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Origin and Consequences

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Based on a symposium cosponsored by the Division of Carbohydrate Chemistry of the American Chemical Society and the Organic Chemistry Division of the Chemical Institute of Canada at the Second Joint Conference of the ACS and CIC in Montreal, Quebec, May 29–June 2, 1977.

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Robert F. Gould, *Editor*

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the SERIES parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that in order to save time the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. As a further means of saving time, the papers are not edited or reviewed except by the symposium chairman, who becomes editor of the book. Papers published in the ACS SYMPOSIUM SERIES are original contributions not published elsewhere in whole or major part and include reports of research as well as reviews since symposia may embrace both types of presentation.

PREFACE

The term "anomeric effect" was introduced by Lemieux in 1958 as a result of a detailed study of the anomerization of acetylated pento- and hexo-pyranoses. The effect is well known to carbohydrate chemists, and refers to the tendency of an electronegative substituent at C-1 of a pyranoid ring to assume the axial rather than equatorial orientation, in contrast to predictions based solely on steric grounds. However, the phenomenon is not restricted to carbohydrate systems, but is displayed in many types of heterocyclic compounds. Thus, the investigation of the anomeric effect has been of considerable interest to a variety of chemists, namely, theoreticians, structural chemists, physical organic chemists, and synthetic chemists. Chemists from all of these areas participated in the Symposium on The Origin and Consequences of the Anomeric Effect. This symposium was the first symposium devoted exclusively to a discussion of the anomeric effect, and it provided a mechanism for interactions between the diverse types of chemists. The chapters in this volume are not merely the texts as presented at the symposium, but they also incorporate some new interpretations by the authors resulting from these interactions.

Several explanations have been proposed to account for the physical origin of the anomeric effect, and, in recent years, this aspect has been the subject of much debate and controversy. The first rationalization attributed the phenomenon to an unfavorable dipole–dipole interaction between the carbon–oxygen bonds on the ring and the bond from C-1 to the equatorial, electronegative substituent. Another interpretation is based on the suggestion that interaction of the ring-oxygen lone pairs with an antibonding σ-orbital of the ligand bond stabilizes the axial orientation of the ligand. The interaction between the oxygen p-type lone pair and adjacent σ-bonds in pyranoid derivatives is discussed by David; the results of ab initio STO-3G molecular orbital calculations on 2-chlorotetrahydropyran are described, and experimental evidence for such an interaction is presented. For several years S. Wolfe and his co-workers have been concerned with the stereochemical consequences of adjacent electron pairs and polar bonds. In the symposium, Wolfe, Whangbo, and Mitchell reported the results of a theoretical study of the magnitudes and origins of the "anomeric effects" associated with X and Y in XCH_2YH molecules. This paper could not be incorporated into this volume, but it appears in *Carbohydrate Research* (1979) **69**, 1. Ab initio molecular orbital calculations were performed at the STO-3G level

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on the series of molecules XCH_2YH in which $X = NH_2$, CH_3, OH, F, and Cl, and $Y = O$ and S. The "anomeric effects" were found to be Cl > F > OH as a function of X, and O > S as a function of Y. Molecules in which $X = CH_3$ and NH_2 exhibit "reverse anomeric effects." The results were analyzed by a quantitative perturbational molecular orbital (PMO) treatment which calculates orbital interactions between XCH_2 and YH in the case of the "anomeric effect," and between X and CH_2YH in the case of the "reverse anomeric effect," using fragments and fragment orbitals generated from the ab initio wave function. The stabilizing interactions between the lone pair of Y and antibonding orbitals of XCH_2, and between the highest lying orbital of X and antibonding orbitals of CH_2YH, were especially examined. In all instances, the trends in these stabilizing orbital interactions parallel the trends in the "anomeric" and "reverse anomeric effects," suggesting that, within the framework of the PMO model, such interactions can be regarded as the "origin" of these effects. Although both σ^* and π^* antibonding orbitals had to be considered to obtain quantitative agreement between the calculated orbital interactions and the total energy differences, only those interactions associated with σ^* varied significantly as X and Y were varied, in accordance with an earlier suggestion (Lucken and Altona).

The exo-anomeric effect has the same electronic origin as the anomeric effect, but it is specifically an orientation effect on the aglycon of a glycopyranoside. The effect may have an important influence on the conformational preferences of glycosides. The exo-anomeric effect and the conformational properties of glycosidic linkages are discussed in the article by Lemieux and co-workers. Probably the most important consequence of the effect concerns the relative disposition of the contiguous sugars of oligo- and polysaccharides; Hall and co-workers have addressed themselves to this problem, and report on the potential of proton spin–lattice relaxation rates for such studies.

The special electronic structure of the anomeric center in pyranoid derivatives results in experimentally significant differences in molecular geometry (e.g., as reflected by bond lengths and valence angles) about the anomeric carbon atom between α- and β-pyranoses and α- and β-pyranosides. In the article by Jeffrey, a discussion of the structural properties of the anomeric center in pyranoses and pyranosides is given, and a comparison is made of crystallographic data of some carbohydrates with the results of theoretical calculations performed on model compounds. Paulsen and co-workers also present x-ray crystallographic data in their discussion of some aspects of the conformational analysis of pentopyranosyl acetates, benzoates, and halides, in comparison with extensive conformational data compiled by Durette and Horton for these compounds in solution.

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The anomeric effect is of prime consideration in synthetic carbohydrate chemistry; in fact, some of the most important problems in this area, for example, the synthesis of oligosaccharides and carbohydrate-containing antibiotics, involve an understanding of the reactivity and properties of the anomeric center. In a detailed article concerned with the influence of reactant structure and solvent on glycoside synthesis, Schuerch explores how the anomeric effect of a number of reactants influences the course of kinetically controlled glycosidations.

Eliel has been involved for many years in heterocyclic conformational analysis, and has made important contributions to investigations related to the anomeric effect. In this volume, Eliel and Juaristi present important data for systems of the type X–C–C–Y (X, Y = heteroatoms), and discuss repulsive gauche effects. Attractive gauche effects have long been known, and a theoretical connection of the gauche effect with the anomeric effect has been made. However, the repulsive interactions were not well recognized until recently.

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The Interaction between the Ring-Oxygen *p*-Type Lone Pair and Adjacent σ-Bonds in Pyranose Derivatives

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In this lecture, the author will attempt not to mix two kinds of approach to the problem of the "Origin and Consequences of the Anomeric Effect", on one side the hard facts of experimental data and calculations conducted with clearly-defined approximations, and on the other side, semi-empirical theories which are more easily grasped and put to use with complex molecules. Discussion of these is reported to the last section. To begin with, the emphasis will be laid on the straightforward utilisation of molecular-orbital calculations to an understanding of some physical and chemical properties of pyranoses.

An *ab initio* STO-3G wavefunction calculation, including all electrons, has been developed with the aid of a program (1) to provide a theoretical basis for the following discussion of experimental results. The model, which is simplified, but represents an actual molecule, 2-chlorotetrahydropyran, contains the skeletal six-membered ring of a pyranose, with a chlorine atom linked to C-2 as the only substituent. Calculations were first made for the two possible chair conformations of this molecule (Table I), one with an equatorial, and the other one with an axial carbon-chlorine bond, with the same carbon-chlorine bond length in both cases. A calculation has also been made with a slightly longer C-Cl bond in the axial case, to follow the known experimental trend according to which axial bonds are longer than equatorial ones (2). The basic assumptions are given in Table I, where the ϕ's are the relevant atomic orbitals of the component atoms. Thus three sets of results were obtained, which correspond to the equatorial conformation, to the axial conformation with the same bond lengths, and to the axial conformation with a longer C-Cl bond. The computation yielded the C_{ij} matrix and the energies of each molecular orbital. The axial conformer was found to be more stable than the equatorial one by 1.2 Kcal, when the length of its C-Cl bond was 177 pm, and by 3.7 Kcal when the length of the C-Cl bond was 182 pm, in approximate agreement xith experimental evidence (3). Henceforward, when dealing with the axial conformer, only the figures corresponding to the

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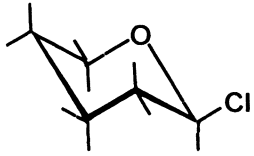
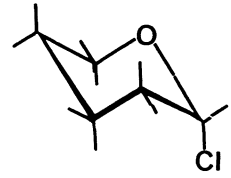
TABLE I

CALCULATION OF MOLECULAR ORBITALS OF 2-CHLOROTETRAHYDROPYRAN IN ITS TWO POSSIBLE CONFORMATIONS





GEOMETRY

Bond angles : 109°28'
Standard bond lengths for C-H, C-C, and C-O bonds
C-Cl bonds : equatorial, 177 pm ; axial, 177 and 182 pm

MOLECULAR ORBITALS

$$\psi_k = \sum_i C_{ik} \phi_i \quad ; \quad \text{energy } E_k$$

Bonding : k = 1, 2, ..., 32 Antibonding : k = 33, ...,64

METHOD

Ab initio STO-3G, giving all C_{ik} and E_k

geometry with relaxed C-Cl bond will be considered.

We shall now discuss some other properties of the molecule which can be derived in a fairly simple manner from the C_{ij} coefficients.

Nuclear Quadrupole Resonance Frequencies

The NQR frequencies of halogenated compounds are related in a very simple manner to the valency *p* orbital populations on the halogen atom by the Townes and Dailey formula (4). For a carbon–chlorine bond, the ^{35}Cl nucleus NQR frequency can be set equal to:

$$\nu = 55\ (b-a)\ \text{MHz} \qquad (1)$$

In this equation, *a* is the population of the $3p_z$ chlorine orbital contributing to the C–Cl bond and *b* is the average population of the two $3p_x$ and $3p_y$ orbitals on chlorine. Then in the case of the two possible conformers of 2-chlorotetrahydropyran the *computed* ^{35}Cl-NQR frequencies of equatorial and axial chlorine are found to be respectively ν_{eq} = 41.2 MHz and ν_{ax} = 37.9 MHz. The direct checking of these figures by measurement is not possible. The actual, *experimental* frequencies for per-*O*-acetylated glycopyranosyl chlorides lie, on the average, 6 MHz lower. However, many approximations are involved in the derivation of the Townes and Dailey formula, so it is generally considered as safer to compare very similar compounds. The difference between the calculated frequencies for the two conformations of 2-chlorotetrahydropyran is :

$$\Delta\nu = \nu_{eq} - \nu_{ax} = 3.5\ \text{MHz} \qquad (2)$$

Such is the order of the frequency difference we may expect between the two anomers, axial and equatorial, of a glycosyl chloride with one configuration. Looking at Figure 1, it may be seen that observed resonances for per-*O*-acetylated glycopyranosyl chlorides are distributed into two non-overlapping groups. The average values of the frequencies of the two groups differ by 2.6 MHz, in qualitative agreement with equation (2). Now NQR frequencies can only be measured on solid samples, and the solid state structure is known with certainty for only three compounds in Figure 1. Nevertheless, discussion of individual cases leaves little doubt that compounds in the higher frequency group have equatorial carbon–chlorine bond, and those in the lower, axial ones.

In the case of hexopyranosyl derivatives, it is generally accepted that the tendency of the side-chain to adopt an equatorial position is dominating in solution, implying that the compounds adopt the $^4\underline{C}_1(\underline{\underline{D}})$ or $^1\underline{C}_4(\underline{\underline{L}})$ conformations. This effect is observed even when it means that four *O*-acetyl groups must adopt axial positions, as in the case of the penta-*O*-acetyl-α-D-idopyranosyl chloride (5). In the case of α-compounds, the presence

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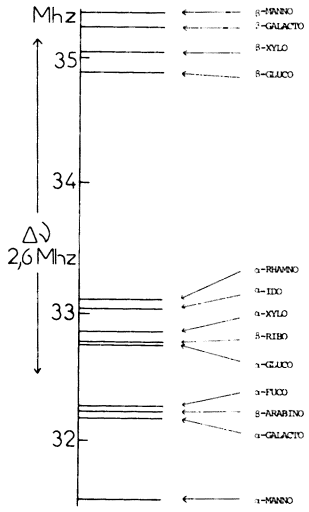

Figure 1. The distribution of the ^{35}Cl NQR frequencies of per-O-acetylated glycopyranosyl chlorides

of a chlorine atom in an axial position acts as an additional stabilizing contribution. Thus it is highly probable that these conformations are retained in the crystalline state,which means that α carbon-chlorine bonds are axial, and β carbon-chlorine bonds equatorial in this state. Now, for hexopyranosyl derivatives, the observed resonances of the α-chlorides are found in the lower, and those of the β-chlorides in the higher, frequency group.

On the other hand, pentopyranoses derivatives in solution do not exhibit the conformational effects observed with hexopyranose derivatives. In a chloroform solution of the β-D-*ribo* derivative, the $^{1}C_{4}(D)$ conformation with an axial chlorine is present at a 92.5 % concentration at room temperature and at 100% at -90°C (6). The same observation has been made for the β-*arabino* derivative. Moreover, *X*-ray studies have established that the bromine atom is axial in the bromo analogue of this compound (7). Thus it seems reasonable to extend to pentopyranose derivatives the statement according to which compounds in the lower-frequency group have a chlorine atom in the axial position, while compounds in the higher-frequency group have an equatorial chlorine atom.

This classification first met with scepticism, as one inference was that tetra-*O*-acetyl-β-D-xylopyranosyl chloride had a $^{4}C_{1}(D)$ conformation, with equatorial chlorine, in the solid state, and the only information available at that time was that the conformation of this chloride was more than 70% $^{1}C_{4}(D)$ in chloroform solution at room temperature (6). However, our prediction from NQR measurements was later on proved true by a solid-state structure determination (8).

Let us now come back to equation (1). So far we have used it to calculate ^{35}Cl NQR frequencies from the computed $3p_z$ orbital populations of two simplified models. Then we compared the calculated figures with the observed resonances of the more complicated pyranosyl chlorides. Conversely, we may start from these observed resonances, and use formula (1) to derive experimental values of the $3p_z$ orbital populations of pyranosyl chlorides, so as to gain direct insight into their electronic structure. If no double bonding is involved, and if a constant value of 2 is adopted bor b, we can accept as an *experimental observation* that on all pyranosyl chlorides examined, *the* $3p_z$ *orbital population on axial chlorine is higher than the* $3p_z$ *orbital population on equatorial chlorine by an amount of about 5% (up to 7% in the case of mannose).* Some people may consider that a statement in terms of ionicity i is more suggestive. Equation (1) may be written :

$$\nu = 55\ (1-i)\ \text{MHz} \qquad (3)$$

So that the statement now reads : *the axial carbon-chlorine bond on C-1 of a pyranose is more ionic by about 5 to 7% than the equatorial one* (9).

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The resonance frequencies of axial chlorides are very scattered. Especially striking are the positions of the *rhamno* and the *manno* compounds, which lie at both extremities of the range, although they have the same ring configuration. From solid-state structure determinations, it appears that the C-Cl bond in the *manno* compound is longer (Table II). Differences in the electronic, intermolecular environment of the chlorine atoms in these two compounds might be responsible for this great difference in ionicity, but this explanation is by no means definitive (10).

TABLE II
^{35}Cl NQR FREQUENCIES AND BOND LENGTHS IN PER-*O*-ACETYLATED HEXOPYRANOSYL CHLORIDES

Configuration	(MHz)	C-1—Cl, pm	Orientation
β-D-*xylo*	35.10	175.4(7)*	equatorial
α-L-*rhamno*	33.10	182.4(6)	axial
α-D-*manno*	31.57	185.6(8)	axial

* from Ref. (8).

Extension of these experiments to ^{79}Br was hampered by the instability of equatorial bromides. Only a few have been described in the crystalline state, and those we could prepare gave no signals. Results with axial bromides parallel those with the corresponding chlorides (11). The use of formulae (4) for ^{79}Br allows an estimation of the $4p_z$ orbital population on bromine and a comparison of ionicity between chlorides and bromides:

$$\nu = 385(b-a) \text{ MHz} \quad \text{and} \quad \nu = 385(1-i) \text{ MHz} \qquad (4)$$

The ^{79}Br NQR frequencies of four axial bromides may be found in Table III.

Carbon-13 Hydrogen Direct Coupling Constants

This study was suggested by the great wealth of experimental data already reported in the literature (12, 13, 14, 15, 16, 17). This led us to examine the percentage of *s*-character, ρ, of the various C-H bonds in the conformers of 2-chlorotetrahydropyran (18). This quantity may be calculated precisely with the use of formula (5). In this formula, b_r, $C_{(1s)r}$, ..., $C_{(2p_z)r}$ are the coefficients of the hydrogen atomic orbital 1*s*, and the carbon atomic orbitals (1*s*), ... , ($2p_z$) in the *r*-th molecular orbital, and $S_{(1s)}$, ..., $S_{(2p_z)}$ are the overlap integrals between this carbon (1*s*), ... , ($2p_z$) orbitals and the bound hydrogen (1*s*) orbital.

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TABLE III

A COMPARISON OF PER-*O*-ACETYLATED GLYCOPYRANOSYL HALIDES WITH THE α-D-GLUCO, α-D-XYLO, β-D-RIBO, AND β-D-ARABINO CONFIGURATIONS

Configuration		NQR Frequency (MHz)	p_z valency orbital population*	Ionicity
α-D-*gluco*				
$\|^{35}Cl\|$	chloride	32.76	1.405	0.40
$\|^{79}Br\|$	bromide	246	1.360	0.36
β-D-*arabino*				
$\|^{35}Cl\|$	chloride	32.149	1.415	0.41
$\|^{79}Br\|$	bromide	240	1.375	0.37
β-D-*ribo*				
$\|^{35}Cl\|$	chloride	32.064	1.416	0.42
$\|^{79}Br\|$	bromide	250	1.349	0.35
-D-*xylo*				
$\|^{35}Cl\|$	chloride	32.863	1.402	0.40
$\|^{79}Br\|$	bromide	246.3	1.359	0.36

* Assuming $p_x = p_y = 2$

$$\rho = \frac{\sum_{r}^{occ} b_r \left(C_{(1s)r} S_{(1s)} + C_{(2s)r} S_{(2s)}\right)}{\sum_{r}^{occ} b_r \left(C_{(1s)r} S_{(1s)} + \ldots + C_{(2p_z)r} S_{(2p_z)}\right)} \qquad (5)$$

The calculated values are reported in Table IV. The quantity ρ has been related (19) to the direct carbon-13 hydrogen coupling constant by a well-known relationship :

$$^1J_{CH} = 500\ \rho \qquad (6)$$

Indiscriminate use of this formula as a mean of assessing *s* character, especially in the comparison of carbons with substituents of different electronegativities has been much criticized in the past. However, numerous measurements to be discussed later show that $^1J_{CH}$ is fairly insensitive to the orientation and even to the nature of the β-substituent within one class of compounds. We shall make only qualitative use of the figures in Table IV to predict a general trend in the comparison of epimeric CH bonds. Thus, assuming that $^1J_{CH}$ and ρ vary in a parallel manner and that the indications given in Table IV can be extended to all pyranose derivatives with similar substitution, we can put forward the following generalizations :

a. For an anomeric pair, the equatorial coupling is higher than the axial one.
b. The same relationship obtains at C-5 of pentopyranoses. Actually, the calculated differences of *s* character between axial and equatorial CH bonds are practically the same at C-1 and C-5.
c. For the methylene groups of deoxypyranoses, the difference between the two constants should be fairly small, except in the case of derivative with axial aglycon, when the axial coupling is predicted to be slightly higher.

The predictions agree with published experimental results. Numerous measurements on anomeric pairs indicate that the difference J_{eq}-J_{ax} lies in the vicinity of 10 Hz. This property was first discovered in D-glucose (12) and further extended, mainly by Pedersen and Bock, to about twenty anomeric pairs of derivatives of D-glucose, D-galactose, D-mannose, 2-deoxy-D-*arabino*-hexose, D-glucosamine, D-arabinose. The distribution into two non-overlapping groups is reminiscent of the similar distribution of the ^{35}Cl NQR frequencies in pyranosyl chlorides. The lower NQR frequencies in axial chlorides reflect their higher 3*p* orbital population in the direction of the C-Cl bond. Our interpretation of the higher values of $^1J_{CH}$ is that this is a consequence of the higher *s* character of the equatorial CH bond, in qualitative agreement with formula (6).

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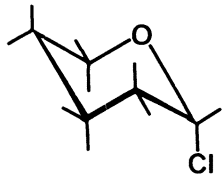
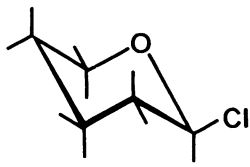
TABLE IV

THE *s* CHARACTER OF THE CARBON ATOM OF C–H BONDS



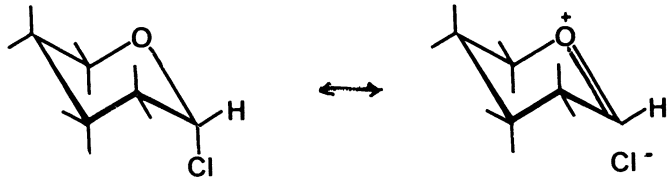
	C-2—H	C-3—H	C-4—H	C-5—H	C-6—H
ax.		28.0	27.8	27.3	26.1
eq.	33.3	27.3	27.5	27.2	31.6



	C-2—H	C-6—H
ax.	28.0	25.6
eq.		31.8

Inspection of Table IV indicates comparable ρ values for the two axial (or the two equatorial) bonds *on either side of the ring oxygen*. In the case of pentopyranoses, two constants differing by *ca.* 8 Hz have been found in most cases, and the lower one was interpreted as the axial one by the authors (15) who stress the effect of the ring oxygen.

The question may then arise whether these variations of *s* character with orientation are specific properties of pyranose-like compounds, or whether they are shared by ordinary ethers in a suitable conformation. We may recall here one popular pictorial interpretation of the Lucken-Altona theory :



This mesomeric picture gives an intuitive explanation of the higher *s* character of the C-H equatorial bond, as it indicates a measure of sp^2 hybridization in this case. One should then be tempted to draw a mesomeric picture showing similar delocalization in axial C-1—H and C-5—H bonds, and moreover to extend such representations to ordinary ethers. However calculations for methanol and dimethyl ether in the staggered conformation predict that the effect should be much smaller for these compounds. In this respect, we may mention that the practical significance of the interaction of the oxygen *p*-type lone pair with the antiperiplanar C-H bond in methanol has been recently questioned (20). So the effect discussed in this section may be restricted to the pyranose-like, acetal or mixed acetal type of compounds.

Chemical Reactivity at the Anomeric Hydrogen

The highest occupied molecular orbital (HOMO) (21) of our models are the ring-oxygen *p*-type lone pairs. These extend to other atoms, as shown in Figure 2. The similarity of the parts played by axial anomeric chlorine and axial anomeric hydrogen is very striking. Atoms with highest orbital populations in the HOMO should be the preferred site of attack by electrophiles. So the models suggest that the electrophilic attack of the axial hydrogen should be much easier than that of the equatorial one which is absent from the HOMO. In fact, several known reactions of pyranose derivatives involving the breaking of a C-1—H bond show remarkable selectivity :

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Aldopyranose anomers with axial C-1—H bond are more readily oxidized by bromine than those with equatorial C-1—H bond. A recent examination of this reaction led to the conclusion that "these rate differences could be reflected in relatively small ground state epimeric differences in the polarization of the CH bond, especially since the polarization could well be magnified in the transition state" (22).

These is even greater selectivity in the chromium trioxide oxidation of pyranose derivative in the conditions described by Angyal et al. (23) (24) : per-*O*-acetyl methyl glycosides with equatorial aglycon give ketoesters, by oxidation of the axial anomeric CH bond; those with axial aglycon have an equatorial anomeric CH bond which is not oxidized in the same conditions, such compounds being rather slowly converted into 1-*O*-formic esters. The reactivity of ozone is parallel to that of the chromium trioxide reagent (25).MO calculations on dihydroxymethane indicate a higher electron density in a CH bond antiperiplanar to an oxygen lone pair (27), and the authors point out that a similar increase may explain the preferential oxidation of β-glucosidic bonds by ozone. Evidence has been given that ozone can give complexes with tertiary CH bonds in hydrocarbons (26) and it is reasonable to assume that in similar cases, preferential complexation will occur on hydrogen with greater negative charge. Thus we assume that the transition state in these reactions is reactant-like. On the other hand, the next steps, that is ozone insertion into the CH bond, or the formation of an ion pair with a pyranosyl cation, may involve, an interaction with the glycosidic oxygen lone pair (25).

More recently, it has been shown that the β-anomeric form of the 4,6-*O*-ethylidenehexoses are oxidized to the corresponding lactones by Fétizon's reagent (28). The α-anomer of the galactose derivative is cleaved between C-1 and C-2 more rapidly than it is anomerized; the reactivity of the α-anomer of the glucose derivative on the other hand seems very low and anomerization to the β-form, followed by oxidation of this anomer to the lactone, occurs more rapidly than degradation. Now the key step in oxidation with Fétizon's reagent is considered to be an electrophilic attack on an hydrogen atom (29). So these results seem to be in keeping with the general theory.

A Survey of Current Interpretation of the Anomeric Effect

Dipole-Dipole Interaction One author has stated : "The factors considered ... show quite clearly that the effect is polar in origin" (30), but pointed out elsewhere that this is in some respect difficult to reconcile with the fact that the anomeric effect of bromine is higher than that of chlorine. Looking at Table III, one sees that bromides are less ionic than chlorides, may be not an unexpected result in view of the relative electronegativities of chlorine and bromine. In this

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respect, there is nothing exceptional in the properties of pyranosyl halides. Anticipating the next section, we may venture the idea that the effect is higher with bromides for the same reason for which organic bromides are as a rule more reactive than the corresponding chlorides: the more diffuse, less energetic carbon–bromine antibonding orbital can interact more efficiently with near nucleophiles.

A good experimental test of the dipole-dipole theory should be the estimation of the energy difference of anomeric glycosylate anions, which bear one unit negative charge on the anomeric oxygen atom. This should be fairly high if dipolar interactions are primarily involved but negligible if electron delocalization is the important factor, as a $C-O^-$ bond should be a very poor electron acceptor. Neuberger and Fletcher found that the D-glucosate ion at equilibrium in an aqueous solvent has a greater preponderance of the β-D-anomer than has the neutral sugar, the difference in ΔG being *ca* 0.3 Kcal.

This, however, is interpreted by the authors as a consequence of differential solvatation (31). When the lithium salt of 2,3,4,6-tetra-*O*-benzyl-D-glucose is prepared in benzene and tetrahydrofuran, there are equal proportions of both anomers, but we do not know whether equilibrium has been reached in this experiment (32).

Interaction between the Oxygen *p*-type Lone Pair and Adjacent σ-bonds The interaction between the oxygen *p*-type lone pair and the adjacent antibonding orbital of a carbon-halogen bond was first considered in 1959 by Lucken as a possible explanation of the abnormally low NQR frequencies of α-haloethers (33). Later on, Altona showed that the same phenomenon could explain the peculiarities of some bond lengths in similar compounds (2). The spectroscopic properties of pyranose sugars which we have described in the first two sections of this article seem to imply that the existence of such an interaction lies beyond all possible doubt in these molecules. It does not follow that they can explain the Anomeric Effect (34) (35). For this, we need a quantitative estimation of the stabilization introduced in a molecule by such interactions.

Molecular-orbital calculations for α-chloroanions, in the two conformations depicted in Figure 3a, indicate that the eclipsed conformation, on the left, is more stable than the bisected, on the right, by 15.7 Kcal (36). If we assume that the axis of the *p*-type lone pair of the ring oxygen in 2-chlorotetrahydropyran lies in the same direction as any axial bond in an ideal chair conformer, we may consider between this model sugar in its two possible conformations, and the α-chloroanion, an analogy which is stressed on Figure 3b. The eclipsed conformation of the chloroanion corresponds to the chair form of 2-chlorotetrahydropyran with axial chlorine, and is also the more stable. There is, however, a great difference in the magnitudes of the two effects,

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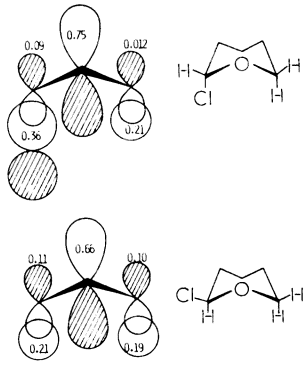

Figure 2. The HOMO of 2-chlorotetrahydropyran in its two possible chair conformations in the vicinity of the ring oxygen. Above, conformation with axial chlorine; below, conformation with equatorial chlorine.

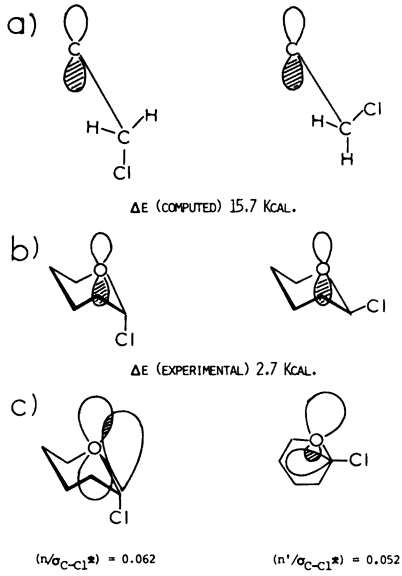

Figure 3. (a) Bisected and eclipsed conformations of an α-chloroanion; (b) corresponding conformations of 2-chlorotetrahydropyran; (c) the overlap between carbon–chlorine antibonding orbitals and the ring-oxygen lone pairs: left, axial C–Cl bond and p-type lone pair; right, equatorial C–Cl bond and σ-type lone pair

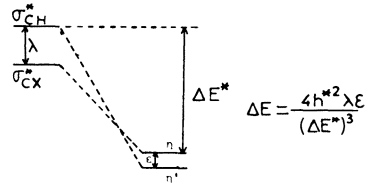

Figure 4. The important interactions in glycopyranosyl halides with axial C–Cl bond, and the corresponding expression for the energy difference between axial and equatorial anomers

the anomeric effect being much smaller.

What is true in the actual sugar model is that there are two lone pairs on oxygen, and that the *p*-type lone-pair axis is not parallel to the σ^*_{CCl} antibonding orbital, being in fact almost perpendicular to the bonds to C-2 and C-6. This is probably the reason why the angle between these bonds has always been found significantly higher than 109° in sugar halides. As a consequence, these is no great difference between the overlap of the *p*-type lone pair with the axial σ^*_{CCl} antibonding orbital in one conformation and the overlap of the σ-type lone pair with the equatorial σ^*_{CCl} in the other conformation, as shown in Figure 3c. The possibility of this second type of interaction had not been considered previously. Its effect is a stabilization of equatorial chlorine. We must also remember that in some respect axial hydrogen plays the same part as axial chlorine (Figure 2). Consideration of all relevant interactions led to the formula given in Figure 4 (37). One important novelty is the introduction of the energy difference between the σ and *p*-type lone pairs of the ring oxygen, a consequence of the fact that one pair stabilizes the conformation with axial chlorine and the other the conformation with equatorial chlorine.

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The Exo-Anomeric Effect

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In 1974, Lemieux and Koto (1), in a review concerning the conformational properties of glycosidic linkages, outlined the origins of the concept now generally referred to as the "anomeric effect" and which amounts to a special bonding effect found in acetal and related structures. The subject has received very extensive experimental and theoretical examination[3].

For the purposes of this lecture, the anomeric and exo-anomeric effects can be simply viewed as extra bonding provided to the carbon to oxygen bonds of acetals through participation of the unshared pairs of electrons when in specific orientations relative to neighboring bonds. The bond is strongest when a lone pair of electrons on an oxygen atom of the acetal grouping is anti-periplanar to the neighboring C–O bond. Although there exists no physical difference between the anomeric (2) and exo-anomeric effects (3), the two different terms for the same general phenomenon were introduced for the simple practical reason that the anomeric effect relates to the preference for the axial orientation of the aglycon of glycopyranosides, as illustrated by the conformational preferences of structures 1c and 1d over structures 1a and 1b for 2-methoxytetrahydropyran whereas the exo-anomeric effect relates to the preference for the aglyconic carbon (the methyl group carbon) to be in near syn-clinal orientation to both the ring oxygen and the anomeric hydrogen; that is, preferences for the conformations 1b and 1d over conformations 1a and 1c,

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[3] Since the presentation of this lecture, Wolfe, Whangbo and Mitchell [*Carbohydr. Res.* (1979) 69, 1] have given an excellent overview of the "anomeric effects," "*exo*-anomeric effects," "reverse anomeric effects" and analyzed the C-X and C-Y bond lengths in XCH_2YH molecules by a quantitative perturbational molecular orbital treatment.

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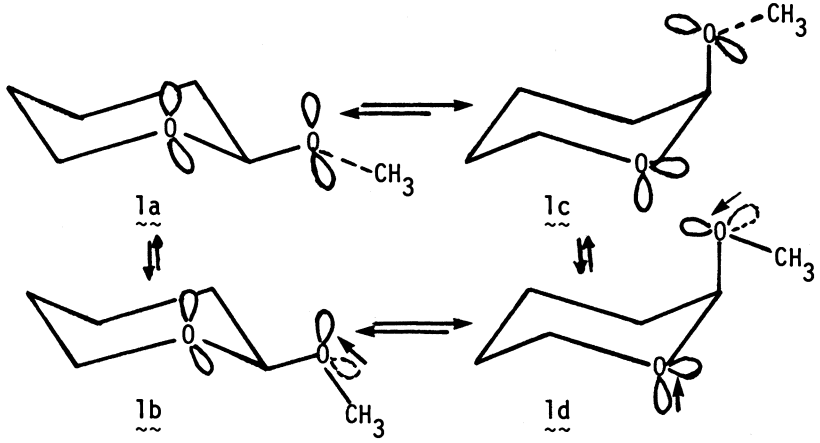
respectively (the arrow near an orbital means that it is anti-periplanar to a C–O bond). In other words, the anomeric effect provides a driving force which affects the conformational preference for the six-membered ring, whereas the exo-anomeric effect provides a driving force which influences the orientation preferred by the aglycon of a glycoside.



Although the origin and nature of the anomeric and exo-anomeric effects appear well appreciated, the importance of these effects on conformational equilibria, especially with regard to the influence of the exo-anomeric effect on the conformational preferences about glycosidic linkages, is not well appreciated. This paper is concerned with experimental investigations which were designed to help clarify this situation.

Jeffrey and coworkers (4) pointed out in 1967 that X-ray investigations showed that both the C1–O1 and C1–O5 bonds of a glycosidic linkage which has the aglycon in axial orientation appeared shorter than average and suggested that there may be a relationship between this observation and the anomeric effect. In 1972, Jeffrey, Pople, and Radom (5) predicted from *ab initio* molecular-orbital calculations on methanediol that the favored orientations and interatomic distances were in accord with the observed anomeric and exo-anomeric effects. "A comparison with experimental data from X-ray crystal-structure determinations, both for conformational angles and bond lengths, of eighteen pyranoses and methyl pyranosides shows agreement with the theory that is surprisingly good when consideration is taken of the experimental errors, the limitations of the theoretical model and the expected differences in the structures of the crystal and the isolated molecule."

At the time, there appeared to be no record in the literature of highly refined X-ray crystal structures for even two anomeric glycopyranosides. Therefore, it was decided to attempt to contri-

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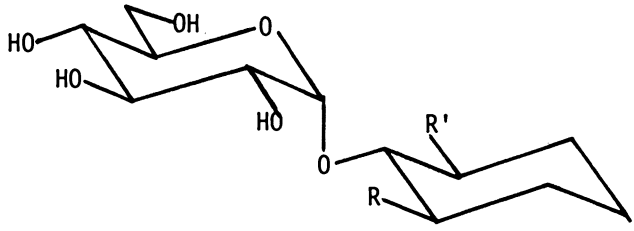
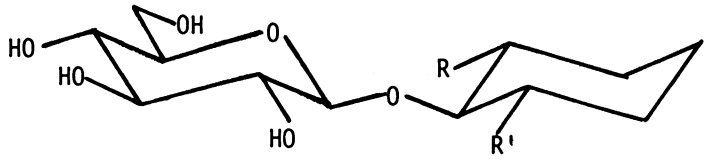


2 (R = R' = H)
4 (R = CH_3, R' = H)
6 (R = H, R' = CH_3)
8 (R = R' = CH_3)



3 (R = R' = H)
5 (R = H, R' = CH_3)
7 (R = CH_3, R' = H)
9 (R = R' = CH_3)

bute such data for at least two such compounds. The collaboration of Drs. Delbaere and James (6) was required in this regard and generously granted. It was decided to examine the crystal structures for 2-R-methylcyclohexyl α-D-glucopyranoside (4) and 2-S-methylcyclohexyl β-D-glucopyranoside (5) for the following reasons. First of all, it was desired to achieve accurate atomic parameters which could be used to assess, on the basis of hard-sphere calculations, the effect on the conformational preference of introducing methyl groups at the positions neighboring (the 2' and 6' positions) to the aglyconic carbon of the anomeric cyclohexyl D-glycopyranosides (2 and 3). Hydrocarbon aglycons were chosen to eliminate other than Van der Waals interactions between the aglycon and the glycosyl group. Secondly, it was hoped that the choice of a rather large, non-polar aglyconic group would help better separate the polar glucosyl groups in the crystal lattice and thereby perhaps eliminate effects on crystal structure that

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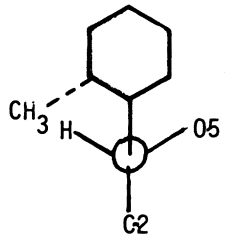
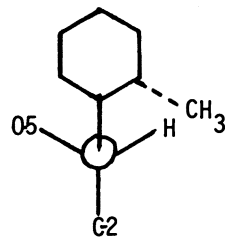
might arise because of a very close packing of highly polar structures only. Thirdly, as shown by the projection formulas 10 and 11, the choice of the trans-2-R-methylcyclohexyl aglycon for the α-anomer and of the trans-S-methylcyclohexyl aglycon for the β-anomer, provides "true" anomeric species in the sense that the steric relationships between atoms about the aglyconic and anomeric carbons are similar for both anomers.



10 (4)



11 (5)

Drs. Delbaere and James were able to refine the structures to the point that every hydrogen atom attached to carbon could be located and C–H bond lengths assigned to within ±5%. The C–C and C–O bond lengths were established to within about 0.4% and the valence angles involving heavy atoms within ±0.3. From this data, torsion angles between heavy neighboring atoms could be determined well within one degree. It was discovered that the α-anomer (4) was present in the unit crystal cell in two conformations; one, the A_{GT} form, which has O-6 syn-clinal to O-5 and anti-planar to C-4 and the other, the B_{GG} form, which has O-6 in syn-clinal orientation to both O-5 and C-4. Although this proved less than convenient to the X-ray crystallographers and, indeed, their resolution of the problem is highly commendable, the achievement of two structures for the same molecule is certainly interesting and useful in the context of this particular project since it shows that the atomic parameters of interest were not appreciably affected by the changes in environment and conformation of the forms in the same crystal.

The bond lengths reported in Table I are seen to be in excellent accord with expectations based on the anomeric and exo-anomeric effects in that strengthening of the C–O bonds at the anomeric center by delocalization of electron density from a p-orbital on an oxygen which is anti-periplanar to a C–O bond will shorten these bonds.

As seen from Table I, the O-1 to C-1' bonds, which join the glycosidic oxygen to the aglyconic carbon, have normal C–O bond lengths for both the anomers. The similar bonds at the other end of the acetal grouping; namely, the C-5 to O-5 bonds appear somewhat shorter than normal. The O-5 to C-1 bonds are definitely shorter

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TABLE I

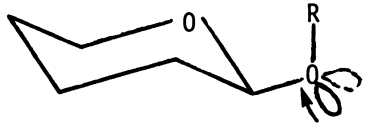
Bond Lengths, Å

	α-Anomer (4)		β-Anomer (5)
	A_{GT}	B_{GG}	
O1–C1'	1.442 (5)	1.447 (5)	1.444 (4)
C5–O5	1.426 (4)	1.439 (5)	1.440 (6)
O5–C1	1.425 (4)	1.419 (4)	1.426 (4)
C1–O1	1.405 (6)	1.400 (5)	1.391 (5)
C1–H1	0.93 (4)	0.99 (4)	1.01 (4)

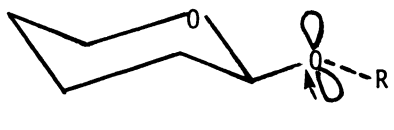
than normal. It must be recognized in this regard that there must exist a rather abrupt limit to the extent that bonds forming a six-membered ring can be shortened and not encounter serious transannular non-bonded interactions. Therefore, it may be considered that the reason for the much shorter lengths for the exo-cyclic C1–O1 bonds being definitely shorter than the endo-cyclic O5–C1 bonds is at least in part due to such a constraint. On the other hand, the relative electronegativities of the carbon atoms at both ends of the acetal linkage (C5 and C1') likely have an important influence in this regard. The important feature of the data presented in Table I is the fact that the exo-cyclic C1–O1 bond for the β-anomer appears definitely shorter than the similar bond for the α-anomer. This infers that the exo-anomeric effect is stronger for the β-anomer. That this should be so seems reasonable since delocalization of electron density from only one oxygen atom (the β-anomer) should be energetically more attractive, per C–O bond, than from two oxygen atoms (the α-anomer) to the same carbon. The fact remains that, as previously recognized by Jeffrey and coworkers (4), the glycosidic C1–O1 bonds are very substantially shorter (0.04–0.05Å) than normal C–O bonds (1.45Å). This appears to mean that the exo-anomeric effect is particularly well expressed in these glycosidic structures. Judging from the theoretical calculations made by Jeffrey, Pople, and Radom (5), as much as 4 to 6 kcal/mole of stabilization can be involved. If so, the exo-anomeric effect can be expected to overcome important non-bonded interactions in order to be most effectively expressed. Therefore, the X-ray crystallographic data require that the exo-anomeric effect be expected to have an important influence on the conformational preferences for glycosidic structures.

The theoretical requirement for a maximum exo-anomeric effect is that the aglycon be so oriented as to place a p-orbital of O1

in anti-periplanar orientation to the O5–C1 bond. Two such orientations are possible as displayed in structures 12 and 13. Structure 13 is expected to be energetically more favorable since the aglycon R is in syn-clinal orientation to H1 and O5 whereas in 12, R is syn-clinal to the grouping about C2 and O5. Lemieux and



12



13

coworkers (7) have examined a number of structures in an attempt to assess the abundance of conformer 12 but were unable to detect an appreciable amount even with the R group as small as a methyl group. Thus, it is apparent that 12 and 13 are separated by over 2 kcal/mole. This rather unexpected situation may be mainly the result of the short C1–O1 bonds present in the glycosides amplifying non-bonded interactions between groups attached to these atoms. Alternately, 13 may be more stable than 12 for stereoelectronic reasons not as yet well defined. The fact remains that there exists no experimental evidence for glycosides assuming but a negligible population of the conformer of type 12 and such conformers can be neglected, in normal circumstances, in considerations of the conformational preferences of glycosides.

It is of interest to note that the valence-bond angles about the anomeric center of the glycosides 4 and 5 are in good accord with expectations based on the anomeric and exo-anomeric effects in that the occurrence of these effects should tend to render the atoms involved more trigonal in character. Thus, as seen from Table II, C5–O5–C1, O5–C1–O1 and C1–O1–C1' bond angles are all substantially greater than the tetrahedral angle of 109.5° in the case of the α-anomer (4). However, for the β-anomer, for which the exo-anomeric effect only is displayed, both C5–O5–C1 and O5–C1–O1 are near the tetrahedral angle but C1–O1–C1' is much greater (115.1°) than 109.5°.

Thus, there can remain no doubt of the importance of the exo-anomeric effect to the orientation of an aglycon. How important is the driving force is the remaining problem. Obviously, if the effect is in the order of 5 kcal/mole, then it would likely dominate over all other factors that are likely to influence the torsion angle defined by O5 and the aglyconic carbon, the so-called ϕ^{O5} torsion angle (1). This would be a great convenience to conformational analyses about glycosidic linkages, since the problem would be essentially restricted to detecting the most favorable rotamer amongst those encountered in rotation about

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TABLE II

Valence-Bond Angles (±0.3°) About the Anomeric Center

	Compound		
	α-Anomer (4)		β-Anomer (5)
	A_{GT}	B_{GG}	
C5-O5-C1	114.5°	114.9°	110.3°
O5-C1-O1	112.3	113.1	108.2
C1-O1-C1'	114.8	115.1	115.1
C2-C1-O1	108.3	108.8	109.2

the O1 to aglyconic carbon bond; that is, a decision as to the most favorable ψ^H torsion angle (1).

Lemieux and Koto (1) assessed the non-bonded interactions by hard-sphere calculations which are present in the cyclohexyl-type α- and β-D-glucopyranosides 2 to 9 as a function of changes in ψ^H and ϕH torsion angles. As previously reported (1), the procedure was to arrive at the ψ^H torsion angle which would produce the minimum non-bonded interaction for a given ϕ^H. These minimum-energy values are plotted against the corresponding ϕ^H values in Fig. 1. It is seen that, for the β-glucopyranosides, the minimum value occurs in the range of ϕ^H values about +60°—the value considered most favorable for expression of the exo-anomeric effect. Therefore, although the hard-sphere calculations provide a rather primitive tool for comparing the energies of conformers, it does seem very probable that, for β-glycopyranosides, there will normally not exist any serious steric hindrance to the exo-anomeric effect. Consequently, it was considered that should the coupling constants between ^{13}C-aglyconic carbons of the β-glucopyranosides (3,5,7 and 9) and the anomeric hydrogens be measured, these would all have very nearly the same values. A Karplus-type relationship between vicinal ^{13}C and ^1H atoms had previously been established by Lemieux and coworkers (8,9).

As seen from Figure 1, the hard-sphere calculations infer a much different situation for the 2,6-dimethylcyclohexyl α-D-glucopyranoside (8) than for the β-anomer (9). For the α-anomer, the ψ^H torsion angle which provides the minimum energy calculated with ϕH = -60° has near 6 kcal/mole of net destabilizing non-bonded interactions whereas that with ϕ^H = -30° involves only about 1 kcal/mole of such interactions. Therefore, based on these calculations, it could be expected that unless the exo-anomeric

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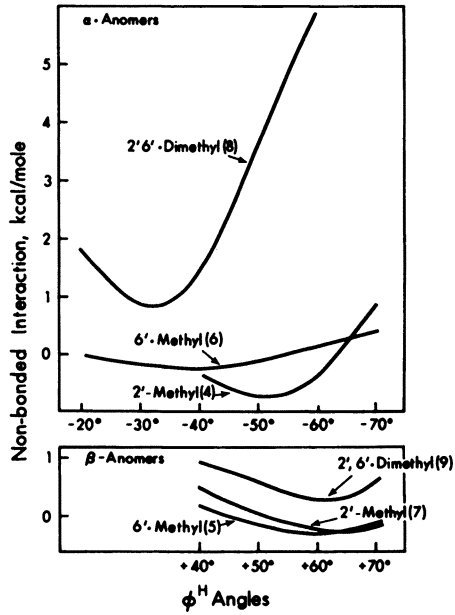

Figure 1. Nonbonded interactions estimated by hard-sphere calculations (1) to be present in the substituted cyclohexyl α- and β-D-glycopyranosides (Compounds 4 to 9) as a function of the ϕ^H torsion angle. The point for a specific ϕ^H angle corresponds to the conformation for which the $\psi^{H'}$ angle provided the minimum nonbonded interaction.

effect is sufficiently strong to maintain ϕ^H = -60°, the ϕ^H torsion angle which would provide the most favorable compromise could tend toward and perhaps achieve -30°.

As will be seen below, a case can be made that the Karplus relationship of the form $^3J_{CH} = 11 \cos^2\phi^H$ may usefully apply for the coupling of an aglyconic carbon with the anomeric hydrogen. On this basis, a change in the ϕ^H angle from -60° to -30° would cause a change in $^3J_{CH}$ from 2.8 Hz to 8.2 Hz. Thus, it seemed useful to attempt to determine the $^3J_{C'H}$ values for the compounds 2 to 9. At the time this research was conducted, the only approach that would provide these values with sufficient accuracy would be that involving the synthesis of the compounds enriched with ^{13}C at the aglyconic carbon position.

Following the procedure described by Reutov and Shatkina (10), reaction of 1,5-dibromopentane with 90% ^{13}C-enriched potassium cyanide provided the 1,5-dicyanide which was hydrolyzed to pimelic acid in aqueous hydrochloric acid (pure in 65% yield). This acid was then reacted with barium carbonate and the product was heated at 340° under distilling conditions for 4 hrs (10). The ether extract of the residue plus the distillate afforded cyclohexanone-1-^{13}C in 85% yield. Reduction with sodium borohydride provided the cyclohexanol-1-^{13}C from which the cyclohexyl-1-^{13}C β-D-glucopyranoside (3) was prepared by reaction with a five-fold excess of tetra-O-acetyl-α-D-glucopyranosyl bromide in methylene chloride and in the presence of mercury cyanide–mercuric oxide as promoters. The crude product was deacetylated using triethylamine in aqueous methanol prior to application to a column of Dowex 1-X8 (hydroxide form). Elution with water provided pure cyclohexyl-1-^{13}C β-D-glucopyranoside (3) in 35% yield. To obtain the α-anomer (2), compound 3 was anomerized to the tetraacetate of 2 using titanium tetrachloride in chloroform. Deacetylation followed by chromatographic purification on silica gel using benzene:ethyl acetate:ethanol (5:5:2) as solvent provided pure cyclohexyl-1-^{13}C α-D-glucopyranoside (2) in high yield.

A sample of racemic 2-methylcyclohexanone-1-^{13}C was prepared by methylation of the lithium cyclohexanolate-1-^{13}C with methyl iodide (11). The enolate was prepared from the cyclohexanone-1-^{13}C by way of the trimethylsilyl derivative following the procedure of House and coworkers (12). A sample of trans-D,L-2-methylcyclohexanol-1-^{13}C was then obtained by reduction of the ketone with lithium aluminum hydride in the presence of aluminum chloride as prescribed by Eliel and coworkers (13).

The D,L-2-methylcyclohexanone-1-^{13}C was also the precursor to the trans,trans-2,6-dimethylcyclohexanol-1-^{13}C required to prepare the β-glucoside 9 from which the α-anomer 8 was obtained by anomerization. The ketone was converted to racemic 2-hydroxymethylene-6-methylcyclohexanone-1-^{13}C in 30% yield following the procedure described by Johnson and Posvic (14). This product was in turn converted, except for the ^{13}C-label, to the known (15) 2-n-butylthiomethylene-6-methylcyclohexanone-1-^{13}C. Reduction and

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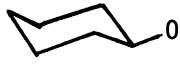
reductive desulfurization of this product to 2,6-dimethylcyclohexanone-1-^{13}C was achieved in 65% yield using Raney nickel in ethanol (13). The reduction of this ketone to afford trans,trans-2,6-dimethylcyclohexanol-1-^{13}C as a near equimolar mixture with the cis,trans-isomer was achieved by reduction in aqueous ether using sodium (15). This mixture was used to prepare the mixture of β-glucosides. Chromatography of the acetylated forms over silica gel using heptane:acetone (1:1) afforded trans,trans-2,6-dimethylcyclohexyl-1-^{13}C tetra-O-acetyl-β-D-glucopyranoside (the tetraacetate of 9). Although not entirely pure, the ^{1}H-n.m.r. spectrum, as compared to an authentic unlabelled sample, left no doubt as to its identity. Deacetylation then provided the desired trans,trans-2,6-dimethylcyclohexyl β-D-glucopyranoside (9). Anomerization provided the α-anomer (8) which was obtained pure by chromatography on a column of Dowex 1-X8 (hydroxide form) using water as eluent.

TABLE III

Estimates of ϕ^H for Alkyl D-glycopyranosides Assuming $^3J_{C'H} = 11 \cos^2\phi^H$

	$^3J_{C'H}$ (found)		ϕ^H (calc)	
	α-Anomer	β-Anomer	α-Anomer	β-Anomer
CH_3O	3.6	4.3	-56°	51°
CH_3CH_2O	3.9	4.4	-54	51
$(CH_3)_2CHO$	4.2	4.7	-52	50
$(CH_3)_3CO$	—	4.0	—	53
	3.8	4.2	-54	52
	3.5	3.3	-55	57
	4.1	4.1	-53	53
	4.2	3.2	-52	57

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In the cases of the trans-2-methylcyclohexyl α- and β-D-glycopyranosides (compounds 4–7), no effort was made to separate the diastereoisomers present in the preparations of each of the anomeric forms. Both the ^{1}H- and ^{13}C-n.m.r. spectra for the unlabelled compounds were known so that the assignments of the signals, from the spectra of the mixtures, could be unequivocally made.

Since the ^{13}C-enrichment of the aglyconic carbons of compounds 2 to 9, inclusive, was over 85%, the doublet of doublets observed for the anomeric hydrogens, knowing the values for $^3J_{H1,H2}$, provided the values for $^3J_{C1'}$. These values are presented in Table III together with those found in earlier studies (7) for simple alkyl glucopyranosides. It is seen that, for present purposes, the values can be accepted as inferring very nearly equal torsion angles for the C-1' and H-1 atoms. Certainly, the value of $^3J_{C1',H1}$ for trans,trans-2,6-dimethylcyclohexyl α-D-glucopyranoside (8) shows no evidence of possessing a substantially different ϕ^H torsion angle as might have been anticipated from the results of hard-sphere calculations presented in Fig. 1.

An assessment of what the $^3J_{CH}$ values presented in Table III may mean can be made using the approximate Karplus relationship $J = k\cos^2\phi$ (16) since evidence exists that J is near zero with $\phi = 90°$ (7,8,9). X-Ray crystallographic data (5) have provided ϕ^H values of 48° and 57° for the methyl β- and α-D-glucopyranosides, respectively. Assuming that these conformations are maintained in solution, and there can be no doubt that very close to these conformations are present (7), then the expression $^3J_{CH} = 11\cos^2\phi^H$ would anticipate $^3J_{C1',H}$ values of 4.9 and 3.3 Hz, respectively. These coupling constants are known to be 4.5 and 3.6 Hz, respectively. These data seem definitely to require that, in fact, the slope of the Karplus curve is steep in the region of $\phi = 50$–$60°$. That the value of $\phi = 180°$ can be as large as 11 Hz is supported by the fact that the average coupling ^{13}C-atoms in the methyl groups of dimethoxymethane with the syn-clinal and anti-periplanar hydrogen atoms of the methylene group is 6.6 Hz and an average coupling constant of 6.9 Hz is obtained using the expression $^3J_{CH} = 11\cos^2\phi^H$ and values of 60° and 180° for the two torsion angles. As seen from Table III, application of this expression to the coupling constants listed provides ϕ^H values in the range 55 ±5°. Thus, it appears definite that, in the absence of important extenuating circumstances such as crystal-field forces, specific solvation effects (3,17) and, perhaps in certain cases, specific intramolecular bonding effects such as a particularly strong hydrogen bond between the glycosyl group and the aglycon; the exo-anomeric effect plus the relatively (for rotamers about the C-1–O-1 bond) favorable steric environment will strongly maintain the ϕ^H torsion angle of glycopyranosides in the range |50°| to |60°|. For example, in the crystal lattice, the A_{GT} and A_{GG} isomers for the α-glucoside (4) possessed ϕ^H torsion angles of -44° and -50°, respectively, and the ψ^H torsion

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angles were 23° and 20°, respectively. However, for the crystalline β-anomer (5), the ϕ^H and $\psi^{H'}$ torsion angles were +32° and +33°, respectively. In view of the steric relationship between these compounds as displayed by the projection formulas 10 and 11, it seems evident that crystal-field forces can indeed strongly influence the conformation about a glycosidic linkage.

Therefore, it is considered that an attempt to establish the conformational preference for a glycopyranoside in solution should start by assuming a value of near |55°| for ϕ^H torsion angle. On this basis, the first approximation would involve assessing which $\psi^{H'}$ angle best accommodates the assumption regarding the ϕ^H angle. Any deviations in the final answer from a value for ϕ^H which is not favorable for the exo-anomeric effect would then require explanation. It may be noted that the observations made (17) regarding the conformation of the terminal trisaccharide for Lewis a human blood group determinant require this compound to possess ϕ^H torsion angles in accord with the exo-anomeric effect. As previously mentioned (1), many publications on the conformation of glycosidic linkages have not taken into consideration the exo-anomeric effect and, therefore, the conclusions reached may require revision.

Lemieux and coworkers (3) obtained evidence that hydration may have an influence on the anomeric and exo-anomeric effects. Painter (18) has studied the influence of cosolutes upon the conformations of carbohydrates in aqueous solution and concluded that the observations made are in general accord with influences on the anomeric and exo-anomeric effects. As recently commented by Painter (18) in connection with the mounting body of evidence that steric preferences are not normally too large for the exo-anomeric effect to have an important influence upon conformation about the C-O bond, "If this is generally true, it is evident that the exo-anomeric effect must be a phenomenon of very considerable, if not profound, biological significance."

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Abstract

Evidence is provided, based in highly refined X-ray crystallographic data and in the near constant (3.7±0.5 Hz) value for the coupling of ^{13}C-atoms at the aglyconic carbon with the anomeric hydrogen for a number of model α- and β-D-glucopyranosides, that, in accordance with expectations based on steric considerations plus the exo-anomeric effect, the torsion angle (ϕ^H) defined by the aglyconic carbon and anomeric hydrogen of glycosides is strongly maintained in the range ±55° ±5° with the aglyconic carbon in syn-clinal relationship to the ring-oxygen atom. Thus, it can be expected that, in general, the conformational preference for a glycosidic linkage can be usefully approximated by thus assigning the ϕ^H angle and considering only those conformations which arise from rotation about the glycosidic oxygen to aglyconic carbon atoms.

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3

Proton Spin-Lattice Relaxation: A New, Quantitative (?) Measure of Aglycon–Sugar Interactions (*1*)

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It is now well known that the anomeric effect of many substituents can dominate the conformations favoured by carbohydrate derivatives in solution. For example, all the pentopyransyl fluoride (2) and chloride derivatives (3) favour in solution that conformation in which the halogen substituent has an axial orientation - even in the case of the β-D-xylopyranosyl derivatives where the $^1C_4$-chair conformation requires that all the substituents be axially oriented. Interesting as it is, the conformational importance of the "anomeric effect" is exceeded by the conformational control exercised by the "exo-anomeric effect" over the relative orientation of an aglycon with respect to the sugar ring of a glycoside (4); and obviously the most important outcome of the "exo-anomeric effect" concerns the relative disposition of the contiguous sugars of oligo- and poly-saccharides. In this discussion we shall direct attention to the potential of proton spin-lattice relaxation rates (R_1-values) for studying the conformational outcome of the exo-anomeric effect, both of simple glycosides and of disaccharides.

Since the first report (5) of a pronounced configurational dependence for the anomeric protons of monosaccharides in aqueous solutions, studies in this laboratory have shown (6), (7), (8), (9) that proton R_1-values have a variety of stereospecific dependencies and reflect the overall steric environment of a proton. In the following discussion, a brief introduction to the phenomenon of spin-lattice relaxation and to the measurement of proton R_1-values by pulse Fourier transform methods, will be

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followed by a brief summary of the protocol we have developed for fully evaluating proton R_1-values in terms of the dipole-dipole relaxation mechanism and hence the solution geometry of the molecule of interest. As will be seen, a critical component of this protocol involves the determination of specific inter-proton relaxation contributions and two of the methods for so doing will provide the major emphasis for the remainder of the discussion.

The process of spin-lattice relaxation involves the interchange of magnetic energy - magnetisation - between the magnetic nuclei of interest (the spins) and their surrounding environment (the lattice), and the spin-lattice relaxation rate (the R_1-value) is the first-order rate constant for this energy interchange. There are many methods for measuring R_1-values but the simplest, the so-called two-pulse, inversion recovery method (10) which is currently available on most pulse Fourier transform n.m.r. spectrometers, suffices for all proton relaxation studies of sugars. This experiment is best visualised with respect to the vectorial model shown in figure 1. At thermal equilibrium between the spins and the lattice, the total magnetisation of the set of nuclei of interest can be represented by a vector directed along the z-axis. Application of a short pulse of radiofrequency power of the appropriate frequency and of sufficient total energy content to tip the magnetisation vector through 180° (a 180°-pulse) serves to "heat" the spins and thereby to destroy their thermal equilibrium with the lattice. This excess energy then "leaks" from the spins to the lattice and this is accompanied by a decrease in the intensity of the magnetisation vector which, after passing through a null (zero intensity), recovers back along the +z-axis to its original thermal equilibrium value: and it is the rate constant of that process which we wish to measure. Since the n.m.r. instrument which is to be used for this experiment has been designed not to detect any component of magnetisation aligned along the z-axis, it is necessary to apply a second pulse - a 90° "monitoring" pulse - to tip the magnetisation vector either up, or down, into the x,y-plane where it induces a signal into the receiver of the spectrometer and is thereby detected.

In practice then, the measurement of an R_1-value involves application of a 180°-pulse to heat the spins, a known delay time (t) during which some of that excess energy is allowed to leak into the lattice and, at the end of that delay time a 90°-pulse to monitor the intensity of the residual magnetisation.

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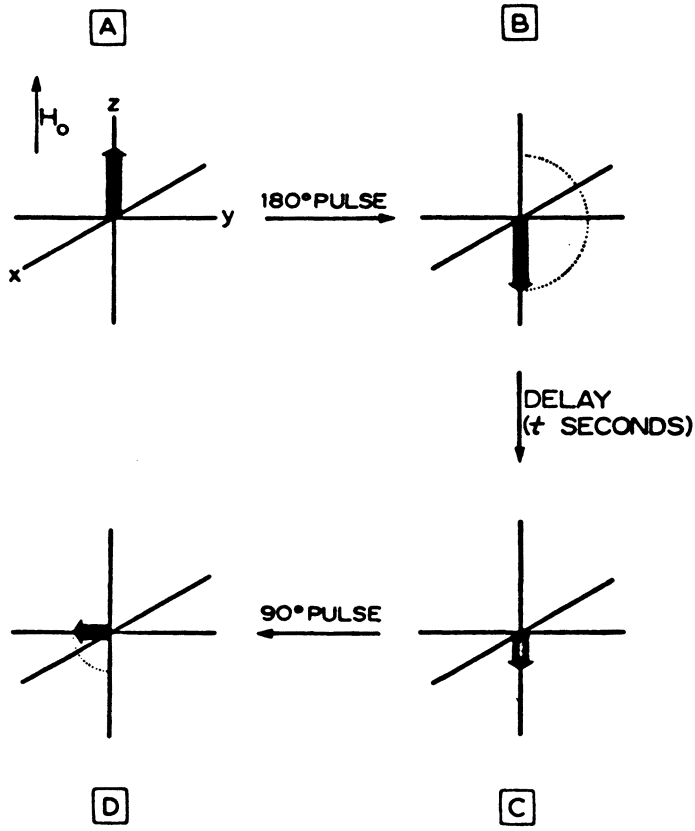

Figure 1. Digram of the rotating reference-frame model of a spin-lattice relaxation time measurement using a two-pulse sequence. (A) The magnetization of the nuclei is at thermal equilibrium with the lattice. (B) This magnetization has been inverted through 180°-pulse; the nuclei are no longer in thermal equilibrium, and the spin-lattice relaxation causes the magnetization to revert back along the z-axis towards its equilibrium position. After a known delay time (t), the residual magnetization (C) is assayed by the application of a 90°-pulse which tips the magnetization up into the x–y plane (D).

The spins are then left to relax during the pulse delay time (PD) back to full thermal equilibrium with the lattice and then the same two-pulse sequence is applied, but with a different value for the interval(t) between them. This process, depicted schematically below, is then repeated for an appropriate number of

$$(180°\text{-}t\text{-}90°\text{-}PD)_n$$

"t-values" and the R_1-values obtained from the relationship between "t" and the magnetisation intensity. Since the pulses of a Fourier-transform instrument are applied simultaneously to all the proton resonances of the sample, the R_1-values of all the protons can be determined from one experiment.

In principle there are many different processes whereby spin-lattice relaxation is mediated - all of them have in common the interaction of the rapidly processing nuclear spin with some fluctuating magnetic field generated in the lattice - but fortunately in practice the relaxation of most protons of sugars occurs exclusively by just one mechanism, the dipole-dipole mechanism. We shall return somewhat later to the full formulation of this mechanism, but for the present the somewhat simplified version shown in [1] will reveal why this particular relaxation mechanism is relevant to studies of the anomeric effect. According to [1] the efficiency with which a donor

$$R_1(j\rightarrow i) \propto \frac{\gamma_j^2 \gamma_i^2}{r_{j\rightarrow i}^6} \tau_c\ (j\rightarrow i) \qquad [1]$$

nucleus j contributes to the relaxation of a receptor nucleus i by the dipole-dipole mechanism is proportional; (a), to the square of the magnetogyric ratios (γ_j,γ_i) of both j and i (since for a normal sugar, the only nuclei having a substantial value of γ are the protons, this feature means that other protons in the same molecule will provide the dominant "lattice"); (b), to the inverse sixth power of the distance ($r_{j\rightarrow i}$) between j and i (which means that the relaxation of any proton will be dominated by its nearest neighbours); and (c), to the motional correlation time ($\tau_c(j\rightarrow i)$) of the vector joining j→i. *This rather simplified formulation contains implicitly the design concept whereby measurements of interproton relaxation contributions can be used to estimate interproton distances:

*Strictly this is only true for a molecule tumbling in the extreme narrowing limit.

If in the molecule of interest two (or more) separate donor protons (j1,j2) each contribute to the relaxation of a common receptor proton i, then relationship [2] holds, and it is the

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$$\frac{r_{j1\rightarrow i}}{r_{j2\rightarrow i}} = \sqrt[6]{\frac{R_1(j2\rightarrow i)}{R_1(j1\rightarrow i)}} \qquad [2]$$

practical realisation of this formulation that has been our concern. As will be seen, all necessary stages have been completed and the sole outstanding consideration is the effect of anisotropic motion of the molecule on the validity of [2]; clearly [2] is valid strictly only if $\tau_c(j\rightarrow i)$ is identical for all $j\rightarrow i$ vectors; we shall return to this point at the end of the discussion.

Practical realisation of the potential of [2] as a measure of the ratios of interproton distances for molecules in solution involves a sequence of four distinct stages.

1. It is necessary to establish the extent to which the dipole–dipole mechanism contributes to the relaxation of each proton.
2. It is necessary to determine the magnitudes of the individual interproton relaxation contributions.
3. It is necessary to establish whether or not the molecule is tumbling isotropically in solution.
4. Finally the simple arithmetic implicit in [2] can be performed.

We shall now briefly summarise aspects of stages 1 and 2 as they pertain to the principal theme of this presentation - determination of the relaxation contributions between the protons of an aglycon and those of a sugar.

Stage 1 involves first the determination of the R_1-value of the protons (A) of interest by the two-pulse sequence (10) referred to earlier, in which the perturbing, 180°-pulse is applied in a non-selective fashion to all the proton resonances (we shall refer to this value as the non-selective relaxation rate R_1^A (ns)). Then the two-pulse sequence is repeated, except that now the 180°-pulse is applied selectively (11), (12) to just the A-resonance, and the recovery back to thermal equilibrium of the magnetisation of A is monitored with the usual non-selective 90° pulse; this gives a new relaxation rate constant, the single-selective relaxation rate ($R_1^A(\widetilde{A})$ where $\widetilde{A}$ indicates the nucleus which has been subjected to the single-selective 180° pulse). It is a trivial matter to show (11), (13), that if the relaxation of A comes exclusively via dipole–dipole interactions with the other protons in the molecule then.

$$\frac{R_1^A\ (ns)}{R_1^A\ (\widetilde{A})} = 1.5$$

In the event that A relaxes exclusively via other mechanisms this ratio will be unity, so the dynamic range of the ratio above is 1.0 - 1.5.

The spectra shown in figures 2 and 3 illustrate the determination of the non-selective and single-selective relaxation rates for the anomeric proton of methyl β-D-glucopyranoside, and the resultant data, along with that of the α-anomer and the two trideuteriomethyl glucosides is given in Table I. It is quite clear that the relaxation of the anomeric protons of all four sugars occurs exclusively via the dipole-dipole mechanism, and it is appropriate to comment at this juncture that this is, in our experience, invariably so far all the sugars we have studied since 1972.

Having established in this way that the relaxation of the protons is dipole-dipole in origin it is then appropriate to factor out from the composite relaxation rates, the magnitudes of the individual interproton relaxation contributions, the so-called ρ-values, or at least those ρ-values which are relevant to the study in hand. Thus in the case of a methyl glucoside we may wish to evaluate the relaxation contribution which the methyl protons make to the anomeric proton ($\rho OCH_3 \rightarrow H\text{-}1$).

We have developed or evaluated four separate methods whereby these values can be measured and these are, briefly, as follows:

1. Apply some form of regressional analysis to the non-selective R_1-values.
2. Compare the non-selective R_1-values of the normal compound with those of its specifically deuterated counterpart.
3. Extend the single-selective pulse method to a double-selective equivalent in which the perturbing pulse is now applied selectively to any two resonances (11), (12), (13).
4. Use the interproton nuclear Overhauser enhancement experiment (14).

The remainder of this discussion will be concerned with the first two of these methods.

There are a number of ways of using the regressional analysis method and the simplest, and for many purposes the most powerful of these can be illustrated with respect to the determination of the relaxation contributions which the anomeric proton of the galactopyranose residue of V receives from the protons of the fructofuranose ring. The non-selective R_1-values

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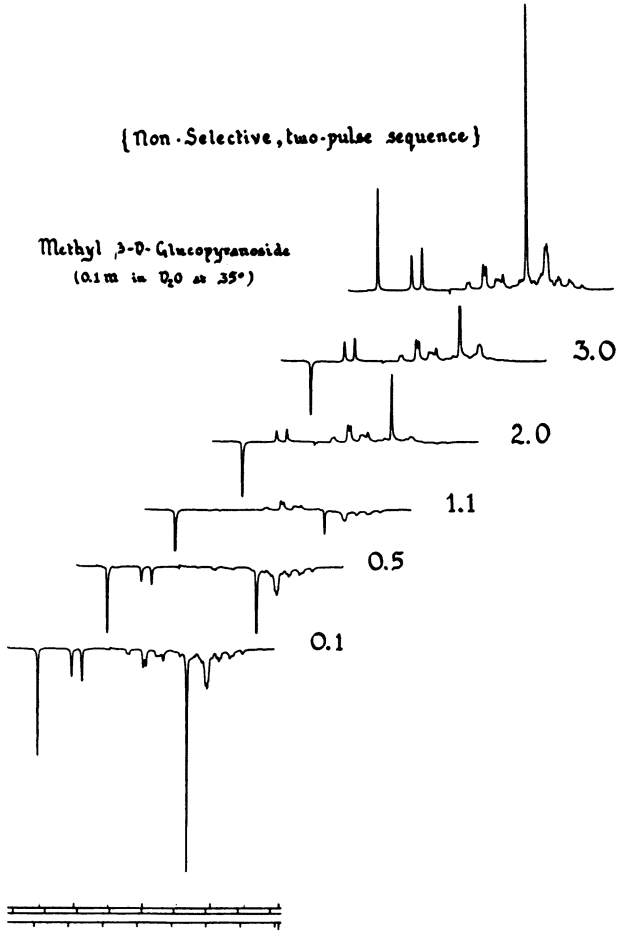


Figure 2. Partial 100-MHz ^1H NMR spectra of methyl β-D-glucopyranoside, showing a two-pulse nonselective inversion–recovery determination of the spin-lattice relaxation rates. All spectra were monitored as follows: pulse width (90°) = 67 μsec; number of transients = 8, pulse delay = 10 sec, acquisition time = 4 sec, data points = 4096, spectral width = 500 Hz, and sensitivity enhancement = 1.5 sec. The time interval (sec) between the 180°- and 190°-pulses are indicated to the right of the respective spectra.

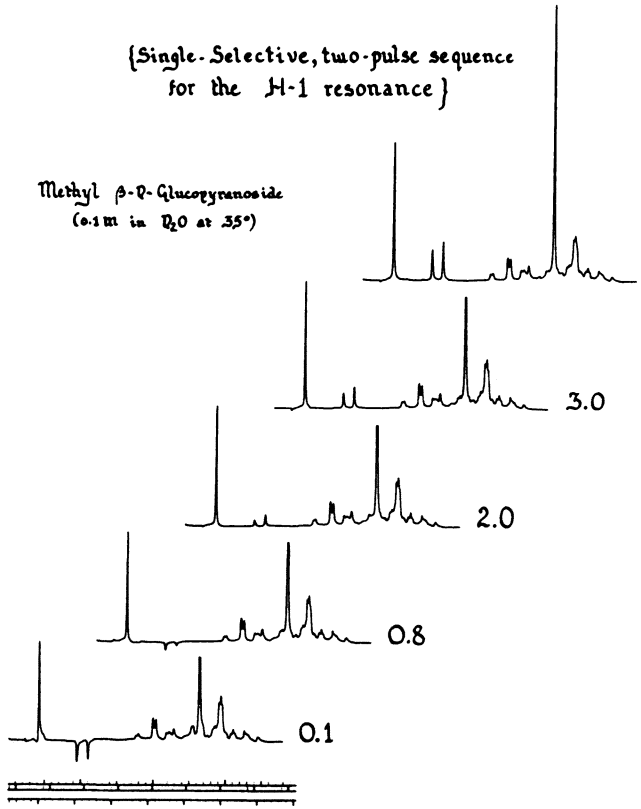
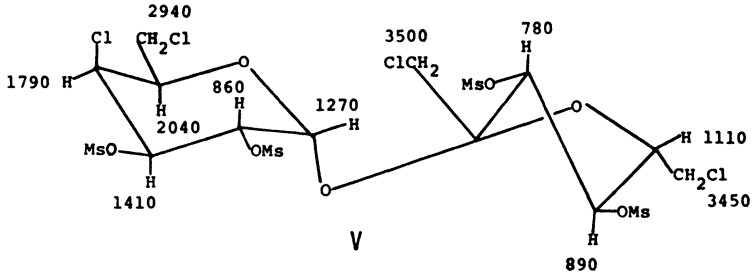


Figure 3. Partial 100-MHz ^1H NMR spectra of methyl β-D-glucopyranoside, showing the single selective determination of the spin-lattice relaxation rate of H-1 using a two-pulse inversion–recovery sequence. All spectra were monitored as for those in Figure 2 except for pulse delay = 15 sec. The duration of the selective 180°-pulse was 38 msec (13 Hz bandwidth). The time interval (sec) between the selective 180°- and 90°-pulses are indicated to the right of each spectrum.

TABLE I. Spin-lattice Relaxation Rates[a] ($10^{-3}sec^{-1}\pm5\%$) for the Anomeric Protons of Methyl Glucopyranosides[b].

Compound	R_1 (ns)	$R_1(\widetilde{H\text{-}1})$	R_1 (ns)/$R_1(\widetilde{H\text{-}1})$
Methyl β-D-glucopyranoside (I)	640	430	1.49
Trideuteriomethyl β-D-gluco-pyranoside (II)	420	280	1.50
Methyl α-D-glucopyranoside (III)	330	220	1.50
Trideuteriomethyl α-D-gluco-pyranoside (IV)	210	140	1.50

[a]Measured using the three-pulse, inversion-recovery sequence with a Varian XL-100 (15) spectrometer fitted with a Varian 620 L (16K) computer and a Linc Tape unit (model CO600); the R_1 values were calculated from the semi-log plots, using a least-square fit, computer program. [b]0.1 molar solutions in D_2O (99.7%) at 35° (degassed).



V

$(10^{-3}sec^{-1})$(15) for the ring protons of the galactopyranose residue can be formulated in terms of the various interproton ρ-values, and as a result of the inverse sixth power dependence on distance, we need only consider nearest-neighbour interactions, namely gauche interactions (ρ_g), 1,3-diaxial interactions ($\rho_{a,a}$) and for the anomeric proton, the inter-ring contribution (ρ inter ring)(strictly we cannot ignore the vicinal trans-diaxial interactions but it is simpler to so do for the present argument). Remembering that because we are dealing with protons which are relaxing via the dipole-dipole mechanism it is necessary to use 2/3 of the experimentally determined relaxation rates when calculating ρ-values, we can make the following formulations.

$$\frac{2}{3} R_1^{H-1} (ns) = \rho_g + \rho_{inter\text{-}ring} = 0.850 \text{ sec}^{-1}$$

$$\frac{2}{3} R_1^{H-2} (ns) = \rho_g = 0.570 \text{ sec}^{-1}$$

$$\frac{2}{3} R_1^{H-3} (ns) = \rho_g + \rho_{aa} = 0.940 \text{ sec}^{-1}$$

$$\frac{2}{3} R_1^{H-4} (ns) = 2\rho_g = 1.190 \text{ sec}^{-1}$$

$$\frac{2}{3} R_1^{H-5} (ns) = \rho_g + \rho_{aa} + \rho_{5,6} = 1.360 \text{ sec}^{-1}$$

Thus the R_1-value of H-2 gives us immediately an estimate of ρ_g (0.570 sec^{-1}) and since these interproton relaxation contributions are mutual, the additional relaxation experienced by H-1 can only come from the protons of the fructofuranose ring, estimated as being 0.280 sec^{-1}, which is ca. 40% of the total relaxation experienced by H-1. Although this simple arithmetic is founded on an extremely simplistic premise it is interesting to note that the above estimate of ρ_g from the H-2 resonance is in excellent accord with the value from H-4 (0.595 sec^{-1}). Furthermore, the ratio of ρ_g/ρ_{aa} = 0.582/0.358 = 1.63 is in excellent

accord with the ratio anticipated on the basis of an undistorted $^4C_1$-conformation for the galactopyranose ring.

Although the above approach obviously has some serious limtations, its application to molecules for which a reasonable number of the individual non-selective R_1-values can be measured, offers much the best return for time invested. Nevertheless for many purposes a more accurate, explicit approach is required and for the practicing chemist having access to a conventional pulse F.t. instrument the selective deuteration (16), (17) method has much to commend it.

In order to fully appreciate this approach it is necessary to return to the formulation (18) of the dipole-dipole mechanism.

For a two spin system, the explicit formulation (18) for dipole internuclear relaxation contribution, $\rho(j\rightarrow i)$, between a receptor nucleus i and donor nucleus j, is shown in [3].

$$\rho(j\rightarrow i) = \frac{\gamma_j^2\gamma_i^2h^2}{r_{j\rightarrow i}^6} I_j(I_j+1)\left[\frac{2}{15}\frac{\tau_c}{1+(\omega_i-\omega_j)^2\tau^2} + \frac{6}{15}\frac{\tau_c}{\omega_i^2\tau_c^2} + \frac{12}{15}\frac{\tau_c}{1+(\omega_i+\omega_j)^2\tau_c^2}\right] \quad [3]$$

where γ_i = gyromagnetic ratio of receptor nucleus i
γ_j = gyromagnetic ratio of donor nucleus j
h = Planck's constant/2π
$r_{j\rightarrow i}$ = internuclear separation between i and j
I_j = total spin quantum number of donor nucleus j
τ_c = rotational correlation time of $r_{j\rightarrow i}$
ω_i = Larmor precession frequency of i
ω_j = Larmor precession frequency of j

In the extreme narrowing limit $(\omega_i+\omega_j)\tau_c<<1$ and expression [3] simplifies to

$$\rho(j\rightarrow i) = \frac{4}{3}\frac{\gamma_i^2\gamma_j^2h^2}{r_{j\rightarrow i}^6} I_j(I_j+1)\tau_c \quad [4]$$

Consider now a system in which the two interacting nuclei are both protons; now expression [4] simplifies to

$$\rho(H\rightarrow H) = \frac{4}{3}\frac{\gamma_H^4h^2}{\gamma_{H\rightarrow H}^6} \tfrac{1}{2}(\tfrac{1}{2}+1)\tau_c \quad [5]$$

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If proton j is replaced by a deuterium substituent, [4] reduces to

$$\rho(D\rightarrow H) = \frac{4}{3} \frac{\gamma_H^4 \gamma_D^2 h^2}{r_{D\rightarrow H}^6} 1(1+1)\ \tau_c \qquad [6]$$

Taking the ratio of [6]/[5], we obtain

$$\frac{\rho(D\rightarrow H)}{\rho(H\rightarrow H)} = \frac{8}{3} \frac{\gamma_D^2}{\gamma_H^2} = 0.063 \qquad [7]$$

Expression [7] is only strictly valid if the replacement of the proton by deuterium causes no alteration in the internuclear separation and if $\tau_c(^1H\text{-}^1H)$ is identical to $\tau_c(^1H\text{-}^2H)$, both of which are perfectly reasonable assumptions. Thus replacement of a proton by a deuterium reduces the dipole-dipole relaxation contribution from that site to ca. 6% of its original value.

Let us now see how this explicit relationship, in conjunction with the initial non-selective relaxation rates, can be used to determine the contribution which the methoxyl protons of a methyl glycoside make to the relaxation of the anomeric proton H-1.

For the methyl glycoside

$$R_1^{H\text{-}1}(ns,OCH_3) = \frac{3}{2}[\rho(OCH_3\rightarrow H\text{-}1) + \rho(others\rightarrow H\text{-}1)] \qquad [8]$$

For the trideuteriomethyl glycoside,

$$R_1^{H\text{-}1}(ns,OCD_3) = \rho(OCD_3\rightarrow H\text{-}1) + \frac{3}{2}\ (others\rightarrow H\text{-}1) \qquad [9]$$

Taking the difference between [8] and [9]

$$\frac{3}{2}\rho(OCH_3\rightarrow H\text{-}1)-\rho(OCD_3\rightarrow H\text{-}1)=R_1^{H\text{-}1}(ns,OCH_3)-R_1^{H\text{-}1}(ns,OCD_3) \qquad [10]$$

Substituting expression [7] into [10] gives

$$\rho(OCH_3\rightarrow H\text{-}1) = 0.696[R_1^{H\text{-}1}(ns,OCH_3)-R_1^{H\text{-}1}(ns,OCD_3)] \qquad [11]$$

Clearly the same treatment can be equally well developed for the single selective R_1-values of H-1.

$$\rho(OCH_3\rightarrow H\text{-}1) = 1.067[R_1^{H\text{-}1}(\tilde{H}\text{-}1,OCH_3) - R_1^{H\text{-}1}(\tilde{H}\text{-}1,OCD_3)] \qquad [12]$$

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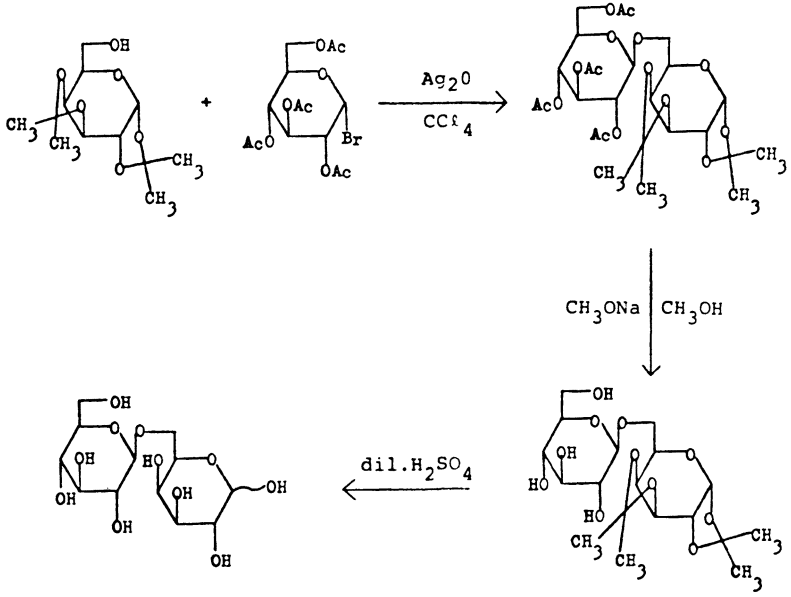
Referring back to the R_1-values given in Table I it is a trivial matter to calculate the relaxation contributions between the methoxyl protons and H-1 for the two methyl D-glucopyranosides and these values are listed below in Table II. Not surprisingly, there is excellent agreement between the values calculated from the non-selective and single-selective relaxation rates.

Because of the poor dispersion of the proton spectra of the methyl D-glucopyranosides in aqueous solution the above deuteration experiment only identified the methoxyl relaxation contribution into the H-1 resonance. However, in the case of the corresponding tetra- acetates, all of the proton resonances were separately resolved and hence a direct comparison could be made of the non-selective R_1-values of all protons of the protio - and deuterio-methyl glycosides. As it happened, only the H-1 and H-5 resonance evidenced any detectable relaxation contribution from the methoxyl group and these values are summarised in Table III.

Encouraged by the above experiments, it was decided to extend this selective deuteration approach to a disaccharide and for reasons of synthetic convenience, β-D-glucopyranosyl-(1→6)-D-galactopyranose and its 6,6-di-deuterio analog were synthesised (see Flow Sheet I). The non-selective relaxation rates for the



Flow Sheet 1. Synthesis of β-D-glucopyranosyl-(1→6)-D-galactopyranose.

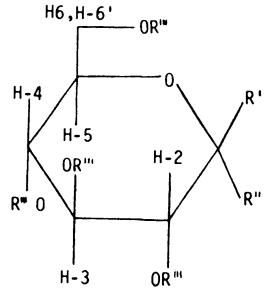
TABLE II. Calculated Values for the Relaxation Contributions ($10^{-3}sec^{-1}$) which H-1 Receives from the Methoxyl Group, $\rho(OCH_3 \rightarrow H\text{-}1)$.

Compound	From R_1 (ns)	From $R_1(\widetilde{H\text{-}1})$	Average Value	$\frac{\rho(\beta OCH_3 \rightarrow H\text{-}1)_{av}}{\rho(\alpha OCH_3 \rightarrow H\text{-}1)_{av}}$
(I)	153	160	157	
				1.9
(III)	84	85	85	

TABLE III. Non Selective Spin-Lattice Relaxation Rates[a] ($10^{-3}sec^{-1}$ ±10%) for the Protons of Methyl Tetra-O-trideuterioacetyl-D-glucopyranosides[b].

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	OCH_3
VI	270	230	150	170	360	670	650	380
VII	160	220	150	180	290	680	670	
VIII	340	160	200	170	480	690	650	360
IX	230	160	190	180	460	680	630	

[a]Measured using the three-pulse, inversion-recovery sequence with a Varian XL-100 (15) spectrometer fitted with a Varian 620 L (16K) computer and a Linc Tape unit (model CO600); the R_1 values were calculated from the semi-log plots, using a least-square fit, computer program. [b]0.1 molar solutions in deuteroacetone at 35° (degassed).



VI R' = H, R" = OCH_3, R''' = $OCOCD_3$

VII R' = H, R" = OCD_3, R''' = $OCOCD_3$

VIII R' = OCH_3, R" = H, R''' = $OCOCD_3$

IX R' = OCD_3, R" = H, R''' = $OCOCD_3$

anomeric protons of these two derivatives are summarised in Table IV. Several sets of intercomparisons can be made. At the non-reducing centre, the pronounced (ca. twofold) differential between the R_1-values for H-1α and H-1β is typical of pyranose derivatives (5) and reflects the greater relaxation contributions which the axial proton at C-1 receives from H-3a and H-5a as compared with its equatorial counterpart (5). More relevant in the present context is the enhanced relaxation of the non-reducing anomeric proton when compared with its counterpart at the reducing centre. The obvious source of this enhanced relaxation is the protons on the reducing ring and confirmation that the protons on C-6 constitute a substantial proportion of that relaxation comes from the R_1-value of H-1'β in the 6,6-dideuterio derivative. Simple calculations following the procedure outlined earlier indicate that the ρ-value between H-1'β and the C-6 protons is 0.470 sec^{-1}, which is 26% of the total relaxation of H-1'β.

Of course it remains that the observed R_1-value for H-1' of the dideuterio derivative is still 0.110 sec^{-1} (ca. 10%) faster than that of the protio derivative and reasons for this must be sought. One possibility is that the remaining enhancement is due to the relaxation contributions emanating from the other remaining protons of the galactopyranose ring; this could be checked experimentally by further deuteration experiments. The alternative explanation is that the disaccharide molecule as a whole is tumbling anisotropically and hence that the correlation times (τ_c-values) of the protons of the reducing ring are different from those of the non-reducing ring. This is a serious possibility because we know (19), (20) from studies of the ^{13}C R_1-values of other disaccharides that their tumbling motion exhibits a small anisotropic component.

It is both necessary and appropriate to terminate this article on this point. It will be recalled that the principle proposal under discussion here is that by evaluating the magnitudes of interproton relaxation contributions it is possible to use relationship [2] to evaluate the magnitudes of interproton distances .... and for glycosides and oligosaccharides this can be performed experimentally either by regressional analyses or by selective deuteration. It is clear that this proposal has considerable practical reality and that qualitative geometric relationships can be readily established. What is unclear at this time is the possibility of fully quantitating the relationship [2], which only holds in its simplest form if the motional correlation times $\tau_c(j \rightarrow i)$ of all $j \rightarrow i$ vectors are identical. All available evidence to date is that simple monosaccharides do tumble essentially isotropically in solution and hence that [2] can be applied directly and quantitatively; more complex monosaccharides and disaccharides do (19), (20), (21) have a detect-

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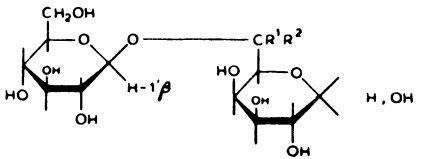
TABLE IV. Non Selective Spin-lattice Relaxation Rates (10^{-3} sec^{-1} ± 5%) for the Anomeric Protons of Disaccharides[a].



(X) $R^1 = R^2 = H$
(XI) $R^1 = R^2 = D$

Compound	H-1 (reducing residue)			H-1' (non-reducing residue)	
	H-1α	H-1β	Ratio H-1β/H-1α	H-1'β	Ratio H-1'β/H-1β
X	450	1060	2.36	1820	1.72
XI	450	950	2.11	1150	1.21

[a] 0.1 molar solutions in D_2O (100.0%) at 35° (degassed).

TABLE V. Ratios of the Interproton Distances for the Ring Protons of X.

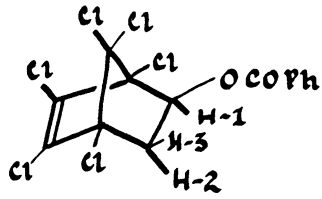
Ratio	Experimental Value[a]	From Model[b]	By Calculation[c]
$\frac{r_{1,2}}{r_{2,3}}$	1.26	1.28	1.25
$\frac{r_{1,3}}{r_{1,2}}$	1.32	1.27	1.28
$\frac{r_{1,3}}{r_{2,3}}$	1.67	1.63	1.60

[a] Based on R_1-values. [b] Dreiding Stereomodels.

[c] Using the programme COORD (ref. 23) and assuming an eclipsed, sp^3-hybridised system with C-C = 1.536Å, C-H = 1.107Å and H-C-H angle 109.3°.

able anisotropic component in their tumbling motion but it is too early for us to decide whether or not this is sufficient to influence the simple use of [2]; obviously the accuracy of distances based on [2] will be less certain for molecules which are tumbling anisotropically, but we have no details of the scaling factors involved.

Clearly though, even a purely qualitative evaluation of the geometric influences of the anomeric and exo-anomeric effects based on a new independent measurement tool, has some considerable relevance and further studies on this topic are being actively pursued at this time. And to leave the more sceptical readers of this article with some positive food-for-thought, we summarise below in Table V the interproton distances, determined (22) by proton relaxation measurement, for an organic molecule, the bicycloheptene portion of XII which is, according to all presently available criteria, tumbling isotropically.



XII

Abstract

A summary is given of the potential of proton spin-lattice relaxation rates as a measure of the steric interactions between the protons of a sugar and those of an aglycon. Particular emphasis is given to the use of specific deuteration as a direct method for quantifying inter-proton relaxation contributions. The method is illustrated for methyl α-D-glucopyranoside, its β-anomer and for β-D-glucopyranosyl-(1→6)-D-galactopyranose.

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4

The Structural Properties of the Anomeric Center in Pyranoses and Pyranosides

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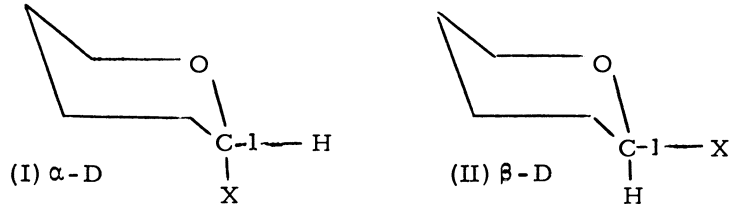
The anomeric carbon atom, C-1, in pyranose and furanose sugars is unique in that it is the only carbon atom in these molecules which is bonded to two atoms which are more electronegative. These more-electronegative atoms necessarily have lone-pair electrons. It is the electronic structure which arises from the electronegativity differences and the presence of these lone-pair electrons that gives rise to the special reactivity and structural properties of the anomeric carbon center.

In this paper, we will be concerned with the molecular geometry, as described by the torsion angles, bond lengths and valence angles associated with the anomeric carbon atom in α and β pyranosyl compounds, I and II. The Pauling



"electronegative difference" (1) between the anomeric carbon, C-1, and the ring oxygen O-5 on one side and the aglycon, X, on the other, leads to a depletion of electrons at the carbon atom; the C–O and C–X σ-bonds are polarized in the direction of the more electronegative atoms. Pauling's rule (1) concerning the "essential electronegativity of atoms" then requires that there be some compensatory electronic shift to re-establish the balance of nuclear and electronic charge in the region of the central carbon atom. This is achieved by a "back-donation" of electrons from the lone-pair orbitals of the flanking oxygen and

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X atoms towards the carbon atom. The electron density of the lone-pair orbitals of X is reduced in order to increase that of a non-bonding O–C σ* orbital, thereby increasing the electron density in the region of the carbon; similarly the electrons from the lone-pair orbitals of the ring oxygen will "back-donate" into a corresponding non-bonding C–X orbital. Since the spatial relationships of the 2p atomic orbitals and the C–O and C–X bonds involved are different for the α and β configurations, there are differences in the energies and bond dimensions between the α and β configurational isomers. When X is a glycosidic substituent, there are also energy and structural differences between different conformational isomers relative to the glycosidic bond. This electronic perturbation from ideal electron-pair bonding will be greatest when the hetero-ring atom is the most electronegative divalent atom, i. e. oxygen, and X is the most electronegative monovalent atom, i. e. fluorine. In consequence, the "anomeric effect" was first clearly identified by Chü and Lemieux (2) when they observed that the α-configuration was the major product in the preparation of pyranosyl fluorides. A remarkably perceptive publication by Edwards (3) had previously pointed out the importance of the spatial arrangement of the oxygen lone-pairs as a basis for explaining the differences in stability to acid hydrolysis of α and β methyl pyranosides.

When X is a hydroxyl or glycosidic group, the lone-pair interaction with the carbon p orbitals, which are involved in the non-bonding orbital, is sensitive to the torsion angle of the glycosidic C-1—O-H or C-1—O-R bond. In consequence, preferred conformations relative to the glycosidic bond are observed in pyranoses and pyranosides in the crystalline state (4) and in solution (5). This effect has been called the "exo" anomeric effect (5), although it is basically a manifestation of the same aspect of electronic structure as the anomeric effect. In 5-thio-pyranoses, where the electronegative difference between the ring hetero-atom and carbon is very small, the anomeric and exo-anomeric effects should be less important and probably non-existent in 1,5-dithio-pyranosides. Some crystal structural work on the 1,5-dithio-ribopyranosides supports this view (6).

Other investigators have studied this aspect of hetero-atom electronic structure in contexts other than carbohydrate chemistry (7-9). The most generally accepted descriptor is the "gauche-effect", originally prompted by the need to explain the unexpected 'gauche' conformation of fluoromethanol (10). The same type of configurational and conformational directing properties can be anticipated, for example, in the carboranes

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containing the bonding sequence C–B–C, since the boron atom is flanked by two or more electronegative atoms, while being deficient in electrons to fill its own 2s and 2p orbitals.

Quantum-mechanical discussions of the "gauche effect" and the "anomeric and exo-anomeric effect" have been published (10-13) which provide a more complete description of these electronic interactions, and the electrostatic repulsions between the vicinal lone-pair electrons.

The most conspicuous structural consequences of the anomeric effect are in the conformational angles of the glycosidic bonds. The change in potential energy with rotation about the glycosidic bonds (Figure 1) calculated by ab-initio quantum-mechanical methods (13) on the model compounds discussed later in this article, suggest that there are energy barriers of 2 to 5 k.cal/mole. In consequence, the glycosidic torsion angles lie within quite narrow ranges for the methyl α and β pyranosides (14). This anomeric conformational energy potential will also apply to the glycosidic linkage-bonds in the (1→n) linked oligosaccharides and its effect is observed in many of the di- and trisaccharides which have been studied by crystal-structure analysis (12). It should be included in the conformational potential-energy maps of polysaccharides containing such linkages.

More subtle differences also occur between α and β pyranoses and pyranosides in the bond lengths and valence angles associated with the hemi-acetal and acetal moieties. These small structural differences of less than 5 pm and 5° do not affect the overall dimensions of a monosaccharide to a large degree, but when multiplied in a linear polysaccharide polymer, they could lead to significant differences in the models used to interpret the somewhat marginal X-ray diffraction data available from oriented fibres and gels. The use of averaged molecular dimensions for monosaccharide components, which do not take into account these small differences, could lead to ambiguities in the interpretation of fibre diagrams by the model-building methods.

More importantly, from the point of view of theoretical chemistry, these small differences provide an excellent criterion with which to test the "nearness to reality" of a particular "ab-initio" quantum-mechanical calculation. This assumes that the best theoretical treatment is that which gives the best agreement with the structural data, which is somewhat of an over-simplification. Some of the wave functions used in the ab-initio calculations are believed to give reliable values

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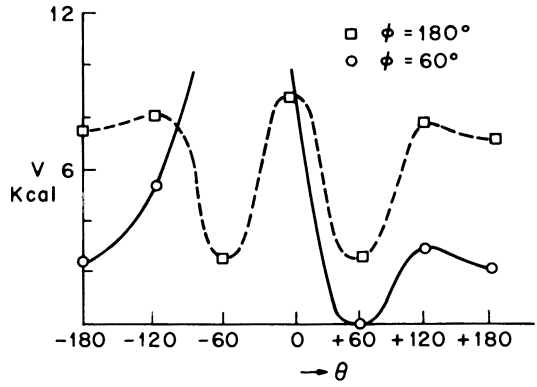

Figure 1. Theoretical potential-energy curves for rotation about the anomeric bond from ab initio Hartree–Fock 431-G calculations on dimethoxymethane. θ is the glycosidic O-5–C-1–O-1–CH_3 torsion angle. Φ is the C-5–O-5–C-1–O-1 torsion angle and is ~ 60° for α-D-pyranosides, ~ 180° for β-D-pyranosides (see Figure 2).

for energies, but poor geometry; others give reliable bond lengths but less reliable bond angles. The most sensitive test will be the comparison of the actual observed and calculated electron-density distribution in these molecules. Significant progress is now being made toward the experimental determination of electron density distributions in molecules as complex as carbohydrates by crystal diffraction methods.

The Experimental Data

There is now a significant amount of excellent molecular structural data on pyranose sugars and methyl pyranosides obtained by 'state of the art' X-ray and neutron-diffraction crystal-structure determinations. All the results quoted herein were obtained from three-dimensional diffractometer measurements. The atomic parameters, which include those describing the anisotropic thermal motion of the atoms, were refined by full-matrix least-squares methods to agreement factors of better than 4%. The more accurate structure determinations also included crystal X-ray or neutron absorption and extinction corrections. In a few of these precise structure analyses, the bond lengths were corrected for rigid-body thermal motion; however, for consistency and because of some uncertainty concerning the significance of these thermal motion corrections, we have reported the uncorrected values in the following tables. The full data for the individual structure determinations have been published elsewhere (13). In Tables I, II, III, and IV, we present a summary of these results in a form suitable for comparison with the results of theoretical ab-initio molecular orbital calculations aimed at predicting the molecular geometry of the hemi-acetal and acetal moiety in pyranoses and pyranosidic molecules.

The experimental standard deviations for individual structure determinations are of the order of 0.5 pm in bond lengths and 0.1° in angles. The accuracy of the X-ray and neutron analyses is comparable, except for the dimensions involving hydrogen atoms. Only in the neutron work are the bond lengths, valence and torsion angles involving hydrogen atoms accurate enough to be relevant for comparison with theory. In the tables we give the extreme values and the mean value observed for each bond length and valence angle. At the level of ~1 pm, there is no reason to expect that the bond lengths and valence angles will be identical from molecule to molecule, because none of the pyranose ring conformations is exactly the

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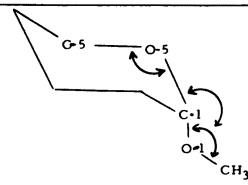
Table I. Acetal Geometry in Methyl α-D-Pyranosides



EXPERIMENTAL		C-5 — O-5	— C-1	— O 1	— CH_3	∠C-5	∠C-1	∠O-1
Methyl α-pyranosides	Max.	145.0	142.1	141.1	144.2	114.3	112.9	113.0
(8 X-ray studies)[a]	Min.	141.8	141.3	139.1	142.3	111.5	111.3	113.5
	Mean	143.54	141.63	140.44	143.05	113.4	112.3	113.1
Methyl α-pyranosides	Max.	143.9	141.8	140.1	142.2	114.3	113.0	114.0
(3 Neutron studies)[b]	Min.	142.8	141.3	140.0	140.7	113.5	112.0	113.9
	Mean	143.53	141.57	140.07	141.70	113.9	112.5	113.9
α-Linkages[c]	Max.	144.1	142.7	142.8	144.2	114.7	111.9	118.9
(5 X-ray studies)[d]	Min.	143.0	140.8	139.8	142.3	113.2	109.8	111.4
	Mean	143.44	141.80	140.75	143.48	114.1	111.2	115.0
α-Linkages		143.7	141.1	142.2	142.9	116.0	110.9	114.3
(2 Neutron studies)[e]		143.4	140.3	141.4	141.9	113.8	110.7	117.8
THEORY[f]		144.4	142.3	(142.3)	(144.4)	115.9	114.0	(115.9)

[a] Methyl α-arabinoside and methyl α-xyloside, molecules 1 and 2 [Jeffrey, G. A. and Takagi, S., (1977), unpublished work.]
Methyl α-glucoside [Berman, H. M. and Kim, S. H., Acta Crystallogr. (1968), 24, 897.]
Methyl α-galactoside [Gatehouse, B. M. and Poppleton, B. J., Acta Crystallogr. (1971), B27, 654.]
Methyl α-mannoside [Gatehouse, B. M. and Poppleton, B. J., Acta Crystallogr. (1970), B26, 1761.]
Methyl α-altroside [Gatehouse, B. M. and Poppleton, B. J., Acta Crystallogr. (1971), B27, 871.]
4-Deoxy-4-fluoro methyl α-glucoside [Choong, W., Stephenson, N. C., and Stevens, J. D., Cryst. Struct. Commun. (1975), 4, 491.]

[b] Methyl α-glucoside and methyl α-mannoside [Jeffrey, G. A., McMullan, R. K., and Takagi, S., Acta Crystallogr. (1977), B33, 728.]
Methyl α-altroside [Poppleton, B. J., Jeffrey, G. A., and Williams, G. J. B., Acta Crystallogr. (1975), B31, 2400.]

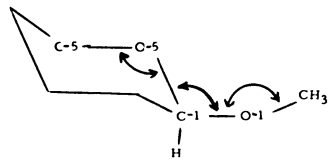
[c] excludes α-linkages which form part of C-O-C-O-C-O-C sequence of bonds.

[d] Methyl β-maltoside [Chu, S. S. C. and Jeffrey, G. A., Acta Crystallogr. (1967), 23, 1038.]
Isomaltulose [Dreissig, W. and Luger, P., Acta Crystallogr. (1973), B29, 514).
Planteose [Rohrer, D. C., Acta Crystallogr. (1972), B28, 425.]
Raffinose [Berman, H. M., Acta Crystallogr. (1970), B26, 290.]
Melezitose [Horotsu, K. and Shimada, S., Chem. Letters (1973), p. 83.]

[e] β-Maltose [Gress, M. E. and Jeffrey, G. A., Acta Crystallogr. (1977), B33, 2490].
Sucrose [Brown, G. M. and Levy, H. A., Acta Crystallogr. (1973), B29, 790.]

[f] Jeffrey, G. A., Pople, J. A., and Binkley, S., J. Amer. Chem. Soc. (1978), 100, 373].

Table II. Acetal Geometry in Methyl β-D-Pyranosides



EXPERIMENTAL		C-5 — O-5	O-5 — C-1	C-1 — O-1	O-1 — CH_3	∠C-5	∠C-1	∠O-1
Methyl β-pyranosides (8 X-ray studies)[a]	Max.	144.2	143.7	139.3	143.4	112.7	107.1	114.4
	Min.	142.6	142.1	137.4	142.1	110.6	108.1	112.4
	Mean	143.29	142.81	138.29	142.70	111.4	107.9	113.4
Methyl β-xylo-pyranoside (Neutron study)[b]		142.1	142.7	138.1	142.6	111.1	107.4	113.0
β-Linkages (3 X-ray studies)[c]	Max.	144.8	142.7	139.7	144.6	112.2	107.7	117.3
	Min.	143.6	142.5	138.4	143.6	111.2	106.9	115.8
	Mean	144.13	142.60	138.93	144.10	111.9	107.4	116.4
THEORY[d]		143.4	142.5	139.9	143.3	115.8	110.9	116.1

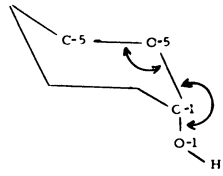
[a] Methyl (α-L)-arabinoside [Jeffrey, G. A. and Takagi, S., (1977), unpublished work.]
Methyl β-xyloside [Brown, C. J., Cox, G., and Llewellyn, F. J., J. Chem. Soc. (1966), p. 922.]
Methyl β-glucoside [Jeffrey, G. A. and Takagi, S., Acta Crystallogr. (1977), B33, 738.]
Methyl β-galactoside [Jeffrey, G. A. and Takagi, S., Acta Crystallogr. (1978), B34, 2006].
6-O-Acetyl methyl β-glucoside [Lindberg, K. B., Acta Crystallogr. (1976), B32, 642.]
6-O-Acetyl methyl β-galactoside [Lindberg, K. B., Acta Crystallogr. (1976), B32, 645.]
3,4-Ethylidene methyl β-galactoside [Lindberg, K. B., Acta Crystallogr. (1976), B32, 639.]
Methyl β-maltoside [Chu, S. S. C and Jeffrey, G. A., Acta Crystallogr. (1967), 23, 1038.]

[b] Takagi, S. and Jeffrey, G. A., Acta Crystallogr. (1977), in press.

[c] Cellobiose [Chu, S. S. C. and Jeffrey, G. A., Acta Crystallogr. (1968), 24, 830.]
Galacto-L-rhamnitol [Jeffrey, G. A. and Takagi, S., Acta Crystallogr. (1977), B33, 2377].
α-Lactose-H_2O [Fries, D. C., Rao, S. T., and Sundaralingam, M., Acta Crystallogr. (1971), 27, 994.]

[d] Jeffrey, G. A., Pople, J. A., and Binkley, S., J. Amer. Chem. Soc. (1978), 100, 373.

Table III. Hemi-acetal Geometry in α-D-Pyranoses

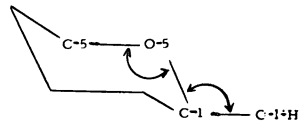


EXPERIMENTAL		C-5—O-5—C-1—O-1—H				O-5	C-1	O-1
α-Pyranoses (10 X-ray studies)[a]	Max.	148.1	144.7	142.1		115.5	113.1	
	Min.	142.6	141.2	138.2		112.1	110.9	
	Mean	144.48	142.77	138.52		113.7	111.9	
α-Pyranoses (3 Neutron studies)[b]	Max.	143.9	142.5	140.4	97.9	114.7	111.9	109.2
	Min.	142.7	141.8	138.9	95.2	113.4	109.8	107.4
	Mean	143.20	142.07	140.03	96.63	113.9	111.1	108.1
THEORY		144.4	142.1	141.7	(96.0)	(109.5)	(109.5)	(109.5)

[a] α-D-Xylose [Morild, E., private communication; Hordvik, A., Acta Chem. Scand. (1971), 25, 2175.]
β-D, L-Arabinose [Kim, S. H. and Jeffrey, G. A., Acta Crystallogr. (1967), 22, 537.]
β-L-Arabinose [Hordvik, A., Acta Chem. Scand. (1961), 15, 16.]
α-D-Galactose [Ohanessian, J. and Gillier-Pandraud, H., Acta Crystallogr. (1976), B32, 2810; Sheldrick, B., Acta Crystallogr. (1976), B32, 1016.]
α-Fucose [Longchambon, F., Ohanessian, J., Avenel, D., and Neuman, A., Acta Crystallogr. (1975), B31, 2623.]
α-L-Rhamnose-H_2O [Killean, R. C. G., Lawrence, J. L., and Sharma, V. C., Acta Crystallogr. (1971), B27, 1707.]
α-D, L-Mannose [Planinsek, F. and Rosenstein, R. D., Abstr. N10, American Crystallogr. Assoc. Meeting, August, 1967.]
α-D-Mannose, molecules 1 and 2 [Longchambon, F., Avenel, D., and Neuman, A., Acta Crystallogr. (1976), B32, 1822.]
α-Talose [Ohanessian, J., Avenel, D., Kanters, J. A., and Smits, D., Acta Crystallogr. (1977), B33, 1063.]

[b] α-D-Glucose [Brown, G. M. and Levy, H. A., Science (1965), 147, 1038.]
β-L-Arabinose [Takagi, S. and Jeffrey, G. A., Acta Crystallogr. (1977), B33, 3033].
α-L-Rhamnose [Jeffrey, G. A. and Takagi, S., (1977), (1978), B34, 2551.]

Table IV. Hemi-acetal Geometry in β-D-Pyranoses



EXPERIMENTAL		C-5—O-5—C-1—O-1-H			O-5	C-1
β-Pyranoses (5 X-ray studies)[a]	Max.	144.0	143.3	139.9	112.7	107.2
	Min.	142.6	141.3	138.4	111.9	106.2
	Mean	143.40	142.52	139.36	112.0	106.8
THEORY		143.5	142.4	139.8	(109.5)	(109.5)

[a] β-L-Lyxose [Morild, E., private communication.]
β-D-Glucose [Chu, S. S. C. and Jeffrey, G. A., Acta Crystallogr. (1968), 24, 830.]
β-D-Galactose [Sheldrick, B., Acta Crystallogr. (1976), B32, 1016; Longchambon, F., Ohanessian, J., Avenel, D., and Neuman, A., Acta Crystallogr. (1975), B31, 2623.]
2-Deoxy-2-fluoro-β-D-mannose [Choong, W., Craig, D. C., Stephenson, N. C., and Stevens, J. D., Crystal Struct. Commun. (1975), 4, 111.]

same. They are all distorted to a greater or lesser degree from the ideal $^4C_1$ conformation, in part by the intramolecular interactions between substituent hydroxyl groups and in part by crystal-field effects. Because the pyranose chair is not a flexible ring (15, 16), some bond lengths and angles must be different when the ring conformational angles are different.

The most obvious feature of the experimental data on the α and β pyranose molecules is the shortening of the anomeric C-1–OH bond length from a normal value of 142.5 pm to 139 to 140 pm. The C-1—O-5 bond length has the normal value, and the O-5–C-5 bond is 143-144 pm. The only significant differences observed between the α and β pyranose molecules are in the valence-bond angles at the ring oxygen, O-5, and at the anomeric carbon atom, C-1. In the α sugars, these angles are 113.8 and 111.5°, respectively, whereas they are significantly less in the β-anomers, i.e. 112 and 107°. There is definite evidence that the O-5—C-1—O-1 valence bond angle is less than tetrahedral in the β pyranoses.

In the methyl pyranosides, in contrast, there is a marked difference in the molecular geometry between the two configurations in both bond lengths and valence angles. The methyl β-pyranosides resemble the free sugars in having a markedly short glycosidic bond of 139 pm. The C-1—O-5 bond is normal, and the two external C–O bonds of the C–O–C–O–C acetal sequence are both longer than normal, 143-144 pm, but not significantly different from each other. Of the three valence angles, that at the carbon atom is less than tetrahedral, while both oxygen angles are greater than tetrahedral.

In the methyl α-pyranosides, the glycosidic bond is still the shortest of the four C–O bonds, but the difference is about 1 pm less. The bond-shortening appears to be shared more equally between the two C–O bonds on either side of the anomeric carbon. As in the β-pyranosides, the external C–O bonds of the acetal sequence are the longest. The differences between the valence angles are similar to the β anomers, except that the C-1 value is tetrahedral rather than less than tetrahedral.

The data relating to the α- and β-linkages observed in di- and trisaccharides tend to be less precise, because of the greater complexity of their structures, and the poorer quality of the crystals that are generally available. There is no evidence that the substitution of a sugar residue for a methyl results in significant differences in the structure of the acetal C–O–C–O–C bonding. We have included only those acetal sequences which are flanked by C–C bonds and have omitted from this listing

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those that form part of a longer chain of C-O bonds, i. e. seven C-O bond sequences as in α,α-trehalose, sucrose, planteose, raffinose and melezitose. The data on these compounds have been published elsewhere (12).

The neutron-diffraction results are in good agreement with the X-ray data for the C-O bond lengths and angles. There is a trend for the C-O bond lengths to be about 1 pm shorter when observed by neutron diffraction. This has been generally observed in studies where both X-ray and neutron-diffraction analyses have been made on the same compound (17-19). We believe that this effect is real and is a consequence of the fact that the thermally smeared electron density of the oxygen atoms is displaced away from the nuclear center in the direction of the lone-pair electrons, thereby tending to increase the observed C-O bond lengths and decrease the observed O valence angles.

The Theoretical Calculations

The theoretical calculations with which these experimental data can be compared are based on the use of methoxymethanol CH_3OCH_2OH (12) and dimethoxymethanol $CH_3OCH_2OCH_3$ (13) as model compounds for the hemi-acetal and acetal moieties in the pyranose and methyl pyranoside molecules, respectively. The analogy to the pyranoses and pyranosides is illustrated in Figure 2.

The calculations were carried out using the ab-initio Hartree-Fock 431-G basis-set molecular orbital method of Ditchfield, Hehre, and Pople (20). Energy calculations have shown that the preferred conformations for the α- and β-anomers were the +sc, +sc and ap, +sc models, respectively (12, 13), and only these conformations were considered. In the experimental data, the torsion angle C-5—O-5—C-1—C-1 is necessarily close to 60° for the α configuration, and close to 180° for the β configuration (they vary from these ideal values by ± 5° since the pyranose rings are not ideal $^4C_1$ chairs). The glycosidic torsion angles lie between 70 and 100° for the free pyranoses and between 60 and 80° for the methyl pyranosides. These values have been reported elsewhere (11, 12).

In the methoxymethanol model only the C-O bond lengths were varied. The C-H bond lengths were fixed at 96 pm and all angles were maintained at tetrahedral values (12).

In the dimethoxymethanol model, both C-O bond lengths and the O-5, C-1, and O-1 valence angles were varied (13). The +sc, +sc conformation is symmetrical, and therefore only

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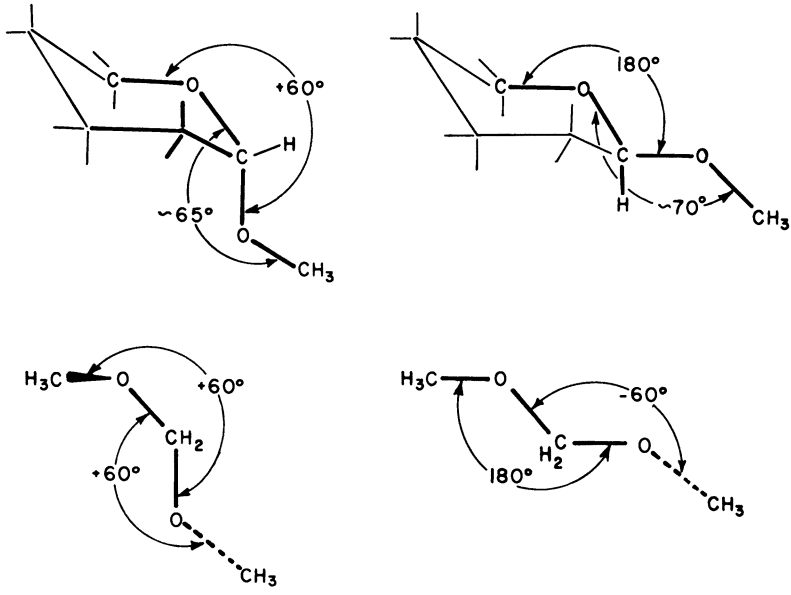

Figure 2. Dimethoxymethane as a model compound for methyl α-D and methyl β-D-pyranosides

two bond lengths and two angles can be varied. In the ap,+sc model, for the β pyranosides, four variable bond lengths and three variable valence angles are possible. The values of these bond lengths and valence angles which optimize the energy of the model molecules are shown under THEORY in Tables I, II, III, and IV.

Comparison Between Experiment and Theory

For the α and β pyranose sugars, the calculations reproduce the shortening of the glycosidic bond very closely and the sequence C-5—O-5 > O-5—C-1 > C-1—O-1 is successfully predicted by the theory. In the β pyranose case, the agreement between theory and experiment is well within the experimental error limits. For the α case, the glycosidic bond calculates ~2 pm longer than the β, but this small discrepancy, which is not observed experimentally, could disappear had the valence angles also been optimized.

The comparison between the dimethoxymethane and the α and β pyranosides is more important because of the more structural features which were optimized in these later calculations (13). The agreement is again very good. The difference in the bond lengths between the two configurations is reproduced to better than 2 pm in most cases. The differences in the theoretical values for the valence angles are in the same sense as those observed. The biggest difference between theory and experiment is the theoretical over-estimate of the C-1 valence angle by 3° in both cases. This agreement shows that the ab-initio Hartree-Fock 431-G approximation, when used with well-chosen models, can give very good descriptions of the hemi-acetal and acetal moieties of the sugar molecules, as far as predicting molecular geometry. It is a fair assumption that this will apply to all molecules involving first-row elements where d-orbital interactions are not important. It also suggests that the substitution of a primary and secondary alcohol group on C-5 instead of two hydrogens does not make any very major changes in the electronic structure of the C-O-C-1—O-C bonds. This is consistent with the chemical experience that the general anomeric effect is a particular property of the anomeric center which applies to all pyranoses and pyranosides and is relatively insensitive to the configuration at the non-anomeric carbon atoms.

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(10) Wolfe, S., Accts. Chem. Res. (1972) 5, 102.
(11) Jeffrey, G. A., Pople, J. A. and Radom, L., Carbohydr. Res. (1972) 25, 117.
(12) Jeffrey, G. A., Pople, J. A. and Radom, L., Carbohydr. Res. (1974) 38, 81.
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(15) Sachse, H., Berichte (1890) 23, 1363.
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(17) Brown, G. M. and Levy, H. A., Acta Cryst. (1973) B29, 790.
(18) Jeffrey, G. A., McMullan, R. K. and Takagi, S., Acta Cryst. (1977) B33, 728.
(19) Takagi, S. and Jeffrey, G. A., Acta Cryst. (1977) B33, 3033.
(20) Ditchfield, R., Hehre, W. J. and Pople, J. A., J. Chem. Phys. (1971) 54, 724.

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Aspects of Conformational Analysis of Pentopyranosyl Acetates, Benzoates, and Halides

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At the beginning of this article, some X-ray data of glycopyranosyl halides will be discussed that refer to the bond lengths at the anomeric center and which are of great importance for discussion of the anomeric effect. As is well known, acylated derivatives of β-xylosyl halides exhibit rather interesting conformational effects because in solution all of them adopt the unusual tetraaxial conformation predominantly or totally (1—6).

By means of X-ray structure-analysis, we were able to determine the conformation and arrangement in the crystalline state both of the benzoates and the acetates. It was demonstrated that the tribenzoates favor the tetraaxial conformation, whereas the triacetates crystallize favorably in the tetraequatorial form, even though the tetraaxial form predominates in solution (4).

Figures 1 and 2 show the aforementioned compounds in the conformations which they adopt in the crystalline state. Of particular interest are the various bond-lengths at the anomeric center. These may be supposed to indicate the amount of back donation that occurs with the halide in the axial disposition and hence strengthens the anomeric effect.

Very interesting are the two fluoro compounds depicted in the top line of Figure 1, where the benzoate crystallizes all axially, and the acetate all equatorially (7). The benzoate is observed as two independent molecules in the symmetrical unit; the interesting distances in both compounds are shown in Figure 1. Obviously, the shortening of the distances between C-1 and the ring-oxygen atom to 1.34—1.36 Å, is quite considerable. Some crystallographic problems were encountered with this compound. The structure was determined centrosymmetrically and subsequently refined asymmetrically to an R-value of 3.9%. Minor undertainties in the bond lengths cannot be entirely

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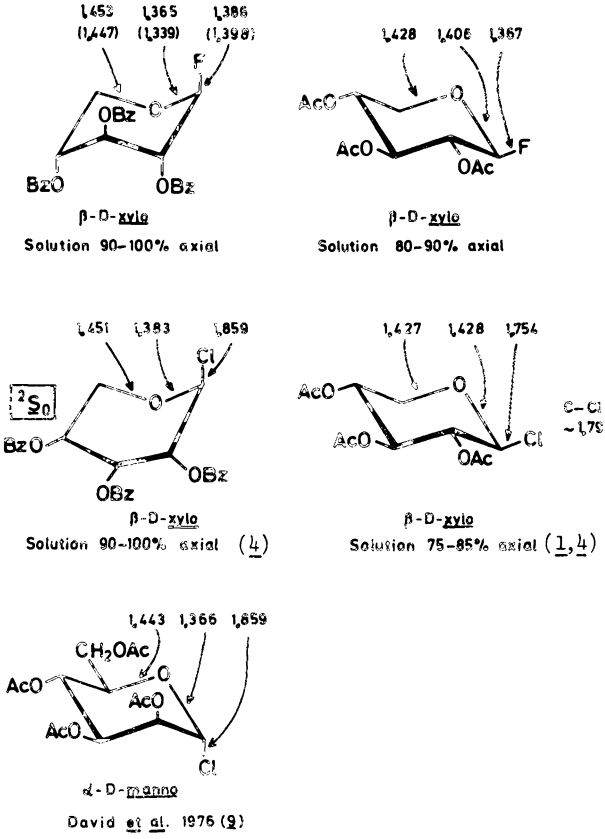

Figure 1

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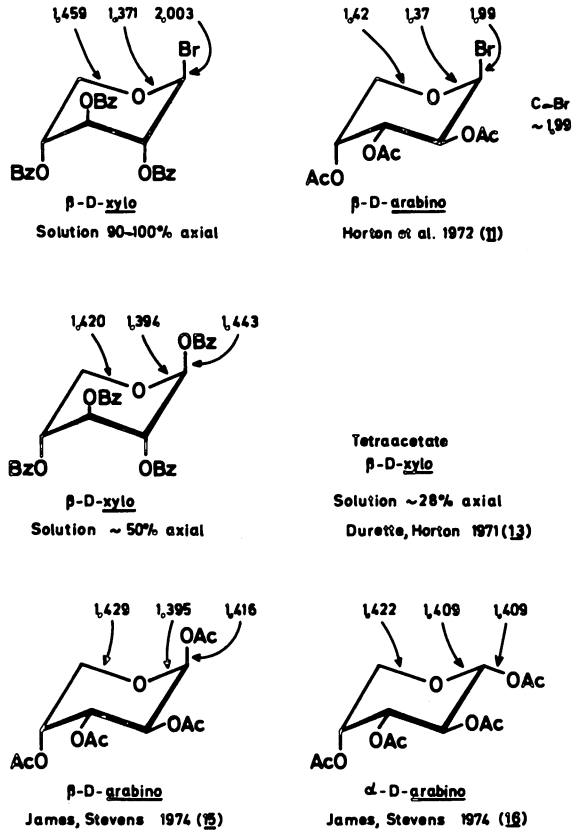

Figure 2

excluded. In the all-equatorially acetylated fluoro compound (Figure 1), the distances approach normal values (7).

In the chloride series, the benzoate (Figure 1, center), crystallizes in a skew conformation $^{2}S_{O}$(8). However, the arrangement around the anomeric center corresponds to a tetraaxial conformation, and thus a comparison of distance data should be permissible. In addition, the α-mannopyranosyl chloride recently determined by David et al. (9) is shown in Figure 1. Obviously, the distances between C-1 and the ring-oxygen atom are about 1.37—1.38 Å, and only slightly larger as compared with the fluoro compound. The tetraequatorial, acetylated chloro compound exhibits almost "normal" data (10).

Figure 2 shows the bromo derivatives (6). In the tetraaxial benzoate, a C-1—ring oxygen distance of 1.37 Å is observed, which corresponds to a considerable shortening of almost the same magnitude as in the fluoro and chloro derivatives. The C-1—bromine bond is concurrently stretched to 2.003 Å.

Other interesting molecules are the β-tetrabenzoate and the β-tetraacetate of xylopyranose. According to Durette and Horton (12, 13), 50% of the benzoate and 28% of the acetate adopt the tetraaxial conformation in solution. This clearly demonstrates that benzoate groups, in contrast to acetate groups, favor the axial disposition. In the crystalline state, the benzoate again shows the tetraaxial conformation (14). The data in Figure 2 demonstrate notably that, in this case, the shortening of the bond (to 1.39 Å) is comparatively small, as might have been expected for an oxygen-bound substituent at C-1. Quite similar distances have been observed by Stevens in the β-D-arabino derivatives (15), and again the corresponding α-D-arabino derivative (16) shows normal bond-lengths. (See Figure 2). By comparison, it may be noted that the variation of bond distances is minor in these cases.

Altogether, the bond-distance data give evidence that, in the case of axial anomeric substituents, a back-donation effect occurs, with the fluoro compound behaving similarly to the chloro and bromo derivatives. The same proves true with oxygen-bound substituents, although here the enhanced bond-distances point to a substantially smaller effect.

We were surprised that, of all the compounds studied, the benzoates, as compared with the acetates, favored the axial arrangement. This is especially obvious when the β-xylopyranose tetrabenzoates and tetraacetates are compared in solution. We supposed as a working hypothesis that the 1,3-diaxial interaction of two benzoates should be even smaller than that of the

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corresponding two acetates. If this were so, a similar effect should generally occur in the manifold acylated pentopyranoses studied by Durette and Horton (13). Here, the splendid and most accurate n.m.r. data of Durette and Horton (13) are at hand.

As shown in Figure 3, an interaction of the phenyl rings in the tetraaxial conformation of 1,2,3,4-tetra-O-benzoyl-β-D-xylopyranose is rather unlikely. In the crystal, the phenyl rings are arranged at random angles to each other. There would be a further possibility for explaining the difference between benzoates and acetates if there were an additional obstruction in the equatorial disposition, but only for the benzoates, which would then lead to a larger gauche interaction.

As key compounds for further studies of this problem, the three 1,5-anhydropentitols shown in Figure 4 are well suited, because here the influence of anomeric effect is eliminated. We prepared the triacetates and the tribenzoates of these compounds and studied the conformational equilibria in detail by n.m.r. spectroscopy (17).

For determination of standard coupling-constants in this series of compounds, as the basis for calculation of the distribution of conformers, the D-arabino compound in Figure 5 turned out to be particularly suitable. The arrangement of C-1 and C-2 of the one and C-5 and C-4 of the other conformation correspond to each other. Thus by a simple calculation, taking into account an average value of the coupling-constants involved, standard coupling-constants are obtained (J_{ee} 1.5 J_{aa} 10.6 for acetates and 10.4 Hz for benzoates.)

The derivatives in the ribo series are very interesting. Figure 6 shows the equilibria of 1,5-anhydroribitols. In this case, 24% of the acetate and 46% of the benzoate are found to adopt the diaxial $^1C_4$ conformation (left). Again, the more-favorable axial arrangement of benzoate groups is observed in this compound. Acetone was used as solvent throughout.

In both conformations (right and left), two gauche interactions between equatorial and axial substituents may be observed. As these should be of comparable magnitude in the different conformers, they were not considered in the energy evaluation. Furthermore, in the left ($^1C_4$) form, a 1,3-diaxial interaction has to be taken into account. This is the one having an equatorial substituent in the middle, and in which the axial groups are opposed by the ring-oxygen atom. The symbols in Figure 6 demonstrate this fact. [(e)OAc//OAc/Or denotes two syn-1,3-diaxial acetoxyl groups (OAc//OAc), opposed by a ring-oxygen atom (/Or) with an equatorial substituent (e) between them].

For the form on the right, only the A-value of the acyloxy group has to be considered. Thus, by means of the experimentally determined magnitude of ΔG° and an A-value of 0.7 kcal/mol,

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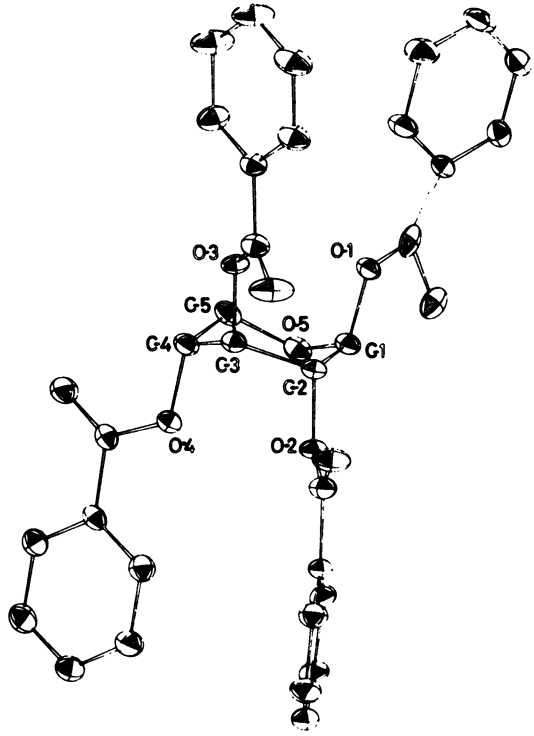


Figure 3

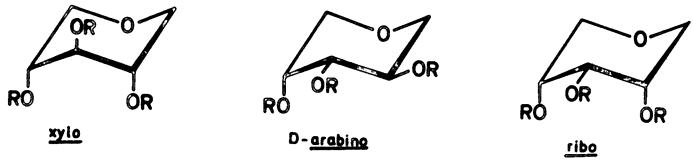


Figure 4

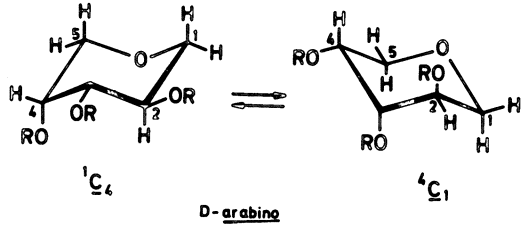
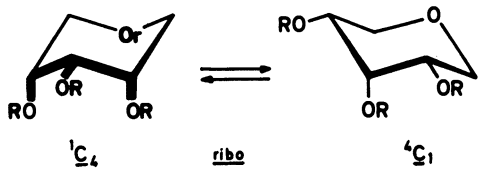


Figure 5



Acetate ~24% $^1C_4$ 76% $^4C_1$ ΔG° -0.7 Kcal/mol
Benzoate ~46% $^1C_4$ 54% $^4C_1$ ΔG° -0.1 Kcal/mol

ΔG° = [syn-1,3-diaxial] (e) OR//OR/Or − A-Value OR

(e) OAc//OAc/Or ~1.4 Kcal/mol
(e) OBz//OBz/Or ~0.8 Kcal/mol

Figure 6

the size of the 1,3-diaxial interaction may be calculated. As a result, for two acetoxyl groups, 1.4, and for two benzoyloxy groups 0.8 kcal/mol, are determined. As had been expected, a considerably lower value resulted for the benzoyloxy groups. It is remarkable for this system that, even in instances of possible angle-distortions, the gauche interactions in both conformers should correspond to each other and thus need not be considered.

It is quite interesting that 2,3,4-tri-O-benzoylribitol which, as already mentioned, adopts to the extent of 50% in solution the diaxial $^{1}C_{4}$ conformation, in the crystalline state favors the diequatorial $^{4}C_{1}$ form. 2,3,4-Tri-O-benzoylxylitol also adopts the triequatorial form in the crystalline state, in contrast to the xylopyranose derivative in Figure 3. Both crystal structures are shown in Figure 7. Both pentitol derivatives lack the anomeric effect, which would otherwise lead to high proportions of the inverse ($^{1}C_{4}$) forms for the β-anomers. From the ring-torsional angles of the ribo and xylo compounds in Figure 7, we may conclude that, in both instances, there are only small deviations from the idealized chair conformations. The torsional angles of the benzoyloxy groups in the ribo compound ($\sim 55^{\circ}$) and the xylo compound ($\sim 65^{\circ}$), also differ only slightly (see Figure 7). A valid assumption should be that the gauche interaction of two substituents in axial—equatorial and equatorial—equatorial disposition is of similar order.

Figure 8 shows the α-D-ribo compounds, where in both acetates and benzoates, the proportion of the $^{1}C_{4}$ conformer is similar (13). This was to be expected, because the 1,3-diaxial interaction in both conformers should be similar. Again, in these derivatives, both conformers exhibit three gauche interactions, which need not be considered. Because of this — in addition to the 1,3-diaxial interactions — only the anomeric effect in the left ($^{1}C_{4}$) form has to be taken into account.

Thus, by calculation using the formerly determined values, the magnitude of the 1,3-diaxial interaction with a central equatorial substituent and an axial hydrogen atom opposing the axial groups is obtained. In this instance, slightly increased values should result, in contrast to the former case with the ring-oxygen atom opposing the two axial groups. This presumption is, in fact, supported by the calculated values, which are found to be 1.9 kcal/mol for the acetoxy, and 1.5 kcal/mol for the benzoyloxy group. As before, a characteristic difference between the two groups may be observed. It should be mentioned that, for both the acetoxy and the benzoyloxy group, the same anomeric effect (1.3 kcal/mol) served as the basis of the calculation. This value may be concluded from the measurements of Durette and Horton (18) on mixed acylated pentopyranoses.

When the situation is examined for the β-ribo compound (Figure 9), the $^{4}C_{1}$ form on the right shows three, and the $^{1}C_{4}$ form on the left, only two gauche interactions. The 1,3-diaxial

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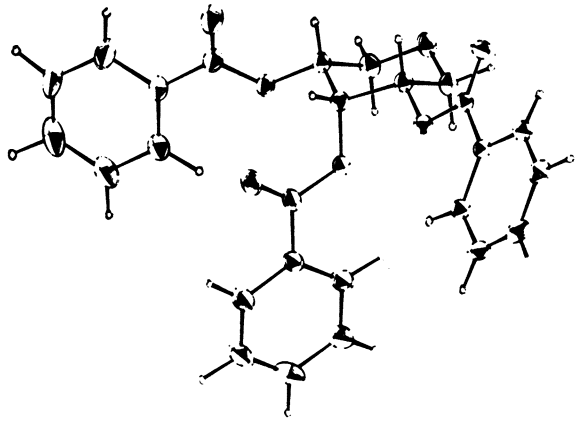
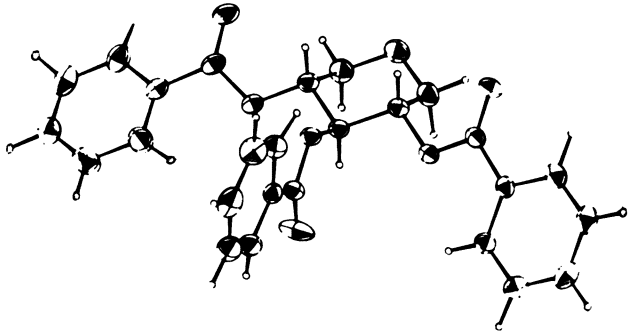


2,3,4-Tri-O-benzoyl-ribitol

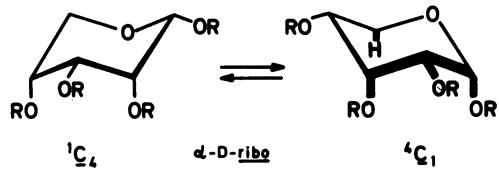
C-1-C-2 — C-3-C-4	-51.9		
C-2-C-3 — C-4-C-5	52.7		
C-3-C-4 — C-5-O-5	-58.4	O-21-C-2 — C-3-O-31	-56.5
C-4-C-5 — O-5-C-1	64.0	O-31-C-3 — C-4-O-41	54.4
C-5-O-5 — C-1-C-2	-63.3		
O-5-C-1 — C-2-C-3	57.2		



2,3,4-Tri-O-benzoyl-xylitol

C-1-C-2 — C-3-C-4	-56.3		
C-2-C-3 — C-4-C-5	56.2		
C-3-C-4 — C-5-O-5	-60.3	O-21-C-2 — C-3-O-31	65.5
C-4-C-5 — O-5-C-1	63.9	O-31-C-3 — C-4-O-41	-65.3
C-5-O-5 — C-1-C-2	-63.1		
O-5-C-1 — C-2-C-3	59.8		

Figure 7

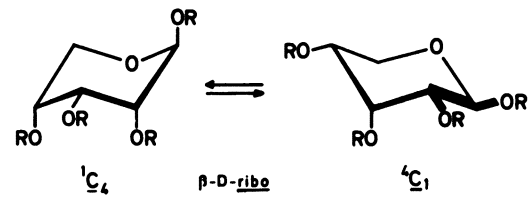


Acetate ~ 23% $^1C_4$ 77% $^4C_1$ $\Delta G°$ -0.74 Kcal/mol
Benzoate ~ 27% $^1C_4$ 73% $^4C_1$ $\Delta G°$ -0.60 Kcal/mol

$\Delta G°$ = (e) OR//OR/Or + anom. Eff. -(e)OR//OR/H

(e) OAc//OAc/H ~ 1.9 Kcal/mol
(e) OBz//OBz/H ~ 1.5 Kcal/mol

Figure 8



Acetate ~ 57% $^1C_4$ 43% $^4C_1$ $\Delta G°$ +0.18 Kcal/mol
Benzoate ~ 77% $^1C_4$ 23% $^4C_1$ $\Delta G°$ +0.72 Kcal/mol

$\Delta G°$ = (e) OR//OR/Or - gauche OR/OR - anom. Eff.

gauche OAc/OAc ~0.3 Kcal/mol
gauche OBz/OBz ~0.2 Kcal/mol

Figure 9

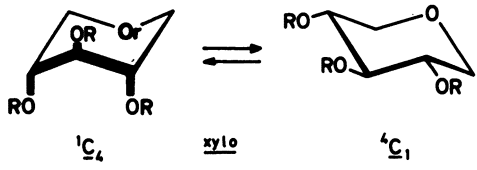
interaction for the left ($^1C_4$) form is known from the 1,5-anhydro ribitol as shown before, the anomeric effect has to be considered, and thus with the experimental ΔG^o-value, the gauche interactions may be calculated. The gauche interaction of two acetoxy groups amounts to 0.3 kcal/mol, and that for the benzoyloxy groups to 0.2 kcal/mol. These values are not substantially different, and are of the same magnitude as calculated by Angyal (19, 20) and Zefirov (21) by their methods. Thus far, these three model compounds investigated form the basis for determination of three values of nonbonding interactions.

In 1,5-anhydroxylitol (Figure 10), the conformational equilibrium is shifted to the equatorial form (right side). By accurate measurements, data could be obtained for determining the equilibrium, according to which the triaxial form amounts to about 13% for the acetate and to about 17% for the benzoate. The two gauche interactions in the $^4C_1$ form on the right, and one 1,3-diaxial interaction plus one A-value in the form on the left, have to be taken into account. The calculations for the 1,3-diaxial interaction of two groups having a middle axial group and an opposing ring-oxygen atom give rise to a smaller value than in the former instance having a middle equatorial group, a fact that was to be expected. For two acetoxy groups, 1.1 kcal/mol and for two benzoyloxy groups 0.6 kcal/mol, were determined. Again, the difference between the two substituents is nearly the same, as observed before. However, because the equilibrium is considerably shifted toward one conformation, these values have a larger margin for error.

The fourth possible 1,3-diaxial interaction may be calculated from the β-xylo compound shown in Figure 11. As mentioned before, 28% of the tetraacetate and 50% of the benzoate adopt the $^1C_4$ conformation shown on the left (13). In the $^4C_1$ form on the right, three gauche interactions and the anomeric effect have to be considered, whereas in the $^1C_4$ form on the left, two 1,3-diaxial interactions of different types occur. The calculation for the 1,3-diaxial interaction to two groups having a middle axial group and opposing hydrogen atoms results in 1.7 kcal/mol for two acetoxy groups and 1.3 kcal/mol for two benzoyloxy groups.

These data correspond well with the results in regard to the other model compound, and are slightly smaller than the comparable interaction in the case of a middle equatorial group. Thus, by this approach, we were able to determine all four different 1,3-diaxial interactions. In all of these instances, comparable and characteristic differences are observed between acetoxy and benzoyloxy groups.

Now the calculated values may be applied to additional, isomeric pentose derivatives. In the α-D-xylopyranose derivative, the equilibrium is practically totally on the side of the $^4C_1$ form (13). Similarly, the β-D-arabinopyranose derivative totally adopts the $^1C_4$ conformation (13). Consequently, neither



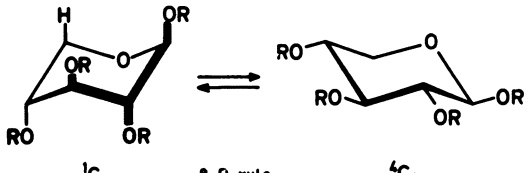
$^1C_4$ xylo $^4C_1$

Acetate ~13% $^1C_4$ 87% $^4C_1$ ΔG° -1.2 Kcal/mol
Benzoate ~19% $^1C_4$ 81% $^4C_1$ ΔG° -0.9 Kcal/mol

ΔG° = (a) OR//OR/Or + A-Value OR - 2gauche OR/OR

(a) OAc//OAc/Or ~ 1.1 Kcal/mol
(a) OBz//OBz/Or ~ 0.6 Kcal/mol

Figure 10



$^1C_4$ β-D-xylo $^4C_1$

Acetate ~28% $^1C_4$ 72% $^4C_1$ ΔG° -0.58 Kcal/mol
Benzoate ~50% $^1C_4$ 50% $^4C_1$ ΔG° ~0 Kcal/mol

ΔG° = (a) OR//OR/Or + (a) OR//OR/H - anom. Eff. - 3gauche OR/OR

(a) OAc//OAc/H ~ 1.7 Kcal/mol
(a) OBz//OBz/H ~ 1.3 Kcal/mol

Figure 11

of these compounds are suitable for further considerations. In 1,5-anhydro-D-arabinitol (Figure 12), closely corresponding data are obtained for the conformational equilibria of the acetate and benzoate, if these are calculated by use of the determined energies of interaction.

However, with α-D-arabino and also α- and β-D-lyxo derivatives, a special effect is observed. In these three compounds a new interaction is at hand, which has not yet been discussed. This is an interaction of an axial acyloxy group with a 1,3-diaxial hydrogen atom and the opposing ring-oxygen atom.

Such an interaction is shown in Figure 13 with the acyloxy group at C-4 in the left column and the acyloxy group at C-2 in the right column. Calculations of the equilibria will give incorrect results if the interaction of both the acyloxy group at C-4 and that at C-2 are considered to be of the same magnitude. If, for this interaction, a difference of 0.7—0.9 kcal/mol is considered, which related to the enhanced interaction of the 2-acyloxy group, the calculation of all of these equilibria according to the energies of interaction determined gives mostly satisfactory results.

Obviously, in the conformation to the right, which shows the characteristic arrangement of an axial 2-acyloxy group with a 1,3-diaxial interaction towards a hydrogen atom and the ring-oxygen atom, an additional destabilizing factor of 0.7—0.9 kcal/mol has to be taken into account. A reason for this additional destabilizing effect cannot be given straightforwardly, although there seems to be a certain similarity to the formerly discussed Δ2-effect (20, 22). In general, most authors tend to incorporate this factor into the anomeric effect; however, it seems to be justified in the pentopyranose series to consider this effect separately.

All of the results are compiled in Figure 14. For the four different possible 1,3-diaxial interactions, slightly different values have been determined. As might have been expected, the interactions are smaller if the ring-oxygen atom opposes the diaxial substituents, in contrast to hydrogen atoms in 1,3-diaxial disposition. Furthermore, the interaction is a little smaller if the middle substituent between the two diaxial groups adopts the axial rather than the equatorial disposition.

The data show clearly that, in all instances for two benzoyloxy groups, the energy of interaction is 0.4—0.6 kcal/mol smaller than for two acetoxy groups. The gauche interaction between two acetoxy and two benzoyloxy groups seems to be of similar magnitude. The difference in the 1,3-diaxial interactions cannot be explained by taking into account an enhanced gauche interaction between two benzoyloxy groups.

For the special arrangement of an axial acetoxy group at C-2 with hydrogen and the ring-oxygen atom in 1,3-diaxial disposition, an additional destabilizing effect has to be considered, as shown in the formula at the bottom of Figure 14.

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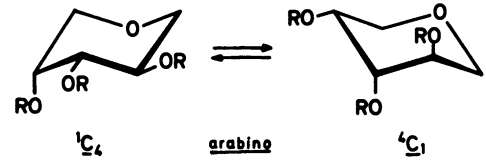
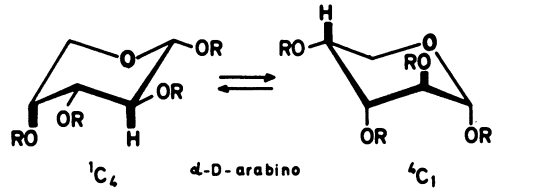
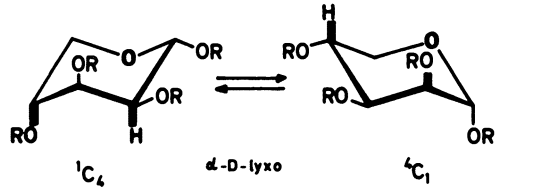


Acetate	calc. 34%	$^4C_1$	found	29%	$^4C_1$
Benzoate	calc. 30%	$^4C_1$	found	25%	$^4C_1$

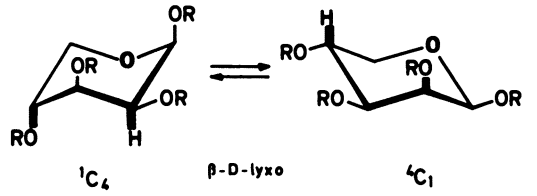
Figure 12



4-OR OR//H/Or + 2-OR OR//H/Or difference ~0.9 Kcal/mol



4-OR OR//H/Or ≠ 2-OR OR//H/Or difference ~0.7 Kcal/mol



4-OR OR//H/Or ≠ 2-OR OR//H/Or difference ~0.7 Kcal/mol

Figure 13

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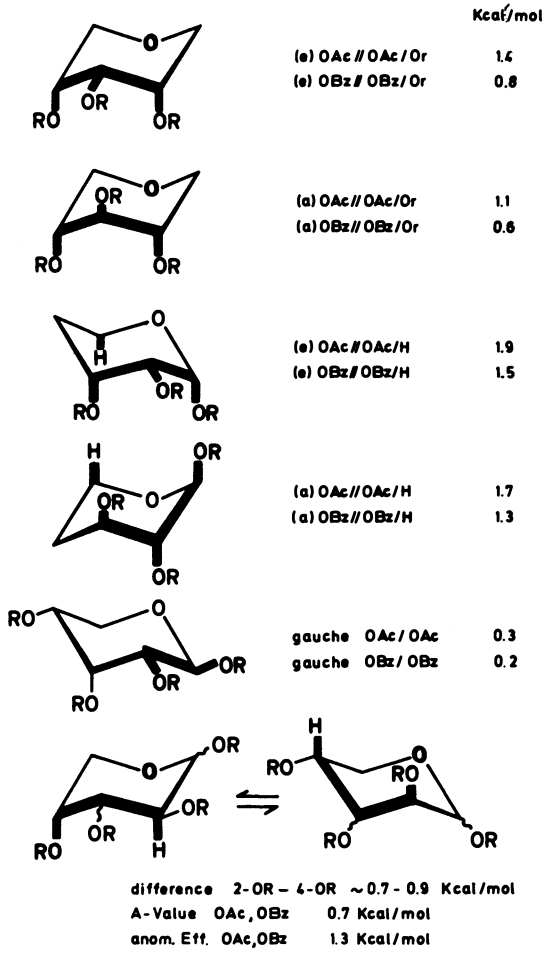

Figure 14

Durette and Horton (18) have also measured conformational equilibria for a series of mixed acetylated and benzoylated pentopyranoses. Our calculations of the conformer distribution corresponds largely to their results. It is quite obvious that there is only a minor difference in the anomeric effect of an acetoxy and a benzoyloxy group. This problem cannot be discussed in detail in the present context.

In any case, it should be kept in mind that pentopyranoses constitute a complex system for conformational studies. Of course, many different forces operate in these compounds, and all of these interactions should be considered. Our studies, having particular emphasis on certain noteworthy effects, are meant to help elucidate significant directions in these systems. According to these results, some further insight into the different factors governing the conformational equilibria in saccharides of this type may be obtained.

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Summary

In the solid state, tri-O-acetyl-β-D-xylopyranosyl halides adopt the all-equatorial $^4C_1$ conformation, whereas tri-O-benzoyl-β-D-xylopyranosyl halides crystallize in the all-axial $^1C_4$ conformation, except for tri-O-benzoyl-β-D-xylopyranosyl chloride, which adopts the ^2S_O (skew) conformation. The variations of bond lengths to the anomeric carbon atom are discussed with regard to the anomeric effect. By comparative studies of the conformational equilibria of acetylated and benzoylated 1,5-anhydropentitols on the one hand, and pentopyranoses exhibiting the anomeric effect on the other, data for the non-bonding interactions may be derived. Based on the principle of additivity of these factors, the conformational distribution of structurally related compound may be estimated. In connection with these results, it is noted that two benzoyl groups show a smaller 1,3-diaxial interaction than two acetyl groups; the difference between these interactions is about 0.4—0.6 kcal/mol. Furthermore, in the lyxo and arabino configurations, a destabilizing influence is observed if the substituent at C-2 adopts an axial disposition. This effect may be compared to the Δ2 effect.

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The Influence of Reactant Structure and Solvent on Glycoside Synthesis

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According to Stoddart (1), the unexpected preference for an electronegative substituent on C-1 of a pyranoid ring to assume the axial orientation, first discussed by Edward (2) and later termed "the anomeric effect" by Lemieux (3), is now a generally recognized phenomenon in the conformational analysis of heterocyclic compounds. The preference for axial orientation is related to destabilization of the equatorial conformer in which a polar bond lies between two electron pairs on a vicinal oxygen atom.

This steric preference is a thermodynamic effect and is exhibited in the classic equilibrium glycosidation of Fischer, in which acid-catalyzed reaction of a free sugar with a simple alcohol takes place in a medium of moderate dielectric constant. Under these conditions, the axial anomer is the favored product. This reaction has synthetic limitations, however, for with most sugars the stereoselectivity is not high, and for practical purposes it can only be applied to form simple glycosides.

The current interest in glycoside synthesis is predominantly in the preparation of complex glycosides, especially oligosaccharides, with specific anomeric configurations and specific linkages between (often) different sugars. For the solution of such problems, one must use kinetically controlled glycosidations under irreversible conditions which do not permit anomerization of product. This paper will explore how the anomeric effect of a number of reactants (rather than products) influences the course of kinetically controlled glycosidations.

We have attempted to investigate model glycoside-forming reactions which could be related to stepwise oligosaccharide syntheses. We have, therefore, looked for reactions of high rate and stereoselectivity which proceed to completion with nearly equivalent amounts of the two reactants: an alcohol and a substituted glycosyl derivative bearing a reactive leaving-group and persistent and temporary blocking-groups. A variety of primary and secondary alcohols have been used, varying in

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structure from methanol to partially blocked sugar derivatives. The number of variables in a systematic study of this type is formidable, so after some exploratory studies, the study was restricted rigorously to reactions in homogeneous solution between two reactants. Although a number of reactions of high rate and stereoselectivity have been found, they are not entirely mutually compatible in stepwise syntheses, which require deblocking reactions as well as glycoside-forming reactions. The main reason for incompatibility is that in our reactions, the persistent blocking groups, ethers, are used in conjunction with non-persistent blocking groups, esters, which are also used as participating groups on C-2 for trans-1,2-glycoside formation. Selective deblocking methods are, therefore, still needed for many conceivable synthetic sequences. We will discuss first the formation of cis-1,2-glycosides of α-D-glucose and α-D-galactose and thereafter trans-1,2-glycosides of α-D-mannose and β-D-galactose, but will limit our remarks to model glycoside reactions and will not discuss complexities involved in the synthesis of specific linkages in trisaccharides or higher oligomers.

Although glycosyl derivatives with non-participating groups on C-2 are usually used for the synthesis of cis-1,2-glycosides, the steric course of their reactions is affected by a variety of other factors, including the structure of the sugar and its leaving group, the pattern and type of its substituents, the solvent, and the concentration and nature of the aglycon alcohol. The early work on these glycosidations, carried out under solvolysis conditions, lead to the original mechanism by Rhind-Tutt and Vernon (4). This proposal has required only minor elaboration to accommodate the results of more recent work directed toward complex-glycoside synthesis.

Since most glycosidation research (including that reported here) is qualitative in nature and synthetic in objective, rigorous evidence supporting the validity of proposed mechanisms is rarely available. The use of the concept of the simultaneous existence of interconvertible ion-pairs, which is basic to the interpretation of glycosidation reactions, is justifiable and profitable only within specific limits of experimental parameters. A definitive statement of these limits has been given by Szwarc (5a). In most glycosidations, the specific limits are unknown. Therefore these glycosidation reactions will be treated "as though" they proceeded through a common set of similar intermediates, but rigorous proof is not implied.

The mechanism of glycosidation of derivatives with an electronegative leaving group on C-1 and non-participating substituents on C-2 is derived from the previously mentioned study by Rhind-Tutt and Vernon on the methanolysis of 2,3,4,6-tetra-O-methyl-α-D-gluco- and mannopyranosyl chloride (4). They found that methanolysis of these compounds proceeded generally by an SN_1 mechanism, but the displacement could acquire more SN_2

character in less-polar media and with stronger nucleophiles. Inversion of configuration at C-1 was essentially complete in the case of the glucopyranosyl chloride, although made slightly less stereoselective because of prior inversion of the glycosyl derivative by chloride ion (Table I, No. 1 and 2). The manno-pyranosyl chloride, in contrast, produced nearly equivalent amounts of the anomeric methyl glycosides (Table I, No. 3 and 4).

They proposed that, under SN_1 conditions, there is a rate-determining ionization of glucosyl chloride to a tight ion-pair (reaction 1, Figure 1), which reacts from the back side with alcohol to form β-glycoside (reaction 2) or with halide ion to form the more reactive β-halide (reaction 3). The latter reacts very much more rapidly than its anomer to form α-glycoside (reaction 5). In contrast, the approach to the back side of the α-mannosyl chloride is shielded, and dissociation to separate ions occurs before reaction with methanol (reaction 6 and 7). As a result most of the stereoselectivity is lost (reaction 8) and no rate enhancement with halide ion is observed. Glaudemans and Fletcher (6) found that a similar interpretation was satisfactory for the methanolysis of anomeric D-arabinofuranosyl halides with non-participating

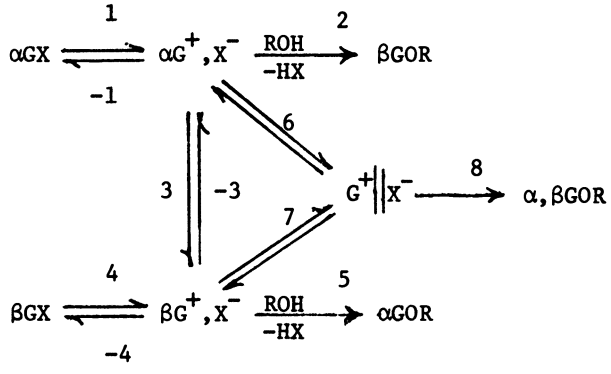

Figure 1. Mechanism of glycosidation (Rhind-Tutt and Vernon (4) modified)

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Table I. Influence of Alcohol and Halide-Ion Concentration on Alpha Selectivity in Glycosidations

No.	Glycosyl Halide	Added Halide X	Rate Enhancement	MeOH:X	%α	Reference
1	Tetra-O-Me-α-D-GlcpCl	--	--	∞ a	6	4
2	"	LiCl	x2	∞	35	4
3	Tetra-O-Me-α-D-ManpCl	--	--	∞	42	4
4	"	LiCl	x1	∞	42	4
5	Tetra-O-Bn-α-D-GlcpBr	--	--	∞	45	7
6	"	$Bu_4N^+Br^-$	x2	∞	72	7
7	"	--	--	4:1	80	10
8	"	--	--	1.5:1	93	10
9	"	$Bu_4N^+Br^-$	--	1.1:1	95	12
10	Tetra-O-Bn-α-D-ManpBr	"	b	1.1:1	89	29
11	Tetra-O-Bn-α-D-GlcpI	NaI	--	40:1	75	11
12	"	NaI	--	2:1	92	11
13	Tetra-O-Bn-α-D-GalpI	NaI	--	40:1	71	11
14	"	NaI	--	2:1	88	11

a. Symbol ∞ indicates undiluted methanol in large excess.
b. Reaction very slow, about half complete in four days at room temperature.

groups on C-2, and further emphasized that the observed rates of reaction were pseudo-first-order and depended on alcohol concentration. Since recombination of the ion pair (reaction 1, Figure 1) competes with glycoside formation (reactions 2, 3, and 5) this observation is easily explained on the basis of the same mechanism.

Two facts of great significance are apparent in the later work of Ishikawa and Fletcher (7). They observed that 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide produced 45% of the α-glycoside on methanolysis in contrast to 6% produced from 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl chloride (Table I, No. 5, cf. No. 1). In our experience, no such differences are observed between compounds with the same skeleton but with different ether functions. Therefore this difference clearly reflects a change from chloride to bromide as leaving group. The α-percentage could, they found, be forced much higher with added halide ion (Table I, No. 6, Cf No. 5).

An even more striking observation was the fact that 2,3,4-tri-O-benzyl-6-O-p-nitrobenzoyl-α-D-glucopyranosyl bromide gave 95% α-glycoside on methanolysis. Thus exchange of an ether group on C-6 for this ester group had a profound influence on the course of reaction at C-1. Probably the rate of anomerization of the ion pair (Figure 1, reaction 3) is enhanced by the presence of p-nitrobenzoate on C-6, but the nature of the influence is not clear.

Fréchet and Schuerch (8) showed that under the same conditions of methanolysis, the substituent effect of a series of C-6 p-substituted benzoates was a function of the corresponding Hammett substituent-constants. Thus the glucopyranosyl bromide with C-6 p-methoxybenzoate produced 84% β-glycoside, in contrast to 95% α with C-6 p-nitrobenzoate. Unfortunately, this difference could not be exploited in solid-phase synthesis for both derivatives gave glycosides high in α content. (Substituent effects have also been observed by Flowers on fucose glycosidations (9)). It soon became apparent from the work of Kronzer and Schuerch (10,11) that the stereoselectivity of glycoside formation as well as its rate was a function of alcohol concentration, and that low alcohol concentration favored high α-stereoselectivity. This observation, which appears to be generally true, can also be readily accommodated in the same mechanism. Reactions 2 and 3 (Figure 1) are in competition and at low alcohol concentrations reaction 3 competes more favorably. Because of the much higher rate of reaction 5, high α-product mixtures are favored at low alcohol concentrations.

The halide ion-catalyzed glycosidation method of Lemieux and coworkers (12-14) takes advantage of two phenomena to enhance the proportion of α-glycoside formed: an increase in halide ion concentration to favor reaction 3 and a low alcohol concentration to disfavor reaction 2 (cf. reactions 6,7,8,9, Table I). Although this methodology is one of the better and

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simplest methods of obtaining α-glycosides, it suffers from the disadvantage of being slow. As a result, the reaction frequently requires two or more days or a substantial excess of glycosyl halide for high conversions of the limiting reagent which is the alcohol (Table I, footnote b). The rate is faster at higher temperatures, but the stereoselectivity poorer (12). The low rate is due in part to the use of a leaving group which is not sufficiently reactive and in part to the relatively low concentration of alcohol which is necessary for stereoselectivity (reaction 6, Table I). It may also be due to suppression of the rate-determining ionization step (reaction 1, Figure 1) by halide ion as pointed out by Glaudemans and Fletcher (6). This at least partly offsets the expected rate enhancement which should result from increasing the rate of anomerization (reaction 3, Figure 1). Thus the two factors that favor high stereoselectivity may favor low rates in this reaction.

Exploratory studies were, therefore, undertaken to find methods of enhancing glycoside-formation rates while retaining or improving α-stereoselectivity. The use of iodide instead of bromide ion catalysis appeared to give somewhat higher rates (11) but still lower than were wanted when nearly equimolar quantities of alcohol and glycosyl halide were used. There also appeared to be some greater tendency toward halide ion-induced side-reactions.

We, therefore, began an examination of metal-assisted glycosidation of α-D-glucopyranosyl halides using silver hexafluorophosphate, tetrafluoroborate, and triflate at low temperature. It was clear that reaction rates were extremely high. Glycosidation was usually complete at -78° with small excesses of methanol in a few minutes to one half hour. The stereoselectivity varied from high β to high α depending on substituent on C-6, solvent, leaving group and whether reaction with silver salt was complete before adding methanol. In a few cases, side reactions were observed leading to anhydro-ring formation (10).

As an alternative approach, it seemed possible that if a leaving group were chosen which had a favored equatorial disposition on C-1, simple inversion might lead with high selectivity to α-glycoside (15). We, therefore, investigated a number of onium salts derived from glycosyl halides and tertiary amines, triphenylphosphine and dimethyl sulfide. The number of possibilities in this group of derivatives is vast and their reactivities are sensitive to both steric and electronic effects. Only a preliminary screening was, therefore, possible. It appeared, however, that the difficulties with these leaving groups were at least comparable to those found with electronegative species. If amines of strong basicity were chosen, elimination became a serious side-reaction. With some leaving groups, reactivities were low. In addition α-stereoselectivity was not reliable, especially with higher

alcohols (16-18). This may be due to an equilibrium of glycosyl onium derivative with the halide ion present, or may be due to the presence of small concentrations of the α-onium salt. If the latter forms, it might be expected to be more reactive than the β anomer (19). It may be, therefore, that the reverse anomeric effect is of little advantage in α-glycoside synthesis, although there are still whole classes of compounds that might be tested (for example, trialkyl phosphines).

We had been convinced by our prior work on iodides and on metal-assisted methanolyses (10) that it was possible to enhance the rate of glycosidation by changing the leaving group, and that it should be possible to control stereoselectivity by proper choice of experimental parameters. We therefore tested a number of alkyl and aryl sulfonates as leaving groups on glucose (20) and galactose (21,22) derivatives having a non-participating group on C-2. With certain patterns of substitution, these compounds formed α-glycosides with high α-stereoselectivity when the reactions were carried out in appropriate solvents. It became clear that it was necessary to produce an ion pair of the right reactivity to be solvent-sensitive or else high α-selectivity was not achieved. Furthermore, it was clear that the solvent was in some way participating in the reaction because in various systems different solvents gave the best stereoselectivity. Early examples of high α-selectivity were achieved by scientists in Japan and by G. Wulff in Germany on metal-assisted glycosidations in dioxane (23) and in ether (24,25). Kronzer (10) and Eby (20) in our laboratory found ethyl ether the preferred solvent on other glucose derivatives, and Marousek, Lucas, and Wheat found dimethoxyethane was superior with various galactose derivatives (22).

Since the influence of solvent is dominant in determining selectivity in α-glycoside synthesis, a correct interpretation of its role should be useful. The solvent might, for example, alter the anomeric effect, increasing the proportion of β-glycosyl derivative. Eby, in fact, found that the ^{1}H-mr spectrum of 2,3,4,6-tetra-O-benzyl-1-O-p-tolylsulfonyl-D-glucopyranose in ether gave evidence of only β-anomeric proton, whereas 2,3,4-tri-O-benzyl-6-O-N-phenylcarbamoyl-1-O-p-tolylsulfonyl-D-glucopyranose appeared to have 15% of its anomeric proton α. This result is consistent with the higher α-selectivity of the latter compound. On the other hand galactose derivatives in dimethoxyethane gave ^{1}H-mr evidence that the leaving group was entirely α, even though high α-selectivity was achieved in this solvent (22).

Wulff has postulated (26) and we have previously implied that these ether solvents act to form incipient or real trialkyloxonium ions that adopt a favored equatorial configuration (the reverse anomeric effect) and are attacked

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from the axial direction by alcohol (20). However since no spectral evidence has been found by us for their existence, it is perhaps useful to think more generally in terms of ion-pair solvation and solvent properties.

Since the desired ion-pair is generated in α-configuration and must be protected from attack by alcohol until it can invert to β-configuration, one must have a solvent which has strong donor properties to compete with alcohol. Donor properties of solvents have been measured by Gordy in hydrogen-bonding systems as "hydrogen-bonding capacity" (27) and in non-hydrogen bonding systems by Gutmann (28) as "donicity numbers." The latter is more pertinent to the reactions under consideration, and it is clear that compounds such as diethyl ether, dioxane, tetrahydrofuran, and dimethoxyethane all have satisfactory donor properties to compete, when present as a solvent, with limited amounts of alcohol (Table II). Solvation of the ion pair lowers its reactivity (5c) and allows time for

Table II. Solvent Properties Significant in α-Glycosidations

Solvent	Donicity[28,5b] Number	Dielectric Constant
Ethyl ether	19.2	4.3
Tetrahydrofuran	20	7.6
Dioxane	a	2.2
Dimethoxyethane	a	7.2
$[(CH_3)_2N]_3$-P-O	38.8	30
Acetonitrile	14.1	38.0
Acetone	17.0	20.7

a. Similar to the two preceding. Dichloromethane, carbon tetrachloride, benzene, and toluene have minimal donicity

rearrangement to the β-anomer. At the same time, structure of the ion pair must be retained and rapid dissociation prevented; otherwise the ion may maintain a conformation approaching half-chair, which would not limit the approach of alcohol (4). To prevent dissociation, a solvent of low dielectric constant is needed. It can be seen that all solvents which allow high α-selectivity have low dielectric constants (Table II). A number of solvents with good donor properties and high or moderate dielectric constants: acetonitrile, acetone, hexamethylphophortriamide have also been tested. None of these give high α-selectivity. In some of these cases, dissociation may occur (reaction 6, Figure 1) and in some cases specific interactions slightly favoring β-glycosidation may be present. It is not possible to define in detail the structure of the intermediate ion-pairs or transition states involved in the formation of α-glycosides. Nevertheless a solvent of good donor properties and low dielectric constant is clearly the sine

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qua non for high α-stereoselectivity.

Although in proper solvents, α-glycosidations of high stereoselectivity and high rate can be achieved in metal-assisted reactions with silver perchlorate (23-25) and other salts, the use of preformed glycosyl sulfonates has a number of advantages, especially for systematic investigations. The reaction is a relatively simple substitution with only two reactants in homogeneous solution, whereas push-pull mechanisms may or may not be operative in reactions with metal ions involved (10). The mechanisms are also probably simpler than the halide ion-catalyzed reactions, which depend on inversion by halide ion before reaction with alcohol (4,7,12). The sulfonates are poor nucleophiles and better leaving groups than bromide. Therefore anomerization of the ion pair presumably proceeds within a solvent cage. We have observed no influence of added sulfonate on the course of the reaction (20).

Three alkyl and three arylsulfonates have been investigated in some detail; methane-, 2,2,2-trifluoroethane-, and trifluoromethanesulfonate, p-toluene-, benzene-, and p-bromobenzenesulfonate. Others are commercially available. In the few cases examined, proton magnetic resonance indicates the configuration of C-1 is largely or completely α. Therefore the anomeric effect of the reactant per se, does not determine product composition. The reactivity of the derivatives increases with the electronegativity of the sulfonate and to avoid side reactions it was advisable to form triflates and allow them to react at -78°. The other derivatives were formed in acetonitrile from glycosyl halide and silver salt at room temperature. The solvent was removed in vacuo and replaced with the solvent of choice for glycosidation. Scrupulously dry conditions must be maintained with all reactive glycosyl derivatives. A measured quantity of bone-dry alcohol was added and glycosidation allowed to proceed. In several cases, the reaction was monitored by n.m.r. and was found to be complete in a few minutes to a few hours. The reaction mixture could be and usually was allowed to stand overnight without added base, and without workup. There was no evidence of anomerization, even though strong acid is generated in the reaction.

The stereoselectivity of the reaction is dependent not only on solvent and C-1 leaving group but also on the pattern of substituents on other carbon atoms. For that reason, optimal conditions may not have been found and observed trends with changes in experimental parameters may not be absolute. With these qualifications, a few generalizations (or oversimplifications) will be made and then some specific cases discussed.

In general, the rates and stereoselectivity of glycosidation reactions were little changed when one ether group on C-2,

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3, 4, or 6 was changed for another. The ethers that were investigated included benzyl, p-methylbenzyl, p-bromobenzyl, allyl, and crotyl. In some cases, the evidence is based on stepwise glycosidation reactions and in other cases on data from the copolymerization of 1,6-anhydro-β-D-glucopypyranose derivatives. The latter is an effective method for investigating the influence of substituents and structure on relative cationic reactivities at C-1. When an ester substituent was present on C-6, C-4, or C-3 and a p-toluenesulfonate group on C-1 of an otherwise etherified glucose or galactose derivative, the glycosidation reaction was more α-selective than when all alcoholic functions were etherified. That is, partial esterification improved α-selectivity. The more effective esters appeared to be those with ample resonance possibilities; p-nitrobenzoate rather than acetate, N-phenylcarbamate rather than N-ethylcarbamate. Esters on C-2, of course, acted as participating groups in proportion to their donor properties; benzoate was more effective than p-nitrobenzoate in forming trans-1,2-glycosides. In the formation of cis-1,2-glycosides, we obtained better stereoselectivity when p-toluenesulfonate (or methanesulfonate) was used as leaving group than when the more electronegative leaving groups were used. The nature of the reacting alcohol also had some influence on stereoselectivity. Methanol and primary alcohols gave highest α-selectivity; secondary alcohols usually gave about 5% less of α-product. Methanolyses of some triflates, hexafluorophosphates, and tetrafluoroborates gave high β selectivity at -78° (10,21). However, in a few glycosidations of the triflates with higher alcohols, the high β selectivity was lost (21). Apparently the rate of reaction 2 (Figure 1) is affected by the nature of the alcohol, and more complex alcohols may allow reaction 3 to compete effectively.

Selected reactions with C-1 p-toluenesulfonates can be seen in Tables III and IV. In the series of 2,3,4-tri-O-benzyl-1-O-p-tolylsulfonyl-D-glucopyranose derivatives, a few examples of the influence of C-6 substituent, solvent, and structure of reacting alcohol can be seen (Table III, no. 1-5). The N-phenylcarbamate derivative (no. 5) has been used in a stepwise hexasaccharide synthesis (30), and has been used to prepare p-aminophenylethyl glucotetraopyranosides for coupling to proteins (31). The stereoselectivity was equally good in the higher members of the series.

The comparable galactose derivative (Table III, no. 6) was notably solvent-insensitive, and in glycosidation reactions gave less than 40% of the α-anomer. However, when the C-6, and C-4 substituents were both N-phenylcarbamate, the proportion of α-glycoside formed in ether was markedly greater (no. 7), the derivative was sensitive to solvent structure, and in dimethoxyethane, glycosidation was comparable in α-selectivity to the best case found with glucose (no. 9). A more extensive

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Table III. Influence of Substituents and Solvents on Alpha Selectivity in Glycosidations[a]

No.	Substituents[b] C-3	C-4	C-6	Solvent 1	Alcohol	Product % α[c]	Reference
	2-O-Benzyl-1-O-tosyl-D-glucopyranose						
1	O-Bn	O-Bn	O-Bn	Acetonitrile	Methanol	60	20
2	O-Bn	O-Bn	O-Bn	Ethyl ether	Methanol	81	20
5	O-Bn	O-Bn	O-CONHPh	Ethyl ether	Methanol, 1°,2°	95-90	20,29,30
3	O-Bn	O-Bn	O-CONHEt	Ethyl ether	Methanol	85	20
4	O-Bn	O-Bn	p-MeOBz	Ethyl ether	Methanol	90	20
	2-O-Benzyl-1-O-tosyl-D-galactopyranose						
6	O-Bn	O-Bn	O-CONHPh	Ethyl ether	Methanol, 1°,2°	37-30	22 Cf. 21
7	O-Bn	O-CONHPh	O-CONHPh	Ethyl ether	Methanol	58	22
8	O-Bn	O-CONHPh	O-CONHPh	Dioxane	Methanol	87	22
9	O-Bn	O-CONHPh	O-CONHPh	Dimethoxyethane	Methanol	94	22
10	O-CONHPh	O-CONHPh	O-Ac	Tetrahydrofuran	Methanol	81	22
11	O-CONHph	O-CONHPh	O-Ac[d]	Dimethoxyethane	Methanol, isobutyl alcohol	93,[d]91	22

[a]Approximately 15% excess alcohol was used, at ambient temperature. [b]O-Bn means O-Benzyl; O-CONHPh, N-phenylcarbamate; O-CONHEt N-Ethylcarbamate; p-MeOBz, p-methoxybenzoate; O-Ac, O-acetyl. [c]The lower values of % α correspond to more complex alcohols. [d]Methanolysis of three similar compounds gave very similar results: 1-O-mesyl (92% α), 2-O-allyl (94% α), 2-O-allyl-1-O-mesyl (94% α) ref. 22.

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Table IV. Rapid Glycosidations on 1-O-Tosyl-D-Mannopyranose Derivatives[32,a]

No.	Substituents C-2	C-3	C-4	C-6	Solvent	Product % α
1	O-Bn	O-Bn	O-Bn	O-CONHPh	Ethyl ether	43[b]
2	O-Bn	O-Bn	O-Bn	O-CONHPh	Acetonitrile	37[b]
3	O-Bn	O-Bn	O-Bn	O-CONHPh	Methylene chloride	53[b]
4	O-Bn	O-Bn	O-Ac	O-Ac	Ethyl ether	50
5	O-Bn	O-Ac	O-Ac	O-Ac	Acetonitrile	54
6	O-Cl_2Ac	O-Bn	O-Bn	O-Bn	Ethyl ether	54
7	O-Ac	O-Bn	O-Bn	O-Bn	Ethyl ether	98[c]

[a]Reaction at room temperature with methanol. [b]Minor variations when benzyl replaced by p-bromobenzyl or other sulfonate leaving groups used. [c]No significant change when C-2 substituent was benzoate or p-methoxybenzoate. Dichloromethane as solvent gives highest yield. p-Nitrobenzoate as C-2 substituent gave lower selectivity.

series of experiments was carried out with 6-O-acetyl-2-O-benzyl-3,4-di-O-N-phenylcarbamyl-1-O-p-tolylsulfonyl-D-galactopyranose and three closely related compounds (Table III, no. 10-12 footnote d.) These gave high proportions of α-galactosides when reaction was carried out in dimethoxyethane. Diethyl ether appeared to give results only slightly inferior.

A number of mannopyranosyl derivatives with a variety of ether and ester substituents and sulfonate leaving groups failed to show any solvent-sensitivity (29) and little or no preference for either anomer on glycosidation (Table IV, no. 1-6). The results could easily be interpreted as Rhind-Tutt and Vernon (4) explained the solvolysis of 2,3,4,6-tetra-O-methyl-α-D-mannopyranosyl chloride: shielding of the back side of C-1 and dissociation prior to reaction. In the absence of any trend which suggested a method of improving α-mannopyranoside selectivity of compounds with non-participating substituents on C-2, it appeared advisable to use a participating group on C-2. This reaction might also serve as a model reaction for rapid trans-1,2-glycoside syntheses.

3,4,6-Tri-O-benzyl-1-O-p-tolylsulfonyl-D-mannopyranose derivatives were made with various ester functions on C-2. With acetate, benzoate, and p-methoxybenzoate on C-2, glycosidation was nearly completely α-stereoselective (Table IV, no. 7, footnote c). It was not clear that any β-isomer was formed. The solvent used in these cases made no difference to the stereoselectivity. It was obvious that solvent did not compete with C-2 ester in participation. As observed previously in other glycosidations (6) p-nitrobenzoate was a less effective participating group. These glycosidations proved to be very rapid and reaction was complete in less than half an hour when 10-20% excess alcohol was used. Application of the reaction to oligosaccharide synthesis has been successful but as always, the reaction tends to be slightly less α-selective with secondary alcohols.

A study of glycosidation of 2-O-acyl-3,4,6-tri-O-benzyl-1-O-p-tolylsulfonyl-D-galactopyranose by E. Rachaman (33) has given comparable results and will be reported. However, the use of the tosylate leaving group on fully esterified sugars has not as yet been fully successful and requires further study.

In conclusion, it appears unlikely that a general method for stereoselective α-glycoside synthesis will be found. However, the rates and stereoselectivity of both α- and β-glycoside syntheses can be controlled independently. By a suitable choice of experimental parameters, reasonably satisfactory syntheses can be devised for either class of glycoside.

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Summary

The rate of glycosidation reactions can be enhanced by using various alkyl and aryl sulfonates as leaving groups on C-1. High cis-1,2-α-selectivity in the reaction of appropriately substituted glucose and galactose derivatives can be achieved by the use of a solvent of strong donor properties and low dielectric constant, typically an ether. The structure of the solvent, and the configuration of the sugar and the pattern of its substitution, all influence the interaction of solvent and C-1 ion-pair. This in turn affects the stereoselectivity of the glycosidation. The course of the reaction is not directly determined by reactant anomeric effects but can be described generally in terms of the Rhind-Tutt and Vernon mechanism.

α-D-Mannopyranosyl and β-D-galactopyranosyl glycosides can be prepared rapidly and stereoselectively from glycosyl sulfonates with C-2 participating groups. The reactions leading to trans-1,2-glycosides appear less sensitive to experimental variables than those leading to cis-1,2-glycosides.

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Conformational Interactions in 1,4-Heterobutane Segments

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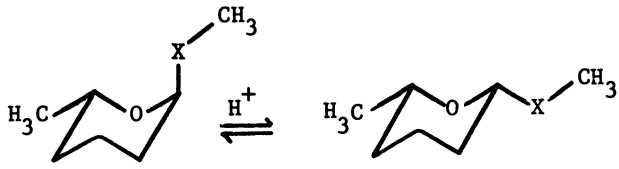
The anomeric effect (relating to X-C-Y interaction) in 2-alkoxytetrahydropyrans and 2-alkylthiotetrahydropyrans was compared some years ago (1). The results are shown in Scheme 1;

O/O and S/O Anomeric Effect (1)



X	Solvent	ΔG° (kcal/mol)
O	CCl_4	0.73
S	CCl_4	0.35
O	CH_3CN	0.35
S	CH_3CN	-0.08

Scheme 1

since the steric component of the CH_3O versus CH_3S axial interaction is not known in these systems, the results unfortunately do not permit evaluation of the relative anomeric effects of S-C-O versus O-C-O. One way out of this difficulty would be through evaluation of the steric part of the interaction by force-field calculation, but unfortunately, such calculations have so far had limited success for oxygen-containing saturated heterocycles.

Comparison of the O-C-O with the S-C-S anomeric interaction has been effected (2,3,4) as shown in Scheme 2. In this case one can tell, unequivocally, that the O-C-O anomeric effect is the larger, for the overall ΔG° in the two systems is nearly the same and from the known conformational energies of 2-alkyl-1,3-dioxanes and -1,3-dithianes (5) it is obvious that the countervailing

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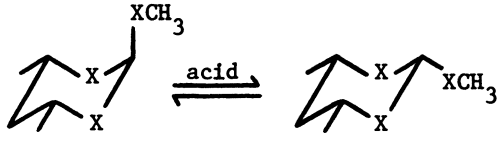
steric effect is much more important in the 1,3-dioxane system.

O/O and S/S Anomeric Effect (2,3)

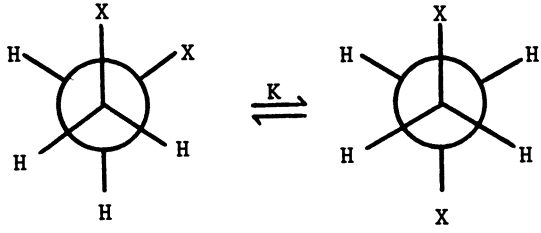


X	ΔG° (kcal/mol)(solvent)
O	0.41 ($C_2H_5OC_2H_5$) (2)
S	0.73 (CCl_4, C_6H_6) (3)
S	0.48 ($CH_3OCH_2CH_2OCH_3$) (3)
S	0.31 (CH_3CN) (3)

Scheme 2

The main subject of this paper is the gauche effect (relating to X-C-C-Y interaction). Referring to Scheme 3, we may consider the gauche effect to be attractive when the gauche conformation

Gauche Effect



attractive: K smaller than expected
repulsive: K larger than expected
} on purely steric grounds

attractive: F/F, O/F, O/O
repulsive: S/S

Scheme 3

is favored more (or the anti less) than calculated on the basis of known steric and polar interactions. Contrariwise, if the anti conformation is favored more (or the gauche less) than the calculations lead one to believe, the gauche effect is repulsive.

Attractive gauche effects have long been known, for example, when X=Y=CH_3O (6) or X=Y=F (7,8,9,10) or X=F, Y=$OCOCCl_3$ (11), and a theoretical connection of the gauche effect with the anomeric effect was made some years ago (12). The repulsive interactions, on the other hand, were not well recognized until recently. However, in 1976 Zefirov and coworkers (13), on the basis of a study

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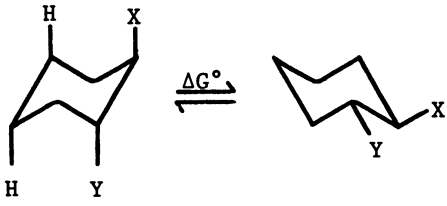
of the conformational equilibrium of certain trans-1,2-disubstituted cyclohexanes (Scheme 4, data derived from measurement of

Repulsive Gauche Effect (13)



$\Delta G_X + \Delta G_Y$ $\qquad$ $E_v^{X/Y} + E_\mu^{X/Y}$

Principle: If there is no additional effect

$\Delta G^\circ_{expt} = (\Delta E_{steric} + \Delta E_{polar})$ calc'd

If $\Delta G^\circ_{expt} > (\Delta E_{steric} + \Delta E_{polar})$ calc'd, there is a repulsive gauche effect [and when

$\Delta G^\circ_{expt} < (\Delta E_{steric} + \Delta E_{polar})$ calc'd, there is an attractive gauche effect]

Scheme 4

vicinal proton coupling constants), concluded that repulsive gauche effects [which Zefirov had earlier (14) termed "hockey-sticks effects"] occur for X=Y=SR; X=SCH_3, Y=Br; X=SCH_3, Y=OCH_3; X=SCH_3, Y=Cl and X=Y=Br. They also concluded that attractive effects existed when X=Y=OR or X=F, Y=I. These conclusions were arrived at by comparing the experimentally determined equilibria with those calculated on the basis of the known ΔG° value (in cyclohexyl-X) of X and Y, and the calculated X/Y interaction. The steric part of the latter was estimated by the Hill equation (15) and the polar part by a charge-charge interaction (16). For CH_3O/Cl, CH_3O/Br, CH_3O/I and Cl/I, the calculated equilibrium agreed with that experimentally found, so there is no gauche effect. An attractive gauche effect was inferred when the equilibrium was further to the right than calculated, a repulsive one when the equilibrium was displaced to the left. As we shall see later, while we agree with Zefirov's conclusions, at least in the case of O/O, O/S and S/S, his approach is not without danger since the calculations tend to underestimate the steric effects even in those cases where no gauche effect comes into play.

Our own investigations involved 5-methoxy- and 5-methylthio-1,3-dithianes (Scheme 5, X=S, Y=O or S); the corresponding 1,3-dioxanes had been studied previously (17).

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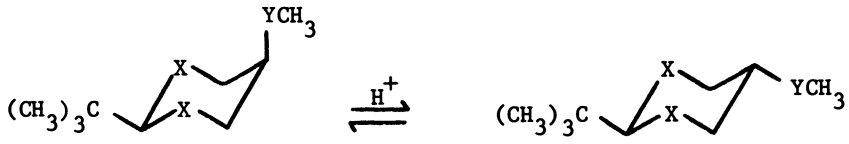
Gauche Effects



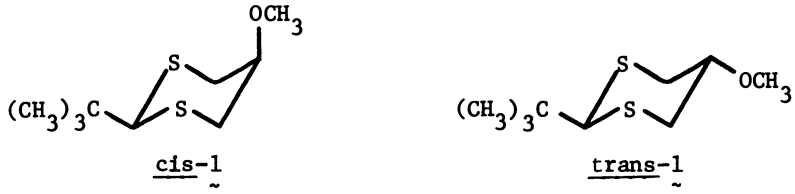
Compd.	X	Y	-ΔG° kcal/mol in $CHCl_3$	in CH_3CN
1	S	O	1.09	1.22
2	S	S	1.49	1.57[b]
3	O	S	(1.55)[a,b]	1.13[b]
4	O	O	0.16[b]	-0.01[b]
5	CH_2	O	0.55	
6	CH_2	S	1.07	

[a]In benzene. [b]Ref. (17).

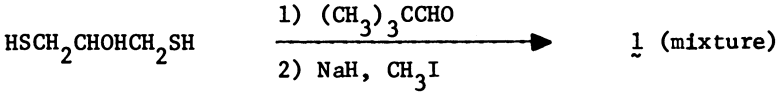
Scheme 5

Synthesis of the methoxy compounds (Scheme 6) was straightforward with the two isomers being best separated by column chromatography at the hydroxy stage. (The cis, or axial, isomer is intramolecularly hydrogen bonded and therefore less strongly adsorbed.)

Synthesis of 5-Methoxy-1,3-dithianes (1)



cis-1 trans-1



Separation at OH stage by column or dry-column chromatography

Scheme 6

The configurational assignment was simple also (Scheme 7): the more easily eluted cis-isomer showed intramolecular hydrogen bonding in the infrared at 3541 cm^{-1} whereas the trans-isomer displayed the free OH stretch at 3640 cm^{-1}. The cis-isomer, by proton NMR spectroscopy, showed only gauche coupling constants for

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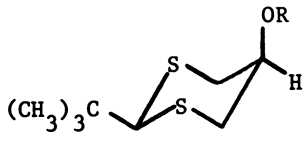
Configurational Assignment of 5-Methoxy-1,3-dithianes (1)



R=H, infrared
(intramolecular H-bonding)
cis: 3541 cm^{-1}, trans: 3640 cm^{-1}

H-5:	R=H	J = 1.7 Hz, 4.5 Hz
	R=Me	J = 4 Hz (quintet)
Isomer:	R=H	J = 10.4 Hz, 4.3 Hz
	R=Me	J = 10.4 Hz, 3.6 Hz

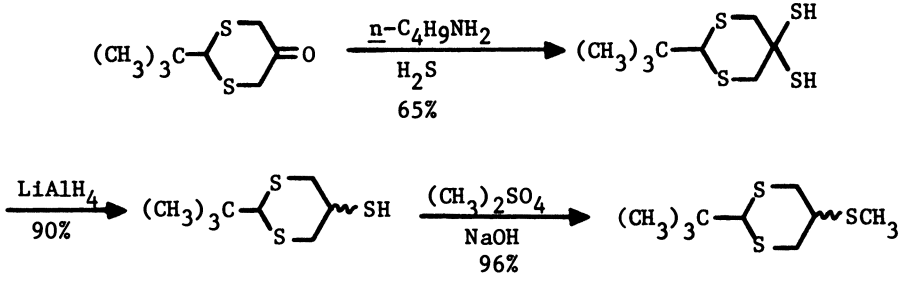
Also X-ray structure of axial isomer ($R=CH_3$);
dipole moments (cis, 2.08D, trans, 1.40D)

Scheme 7

H-5 (triplet of triplets at 3.86 ppm, J = 4.5 Hz, 1.7 Hz) and the corresponding methyl ether displayed a (degenerate) quintet at 3.48 ppm, J = 4 Hz. In contrast, the trans hydroxy compound showed a large (anti) coupling constant of 10.4 Hz and a small (gauche) coupling constant of 4.3 Hz for H-5 at 4.01 ppm, the corresponding coupling constants for the methoxyl analog being 10.4 and 3.6 Hz (at 3.53 ppm). The dipole moment of the axial and equatorial methoxyl compounds were 2.08 and 1.40D, respectively and the structure of the cis isomer was confirmed by X-ray crystallography (see below).

Synthesis of the methylthio compounds followed a route previously used for the cyclohexyl analogs (18) and is depicted in Scheme 8; the starting material is readily available (19) by a Dieckmann condensation of the acetal $(CH_3)_3CCH(SCH_2CO_2C_2H_5)_2$.

Synthesis of 5-(Methylthio)-1,3-dithianes (2)



cis by crystallization; trans by glpc or column chromatography

Scheme 8

The structural assignment follows from the dipole moment (cis, 2.08D, trans, 1.53D), from the proton NMR spectra (at C-4,6) of the 5-deuterated compound (Scheme 9) and from the crystal-structure analysis (see below) of the cis-isomer. Since the proton spectra of the 5-(methylthio)-1,3-dithianes were degenerate in the region of the protons attached to C-4,5,6 we examined, instead, the 5-deuterio analogs synthesized by replacing $LiAlH_4$ in Scheme 8 by $LiAlD_4$. As seen in Scheme 9, the trans-isomer displays a broad signal for the upfield leg of the AB pattern of the protons attached to C-4,6 due to the sizeable (ca. 1.6 Hz) coupling constant between the axial H and the axial D. The signal sharpens when the deuterium is decoupled. No such broad signal is seen in the (undecoupled) spectrum of the cis-isomer, which lacks the 180° vicinal coupling constant ($^3J_{H/D}$).

Equilibration of the 5-methoxy- and 5-(methylthio)-1,3-dithianes was effected by means of trifluoroacetic acid in either chloroform or acetonitrile with the results shown in Scheme 5. [The previously determined equilibria for the corresponding 1,3-dioxanes (17) and cyclohexanes (18,20) are included for comparison.] Equilibration in these solvents proceeded rapidly (in a matter of a few hours or less) and reasonably smoothly, although on prolonged contact time there is some decomposition of the 5-methoxy compounds and some ring contraction in the 5-methylthio compounds which leads to their conversion to the more stable 4-(methylthio)methyl-1,3-dithiolanes. Excessive decomposiiton occurred in pure CF_3CO_2H and equilibration was inconveniently slow in ether. The equilibrium for both the CH_3O- and CH_3S-compounds depended on the ratio of acid to solvent, with $-\Delta G°$ increasing upon increasing dilution. The results in Scheme 5 refer to a volume dilution of 1:19 in $CHCl_3$ or 1:57 in CH_3CN.

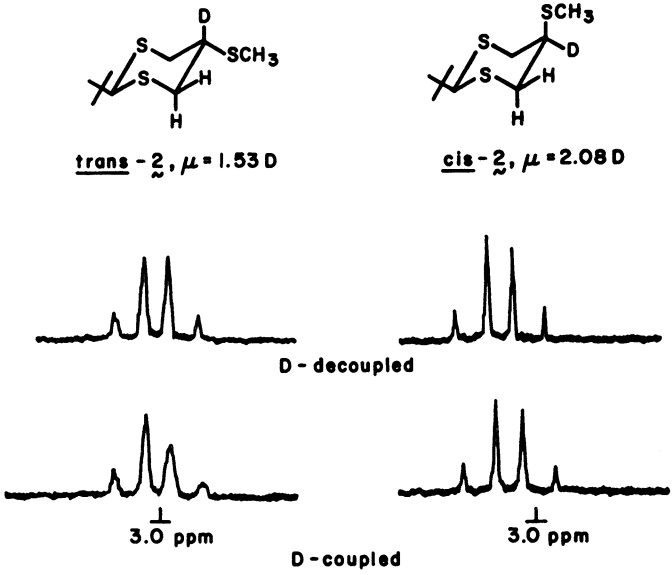
The equilibration results are summarized in Table 1. The second column ($\Delta G°$) gives experimental $\Delta G°$ values, the third column ΔE-values ($E_{ax} - E_{eq}$) calculated on the basis of Hill's equation (15) using Allinger's recent parameters (27).

Table 1

$\Delta G°$ for Equilibrations (in CH_3CN)[a]

Compound	$-\Delta G°_{expt}$	ΔE^{b}_{steric}	$\Delta\Delta_{steric}$	$\Delta E_{elec.}$	$\Delta\Delta^{c}_{total}$
CH_2/O (5)	+0.55	+0.55	0.00	0	0.00
CH_2/S (6)	+1.07	+3.24	-2.17	0	-2.17
O/O (4)	-0.01	+0.18	-0.19	+2.22	-2.41
O/S (3)	+1.13	+0.01	+1.12	+1.49	-0.37
S/O (1)	+1.22	-0.37	+1.59	+0.64	+0.95
S/S (2)	+1.57	-1.05	+2.62	+0.36	+2.26

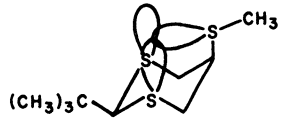
[a] kcal/mol. [b] Difference between experimental and calculated steric energy. [c] Difference between experimental and total calculated energy.



Proton Spectrum (H-4, 6)

Scheme 9

Gauche - repulsive interaction



Scheme 10

Poor agreement between experimental and calculated values is found for the methyl sulfide 6: the calculated repulsion is far too large, no doubt because energy minimization was not attempted in the calculation. For the methoxy compound (5), on the other hand, agreement between the two values is surprisingly good.

Column 4 ($\Delta\Delta_{steric}$) suggests attraction in the case of O/O (compound 4) and repulsion in the three other cases (1-3) over and above that calculated on the basis of steric factors. (If the calculated repulsion for the sulfur compounds is too low - vide supra - the excess repulsion is even greater than shown.) At first glance, the excess repulsion may be ascribed to well-understood electrostatic causes. To test this possibility, the electrostatic interactions between the exocyclic heteroatom Y and the endocyclic atoms X as well as C-2 in compounds 1-3 were computed by calculating the charges on the heteroatoms and C-2 and then the interaction between them assuming a dielectric constant of unity (16). (If the effective dielectric constant is larger, the electrostatic interaction is less than indicated.) The differences in electrostatic interactions between stereoisomers thus calculated are indicated as $\Delta E_{elec.}$ in column 5 and the total final difference $\Delta\Delta_{total}$ between calculated (steric plus electrostatic) and experimental values is entered in column 6. (Column 6 = column 4 - column 5 = column 2 - sums of columns 3 and 5.)

It is quite clear from the data that there is substantial "excess" attractive interaction in compound 4; i.e. the slight experimental preference for the axial conformation contrasts with a substantial calculated preference for the equatorial one; the difference has been ascribed to the "gauche attractive effect" between oxygens (14,17). In contrast, for compounds 1 and 2 there is a substantial "excess" repulsion, i.e. the equatorial conformation is preferred more than calculated. The effect, which has been called "gauche repulsive effect" (14) is especially marked for gauche interactions between sulfur atoms, as in 2. Only in the case of compound 3 is the difference between calculated and observed preference for the equatorial position sufficiently small to make any conclusion uncertain, especially in view of the fact that, in the absence of energy minimization, the calculated energy difference (1.50 kcal/mol) may be somewhat overestimated.

This is not the place to discuss the origin of the gauche attractive effect about which there has been much controversy (21, 22). On the other hand, as to the gauche repulsive effect, we agree with Zefirov in ascribing it to a (repulsive) overlap of the 3p orbitals on sulfur (Scheme 10). These orbitals extend outward much further than the 2p orbitals of oxygen and the repulsive overlap situation for O/S is marginal and may depend on the exact geometry of the system.

It ought to be possible to put in evidence the interaction of the unshared electrons on the ring and exocyclic sulfur atoms in a compound such as cis-2. Efforts to do so by photoelectron

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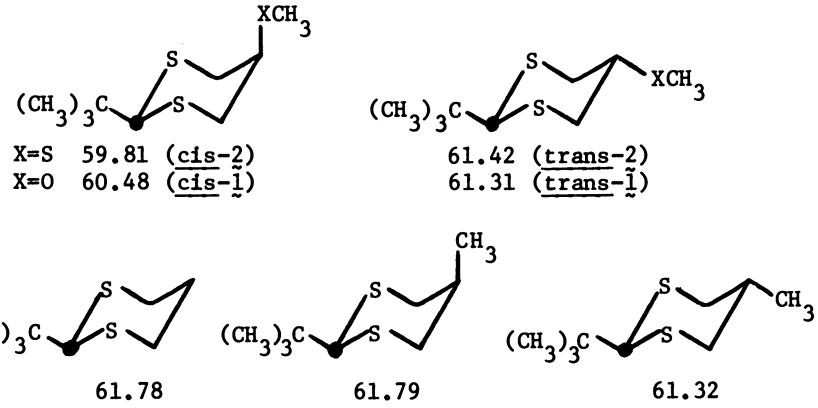
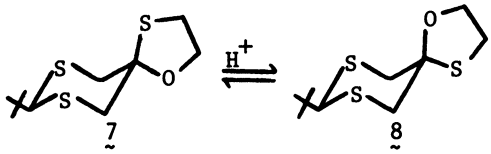
spectroscopy have so far been to no avail, the spectra being too complex. However, an effect, albeit somewhat marginal, may be seen in the effect of an axial 5-methylthio group (in cis-2) and, to a lesser extent, of an axial 5-methoxy group (in cis-1) on the ^{13}C NMR signal at C-2 in a 1,3-dithiane. As seen in Scheme 11,



Scheme 11

the axial isomers cis-2 and cis-1 display a palpable upfield δ-shift caused by the XCH_3 group; no such shift (relative to the reference compounds shown at the bottom of Scheme 11) is shown by trans-2 and trans-1. There is at least a suspicion that the effect of the axial oxygen or sulfur at C-5 is transmitted through space (via the ring sulfur atoms) to C-2 whose chemical shift is affected.

In the course of this research we synthesized the oxathia-spiro systems shown in Scheme 12 and equilibrated them with acid.



7 8

Solvent	Temp. (°C)	7/8 (K)	ΔG° (kcal/mol)[b]
$CHCl_3$ - TFA[a] (3:1)	25	1.36±0.05	0.18±0.02
$CHCl_3$ - TFA[a] (19:1)	61	1.34±0.06	0.19±0.03
$CHCl_3$ - cat. TFA[a]	25	1.38±0.09	0.19±0.04

[a]Trifluoroacetic Acid. [b]Expected ΔG° = -0.42 kcal/mol.

Scheme 12

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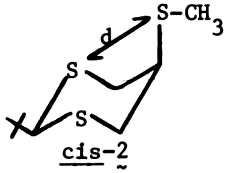
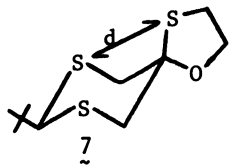
It became obvious that the experimental $\Delta G°$ value was not the difference of $\Delta G°_{SCH_3}$ and $\Delta G°_{OCH_3}$. The situation resembles one detected some 15 years ago in the corresponding spiro systems derived from cyclohexane (23,24). Additivity was found in the (6.6) but not in the (6.5) spiro systems. The explanation then given was one of outward bending of the 5-membered spiro ring which was believed to relieve the syn-axial S/H more than O/H because of the longer C-S bond. McPhail and Hargrave (25) have now compared the crystal structures of pertinent axial SCH_3 (and OCH_3) analogs with those of the oxathianes 7 and 8 (Scheme 13) and



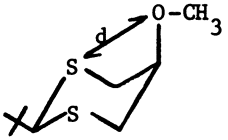
cis-2

d = 3.46±0.003 Å



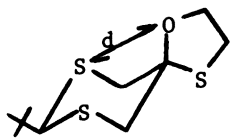
7

d = 3.44±0.002 Å



cis-1

d = 3.214±0.005 Å



8

d = 3.232±0.004 Å

Scheme 13

have found that the salient distances (marked d in Scheme 13) are virtually the same in the monocyclic and spirobicyclic systems. Thus there can be no question of "outward bending" in spirobicycles — if anything the effect is in the wrong direction since the axial S is slightly closer to the ring S in 7 than in cis-2 (and the axial O is slightly further away from the ring S in 8 than in cis-1).

Availability of low-temperature ^{13}C-NMR spectroscopy and a gift of various spiro compounds (from F. W. Vierhapper and P. Picard) enabled us to survey several additional systems with the results shown in Scheme 14. There is additivity for CH_2 and S but not for CH_2 and O or for O and S.

An explanation for the CH_2/O case has been suggested by Picard (26) and is summarized in Scheme 15.

For an axially substituted CH_3 compound, the torsionally favored conformation is the staggered one (A) but in this conformation there is a sizeable steric interaction of the "inside-H" (underlined) with the syn-axial hydrogen atoms of the ring. No such interaction exists for oxygen, hence $O<<CH_3$ in size. But in

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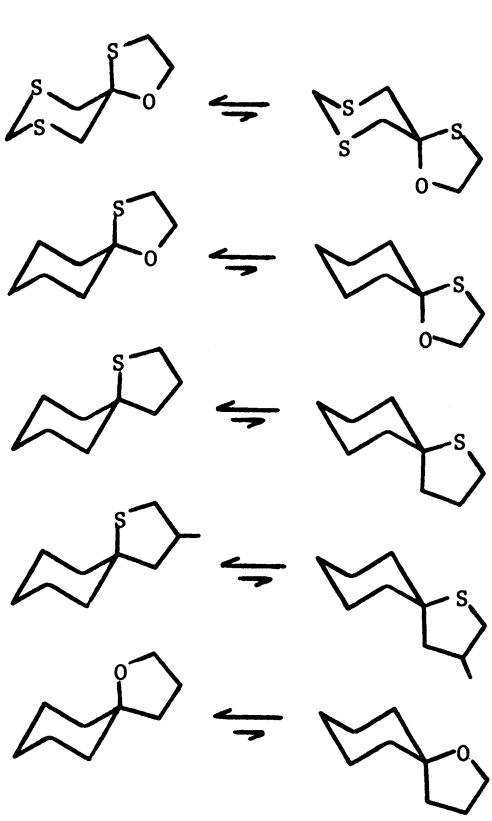

ΔG° calcd		ΔG° found
-0.42	≠	+0.45±0.02
-0.47	≠	+0.36±0.01
+0.7	≈	+0.73±0.01
+0.7	≈	+0.78±0.03
+1.15	≠	+0.23±0.10

Scheme 14

a 5-membered ring the CH bonds become by necessity nearly eclipsed (B) and while this leads to an increase in torsional interaction (which does not affect ΔG° since it comes into play for both the axial and the equatorial group), it leads to a diminished H/H steric interaction. This makes the axial CH_2 less unfavorable (vis-à-vis O) in B than it was in A (O<CH_2) and hence the conformational energies of B (CH_2 versus O axial) are not the sum of those in A (CH_3 versus O axial).

If this interpretation is correct, it must mean (Scheme 14, first four entries) that S behaves like CH_2 and not like O. In other words, the extended filled p-orbitals on sulfur must interact with the axial H's (or C-H bonding electrons) of the ring much like the C-H bonds of the methyl group do.

Both this hypothesis and the finding of the gauche repulsive effect tend to throw new light on the "steric requirements" of unshared electrons on atoms below the second row of the Periodic Table.

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C

D

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T

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