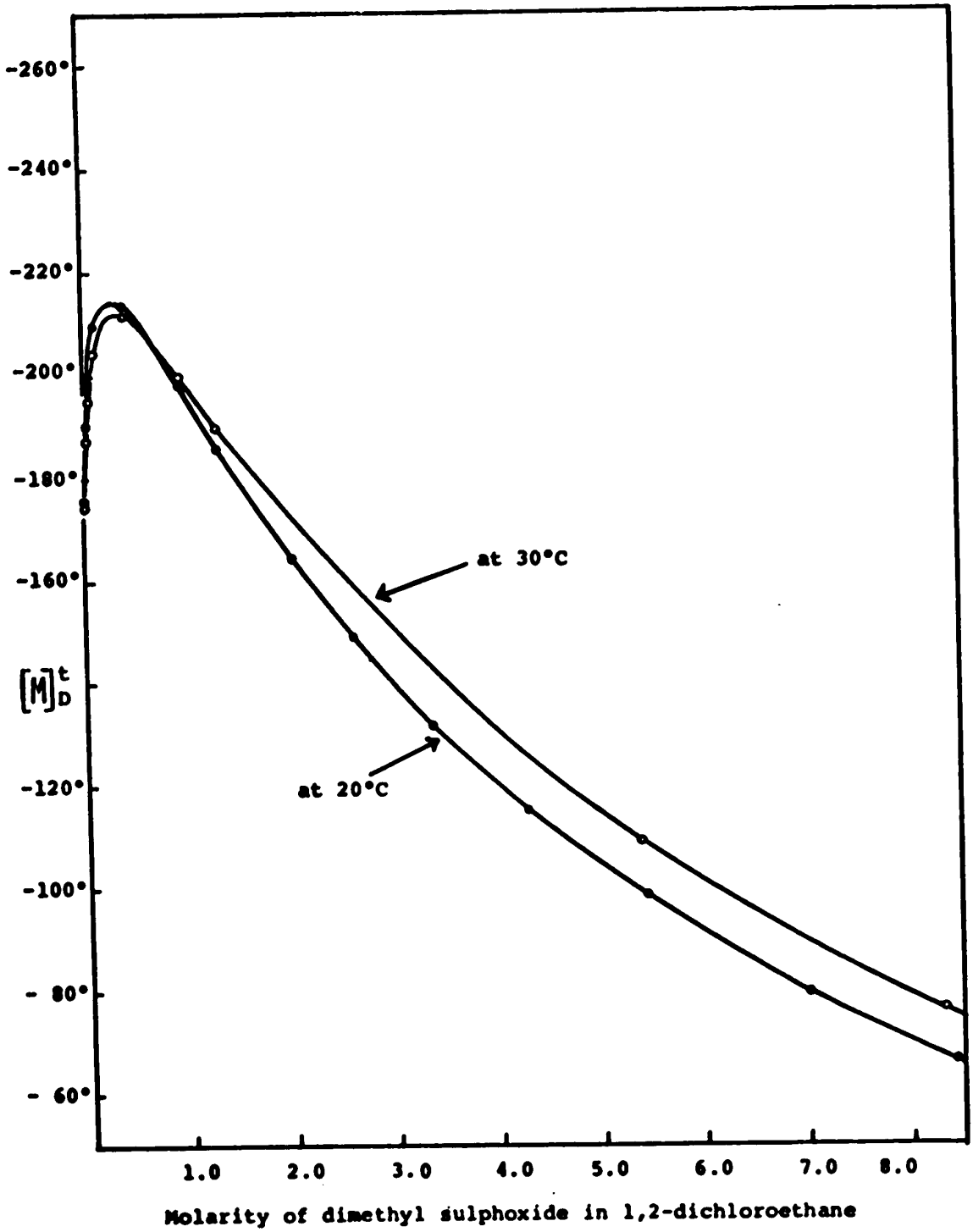

Fig. 27: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotations at 20°C and at 30°C of solutions of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) in 1,2-dichloroethane.

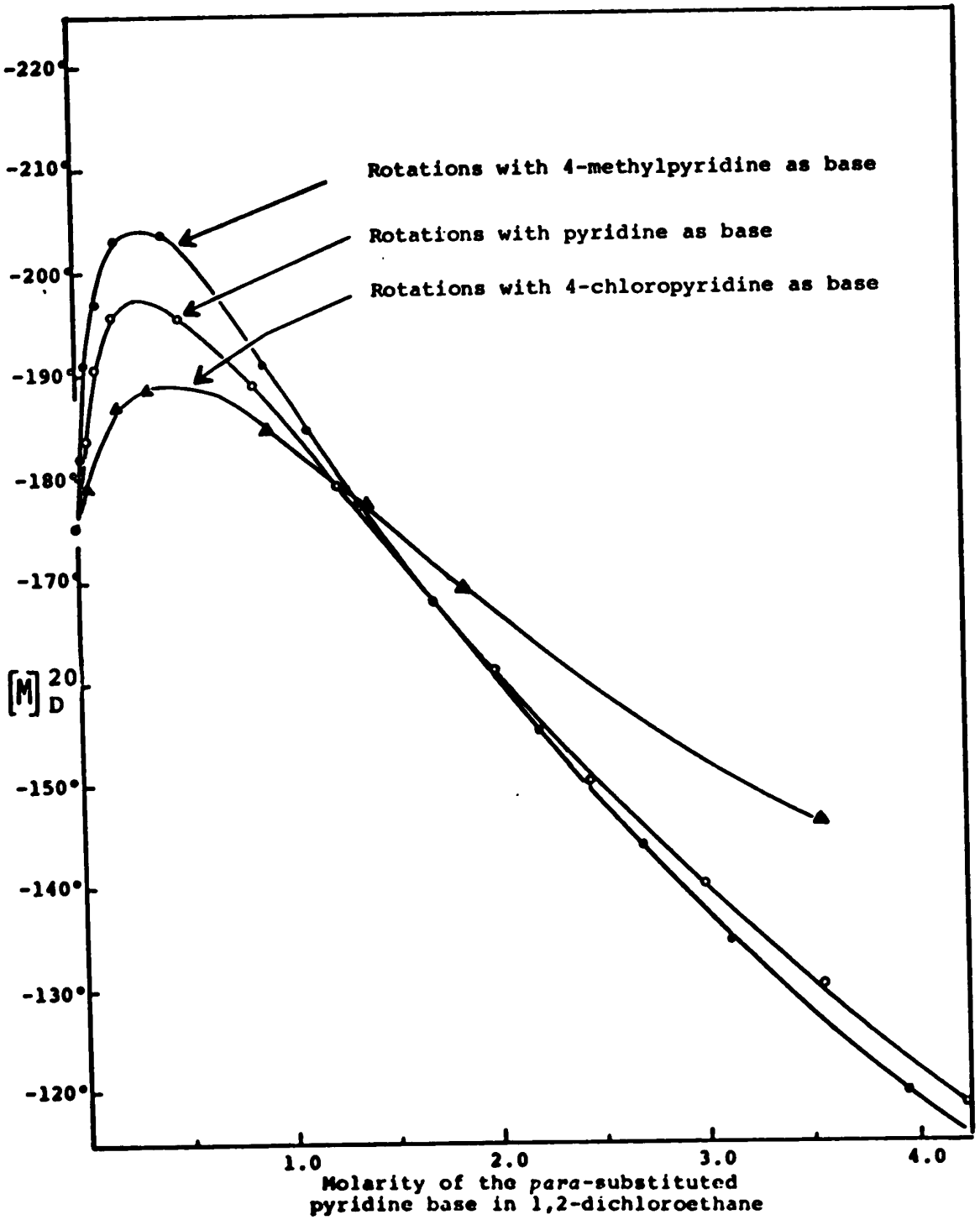

Fig. 28: The effect of increasing concentration of different *para*-substituted pyridine bases on the molecular rotations at 20°C of solutions of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) in 1,2-dichloroethane.

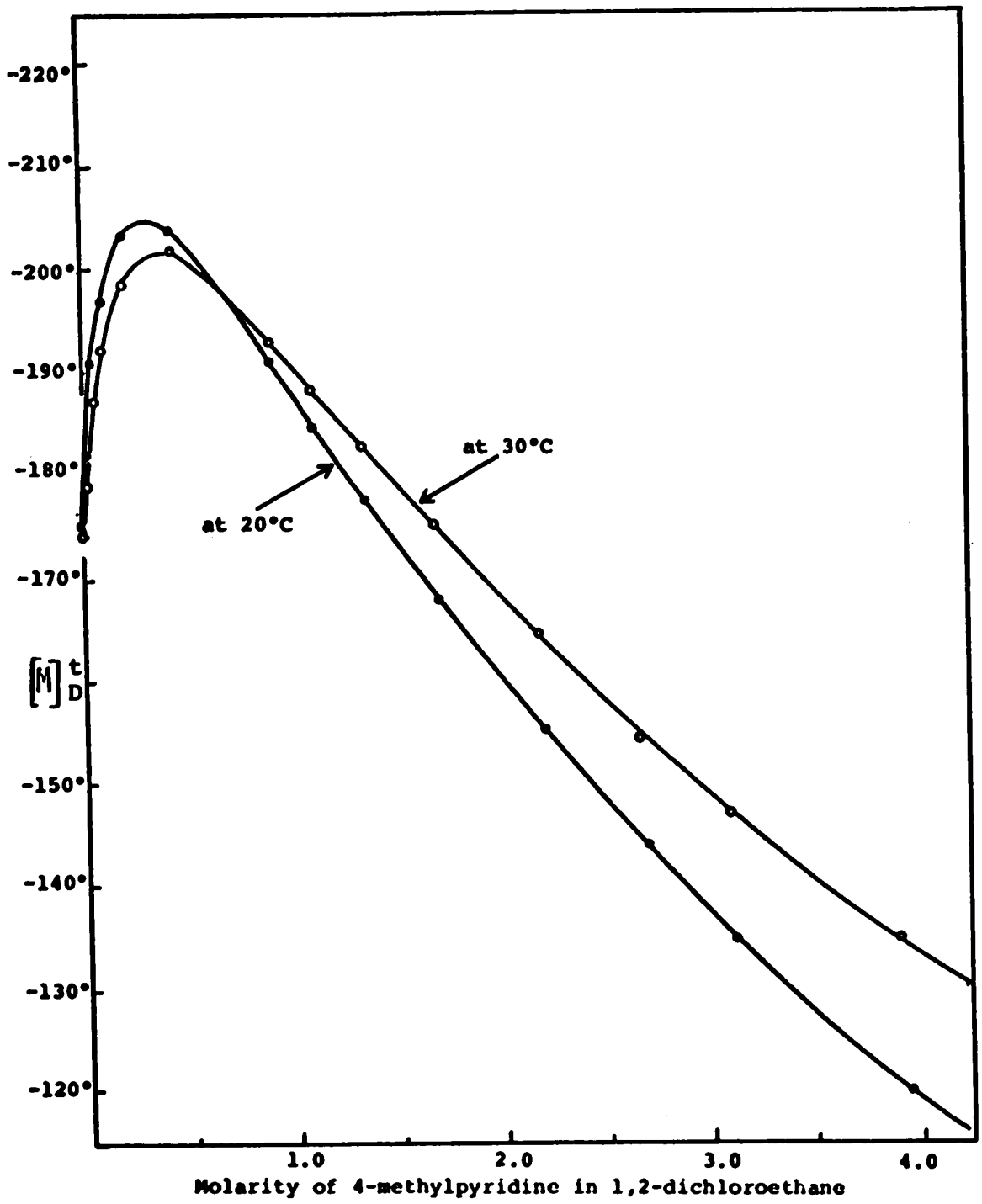

Fig. 29: The effect of increasing concentration of 4-methylpyridine on the molecular rotations at 20°C and at 30°C of solutions of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) in 1,2-dichloroethane.

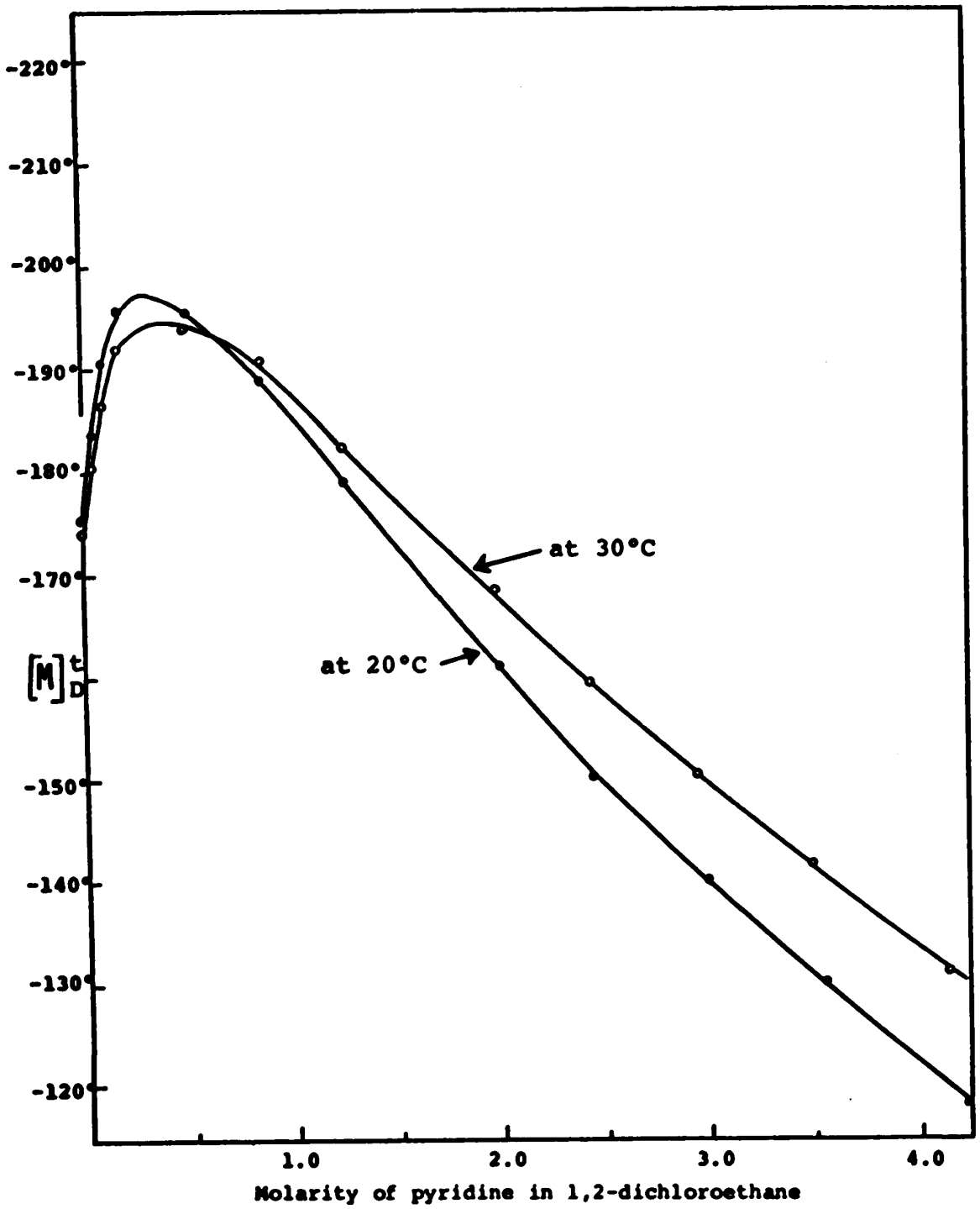

Fig. 30: The effect of increasing concentration of pyridine of the molecular rotations at 20°C and at 30°C of solutions of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) in 1,2-dichloroethane.

changes were once again necessary in the calculations of molecular rotations. Average values of 1.005 and 0.995 were used for $(\frac{d_{20}}{d_{25}})$ and $(\frac{d_{30}}{d_{25}})$ respectively, in the general calculation on page 54.

Table 12 (p. 112) lists the average molecular rotations of four solutions of 7 in pure 1,2-dichloroethane; obtained at 5° intervals between temperatures of 10°C and 35°C. These individual solutions were all prepared at 25°C. The density ratios of pure 1,2-dichloroethane that were incorporated into calculations of their molecular rotations can be found in Table 4 (p. 104).

By assuming that the molecular rotation $[M]_D^t$ of a solution of 7 is governed principally by the chair-chair equilibrium position of this compound, it is possible to derive equation (5),* which relates the equilibrium constant K_1 (at t°C) to the molecular rotation of 7 in an "inert" solvent such as 1,2-dichloroethane. The molecular rotations of the 7d and 7e chair conformations ($[M_d]$ and $[M_e]$) also appear in equation (5), so that a knowledge of their values is a prerequisite for its solution.

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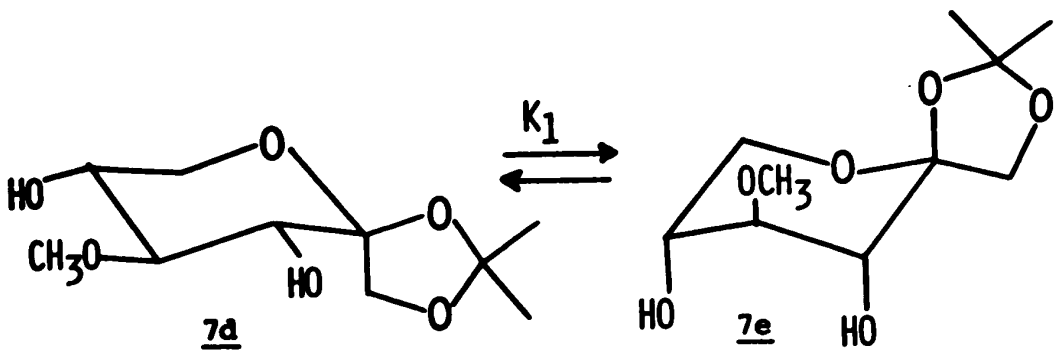
* See page 131.



7d 7e

$$K_1 = \frac{X_e}{X_d} \tag{1}$$

where X_e and X_d are the mole fractions of the 7e and 7d conformations

$$K_1 = \frac{X_e}{1-X_e} \tag{2}$$

$$[M]_D^t = X_d[M_d] + X_e[M_e]$$

$$= (1-X_e)[M_d] + X_e[M_e] \tag{3}$$

$$\therefore X_e = \frac{[M]_D^t - [M_d]}{[M_e] - [M_d]} \tag{4}$$

Combining (4) and (2)

$$K_1 \text{ (at } t°C) = \frac{[M]_D^t - [M_d]}{[M_e] - [M]_D^t} \tag{5}$$

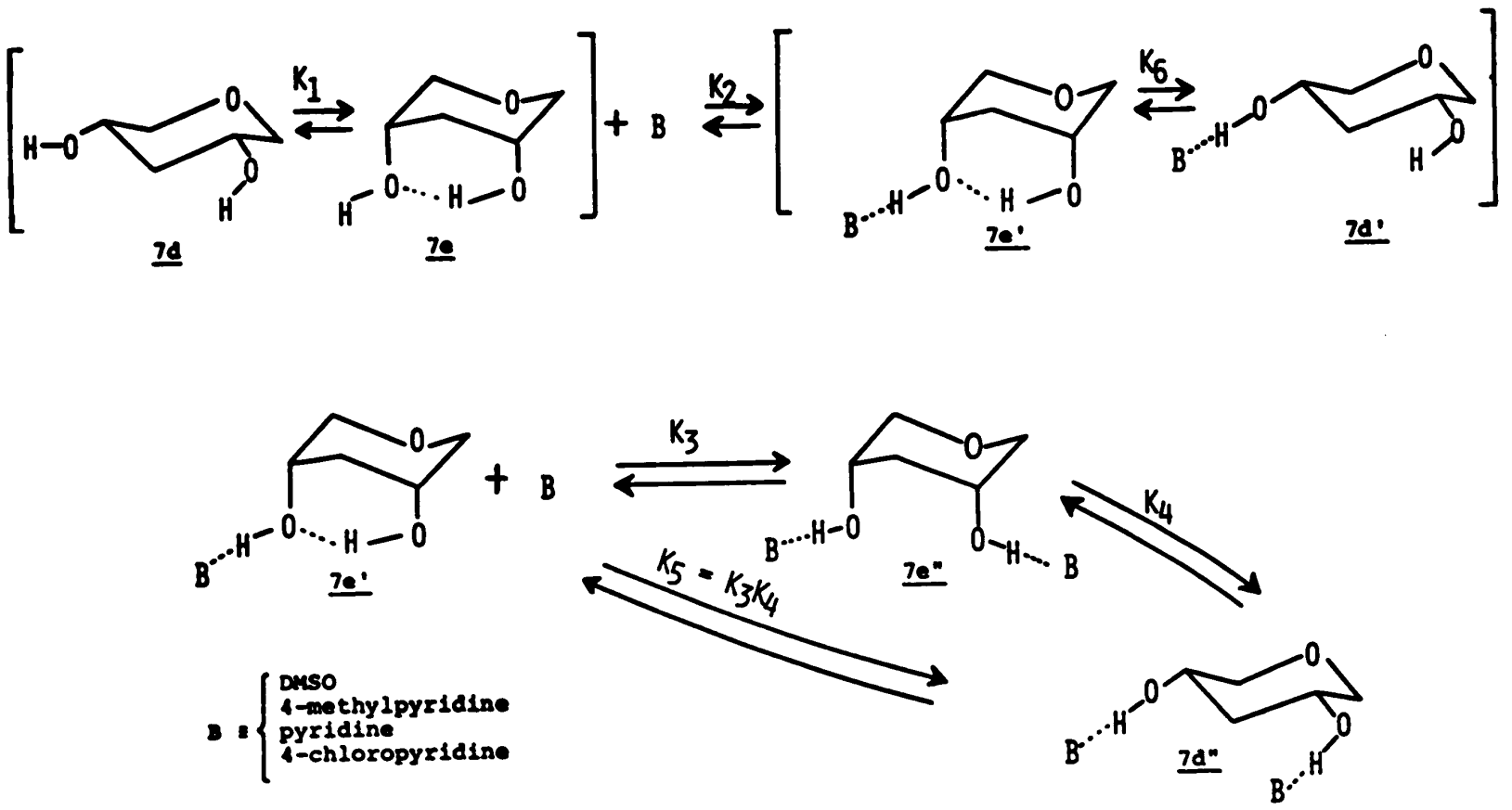


Fig. 31: Conformational equilibria depicted in the form of abbreviated formulae for 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose, when dissolved in 1,2-dichloroethane containing a hydrogen-bond-accepting base, (B).

Values for $[M_{\underline{d}}]$ and $[M_{\underline{e}}]$ cannot be reliably estimated by simple empirical procedures (9,10,12) due to the rather complex structures of 7d and 7e. However, experimental estimates of their values can be obtained from the molecular rotations of 7 in solutions whose DMSO concentrations are large enough that the chair-chair equilibrium is controlled by the equilibrium constant designated as K_5 in Fig. 31.

The following analysis of the K_5 equilibrium of 1,2-dichloroethane/DMSO solutions of 7 involves certain assumptions. It is assumed that $[M_{\underline{d}''}]$, the molecular rotation of 7d", is approximately equal in value to $[M_{\underline{d}}]$, and that $[M_{\underline{e}'}]$, the molecular rotational 7e', is about equal to $[M_{\underline{e}}]$. Structure 7e", which is no longer stabilized by a 1,3-type hydrogen bond, but instead has two opposing DMSO-solvated hydroxyl functions, may be considered to be so unstable that it exists only in negligible amounts at any DMSO concentration. It is also proposed that the first molecule of DMSO will hydrogen bond with 7d or 7e to form 7e' almost quantitatively with respect to 7d'. In other words, K_6 will be much less than unity. Structure 7d' has been assigned this small population on the assumption that the conjugated hydrogen bonds impart a particular stability to 7e'. Once the DMSO concentration has reached the point that there are only small amounts of the non-solvated 7d and 7e conformations in solution, the principal structures

will be 7e' and 7d", and the molecular rotation will be determined by K_5. Subject to the validity of these assumptions, the sum of the mole fractions of 7e' and 7d", ($X_{e'} + X_{d"}$), can be equated to unity.

The following analysis relates $[M_d]$, $[M_e]$, and K_5 to the observed molecular rotations, $[M]_D^t$, and the concentration of DMSO, referred to as [B].

$$7e' + B \overset{K_5}{\rightleftharpoons} 7d" \tag{7}$$

$$K_5 = \frac{X_{d"}}{[B]\ X_{e'}} = \frac{1-X_{e'}}{[B]\ X_{e'}} \tag{8}$$

$$[M]_D^t = [M_d"]\ X_{d"} + [M_e']\ X_{e'}$$

$$= [M_d]X_{d"} + [M_e]X_{e'} \tag{9}$$

Substituting $X_{d"} + X_{e'} = 1$ into (9), and rearranging,

$$X_{e'} = \frac{[M]_D^t - [M_d]}{[M_e] - [M_d]} \tag{10}$$

Substituting (10) into (8),

$$K_5 = \frac{1}{[B]} \times \frac{[M_e] - [M]_D^t}{[M]_D^t - [M_d]} \tag{11}$$

and rearranging (11),

$$[B]K_5[M]_D^t - [B]K_5[M_d] = [M_e] - [M]_D^t \tag{12}$$

Equation (12) contains three unknown physical constants, namely, K_5, $[M_{\underline{d}}]$ and $[M_{\underline{e}}]$, as well as two experimental variables, $[M]_D^t$ and the DMSO concentration associated with it. Three points on the rotation curve provide three simultaneous equations in the three unknown values of K_5, $[M_{\underline{d}}]$ and $[M_{\underline{e}}]$.

Table 22 lists nine sets of three points that were used in nine separate calculations of $[M_{\underline{d}}]$, $[M_{\underline{e}}]$ and K_5. These points were obtained from the rotational data of 7 in binary 1,2-dichloroethane and DMSO solutions at 20°C. Table 23 lists the calculated $[M_{\underline{d}}]$, $[M_{\underline{e}}]$ and K_5 values that were obtained in this manner. The constancy of these values clearly appears to justify the approach taken.

The average calculated values of $[M_{\underline{d}}]$ and $[M_{\underline{e}}]$ that are shown in Table 23 were assumed to be independent of temperature and were inserted into equation (5). Values of K_1 (Fig. 31) were then calculated at several temperatures using the molecular rotational data for solutions of 7 in pure 1,2-dichloroethane. These values, and the free energy, entropy and enthalpy changes that are associated with them, are presented in Table 24.

TABLE 22

Rotational data for 7, in 1,2-dichloroethane and DMSO solutions, used to solve equation (12) for $[M_d]$, $[M_e]$ and K_5 (at 20°C)

a. Data from individual solutions (at 20°C)+

Concentration of DMSO ⟶	1.27	1.97	2.55	3.35	4.24	5.39	6.96	8.37	9.96
$-[M]_D^{20}$ ⟶	185.6	164.2	148.9	131.6	115.2	98.2	79.7	66.7	54.1

b. Sets of above data used to obtain three equations in K_5, $[M_d]$ and $[M_e]$

Set*									
1.			✓		✓			✓	
2.	✓		✓			✓			
3.		✓		✓			✓		
4.	✓			✓					✓
5.	✓				✓		✓		
6.		✓				✓		✓	
7.				✓		✓			✓
8.					✓		✓	✓	
9.		✓		✓		✓			

+ Obtained from Table 5.

* Each ✓ refers to the two figures above it in section a of this Table.

TABLE 23

The values of $[M_{\underline{d}}]$, $[M_{\underline{e}}]$ and K_5 calculated from the rotational data of 7 in 1,2-dichloroethane/DMSO solutions at 20°C

Set[+]	$[M_{\underline{d}}]$ (°)	$[M_{\underline{e}}]$ (°)	K_5 (moles^{-1})
1.	+51.0	-237.0	0.173
2.	+46.3	-238.5	0.180
3.	+53.2	-236.9	0.170
4.	+54.3	-237.5	0.170
5.	+50.1	-237.8	0.175
6.	+52.5	-236.6	0.170
7.	+57.2	-234.7	0.163
8.	+49.9	-238.4	0.176
9.	+51.5	-237.1	0.172

Average value for $[M_{\underline{d}}]$ = +51.8 ± 2.2

Average value for $[M_{\underline{e}}]$ = -237.2 ± 0.8

Average K_5 = 0.172 ± 0.004 (at 20°C)

[+] See Table 22.

TABLE 24

Values of ΔG_1, ΔH_1 and ΔS_1, calculated from values of K_1 for solutions of compound 7 in pure 1,2-dichloroethane

Temperature, °C	K_1 +	ΔG_1 (kcal/mole)	ΔS_1 (e.u.)	ΔH_1 (kcal/mole)
10	3.76	-0.74	+1.2	
15	3.72	-0.75	+1.2	
20	3.67	-0.76	+1.3	-0.4*
25	3.64	-0.76	+1.2	
30	3.59	-0.77	+1.2	
35	3.55	-0.77	+1.2	

+ This was calculated by substituting the average molecular rotations in Table 12 into equation (5), and solving it using $[M_d]$ = +51.8° and $[M_e]$ = -237.2°.

* This was calculated from the slope of the plot of log K_1 vs 1/T (°K) that is shown in Fig. 32.

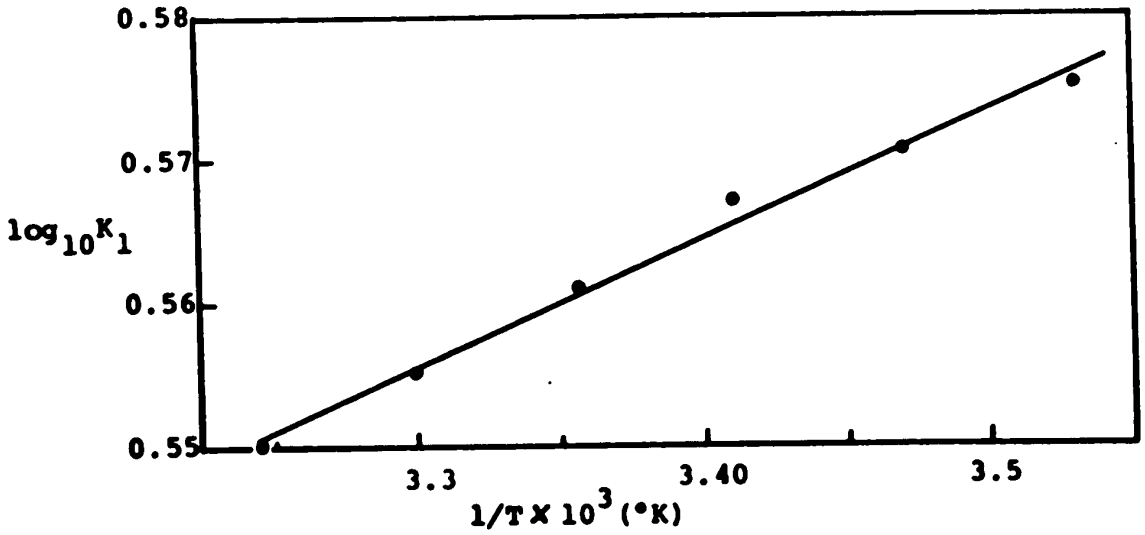


Fig. 32: Log K_1 vs 1/T(°K) for compound 7 in 1,2-dichloroethane.

The value of K_1 that is obtained by this molecular rotation analysis (3.64 at 25°C) corresponds to an equilibrium mixture that is 78.5% 7e and 22.5% 7d at 25°C. The general validity of this estimate is supported by the following discussion of the i.r. spectral data of the solution of 7 in 1,2-dichloroethane.

This i.r. spectrum of 7 contains two overlapping absorption bands in the hydroxyl stretching region (Table 35 p. 206). The first band, which is 1.75 more intense than the second, is centred at 3565 cm^{-1}, with a shoulder at about 3585 cm^{-1}. In 1,2-dichloroethane, such an absorption can correspond to either free hydroxyl functions or to hydroxyl functions that are engaged in 1,2-intramolecular hydrogen[+] bonds (see p. 211). Therefore, it represents the two hydroxyl functions of 7d, as well as that hydroxyl function of 7e whose proton is not a part of the 1,3-intramolecular hydrogen bond. The second, and less intense band is centred at 3490 cm^{-1}. In 1,2-dichloroethane absorption bands centred at about 3500 cm^{-1} appear to be

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[+] The hydroxyl functions that give rise to this second band are most likely extensively engaged in 1,2-intramolecular hydrogen bonds with neighbouring *vicinal* oxygen atoms. The shoulder absorption at 3585 cm^{-1} may represent what free OH there actually is. Because a hydrogen-bond accepting base such as DMSO is capable of strengthening only the 1,3-type hydrogen bond between the two OH groups, it is the only one that has been indicated in the structural diagrams of 7. Neither these diagrams or their discussion are meant to imply that 1,2-type bonds do not exist in a solution of 7.

characteristic of hydroxyl functions that are engaged in 1,3-intramolecular hydrogen bonds (see pp. 26 and 209). Therefore this band represents only that hydroxyl group of 7e whose proton bridges the two opposing oxygen atoms.

If one accepts the concept (41,49) that the relative intensities, per mole, are *approximately* the same for both the intramolecularly hydrogen-bonded and the free hydroxyl functions of diols such as $\underline{7}^{+}$, the i.r. data obtained for the solution of 7 in 1,2-dichloroethane can be used to estimate a value for K_1.

$$\frac{1.75}{1} = \frac{\text{the intensity of the absorption band at 3565 cm}^{-1}}{\text{the intensity of the absorption band at 3490 cm}^{-1}}$$

$$= \frac{\text{contributions from the two OH groups of 7d + one of the OH groups of 7e}}{\text{contributions from one of the OH groups of 7e}}$$

$$= \frac{2X_d+X_e}{X_e} \text{ ; where } X_d+X_e = 1$$

$$= \frac{2-X_e}{X_e} \text{ ; from which } X_e = 0.725 \text{ (7e = 72.5\%)}$$

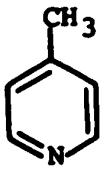
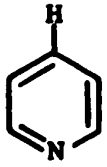
$$X_d = 0.275 \text{ (7d = 27.5\%)} \qquad K_1 = \frac{X_e}{X_d} = 2.6$$

This value of K_1 (2.6 at room temperature) and the fractional populations that are associated with it are not substantially different from the corresponding values that were obtained by molecular rotation analysis.

+ Further support for this concept can be found on pages 209 and 210.

TABLE 25

Pyridine bases, and their pK_b values

Compound	pK_b	ref.
	8.2	73
	9.0	73
	11.3	74

The molecular rotations of solutions of 7 that contain only a small amount of a hydrogen-bond-accepting base will now be discussed. It has been shown that both ΔG and ΔH values associated with hydrogen bond formation between substituted pyridines and simple alcohols become more negative as the pyridine basicities increase (75). This is certainly reasonable, as both hydrogen bond formation and conjugate acid formation involve the lone pair electrons of the nitrogen atom. Both will be promoted as the ability of the nitrogen to share its electrons increases. The choice of *para*-substitution for the pyridines used in this

present investigation (Table 25) was based on the concept that such remote substitution effects the electronic properties of the nitrogen atom without substantially altering the steric requirement for hydrogen bond formation.

Fig. 28 shows that the three pyridines in Table 25 all have the ability (in low concentrations) to shift the absolute rotations of solutions of 7 in 1,2-dichloroethane towards the value expected for the intramolecularly hydrogen-bonded conformation (7e). It is, however, apparent that this ability, like the intermolecular hydrogen bond energy for these bases, increases with the basicity of the substituted pyridines.

The size of the increase in the rotation of 7 that accompanies the addition of a small amount of these bases will obviously depend on the stability of 7e' relative to 7d' (Fig. 31). The greater this stability, or the smaller the value of K_6, the greater will be the increase in the rotation of the solution. Of course, the stability of 7e' relative to 7d' must be greater than that of 7e relative to 7d in order for any increase to occur. It is apparent from Fig. 28 that this condition is met by all three of the *para*-substituted pyridines.

Consider structure 7e'. If the basicity of the substituted pyridine is increased by a change of the *para*-substituent, the strength of the intermolecular hydrogen

bond between the nitrogen atom and the H-O5 proton[+] should increase (75). This will increase the induced polarization in H-O5 (see p. 21), which, in turn, will improve the ability of O5 to act as the acceptor for the H-O3 proton. On this basis, the intramolecular hydrogen bond strength in 7e' will increase with increasing pyridine basicity. This means that the stability of 7e' relative to 7d', and therefore the size of the increase in rotation, should be greater for 4-methylpyridine than for 4-chloropyridine, as was found (Fig. 28).

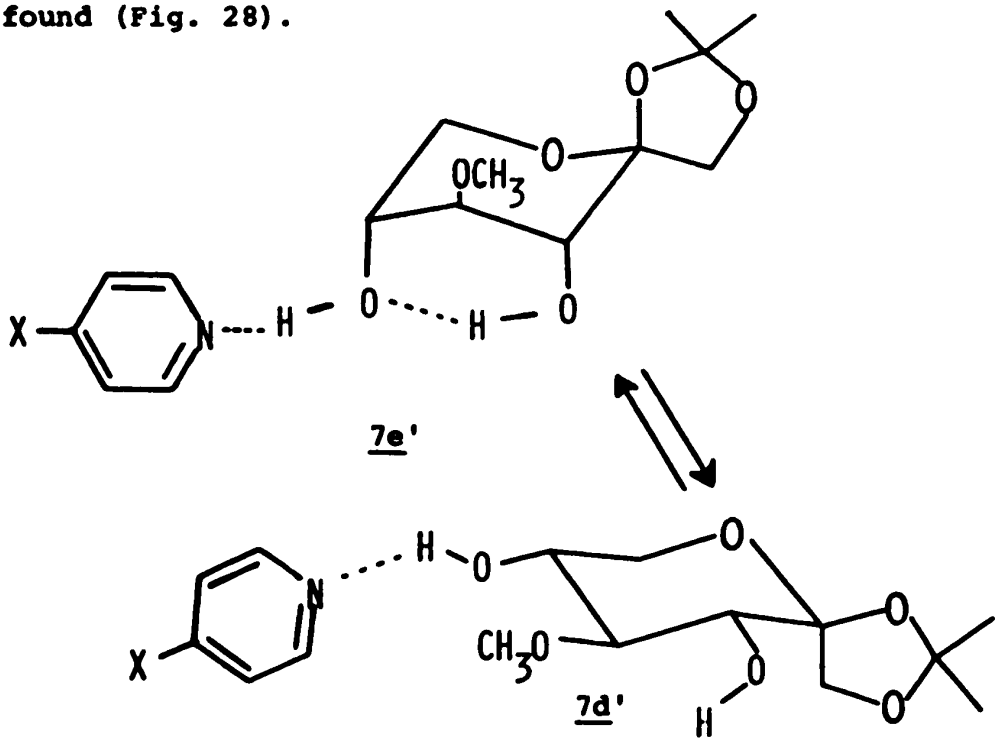


Fig. 33: Compound 7, hydrogen-bonded to a *para*-substituted pyridine.

[+] An n.m.r. study of 7 in benzene/DMSO solutions indicated that the H-O3 proton is the one engaged in the intramolecular hydrogen bond at low concentrations of DMSO (35). It is reasonable to expect that such behaviour will also apply to the solvent systems under discussion here.

The increase in the absolute rotation of 7 will not only depend on the relative stabilities of 7e' and 7d', but also on the total amount of 7e' and 7d' in the solution. For small amounts of the pyridine bases, this second factor is controlled by the equilibrium that is designated by K_2 in Fig. 31.

$$(7d \overset{K_1}{\rightleftharpoons} 7e) + \text{base} \overset{K_2}{\rightleftharpoons} (7e' \rightleftharpoons 7d')$$

This equilibrium involves the formation of an intermolecular hydrogen bond with base, so that the magnitude of K_2 should increase if the basicity of the substituted pyridine is increased. This means that more of the 7e' ⇄ 7d' equilibrium mixture can form from a given amount of 4-methylpyridine than can form from the same amount of 4-chloropyridine.

The preceding discussions account for the differing abilities of the *para*-substituted pyridines in Table 25 to increase the rotation of 7. Fig. 27, 29 and 30 show that the solution temperature is also a factor in determining the rotation of solutions of 7 that contain a small amount of a hydrogen-bond-accepting base; specifically, DMSO, 4-methylpyridine or pyridine. It is seen that the rotations of these solutions are shifted to greater absolute values by a 10° decrease in temperature. In view of the data in Table 12, this effect is too big to be explained by a temperature effect on the 7d ⇄ 7e equilibrium. It can

however be rationalized on the basis of a shift in the 7d' ⇌ 7e' equilibrium. That is, the decrease in temperature should shift this equilibrium to the right, if, as expected, 7e' is more stable than 7d'.

A second contributing factor could be an increase in the value of K_2. From an enthalpy standpoint, intermolecular hydrogen bond formation is a favourable process. For example, ΔH values of about -4 kcal per mole have been reported for the energies of intermolecular hydrogen bonds between both pyridine and 4-methylpyridine and simple alcohols (75,76,77,78). Because of the intermolecular hydrogen bond formation, the ΔH value that is associated with the K_2 equilibrium should be negative. According to the van't Hoff equation, this means that a decrease in solution temperature should result in an increase in the magnitude of K_2. This produces more of the equilibrium mixture of 7e' and 7d', and, as a result, the absolute rotation of the solution increases.

This temperature effect is reversed for moderate to high concentrations of hydrogen-bond-accepting bases. The rotations of such solutions are shifted to lower absolute values by a 10° decrease in temperature (see Figs. 27, 29 and 30). These shifts, for the following reasons, are attributed to changes in the equilibrium constant that is designated K_5 (see Fig. 31).

$$\underline{7e}' + B \overset{K_5}{\rightleftharpoons} \underline{7d}''$$

Equation 12 (p. 134) was solved for K_5 (at 30°C) using the average values of $[M_{\underline{d}}]$ and $[M_{\underline{e}}]$ that appear in Table 23 and the rotational data of $\underline{7}$ in 1,2-dichloroethane/DMSO solutions at 30°C. The individual and average K_5 values that were obtained are listed in Table 26. Free energy, entropy and enthalpy changes (ΔG_5, ΔS_5, ΔH_5) derived from the average K_5 values (at 20° and 30°C) of the 1,2-dichloroethane/DMSO solutions of $\underline{7}$ appear in Table 27.

TABLE 26

Calculated K_5 values ($moles^{-1}$) for solutions of $\underline{7}$ in 1,2-dichloroethane and DMSO at 30°C

Concentration of DMSO in moles per litre	$[M]_D^{30}$	K_5 + (at 30°)
1.25	-189.7	0.157
5.34	-108.5	0.150
8.29	- 76.6	0.151
11.08	- 55.9	0.152
Average K_5 (at 30°) = 0.152 ± 0.002		

+ Calculated from equation (12), using $[M_{\underline{d}}] = +51.8°$ and $[M_{\underline{e}}] = -237.2°$.

TABLE 27

Values of ΔG (kcal per mole), ΔH (kcal per mole) and ΔS (e.u.) that are associated with the K_5 equilibrium of compound 7

Solvent base	Temperature; 20°C			Temperature; 30°C			
	ΔG_5	ΔS_5	K_5 (moles^{-1})	ΔG_5	ΔS_5	K_5 (moles^{-1})	ΔH_5
DMSO	+1.01	-10.9	0.172 ±0.004	+1.13	-10.9	0.152^{+} ±0.002	-2.2
4-methylpyridine	+1.01	-14.2	0.175^{+} ±0.004	+1.16	-14.2	0.146^{+} ±0.004	-3.15
pyridine	+1.02	-13.2	0.167^{+} ±0.006	+1.13	-13.2	0.142^{+} ±0.006	-2.83

$^{+}$ The values of K_5 are an average of individual values that were obtained by solving equation (12); using $[M_e] = -237.2^{\circ}$, $[M_d] = +51.8^{\circ}$ and the appropriate rotational data from Tables 5 to 10.

Calculations of K_5 were also carried out using the rotational data of 7 in 1,2-dichloroethane solutions that contained pyridine or 4-methylpyridine as the hydrogen-bond accepting base. The asterisked data in Tables 7,8,9 and 10 were used to obtain the appropriate average K_5 values that appear in Table 27. Also listed in Table 27 are the ΔG_5 ΔS_5 and ΔH_5 values that were derived from them.

The ΔS_5 values that appear in Table 27 represent both intermolecular hydrogen bond formation as well as a change in chair conformation. The entropy difference between the 7e and 7d conformations of 7 in pure 1,2-dichloroethane, ΔS_1, has a value of only +1.2 e.u. (Table 24). For this reason, the change in chair conformation associated with K_5 is probably not a large contributor to the observed ΔS_5 values. The principal reason for these negative entropy changes should be the "pairing" of the OH function of 7 with the DMSO or pyridine bases to form a single intermolecularly hydrogen-bonded complex.

Several i.r. studies have been reported for intermolecular hydrogen bond formation between simple aliphatic alcohols and various pyridine derivatives in CCl_4 (75,76, 77,78). The hydrogen-bonded complexes are proposed to consist of one molecule of the pyridine base and one molecule of the alcohol. The investigators report ΔS values in the order of -12 e.u. for intermolecular hydrogen bonds that

involve pyridine or 4-methylpyridine. These values compare favourably with the data in Table 27. Although suitable reference data for complexes of DMSO and alcohols could not be found, the value of ΔS_5 that was obtained from the DMSO/1,2-dichloroethane solutions lies within the range of values reported for intermolecular hydrogen bonds between alcohols and general base types such as dioxane and dimethylformamide (29,78).

The enthalpy changes, ΔH_5, that are reported in Table 27 consist of two probable terms. The first is the enthalpy associated with the formation of just the intermolecular hydrogen bond. The second is the energy that is required for the combined rupture of the existing intramolecular hydrogen bond in 7e' and the shift to the 7d" conformation. It is, therefore, not surprising that the ΔH values of about -4 kcal per mole that have been reported for the intermolecular hydrogen bond strengths of pyridine, or 4-methylpyridine and alcohol complexes (75,76,77,78) are somewhat larger than the ΔH_5 values in Table 27. These ΔH_5 values are not big enough to offset the values of $-T \times \Delta S_5$, with the result that the ΔG_5 values are greater than zero and the K_5 values are considerably less than unity.

This concludes the discussion of compound 7. These interpretations of its rotational behaviour will be referred to in the discussion of the rotation curves of compounds 3 and 5. The work with 7 justifies the use of DMSO/1,2-dichloroethane as a convenient solvent system for the studies of "hydrogen-bond conjugation" in such diols. The results have demonstrated that this phenomen is not restricted only to solutions that contain DMSO as the hydrogen-bond-accepting base. However, of the four bases that were used, DMSO possesses the greatest ability to increase the population of the intramolecularly hydrogen-bonded conformation of 7 (*cf.* Figs. 27 and 28).

2. Empirical rules for determination of the molecular rotations of 1,5-anhydro-deoxyhexitols and related carbocyclic compounds

Interpretations of molecular rotations plays an important part in the ensuing discussions of the preferred orientations of the bonds of the hydroxymethyl function of model carbohydrate compounds. Empirical rules that will be used to assess the molecular rotations of the individual rotamers of these compounds will be developed at this point.

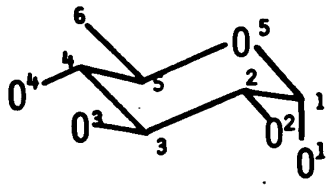
Procedures for determining these rotations, developed by Brewster (12) and Whiffen (10), have been available for many years. Attempts to use them are

hampered by the rather complex presentation of the rotation parameters (*cf.* Table 1). The system developed by Lemieux and Martin (9) requires the tabulation of only those *gauche* three-bond units of conformational assymetry that do not terminate in a hydrogen atom (Fig. 8, p. 17) and is much simpler to use. This latter approach will in part be used here, although it must be extended to include the structural feature that gives rise to Whiffen's I parameter, or Brewster's"permolecular pattern".

One difficulty that is encountered with any theoretical treatment of optical activity is the lack of a precise correspondence of the actual conformations with the ideal staggered conformations that are used for the calculations. As X-ray data have accummulated on the conformation of carbohydrate structures in the crystalline state, it has become quite evident that ideal chair conformations are not realized, and that, as a result, dihedral angles vary from one point to another on the ring. This is well displayed by the data in Table 28. There are no assurances that the same differences will occur in solution, but clearly one must expect similar deviations. As Brewster has pointed out (12,14), the contribution made by asymmetric three-bond units should be proportional to the sine of their dihedral angle, which in the present case is assumed to have an ideal value of 60°. As a result of the

TABLE 28

Torsional angles for neighboring atoms in crystalline derivatives of α-D-glucopyranose*

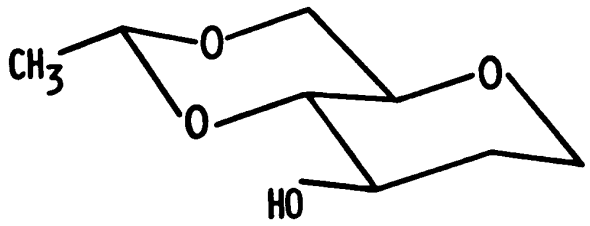


	Sucrose	Methyl β-D-Maltoside	Methyl α-D-Glucopyranoside
O1-O2	54.7°	56.1°	61.5°
O2-O3	62.7	60.0	58.7
O3-O4	-64.2	-60.2	-67.7
O4-C6	64.4	61.0	64.3
C1-C4 (Via C2-C3)	-55.9	-58.5	-55.5
C1-C4 (Via O5-C5)	55.2	58.2	58.0
C2-C5 (Via C3-C4)	56.0	60.5	54.2
C2-C5 (Via C1-O5)	-55.0	-56.1	-60.1
C3-O5 (Via C4-C5)	-54.8	-60.6	-54.1
C3-O5 (Via C2-C1)	54.9	56.3	58.2
O1-C3	-68.1	-65.9	-64.7
O1-C5	67.7	63.9	59.3

* From reference 55.

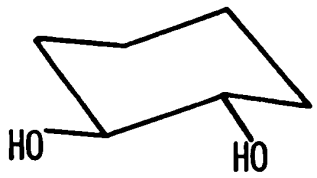
deviations of the actual bond angles from 60°, the values assigned to the individual parametric units can only be regarded as average, rather than precise, values.

A second problem encountered with the estimation of optical activity is a possible variation in the values of the individual rotational parameters from one solvent system to another. For example, an O/O unit in DMSO may not have exactly the same value that it does in water. Lemieux has helped to dispell such fears, noting, for example, that the rotation of 1,5-anhydro-2-deoxy-4,6-*O*-ethylidene-D-*arabino*-hexitol (48), which should be a conformationally rigid compound, is not appreciably dependent on the solvent (9).



48

The empirical rules developed here are based in part on the molecular rotations, in water, of certain compounds prepared during the course of this research. Additional data have been obtained from literature sources, which are usually given for aqueous solutions.



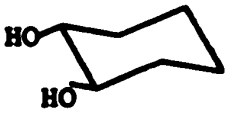
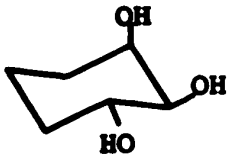
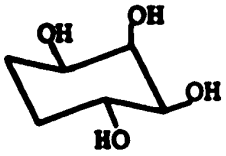
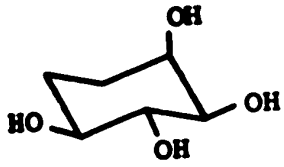
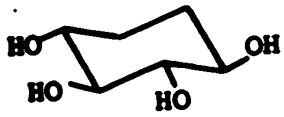
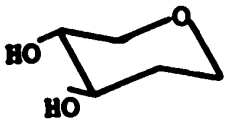
49

According to the present procedure, a single O/O unit generates essentially all of the optical activity of (+)- or (-)-*trans*-1,2-cyclohexanediol (49). There are two different literature values for the rotation of this compound. Previous authors (9,10,12) have referred only to the value of +48.9° that has been reported for the dextrorotatory isomer (79), and not to the values of ±53.9° that are reported for each of the two enantiomers of this compound (80). It would appear, on reading references 79 and 80, that the values of ±53.9° are the more accurate indications of the rotation of this compound. This suggests that the value of 45° that was previously used for the O/O, and related parameters (9,10,12), may have been too small. In this thesis each O/O unit will be assessed 55° of molecular rotation. The rotations of the compounds in Table 29 show that this is a more realistic estimate of its value.

A single O/C unit of molecular rotation should generate most of the optical activities of (+)-*trans*-2-methylcyclohexanol (50) and 1,5-anhydro-2,3,6-trideoxy-D-

TABLE 29

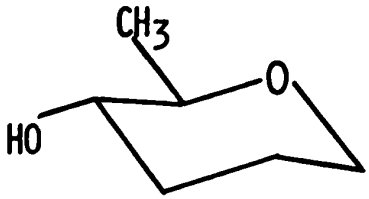
Molecular rotations (°) of selected cyclitols, in water

Compound	Analysis	Molecular Rotation		Reference
		Calculated	Observed	
	-0/0	-55	-54 -49	80 79
	-20/0[+]	-110	-91	81
	+0/0-20/0 = -0/0	-55	-53	82
	-20/0+0/0 = -0/0	-55	-57	82
	-20/0+0/0 = -0/0	-55	-43	81
	-0/0	-55	-53 -46	83 84

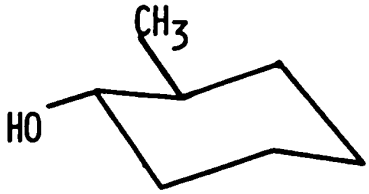
* For ±0/0 = ±55°.

\+ This compound will almost certainly have a sizeable population of the alternate chair conformation (85).

erythro-hexitol (10).

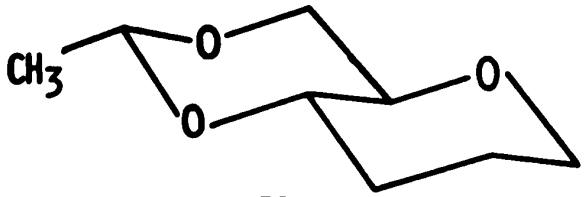


10



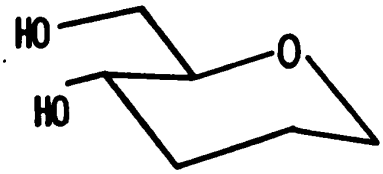
50

Two literature values have been reported for the molecular rotation of 50. The first, and older value of +44° is for a neat solution (86) whereas the more recent value of +48.9° is for a methanol solution (20). The rotation of a water solution of compound 10, recorded as part of this research, is +39.0°. In this thesis an averaged value of 45° will be given to O/C units. Table 30 contains the estimated and observed rotations of several compounds that contain this rotational parameter. The rotation of 1,5-anhydro-2,3-dideoxy-4,6-*O*-ethylidene-D-*erythro*-hexitol (51) is of particular interest. The fact that it is only 2° (9) justifies the empirical prediction of a rotation of zero for the a conformations of compounds 5 and 3.



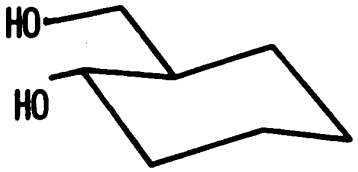
51

[M] = +0/C-0/C = 0°



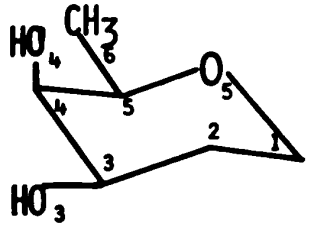
3a

[M] = +0/C-0/C = 0°



5a

[M] = +0/C-0/C = 0°



33

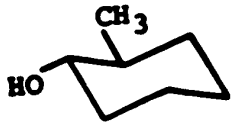
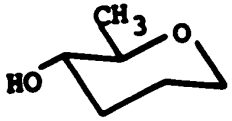
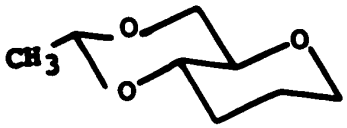
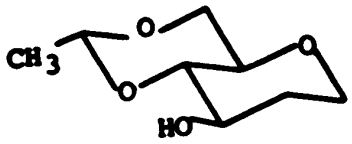
The molecular rotation of 1,5-anhydro-2,6-dideoxy-D-*lyxo*-hexitol (33)[+] is +55°[*] in water at 25°C. The +0/0

[+] This compound can be assumed to exist in the chair conformation that is illustrated. The alternate chair form, with its opposing methyl and hydroxyl functions, must be in very low abundance at room temperature.

[*] From the rotation of the enantiomer (Table 14).

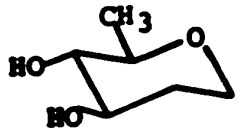
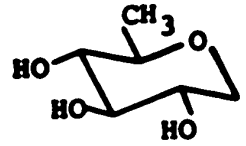
TABLE 30

Molecular rotation (°) of compounds that contain only O/O and O/C parameters; recorded in water unless otherwise specified

Compound	Analysis	Molecular Rotations			Reference
		Calculated†	Observed	Whiffen's Method*	
	+0/C	+45	+48.9 (CH_3OH) +44 (neat)	+34	20 86
	+0/C	+45	+39.0	+34	-
	+0/C-0/C	0	+ 2	0	9
	+0/C-0/C-0/0	-55	-44+	-45	9

Continued ...

TABLE 30 (continued)

Compound	Analysis	Molecular Rotations			Reference
		Calculated†	Observed	Whiffen's Method*	
	+0/C-0/0	-10	-14.5	-11	-
	+0/C-0/0+0/0	+45	+43 (CH_3OH)	+34	87

† For 0/0 = 55° and 0/C = 45°.

* Determined using Whiffen's procedure; outlined in Table 1 (p. 11).

+ This is erroneously listed in ref. 9 as a specific rotation. According to the notebook of J.C. Martin, -44° is the molecular rotation of this compound.

unit between C3-03 and C4-04 combines with the -0/C unit between C4-04 and C5-C6 to produce only +10° of this rotation. The remaining partial structure of 33 (Fig. 34a), which still contains a +0/0 unit between C4-04 and C5-05 (04/05) and a -0/C unit between C4-04 and C3-C2 (04/C2), has an apparent rotation of +45°. Obviously, the +04/05 unit, if valued at +55°, and the -04/C2 unit, if valued at -45°, are not enough to account for this +45° of rotation. About +35° of rotation are "left-over".

For this reason, the partial structure in Fig. 34a, with its rotation of +45°, is best considered as a third, and distinct rotational parameter.+ Whiffen's I parameter, which he assessed a value of 43°, covers this same structural feature, namely, an axial OH group at C4 (or C2) of a pyranoid ring. Because of the similarity of Whiffen's empirical value and the empirical value obtained here (45°), it seems appropriate to refer to this third parameter by the letter I.

(a) + I = +45° (b) - I = -45°

Fig. 34: Partial structures that define the I parameter.

+ The enantiomeric structure, shown in Fig. 35b will contribute -45° of rotation to compounds that contain it.

Different explanations of the rotational power of this I parameter can be proposed. For example, it is possible that the +04/05 unit is somewhat larger than a "normal" +0/0 unit, or that the -04/C2 unit is smaller than a normal -0/C unit, so that their difference is greater than +10°. This is reminiscent of the manner in which Whiffen approached this problem (10). A second cause of the rotation of the I parameter could be the result of the permolecular pattern of 05, C3, and the axial H and OH substituents at C2 and C4. This permolecular pattern need not, of course, produce all the 60° of rotation proposed by Brewster (12). However, it could have some rotational power and thereby account for some or all of the rotation of I.

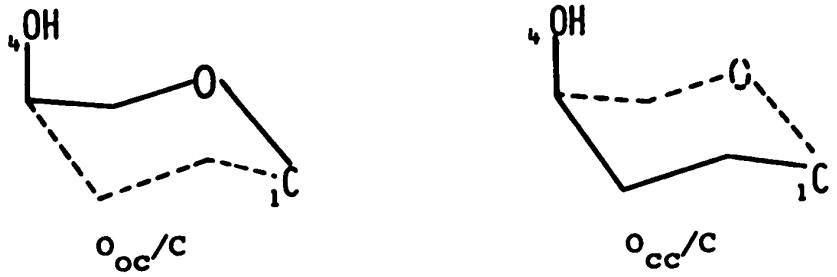


Fig. 35: Four bond units of conformational asymmetry.

The present treatment does not include contributions from four-bond units of conformational asymmetry.+

+ For a detailed, but rather complex treatment of such units, see references 15, 16 and 17.

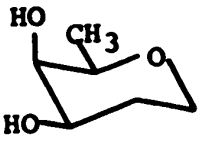
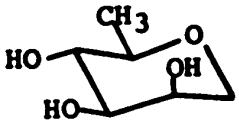
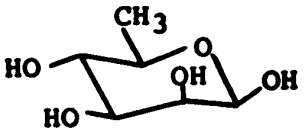
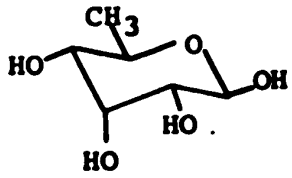
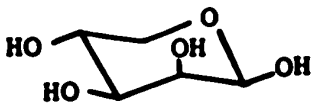
However, such units could make a contribution to the value of I. For example, the axial oxygen, 04, "sees" the C1 carbon in two different ways (Fig. 35). One of the four-bond chains connecting 04 and C1 includes the ring oxygen and can be symbolized as O_{CO}/C. The other chain, designated as O_{CC}/C, contains three central carbon atoms. The difference between the rotational powers of these two chains ($O_{OC}/C - O_{CC}/C$) may be greater than zero.

At this time, such discussions of the theoretical basis of the I parameter are only speculative in nature and illustrate the need for continued investigations into the reasons for the optical activities of molecules. One, or all of the above-mentioned theoretical effects could generate the empirically observed value of I and at present it is not possible to distinguish between them.

The empirical values of the O/C, O/O and I parameters presented to this point give an adequate account of the rotations of compounds in Tables 29, 30 and 31, and therefore appear to be suitable for discussions of the rotations of the diols that are considered in the next sections. A fourth unit, C_O/C, will be discussed in a separate section on the rotational behaviour of the methyl ethers of compound 3.

TABLE 31

Molecular rotations (°) of sugars with axial hydroxyl functions at C2, C3 or C4

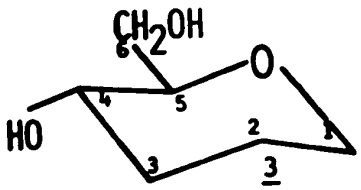
Compound	Analysis	Molecular Rotations			Ref.
		Calcd.+	Obs.	Whiffen's Method*	
	0/0-0/C+I	+ 55	+54.9	+54	-
	+0/C-20/0-I	-110	-124	-99	9
	0/C-0/0-I	- 55	-63	-57	9
	0/C-0/0	- 10	-20	+ 2	9
	-0/0-I	-100	-109	-101	9

+ For 0/0 ≡ 55°, 0/C ≡ 45° and I ≡ 45°.

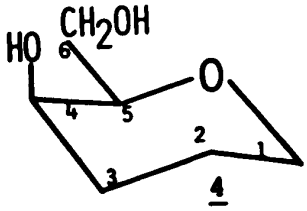
* From Whiffen's empirical rules, Table 1.

3. The conformational preferences of the hydroxymethyl functions of 1,5-anhydro-deoxyhexitols and related carbocyclic compounds in water

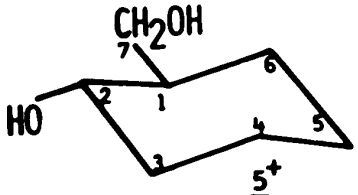
As was mentioned previously, the object of this research was to acquire information on solvation effects on the conformational equilibria of compounds which are simple analogs of hexopyranoses and hexopyranosides. A basic element of this procedure was to compare properties of 3 and 4 with those of their carbocyclic counterparts, 5 and 6. For example, differences in the molecular rotations of 3 and 5 help to establish the effect that the ring oxygen has on the preferred orientations of the bonds of their hydroxymethyl functions. It is considered best to first discuss the insight that was gained on the conformational properties of these compounds in water and then to extend the discussion to non-aqueous solvents.



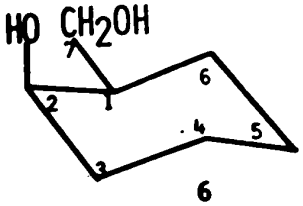
3



4



5+



6

+ Data were obtained from the enantiomer.

The molecular rotations, in water, of the compounds that will be considered in this section are listed in Tables 13 and 14 (pp. 113 and 114). Each of the solutions was prepared at 25°C and then its rotation was measured at the various temperatures that are listed. The calculations used to obtain the molecular rotations included adjustments for the change of the solution volumes relative to their values at 25°C.

Portions of the n.m.r. spectra of compounds 3, 5 and 6 in D_2O (220 MHz) are reproduced on pages 177 and 187. Approximate, average coupling constants are listed in Table 32. Estimates of the average coupling constants between the exocyclic methylene and H5 protons of compound 4 could not be obtained from its complex n.m.r. spectrum, which is reproduced on page 192.

It is convenient to begin with the two carbocyclic compounds, 5 and 6. Each of these diols was recrystallized to constant optical activity following its preparation from the configurationally related 2-hydroxycyclohexanecarboxylic acid. These two optically active acids, (1R,2R)-(-)-*trans*-2-hydroxycyclohexanecarboxylic acid (25) and (1S,2R)-(-)-*cis*-2-hydroxycyclohexanecarboxylic acid (24) were prepared according to the procedure of Torne 61. The general scheme that was followed is illustrated in Fig. 36.

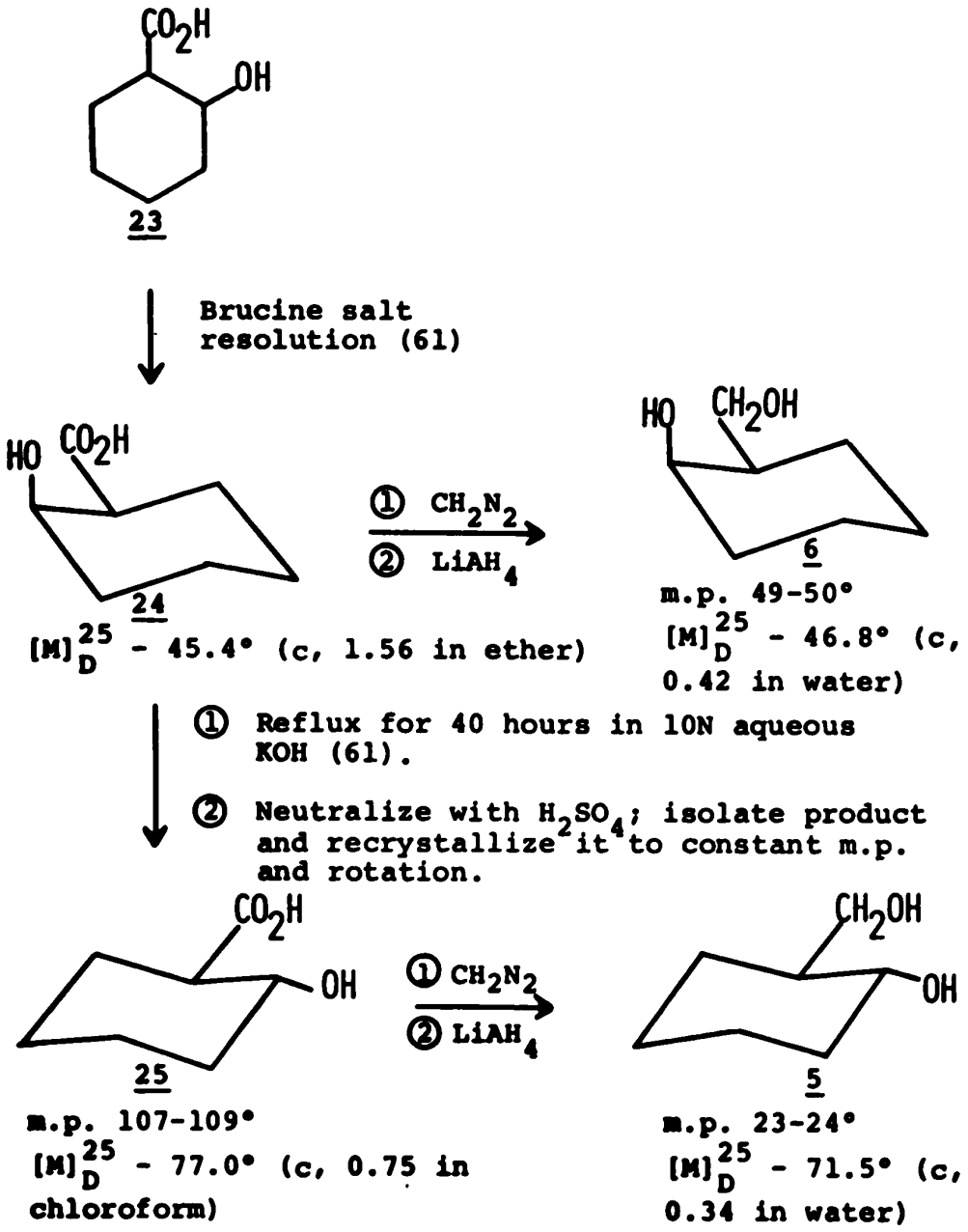
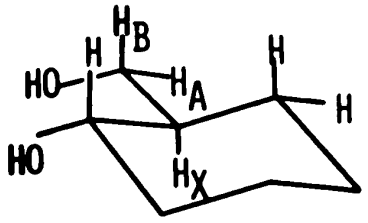


Fig. 36: The preparation of (1R,2S)-(-)-*trans*-2-hydroxymethylcyclohexanol (5) and (1R,2R)-(-)-*cis*-2-hydroxymethylcyclohexanol (6).

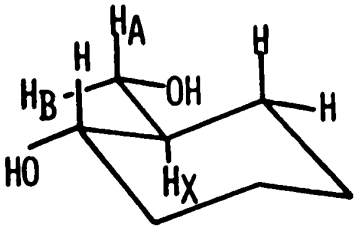
The enantiomer of compound 5 that was prepared experimentally is the "*quasi* mirror-image" of 3. The author feels that it is better to refer to the structure of the other enantiomer of 5 in order to better illustrate the relationship to compound 3. Consequently, the structural diagrams of 5 in the text that follows represent its dextrorotatory epimer. Similarly, the molecular rotations of 5 that are discussed will have *opposite* signs to the experimentally determined values that are listed in Tables 13 and 15.

Conformational preferences resulting from rotation about the exocyclic C-C bond of compounds 5 and 6 can be anticipated by so-called quantitative conformational analysis. This technique is of course only an approximate procedure but it does provide a guide for the interpretation of their n.m.r. spectra and molecular rotations.



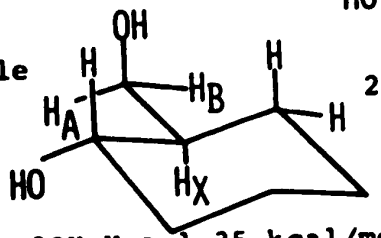
OH:OH ≡ 1.5 kcal/mole

5a



2OH:H ≡ 0.9 kcal/mole

5c



3OH:H ≡ 1.35 kcal/mole

5b

Fig. 37: Interaction free energies involving the hydroxymethyl group of *trans*-2-hydroxymethyl-cyclohexanol.

The three rotamers[+] of 5 are shown in Fig. 37 along with the estimates of their *relative* conformational free energies.

The OH:H symbol represents the interaction free energy generated by opposing C-H and C-OH bonds, although it is often referred to simply as the repulsive energy between *syn*-axial hydrogen and hydroxyl functions. It may be considered as nearly equal to one half of the free energy difference between the chair forms of cyclohexanol, whose hydroxyl function opposes two hydrogen atoms in its axial orientation. The total contributions that the *two* OH:H interactions make to the free energies differences of cyclohexanols and related structures have "best" values of 0.87 kcal per mole in polar hydrogen-bonding solvents (85). In aprotic solvents such as CS_2, hydrocarbons and halogenated hydrocarbons it is somewhat smaller, averaging 0.52 kcal/mole (85). In this thesis, a *single* OH:H interaction, in water, is given Angyal's value of 0.45 kcal per mole (88,89), approximately one half of the 0.87 kcal referred to above. The OH:OH symbol represents the interaction free energy of two opposing C-OH bonds. Angyal first assigned this a value of 1.9 kcal per mole in water, using as models

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[+] Because of the different nomenclature and numbering convention for 3 and 4 compared to that of 5 or 6, the exocyclic methylene and *vicinal* ring protons of these four compounds will be referred to as H_A, H_B and H_X in order to simplify discussions of the n.m.r. spectra.

the conformations of cyclitols that contained opposing axial C-OH bonds (88). He has subsequently reported (89) that a lower value, 1.5 kcal per mole, appears to be better suited for the analysis of pyranose conformations, noting that angular distortions in such structures can relieve some of the steric strain contained in this OH:OH interaction. In a conformation such as 5a, the steric repulsion terms between the opposing oxygen atoms can probably be reduced by a slight rotation of the hydroxymethyl function about the exocyclic C-C bond. With this in mind, Angyal's smaller value of 1.5 kcal per mole is probably a more appropriate estimate of the OH:OH interaction in this structure. Again, this value refers only to aqueous solutions.

Using these values for OH:H and OH:OH interactions, the differences in the free energies of conformations 5a, 5b and 5c can be estimated and then used to predict their relative populations. For example, 5c should be about 0.45 kcal per mole more stable than 5b. Using the simple free energy-equilibrium relationship, the ratio of the mole fraction of these two conformations can be estimated to be 2.1 at 25°C.

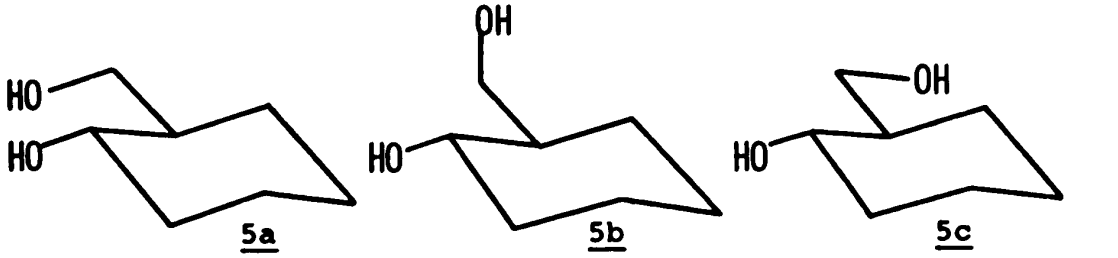
$$(1)\quad \Delta G^{\bullet}_{25}{}_{b\rightarrow c} = -RT\ \ln K = 1.985 \times 298 \times 10^{-3} \times \ln \frac{X_c}{X_b}$$

where X_c and X_b are the mole fractions of 5c and 5b

(2) for ΔG°_{25} = -0.45 kcal per mole; $\frac{X_c}{X_b}$ = 2.1

$b \rightleftarrows c$

Similarly, the ratio of X_c to X_a should be 2.8 at 25°C. Equating the sum of X_a, X_b and X_c to unity supplies the necessary third relationship for the calculation of their individual values. The conformational populations of 5, in water at 25°C, calculated on this basis, are: 5a, 20%; 5b, 26%; 5c, 54%.



5a 5b 5c

[M] = +0/C-0/C=0 [M] = +0/C=+45° [M] = +20/C=+90°

Fig. 38: The rotational units contained in the conformations of compound 5.

Fig. 38 shows the analysis of the molecular rotations of the individual conformations of 5. The observed rotation of this compound, at 25°C in water, is +71.5°. According to the conformational distribution predicted for 5, its molecular rotation should be only 60.3° (at 25°C), if the following equation is solved for 0/C = 45°.

$$[M]_D^{25} \text{ (predicted for } \underline{5}) = X_a(0) + X_b(+0/C) + X_c(+20/C)$$

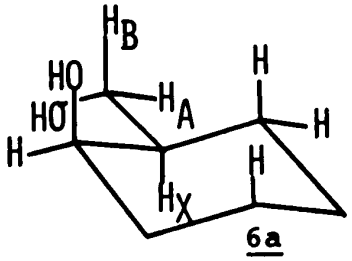
$$= 0.20\ (0) + 0.26\ (+45°) + 0.54\ (+90°)$$

$$= +60°.$$

An 11.5° discrepency between the predicted and observed rotations of a conformationally flexible molecule such as 5 should not be considered serious. For example, if 0/C had been given a value of 50°, the predicted rotation would have been 67°, which is much closer to that which is observed. The important result here is that both the conformational analysis, and the molecular rotation, indicate that the total population of 5b and 5c is much larger than that of 5a in a solvent such as water. This is also supported by the n.m.r. spectrum of 5, which will be discussed shortly.

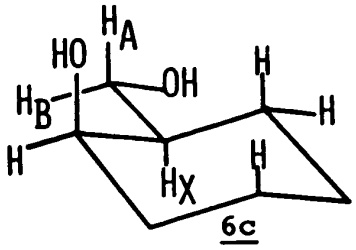
The molecular rotation of the aqueous solution of 5 was recorded at temperatures that ranged from 5° to 80°C (Table 13, p. 113). As the solution temperature was raised the absolute rotational values decreased, most probably indicating increases in the total population of the 5a and 5b conformations. The relative insensitivity of the rotations of compounds such as 9, 10 and 33 to such changes in temperature (Table 14, p. 114) rules out the possibility that the changes observed for 5 are the result

of variations in the values of the actual 0/C parameters themselves. As will be seen shortly, the n.m.r. spectra of 5, recorded at 5°, 40° and 80°, also indicate that these rotational shifts are the result of changes in the relative populations of the 5a, 5b and 5c conformations, toward decreasing abundance of 5c.



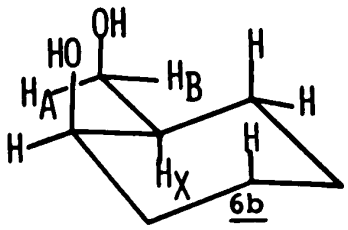
6a

4OH:H ≡ 1.8 kcal per mole



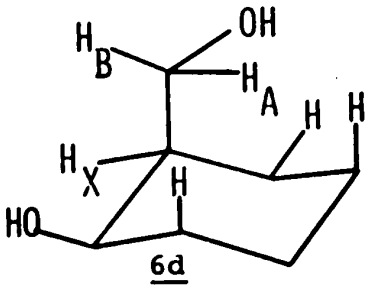
6c

4OH:H ≡ 1.8 kcal per mole



6b

3OH:H+OH:OH ≡ 2.85 kcal per mole



6d

2OH:H+2"CH_3:H" ≡ 2.9 kcal per mole

Fig. 39: Interaction free energies involving the hydroxymethyl function of *cis*-2-hydroxymethylcyclohexanol.

There are four conformations of *cis*-2-hydroxymethylcyclohexanol that could have significant populations in water. These, together with the important interactions

that determine their relative populations, are illustrated in Fig. 39.

The two minimum energy conformations, 6a and 6c should occur in about equal amounts, as they contain the same interaction terms. At 25° in water, they will be about 1.05 kcal per mole more stable than 6b, which has opposing hydroxyl functions.

The relative importance of 6d depends in part on the instability of its axial hydroxymethyl function. As far as its interactions with the two opposing axial C-H bonds are concerned, this function should have about the same instability as an axial methyl function would have, namely, the value of two CH_3:H interactions. For this discussion, these interactions are assessed values of about 1.0 kcal per mole each.[+] They combine with the two OH:H interactions that are also present in 6d to make this conformation only slightly less stable than 6b, and 1.1 kcal per mole less stable than either 6a or 6c.

The following populations (at 25°C) of these four conformations of 6 have been calculated from the above estimates of their relative conformational free

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[+] This is slightly larger than the CH_3:H interaction value of 0.9 kcal per mole that is recommended on p. 354 of reference 1.

energies. The method of calculation was the same as that described for the conformations of 5.

6a, 43%; 6b, 7.5%; 6c, 43%; 6d, 6.5%.

The analysis of molecular rotation units contained in each of these four conformations is as follows.

6a	-20/C = -90°	6b	-0/C = -45°
6c	+0/C-0/C = 0°	6d	+20/C = 90°

By solving the following equation, using an 0/C value of 45° and the above estimates of the fractional populations of 6, a value of -36° is obtained for the predicted rotation of 6 in water.

$$[M]_D^{25}(\text{predicted for } 6) = X_a(-20/C) + X_b(-0/C) + X_c(0) + X_d(+20/C)$$
$$= 0.43(-90°) + 0.075(-45°) + 0.43(0) + 0.065(+90°)$$
$$= -36°$$

The observed rotation of a solution of 6 in water is -46.5° at 25°C. Considering the approximate natures of both the conformational analysis and the estimate of the value of an 0/C parameter, the discrepency between the predicted and observed rotations is not surprising. One possible reason for the "low" predicted value of $[M]_D^{25}$ could be an error in the assumption that 6a and 6c

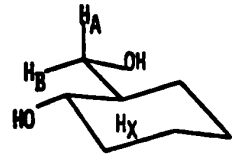
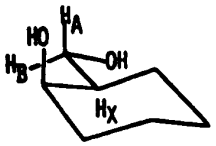
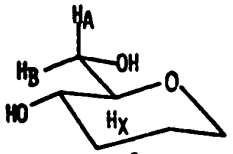
have equal populations. In actual fact, the 6a conformation could be more stable than 6c due to some solvation effect that necessarily crude conformational analysis does not foresee. This would give the solution a more negative rotation than that which is predicted. Another reason could be the importance that conformational analysis gives to 6d. Its population could be smaller than that predicted if the axial hydroxymethyl function interacts more strongly with the opposing C-H bonds than was proposed.

The molecular rotation of the solution of 6 shifts, with increasing temperature, towards the rotation of +20/C (+90°) that is predicted for 6d. However, the net shift in rotation is only +7.4° in the temperature range between 5° and 80°C (Table 13, p. 113). Evidently this increase in thermal energy is unable to effect a substantial increase in the small percentage of 6d. This will also be evident from the discussion of its n.m.r. spectra, which were recorded at 5°, 40° and 80°C.

The molecular rotations and predicted conformational distributions of 5 and 6 will now be related to the n.m.r. spectral parameters of these two diols. The two exocyclic methylene protons of both structures are deshielded by oxygen atoms, and, as a result, are well separated from the signal of H_X. The values for J_{AX} and J_{BX} that appear in Table 32 were taken directly from the

TABLE 32

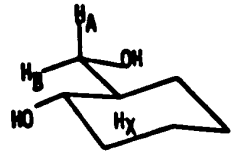
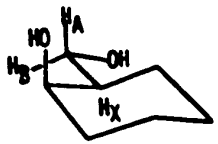
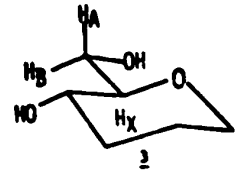
Nuclear magnetic resonance parameters* for the exocyclic methylene protons of compounds 5, 6 and 3, in D_2O

Compound	Temperature (°C)	Chemical shifts (τ) from an external HMDS reference			Coupling constants (±0.1 Hz)	
		H_B	H_A	H_X	J_{AX}	J_{BX}
 5	5	6.04	6.22	-	6.5	4.3
	40	5.99	6.16	-	6.2	4.5
	80	5.94	6.09	-	6.0	5.0
 6	5	6.28,6.41		-	7.0	7.0
	40	6.23,6.36		-	7.0	7.0
	80	6.16,6.29		-	7.0	7.0
 3	5	5.94	6.16	6.57	6.6	2.4
	40	5.89	6.09	6.51	6.4	2.6
	80	5.81	5.99	6.43	6.2	2.8

* Coupling constants were taken from 220 MHz n.m.r. spectra (Figs. 40, 41 and 43). The chemical shifts were determined from 100 MHz n.m.r. spectra.

TABLE 32

Nuclear magnetic resonance parameters* for the exocyclic methylene protons of compounds 5, 6 and 3, in D_2O

Compound	Temperature (°C)	Chemical shifts (τ) from an external HMDS reference			Coupling constants (±0.1 Hz)	
		H_B	H_A	H_X	J_{AX}	J_{BX}
 2	5	6.04	6.22	-	6.5	4.3
	40	5.99	6.16	-	6.2	4.5
	80	5.94	6.09	-	6.0	5.0
 6	5	6.28,6.41		-	7.0	7.0
	40	6.23,6.36		-	7.0	7.0
	80	6.16,6.29		-	7.0	7.0
 3	5	5.94	6.16	6.57	6.6	2.4
	40	5.89	6.09	6.51	6.4	2.6
	80	5.81	5.99	6.43	6.2	2.8

* Coupling constants were taken from 220 MHz n.m.r. spectra (Figs. 40, 41 and 43). The chemical shifts were determined from 100 MHz n.m.r. spectra.

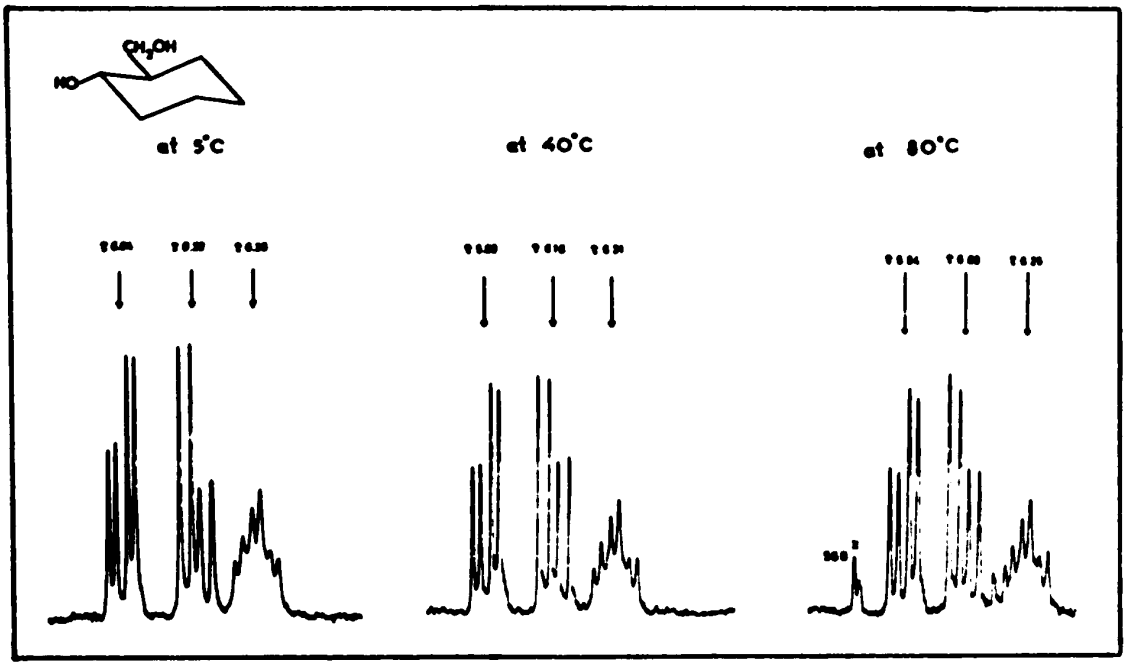


Fig. 40: Portions of the n.m.r. spectra (220 MHz) of *trans*-2-hydroxymethylcyclohexanol (5), in D_2O, at 5°, 40° and 80°C (see Table 32).

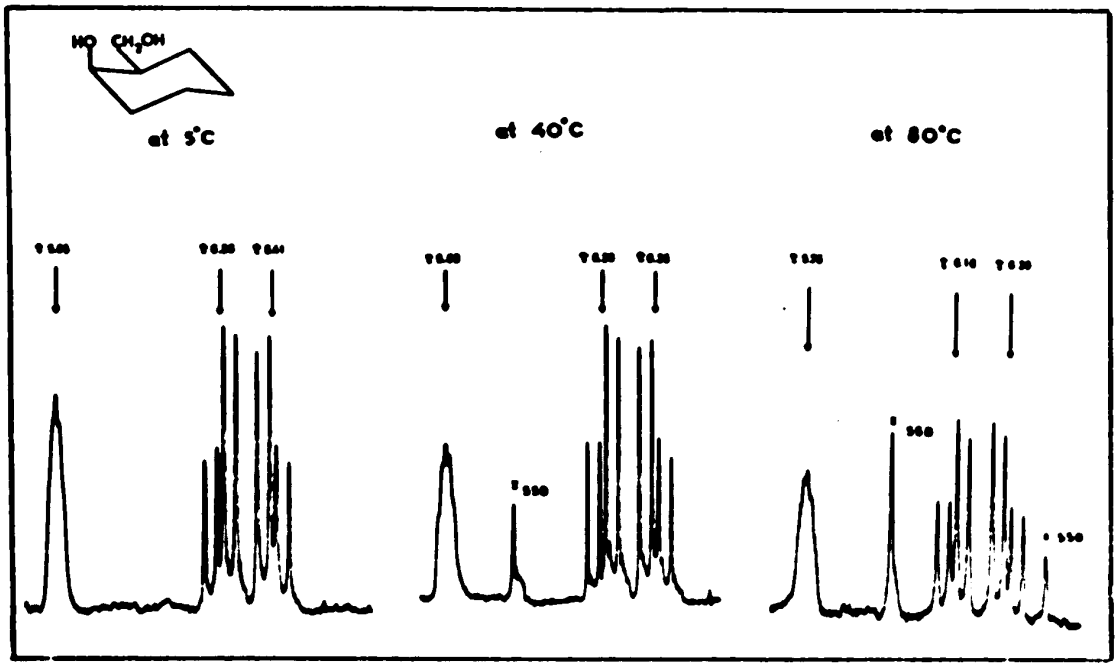


Fig. 41: Portions of the n.m.r. spectra (220 MHz) of *cis*-2-hydroxymethylcyclohexanol (6), in D_2O, at 5°, 40° and 80°C (see Table 32).

portions of the 220 MHz n.m.r. spectra of these two diols that are reproduced in Figs. 40 and 41.

Soon after the discovery (90) that *vicinal* hydrogens which define a dihedral angle of 180° are coupled three to four times more strongly than when the dihedral angle is 60°, it was established that coupling was also large when the angle was 0°, but small in the range of angles between 80° and 100° (91). These observations led to Karplus' proposal (92,93) that there exists a relationship of the form

$$J = a \cos^2 \phi + b$$

where J = coupling constant, ϕ is the dihedral angle and a and b are constants of the particular system under study. Meanwhile it had become apparent that the magnitude of a coupling constant was also dependent on other parameters, including, for example, the electronegativity of substituents (94). Therefore, it is important to recognize that coupling constants calculated from this relationship are only very approximate. Nevertheless, the Karplus type relationship appears definitely to be of value in the study of conformational differences between closely related compounds, such as 5 and 6.

One problem in using Karplus' equation to predict the J_{AX} and J_{BX} values for the individual

conformations of compounds 5 and 6 is the choice of values to be given to the a and b constants. A second problem, discussed shortly, is the assessments of ϕ, the actual rather than theoretical dihedral angle.

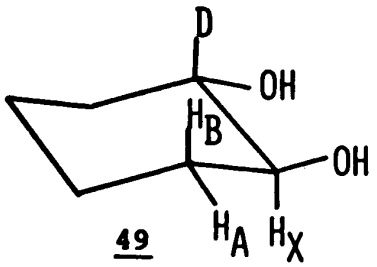
The two Karplus-type expressions

$$J = 11 \cos^2\phi \quad (90 \leq \phi \leq 180°)$$

and

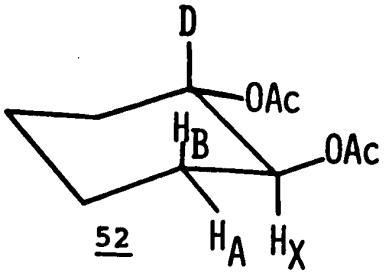
$$J = 14 \cos^2\phi \quad (0 \leq \phi \leq 90°)$$

will be employed in the following discussion to estimate the coupling constants of the conformations of 5 and 6. For the present purposes the small constant b has been equated to zero. This constant is mainly of interest when dihedral angles approach zero degrees, which is almost certainly not the case here. The values used for the a constant have been derived from the n.m.r. spectral data of the conformationally rigid compounds, 49, 52 and 53 (95). Their observed values of J_{BX} are the basis for the a of 11 that is used in the first expression. This involves the reasonable assumption that the dihedral angle between the B and X protons is approximately 180° in these structures. The value of 3.5 Hz, reported for the J_{AX} of the isopropylidene compound (53), is the basis for the a of 14 used in the second relationship. For $\phi = 60°$, the expression affords a J value of 3.5 Hz.



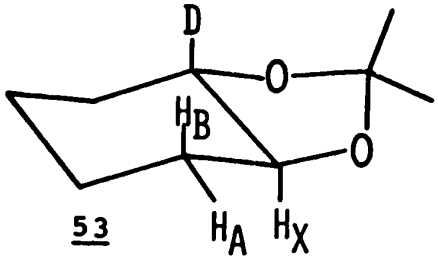
49

J_{BX} = 11 Hz in $CDCl_3$
= 10.5 Hz in D_2O



52

J_{BX} = 11 Hz in CCl_4



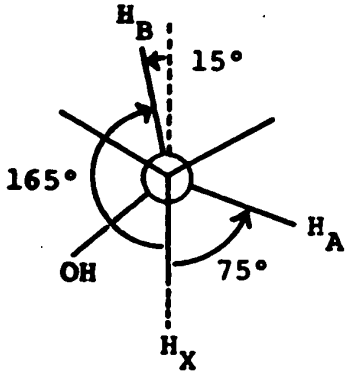
53

J_{BX} = 11 Hz in CCl_4
J_{AX} = 3.5 Hz in CCl_4

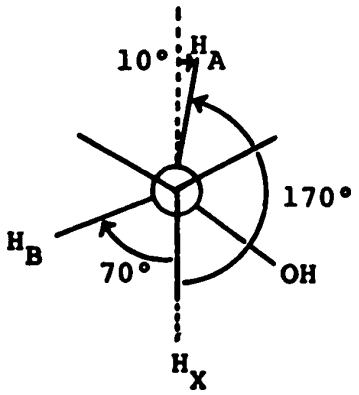
Now consider the three rotamers of compound 5 (Fig. 37, p. 167). It would be naive to propose that these rotamers all define the ideal dihedral angles of 60° or 180°. This assumption is probably only valid for 5b, in which the "axial" exocyclic C-OH bond is buttressed by the two opposing C-H bonds of the ring. Therefore, only in 5b can J_{AX} and J_{BX} be given the value of 3.5 Hz that the proposed relationships predict for ϕ = 60°.

The situations in 5a and 5c are undoubtedly less ideal. Inspection of the structures in Fig. 37 shows that the primary OH group of 5a can probably relieve some of the non-bonding steric interaction with the opposing secondary OH group by undergoing an angular deviation from

the ideal staggered orientation. For the same reason, the primary OH group in 5c will most likely be skewed slightly away from the H atom that opposes it. In both cases the angular distortion of the C-OH bond should be towards the *vicinal* C-H bond rather than towards the more space demanding *vicinal* C-C bond systems of the ring. The actual dihedral angles will obviously represent the best compromise between torsional strain and non-bonding interactions.



J_{AX} = 0.9 Hz
J_{BX} = 10.3 Hz



J_{AX} = 10.7 Hz
J_{BX} = 1.6 Hz

To illustrate this point, assume that the "real" dihedral angles in 5c are 70° and 170°. The values of J_{BX} and J_{AX} become 1.6 and 10.7 Hz respectively. The OH:OH interaction in 5a will probably result in a somewhat greater distortion. If dihedral angles of 75° and 165° are proposed for this conformation, J_{AX} becomes 0.9 Hz and J_{BX} 10.3 Hz.

At 25°C, the average J_{BX} for the D_2O solution of 5 has an actual value that lies between 4.3 and 4.5 Hz.[+] Similarly, the average J_{AX} for the solution has a value between 6.5 and 6.2 Hz.[+] The average values of J_{BX} and J_{AX} that are predicted for the solution of 5 in water at 25°C, using the estimated conformational distribution on page 170 and the above estimates of the individual conformational values of J_{AX} and J_{BX}, are 6.8 and 3.8 Hz respectively.

$$J_{AX} = 0.54 \times 10.7 + 0.26 \times 3.5 + 0.20 \times 0.9$$
$$= 6.8 \text{ Hz (predicted for 25°C)}$$
$$J_{BX} = 0.54 \times 1.6 + 0.26 \times 3.5 + 0.20 \times 10.3$$
$$= 3.8 \text{ Hz (predicted for 25°C).}$$

The author points out that these calculated values of J_{AX} and J_{BX} could have been made to correspond more closely to the observed values had different a values been used in the Karplus-type relationships that were proposed on page 178. For example, an a value of 9 in the $0° < \phi < 90°$ expression would have produced a smaller calculated average value of J_{AX}. However, such procedures are basically fruitless and are not warranted. In fact, it is this uncertainty in both the a value and in the actual

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[+] These values are observed for solutions at 5° and 40°C respectively (see Table 32).

conformational dihedral angles that makes n.m.r. spectroscopy, by itself, only a very approximate tool for this type of conformational analysis. This is one reason for the present attempt to develop molecular rotation analysis as an alternate approach to the problem.

The n.m.r. spectral data for 5 that are listed in Table 32 indicate that a change in conformational equilibria occurs on raising the solution temperature from 5° o 80°C. The increase in the average value of J_{BX} presumably represents an increase in the population of 5a, in which H_B and H_X are *trans* to one another and have a large coupling constant. Coincident with the increase in J_{BX} is a decrease in J_{AX}. In 5a, H_A and H_X are *gauche* to each other and should have a much smaller coupling constant than they do in 5c. Therefore, the decrease in the observed value of J_{AX} suggests a decrease in the amount of 5c, which in effect also signifies an increase in the abundance of 5a. These temperature effects are in accordance with the shift in conformational equilibria that was indicated by the decrease in the molecular rotation of 5 as the temperature of its solution in water was increased from 5° to 80°C.

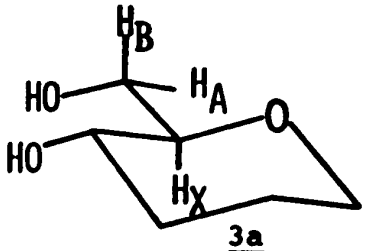
The n.m.r. spectra of *cis*-2-hydroxymethylcyclohexanol (6) in D_2O show that at 5°, 40° and even at 80°C the average coupling constants, J_{AX} and J_{BX}, have the

same value, namely 7.0 Hz (see Table 32 and Fig. 41).

The conformational value of J_{AX} in 6c should lie between 9 and 12 Hz, whereas in 6a, where H_A and H_X are *gauche* to each other, J_{AX} should have a value between 1 and 4 Hz (see Fig. 39). The exact value will, of course, depend on the actual conformational dihedral angles and on the a values in the Karplus-type relationship. The values of J_{BX} will be the reverse, 1 to 4 Hz in 6c and 9 to 12 Hz in 6a. The average values of J_{AX} and J_{BX} that are observed are almost halfway between the "ideal" *gauche* value of 3.5 Hz and *trans* value of 11.0 Hz. Clearly, this does not permit a very large population of 6b, the conformation in which both J_{AX} and J_{BX} have the *gauche* value of 1 to 4 Hz. The reader should note that this was predicted in the preceding discussion of the relative interaction free energies of 6a, 6b and 6c.

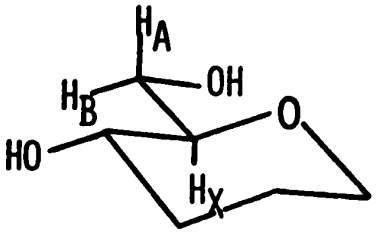
In conformer 6d, J_{AX} should have a value between 9 and 12 Hz and J_{BX} a value between 1 and 4 Hz. Provided that the mole fractions of 6a and 6c remain equal over the temperature range from 5° to 80°C, there cannot be a substantial population of 6d in solution, as this would have produced an average J_{AX} value that was greater than that of J_{BX}. Even at 80°C, this was not observed. Evidently, the shift towards 6d that was indicated by the change in the molecular rotation (see p. 175) was too

small for n.m.r. spectroscopy to detect.



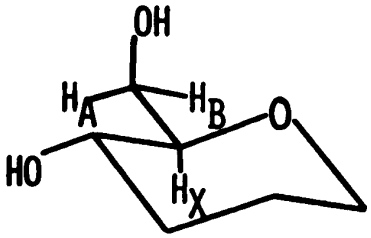
3a

[M] = +0/C-0/C = 0°



3c

[M] = +0/0+0/C = +100°



3b

[M] = +20/C-0/0 = +35°

Fig. 42: The predicted molecular rotations of the three rotamers of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3).

The three principal conformations of compound 3 are illustrated in Fig. 42, along with estimates of their molecular rotations. The observed molecular rotation of 3 is +70.5° in water at 25°C, which compares to +71.5° that is observed for its carbocyclic analog, compound 5. Like the rotation of 5, the rotation of 3 decreases with an increase in solution temperature, which suggests a decrease in the abundance of 3c (see Table 13, p. 113).

As can be seen from Fig. 42, the primary hydroxyl function of 3c is *gauche* to the ring oxygen atom. In 3b, where this hydroxyl function is also *gauche* to the ring oxygen, it encounters an OH:H interaction with the axial C4 hydrogen atom. As a result, 3b should be less stable than 3c by the value of an OH:H interaction, estimated at 0.45 kcal per mole in water (89,90). This means that 3c should have 2.1 times the population that 3b does at 25°C, the same ratio as was calculated on page 169 for the two corresponding conformations of 5. Considering this anticipated ratio of 3c to 3b, the observed rotation of 3 suggests that 3a, with its two opposing hydroxyl functions, cannot be a very important conformation in water. This is expected, as the opposing hydroxyl functions should destabilize this conformation in water, as they do 5a (see p. 169), by about 1.5 kcal per mole (90).

The partial n.m.r. spectra of 3 that are reproduced in Fig. 43 are somewhat more complex than those of 5 (*cf.* Fig. 40). Because of the deshielding effect of the ring-oxygen atom, there are four other protons, including H_X, that absorb in the region of H_A and H_B. The values of J_{AX} and J_{BX} that appear in Table 32 were obtained by analyzing the signals for H_A and H_B as the AB portion of an ABX pattern, in spite of the proximity of the signal from H_X.

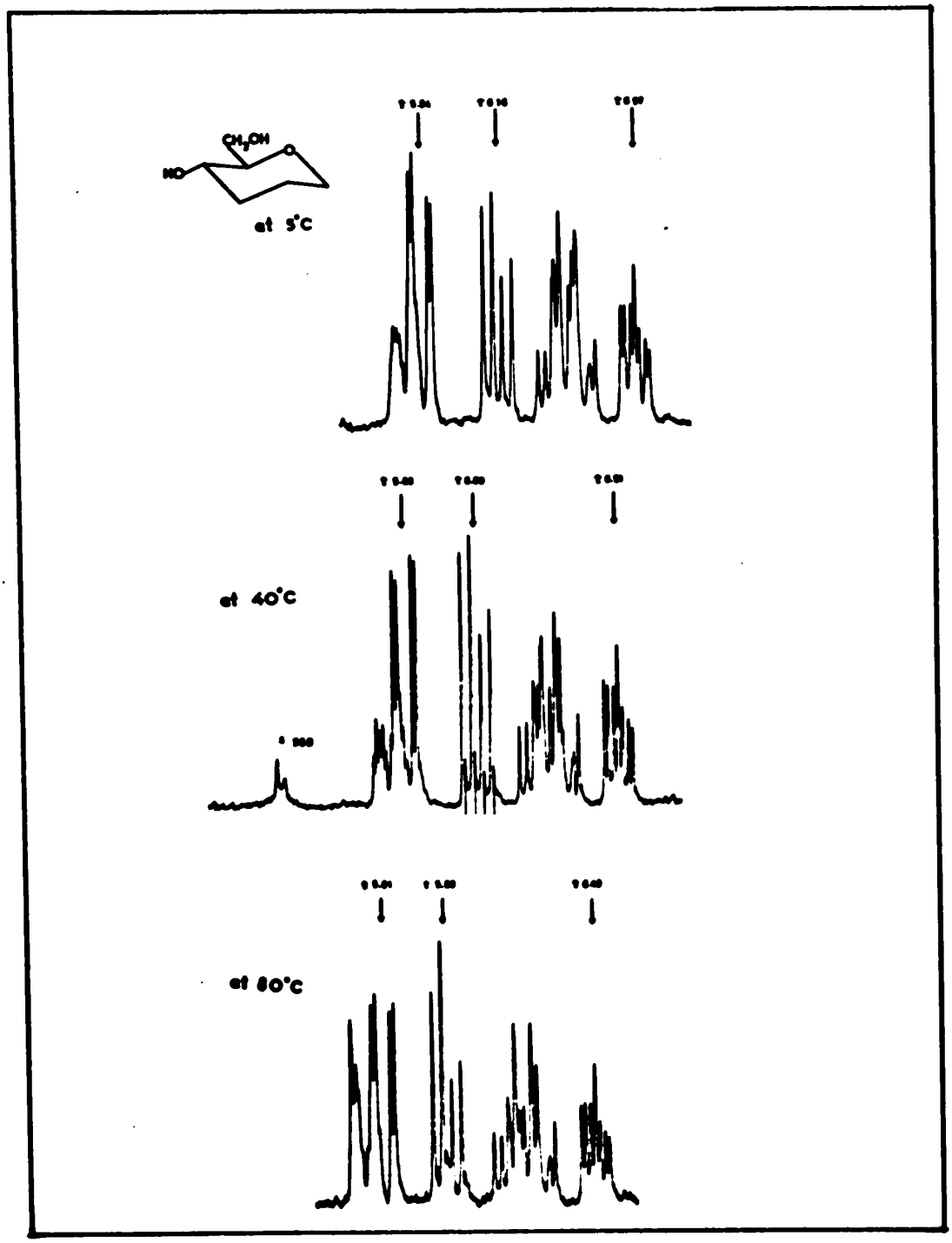


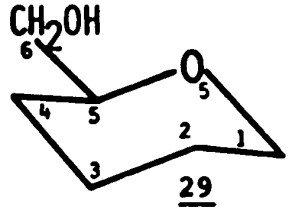
Fig. 43: Portions of the n.m.r. spectra (220 MHz) of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3), in D_2O, at 5°, 40° and 80°C (see Table 32).

The average value of J_{AX} at 25°C lies between 6.4 and 6.6 Hz (Table 32). Obviously, all of 3 cannot exist in the 3c conformation at room temperature, or this value (as well as the molecular rotation of the solution) would have been larger. As was just mentioned, conformational analysis requires about one 3b conformer (J_{AX}; from 1 to 4 Hz) for every two 3c conformers (J_{AX}; from 9 to 12 Hz). This anticipated population of 3b, plus what population there is of 3a (J_{AX}; from 1 to 4 Hz), help to explain the intermediate nature of the average observed value of J_{AX}.

The value of J_{BX} can only be large (9 to 12 Hz) in conformation 3a, where H_B and H_X are *trans* to each other. The value of J_{BX} at room temperatures lies between 2.4 and 2.6 Hz, (Table 32), and obviously does not permit a large population of 3a, a result that reinforces the interpretation of the molecular rotation of 3.

An increase in the temperature of the solution of 3 causes both a decrease in the value of J_{AX} and an increase in the value of J_{BX} (Table 32). The decrease in J_{AX} indicates a decrease in the amount of 3c, whereas the increase in J_{BX} represents the concomitant increase in the abundance of 3a. These results support the above interpretation of the effect that increases in temperature have on the molecular rotation of 3, in water.

It is of interest to note that the values of J_{BX} that were obtained from the n.m.r. spectra of 5 are larger than the J_{BX} values obtained from the n.m.r. spectra of 3 (see Table 32). Compounds 3 and 5 differ in their molecular structure at a point that is adjacent to the carbon atom which bears their hydroxymethyl function. Because of this, there will undoubtedly be some differences in the conformational dihedral angles that are defined by their respective a, b and c rotamers, as well as in the Karplus expressions required to relate these angles to conformational values of J_{BX} and J_{AX}. Therefore, it is difficult to say whether or not these observed differences in the average J_{BX} values of the solutions of 3 and 5 reflect a difference in the respective populations of their a conformations. *If* the difference *does* reflect a lower population of 3a relative to 5a, it would imply that the interaction between the primary hydroxyl function and the ring-oxygen atom of 3a is smaller (in water) than the corresponding OH:H interaction between the primary hydroxyl function of 5a and the methylene proton of the ring.



29

$[M]_D^{25}$ = +26.1° (in water)

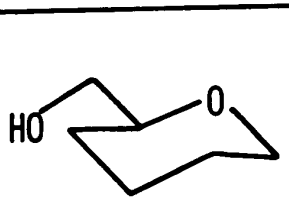
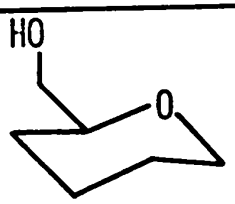
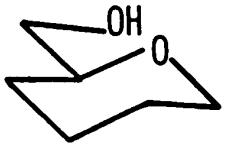
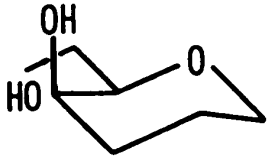
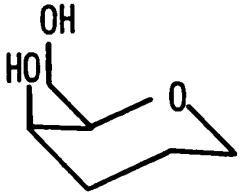
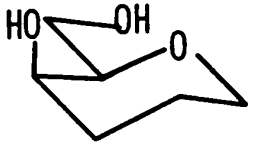
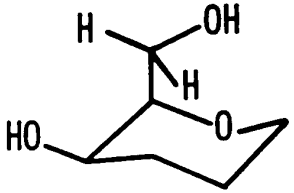
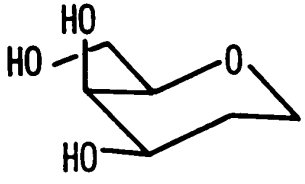
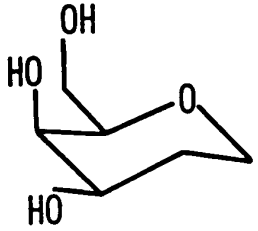
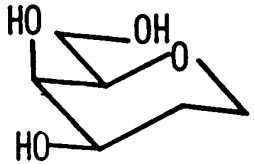
The molecular rotation of 1,5-anhydro-2,3,4-trideoxy-D-*glycero*-hexitol (29) in water provides additional evidence that the interaction between *gauche*-oriented oxygen atoms, in water, is definitely smaller, and possibly attractive, relative to the value of an OH:H interaction.

Consider the three rotamers of this compound, and their predicted rotations, that are shown in Table 33. The hydroxyl group of 29c is *gauche* to the ring-oxygen atom. In 29b, this group is also *gauche* to the ring oxygen, but at the same time is opposed to the axial hydrogen at C4. Because of this OH:H interaction, there should be 2.1 times more 29c than there is 29b in the water solution at 25°C. In 29a, there is only the destabilizing OH:H interaction, between the hydroxyl group and the equatorial proton at C4. The relative amounts of 29a and 29b will depend on the nature of the interaction between the *gauche*-oriented oxygen atoms of 29b. If it is attractive, as compared to the repulsive OH:H interaction energy of 0.45 kcal per mole, there will be more 29b, and much more 29c in solution than there is 29a.

The observed rotation of the aqueous solution of 29, which is +26.2° at 25°C, requires that this be so. For example, if 62% of the molecules of 29 adopt the 29c conformation, there must be 62 ÷ 2.1 or 29% of 29b.

TABLE 33

The estimated molecular rotations of conformations of compounds 4, 9 and 32

Compound	Observed $[M]_D^{25}$ (water)	Conformational rotations; for 0/0 = 55°, 0/C = 45° and = 45°			
		a	b	c	d
29	+26.2°	 -0/C = -45°	 +0/C-0/C = -10°	 +0/0 = +55°	
4	+ 6.8°	 -20/C+I = -45°	 -0/0+I = -10°	 +0/0-0/C+I = +55°	 +0/C+0/0 = +100°*
32	+70.8°	 -20/C+0/0+I = +10°	 +I = +45°	 +20/0-0/C+I = +110°	

* See page 195.

Fig. 44: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (4) (D_2O).

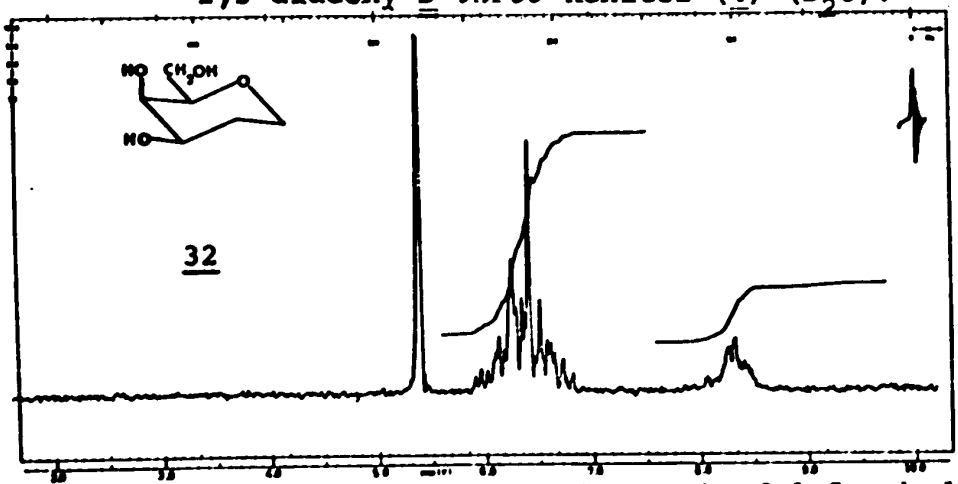


Fig. 45: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2-deoxy-D-*lyxo*-hexitol (32) (D_2O).

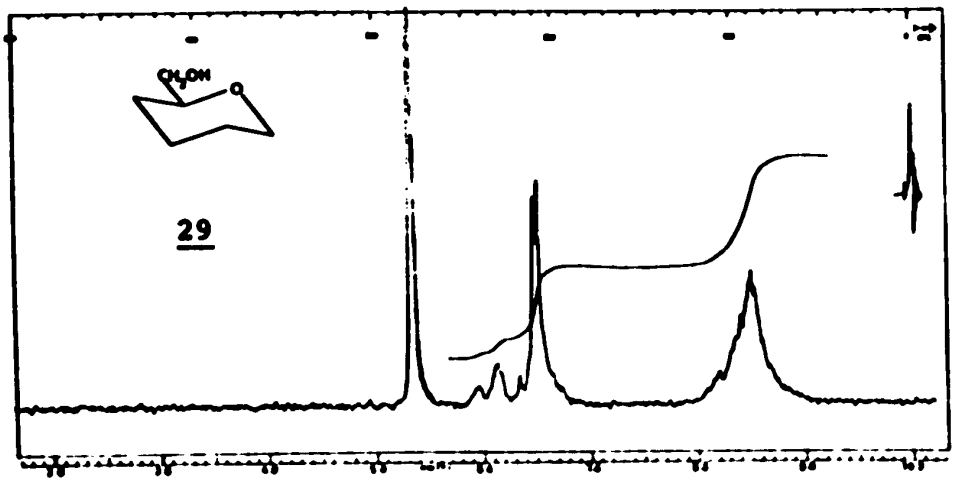
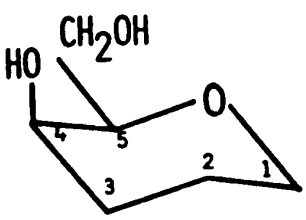


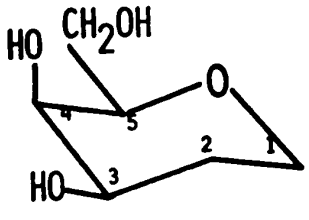
Fig. 46: The n.m.r. spectrum (60 MHz) of 1,5-anhydro-2,3,4-trideoxy-D-*glycero*-hexitol (29) (D_2O).

This leaves about 9% of the compound as 29a. The predicted rotation for this conformational distribution is very close to the rotation that is observed.

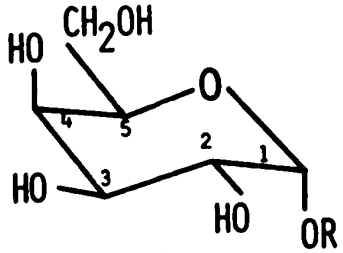
$$[M]_D^{25} \text{ (predicted for 29)} = 0.62\times(+0/0)+0.29\times(+C/0-0/0) + 0.09\times(-0/C)$$
$$= +0.62(55°) - 0.29(10°) - 0.09(45°)$$
$$= +26.8° \text{ (compared to +26.2°, observed at 25°C).}$$



4



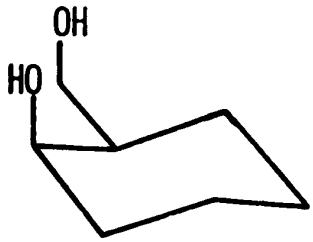
32



2

Compounds 4 and 32, whose conformations are also illustrated in Table 34, are simple analogs of more complex structures such as α-D-galactopyranosides (2). In D_2O, n.m.r. spectra of these two compounds, as well as that of compound 29, did not afford the averaged coupling constants between the exocyclic methylene protons and H5. As can be seen from Figs. 44, 45 and 46, the difference between the average chemical shift of the two methylene protons is, in each case, apparently very small. This proved to

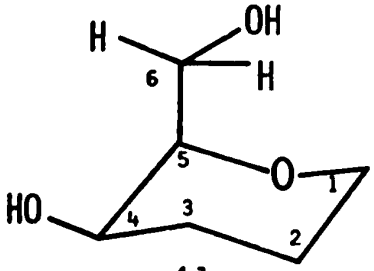
be most unfortunate, as the molecular rotations of 32 and 4 are somewhat anomolous with respect to that of 29, as will become apparent from the following discussion.



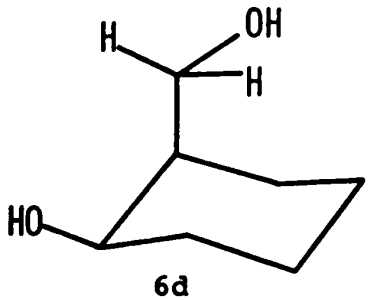
6b

According to n.m.r. spectroscopic data, the 6b conformation of the carbocyclic analog of 4 is not important in water (see p. 184). Because of this, it might be argued that 4b, or 32b, should also have a low percentage population in water. Now, the primary hydroxyl function of the 4a or 32a conformations has the same steric environment as the hydroxyl function of 29a. Similarly, this function has the same environment in 4c, or 32c, as it does in 29c. Therefore, just as 29c was shown to have a much higher percentage population than 29a, 4c or 32c should have much higher percentage populations than 4a or 32a. If their b conformations have small populations in water, this means that the molecular rotations of 4 and 32 should be much closer to the values predicted for their respective c conformations than to the values predicted for their respective a conformations. Some of this expected bias can be seen in the molecular rotation of compound 32,

although it is not as large as might be expected.[+] The rotation of 4 is even more anomolous, as it lies almost exactly half-way between the values predicted for the rotations of 4a and 4c (Table 33).



4d



6d

It could be argued that this "low" rotation of 4 is due to the presence of 4d. However, it is unlikely that this conformation will be any more important in water than was the corresponding conformation of the carbocyclic compound (6d). In any case, the rotation of 4d should be dextrorotatory*, so that the presence of a small amount

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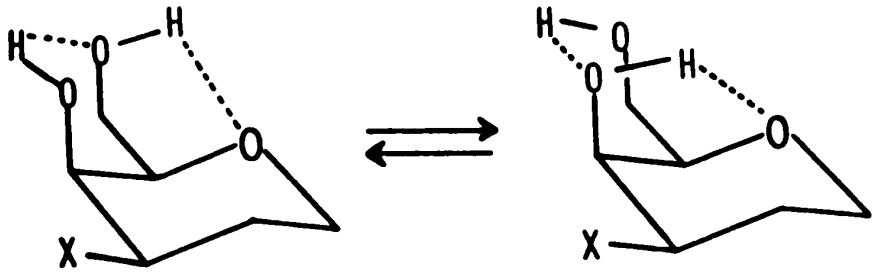
+ The interpretation of the rotation of 29 suggests that there is about six times as much of the 29c conformation as there is the 29a conformation (p. 190).

* Conformation 4d has been assigned a tentative rotation of +100° in Table 33. This is the rotation that is contributed by the +O/O and +O/C units that are produced as a result of the orientations of its two C-OH bonds. Because of the ring oxygen atom, the axial C5-C6 bond could generate additional molecular rotation. Whiffen's K parameter (Table 1) covers that situation, although he points out that the empirical value of -29° that is given to it is "uncertain" (10). On the other hand, if C6 were to be replaced by an oxygen atom, it would generate Whiffen's J parameter, which has a value of +113°. Therefore, although the rotation of 4d is almost certainly dextrorotatory, +100° should be regarded as only a rough approximation of its value.

of this conformation cannot account for the fact that the observed rotation of 4 is "too low".

There is the possibility that 4b and 32b are actually the most abundant conformations in water solutions. Because of the intermediate nature of their rotations (Table 33), the presence of substantial amounts of these b conformations would reduce the effect that the anticipated c to a ratios have on the solution rotations. In preceding discussions it was shown that 6b, 5a and 3a, which all contain opposing hydroxyl functions, cannot be regarded as having substantial populations in water. The reason for such unexpectedly large percentages of 4b and 32b could be the cumulation of two intramolecular hydrogen bonds that can occur in these conformations. If this intramolecular hydrogen bond pattern is particularly favourable, 4b or 32b could predominate in water, a solvent that can normally be expected to disrupt intramolecular hydrogen bonds.



X ≡ H ; 4b

X ≡ OH ; 32b

In the absence of useful n.m.r. data the above proposal must be regarded as only tentative. The technique of analyzing conformational equilibria by interpretation of molecular rotation is admittedly crude, as it is still only in its development stages. The reader will realize that the anomaly in the observed molecular rotations of 4, 32 and 29 could simply be the result of errors in the predictions of the molecular rotations of their respective conformations.

Fig. 47 illustrates the effect that an increase in solution temperature has on the molecular rotations of 4, 29 and 32 in water. As the temperature is increased, the molecular rotations of all three compounds decreases. It had been hoped that this temperature effect could be unambiguously interpreted through corresponding changes in the n.m.r. spectra of these compounds. However, this was not possible. It is most likely that increases in temperature result in changes in the conformational distribution of these compounds. The fact that the solution rotations decrease implies an increase in the percentage of the least stable a conformations (see Table 33). This conclusion is supported by the insensitivity of the rotation of the reference 6-deoxy compound (33) to the same temperature changes.

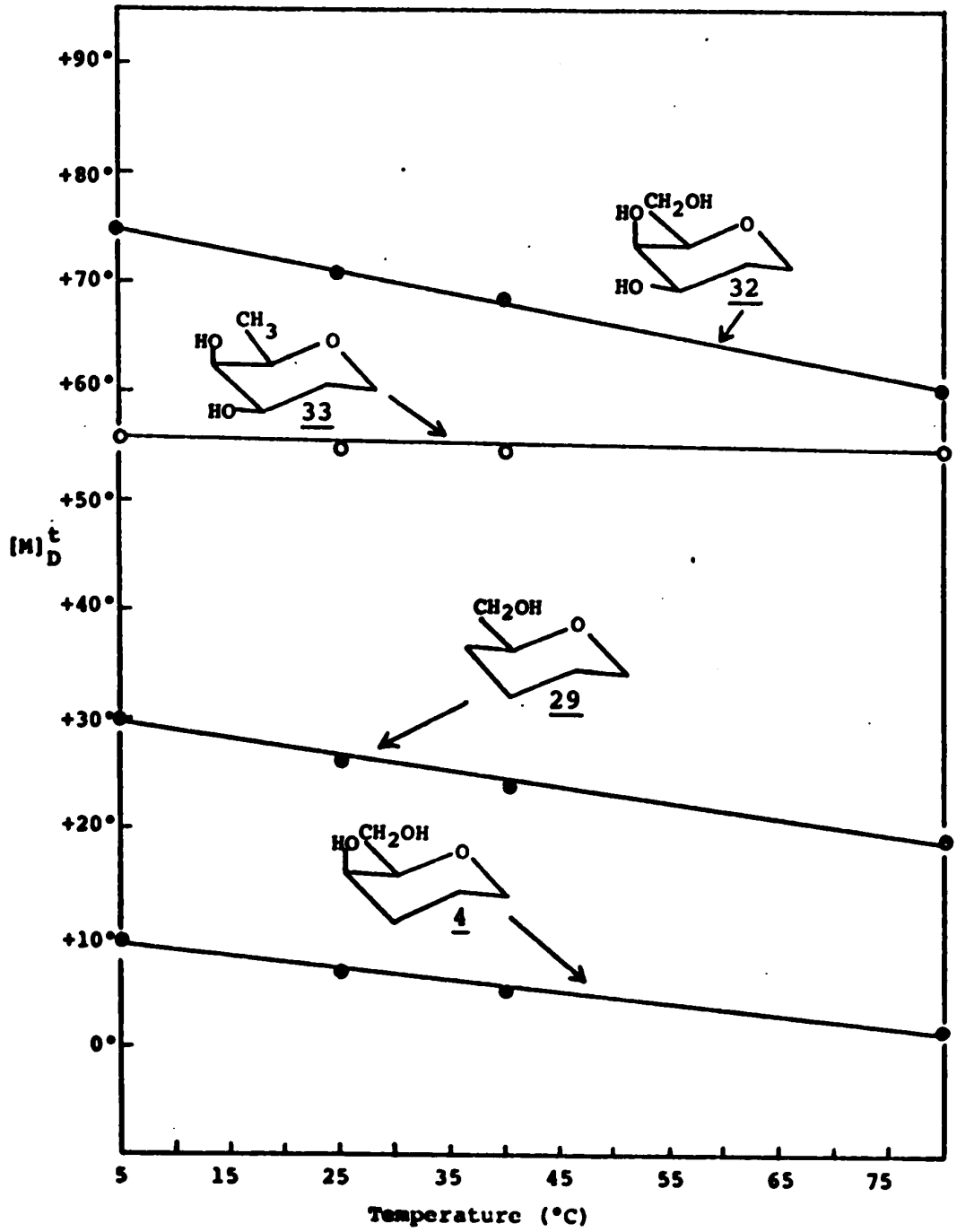


Fig. 47: The effect of increasing temperature on the molecular rotations of related 1,5-anhydro-deoxy-hexitols in water.

4. The conformational preferences of hydroxymethyl functions in binary solutions of 1,2-dichloroethane and dimethyl sulphoxide (DMSO).

In this section the effect that intramolecular hydrogen bond formation has on the conformational equilibria of compounds 3, 4, 5 and 6 in non-aqueous solvents will be discussed. Infrared and molecular rotational data obtained from compounds 3 and 4 will be compared with data obtained from their respective carbocyclic analogs, compounds 5 and 6.

Solutions of 1,2-dichloroethane and DMSO were chosen as the solvent system for these investigations. In pure 1,2-dichloroethane, intramolecular hydrogen bond formation was not expected to have to compete with strong solvent-solute interactions, whereas for low concentrations of DMSO, hydrogen-bond conjugation (9,35,55) was expected to increase the populations of conformations that contained a 1,3-type intramolecular hydrogen bond. The study of the rotational behaviour of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) demonstrated that DMSO is not the only hydrogen-bond-accepting "base" that can increase the strength of a 1,3-type intramolecular hydrogen bond between opposing hydroxyl functions, although it was the most effective of the bases that were used for the purpose.

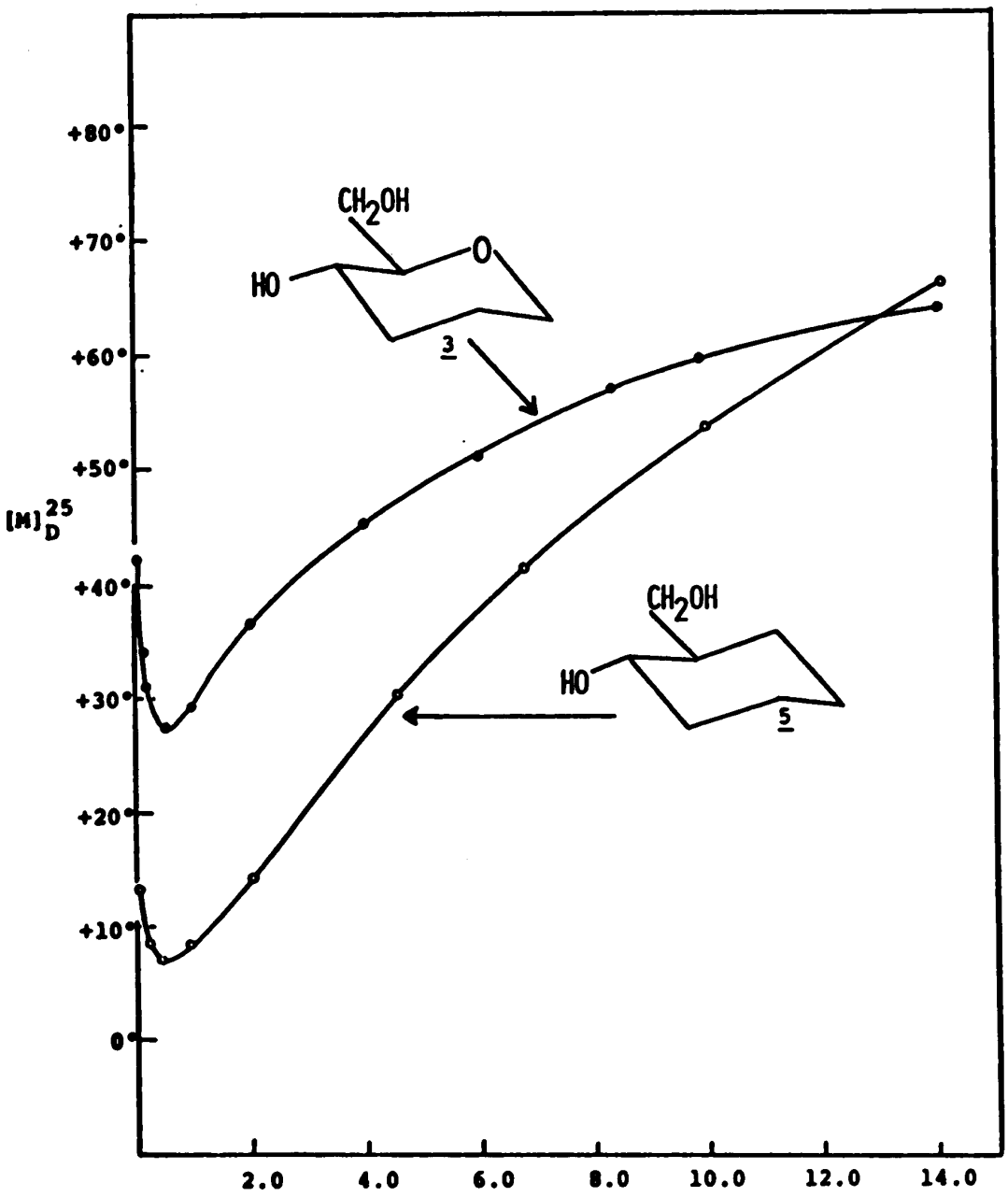


Fig. 48: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotation at 25°C of solutions of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) and (1S,2R)-(+)-*trans*-2-hydroxymethylcyclohexanol (5) in 1,2-dichloroethane.

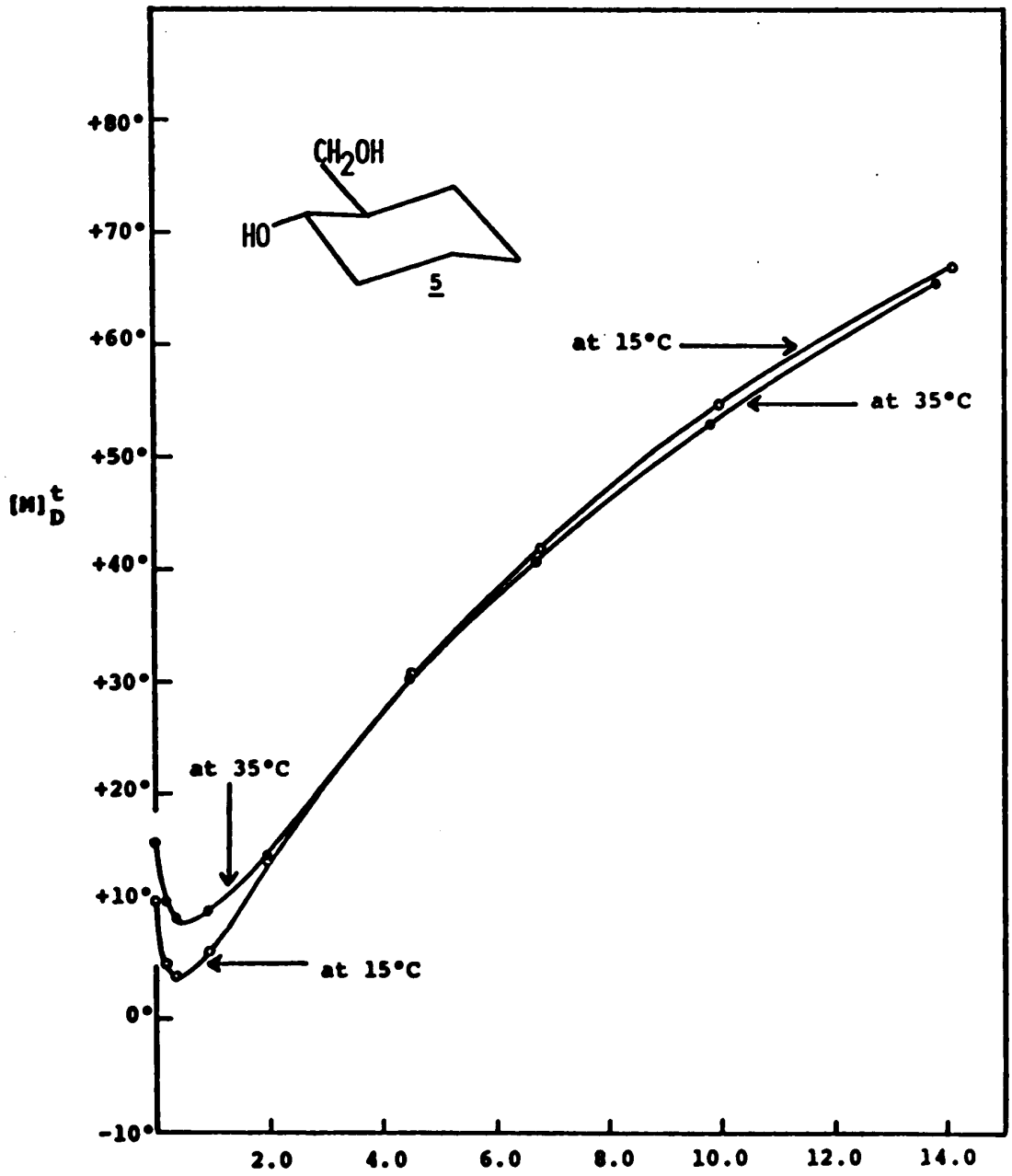


Fig. 49: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotations at 15°C and at 35°C of solutions of (1S,2R)-(+)-*trans*-2-hydroxymethylcyclohexanol (5) in 1,2-dichloroethane.

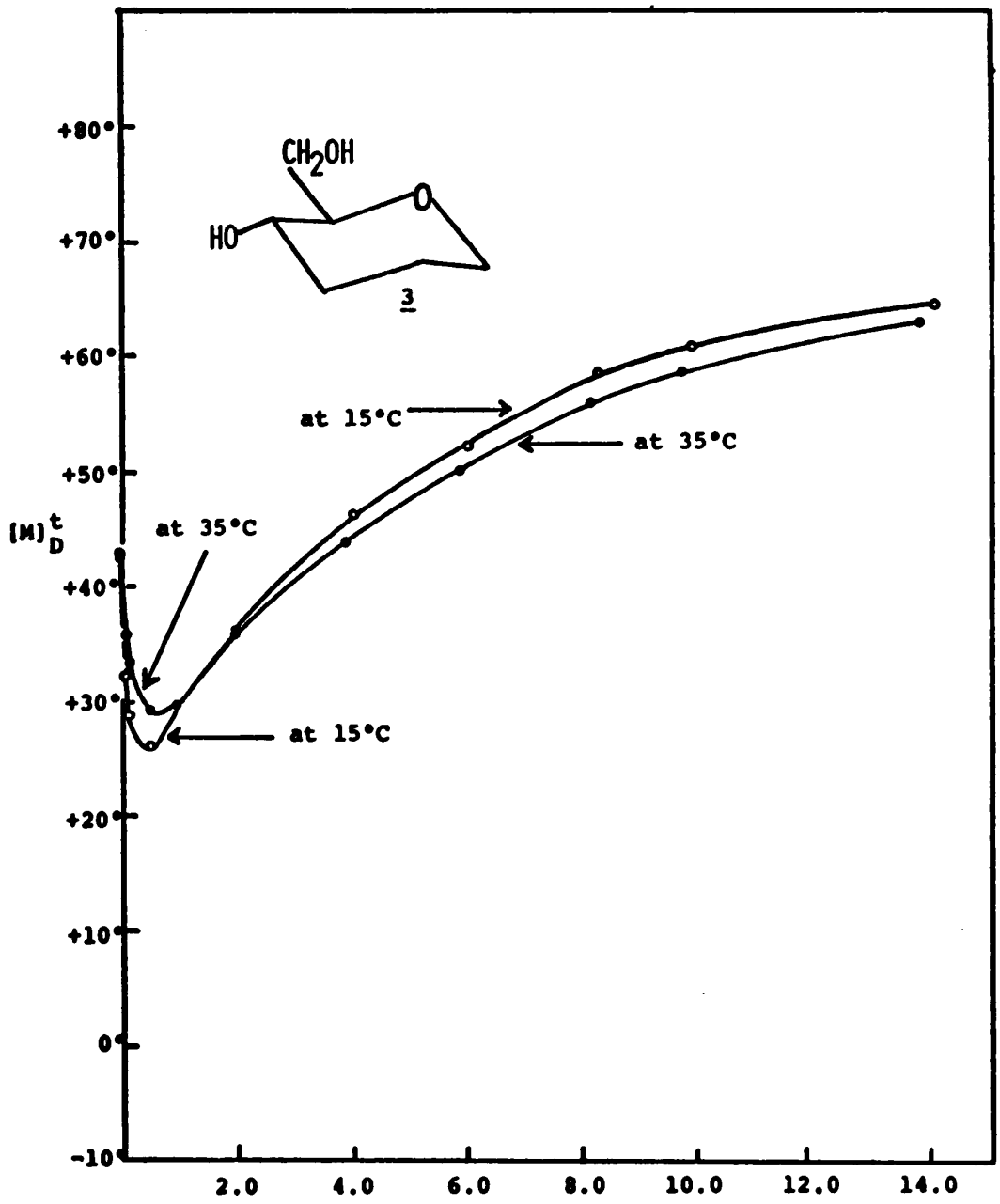


Fig. 50: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotations at 15°C and at 35°C of solutions of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) in 1,2-dichloroethane.

The results of the studies of the conformational equilibria of 3 and 5 will be compared first. As can be readily seen from Figs. 48, 49 and 50, the amount of DMSO in their solutions has a profound effect on their molecular rotations. To a lesser extent, the solution temperature is also a factor in determining the molecular rotation.

The rotational data* that were used to plot these curves can be found in Tables 15 and 16 (pp. 115 and 116). Each of these solutions was prepared at 25°C and its rotation measured at 15°, 25° and 35°C. For solutions whose DMSO concentrations were less than 7 moles per litre, the density ratios, $\frac{d_{15}}{d_{25}}$ and $\frac{d_{35}}{d_{25}}$, that were substituted into the formula on page 54 were given values of 1.012 and 0.989 respectively. For solutions whose DMSO concentrations were greater than 7 moles per litre, $\frac{d_{15}}{d_{25}}$ and $\frac{d_{35}}{d_{25}}$ were assessed values of 1.009 and 0.991 respectively. (See Table 4.)

Fig. 51 compares the structures and predicted rotations of conformations of 3 and 5. Where they can occur, intramolecular hydrogen bonds have also been

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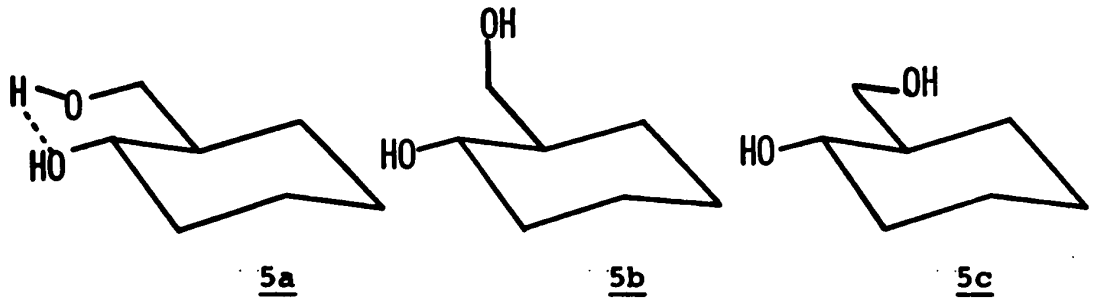
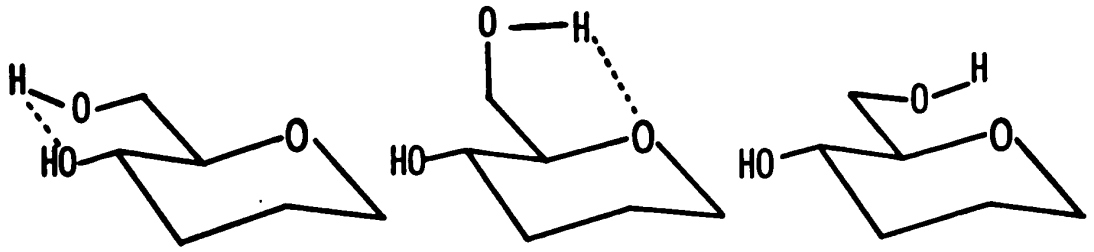
* Lemieux and Martin (9) have reported a curve for 3 that is qualitatively the same in shape to the ones in Figs. 48 and 50. However, the rotational values of the solutions of 3 that are reported in this thesis are somewhat larger than their values. This is presumably due to precautions that were taken in the present work to ensure the purity of this compound.

indicated. It is reasonable to expect that the proton of the primary hydroxyl function, being the more acidic of the two O-H protons, will be the one that "bridges" the two opposing hydroxyl functions of 5a or 3a (41,51).



5a 5b 5c

[M] = 0/C-0/C = 0° [M] = +0/C = +45° [M] = +0/C+0/C = +90°



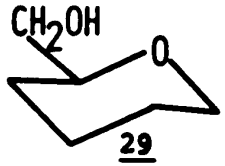
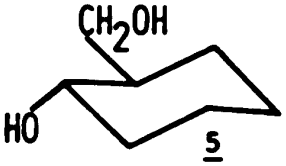
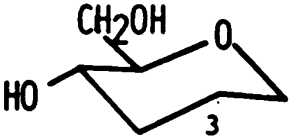
3a 3b 3c

[M] = +0/C-0/C = 0° [M] = +20/C-0/0 = +35° [M] = +0/C+0/0 = +100°

Fig. 51: The estimated molecular rotations of conformations of 3 and 5.

TABLE 34

Infrared spectral data on compounds dissolved in carbon tetrachloride (5 mm cells)

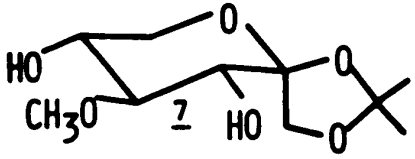
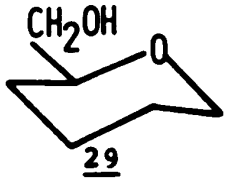
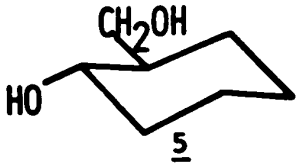
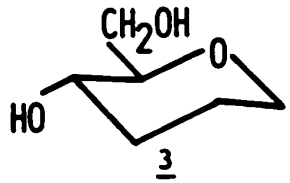
Compound	Approximate concentration in moles per litre	Fundamental hydroxyl stretching frequencies, cm^{-1}, and (absorbances)	
		Free OH	Hydrogen bonded OH
 29 +	0.01	3637 (0.04)	3595 (0.26)
 5 *	0.01	3630, sh.$^{\nabla}$ 3618 (0.17)	3635 (0.22) 3375$^{\Phi}$b$^{\Delta}$ (0.06)
 3	0.01	*ca.* 3630 (0.19); 3600 (0.21); 3525,b (0.11); 3450$^{\Phi}$b (0.09)	

\+ Also see ref. 46.
* Also see ref. 51.

$^{\Delta}$ b ≡ broad
$^{\Phi}$ This signal probably corresponds to intermolecularly bonded OH groups (40).
$^{\nabla}$ sh ≡ shoulder

TABLE 35

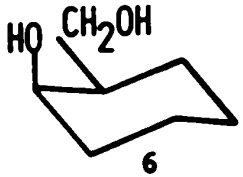
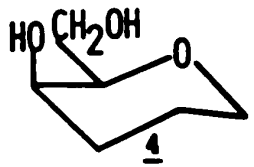
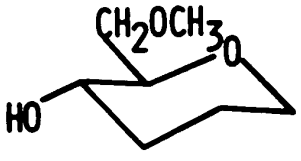
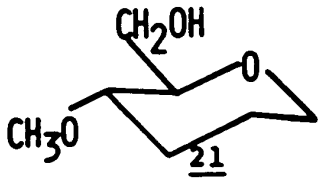
Infrared spectral data on compounds dissolved in 1,2-dichloroethane (1 mm cells)

Compound	Concentration, in moles per litre	Fundamental hydroxyl stretching frequencies, cm^{-1}, and (absorbances)		
	0.04	3585, sh[+] 3565 (0.37)	3490 (0.21)	
	0.03	3580 (0.41)		3460,b* (0.06)
	0.03	3590 (0.24)	3505 (0.22)	3400,b(0.04)
	0.03	3590 (0.39)	3510,b(0.1)	

continued .....

TABLE 35 (continued)

Infrared spectral data on compounds dissolved in 1,2-dichloroethane (1 mm cells)

	Concentration, in moles per litre	Fundamental hydroxyl stretching frequencies, cm^{-1}, and (absorbances)	
 6	0.03	3590 (0.13)	3500 (0.11)
 4	0.03	3565 (0.21)	3500 (0.18)
 20	0.02	3585 (0.11)	3500 (0.13)
 21	0.02	3565 (0.14)	3510, sh (0.07)

+ sh = shoulder

* b = broad

The strengths of their 1,3-intramolecular hydrogen bonds, as well as the steric environments of their primary hydroxyl functions, should be about the same for both the 3a and 5a conformations. For this reason, their absolute conformational stabilities should be about the same. There is a repulsive OH:H interaction between the primary hydroxyl group and the equatorial methylene proton of the ring in conformation 5c. On the other hand, 3c can be stabilized in inert solvents by the formation of a 1,2-type intramolecular hydrogen bond between the primary hydroxyl function and the oxygen atom of the ring. For the same reason, 3b will also have a greater absolute conformational stability than its carbocyclic analog, 5b. Therefore, in inert solvents that permit intramolecular hydrogen bonding, the presence of the ring oxygen should result in compound 3 having a greater total percentage of the c and b conformations than compound 5.

The molecular rotation of 5 in 1,2-dichloroethane is +13.9° at 25°C,[+] and indicates a high percentage of 5a, which is stabilized by the 1,3-intramolecular hydrogen bond. The corresponding molecular rotation of 3 is much bigger; +42.4° at 25°C. This means that the fractional population of the 3a conformation is smaller than that of 5a, which

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[+] The reader is reminded that this value is taken from the enantiomer.

is experimental evidence of the importance of the 1,2-type intramolecular hydrogen bonds between the primary hydroxyl function and the ring oxygen of 3b or 3c. In fact, this rotation of 3 in pure 1,2-dichloroethane suggests that 3c and 3a have similar populations.

This apparent difference in the conformational distributions of 3 and 5 is consistent with the hydroxyl function stretching absorptions in their i.r. spectra in carbon tetrachloride (CCl_4) and 1,2-dichloroethane. Data from these spectra are listed in Tables 34 and 35.

The i.r. spectrum of 5 in CCl_4 contains an absorption centred at 3525 cm^{-1}, which corresponds to the 1,3-type intramolecular hydrogen bond of 5a (see pp. 23 to 25). This absorption is shifted by 83 cm^{-1} from the maximum absorption, and 95 cm^{-1} from the shoulder absorption of a slightly less intense band that lies in the region of free hydroxyl group stretching frequences. Mori and Tsuzuki have reported very similar data for a sample of racemic 5 (51).

The i.r. spectrum of 5 in 1,2-dichloroethane[+] has an absorption for free OH at 3590 cm^{-1} and a second,

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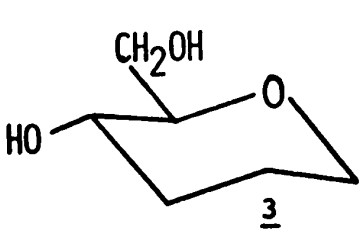
[+] The i.r. spectrum and molecular rotation of 5 in 1,2-dichloroethane were obtained from solutions that contained the same concentration of the diol.

slightly less intense absorption at 3505 cm^{-1} ($\Delta\nu_{OH}$; 85 cm^{-1}) that corresponds to the intramolecularly hydrogen-bonded hydroxyl group of 5a. Both of these absorptions occur at lower wave numbers than in the CCl_4 solution, although the difference between them is about the same for both solvents. This is in accordance with the predictions of von R. Schleyer (44).

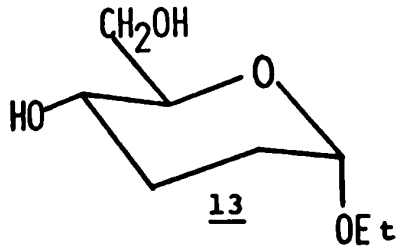
Provided that free and intramolecularly hydrogen-bonded hydroxyl functions have similar absorbances, per mole, (41,49), these i.r. spectra of 5 indicate that it exists mainly in the 5a conformation, where one hydroxyl group is free and the other is engaged in a 1,3-type of intramolecular hydrogen bond. This is also what its molecular rotation in 1,2-dichloroethane suggests.

The i.r. spectrum of 3, recorded in carbon tetrachloride, provides direct evidence of a substantial amount of 1,2-type hydrogen bonding. The absorption at about 3630 cm^{-1} is assigned to free OH groups. A second absorption, of comparable intensity to the first, occurs at 3600 cm^{-1} ($\Delta\nu_{OH}$; 30 cm^{-1}) and can be assigned to the hydroxyl functions that form the 1,2-intramolecular hydrogen bonds in 3b and 3c (see pp. 23 to 25). A third absorption, only about half as intense as the first two, and centred at approximately 3525 cm^{-1} ($\Delta\nu_{OH}$; 105 cm^{-1}), belongs to the hydroxyl function that forms the

1,3-intramolecular hydrogen bond in 3a. These results are very similar to those that Foster and co-workers (50) have reported for the i.r. spectrum of the related structure, ethyl 2,3-dideoxy-D-*erythro*-hexopyranoside (13) (see p. 33).

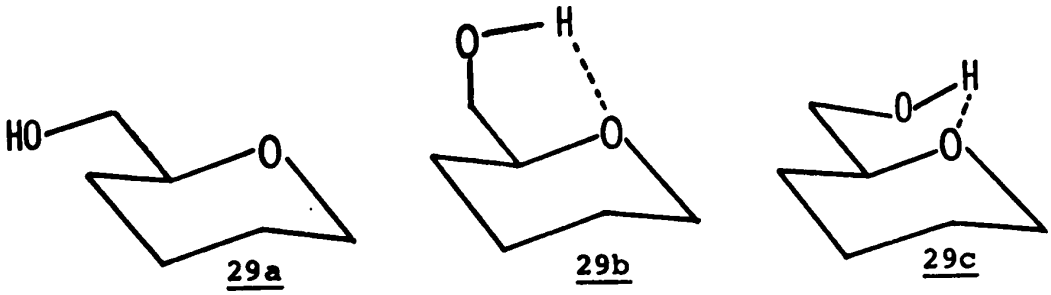


3



13

Unfortunately, frequency shifts ($\Delta\nu_{OH}$) appear to be a rather unreliable test for the existence of 1,2-intramolecular hydrogen bonding in 1,2-dichloroethane solutions. For example, the free hydroxyl function of 5 absorbs at 3590 cm^{-1} in this solvent. However, the hydroxyl group of 1,5-anhydro-2,3,4-trideoxy-D-*glycero*-hexitol (29), which appears to be almost quantitatively hydrogen bonded to the ring oxygen atom in CCl_4 (1,2-type hydrogen bonding), absorbs at 3580 cm^{-1} in 1,2-dichloroethane (*cf.* Tables 34 and 35). Assuming that this hydroxyl function of 29 is extensively hydrogen bonded to the ring oxygen in 1,2-dichloroethane, the formation of this 1,2-intramolecular hydrogen bond has not significantly lowered its absorption frequency relative to that of the free hydroxyl function of 5.



29a 29b 29c

Therefore, it is not surprising that only two absorptions bands for hydroxyl functions occur in the i.r. spectrum of 3 in 1,2-dichloroethane. The first band, centred at 3590 cm^{-1}, probably contains the absorptions of free hydroxyl functions as well as the absorptions of the primary hydroxyl functions of 3b and 3c, which should be engaged 1,2-type intramolecular hydrogen bonds. The second, and substantially weaker absorption band, that appears to be centred at approximately 3510 cm^{-1}, is assigned to the hydroxyl function that forms the 1,3-type intramolecular hydrogen bond in 3a. On comparison of the ratio of the intensities of these two absorption bands (*ca.* 4 to 1) with the ratio of the intensities of the two corresponding bands in the spectrum of 5 (*ca.* 1 to 1), it is evident that 3a cannot have as large a population in 1,2-dichloroethane than 5a does. This is the same conclusion that was reached on comparison of the molecular rotations of the dichloroethane solutions of 3 and 5.

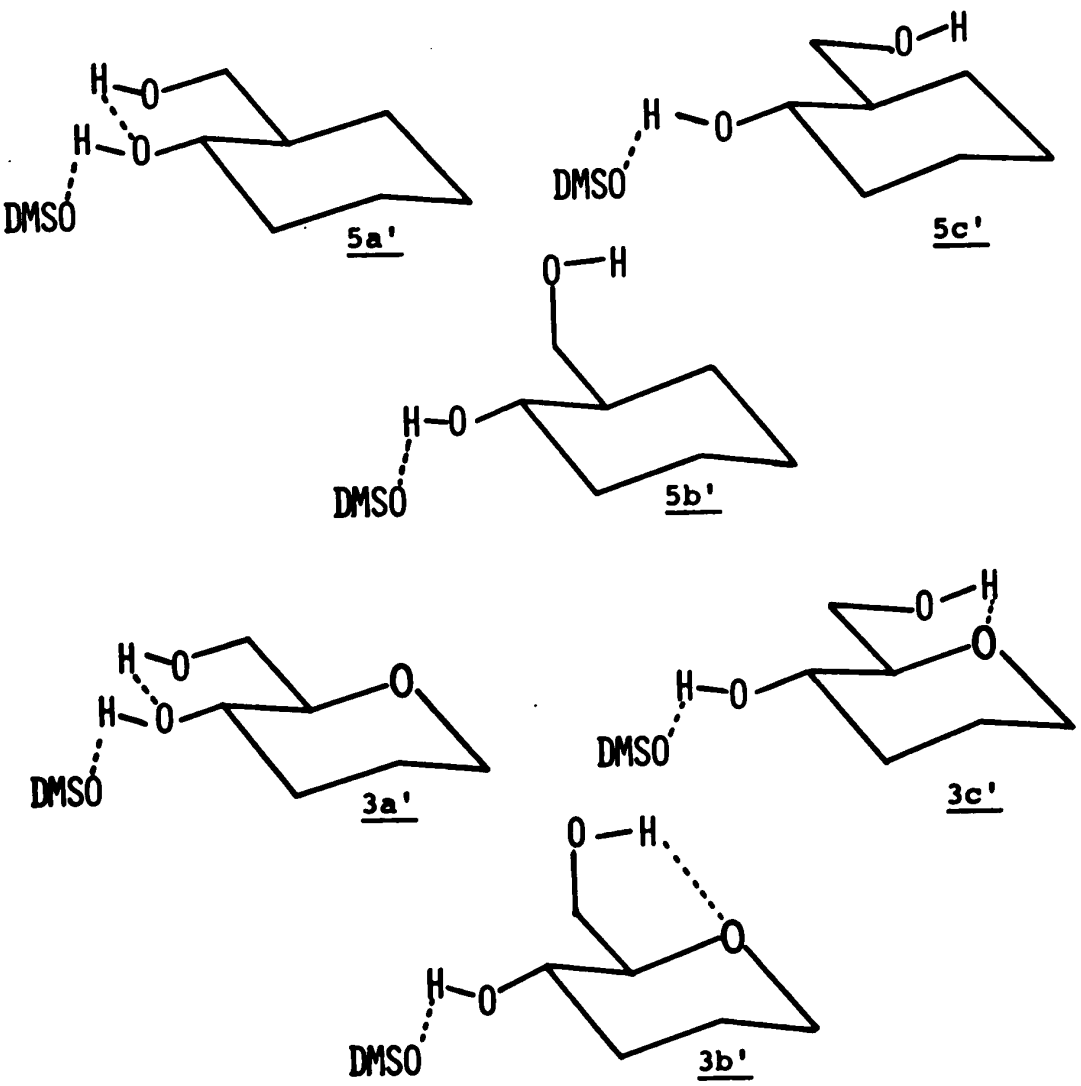


Fig. 52: Conformations of compounds 3 and 5 that are hydrogen-bonded to one molecule of dimethyl sulphoxide.

The molecular rotations of solutions of 3 and 5 in 1,2-dichloroethane are both decreased by the introduction of a small amount of DMSO (Fig. 48).

Fig. 52 shows some of the possible ways in which one DMSO molecule can form an intermolecular hydrogen bond

with the a, b and c rotamers of 3 and 5. To distinguish these mono-solvated conformations from the conformations of these compounds in pure 1,2-dichloroethane, they are referred to by the primed letters a', b' and c'.

According to Lemieux' proposals (9,35,55) (see also p. 42), the formation of an intermolecular hydrogen bond between the free hydroxyl functions of 3a or 5a should strengthen the existing intramolecular hydrogen bond between their opposing hydroxyl functions. As a result, 3a' and 5a' will have greater conformational stabilities than 3a and 5a. Intermolecular hydrogen bond formation cannot be predicted to generate a similar increase in the stabilities of the b' and c' conformations of 3 and 5. However, the 3b' and 3c' structures can be expected to form as shown in Fig. 52, so that the 1,2-type intramolecular hydrogen bonds between the primary hydroxyl functions and the ring oxygen atom are not disturbed. Therefore, 3b' and 3c' will continue to be more stable than 5b' and 5c', just as 3b and 3c were more stable than 5b and 5c.

As the small amount of DMSO is increased, the collective mono-solvation equilibrium

$$\text{DMSO} + (\underline{a} \rightleftarrows \underline{b} \rightleftarrows \underline{c}) \overset{K_1}{\rightleftarrows} (\underline{a}' \rightleftarrows \underline{b}' \rightleftarrows \underline{c}')$$

will shift to the right, increasing the total amount of

a', b' and c' in solution. Because of the increased stabilities of 3a' and 5a' relative to 3a and 5a, this will result in a decrease in solution rotation. However, at its minimum point (0.5 moles per litre of DMSO) the rotation curve of the solutions of 3 suggests that the 1,2-intramolecular hydrogen bonds in 3b' and 3c' continue to give these conformations enough stability to prevent the solvent-stabilized 3a' conformation from becoming the dominant species in solution. On the other hand, at its minimum value (0.5 moles per litre of DMSO) the rotation curve of 5 indicates that in the absence of the ring oxygen, most of the molecules prefer the 5a' conformation, with its conjugated hydrogen bond.

The rotations of solutions of 3 and 5 that contain relatively small amounts of DMSO are decreased by a decrease in temperature (Figs. 49 and 50). There are two probable reasons for this behaviour.

The decreases in temperature could alter the a' $\rightleftarrows$ b' $\rightleftarrows$ c' equilibria, increasing the amount of a' relative to c' and b'. Similarly, the a $\rightleftarrows$ b $\rightleftarrows$ c equilibria could be altered. This change in the a $\rightleftarrows$ b $\rightleftarrows$ c equilibria does not appear to apply to 3, as its rotation in pure 1,2-dichloroethane is not effected by changes in solution temperature. However, it does apply to 5. In pure 1,2-dichloroethane, the rotation of 5 decreases with

a decrease in temperature, thereby indicating an increase in the percentage of 5a. (*cf.* Tables 15 and 16.)

$$(\underline{a} \rightleftarrows \underline{b} \rightleftarrows \underline{c}) + \text{DMSO} \overset{K_1}{\rightleftarrows} (\underline{a}' \rightleftarrows \underline{b}' \rightleftarrows \underline{c}')$$

A second cause of this temperature effect is a probable increase in the value of the collective equilibrium constant, K_1. In as much as formation of intermolecular hydrogen bonds has negative ΔH values, K_1 should increase as temperature is decreased. This will increase the total amount of a', b' and c' in solution, and consequently the solution rotation will decrease.

The molecular rotation of corresponding solutions of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) also indicated the formation of more of the intramolecularly hydrogen-bonded conformation as the temperature was decreased (*cf.* Figs. 27, 29 and 30). However, because this conformation of 7 (7e') had a large absolute rotation, the effect was indicated by increases in absolute rotation, rather than the decreases that are observed for 3 and 5.

As the DMSO concentrations in the solutions of 3 and 5 is increased from 0.5 moles per litre to 14 moles per litre (100%), the molecular rotations of the compounds increase. This is the result of their forming intermolecular hydrogen bonds with a second molecule of DMSO.

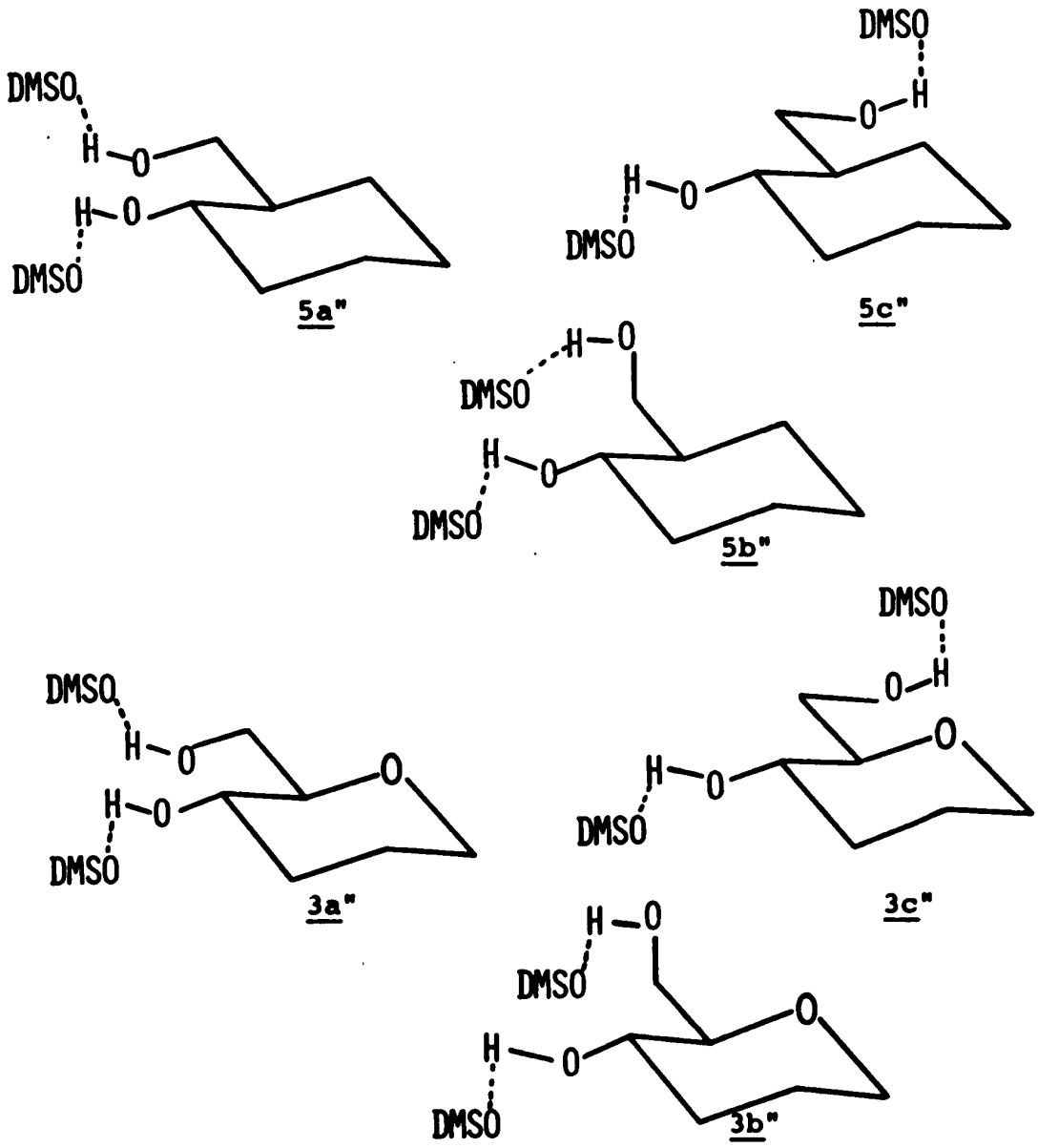


Fig. 53: Conformations of compounds 5 and 3 that contain two intermolecular hydrogen bonds.

Consider the possible di-solvated conformations of these compounds that are shown in Fig. 53. Unlike their mono-solvated counterparts, 3a" and 5a" no longer contain an intramolecular hydrogen bond. In fact, they should be

particularly unstable due to the opposition of the two solvent-induced dipole moments (35,55) and cannot be expected to have significant populations at any DMSO concentration. Therefore, for moderate to high DMSO concentrations, the molecular rotation of 5, and, to a lesser extent, 3,[+] will be primarily a function of the following three equilibria

$$\underline{a}' + \text{DMSO} \overset{K_2}{\rightleftarrows} \underline{c}''$$

$$\underline{a}' + \text{DMSO} \overset{K_2'}{\rightleftarrows} \underline{b}''$$

$$\underline{b}'' \overset{K_3}{\rightleftarrows} \underline{c}''$$

According to the first two equilibria, the ratios of c" to a', and b" to a' will be increased by increases in the DMSO concentration. Notice that each of these processses is formally the same as that proposed for solutions of 7 that contained moderate to high percentages of DMSO (*cf.* p. 132). In the present case, however, there are two stable di-solvated conformations that can form (b" and c"), so that two similar processes must be considered.

[+] At 0.5 molar concentrations of DMSO, the solution of 3 has a modest population of the mono-solvated b' and c' conformations. According to its molecular rotation, the corresponding solution of 5 contains mostly the mono-solvated a' structure.

The ratio of the populations of c" and b" will be determined by the relative conformational free energies of these two di-solvated conformations. The b" conformations of both 5 and 3 are less stable than their respective c" conformations by the value of an OH:H interaction (see p. 168). If 0.45 kcal per mole is used to estimate the value of an OH:H interaction in DMSO,[+] the ratio of the populations of c" and b" will be 2.1 to 1 at 25°C. Therefore, as the DMSO concentrations approach values that are large enough to reduce the a' populations to an insignificant level, c" and b" will approach mole fractions of 0.68 and 0.32 respectively. According to the following calculations, the rotations of such solutions of 3 and 5 would approach +80° and +76° respectively at 25°C.

$$[M]_D^{25} \text{ (for } \underline{3}) = X_{b"} \times (+20/C-0/0) + X_{c"} \times (+0/0+0/C)$$
$$= 0.32(+35°) + 0.68(+100°)$$
$$= +79° \text{ (predicted for } X_{b"} = 0.32 \text{ and } X_{c"} = 0.68)$$

[+] The difference between the conformational free energies of the two chair forms of cyclohexanol, which can be equated to the value of two OH:H interactions has been assessed values that range from 0.77 to 0.99 kcal per mole in DMSO (96,97,98). Therefore, one OH:H interaction in water will have a "best" value of 0.45 kcal per mole.

$$[M]_D^{25} \text{ (for } \underline{5}) = X_{b''} \times (+0/C) + X_{c''} \times (+20/C)$$

$$= 0.32(+45°) + 0.68(+90°)$$

$$= +76° \text{ (predicted for } X_{b''} = 0.32 \text{ and } X_{c''} = 0.68)$$

The observed rotations of $\underline{3}$ and $\underline{5}$ that are plotted in Fig. 48 indicate that even 100% DMSO is unable to force these compounds exclusively into their $\underline{b}''$ and $\underline{c}''$ conformations. However, the rotations of both compounds in pure DMSO do require that the $\underline{b}''$ and $\underline{c}''$ conformations have a total population that is much larger than that of the $\underline{a}'$ conformation.

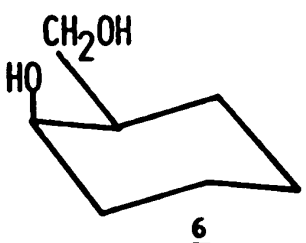
For moderate to high DMSO concentrations, a decrease in temperature causes a slight increase in the rotations of the solutions of both $\underline{3}$ and $\underline{5}$, which suggests an increase in the amount of their $\underline{c}''$ conformations. This could imply that the ΔH associated with the equilibrium

$$\underline{a}' + \text{DMSO} \overset{K_2}{\rightleftharpoons} \underline{c}''$$

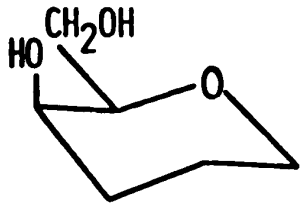
is negative, which was the reason for the temperature effects on corresponding solutions of $\underline{7}$ (*cf.* pp. 145 to 149). However, in the case of $\underline{3}$ or $\underline{5}$, decreases in temperature could also increase the value of K_3, the $\underline{b}'' \rightleftharpoons \underline{c}''$ equilibrium constant, which could also account for

some or all of the effect that is observed. In short, it is not possible to interpret the shift in rotation as the result of a change in any one of K_2, K_2' or K_3. Rather, it represents the net effect that a temperature change has on all of their values.

A recent publication (66) has attempted to interpret the rotation of 5 in an ether solution ($[M]_D$ = +27°) solely on the basis of optical activity generated by the *gauche* hydroxyl and hydroxymethyl functions. The three possible orientations of the bonds of the hydroxymethyl group were not included in the analysis. This present study of the rotational behaviour of 5 and 3 in 1,2-dichloroethane/DMSO solutions, and in water solution; aided by the interpretations of n.m.r. spectra in D_2O and i.r. spectra in both CCl_4 and 1,2-dichloroethane, has related the molecular rotations of both of these compounds to the preferred orientations of their exocyclic CH_2-OH bond.



6



4

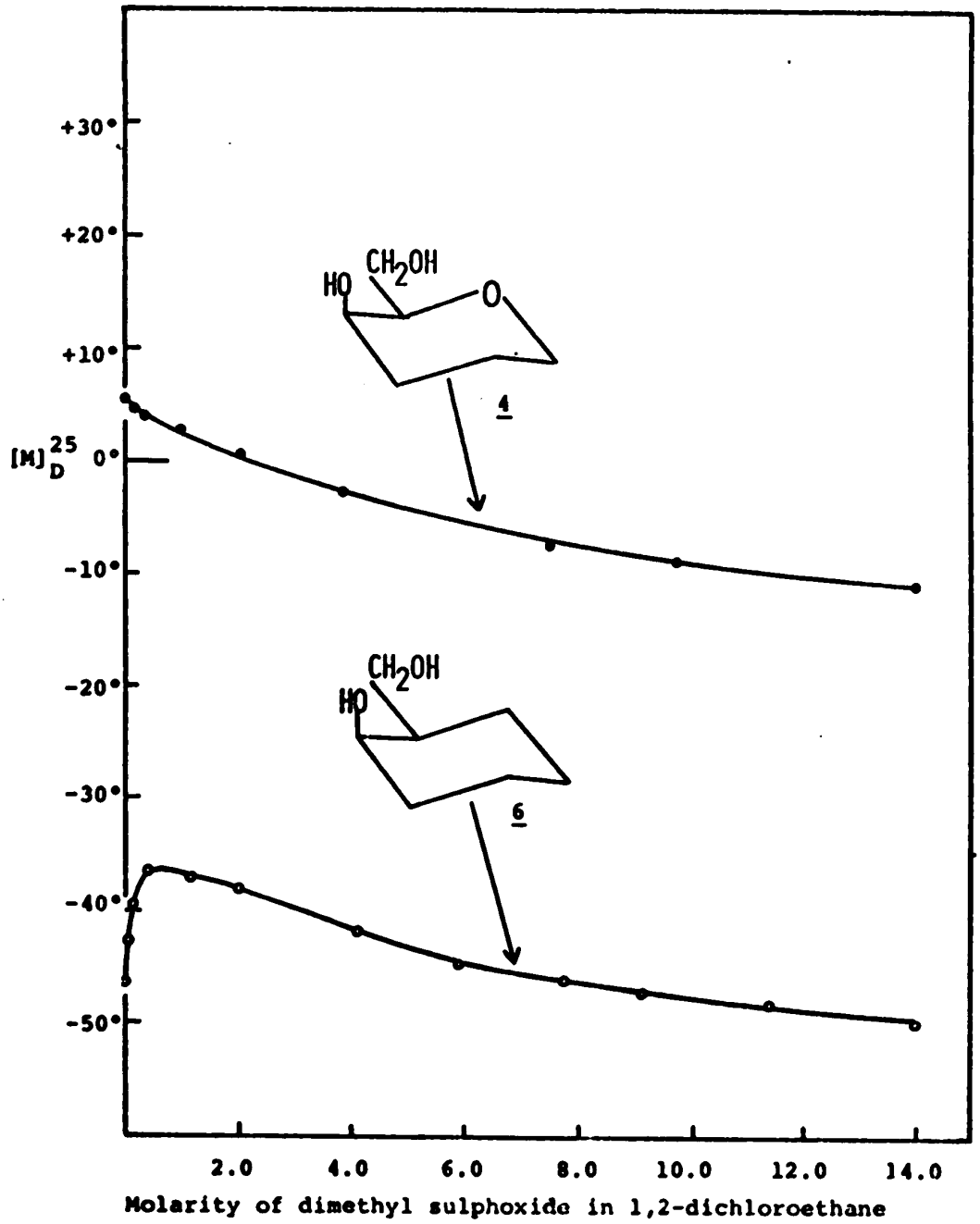
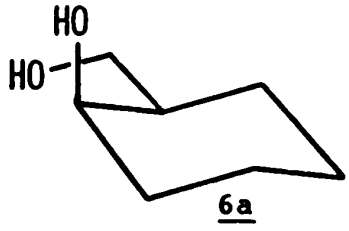


Fig. 54: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotation at 25°C of solutions of 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (4) and (1R,2R)-(-)-*cis*-2-hydroxymethylcyclohexanol (6) in 1,2-dichloroethane.

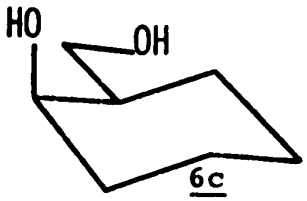
The molecular rotations of the structurally related compounds, 4 and 6, in solutions of 1,2-dichloroethane that contain increasing amounts of DMSO, are compared in Fig. 54. Data that were used to plot these rotation curves can be found in Tables 17 and 18 (pp. 117 and 118).

The rotations of the carbocyclic compound, (6), will be discussed first. There are four conformations of this compound that require consideration in a solvent that permits the formation of intramolecular hydrogen bonds. These are shown in Fig. 55, along with estimates of their molecular rotations.



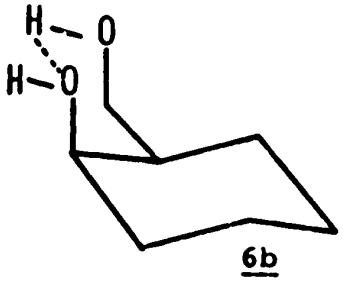
6a

[M] = -20/C = -90°



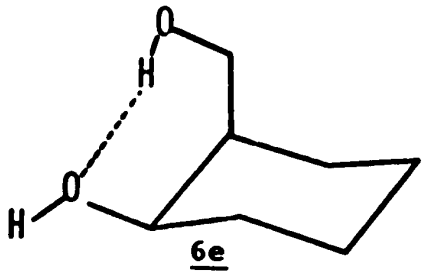
6c

[M] = -0/C+0/C = 0°



6b

[M] = -0/C = -45°



6e

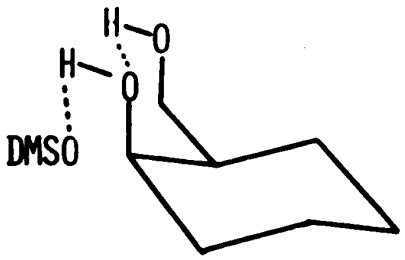
[M] = -0/C+0/C = 0°

Fig. 55: The calculated molecular rotations of conformations of (1R,2R)-(-)-*cis*-2-hydroxymethylcyclohexanol (6).

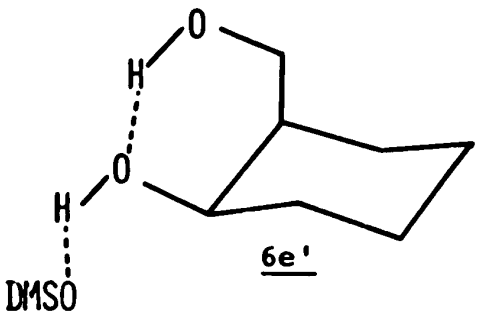
The observed molecular rotation of 6 in pure 1,2-dichloroethane is -46.7° at 25°C, which is very close to the value of -45° that is predicted for the intramolecularly hydrogen-bonded 6b conformation. However, this predicted rotation of 6b is exactly halfway between the rotations that are expected for 6a and 6c. Because 6a and 6c should have the same relative stabilities (see p. 113), they should have about the same populations, and should therefore have an "average" molecular rotation of -45°. For this reason, the observed rotation of 6 in 1,2-dichloroethane is not direct evidence of a high percentage of the 6b conformation. On the other hand, this rotation would have been smaller if 6e, which also contains a 1,3-intramolecular hydrogen bond, but which has a predicted rotation of zero, had a significant population in this solvent.

The infrared spectrum of the 1,2-dichloroethane solution of 6 contains an absorption centred at 3590 cm^{-1}, which corresponds to free hydroxyl functions, and a second absorption, of comparable intensity, centred at 3500 cm^{-1} ($\Delta\nu_{OH}$; 90 cm^{-1}), which is assigned to hydroxyl functions that are engaged in a 1,3-intramolecular hydrogen bond (*cf.* p. 209). This is a more direct indication of a high percentage of 6b, which has one free and one bound hydroxyl function.

As a small percentage of DMSO in introduced into the 1,2-dichloroethane solution of 6 it should engage in an intermolecular hydrogen bond with the free hydroxyl function of 6b. According to the concept of hydrogen-bond conjugation (35,55) (see p. 22), this should strengthen the intramolecular hydrogen bond, and thereby increase the stability of this conformation. However, this solvent-stabilized 6b' structure has a predicted rotation that is virtually the same as the rotation of 6 in pure 1,2-dichloroethane. In fact, the solution rotation should not change if 6b' were the only material that forms on the addition of DMSO. The decreases in the absolute rotation that are observed suggest instead that the DMSO generates some of the 6e' conformation as well as 6b'.



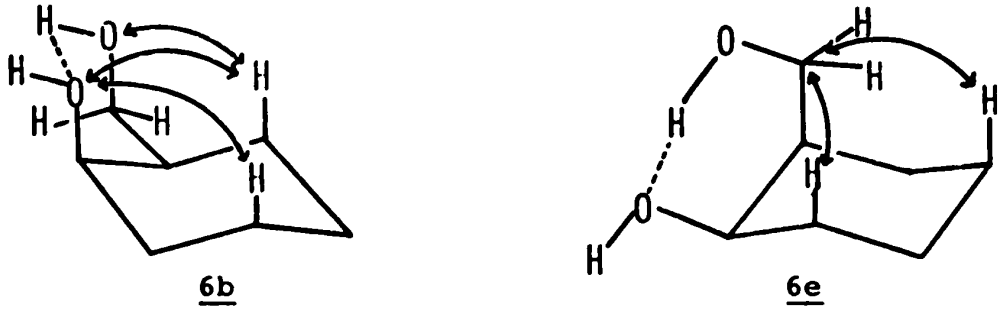
6b'



6e'

This would require that the difference between the conformational free energies of 6b' and 6e' be smaller than the difference between the conformational free energies of 6b and 6e. This could occur if the formation of the intermolecular hydrogen bond with the DMSO effects a

greater increase in the strength of the intramolecular hydrogen bond in 6e than it does in the strength of the intramolecular hydrogen bond of 6b. It is also possible that the formation of the intermolecular hydrogen bond with the DMSO increases the magnitude of the repulsive interactions that are initially present in 6b without substantially increasing those in 6e. The ensuing discussion illustrates how this second situation could arise.



6b 6e

Fig. 56: The relative repulsive interactions in the 6b and 6e conformations of compound 6.

When the DMSO forms the intermolecular hydrogen bond with 6b, it induces additional polarization in the O-H bonds. As a result of this increase in their negative charge, the oxygen atoms of these functions should become more space-demanding, so that the magnitude of their interactions with the opposing hydrogen atoms of the ring will increase (Fig. 56). For this reason, the average values of the three OH:H interactions in 6b'

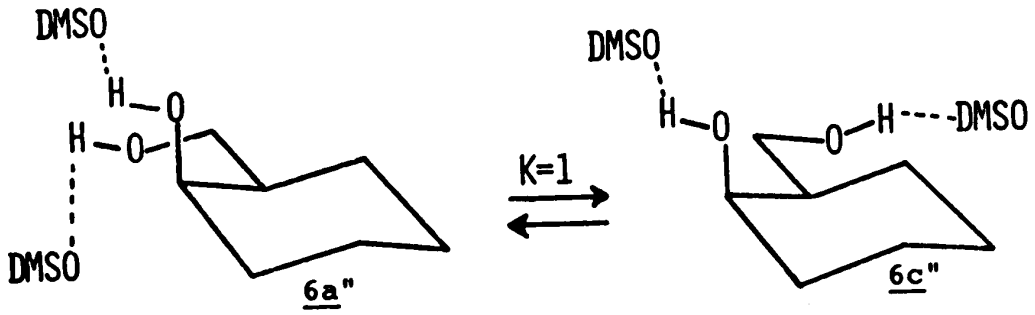
should be greater than they are in 6b. An increase in the "size" of the oxygen atoms will not be as important in 6e'. This conformation has no OH:H non-bonded interactions, and the two axial C-H bonds that oppose the axial hydroxymethyl function are well separated from its O-H bond. Therefore, although the size of the repulsive interaction energy could be bigger in 6b' than it is in 6b, it should be about the same in 6e' as it is in 6e. This, in effect, means that the energy difference between 6b' and 6e' will be smaller than that between 6b and 6e.

An indication of the relative amounts of 6b' and 6e' that are formed on the addition of DMSO can be obtained from the molecular rotation at the minimum point of the curve in Fig. 54 (DMSO = 0.5 moles per litre). If at this point most of the molecules exist as one or the other of these two structures, the rotation of -36.4° requires that there be about 78% of 6b' and 22% of 6e' in solution. On this basis, these structures are formed in a ratio of about 3.5 to 1.

As the DMSO concentration is increased beyond 0.5 moles per litre,[+] it should begin to saturate both of the hydroxyl functions of 6 with intermolecular hydrogen bonds.

[+] For DMSO concentrations that were greater than this, the rotation curves of 3 and 5 indicated the formation of material that was hydrogen-bonded to two molecules of DMSO.

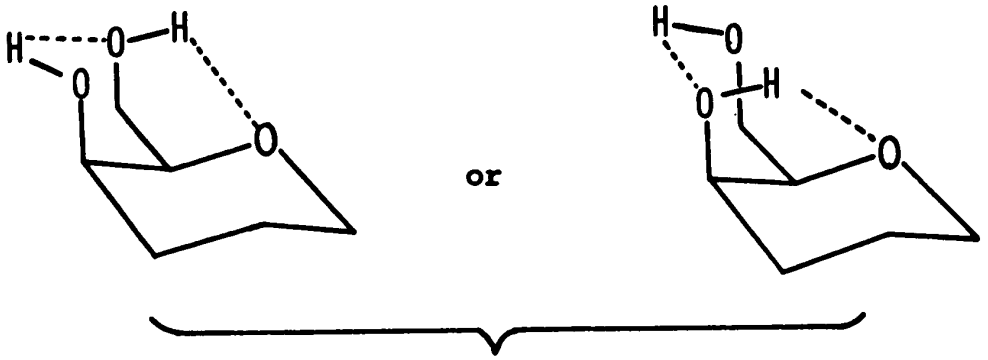
Because of the unfavourable interactions between opposing hydroxyl functions that are both intermolecularly hydrogen bonded to DMSO, 6a" and 6c" should be the only important di-solvated structures of 6.



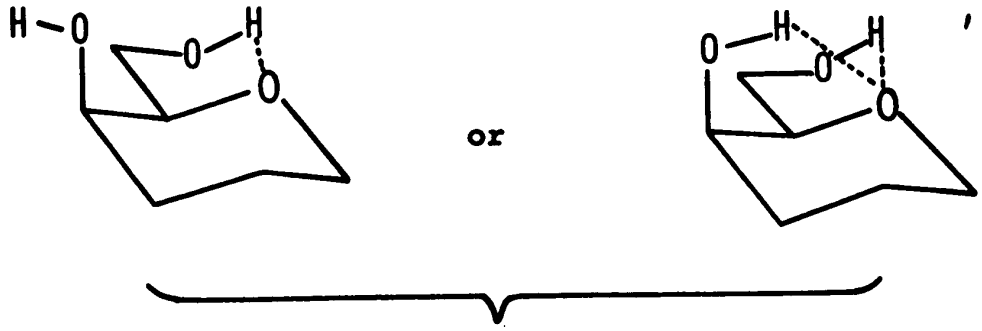
The stabilities of 6c" and 6a" should be about the same, so that they should have an average molecular rotation that is close to -45°. The transfer of 6b' to equal amounts of 6c" and 6a" will not be indicated by a change in rotation. The gradual increase in absolute rotation that is observed as the DMSO concentration increases reflects the diminishing population of 6e', which is formed along with 6b' in the mono-solvation step.

$$(6e' \rightleftarrows 6b') + DMSO \rightleftarrows (6c'' \rightleftarrows 6a'')$$

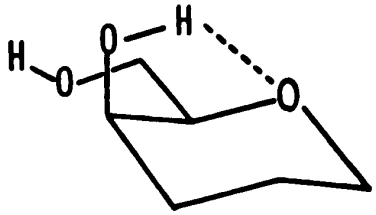
The molecular rotation of 4, a compound that has a ring oxygen in place of the methylene function of 6, is +5.5° in pure 1,2-dichloroethane. Structures that could make possible contributions to this rotation are



4b; [M] = -0/0+I = -10°



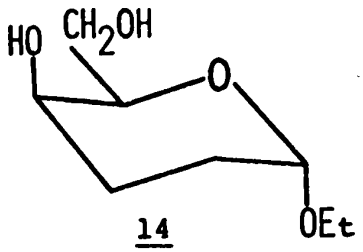
4c; [M] = +0/0-0/C+I = +55°



4a; [M] = -20/C+I = -45°

Fig. 57: Conformations, and their molecular rotations, of 1,5-anhydro-2,3-dideoxy-D-*threo*-hexitol (4).

shown in Fig. 57 along with estimates of their molecular rotations.



14

Of the three rotamers, 4b should be the most abundant, as both of its hydroxyl functions can simultaneously engage in intramolecular hydrogen bonds. Foster and co-workers (50) have reported this type of hydrogen bond pattern for a carbon tetrachloride solution of the structurally related compound, ethyl 2,3-dideoxy α-D-*threo*-hexopyranoside (14) (see p. 29). The 4c conformation can also be expected to have a modest population because of the opportunity for the formation of an intramolecular hydrogen bond between the primary hydroxyl function and the ring oxygen atom.[+] The importance of this 1,2-type of intramolecular hydrogen bond was noted in the comparison of the rotational behaviour of 3 and 5. Because its primary hydroxyl function cannot form an intramolecular hydrogen bond, but instead experiences a repulsive OH:H

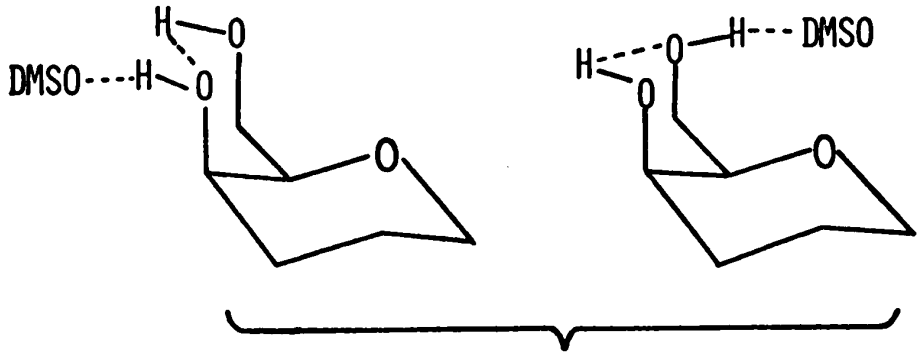
[+] The ring oxygen could conceivably function as a proton acceptor for both hydroxyl groups of 4c, as is shown in Fig. 57.

non-bonded interaction with H4, 4a should have a population that is much smaller than that of 4c. If the actual percentage of 4a is assumed to be small enough that it can be neglected (<5%), the observed molecular rotation of +5.5° suggests that there is about a 4 to 1 mixture of 4b and 4c in the 1,2-dichloroethane solution.

Infrared spectroscopy confirms that a high percentage of 4 exists as 4b in 1,2-dichloroethane. The spectrum contains two bands that are the result of O-H stretching (Table 35). The band at 3500 cm^{-1} corresponds to the OH group of 4b that is engaged in the 1,3-type intramolecular hydrogen bond (*cf.* pp. 209 and 224). The other hydroxyl function of 4b, which is engaged in a 1,2-type intramolecular hydrogen bond with the ring oxygen, should account for the greater part of the somewhat larger absorption at 3565 cm^{-1}. What remains of this larger absorption can be related to the two hydroxyl functions of 4c.

If the proposed 4 to 1 mixture of 4b and 4c was almost quantitatively converted to the solvent-stabilized 4b' structure by the addition of a small amount of DMSO, the rotation of the solution would decrease sharply, towards a value of about -10°. As can be seen in Fig. 54, this does not occur. Instead, the presence of a small amount of DMSO in the solution results in only a slight

decrease in rotation. There is a possible drawback to the



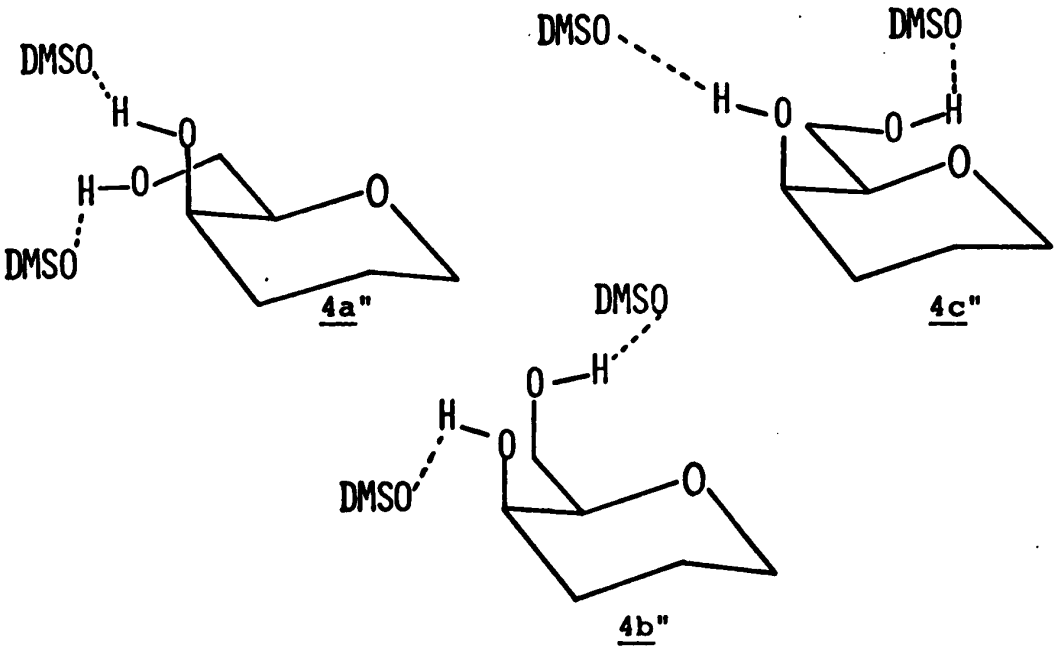
4b'

[M] = -0/0+I = -10°

formation of 4b', even with its conjugated hydrogen bonds. In order that this structure can form from either 4b or 4c, an existing intramolecular hydrogen bond must be sacrificed. This could be one reason why the proposed initial population of 4c (20%) is not dramatically reduced by the small amounts of DMSO.

As the concentration of DMSO is built up in the solution, the rotation of 4 becomes increasingly more negative. These increased concentrations of DMSO can act as a driving force for the formation of conformations of 4 that are hydrogen-bonded to two molecules of DMSO. Specifically, these structures are 4a" and 4c". Because of the anticipated unfavourable electrostatic interactions between two opposing hydroxyl functions that are both

hydrogen bonded to DMSO molecules, 4b" should be strongly destabilized.



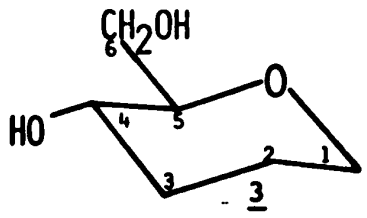
4a" 4c" 4b"

The predicted rotation of 4b is intermediate between those of 4a" and 4c", so that it is not possible to tell how much of this intramolecularly hydrogen-bonded conformation persists in pure DMSO. Previously, it was pointed out that its cumulated intramolecular hydrogen bonds could stabilize 4b to the extent that it is actually the most abundant conformation of 4 in water, even though this solvent, like DMSO, is capable of acting as a hydrogen-bond-accepting base. This situation may also apply to the DMSO solution. On the other hand, the population of 4b (and 4b') may be small enough in pure DMSO that the molecular rotation of the solution is primarily determined by the 4a" $\rightleftarrows$ 4c" equilibrium position.

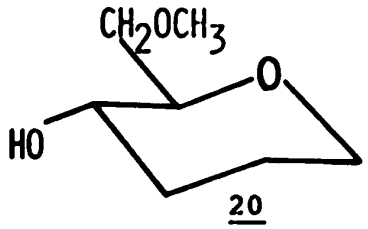
The observed molecular rotation of the solution does not permit a distinction between these two possibilities.

5. Studies of the conformational equilibria of the *O*-methylated derivatives of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3)

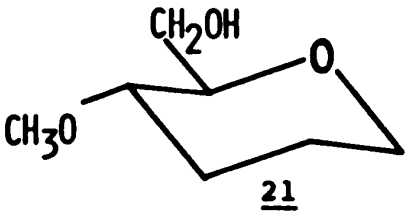
In the preceding discussion, the conformational preference of 3 was shown to be strongly influenced by the existence of intramolecular hydrogen bonds between its two hydroxyl functions and between its primary hydroxyl function and the ring-oxygen atom. This section will show how modifications to the intramolecular hydrogen bonding ability of 3, *via* preparation of its *O*-methylated derivatives, 20 and 21, can effect the preferred orientations of the C6-O6 bond.



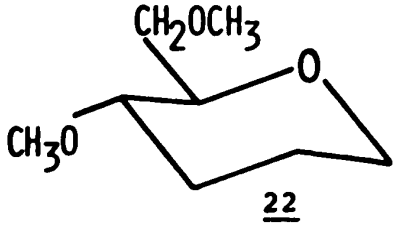
3



20



21



22

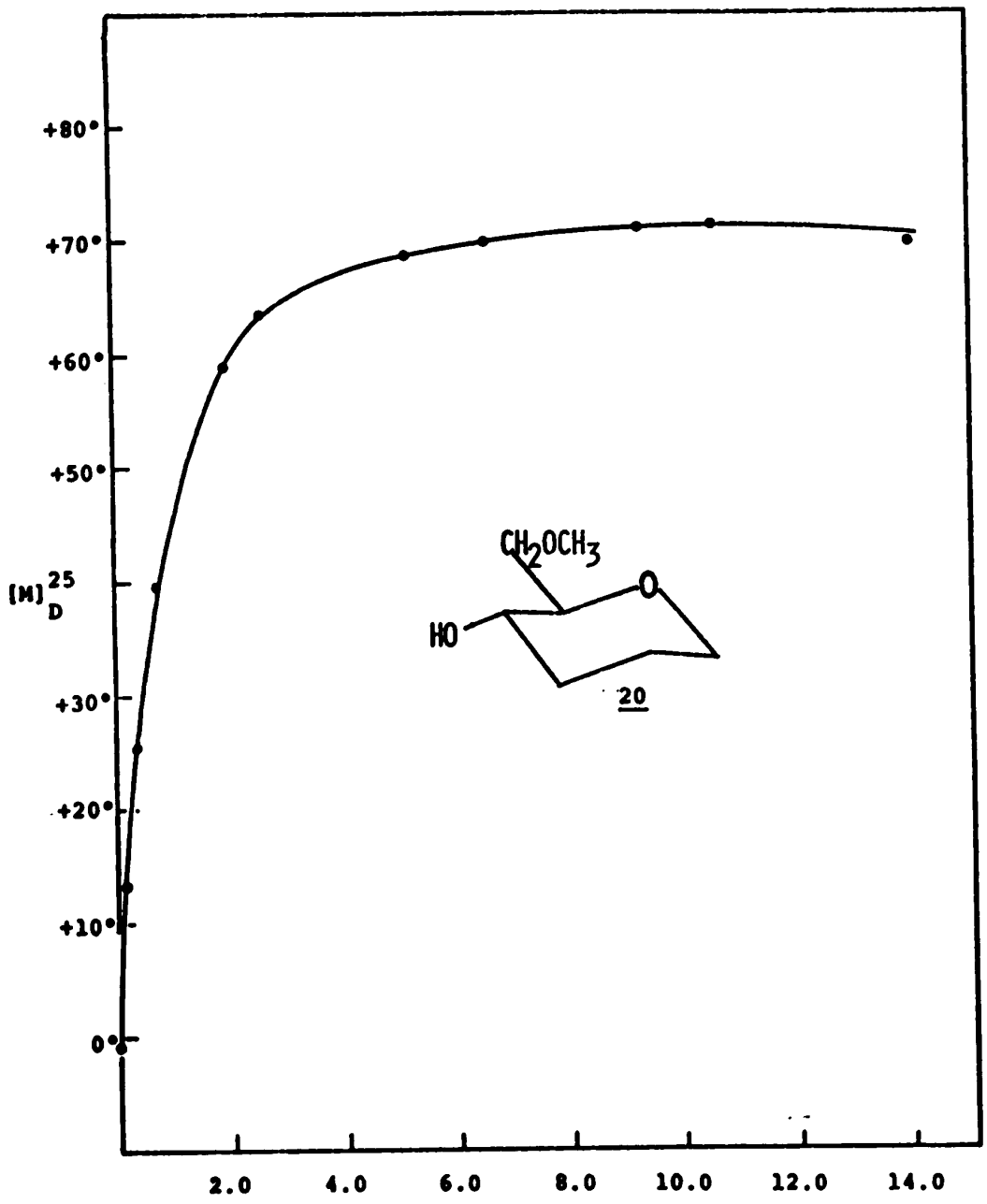


Fig. 58: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotation at 25°C of solutions of 1,5-anhydro-2,3-dideoxy-6-*O*-methyl-D-*erythro*-hexitol (20).

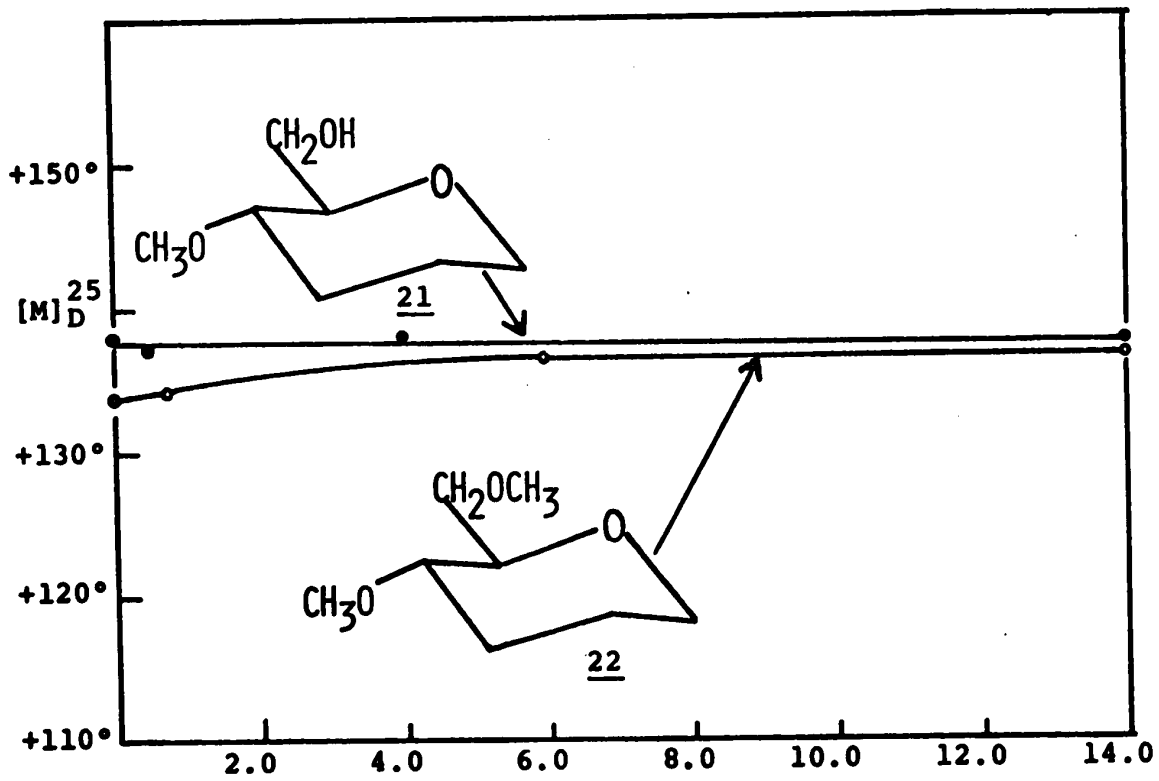
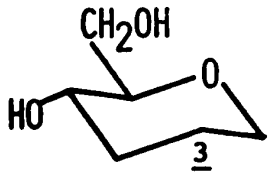
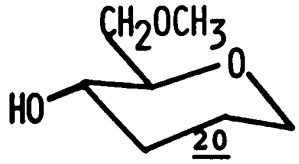
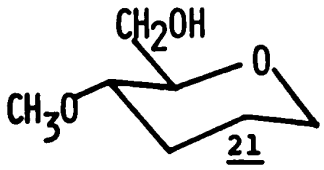
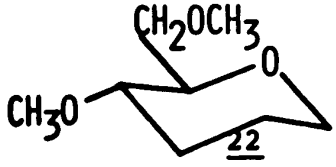


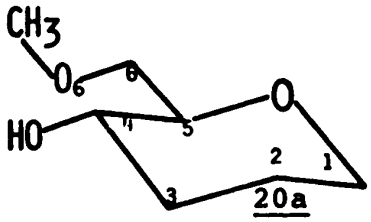
Fig. 59: The effect of increasing concentration of dimethyl sulphoxide on the molecular rotations at 25°C of solutions of 1,5-anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol (21) and 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol (22) in 1,2-dichloroethane.

TABLE 36

The molecular rotations (°) in water, of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol (3) and its *O*-methylated derivatives at 25°C

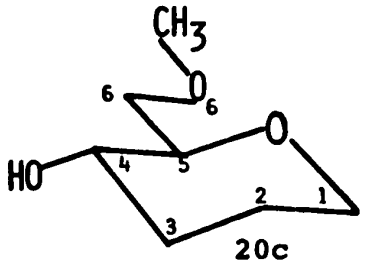
Compound	$[M]_D^{25}$
 3	+ 70.9
 20	+ 84.4
 21	+136.0
 22	+147.0

The molecular rotations of 20 and 21 were recorded in solutions of 1,2-dichloroethane that contained increasing amounts of DMSO. For comparison, the rotational behaviour of the di-*O*-methyl ether of 3, compound 22, was also investigated. These rotations are plotted in Figs. 58 and 59. Data for the individual solutions appear in Tables 19, 20 and 21 (pp. 119, 120 and 121). The rotations of these compounds in water are compared in Table 36.



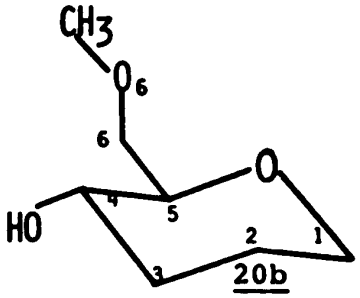
20a

[M] = +0/C-0/C = 0°



20c

[M] = +0/0+0/C = +100°



20b

[M] = +20/C-0/0 = 35°

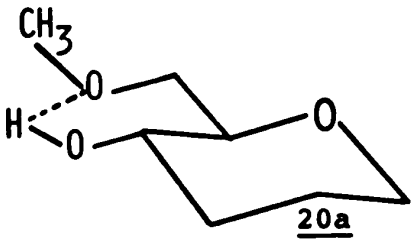
Fig. 60: The predicted rotations of conformations of compound 20.

The three conformations of compound 20 in which the O-CH_3 bond is *anti*-periplanar to the C5-C6 bond (Fig. 60) contain no significant steric interactions in addition to those present in the corresponding 3a, 3b and 3c rotamers of the parent diol. Because their O-CH_3 bond is in a symmetric environment, the predicted molecular rotations of these conformations should have the same values as those of the corresponding conformations of 3. If the O-CH_3 bond adopts either of its other staggered orientations it is in opposition to at least one other bond. Therefore, as a first approximation, the rotation of 20 will be discussed solely in terms of the relative populations of the three conformations in Fig. 60.

Like the 3a conformation of the parent diol (see pp. 185 to 189), 20a should be destabilized in water. Therefore, 20b and 20c should represent the most important orientations of the C6-O6 bond in this solvent. Of these, the 20b conformation should be the less preferable because of its opposing C6-O6 and C4-H4 bonds. The observed rotation of 20 in water is +84.4°, which confirms that 20c, together with the smaller attendant population of 20b, are the most abundant conformations in solution.

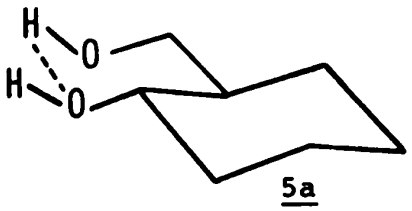
Fig. 58 illustrates that the nature of the solvent is very important in determining the rotation of 20. For example, in 1,2-dichloroethane the molecular

rotation indicates that 20a is very much the preferred conformation. This conformation can be expected to predominate in pure 1,2-dichloroethane, which is a solvent that should not interfere with its ability to stabilize itself by formation of a 1,3-type intramolecular hydrogen bond. For example, such a bond was shown to give a dramatic stabilization to 5a under the same circumstances. Indeed, compound 20 should behave more like 5 than its parent diol (3) in this solvent. Compound 3 is able to stabilize its 3b and 3c conformations by the formation of 1,2-intramolecular hydrogen bonds between its primary hydroxyl function and ring oxygen. This option is not open to 20 or 5.



20a

[M] = +C/O-O/C = 0°



5a

[M] = +C/O-O/C = 0°

The molecular rotation of 20 in pure 1,2-dichloroethane is by itself somewhat misleading, as it indicates that almost all of the compound prefers the 20a conformation. Infrared spectroscopy shows that this is not entirely so (Table 35). There is an absorption in the i.r. spectrum of 20 in 1,2-dichloroethane that occurs

at 3500 cm^{-1}. This can be equated to the hydroxyl group which forms the 1,3-type intramolecular hydrogen bond of 20a. There is also a band at 3585 cm^{-1} that is about 85% as intense as the first band. In 1,2-dichloroethane, such an absorption corresponds to either free hydroxyl groups or to hydroxyl groups that are engaged in 1,2-intramolecular hydrogen bonds. (*cf.* p. 211). In the case of 20, it can originate from the free hydroxyl group in either of 20b or 20c. Now, the relative intensities of these two absorption bands are not necessarily an exact indication of the amount of 20a with respect to 20b and 20c. However, they do indicate that 20a, although probably the most abundant conformation, is certainly not the exclusive conformation in pure 1,2-dichloroethane. In as much as the 1,2-dichloroethane solution of 20 contains this modest percentage of dextrorotatory 20c and 20b, its observed rotation of almost zero degrees requires that 20a have an actual rotation that is negative. This is not unexpected, as the empirical rules that were used to estimate a rotation of zero for this conformer are only approximate in nature. It would be remarkable if such a first-order approach to optical rotation were able to give a precise estimate of the rotation of 20a, whose structure includes an acyclic chain of three bonds. For example, a partial rotation about the C5-C6 bond or the C6-O6 bond may occur in order to achieve a better

intramolecular hydrogen bond. Because of the sinusoidal dependence of rotational parameters[+] (12,14), this would result in additional contributions to the rotation of this conformation.

The rotation of 20 rises sharply as a small amount of DMSO is introduced into the 1,2-dichloroethane solution. Evidence presented earlier in this discussion demonstrated that a small amount of DMSO could actually stabilize the a conformations of 5 and 3 by the formation of an intermolecular hydrogen bond with their free hydroxyl function. This hydrogen-bond conjugation is no longer possible in 20, as it has only one hydroxyl function, and it is already engaged in an intramolecular hydrogen bond. In order for this function to hydrogen bond to the DMSO molecule, the 1,3-intramolecular hydrogen bond that stabilizes the conformation must be sacrificed. Lemieux and Pavia (35) have shown that opposing methoxyl and DMSO-solvated hydroxyl functions constitute an electrostatically and sterically unfavourable situation, so that 20a' cannot be regarded as an energetically important structure. Of the three DMSO-solvated conformations of 20,

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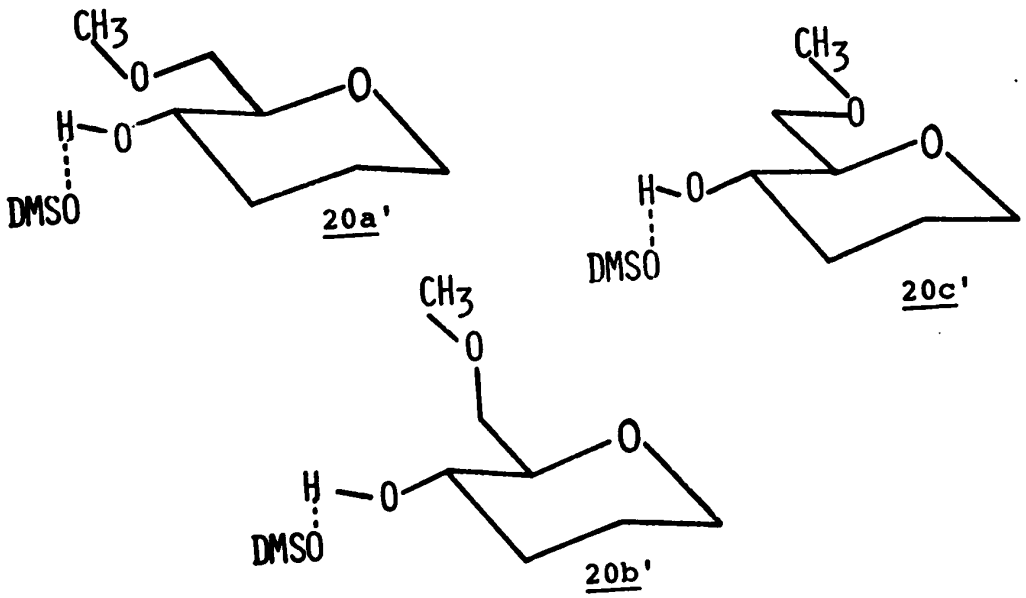
+ For example, if the dihedral angle between C5-O5 and C6-O6 is not 180°, these bonds will be conformationally asymmetric, and additional rotation will result.

only 20c' and to a lesser extent 20b' require consideration.



The amount of these two species that exist in equilibrium with the intramolecularly hydrogen-bonded 20a conformation will be a function of the DMSO concentration.

$$\begin{array}{ccc} \underline{20a} + \text{DMSO} & \rightleftarrows & \underline{20c'} \\ & & \uparrow\downarrow \\ \underline{20a} + \text{DMSO} & \rightleftarrows & \underline{20b'} \end{array}$$

In concentrations that are greater than about 5 moles per litre the DMSO appears to be able to hold 20 extensively in its 20c' and 20b' conformations. The rotations of such solutions, which are virtually insensitive to the DMSO concentration, should be determined by the relative conformational free energies of 20c' and 20b'. The interaction between the C6-O6 bond and the opposing C5-H5

bond of 20b' will destabilize it in relation to 20c'. If this interaction is given the value that was assigned to an OH:H interaction in DMSO (0.45 kcal per mole; see p. 219), 20b' and 20c' will have mole fractions of 0.32 and 0.68 respectively at 25°C. The molecular rotation of +79° that is calculated from these estimated fractional populations is not substantially different from the observed rotations of about +70°.

$$[M]_D \text{ (for 20)} = X_{b'}(+2C/0\text{-}0/0) + X_{c'}(0/0+0/C)$$

$$= +0.32(+35°) + 0.68(+100°)$$

$$= +79° \text{ (predicted for solutions containing only 20b' and 20c')}.$$

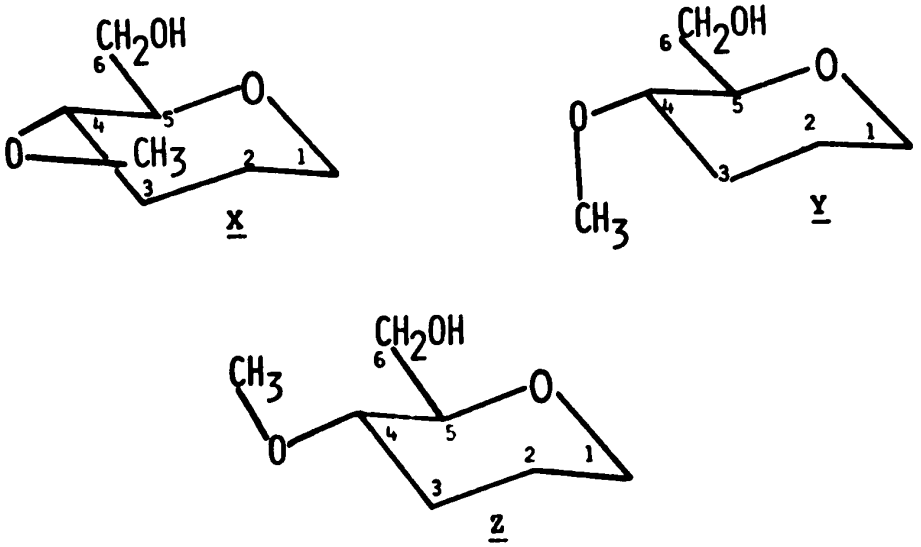


Fig. 61: Staggered orientations of the O-CH_3 bond of 1,5-anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol.

Consider the three staggered orientations that the O-CH_3 bond of compound 21 can adopt (Fig. 61). In Z, the methyl function opposes C6, which is sterically a very unfavourable arrangement.[+] This conformation will therefore occur in insignificant amounts. The X orientation should be the more stable of the two remaining possibilities. In this equatorial orientation, the O-CH_3 bond opposes only one C-H bond. At the same time it is *gauche* to the C3-C4 bond and therefore defines a $+C_o/C$ rotational parameter (*cf.* Fig. 8, p. 17). In the axial orientation, Y, the O-CH_3 bond is sterically opposed by two C-H bonds. It generates no molecular rotation in this orientation since it is symmetrically positioned with regard to the two *gauche* C-C bonds of the ring.

These considerations help to account for the observed rotation of the solution of 21 in water, which is 136° at 25°C. Because it is restricted to the X and Y orientations (mostly X) the OCH_3 group should not interfere sterically with any of the rotameric positions of the C6-O6 bond. As a result, the C6-O6 bond of 21 should have the same conformational distribution in water as the corresponding C6-O6 bond of 3. The contribution to

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[+] The repulsive interaction between opposing methyl functions is given a value of 3.7 kcal per mole on page 52 of reference 1.

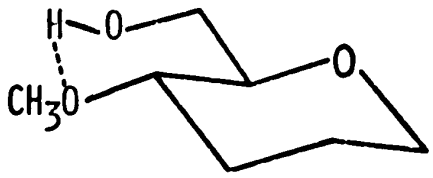
the rotation of 21 that originates in the averaged orientation of the C6-O6 bond, plus the contribution from the fixed O/C unit between C4-O4 and C5-O5, should equal the observed rotation of 3 in water, which is +70.9° at 25°C. The 65° difference between the rotations of 20 and 3 must therefore originate in the asymmetry of those $O-CH_3$ bonds of 20 that adopt the X orientation, where they generate a $+C_o/C$ rotational parameter. Because of the small percentage of the $O-CH_3$ bonds that should be in the symmetric axial orientation (Y), the value of a $+C_o/C$ unit is probably somewhat greater than +65°. This supports Lemieux and Martins' proposal that it is at least +60° (9).

The rotations of 22 and 20 differ by +62.6° in water (Table 36), a value that is very similar to the difference between the rotations of 21 and 3. This shows that the contributions to molecular rotation from the OCH_3 groups at C4 of 21 and 22 are approximately the same, namely, 65°.

Fig. 62 illustrates the staggered orientations of the hydroxymethyl function of compound 21. It is assumed that the conformational distribution of the $O-CH_3$ bonds will be the same for each orientation of the C6-O6 bond, and for different solvents. Therefore, +65°, the average contribution that this $O-CH_3$ bond makes to

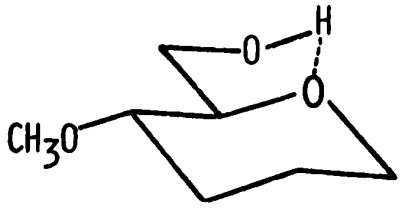
the rotation of 21 in water, has been used to estimate the contribution that the OCH_3 function makes to the molecular rotation of each of the rotamers in Fig. 62.

The hydroxyl functions of 21b and 21c can engage in 1,2-type intramolecular hydrogen bonds with the ring oxygen. As a result, these conformers should be somewhat more stable than their counterparts in compound 20. The i.r. spectrum of 21 in 1,2-dichloroethane contains an absorption at 3865 cm^{-1} that can be equated to the hydroxyl functions of these two conformations. There is a weaker "shoulder" absorption adjoining this band, which is



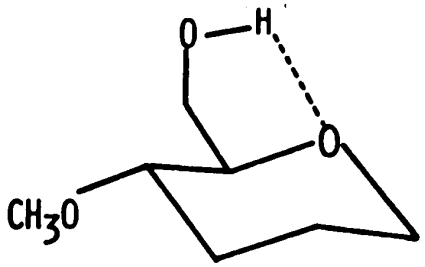
21a

[M] = +C/O-C/O+65° = +65°



21c

[M] = +O/C+O/C+65° = +165°



21b

[M] = +2O/C-O/O+65° = 100°

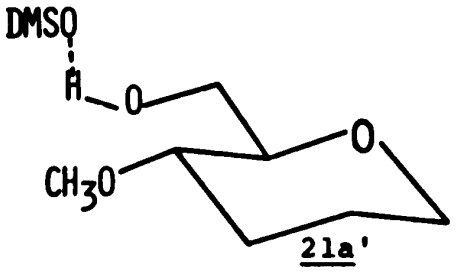
Fig. 62: Staggered orientations of the hydroxymethyl function of 1,5-anhydro-2,3-dideoxy-4-*O*-methyl-D-*erythro*-hexitol (21)

centered at 3500 cm^{-1}. This serves as an indication of the relative amount of 21a, whose OH function is engaged in a 1,3-type intramolecular hydrogen bond with the oxygen atom of the methoxyl group. The fact that this shoulder absorption is roughly half as intense as the absorption at 3565 cm^{-1} is qualitative evidence that 21c and 21b have a combined population that is substantially greater than that of 21a.

The molecular rotation of 21 in pure 1,2-dichloroethane is +138°, which does not allow for a substantial population of 21a, and therefore supports the interpretation of the i.r. spectrum. Notice the remarkable difference between this molecular rotation and that of compound 20, which has a value of almost zero in pure 1,2-dichloroethane. About 65° of the difference between these rotations originates in the asymmetric orientation of the 4-*O*-methyl function of 21 as compared to the proposed symmetric *anti*-periplanar orientation of the 6-*O*-methyl function of 20. The remainder reflects the differing conformational preferences of the C6-O6 bonds of the two compounds in this solvent. The most abundant rotamer of compound 20 is 20a, which is stabilized by a 1,3-type intramolecular hydrogen bond. Although the 21a conformation can also contain such a bond, it is forced to compete against 21b and 21c conformations

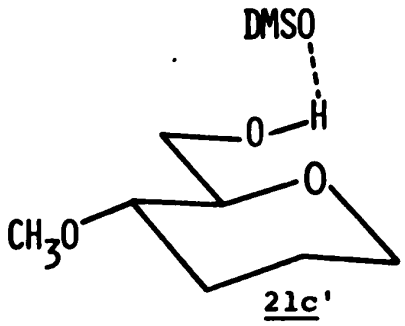
that are stabilized by 1,2-type intramolecular hydrogen bonds.

When DMSO is introduced into the 1,2-dichloroethane solution of 21 it will form an intermolecular hydrogen bond with the hydroxyl function of this compound. The 21a' conformation will be destabilized by the electrostatic and steric interactions between the opposing methoxyl and DMSO-solvated hydroxyl functions (35). As a result, the addition of DMSO should convert what population there is of 21a into the more dextrorotatory 21b' and 21c' structures. This should produce an overall increase in



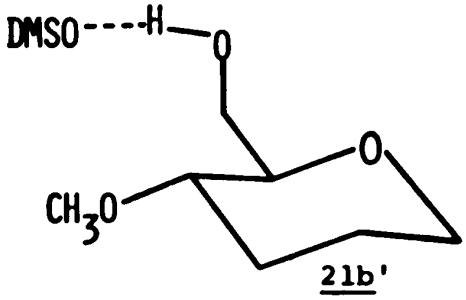
21a'

[M] = +0/C-0/C+65 = 65°



21c'

[M] = +0/0+0/C+65 = 165°

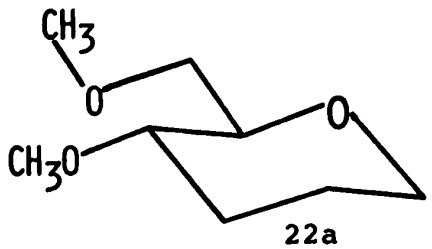


21b'

[M] = +20/0-0/C+65 = 100°

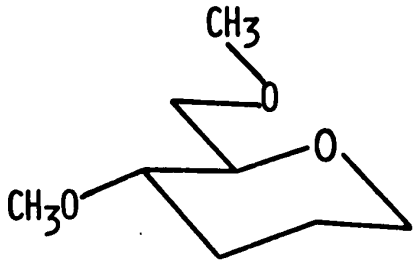
rotation. As can be seen from Fig. 59, this has no experimentally detectable effect on the rotation of 21, which is additional evidence that the population of 21a in pure 1,2-dichloroethane cannot be very large. However, it must be remembered that the rotations that are predicted for the rotamers of 21 are only approximations and that the change in the nature of the solvent may have some effect on their values. For example, the averaged orientation of the O-CH_3 bond and therefore its contribution to rotation may not be completely independent of the solvent. If the actual molecular rotation of 21c' were to be somewhat smaller than that of 21c, the effect of the conversion of 21c to 21c' would cancel out the effect of the conversion of small to moderate amounts of 21a to 21c'.

The most important aspect of the rotational behaviour of 21 is that its rotation is not decreased by the addition of a small amount of DMSO to the 1,2-dichloroethane solution. This means that the small amount of DMSO does not produce a dramatic increase in the stability of 21a (or 21a'). If such an effect had been observed, it would have necessitated a re-evaluation of the rotational behaviour of compounds 3, 5 and 7, since hydrogen bond conjugation is not possible in compound 21.



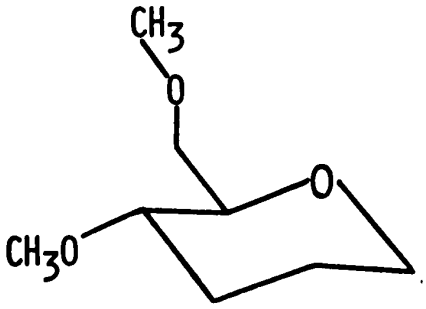
22a

[M] = +0/C-0/C+65 = +65°



22c

[M] = 0/0+0/C+65 = +165°



22b

[M] = 20/C-0/0+65 = +100°

Fig. 63: Staggered orientations of the hydroxymethyl function of 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol (22)

Fig. 59 shows that the rotation of 1,5-anhydro-2,3-dideoxy-4,6-di-*O*-methyl-D-*erythro*-hexitol is independent of the concentration of DMSO in its 1,2-dichloroethane solutions. The 3° increase in rotation as the DMSO concentration is increased from 0 to 14 moles per litre cannot be regarded as significant.

The three rotameric orientations of the C6-O6 bond of 22 are illustrated in Fig. 63. The O6-CH_3 bond should be mostly *anti*-periplanar to C5-C6, since it

encounters the minimum steric interaction in this orientation. The contribution that the averaged orientation of the O4-CH_3 bond makes to the rotations of the individual structures in Fig. 63 should be about +65°, the approximate contribution that it makes to the rotations of both 21 and 22 in water.

Both of the original hydroxyl functions of 3 have been blocked by methyl functions in 22, so that in inert solvents, such as 1,2-dichloroethane, 22a cannot acquire any stabilization through the formation of an intramolecular hydrogen bond. In fact, Lemieux and Pavia have presented evidence that shows opposing methoxyl functions to be clearly disfavoured (35). In addition to the unfavourable steric interactions that are present, the O-CH_3 dipole moments oppose each other electrostatically. For these reasons, 22a was not expected to have a large population in any of the solutions.

The magnitude of the repulsive interactions between its C6-O6 and C4-H4 bonds will determine the size of the population of 22b relative to that of 22c. This interaction should have a value that is close to 0.45 kcal per mole (*cf.* p. 219) which means that there should be about 2:1 times as much 22c as there is 22b at 25°C. For example, if the percentage population of 22a is only 10%, 22b and 22c will have populations of 29% and

61%[+] respectively. With this conformational distribution 22 would have a molecular rotation of +135°, which is very similar in value to the molecular rotations that are observed. These observed rotations therefore serve as an indication that the percentage populations of 22a cannot be substantially greater than 10%, even in 1,2-dichloroethane.

$$[M]_D^{25} \text{ (for 22)} = X_a(+65°) + X_b(+100°) + X_c(+165°)$$

$$= +135.3° \text{ (predicted for } X_a = 0.10;$$

$$X_b = 0.29 \text{ and } X_c = 0.61).$$

The fact that the rotation of 22 does not change significantly as the DMSO concentration is increased in the solutions is in itself an important result. This serves as indirect support for the theory that the rotational changes that are observed in the corresponding solutions of 3, 5, 20 and 7 reflect the changes in conformational equilibria that result as intramolecular hydrogen bonds are replaced by intermolecular hydrogen bonds.

[+] 61% = 2.1 X 29%.

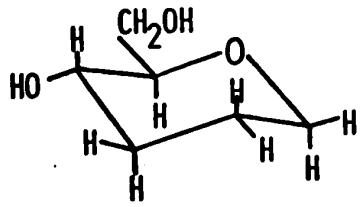
CONCLUSIONS

This project has used optical activity, at the D line of sodium, to study the conformational equilibria of molecules in solution. The effects that solvent and temperature changes have on the rotations of simple molecules that are models for hexopyranose compounds were examined and interpreted in terms of changes in conformational equilibria. It is concluded that interpretation of optical rotation represents a promising approach to conformational analysis.

In section 1 of the Discussion (p. 122), it is demonstrated that the addition of a *para*-substituted pyridine to a 1,2-dichloroethane solution of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-sorbopyranose (7) results in a reinforcement of the 1,3-type intramolecular hydrogen bond between the opposing hydroxyl groups of the $^{1}C_{4}$ conformation. The ability to strengthen this intramolecular hydrogen bond increases with increasing base strength. Thus, the work provides additional experimental confirmation of the Lemieux-Pavia theory of hydrogen-bond conjugation (35).

In section 2 (p. 150), empirical procedures are proposed for the estimation of the molecular rotations of the individual conformations of the model hexopyranose compounds that are shown below. The simplified approach to the interpretation of optical rotation that was developed by Lemieux and Martin (9) is partially adopted. However,

certain modifications to their rules are necessary in order to provide a better agreement between the predicted and observed rotations of test compounds. The O/O and O/C parameters (Fig. 8) are assigned new values of 55° and 45° respectively. An additional parameter is proposed, designated as I (Fig. 34), and assessed a value of 45°.



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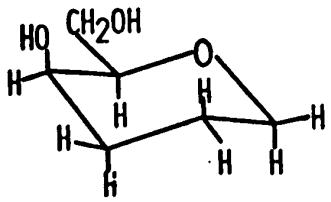

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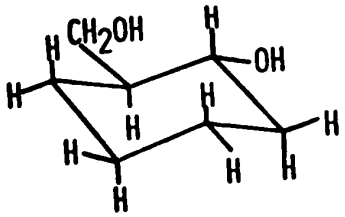

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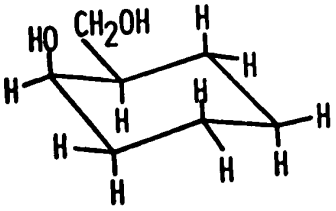

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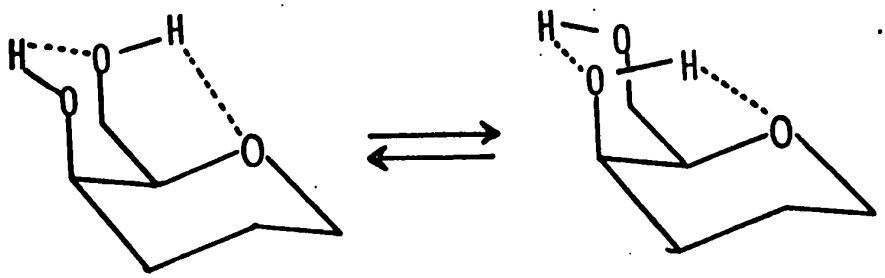
Section 3 (p. 164) deals with the conformational equilibria of the above four compounds in water, as revealed by their molecular rotations and their proton magnetic resonance spectra. It is concluded that the conformations of 3, 5 and 6 that contain opposing hydroxyl functions are not abundant in this solvent. Compound 4 is an exception. In water, its molecular rotation requires that it prefer the conformation shown below, which is probably stabilized

by a cumulation of two intramolecular hydrogen bonds. A



second conclusion reached in this section is that the interaction between two *gauche*-oriented oxygen atoms is smaller, in water, than the interaction between a *gauche*-oriented oxygen atom and methylene group.

In section 4, the conformational preferences of the hydroxymethyl function of the model compounds in binary 1,2-dichloroethane/dimethyl sulphoxide solutions are investigated. In pure 1,2-dichloroethane, molecular rotation analysis, aided by infrared spectroscopy, leads to the conclusion that intramolecular hydrogen bonding is of fundamental importance in determining the rotameric populations of these compounds. In this regard, the rotameric populations for both 3 and 4 are determined by 1,2-type hydrogen bonding between their C6 hydroxyl function and ring-oxygen atom as well as by 1,2-type intramolecular hydrogen bonding between their two hydroxyl groups. The addition of dimethyl sulphoxide to the pure 1,2-dichloroethane solutions of 3 and 5 results in experimentally

detectable increases in the population of the conformation that has two opposing, 1,3-intramolecularly hydrogen-bonded hydroxyl groups. This demonstrates that the Lemieux-Pavia theory of hydrogen bond conjugation also applies to this class of compound. In 1,2-dichloroethane solutions that contain moderate to high concentrations of dimethyl sulphoxide, the conformational populations of the model compounds revert to values that are similar to those observed in water.

Section 5 (p. 234) evaluates the changes in conformational equilibria that result on methylation of one, or both of the hydroxyl groups of compound 3. The data show that methylation of the C4 hydroxyl function inhibits the ability of O4 to act as an acceptor for a 1,3-type intramolecular hydrogen bond with the C6 hydroxyl group. On the other hand, the 6-*O*-methyl ether of 3 exists mainly in the 1,3-intramolecularly hydrogen-bonded conformation in pure 1,2-dichloroethane solution.

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