NEWER DEVELOPMENTS IN THE CONFORMATIONAL ANALYSIS OF CARBOHYDRATES

R. U. LEMIEUX

Department of Chemistry, University of Alberta, Edmonton, Canada

ABSTRACT

The lecture is mainly concerned with research from the author's laboratory on substitutional and solvation effects on conformational equilibria as estimated from NMR and optical rotation data. Reference is made to the use of empirical rules of rotation for estimating conformational preferences and to how x-ray crystallographic data on the torsional angles defined by vicinal atoms may become of importance to both the interpretation of rotation and NMR data. The anomeric and reverse anomeric effects on glycoside conformation are considered and reference is made to solvation effects on the interaction between oxygen atoms in *gauche* and in *syn*-axial relationships. Effects of solvation on the orientation of the hydroxymethyl group of hexopyranoses and on intramolecular hydrogen bonding are presented.

Remarkable advances were made in the past fifteen years in observing the conformational properties of carbohydrate structures. However, we are only beginning to probe the effects of the solvent in establishing the conformational preferences observed. The real value of conformational analysis will only be realized with a thorough understanding of how the carbohydrate solute interacts with the molecules in its environment and how this is related to conformational preferences as well as to how such interactions affect the energy requirements for changes in the environment of the carbohydrate. Answers to these questions are obviously of basic importance towards the eventual understanding of the enzyme-catalysed transformations of the carbohydrates, the antigenic properties of carbohydrate structures, the structure-activity relationships for carbohydrate antibiotics, etc. This lecture will be mainly concerned with our efforts to make contributions to this aspect of conformational analysis. Basic to our approach is the synthesis of model structures for which there should exist a substantial population of more than one conformation. Thus, solvation effects on the conformational equilibria for such compounds can be expected to be sufficiently large, to allow their observation, particularly through changes in nuclear magnetic resonance spectra and changes in optical rotation.

As seen in *Figure 1*, this objective was realized by the preparation of methyl 3-deoxy-β-L-*erythro*-pentopyranoside[1]. It could be expected that in non-basic media, such as chloroform, an intramolecular hydrogen bond

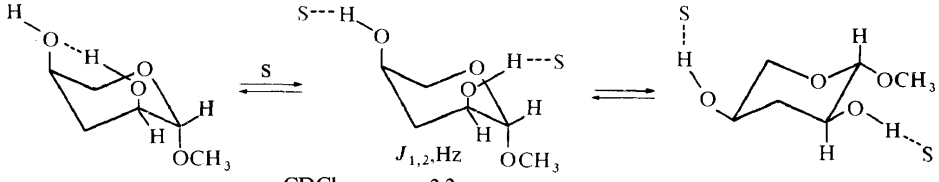
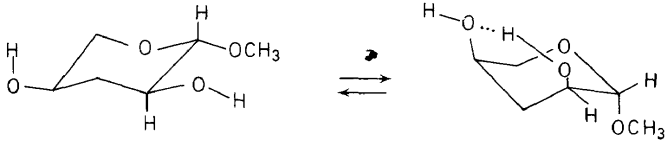


Figure 1. Effect of solvent on the conformational equilibrium for methyl 3-deoxy-β-L-*erythro*-pentopyranoside[1].



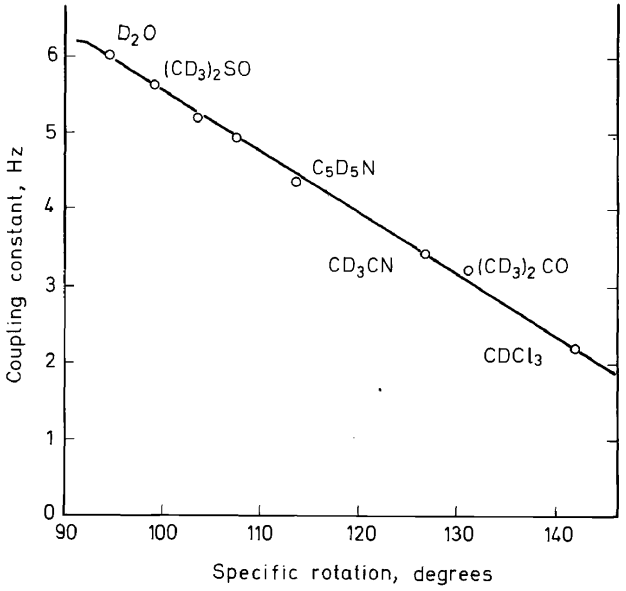


Figure 2. Correlation of the effect of change of solvent on the conformational equilibrium for methyl 3-deoxy-β-L-*erythro*-pentopyranoside as determined by NMR with that indicated by change in optical rotation[6].

between the 2- and 4-hydroxyls together with the anomeric effect[2] would help stabilize the C1-conformation at the left. However, breaking of the intra-molecular hydrogen bond by adding, for example, dimethylsulphoxide or water, should result in considerable repulsion between the two opposing solvated hydroxyl groups and, as a consequence, shift the equilibrium toward the 1C conformation where the two hydroxyl groups are in equatorial orientation. For a high population of the 1C conformation to result, the repulsion between the two solvated axial hydroxyl groups in the C1 conformation would have to be much greater than the *gauche* interaction between the 1-methoxy and the 2-hydroxy group plus the anomeric effect. The NMR data confirmed substantial change in conformational equilibrium with change in solvent. It is seen that in chloroform a small coupling constant was observed between the 1 and 2 protons indicating these protons to be largely in the *gauche* relationship and, therefore, the molecule in the C1 conformation. When the NMR spectrum was taken in dimethylsulphoxide, the coupling constant increased to 5.6 Hz, a value which requires a high population of the 1C conformer wherein both the 1 and 2 hydrogens are in axial orientation. This situation appears even more pronounced in water but less so in acetone which presumably forms a weaker hydrogen bond with hydroxyl than does dimethylsulphoxide.

NMR spectroscopy, for many reasons, is severely limited in scope for the study of conformational equilibria especially for complex structures at low concentrations. As was anticipated many years ago[3], an ability to interpret optical rotation would provide an excellent method for establishing conformational properties. The publication in 1956 by Whiffen[4] of his empirical rules for the optical rotation of certain carbohydrates confirmed these anticipations and established a new approach to the study of conformational equilibria. These rules were modified and presented in a somewhat different manner by Brewster[5] in 1959 and it was shown that a least for the saturated carbohydrate structures the empirical rules allowed the anticipation of molecular rotation to an impressive degree. In order to test this approach we undertook the experiment reported in *Figure 2*[6].

It is seen that when a plot was made of the specific rotation of the solution used for the NMR experiment and the coupling constant for the 1 and 2 protons, a linear relationship was obtained[6]. The rotation tended in water towards the expected rotation based on either Whiffen's or Brewster's rules for the triequatorial 1C conformation. As the basicity of the solvent was reduced, the rotation tended towards that expected for the triaxial C1 conformation which is stabilized by the intra-molecular hydrogen bond. Thus, the changes in optical rotation which occurred appeared to arise mainly from the changes in the torsional angles defined by the atoms in the molecule as a result of the change in the conformational equilibrium and that contributions to rotation by the solvent molecules themselves were relatively minor. This latter conclusion was subsequently tested through the preparation of a number of optically active conformationally rigid substances[7]. Indeed, it was found that their optical rotations were substantially solvent independent.

At this point, I wish to comment on the simplified rules for optical rotation which we have previously published[7]. These rules are virtually precisely

those originally presented by Whiffen. The central concept is identical. Our attempts at simplification were not proposed for improvement but instead to render the application of such empirical rules more simple and thereby, hopefully, stimulate the testing and eventual improvement of this approach to information on conformation. Although Whiffen's rules have been available for over fourteen years few attempts to use the rules for the examination of solvation effects on conformation have been made. This was probably at least in part due to the rather generalized and, as a consequence, complex presentation of parameters made by Whiffen. Our simplified rules are presented in *Figure 3*.

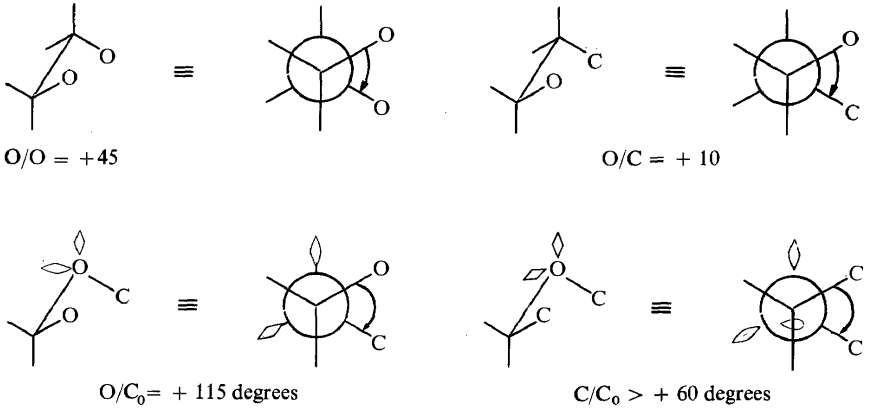


Figure 3. Parameters suggested for the estimation of the molecular rotations of saturated sugars and methyl glycopyranosides from a consideration of *gauche* interactions between the oxygen and carbon atoms only[7].

It is seen that permolecular contributions to rotation as proposed by Brewster[5] are not included. This is not to be interpreted that such contributions do not exist.

For classical glycopyranoside structures, the simplified rules require only three parameters, the so-called O/O which refers to oxygen in *gauche* relationship and bridged by two carbon atoms, the O/C relationship which refers to an oxygen and a carbon atom in *gauche* relationship and bridged by two carbon atoms, the O/C$_0$ which refers to an oxygen and a carbon in *gauche* relationship but bridged by carbon and an oxygen atom. The C/C$_0$ relationship occurs for example in methyl ethers and probably contributes to some extent in glycopyranosides. This latter contribution is undoubtedly large and $\pm$ 60 degrees (depending on sign of the torsional angle) appears a minimum numerical value.

The value of only $\pm$ 10 degrees for the O/C contribution is undoubtedly an artefact of the simple approach used to account for the rotations of these complex structures. Thus, as pointed out by Brewster[5], the molecular rotation of *dextro-trans*-2-methylcyclohexanol is 44 degrees and not $\pm$ 10 degrees as would be expected from the simplified rules. Thus, the O/C

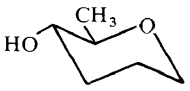
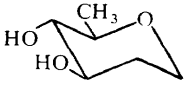
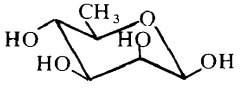
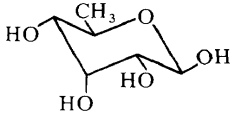
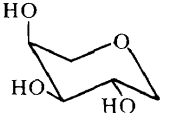
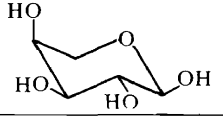
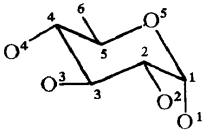
	Analysis	Molecular rotation *Calc.*	*Found*	*Brewster*
	O/C	(degrees) +10	(degrees) +13	(degrees) +50
	O/C–O/O	−35	−32	+5
	2O/C–2O/O	−70	−63	−55
	O/C–O/O	−35	−20	+5
	3O/O–O/C	+125	+132	+150
	2O/O–O/C	+80	+82.5	+105

Figure 4. A comparison of the predictions based on the simplified empirical rules[7] with those proposed by Brewster[5].

contribution of ± 10 degrees must be reserved for the tetrahydropyran derivatives represented by sugars and glycosides, as shown in *Figure 4*, where it is seen that its use accounts at least as well as Brewster's approach for the rotations of the compounds listed. Assuming a basic validity to the approach represented by the simplified rules, the problem is then to establish why the O/C contribution appears to be numerically so low under these circumstances. The answer will undoubtedly require a number of adjustments and this matter is presently under investigation. The refinements conceivably may arise from varying effects on rotation at the D-line of sodium arising from the chromophoric acetal and hemiacetal groupings, important contributions to rotation arising from the presence of hydrogen atoms as indicated by Whiffen[4], the presence of permolecular effects as proposed by Brewster[5] and Englard and coworkers[8], the lack of a precise correspondence of the actual conformation and the idealized conformations used for the calculations, and substantial contribution to observed rotation by other conformers although present in only relatively much lower concentrations. It is hoped that the publication of our admittedly controversial

simplified rules[7] will provide a further impetus to investigation in these directions.

As the x-ray data have accumulated on the conformation of carbohydrate structures in the crystalline lattice it has become quite evident that ideal chair conformations are not realized. This is well displayed, for example, by the torsional angles reported in *Figures 5* and *6*.

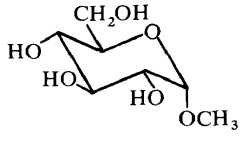


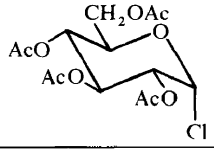
	Sucrose	Methyl β-D-maltoside	Methyl α-D-glucopyranoside
	(degrees)	(degrees)	(degrees)
O_1O_2	54.7	56.1	61.5
O_2O_3	62.7	60.0	58.7
O_3O_4	−64.2	−60.2	−67.7
O_4C_6	64.4	61.0	64.3
C_1C_4 (via C_2C_3)	−55.9	−58.5	−55.5
C_1C_4 (via O_5C_5)	55.2	58.2	58.0
C_2C_5 (via C_3C_4)	56.0	60.5	54.2
C_2C_5 (via C_1O_5)	−55.0	−56.1	−60.1
C_3O_5 (via C_4C_5)	−54.8	−60.6	−54.1
C_3O_5 (via C_2C_1)	54.9	56.3	58.2
O_1C_3	−68.1	−65.9	−64.7
O_1C_5	67.7	63.9	59.3

Figure 5. Torsional angles for neighbouring atoms in crystalline derivatives of α-D-glucopyranose[9].

It is seen in *Figure 5* that very substantial differences exist for the torsional angles as determined by x-ray crystallography for the α-D-glucopyranosyl group in sucrose, methyl β-D-maltoside and methyl α-D-glucopyranoside depending on the aglycon. Of course, we have no assurance that the same differences will occur in solution but clearly one must anticipate similar deviations from the ideal chair form.

As seen in *Figure 6*, the deviations are even greater on acetylated structure. For α-acetochloroglucose, the deviations are about ± 15 degrees from the 60 degrees torsional angles anticipated on the basis of the ideal chair form. It may be noted at this point that the Karplus curve[10] was established on the basis of structures such as the acetylated sugars which most likely also deviate from ideality very substantially. It is probably for this reason that there has been a tendency[11] to displace the Karplus curve upwards in order to better accommodate the experimental data. It is to be expected that the contribution made by two atoms which define a screw pattern of asymmetry would vary with the pitch of the screw, that is, the torsional angle. Brewster[5] has suggested that it should be proportional to the sine of the angle. On this basis, we may expect, especially for a large contribution to rotation as





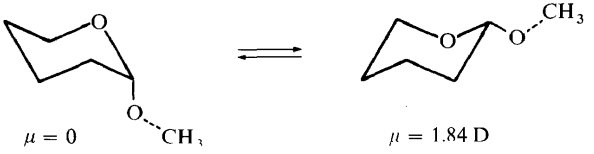
	(degrees)		(degrees)
O_1O_2	61.5	Cl_1O_2	48.3
O_2O_3	58.7		73.6
O_3O_4	−67.7		−76.0
O_4C_6	64.3		76.0
C_1C_4 (via C_2C_3)	−55.5		−47.2
C_1C_4 (via O_5C_5)	58.0		59.0
C_2C_5 (via C_3C_4)	54.2		47.3
C_2O_5 (via C_1C_5)	−60.1		−60.0
C_3O_5 (via C_4C_5)	−54.1		−51.0
C_3O_5 (via C_2C_1)	58.2		52.9
O_1C_3	−64.7	Cl_1C_3	70.4
O_1C_5	59.3	Cl_1C_5	64.0

Figure 6. Torsional angles for neighbouring atoms in crystalline derivatives of α-D-glucopyranose[9].

represented by the O/C_0 contribution, only a relatively small distortion will strongly affect the magnitude of the contribution to rotation.

Evidently, then, there still exist both experimental and theoretical deficiencies with regard to attempts to correlate structure and conformation with optical rotation. Nevertheless, the advances made to date appear to allow fruitful application of the available empirical rules to problems such as solvation effects on conformational equilibria as well as determination of conformation and absolute configuration.

One of the effects we would like to learn more about is the effect of solvent on the interaction between oxygen atoms in *gauche* relationship. Unless one of the oxygen is a hydroxyl group and can form a strong intramolecular hydrogen bond with the other *gauche* oxygen one would expect a strong



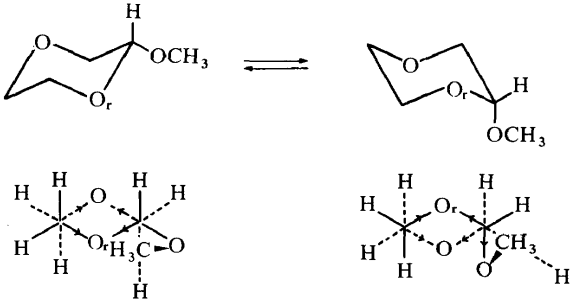
$\mu = 0$ $\mu = 1.84$ D

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 7. Effect of solvent on the conformational equilibrium for 2-methoxytetrahydropyran[12].

electrostatic repulsion between the two oxygen atoms. I would like now to present some NMR data which have suggested to us that this is indeed the case for certain methoxy derivatives of tetrahydropyran[12] and dioxan[13] in non-polar solvents. However, we are led to the tentative conclusion that water tends to substantially stabilize that conformation with the oxygens in *gauche* relationship as compared to other solvents and that this may be for reasons of specific solvation effects.

Figure 7 shows our interpretation of NMR data for 2-methoxytetrahydropyran and these data were well substantiated by studies of the optical changes which occurred using optically active material[12]. It is seen that for 2-methoxytetrahydropyran the equatorial conformer is preferred in larger amounts with increasing dielectric constant for the solvent with the hydrogen-bonding solvent chloroform a notable exception. We consider the effect of this solvent likely to be a specific solvation effect on the magnitude of the anomeric effect which, of course, is responsible for the preference of the axial conformer in all the solvents. The trend is in line with the general anticipation that, the more polar the solvent, the better it can stabilize the more polar conformation. However, a non-bonded interaction such as the anomeric effect which must arise from dipole interactions must be expected to be also affected by changes in solvation which involve the bonding of the oxygen atoms as proton acceptors in hydrogen bonds.

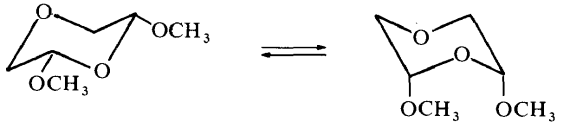


	Dielectric constant	*% Axial conformer*
Carbon disulphide	2.6	60
Pyridine	12	65
Dimethyl sulphoxide	45	67
Chloroform	4.8	70
Water	80	80

Figure 8. Effect of solvent on the conformational equilibrium for 2-methoxydioxan[13].

In *Figure 8* the effect is shown of change in solvent on the conformational equilibrium for 2-methoxydioxan, as derived from interpretations of NMR data[13]. It is at once seen that, in contrast to the 2-methoxytetrahydropyran where increasing solvent polarity favoured the equatorial conformer, in the case of 2-methoxydioxan increased polarity for the solvent favours the axial conformer. Again, chloroform is an exception. In this case we cannot

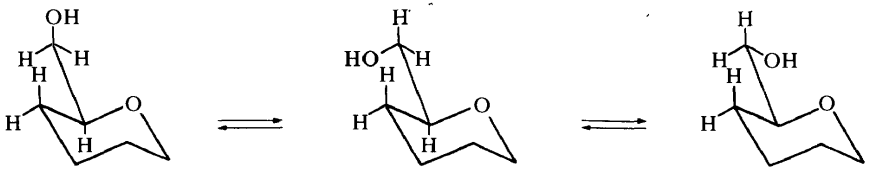
expect the two conformers to differ appreciably in polarity. Therefore, the rather pronounced effect of water must result in some way from a specific solvation effect which is perhaps most favourably expressed with the vicinal atoms in *gauche* orientation.



	% *Diaxial conformer*
Carbon disulphide	7
Pyridine	12
Chloroform	24
Water	57

Figure 9. Effect of solvent on the conformational equilibrium of *cis*-2,6-dimethoxydioxan[13].

Figure 9 shows an even more remarkable example of this phenomenon. Here we show the conformational equilibrium for *cis*-2,5-dimethoxydioxan. Again, we see water apparently stabilizing a conformation which must be highly unfavourable in the gaseous state as reflected by the small amount of the diaxial conformer in carbon disulphide. Indeed, the solvation effect of water on this conformational equilibrium must be of the same magnitude as the strongest intramolecular non-bonded interaction. Judging from the results obtained for the 2-methoxydioxan we tend to expect that the driving force is at least in part the bringing of the methoxy oxygen atoms in *gauche* relationship with the vicinal ring oxygen atom. This seems also to be the case when the vicinal oxygens are hydroxyls or one is hydroxyl and the other an ethereal oxygen.



Expected ~ 0 degrees ~ − 45 degrees ~ + 45 degrees

Found + 22 degrees (H_2O), − 6.5 degrees (DMSO), + 8 degrees (CH_2ClCH_2Cl)

Figure 10. Effect of solvent on the conformational equilibrium for s-2-hydroxymethyltetrahydropyran[7].

It was mentioned above regarding the O/C contribution to the rotation of sugars and glycosides that the magnitude of the contribution was substantially less than that expected from the model compound, *trans*-2-methylcyclohexanol. In situations not involving the presence of an axial

oxygen on a tetrahydropyran ring, it is probably better to assign a near equality of the O/C and O/O contributions as proposed by Whiffen[4] and Brewster[5]; namely ± 45 degrees. On this basis, the rotations shown in *Figure 10*, are calculated for the three conformers of s-2-hydroxytetrahydropyran. The molecular rotation of + 22 degrees in water clearly favours, on this basis, the conformer for which a rotation of + 45 degrees is calculated. Lemieux and Martin[7] reached the same conclusion using the smaller O/C contribution proposed for pyranose structures. The point then is that a definite conclusion appears possible as to which of the conformers shown in *Figure 10* is most prevalent in the absence of a highly precise knowledge of the value for the O/C contribution and other contributions neglected in this simple approach. Much improved insight will be required, however, to reach a definite decision on the relative populations of the other two conformers. Information concerning this problem is presented with reference to *Figure 19*.

Thus, in water, a *gauche* interaction between the two oxygen atoms seems

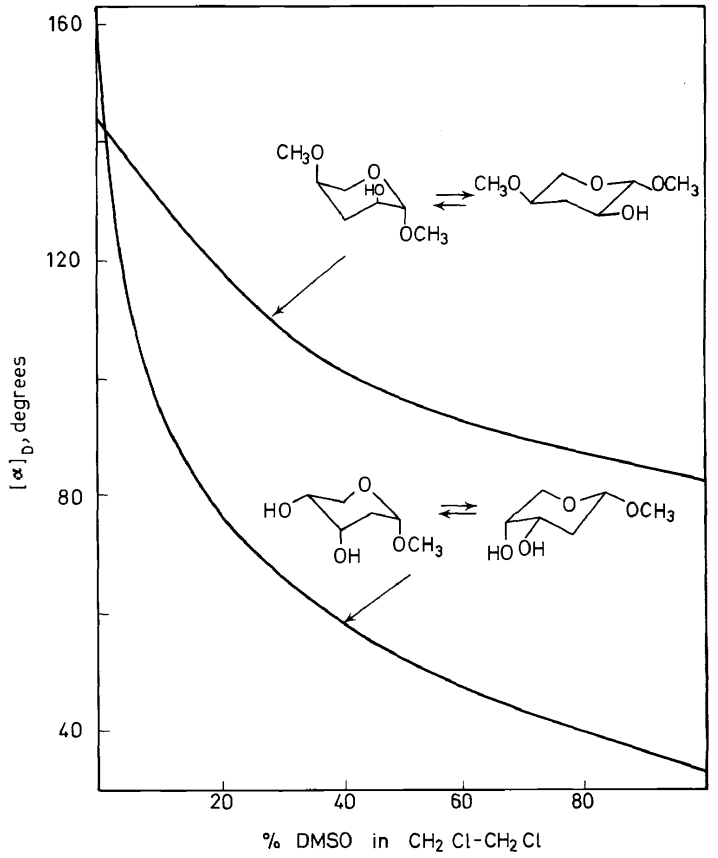


Figure 11. Plots of the change in specific rotation which occurs with increasing amounts of dimethylsulphoxide for solutions of methyl 4-*O*-methyl-3-deoxy-β-L-*erythro*-pentopyranoside and methyl 2-deoxy-*erythro*-α-D-pentopyranoside in ethylene chloride[1].

preferred over an orientation which would place the hydroxyl group in *syn*-axial-like relationship with a hydrogen atom. This conclusion is in line with the data reported in *Figure 8* for the 2-methoxydioxan. Furthermore, the conclusion is in line with the suggestion by Brimacombe and coworkers[14] that 1,5-anhydro-2-deoxy-L-*erythro*-pentitol exists largely in solution in the conformation which has the 4-hydroxyl group in axial orientation and *gauche* with the ring oxygen. In view of the data presented in *Figures 8* and *9*, the explanation of these results need not involve a hydrogen bond between the hydroxyl and the oxygen in *gauche* relationship. Instead, the highly polar grouping can be expected to be well accommodated by the highly polar water especially should the oxygen atoms in *gauche* relationship be particularly favourable to solvation by water. In contrast, the laevorotation for the compound (*Figure 10*) in dimethylsulphoxide appears to indicate that when the hydroxyl group is hydrogen bonded to dimethylsulphoxide, substantial repulsion between the two hydroxyl groups is experienced and, although the solvent is highly polar, a substantially greater population of the laevorotatory conformer is present than when the solvent was water.

In *Figure 11*, two compounds are shown which when dissolved in ethylene chloride demonstrated strong intramolecular hydrogen bonding and as a consequence we expect these compounds to exist largely in the conformation shown on the left[15]. Furthermore, the rotations of the compounds, to the extent that they could be anticipated from the empirical rules, were in support of this contention. On adding dimethylsulphoxide to this solution,

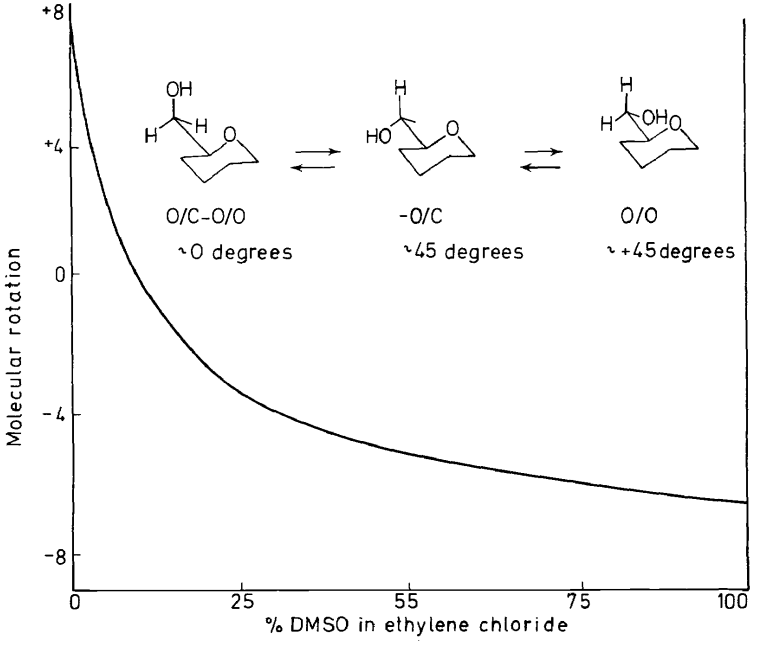


Figure 12. Plot of the change in the molecular rotation of s-2-hydroxymethyltetrahydropyran with increasing amounts of dimethylsulphoxide in ethylene chloride as solvent[7].

it is expected that the intramolecular hydrogen bond is disrupted and, as a result, the conformational equilibrium would change toward the conformation which does not have the oxygens in *syn*-axial relationship. Indeed, as seen, the rotations fell towards the rotations expected for the compounds in the conformations shown at the right. We have seen then that a strong repulsion exists between *syn*-hydroxyl groups hydrogen bonded to dimethylsulphoxide and also between a hydroxyl group bonded to dimethylsulphoxide and an opposing axial methoxy group. If such a strong repulsion exists between groups in *syn*-axial orientation one might expect a similar one between such groups in *gauche* orientation. This seems well displayed by the data for the 2-hydroxymethyltetrahydropyran shown in *Figure 12*[7].

It is seen that there was a sharp drop in rotation on adding dimethylsulphoxide to a solution of the compound in ethylene chloride. We interpret these observations as indicating that, when the hydroxyl is hydrogen-bonded to dimethylsulphoxide, the compound adopts the laevorotatory

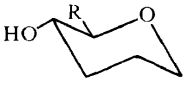
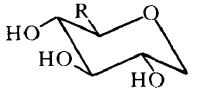
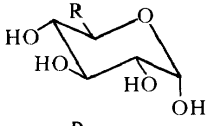
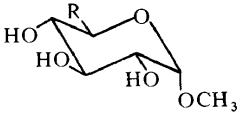
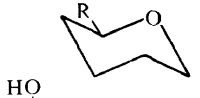
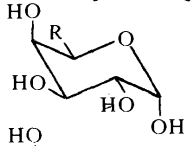
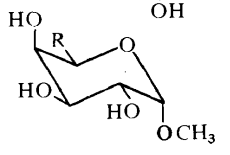
	Molecular rotation		
	$R = CH_2OH$	$R = CH_3$	*Difference*
	+53	+13	+40
	+83	+43	+40
	+202	+163	+39
	+309	+271	+38
	+22	+4	+18
	+271	+249	+22
	+384	+351	+33

Figure 13. The effect of introducing the 6-hydroxyl group on the rotation in water of a hexopyranose derivative[7].

conformation which has the two oxygen atoms in anti-parallel orientation. We see no reasons on conformational grounds to assigning an important contribution to rotation by the conformer which has the hydroxyl group both *gauche* with the ring oxygen and the vicinal methylene group. The fact that this conformer is often found in the crystalline state for carbohydrate structures, is likely the result of favourable intermolecular hydrogen bonds in the crystalline lattice.

Figure 13 shows the difference in rotation between a sugar or glycoside and certain deoxy derivatives with either a methyl group or a hydroxymethyl group at the 5-position[7]. The rather large positive difference found in all cases must, we believe, be a reflection of the contribution to rotation made by the hydroxyl group of the hydroxymethyl group and the pyranose ring. We must expect then that the ring oxygen and the hydroxyl group define a positive torsional angle, that is, that the preferred conformation is that which has the hydroxyl group in *gauche* orientation with the ring oxygen and the hydrogen at the 5-position.

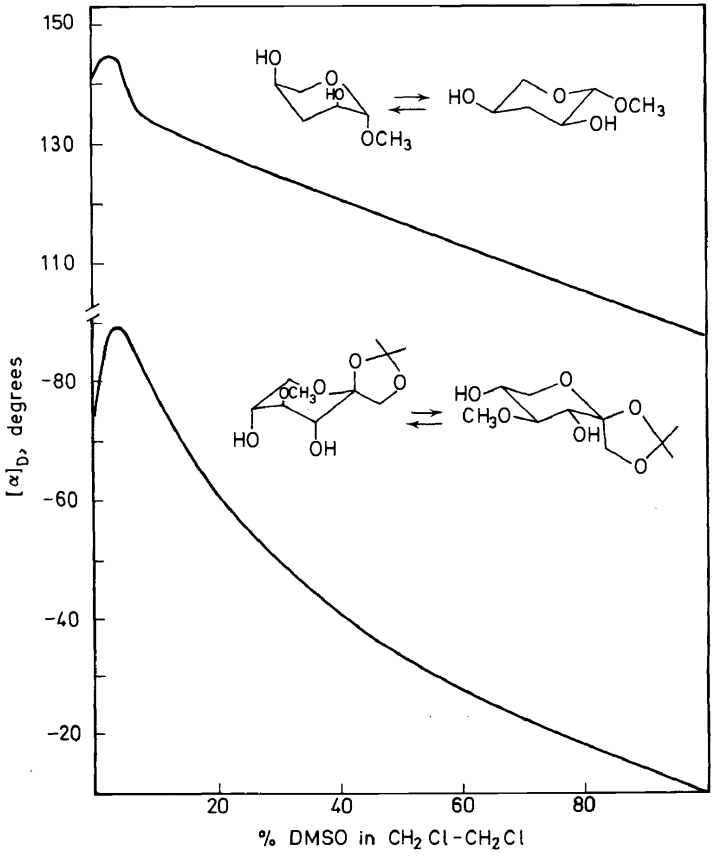


Figure 14. The effect of increasing amounts of dimethylsulphoxide on the specific rotations of methyl 3-deoxy-β-L-*erythro*-pentopyranoside and 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-*xylo*-hexopyranulose in ethylene dichloride[1].

I wish now to describe some rather unusual solvation effects on the conformational equilibria for certain 1,3-diols which we have prepared. In all such structures that we have synthesized, and two are presented in *Figure 14*, the discontinuity in the sign of the rotational change shown was found. Namely, on adding small amounts of dimethylsulphoxide to the diol dissolved in ethylene chloride there was initially a change in rotation towards that expected for the diol in the intra-molecularly hydrogen bonded form. However, on adding larger amounts of dimethylsulphoxide the rotation changed towards that expected for the compound in the alternate chair form[1].

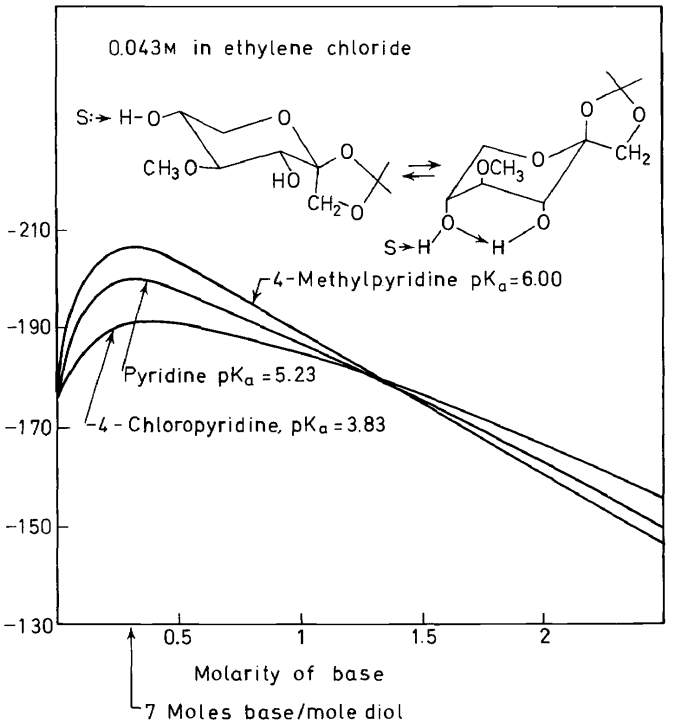


Figure 15. The effect of changes in the basicity of pyridines on the change in molecular rotation at 25° for 1,2-isopropylidene-4-*O*-methyl-β-D-*xylo*-hexopyranulose at various concentrations of the base in ethylene dichloride[15].

The phenomenon involving the sorbose derivative has been studied in detail. First of all, as seen in *Figure 15*, we examined the rotational change with other bases, particularly with pyridines differing by virtue of substitutional changes at the 4-position in their basicities. It is seen that the stronger the base, the more pronounced was the effect. In all cases the maximum effect at the concentrations studied involved about 7 moles of the pyridine per mole of the diol.

The effect of temperature on the phenomenon was readily measured and,

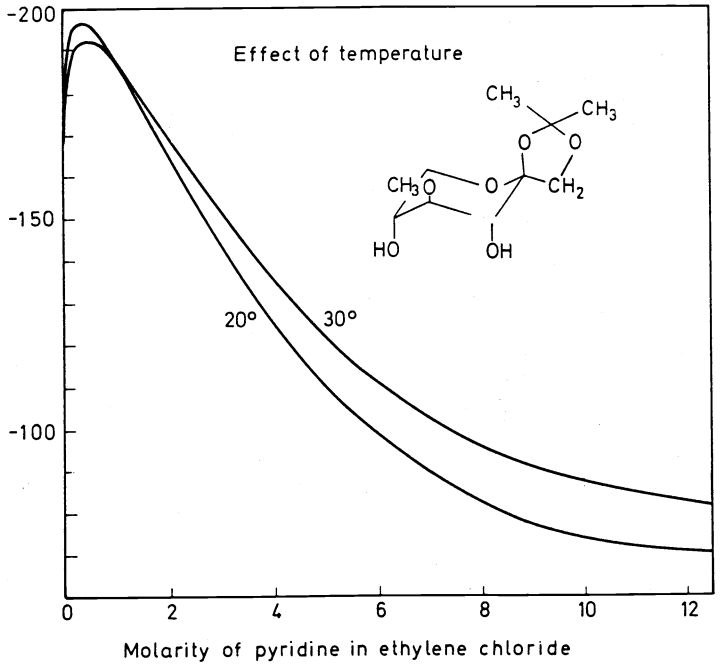
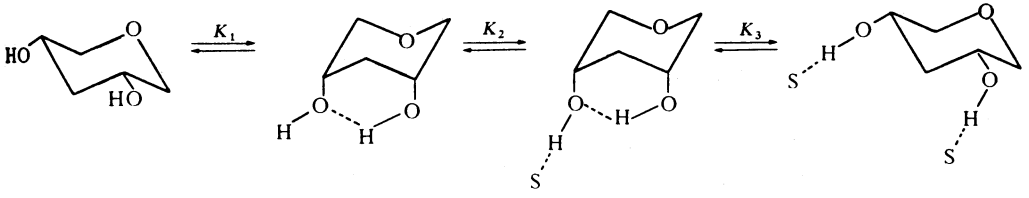


Figure 16. The effect of temperature on the molecular rotation of 1,2-*O*-isopropylidene-4-*O*-methyl-β-D-*xylo*-hexopyranulose in ethylene chloride containing varying amounts of pyridine[15].

for example, the curves obtained at 20 and 30° are shown in *Figure 16*. In order to obtain the thermodynamic data presented in *Figure 17*, differences over a temperature range of 20° were employed. It is seen that the lower the temperature the more pronounced the initial increase in rotation and the more rapidly it fell off with increasing amount of pyridine. Using abbrev-



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 17. Thermodynamic constants derived for conformational equilibria depicted in the form of abbreviated formulae for 1,2-isopropylidene-4-*O*-methyl-β-D-*xylo*-hexopyranulose when dissolved in ethylene chloride containing pyridines of different basicities[15].

iated formulae we consider the phenomenon to be a result of changes in equilibria as indicated in *Figure 17*.

The data presented in *Figure 17* were obtained by curve fitting using appropriate extrapolations. The equilibrium constant K_1 is taken as the equilibrium in the solvent ethylene chloride. The equilibrium constant K_2 refers to a stabilization of the intramolecular hydrogen bond through hydrogen bonding of the free hydroxyl group by the solvent. We see the driving force to be substantial and greater, the stronger the base. A large negative change in entropy is noted as expected for the engagement of a solvent molecule in the complex. It is to be noted that the intramolecular process represented by K_1 involved a relatively small change in entropy as expected. K_3 refers to the cleavage of the intramolecular hydrogen bond by the mass effect of excess dimethylsulphoxide. Here, again, a large negative entropy change is noted, as required for the process. Thus, we consider having achieved unequivocal evidence for the nature of the process and, as a corollary, the significance of the optical changes noted.

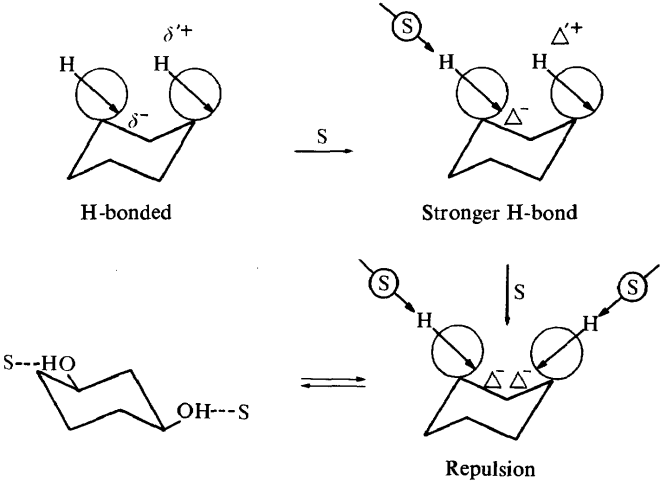


Figure 18. An interpretation of the apparent strengthening of a hydrogen bond between two hydroxyl groups when the free hydroxyl becomes hydrogen bonded to proton acceptor S.

We interpret these results as depicted in *Figure 18*[1]. The intramolecularly hydrogen-bonded conformer is the main species with ethylene chloride as solvent. When the free hydroxyl group of this conformer becomes bonded to dimethylsulphoxide, the polarization in the O—H bond increases the partial negative charge on oxygen. As a result, the intramolecular hydrogen bond is strengthened. In the presence of a large excess of dimethylsulphoxide both hydroxyls are forced into intermolecular hydrogen bonding. These do not stay in the *syn*-axial relationship since there now exists a strong repulsion between the two oxygen atoms. In *Figure 1*, similar effects in destabilizing *syn*-axial groups were noted both for water and dimethylsulphoxide. Therefore, water most certainly does not tend to stabilize the

hydroxyl group in this stereochemical relationship. This, of course, has been well demonstrated, for example by the work of Angyal in his studies of the extents of borate complexing of inositols[16] and is in direct contrast with the conclusions reached by Yamana[17].

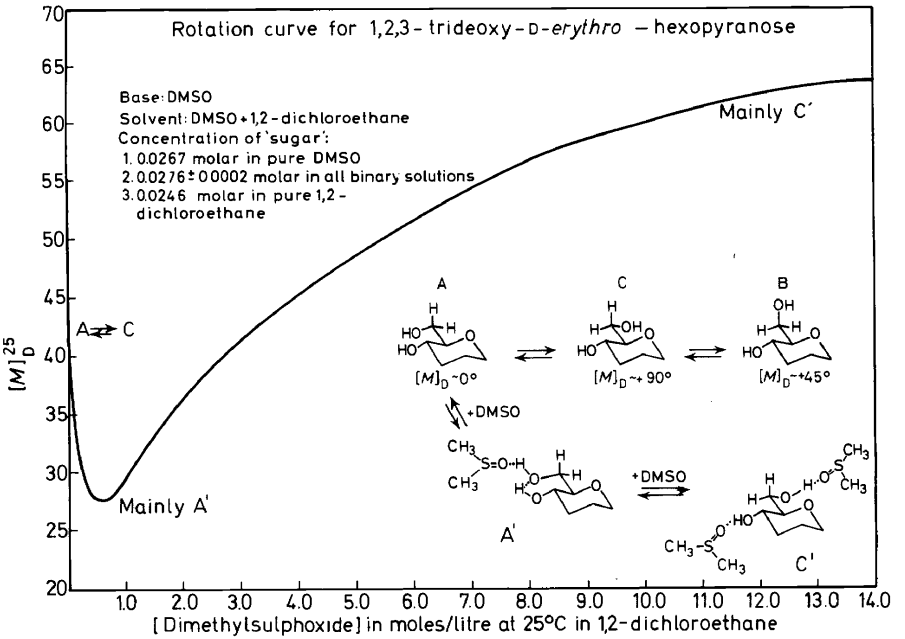


Figure 19. Effect of dimethylsulphoxide on the molecular rotation of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol in ethylene chloride[15].

The effect for the 1,3-diol represented by 1,2,3-trideoxy-D-*erythro*-hexopyranose is shown in *Figure 19*. In ethylene chloride from the magnitude of the rotation we expect substantial amounts of both conformations A and C. Conformation B is expected to make only a relatively small rotation because of its inherent instability as a result of the *gauche* interaction of the hydroxyl with the ring oxygen and its *syn*-axial-like relationship to the hydrogen at position 4. The indication that substantial amounts of conformation A is present clearly indicates that the intramolecular hydrogen bond between the two hydroxyl groups is preferred over that of the 6-hydroxyl group with the ring oxygen. On adding dimethylsulphoxide, the rotational change, for reasons already discussed, indicates an increase in the concentration of the solvated conformer A; namely, that designated A'. On increasing the dimethylsulphoxide concentration the rotation then rises to a strongly dextrorotation indicating a strong preference of the solvated conformer C' over the other possible solvated staggered conformations. Of course, the dipole–dipole interactions between the oxygen atoms in *gauche* relationship in conformer C' where both hydroxyls are hydrogen bonded to DMSO are expected to be much less favourable than in conformation C.

The molecular rotation of the compound in water is + 71 degrees and under these conditions the coupling constants of H_5 with the two H_6's are 2.5 and 6.1 Hz. Thus, the indication is clear that in water hydrated C is the preferred conformer. Otherwise the presence of both the high positive rotation and the large coupling constant are not compatible.

In conclusion, we contend to have gained experimental support in favour of the orientation of the hydroxyl of the hydroxymethyl group at the 5-position of pyranose structures in aqueous solution. Furthermore, we have gained experimental evidence that this conformational preference may be seriously altered depending on the nature of the solvation effects. I would now like to discuss briefly certain results we have gained related to possible solvation effects on the phenomenon we have termed the anomeric effect[2].

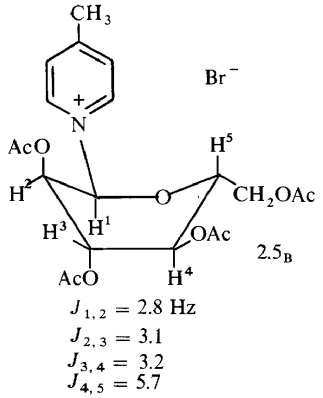


Figure 20. The boat conformation of *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide[19] as a result of the reverse anomeric effect[18].

I have alluded to solvation effects on the magnitude of the anomeric effect. We have achieved further evidence for this type of phenomenon through a study of the effect of protonation or alkylation of the imidazole group of a number of glycosyl imidazoles. This study arose out of the discovery of the reverse anomeric effect through the observation that the pyridine ring, of compounds such as the *N*-tetra-*o*-acetyl-α-D-glucopyranosyl derivative of 4-methylpyridine, is forced from the axial orientation normally found in α-gluco-pyranosides to an equatorial orientation[18]. James[19] has recently established that indeed this compound exists in the crystalline form in the boat conformation shown in *Figure 20*. There must, therefore, exist a powerful driving force for the pyridinium group to become equatorially oriented in such compounds. It is interesting to note that the NMR data given in *Figure 20*, agree well with the compound possessing this boat form in the dissolved, as well as the crystalline state. The driving force toward this conformation could be mainly of steric origin because of the large bulk of the pyridinium grouping. It was in an effort to separate steric from polar effects that we studied the imidazole glycosides[20].

Figure 21 depicts possible origins for the anomeric and reverse anomeric

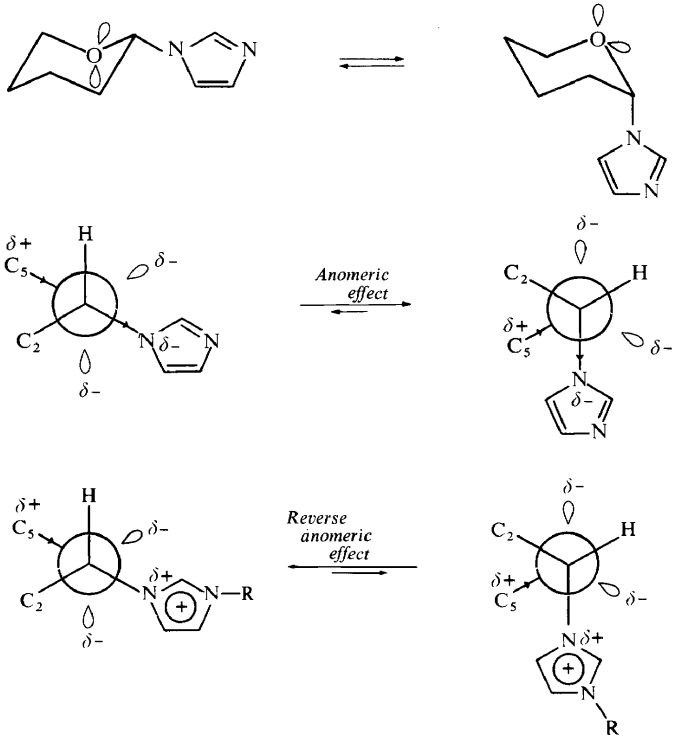
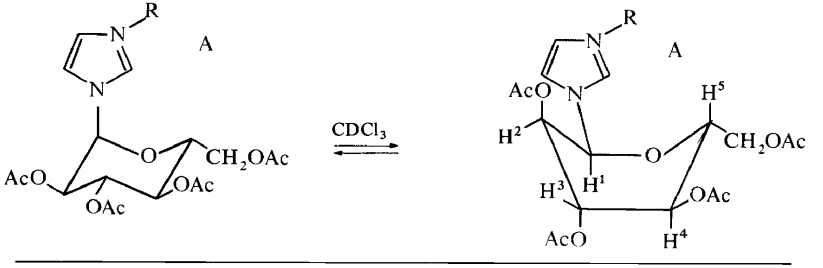


Figure 21. The possible origins of the polar anomeric and reverse anomeric effects.

effects. Should the nitrogen atom attached to the anomeric centre of an imidazole glycoside as a result of inductive effects cause a polarization of the C_1—N bond such that the nitrogen possesses a partial negative charge,



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 22. The effect on the conformational equilibrium for *N*-(tetra-*O*-acetyl-α-D-gluco-pyranosyl)-imidazole of either *N*-protonation or *N*-methylation of the imidazole ring[20].

then the glycoside would be expected to display an anomeric effect; that is, the more favourable disposition of the dipoles about the anomeric centre will be experienced with the imidazole group in axial orientation. On the other hand, if, by either protonation or alkylation of the imidazole ring, the ring adopts a positive charge, then the more favourable disposition of the dipoles about the anomeric centre should become that with the imidazolium group in at least *quasi*-equatorial orientation. Thus, the compound should experience the reverse anomeric effect. It was considered that such experiments with imidazole glycosides would unequivocally separate steric from polar effects on conformation since the protonation or alkylation is at a nitrogen atom remote from the pyranose ring. Thus, the steric effects should remain virtually constant.

We have established that *N*-protonation or *N*-methylation of the imidazole group of imidazole glycopyranosides invariably creates a driving force for an axial imidazole group to adopt a more equatorial-like orientation. The hexopyranosides studied were of the *gluco* and *manno* configurations. *Figure 22* illustrates the type of data obtained. Neither protonation nor methylation affected the conformational equilibrium to a detectable degree in the case of the β-glycosides[20].

As seen in *Figure 22*, the acetylated α-imidazole glucoside gave NMR parameters in chloroform in very good agreement with those expected for the compound in the C1 chair conformation. The large value for $J_{1,2}$ shows substantial steric interaction causing a torsional angle between the 1- and 2-protons somewhat smaller than 60 degrees and probably about 50 degrees. The addition of an equimolar amount of the weak acid acetic acid caused little change but on addition of an equimolar amount of the strong trifluoroacetic acid greatly reduced the magnitudes of the coupling constant between the 3- and 4-hydrogens and the 4- and 5-hydrogens. Better NMR evidence was obtained for the methiodide derivative. It is seen that the coupling constant for the 1 and 2 hydrogens is now much lower as are those for the 2,3, 3,4, and 4,5 hydrogens. Much more spectacular changes in the conformational equilibria were observed for the corresponding mannosides but the conclusion is the same and one which had to be logically expected; that is, that changes in the electrical character of the atom attached to the anomeric centre of a sugar will affect the magnitudes of the dipole interactions responsible for the anomeric effect and, depending on the direction of the charge separation, the change may provide a driving force for the aglycon to achieve the axial orientation as demanded by the anomeric effect, or the equatorial orientation as demanded by the reverse anomeric effect. We have gathered information that seems to show these considerations to be of prime importance in establishing the conformational preferences for nucleosides[20].

The subject of this lecture was chosen particularly to draw attention to the importance of solvation effects on conformational equilibria. The significant advances toward a thoroughly useful theoretical basis for the conformational analysis of carbohydrates and their reactions to be made in the future will inevitably be concerned with this aspect of the problem, an aspect which to date has been largely neglected.

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