EFFECTS OF UNSHARED PAIRS OF ELECTRONS AND THEIR SOLVATION ON CONFORMATIONAL EQUILIBRIA

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ABSTRACT

The empirical rules for estimating molar rotations of carbohydrate structures proposed by Whiffen and elaborated by Brewster provided interpretations of solvent effects on optical rotation with changes in conformational equilibria which in certain cases were confirmed by n.m.r. Conversely, it was found that only slight changes in rotation occur on changing the solvent for conformationally rigid molecules. Thus, studies involving optical rotations measured at the D-line of sodium and n.m.r. spectra provided the experimental support for the following solvation phenomena which are related to the role of unshared pairs of electrons in conformational equilibria.

(a) The reverse anomeric effect was substantiated by the effect of introducing a positive charge on the imidazole ring of certain *N*-glycosides of imidazole.

(b) The magnitude of the anomeric effect was influenced as expected by changes in the polarity of the solvent but hydrogen bonding of the solvent with the acetal oxygen atoms had a more pronounced effect.

(c) The orientation of oxygen atoms in *gauche* relationship appears particularly favourable with water as solvent.

(d) An intramolecular hydrogen bond between two hydroxyl groups is strengthened by hydrogen bonding of the free hydrogen to a basic solvent.

(e) The non-bonded interaction between two opposing axial oxygen atoms is dependent on the nature of the substituents. The repulsion is substantially greater when the oxygen atoms are either bonded to methyl groups or hydrogen-bonded to the solvent than when attached to acetyl, benzoyl or methane-sulphonyl groups.

THE first statement that unshared pairs of electrons may play an important role in establishing conformational preferences was made by Edward[1] with reference to the apparent stability of that anomeric form for a glycosyl halide which has the halogen in axial orientation. The statement made was, as seen in *Figure 1*, that by going axial the polar C_1 to X bond avoids an interaction with the axially oriented orbital of the ring oxygen. Later this was discussed by Kabayama and Patterson[2] who pointed out that the unfavourable interactions could, indeed, involve repulsions between the orbitals occupied by lone pairs of electrons in the aglycon X with those of the ring oxygen. Such interactions equivalent to *syn*-axial interactions, would be released on passing from the equatorial to axial anomer.
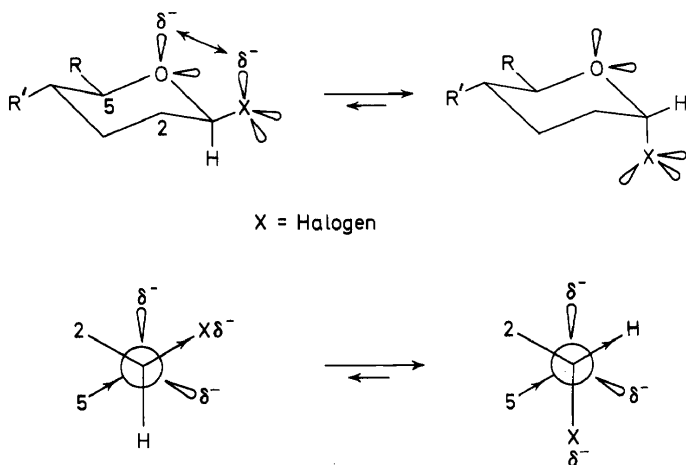
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X = Halogen

Figure 1. Origin of the anomeric effect[1, 2, 4].

We introduced the term 'anomeric effect' after having placed these conjectures on a sound basis by obtaining direct evidence through n.m.r. spectroscopy on the conformations of relevant glycosidic structures[3]. In the case of the sugar acetates, the rationalization of their anomerization equilibria[4, 5] required the presence of a non-bonded interaction free energy of electrostatic origin which was termed the 'anomeric effect'.

The anomeric effect was discussed in detail in a 1964 review article[5] when it was pointed out that the preferred conformations of glycosides minimize the number of interactions between opposing unshared pairs of electrons which were termed the e//e component of the anomeric effect. Thus, for glycosides with an axial aglycon (OR group), as seen in *Figure 2*, the preferred orientation is that depicted in Ic where no e//e interaction is present. All staggered orientations for an equatorial aglycon involve at least one e//e interaction and studies of anomerization equilibria have shown the axial orientation is preferred by an alkoxy group at the anomeric centre
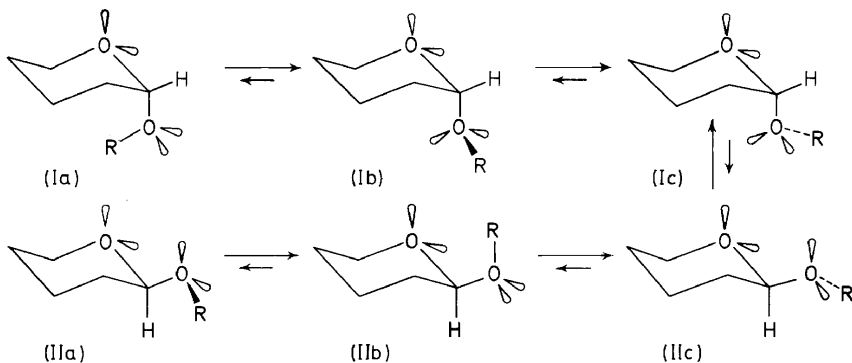

Figure 2. Influence of the *exo* anomeric effect on the orientation of an alkoxy aglycon[5, 6].

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of a glycopyranoside. It was pointed out[5] that the conformation of the simple model compound methylal was in accord with the relative stabilities of α- and β-glycopyranosides. Indeed, in 1959[6], for reasons of what we have termed the *exo* anomeric effect; namely, the tendency for the R group of both α and β anomers to be antiparallel to C_2, it was predicted that all homopolysaccharides should tend to possess helical structures.

Recent work in our laboratory[7] with six-membered perhydro-1,3-oxazoline and 1,3-diazine compounds has shown (*Figure 3*) that that conformer
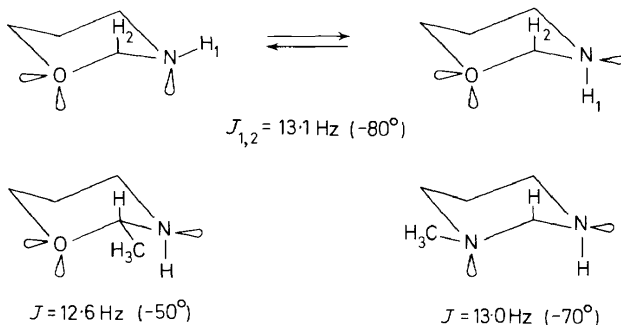

$J_{1,2} = 13 \cdot 1$ Hz ($-80°$)

$J = 12 \cdot 6$ Hz ($-50°$) $J = 13 \cdot 0$ Hz ($-70°$)

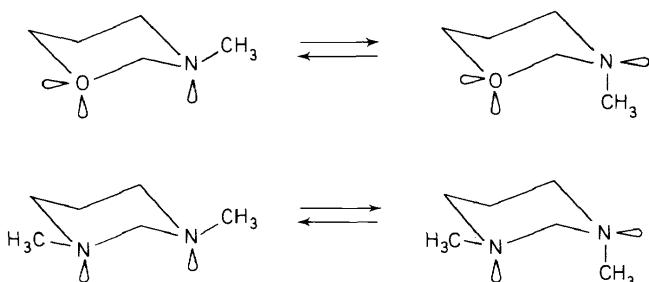Figure 3. The generalized anomeric effect[7].

Figure 4. Further evidence for the generalized anomeric effect[8].

is the more stable, which avoids placing orbitals of both the heteroatoms in axial orientation. This conclusion is drawn in view of the magnitude of the coupling constants between the N-hydrogens and the vicinal hydrogen in axial orientation. In the course of this work, Eliel[8] proposed the term 'rabbit-ear effect' for the $e//e$ component of the anomeric effect. As seen in *Figure 4*, mention was made of how interpretations of chemical shift were in support of the equilibria shown. We propose for historical reasons that the occurrence of phenomena which are the result of the same kinds of interactions as were proposed for explaining the anomeric effect but present in non-carbohydrate structures be referred to as the result of the 'generalized anomeric effect' rather than the 'rabbit-ear effect'.

Figure 5 shows the relationship between conformational equilibrium and optical rotation which stimulated us greatly towards the application of optical rotations measured at the D-line of sodium in studies of conforma-
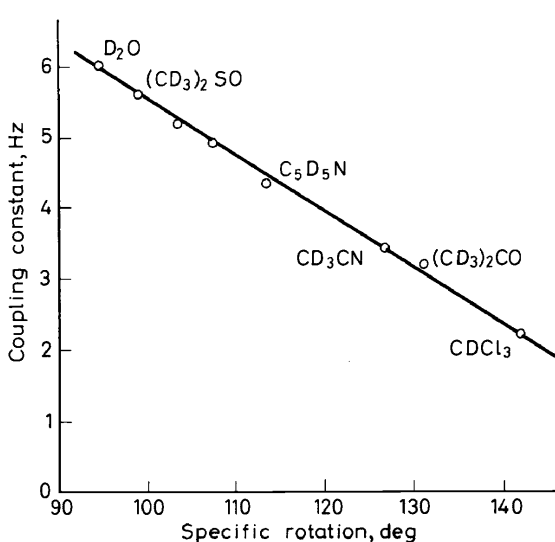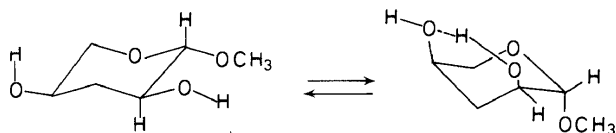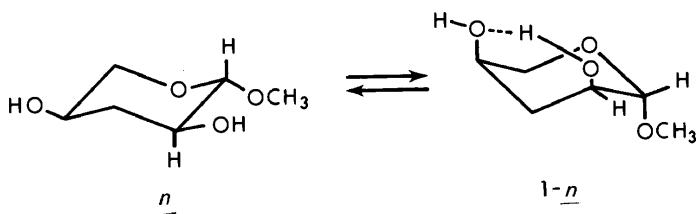
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Figure 5. Relationship between change in a conformational equilibrium and change in optical rotation as evidenced by the linear relationship between specific rotation at the D-line of sodium and the coupling constant for H_1 and H_2 of methyl 3-deoxy-β-L-*erythro*-pentopyranoside with change in solvent[10].

$$nJ_t + (1 - n) J_g = J_{obs.}$$

$$n[\alpha]_t + (1 - n) [\alpha]_g = [\alpha]_{obs.}$$

$$\therefore n = \frac{J_{obs.} - J_g}{J_t - J_g} = \frac{[\alpha]_{obs.} - [\alpha]_g}{[\alpha]_t - [\alpha]_g}$$

Figure 6. The theoretical basis for the linear relationship between $J_{1,2}$ and optical rotation.

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tional equilibria. It is seen that the plot of specific rotation measured in a variety of solvents against the coupling constant between the 1- and 2-hydrogens of the methyl glucoside in the various solvents provided a straight line. That a linear relationship should occur is at once evident from the expressions in *Figure 6*. Calculation of the molecular rotation for the compound in the triaxial chair form using Brewster's rules[9] gives a molecular rotation ($+205°$) in good agreement with that ($+210°$) measured in chloroform. The observed molecular rotation in water ($+139°$) compares well with that calculated ($+150°$) for the compound in the triequatorial form. Of course, the triaxial form is preferred in chloroform primarily for reasons of the anomeric effect and the intramolecular hydrogen bridge between the two axial hydroxyl groups. This hydrogen bridge is destroyed by the hydrogen-bonding solvent molecules such as those of water and dimethylsulphoxide and a resulting repulsion between the two oxygen atoms can override the anomeric effect to provide the triequatorial conformation as the major conformation in these solvents.

In view of these results, we became interested in applying changes in optical rotation with changes in solvent to investigate solvation effects on conformational equilibria. As a first stage it was decided to examine conformational changes for the simple model compound, 2-methoxytetrahydropyran.
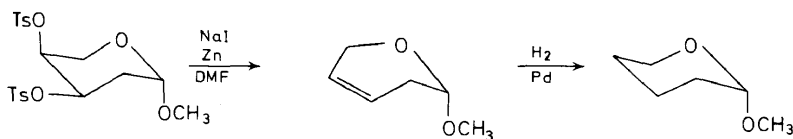

Figure 7. Synthesis of optically active s-2-methoxytetrahydropyran[10].

Figure 7 shows how optically active 2-methoxytetrahydropyran was obtained from the di-*O*-tosylate of methyl 2-deoxy-β-L-ribopyranoside[10]. The method for reducing *cis*-di-tosylates described by Tipson[11] which employs sodium iodide and zinc in dimethylformamide was used to prepare the olefin which actually was not characterized but reduced without isolation with hydrogen over palladium to give optically active 2-methoxy-tetrahydropyran which was purified by gas chromatography. The ditosylate was a pure crystalline material but we have no evidence that some degree of racemization did not occur on working up the extremely acid-labile final product.

Our plan was to make a study of the chair–chair equilibrium for 2-methoxytetrahydropyran using nuclear magnetic resonance, then to attempt to relate these changes to the changes in optical activity. Because of virtual coupling between the 2- and 4-protons of ordinary 2-methoxytetrahydro-pyran, the desired n.m.r. parameters could not be obtained. However, the preparation of 4,4,5,5-tetradeuterio-2-methoxytetrahydropyran[10] (see *Figure 8*) provided a substance which allowed the desired coupling constants between the 2- and 3-protons to be measured with precision. As is seen in *Figure 8*, it proved possible, for example, to establish precisely the width of the band for the anomeric signal as 6·4 Hz in carbon tetrachloride, 6·6 Hz in carbon

$$n(J_{aa} + J_{ae}) + (1 - n)(J_{ee} + J_{ea})$$

$$= 6\cdot4\ (CCl_4),\ 6\cdot6\ (CS_2)\ \text{and}\ 8\cdot4\ Hz\ (D_2O)$$
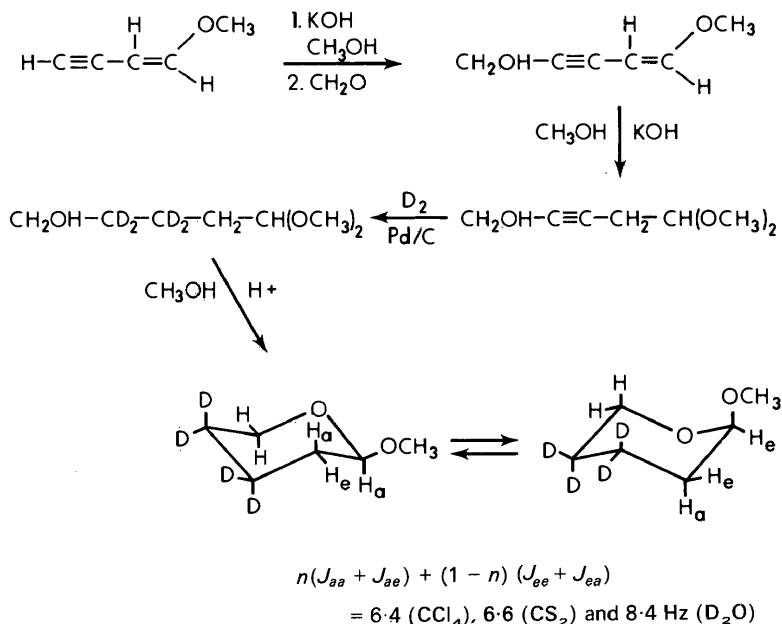
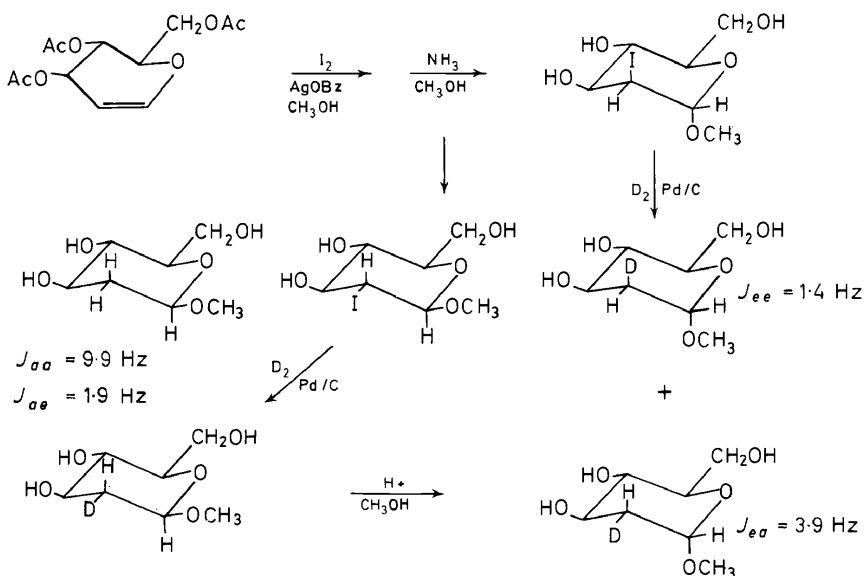*Figure 8.* Synthesis of 4,4,5,5-tetradeuterio-2-methoxytetrahydropyran[10].

Figure 9. Determination of the coupling constants between H_1 and the hydrogens at the 2-position for both the anomers of methyl 2-deoxy-D-glucopyranoside[12].

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disulphide, solvents of about equal polarity, but to rise to 8·4 Hz in water. Thus, the chair form which has the methoxy group in equatorial orientation is favoured substantially more by the more polar solvent, water, than by the more weakly polar solvents—carbon tetrachloride and carbon disulphide.

In order to interpret these time-averaged coupling constants measured for the 2-methoxytetrahydropyran in various solvents it is necessary to know the actual coupling constants which are time-averaged. Values for these coupling constants were obtained[12] for the closely related methyl 2-deoxy-D-glucopyranosides in the manner depicted in *Figure 9*.

It is seen in *Figure 9* that the treatment of D-glucal triacetate with iodine in the presence of silver benzoate in methanol followed by deacetylation gave as one of the products methyl 2-deoxy-2-iodo-α-D-mannopyranoside. Reduction of this iodide with deuterium gas in the presence of palladium on charcoal provided an about equal mixture of the epimers differing in configuration at position 2[12]. These isomers were distinguished by preparing the 1,2-*cis* compound as follows. The iodomethoxylation reaction gave, as a minor product, methyl 2-deoxy-2-iodo-β-D-glucopyranoside. In this compound, the iodine is equatorial and it was found that the reduction with deuterium in the presence of palladium went virtually completely with retention of configuration. This, then, provided a sample of the methyl 2-deoxy-2-deuterio-β-D-glucopyranoside whose configuration was evident from the large coupling constant of 9·9 between the 1- and 2-protons. When this substance was treated with acid in methanol it was readily anomerized to one of the compounds formed earlier and the epimers formed on the reduction of the iodo-mannoside were sorted out. Thus, as seen in *Figure 9*, we arrived at the conclusion that for the methyl 2-deoxy-D-*arabino*-hexopyranosides the coupling constants for the anomeric hydrogen with hydrogens at position 2 are $J_{aa} = 9·9$, $J_{ae} = 1·9$, $J_{ea} = 3·9$ and $J_{ee} = 1·4$ Hz. It is these coupling constants then that were used to interpret the n.m.r. data obtained for the 2-methoxytetrahydropyrans.

The effects of changes of solvent on the chair–chair equilibrium for 2-methoxytetrahydropyran as determined by n.m.r. are given in *Figure 10*.

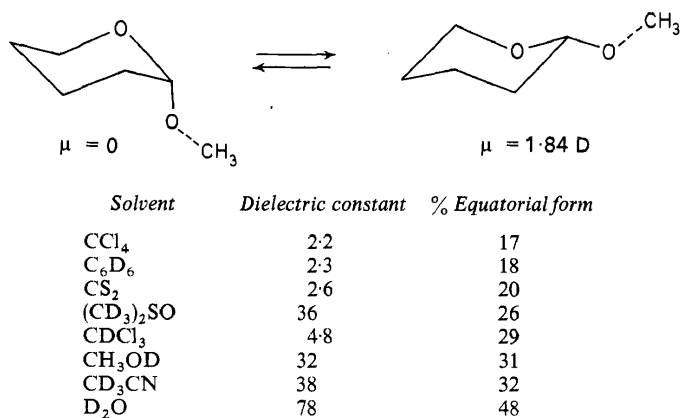| Solvent	Dielectric constant	% Equatorial form
CCl_4	2·2	17
C_6D_6	2·3	18
CS_2	2·6	20
$(CD_3)_2SO$	36	26
$CDCl_3$	4·8	29
CH_3OD	32	31
CD_3CN	38	32
D_2O	78	48

Figure 10. Effect of solvent on the chair–chair equilibrium for 2-methoxytetrahydropyran[10].

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It is seen that, in general, the higher the dielectric constant of the solvent the larger the amount of the more polar equatorial form. It is to be noted, however, that chloroform had a larger effect than dimethylsulphoxide and is next only to methanol, although its dielectric constant is substantially lower than any of these solvents.

The effect by chloroform is thought to arise from its ability to hydrogen-bond with the oxygens of the 2-methoxytetrahydropyran. Of course, the methoxy group in this compound can occupy three orientations relative to the pyranose ring which are staggered and three such orientations are possible for each conformation of the pyranose ring. The conformations shown in *Figure 10* are undoubtedly the most stable ones for the axial and equatorial conformers. This is because both electrostatic (what may be termed the *exo* anomeric effect[10]) and steric factors are energetically minimal in these conformations.

Using the chair–chair equilibria as determined by n.m.r. (*Figure 10*) and the rotations of methyl 2,3-dideoxy-4,6-*O*-ethylidene-α-D-*erythro*-hexopyranoside and its β-anomer (opposite sign) as representative rotations for s-2-methoxytetrahydropyran, the rotations expected for the latter compound in the various solvents were calculated and are given in *Figure 11*.
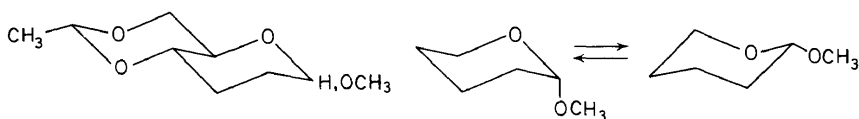
Solvent	α Anomer	β Anomer	s-2-Methoxytetrahydropyran		
			Calc.	Obs.	Difference
CCl₄	261	− 144	241	182	59
CHCl₃	258	−152	227	167	60
CH₃COCH₃	251	− 152	231	177	54
CH₃OH	257	− 155	224	166	58
CH₃SOCH₃	260	− 142	229	171	58
H₂O	218	− 144	183	127	56

Figure 11. Effect of solvent on the rotation of s-2-methoxytetrahydropyran[10].

$[M]_D^{25}$ (CHCl₃)	1·8	− 38	258	167
Change in molar rotation from that in chloroform				
CCl₄	0·3	0·6	3	15
CH₃COCH₃	−0·2	0·4	− 7	10
CH₃OH	—	0·1	−1	−1
(CH₃)₂NCHO	—	− 0·2	− 3	+ 3
CH₃SOCH₃	0·1	5	2	4
H₂O	0·2	− 5	−40	−40

Figure 12. Effect of solvent on the optical rotation of two conformationally rigid compounds and structurally related methyl glycosides.

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Following Brewster's rules, the rotations of these two ethylidene compounds should arise only from the asymmetric conformational units involving the methoxy group. Indeed, the desmethoxy derivative was virtually optically inactive (see *Figure 12*).

The fact that the rotations thus calculated for the 2-methoxytetrahydropyran are $57 \pm 3°$ higher than those found cannot be explained. Nevertheless, it may be noted that only a 15 per cent racemization of the highly labile 2-methoxytetrahydropyran could cause the observed discrepancy. However, the fact that the discrepancy was constant for each solvent infers that the effect of a given solvent on the distribution of the conformers involving rotation about the $CH_3O—C_1$ bond is the same for a given conformer of 2-methoxytetrahydropyran as for the glycoside (*Figure 11*) which has the same orientation for the methoxy group. This conclusion is of interest in view of the relatively large effect on rotation displayed by water in the case of the α anomer which has the methoxy group in axial orientation and which is also present in the rotations for the 2-methoxytetrahydropyran. Evidence that the effect arises from changes in conformation about the $CH_3O—C_1$ bond is provided by the data given in *Figure 12*.

The specific effect of water on rotation displayed in *Figure 12* may well arise from the fact that for such glycosides the most stable conformer (CH_3 is antiparallel to C_2) does not have orbitals for the unshared pairs of electrons in orientations which are parallel and opposing. As seen in *Figure 13*, the
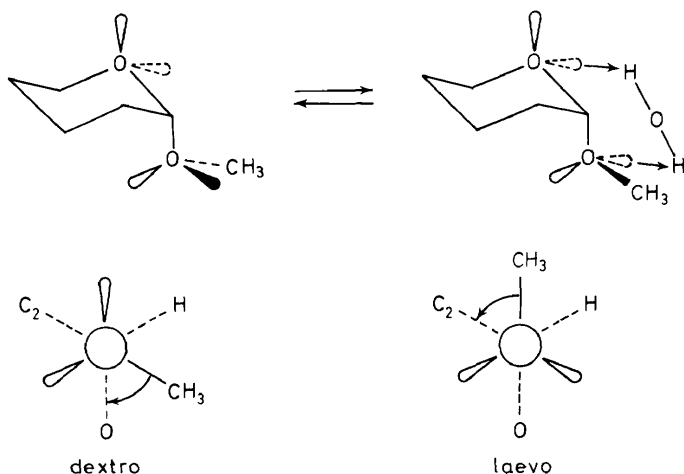

Figure 13. Possible effect of water on the conformational equilibrium involving an axial methoxy group at the anomeric centre of a 2-deoxyglycoside[10].

conformer in which the CH_3 group is antiparallel to the ring-oxygen atom offers parallel orbitals and it is conceivable that this arrangement is more favourable in water than in the other solvents because the dihydric nature of water allows unique possibilities for stabilizing this arrangement of the orbitals. Certainly, following Brewster's rules, a decrease in rotation is expected for an increased abundance of the conformer with the CH_3 group defining a

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left-handed screw pattern with C_2. The conformer with the CH_3 group antiparallel to the anomeric hydrogen is considered so highly strained as to have negligible existence.
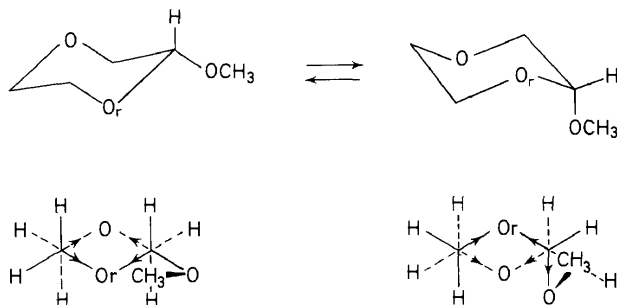
	Dielectric constant	% Axial conformer
Carbon disulphide	2·6	60
Pyridine	12	65
Dimethyl sulphoxide	45	67
Chloroform	4·8	70
Water	80	80

Figure 14. Effect of solvent on the chair–chair conformational equilibrium of 2-methoxy-1,4-dioxan[19].

Figure 14 shows our estimates of the chair–chair equilibria for 2-methoxy-dioxan by n.m.r.[19]. The reason for showing these data at this time is to show that chloroform has an effect on the conformational equilibrium similar to that demonstrated for 2-methoxytetrahydropyran in the sense that chloroform shifts the equilibrium in the same direction as water and more effectively than much more polar solvents. The percentage axial conformers given in Figure 14 may not be precise because of certain assumptions regarding the magnitudes of the coupling constants between the anomeric hydrogen and the vicinal hydrogens in this compound. However, such errors do not affect our conclusion that the magnitude of the anomeric effect for a given compound can be significantly altered by engagement of the oxygen atoms present in the acetal linkage in hydrogen bonds with the solvent. Although we cannot make any but thoroughly speculative statements on the possible origins of these effects, it seems likely that these are related to the 'reverse anomeric effect' which we suggested some years ago[13].

I now wish to present experimental data which definitely establish the reverse anomeric effect. Therefore, this effect must, in some way, be present whenever the oxygen atoms of acetals gain positive charge such as through hydrogen bonding or protonation[13].

A study of the protonation of N-glycosyl imidazoles has established[14] that the involvement of an atom at the anomeric centre in a change in the disposition of its unshared pairs of electrons can have an effect on the conformation of a glycoside. This effect is considered to arise from the change in the electrical properties of the atoms responsible for the anomeric effect.
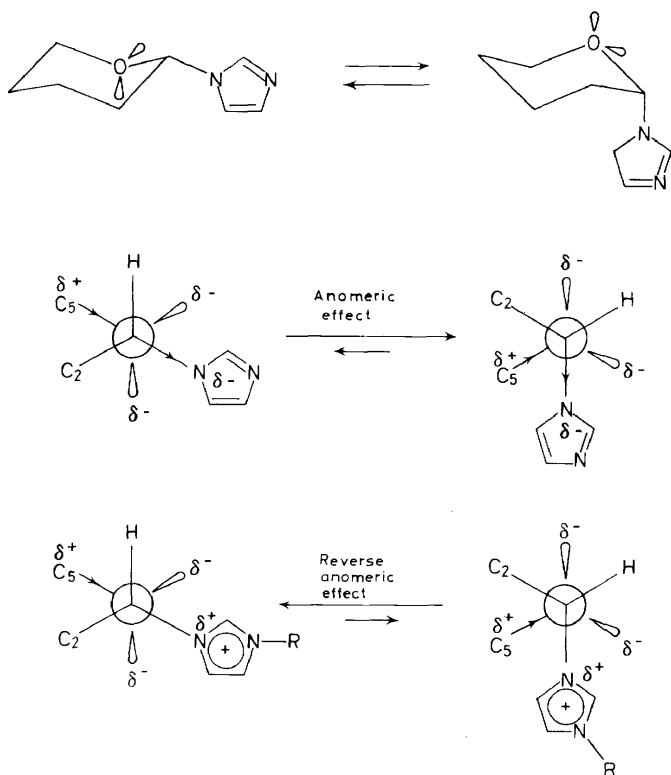
Figure 15. The reverse anomeric effect[13, 14]

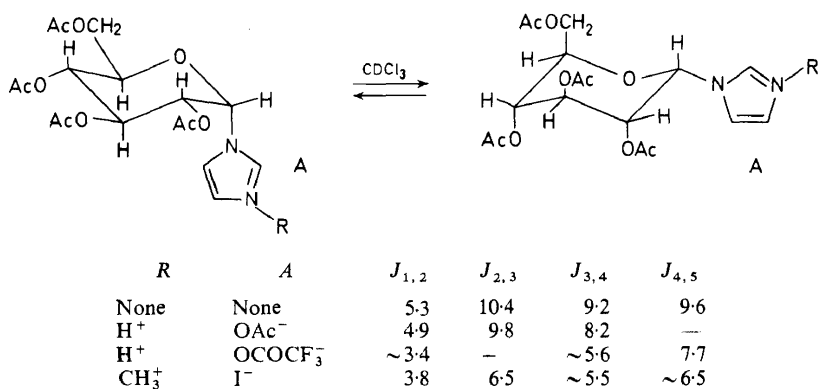| R	A	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
None	None	5·3	10·4	9·2	9·6
H$^+$	OAc$^-$	4·9	9·8	8·2	—
H$^+$	OCOCF$_3^-$	~3·4	—	~5·6	7·7
CH$_3^+$	I$^-$	3·8	6·5	~5·5	~6·5

Figure 16. The effect of *N*-protonation and of *N*-methylation of *N*-(tetra-*O*-acetyl-α-D-gluco-pyranosyl) imidazole on the coupling of vicinal hydrogens of the pyranose ring—the reverse anomeric effect[14].

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Lemieux and Morgan[13] postulated that the presence of positive charge on the atom attached to the anomeric centre may lead to a driving force for the aglycon to adopt the equatorial orientation, and termed this the 'reverse anomeric effect'. These remarks were based on observations made on the conformations of N-glycopyranosyl pyridinium salts and are illustrated for N-glycosyl imidazoles in *Figure 15*. It is seen that the distribution of electrical charge is more favourable with the imidazole group in axial orientation when the nitrogen attached to the anomeric centre carries a partial negative charge and this is the anomeric effect. However, the distribution of electrical charge is more effective in the anomer with the imidazole group in equatorial orientation when the imidazole ring has acquired a positive charge either through protonation or alkylation, and this is the reverse anomeric effect.

As seen in *Figure 16*, the protonation of the imidazole ring in N-(tetra-O-acetyl-α-D-glucopyranosyl) imidazole in chloroform through the addition of an equimolar amount of acetic acid had a smaller effect on the n.m.r. spectrum than the addition of an equimolar amount of the much stronger acid, trifluoroacetic acid. Indeed, the latter acid had an effect nearly equivalent to methylation of the imidazole group in decreasing the observed coupling constants $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$. These observations are interpreted to mean that the establishment of positive charge on the imidazole ring changes the conformational equilibrium for the N-glycoside in chloroform to favour the conformer which has the imidazole group in equatorial orientation in accordance with the principle of the reverse anomeric effect.

As seen in *Figure 16*, the n.m.r. spectrum of N-(tetra-O-acetyl-α-D-glucopyranosyl) imidazole in chloroform is in excellent accord with that expected for the compound in the conformation with the imidazole group in axial orientation. This is at once evident from the magnitudes of values for $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ which require the hydrogens at positions 2, 3, 4 and 5 to be in axial orientation. The value of $J_{1,2} = 5.5$ requires the hydrogens at positions 1 and 2 to define a dihedral angle of less than 60°. A distortion of the chair form for the pyranose ring which would relieve the non-bonded interaction between the imidazole ring and the hydrogens at positions 3 and 5 must be expected and should lead to a decrease of this angle as is inferred by the n.m.r. data. Indeed, the coupling constants reported in *Figure 16* for the compound in chloroform require that the compound be very extensively in the conformation with the imidazole group in axial orientation†. It follows, therefore, that the protonation or methylation of the imidazole ring does establish an important driving force for conformational change.

Similar results were obtained with N-(tetra-O-acetyl-α-D-mannopyranosyl) imidazole. As for the *gluco*-isomer, the values of $J_{3,4}$ and $J_{4,5}$ decreased on either protonation or methylation of the imidazole group. As seen in *Figure 17*,

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† It could be debated whether or not this orientation should be termed *quasi*-axial because of obvious distortion away from the perfect axial orientation. However, it seems unnecessary to so encumber the language of conformational analysis when in *practice* virtually all statements are meant only as approximations to the extent that staggered conformations do not necessarily involve dihedral angles of exactly 60°, a chair conformation need not be and normally is not considered to be free of distortions and axial substituents cannot normally be expected to be bonded in the direction exactly perpendicular to the mean plane of the six-membered ring. It is in this context that the chair conformations are assigned to the imidazole glycosides.

	R	A	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
$In\,(CD_3)_2CO$						
	None	None	5·1	2·9	7·0	~6·0
	H^+	$OCOCF_3^-$	6·8	3·2	5·3	4·7
$In\,CDCl_3$						
	CH_3^+	I^-	6·8	3·0	5·5	4·1

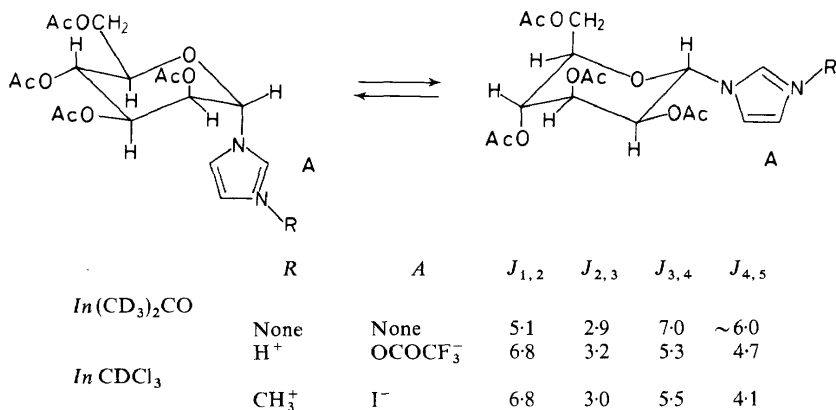*Figure 17.* The effect of N-protonation and of N-methylation of N-(tetra-O-acetyl-α-D-manno-pyranosyl) imidazole on the coupling of vicinal hydrogens of the pyranose ring—the reverse anomeric effect[14].

the value for $J_{1,2}$ increased on either protonation or methylation in accordance with our postulate that the protonated imidazole group has a greater affinity for the equatorial than the axial orientation *as compared* to the unprotonated form.

In view of this evidence for solvation effects on the magnitude of the anomeric effect, we conclude that the conformational properties of a glycoside in solution can depend on specific solvation effects. These considerations are of obvious interest to structure–activity correlations involving glycosidic structures and have a bearing on any consideration of the energetics of the hydrolysis of glycosides catalysed either by acids or by enzymes.

2,6-*cis*-Dimethoxytetrahydropyran is reported to exist extensively in carbon disulphide in the chair conformation with both methoxy groups in equatorial orientation[15]. The data in *Figure 18* show this is also the case for 2,6-*cis*-dimethoxy-1,4-dioxan in this solvent[19]. However, it is seen that, as found for 2-methoxydioxan (*Figure 14*) but not for 2-methoxytetrahydropyran (*Figure 10*), water and chloroform favour the diaxial conformer to a much greater extent than do carbon disulphide or pyridine. The percentages
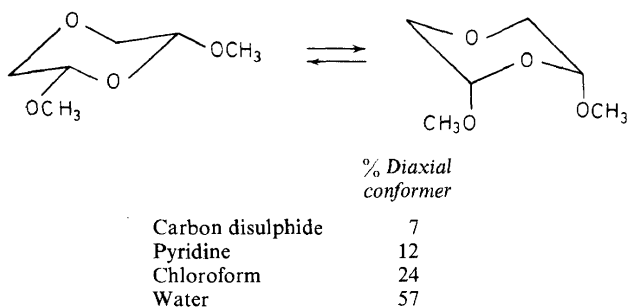

%·Diaxial conformer

Carbon disulphide	7
Pyridine	12
Chloroform	24
Water	57

Figure 18. Effect of solvent on the chair–chair equilibrium of 2,6-dimethoxy-1,4-dioxan[19].

of the diaxial conformer given in *Figure 18* were calculated on the arbitrary assumption that $J_{aa} + J_{ae} = 11$ Hz and $J_{ee} + J_{ea} = 3.6$ Hz. The sum, $J_{aa} + J_{ae} + J_{ee} + J_{ea} = 14.6$ Hz, was found for 2,6-*trans*-dimethoxydioxan and it is of interest to note that this sum did not vary for a large number of solvents, which supports our general contention that changes in coupling constant with changes in solvent are due to changes in conformation and not changes in coupling constant for the compound in the same conformation.

Calculations of the dipole moments expected for 2,6-*cis*-dimethoxy-dioxan show that the diequatorial form has more polar conformations than does the diaxial form, and on this basis it may have been expected that the solvent effects on the compound's conformational equilibria would be opposite to those determined (*Figure 18*). Since we saw earlier that the general effect of water is to decrease the magnitude of the anomeric effect (see *Figure 10*), the stabilization of the diaxial form of 2,6-*cis*-dimethoxy-1,4-dioxan and of the axial form of 2-methoxy-1,4-dioxan by water, relative to that by non-polar aprotic solvents, appears best rationalized by assuming that water best solvates vicinal oxygen atoms in *gauche* relationship. Certainly, the *gauche* relationship for two C—O bonds is more polar than when these are antiparallel and should, therefore, be favoured by the more polar solvent. However, it seems necessary to anticipate a special ability by water to stabilize oxygen atoms in *gauche* relationship which is related to its ability to become engaged in hydrogen bonds since chloroform had effects on the conformational equilibria (*Figures 10* and *18*) similar to those of water. Certainly, these results could not have been anticipated and form an excellent example of the importance of the solvation of unshared pairs of electrons on conformational equilibria.

We now wish to present evidence of substitutional effects on non-bonded interactions involving oxygen atoms. We see in *Figure 19* that, for the methyl
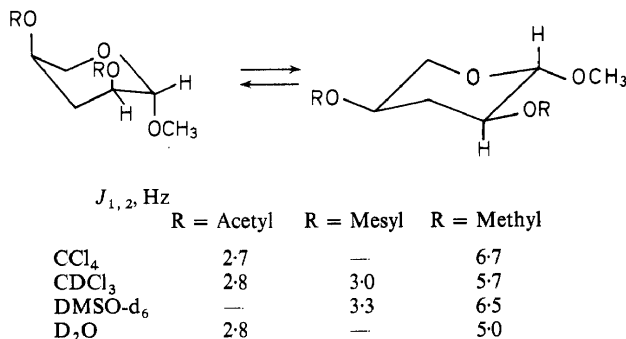

$J_{1,2}$, Hz			
	R = Acetyl	R = Mesyl	R = Methyl
CCl_4	2.7	—	6.7
$CDCl_3$	2.8	3.0	5.7
$DMSO-d_6$	—	3.3	6.5
D_2O	2.8	—	5.0

Figure 19. Substitutional effects on the conformational equilibria for derivatives of methyl 3-deoxy-β-L-*erythro*-pentopyranoside[16].

β-L-*erythro*-pentopyranoside derivatives shown, the conformational equilibrium is strongly dependent on the nature of the R-substituents on the oxygen atoms at positions 2 and 4. The magnitude of the coupling constants for $J_{1,2}$ in the case where both R groups are acetyl or mesyl clearly requires the favoured conformation to be that which has the three substituents in axial

orientation. This conclusion was supported by other coupling constants about the molecule[16]. However, it is seen that, with the R substituent the methyl group, the preferred conformer is that which has the three substituents in equatorial orientation. Since there cannot reasonably be any interaction between the R groups themselves in any plausible conformation, it is apparent that the nature of the R groups can appreciably affect the magnitude of the repulsion between the two opposing axial oxygen atoms with the more electronegative and electron-attracting acyl substituents leading to a weaker repulsion than that between the relatively more electron-donating methyl group. Of course, the energy of the triequatorial form will vary depending on the interaction of the OR group at the 2-position with the 1-methoxy group and this interaction may be greater for the acetyl and mesyl derivatives than for the methyl derivatives. However, this relatively weak non-bonded interaction is not expected to control the positions of these equilibria.

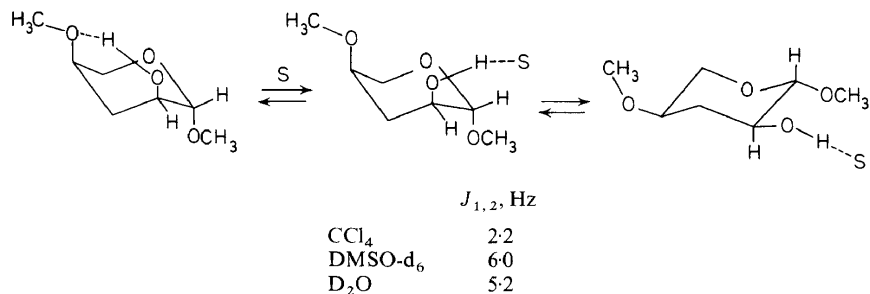As seen in *Figure 20*, the solvation of the axial hydroxyl group which

$J_{1,2}$, Hz

CCl_4	2·2
DMSO-d_6	6·0
D_2O	5·2

Figure 20. Effect of solvent on the conformational equilibrium for methyl 3-deoxy-4- O-methyl-β-L-*erythro*-pentopyranoside[16].

opposes an axial methoxy group and which leads to cleavage of the intra-molecular hydrogen bond results in the unstable chair conformation for the compound. Thus, the repulsion between the two axial oxygen atoms is of the same magnitude as that between two axial methoxy groups to the extent that it successfully counters both the anomeric effect and the introduction
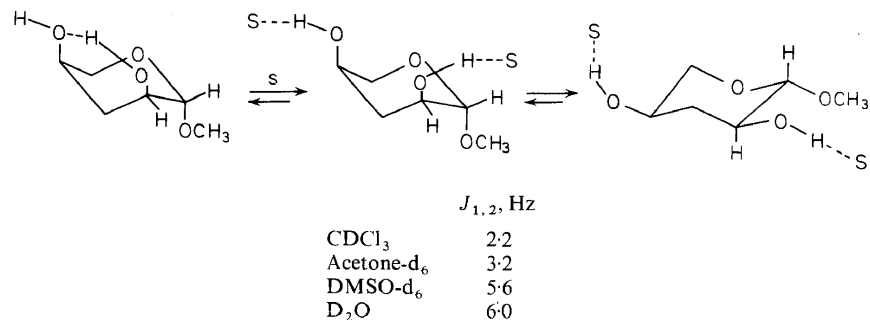

$J_{1,2}$, Hz

CDCl$_3$	2·2
Acetone-d_6	3·2
DMSO-d_6	5·6
D_2O	6·0

Figure 21. Effect of solvent on the conformational equilibrium for methyl 3-deoxy-β-L-*erythro*-pentopyranoside[16].

of a *gauche* interaction between the 1 and 2 substituents. This seems reasonable, since hydrogen bonding of the hydroxyl group with solvents leads, as will be seen later, to an enrichment of electron density about the oxygen and thereby should lead to a stronger repulsion with an opposing oxygen atom. It could be predicted on this basis that the parent 2,4-diol would also occupy the triequatorial conformation when both hydroxyl groups are bonded to solvent. As seen in *Figure 21*, this was the case. Evidently, cleavage of the intramolecular hydrogen bond by the dimethylsulphoxide or water leads to the conformer with the two solvated hydroxyl groups in axial orientation. However, the repulsion between the two hydroxyl groups is sufficiently great to require the compound to exist largely in the alternate chair form wherein the hydroxyl groups are in equatorial orientation but the methoxy group at the anomeric centre is in equatorial orientation and *gauche* to the 2-hydroxyl group.

It was desired to study these effects of hydrogen bonding on conformational
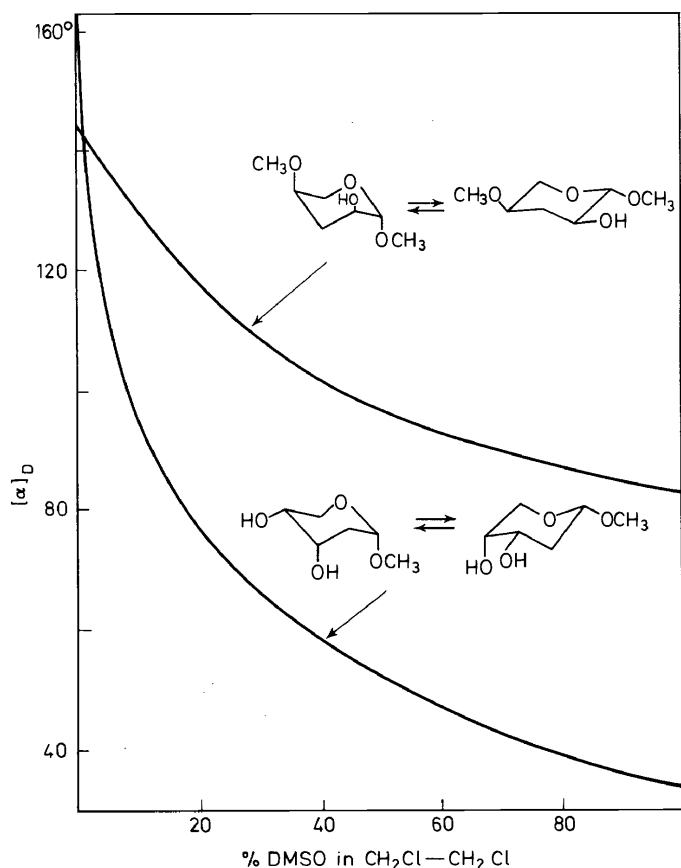

Figure 22. Effect of the concentration of dimethylsulphoxide on the optical rotations of solutions of methyl 3-deoxy-3-O-methyl-β-L-*erythro*-pentopyranoside and methyl 2-deoxy-α-L-*erythro*-pentopyranoside in ethylene chloride[16].

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equilibria more closely and at higher dilutions than is possible using n.m.r. For this reason, the possible use of changes in optical rotation at the D-line of sodium was examined[16]. Ethylene chloride was chosen as the solvent because it appeared to provide the best compromise of physical properties for a solvent which would form only very weak hydrogen bonds and still dissolve appreciable amounts of quite polar substances. Initially, dimethylsulphoxide was chosen as the base since it forms strong hydrogen bonds with the hydroxyl group.

As seen in *Figure 22*, solutions of two compounds which have a hydroxyl group which can form an intramolecular hydrogen bridge with an opposing axial methoxy group showed rotations in ethylene chloride in good agreement
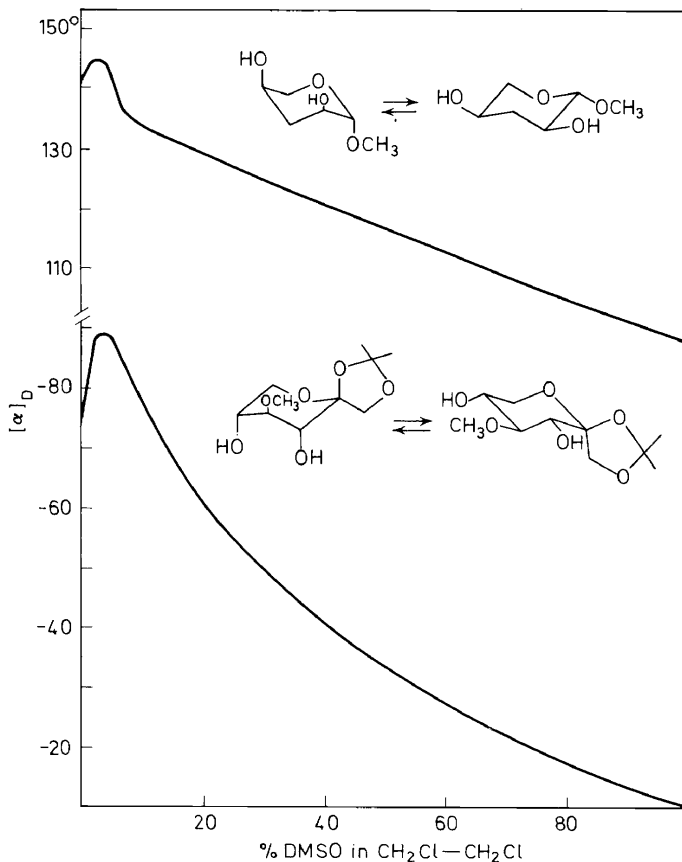

Figure 23. Effect of the concentration of dimethylsulphoxide on the optical rotations of solutions of methyl 3-deoxy-β-L-*erythro*-pentopyranoside and 1,2-*O*-isopropylidene-3-*O*-methyl-β-D-*xylo*-hexopyranos-2-ulose[16].

with the rotations expected from Brewster's rules for the conformation with the intramolecular hydrogen bond. On adding dimethylsulphoxide to the solutions the rotations decreased and tended toward the rotations expected for the compounds in the conformations which have the hydroxyl and

methoxy group in equatorial orientation. This is, of course, what was expected since, in each case, the dimethylsulphoxide in high concentrations can compete effectively with the methoxyl group for hydrogen bonding with the hydroxyl group and, once bonded to dimethylsulphoxide, as we saw in *Figure 20*, the opposition between the two axial oxygen atoms is sufficiently great to force the compound against the anomeric effect into the conformation which has the hydroxyl and methoxy groups in equatorial orientation.

As seen in *Figure 23*, the effect on rotation of adding dimethylsulphoxide to two intramolecularly hydrogen-bonded diols in ethylene chloride was more complex. It is seen that at very low concentrations of dimethylsulphoxide the rotations were higher than in pure ethylene chloride. However, with additional increases in the concentration of dimethylsulphoxide, the rotations began to decrease in the manner expected to achieve the rotations of the compounds in pure dimethylsulphoxide. This phenomenon has been observed for a variety of other diols and appears general when the breaking of an intramolecular hydrogen bond by the addition of dimethylsulphoxide or other hydrogen-bonding base leads to a change in conformation. We attribute the initial change in rotation to an increase in the population of the intramolecularly hydrogen-bonded conformation for the reasons outlined in *Figure 24*.

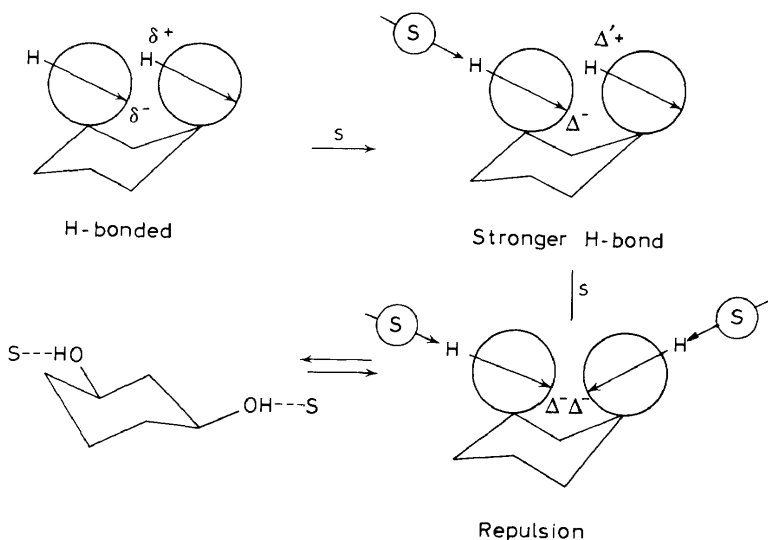The bonding of the hydrogen of an hydroxyl group to solvent is well

Figure 24. Theory for the conjugation of hydrogen bonds[16].

known to polarize the O—H bond so as to increase the electron density at the oxygen atom. The deshielding of hydrogen through hydrogen bonding in the n.m.r. spectrum is a related phenomenon. It is reasonable to expect, then, that the increase in electron density at the oxygen atom will enable this particular oxygen atom to form a stronger hydrogen bond than it could prior to its hydrogen having become bonded to the solvent. The strong

acidity of O-hydroxybenzoic acid as compared to m- and p-isomers has been attributed[17] to the increased strength of the intramolecular hydrogen bridge
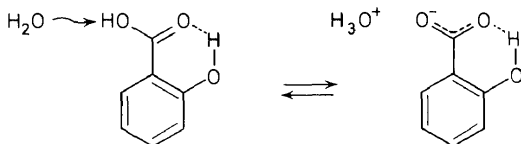
as a result of the dissociation of the carboxyl group and is a comparable phenomenon. Thus interpreted, the phenomenon displayed in *Figure 23* provides further evidence that the electrical properties of oxygen atoms are appreciably affected through hydrogen bonding and confirms our general conclusions on the influence of hydrogen bonding on the anomeric effect. Indeed, the repulsion between two axial and opposing hydroxyl groups can now be expected to be especially great when both hydroxyl groups are bonded to the solvent and this repulsion is considered primarily responsible for the compound adopting the conformation which has both solvated hydroxyl groups in equatorial orientation.

The 'conjugation' of hydrogen bonds as proposed in the first stage of the transformations shown in *Figure 24* found strong support in experiments[18] using pyridines as bases in shifting the conformational equilibria for 1,2-O-isopropylidene-3-O-methyl-β-D-sorbopyranoside from the triaxial conformer in ethylene chloride.

As seen in *Figure 25*, as was expected from the simple theory of *Figure 24*, increasing the base strength of pyridine by changing the 4-substituent led to a larger increase in rotation. This is interpreted as the system achieving a relatively higher concentration of the intramolecularly bonded form as a result of the greater strengthening of the intramolecular bond by the stronger base.

As seen in *Figure 26*, an increase in temperature shifts the equilibria in the way expected from the simple theory presented. An increase in temperature would obviously tend to decrease the maximum amount of the intramolecularly bonded form, since the increased thermal agitation would work against the association of the base with the diol to reinforce the intramolecular bridge. For similar reasons, the extent of conformational change to the di-equatorial diol for a given amount of base should decrease with increase in temperature and this is reflected by the plots shown. Indeed, as is shown in *Figure 27*, the data obtained could be treated to provide thermodynamic constants for the variety of equilibria postulated using abbreviated formulas for 1,2-O-isopropylidene-3-O-methyl-β-D-sorbopyranoside. As expected, the first equilibrium, which is simply between the diol conformers, involves a small change in entropy. The changes in enthalpy in the second stage (ΔH_2) are very interesting since their values should correspond to the strength of the hydrogen bond established between the 4-methylpyridine and the free hydroxyl group in the intramolecularly hydrogen-bonded form of the diol. Indeed, the value of about -4.5 for this hydrogen bond is much in line with values normally provided for this kind of hydrogen bond. Certainly the change in entropy for this equilibrium corresponds well with expecta-
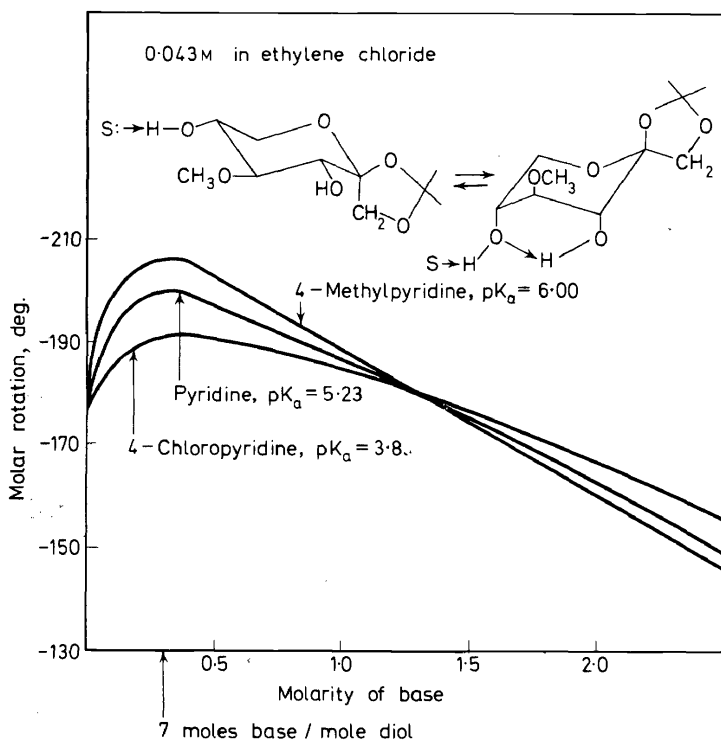
Figure 25. Effect of base strength on the rotation of a 0·043 molar solution of 1,2-*O*-isopropylidene-3-*O*-methyl-β-D-*xylo*-hexopyranos-2-ulose in ethylene chloride at 20°[18].

tion for a process which involves the bringing together of two molecules. The change in entropy obtained for the third process is also in the range expected. Thus we see that the changes in equilibrium constant which occurred with changes in temperature are in accord with the idea that the formation of the bond between the diol and solvent molecule in stage 2 (*Figure 27*) reinforces the hydrogen bridge. The excellent relationship between the pK_a of the base and the change in free energy for this second stage is in accord with the expectation that the reinforcement should increase with increasing strength for the base.

In conclusion, then, we believe we have demonstrated that the conformational analysis of polar compounds will necessarily require close attention to non-bonded interactions involving unshared pairs of electrons and especially as to how these interactions are influenced by the solvent. From the point of view of the terms of reference for this Symposium: namely, the scope and present limitations of conformational analysis, it should be kept well in mind, I believe, that the most important aspects of conformational analysis will necessarily involve highly polar compounds such as are represented by the proteins, the carbohydrates, the nucleic acids and their precursors in the presence of water. The kinds of investigations which I reported represent some of our efforts in this direction. Certainly, it is quite evident
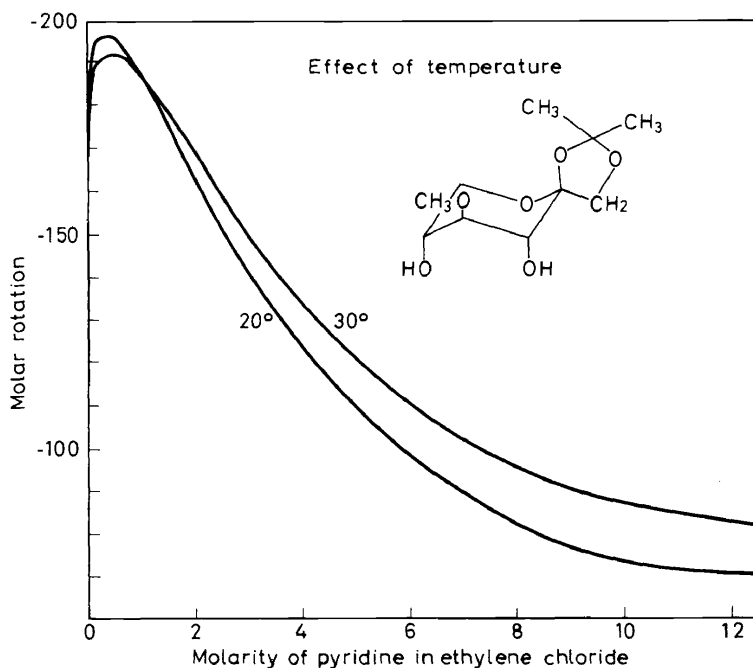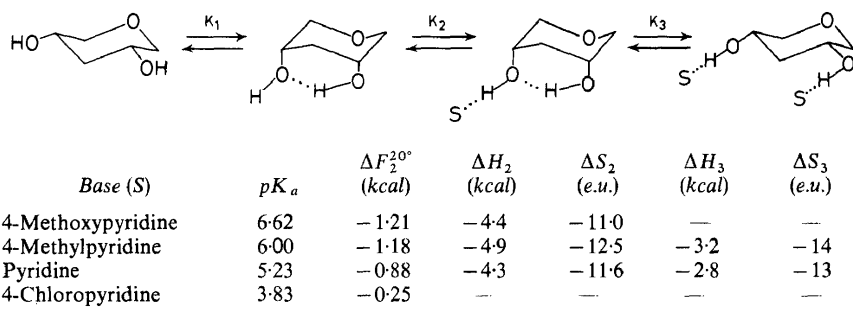
Figure 26. Effect of temperature on the change in rotation observed when pyridine is added to a 0·043 molar solution of 1,2-O-isopropylidene-3-O-methyl-β-D-*xylo*-hexopyranos-2-ulose in ethylene chloride[18].

Base (S)	pK_a	$\Delta F_2^{20°}$ (kcal)	ΔH_2 (kcal)	ΔS_2 (e.u.)	ΔH_3 (kcal)	ΔS_3 (e.u.)
4-Methoxypyridine	6·62	− 1·21	− 4·4	− 11·0	—	—
4-Methylpyridine	6·00	− 1·18	− 4·9	− 12·5	− 3·2	− 14
Pyridine	5·23	− 0·88	− 4·3	− 11·6	− 2·8	− 13
4-Chloropyridine	3·83	− 0·25	—	—	—	—

† $\Delta H_1 = -0·4$ kcal/mole, $\Delta S_1 = 1·2$ entropy units

Figure 27. Some thermodynamic constants estimated for the chair–chair equilibrium for 1,2-O-isopropylidene-3-O-methyl-β-D-*xylo*-hexopyranos-2-ulose (shown as a partial formula) in ethylene chloride and the effect of adding bases to this equilibrium as derived from temperature effects on rotation[18].

that much remains to be learned and, indeed, it seems fair to say that we are just beginning to gain a basis for proper conformational analysis in these areas which in the end will be a prime requirement for the understanding of biological processes, especially protein synthesis and structure and enzyme catalysis.

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