THE ROLE OF LONE PAIR INTERACTIONS IN THE CHEMISTRY OF THE MONOSACCHARIDES. THE ANOMERIC EFFECTS

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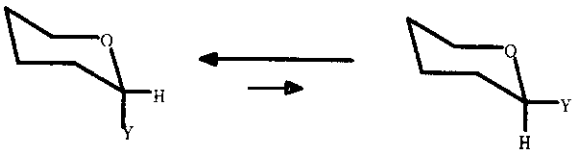
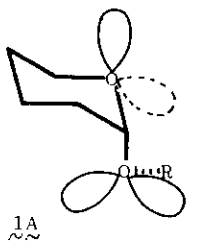
Abstract - The electronic factors which contribute to the anomeric effects have been attributed to the destabilizing n-n (lone pair - lone pair), or/and the stabilizing n-σ*, interactions of the non-bonded electron pairs of geminal heteroatoms. Predictions of the chemistry of the simple monosaccharide acetals, based on a n-σ* hypothesis, are not consistent with the experimentally observed chemistry. Thus, the n-σ* hypothesis is not a useful model for rationalizing the chemical reactivity of acetals, or the closely related anomeric effects. A study of the X-ray crystallographic data of some monosaccharides also casts considerable doubt on the validity of the bond length and bond angle criteria that have been used to assert the importance of the n-σ* hypothesis. A hypothesis based on dominant n-n interactions, with a minor contribution from the n-σ* interactions, is a better model for rationalizing the chemistry of the simple acetals. This combination of electronic factors illuminates both the anomeric effects and the chemistry of the acetals.

INTRODUCTION

The anomeric effects are among the most discussed and most important areas in carbohydrate chemistry (ref. 1). The anomeric effects (ref. 2) are encountered in the solution equilibria of glycopyranosyl compounds, and other similar acetals, and confer a greater stability on those molecules that have an axial C1 heteroatom





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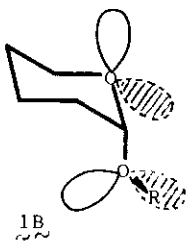

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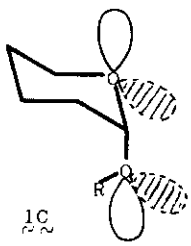

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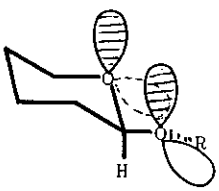

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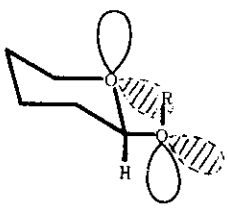

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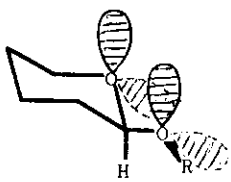

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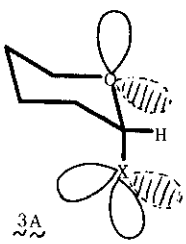

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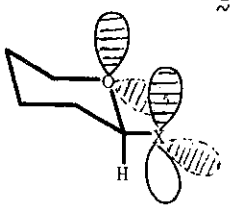
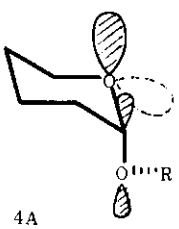
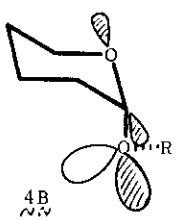


3B

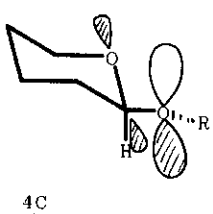
Scheme 1



4A



4B



4C

Scheme 2

substituent (α-anomers), over their equatorial isomers (β-anomers); Scheme 1. This "unusual" stability of the axial heteroatom (or group) is opposite to that encountered in the analogous cyclohexanes (ref. 3).

The anomeric effects must be the outcome of the dynamic interplay of steric and electronic factors which are present at, and close to, the anomeric center of the host molecule. The anomeric effects are small in magnitude, with estimates of their value ranging from 1 to 3 kcals. The steric component is the free energy difference between the glycosidic group in the axial and the equatorial orientations. This energy difference is usually about 1 kcal and favours the equatorial isomer. The electronic factors, which favour the axial isomer, must therefore contribute about 2 to 4 kcals. These small effects can easily be masked by energy changes due to molecular solvation etc. Indeed, the sizes of the anomeric effects vary from solvent to solvent.

The term "anomeric effect" defines a stereochemical feature of acetals and the heteroatom analogues. The term does not properly refer to the stereochemical preferences of hydrogen, radical, or n orbitals which are borne by the anomeric carbon.

Traditionally, the anomeric effects have been regarded as phenomena which bear little, if any, relationship to the chemistry at the anomeric center. However, both the anomeric effects and the chemistry at the anomeric center are intimately associated with the lone pairs of electrons borne by the heteroatoms which define the anomeric center. All stereo-electronic effects which result in the redistribution of electron density must modify the structure and reactivity of their host molecule. Therefore, there must be experimental chemistry which will provide evidence to define the existence and origins of these effects. Many investigators have examined the structural features of the saccharides in the solid phase for clues to the origins of the anomeric effects, while the relevance and importance of the CHEMISTRY at the anomeric center has received little attention.[4] The glycopyranoses and their simple derivatives will be the focal point of this discussion since the effects were first noticed, and are best appreciated, in these molecules. For clarity and convenience the diagrams will show sp3-like hybrid atomic orbitals for the lone pairs on oxygen, rather than the now widely accepted σ, π pair of orbitals.

Two hypotheses, or some combination of them, seek to define the origin of the electronic factor(s) that is most important to the manifestation of the anomeric

effects. Edwards (ref. 2a) originally proposed by that the anomeric effect was the consequence of the dipolar interactions involving the acetal oxygens of the glycopyranosides. This idea eventually focused attention on the interactions of the lone pairs of electrons on the oxygen atoms. Scheme 1 shows the chair conformations of the α- and β-anomers of a glycopyranoside and the n orbitals. By considering the nature of the n-n interactions and the degree to which each anomer is affected by these interactions, the relative stabilities of the anomers have been rationalized (refs. 4a and 5).

More recently, theoreticians have suggested that stabilizing n-σ* delocalizations, for example that of the lone pair of O5 into the coplanar σ* orbital of the adjacent C1-O1 bond, could be the origin of the anomeric effect. The n-σ* hypothesis requires that these interactions be more significant in the α-anomer than in the β-anomer. The theoreticians have sought to develop algorithms, based on these orbital interactions, that simulate the structural features of acetals and hence the anomeric effects.

A few theoreticians have continued to express some support for both models. For example, Wolfe et al. (ref. 6) suggested that algorithms based on a n-n interaction model will also simulate the anomeric effects, but that these algorithms are more difficult to formulate. Tvaroska has stated that, for acetals, the n-n interaction model is of greater validity than a n-σ* model (ref. 7). The orbital energies of β-anomeric acetals have been measured by Jorgensen et al., using photoelectron spectroscopy (ref. 8), and these energies are consistent with the dominant role of n-n interactions, as will be discussed below.

1.0.0 THE n-σ* STABILIZATION HYPOTHESIS

The n-σ* model has been developed by theoretical chemists in order to simulate the X-ray crystallographically determined structural features of the saccharides. The assumption that the structure in the solid phase is the most stable structure of the molecule is of prime importance to the validity of this model. The structural features that are deemed to be consequences of the n-σ* interactions will be outlined below.

There are many examples of molecules which crystallize in more than one conformation, which often have different dimensions. Further, some molecules are apparently grossly distorted in their unit cells because of packing and dipolar interactions (ref. 9). Even when these factors are taken into consideration, there

are many molecules whose data do not support the n-σ* hypothesis. Nevertheless, by selecting suitable X-ray data and adjusting their algorithms accordingly, some aspects of the structural features of some simple acetals have been simulated. To date, these efforts fail to simulate the variation of the size of the anomeric effects with the presence of other oxygen functional groups in the molecule.

1.1.0 THE MONOSACCHARIDE IN THE SOLID PHASE

1.1.1 n-σ* DELOCALIZATIONS IN THE α-ANOMERS

The orbitals which can participate in the n-σ* processes are shown in the Scheme 2 for the chair conformations of the sugar. Conformation (1A) of α-anomers is the most stable and most frequently observed in the solid phase.

There can be two independent n-σ* processes in (1A). One of these interactions can occur between the axial lone pair of O5 and the coplanar axial σ* orbital of the C1-O1 bond, diagram (4A). While the molecule remains in the chair conformation, these orbitals are fixed in space relative to each other. Thus, the efficiency of overlap of these orbitals ought to be maximal. The other interaction can occur between the lone pair on O1 and the coplanar σ* orbital of the C1-O5 bond, diagram (4B). In the crystal, the aglyconyl atom(s) can be regarded as being fixed in space, although not necessarily in the geometry best suited for maximal n-σ* orbital overlap. Thus, the O1 lone pair delocalization could be as efficient as the O5 lone pair delocalization, but it could also be much less efficient, depending on the conformation at the C1-O1 bond. The O5 lone pair delocalization can occur simultaneously with the O1 lone pair delocalization, since they involve different orbitals, and so they should reinforce each other in their stabilizing influence. The delocalizations discussed above should cause the bond linking the donor atom to the receptor atom, for example the C1-O5 bond in diagram (4A), to acquire some π-character and to become shorter. The receptor bond, the C1-O1 bond, should simultaneously become longer. There should also be a change in the size of the O5-C1-C2 bond angle. More efficient delocalizations should produce greater geometrical changes.

The X-ray crystallographic data of the α-pyranoses and pyranosides show that their C1-O1 bonds are usually, but not always, shorter than the C1-O5 acetal bonds (ref. 10). Thus, the n-σ* hypothesis suggests that the O1 to C1-O5 n-σ* process is usually dominant in the solid phase.

1.1.2 n-σ* DELOCALIZATIONS IN THE β-ANOMERS

The O5 lone pairs and the C1-O1 orbitals of β-glycopyranosides in chair conformations cannot become anti-coplanar. Thus, β-anomers cannot display O5 to C1-O1 delocalizations in chair conformations. However, an O1 to C1-O5 delocalization is possible (Scheme 2, diagram (4C)) and so the C1-O1 bond of the β-anomer should always be shorter than the C1-O5 bond, and the C1-O1 bond of the corresponding α-anomer.

1.1.3 n-σ* DELOCALIZATIONS AND THE ANOMERIC EFFECT

This discussion above leads to the conclusion, the n-σ* hypothesis, that the anomeric effects are the result of the stability gained by the α-anomer from the two possible n-σ* delocalizations, opposed by the sum of the steric liability of the axial substituent at C1 and the single n-σ* delocalization of the β-anomer.

1.2.0 THE MONOSACCHARIDE IN SOLUTION

A glycopyranoside in solution must be conformationally mobile, but it is often assumed that a monosaccharide has the same geometry in solution as in the solid phase. Recent studies of the high field nmr spectra of some sugars (ref. 1b) have cast doubt on this assumption. If n-σ* interactions are important, conformational mobility, particularly rotation about the C1-O1 bonds, should affect the lengths of the bonds at the anomeric center, especially those of α-anomers. The possible consequences of these conformational changes will therefore be discussed for the α-anomer.

1.2.1 α-ANOMERS

In solution, the axial n orbital of O5 will be anti-coplanar to the axial O1-C1 orbital when the molecule is in a stable chair-like conformation. Thus, most of the molecules of the α-anomer will have an O5 lone pair properly oriented for delocalization into the C1-O1 σ* orbital. On the other hand, free rotation about the C1-O1 single bond will ensure that an O1 lone pair will not always be properly aligned for delocalization into the C1-O5 σ* orbital. Thus, the O1 to C1-O5 delocalization must be attenuated and it must be less efficient than the longer-lived O5 to C1-O1 delocalization.

This analysis suggests that the n-σ* delocalization that is thought to be dominant in the solid phase cannot be dominant in solution. If these stereo-electronic

effects are important, then the geometrical features of the sugars must be different in the solid phase from in solution.

No attempt will be made to examine the consequences of solvation on the geometrical features of sugars in solution. Since the energy of solvation can easily surpass the accepted magnitude of the anomeric effect, caution must also be exercised in assuming that the geometrical features of the sugars are constant in different solvents.

At present, we cannot measure the bond lengths/angles of complex molecules in solution. Until the correspondence of bond lengths/angles in different phases has been demonstrated, there is no basis for assuming that these parameters can remain constant. Thus, a rationalization of the anomeric effect based on observations of the solid phase might have no validity in solution.

1.3 THE CHEMISTRY OF THE ANOMERS IN SOLUTION

Deslongchamps has alluded to the chemistry that ought to be observed if the n-σ* delocalizations were present in acetals (ref. 5). In addition to the changes in the bond lengths discussed above, the delocalization of electron density from O5 into the σ* orbital of the C1-O1 bond should cause O5 to acquire a partial positive charge and O1 to acquire a partial negative charge. On the other hand, the delocalization of electron density from O1 into the σ* orbital of the C1-O5 bond should cause O5 to acquire a partial negative charge, and O1 to acquire a partial positive charge. Any lone pair that effectively participates in a n-σ* interaction will become more stable, less available and the parent atom less nucleophilic.

For β-glycopyranosides in the chair conformation, since there can only be an O1 to C1-O5 delocalization, the O1 should develop a partial positive charge and the O1 should show an attenuated nucleophilicity, less than that of any other unaffected oxygen of the sugar. However, the nucleophilicity of O5 should be enhanced.

For the isomeric α-glycopyranosides in the chair conformation, if the O5 donation is the dominant process, then the O1 will become a good nucleophile, while the nucleophilicity of O5 should be decreased. On the other hand, if the O1 to C1-O5 delocalization is dominant, then O1 will become a poor nucleophile and the nucleophilicity of O5 should be increased. Both delocalization processes are thought to occur in α-anomers, thus the O1 and O5 of α-anomers ought to be an attenuated nucleophiles. However, the back-donation by the O5 should make the O1 of α-anomers more nucleophilic than the O1 of β-anomers (which cannot experience

this effect).

Experiments done in our laboratory and elsewhere clearly show that the O1 of both anomers are usually more nucleophilic than any other oxygen of the monosaccharide. Instead of showing a reduced nucleophilicity, the O1 actually shows an enhanced nucleophilicity. Further, the O1 of ß-anomers are very much more nucleophilic than those of the α-isomers, in dramatic contradiction to the predictions above. However, if we still assume that the n-σ* delocalizations play a dominant role in the structure and chemistry of the sugars, then the experimental facts can only be interpreted as follows:

a) In solution, the O1 to C1-O5 delocalization must be relatively unimportant. Rather the O5 to C1-O1 delocalization must be the dominant process for the α-anomers, the reverse of the situation in the solid phase.

b) The dramatically enhanced nucleophilicity of the ß-O1 shows that the O1 to C1-O5 delocalization cannot occur in ß-anomers, or is of much less importance than the O1 to C1-O5 delocalization in the analogous α-anomers.

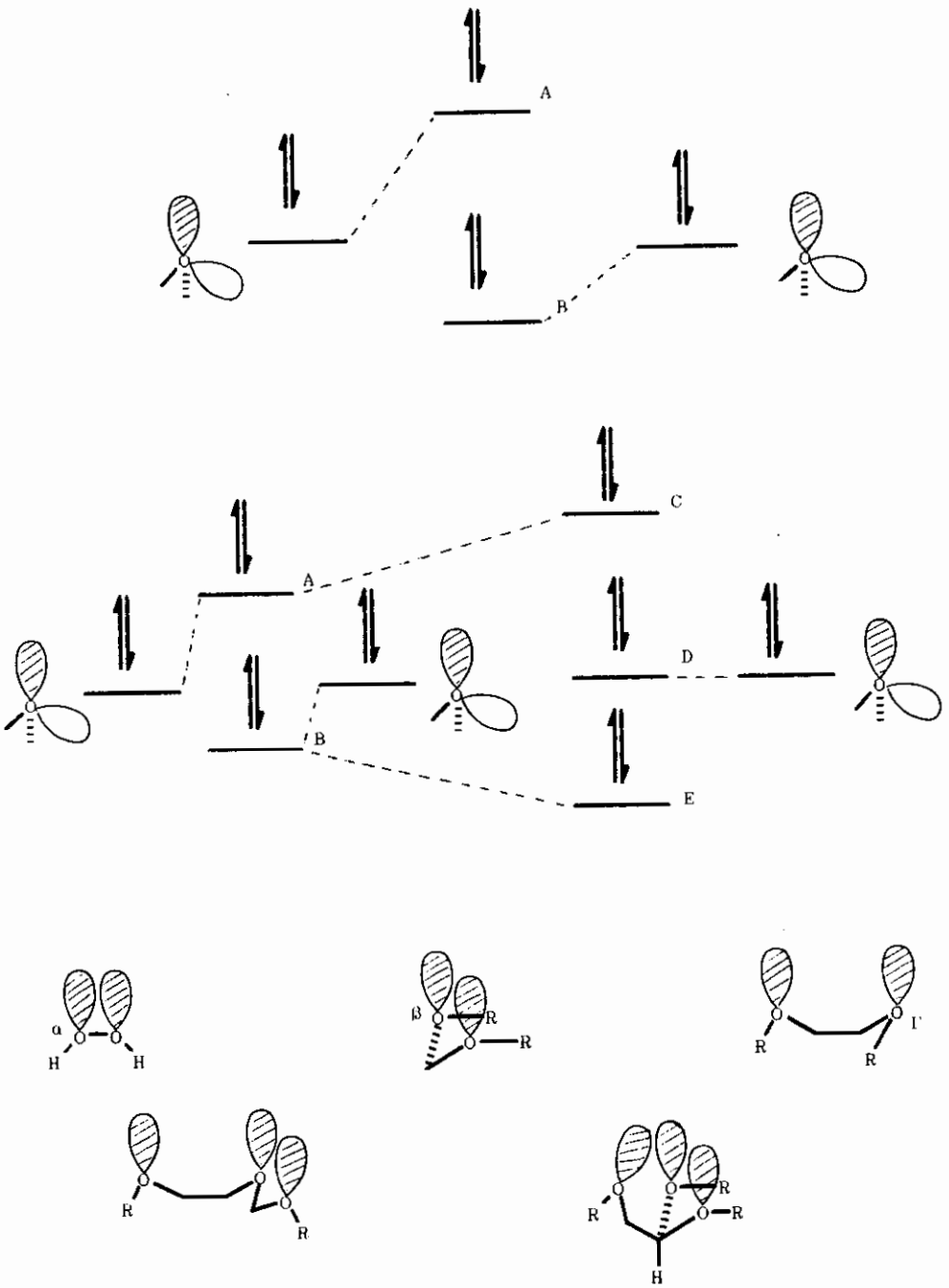
2.0.0 THE n-n INTERACTION HYPOTHESIS

The n-n interaction hypothesis is based on the widely accepted premises of bonding theory. When two orbitals of similar energy approach each other closely and with the proper orientation to interact through space, then the two orbitals will mix and produce new orbitals. This direct, through-space interactions of the n orbitals will be destabilizing and one of the two new orbitals will be elevated in energy, while the other will be depressed in energy, relative to the parent orbitals (Scheme 3).

Scheme 1 shows that every chair conformation available to the ß-anomer of an acetal has at least one n-n interaction and the three important conformations about the C1-O1 bond have a total of 4 n-n interactions. On the other hand, the two (1A and 1B) important conformations of the α-anomer have a total of one n-n interaction (if we ignore conformation (1C), which suffers from the steric crowding of the aglycone).

Molecules, like the glycopyranosyl halides, having heteroatoms attached to the anomeric center that bear three lone pairs, will always possess n-n interactions. The ß-anomer will always have two n-n interactions, while the α-anomer will have one n-n interaction.

Jorgensen's work (ref. 8) clearly shows that as the conformation of an acetal



Scheme 3

becomes more favourable for the direct, through-space interactions of its lone pairs, so does the extent of destabilization in the system increase. This destabilization is shown by the energy of splitting of the n orbitals. 1,8-Dioxadecalin is fixed in a β-anomeric-like arrangement which is best suited for these direct, through-space interactions. The energy separation of the n orbitals shown by this molecule is, remarkably, 0.85 eV. Jorgensen did not elaborate on the contribution of the through-space interactions to this large splitting. However, since through-bond interactions are usually stabilizing, then the contributions of the through-space destabilizing interactions were undoubtedly quite large. These studies also revealed that the energy separation of the n orbitals of the α-anomeric-like, gauche-gauche, conformation of dimethoxymethane was only 0.02 eV. These results showed that the β-anomeric arrangements are less stable than the α-anomeric arrangements, and demonstrated that the dominant contribution to this energy difference is the through-space interactions which can occur more efficiently in the β-anomers.

A stereochemical consequence of the presence of destabilizing n-n, or any other, interaction in a flexible acetal molecule is that the system will adjust its geometric parameters in order to minimize these interactions. The anomer which experiences the smaller number of unfavourable interactions will be more stable. Further, for a given configuration, the molecular geometry which possesses the smallest number of n-n through-space interactions should be the most stable conformation of that anomer (refs. 4a and 5). A chemical consequence is that the "new" n orbital, which is higher in energy than the parent n orbital, will show an enhanced nucleophilicity relative to a simple ether/alcohol oxygen. This phenomenon is known as the "α-Effect" when two lone pair bearing atoms are attached to each other (ref. 11), and by analogy, the "β-Effect" when the atoms are separated by one common atom, the "Γ-Effect" when the two atoms are separated by two common atoms, etc. (ref. 4a). These orbital interactions are figuratively represented (using sp3-like hybrid orbitals for diagrammatic simplicity) in Scheme 3.

The configuration and conformation (1A), which has no lone pairs eclipsed, is the most stable geometry of the α-anomeric sugars, their simple esters and their glycosides. Since the n-σ* delocalizations cannot be used to rationalize the solution chemistry, and hence equilibria, of the sugars, the stability of (1A) in solution must be regarded as a consequence primarily of the n-n through-space interaction.

The sum of the energies of the n-n interactions in the β-anomer, plus that due to the steric liability of the axial group of the α-anomer, is greater than that due to the small number of n-n interactions in the α-anomer, so leading to the manifestation of the anomeric effects in solution. n-σ* Interactions play only a minor role in the anomeric effects and their chemical manifestations in solution. There are glycopyranosidic compounds that show the normal cyclohexane-like stereochemical features (ref. 12). These compounds, which are influenced by the reverse anomeric effect and are quite different from the simple esters and acetals of sugars, will be discussed below.

2.1.0 THE GEOMETRICAL FEATURES OF THE MONOSACCHARIDES

It requires less energy to change a bond angle than to change a bond length (ref. 13), but both processes are unfavourable. The dynamics of minimizing the distance dependent n-n interactions by some combination of lengthening of the acetal C-O bonds and/or increasing the acetal O-C-O bond angle is therefore not immediately clear and will require detailed analysis.

Acetal C-O bonds are much shorter than C-C bonds, and so a pyran will possess larger steric interactions than a similarly substituted cyclohexane. The C-C bonds of a sugar are also quite short in comparison to those of an alkane, because of the inductive effect of the oxygens (ref. 10). This further exaggerates the steric interactions in glycopyranosidic molecules.

If a bond lengthening process must occur in order to minimize an interaction involving the ring oxygen atom of a pyranosidic compound, then the ring C-O bond will be lengthened rather than the mobile exocyclic C-O bond. This single action will help to minimize not only the n-n interactions, but also the steric interactions in the whole pyran ring. The lengthening of the acyclic C-O bond will possibly reduce the n-n interactions, but will not minimize any other unfavourable intra-annular effects which do not involve this oxygen.

The lengthening of ring bonds, in order to minimize intra-annular interactions, is a very general phenomenon. If one of the carbons of a monosaccharide is converted into a quaternary center, then the flanking C-C bonds increase in length markedly in order to offset the increased steric interactions. The X-ray data of the di-p-bromobenzoate of methyl gibberellate (ref. 14a) and methyl 4,6-O-benzylidene-2,3-di-C-methyl-2-O-(methylthio)methyl-α-D-allopyranoside (ref. 14b) provide good examples of these annular distortions.

Thus, the glycopyranosidic molecule, like all other organic molecules, will accommodate any unfavourable stereo-electronic interactions by a dynamic combination of:

a) adopting conformations which minimize the interactions

b) varying the lengths of the intra-annular, including the C-O, bonds

c) varying the size of the bond angles, including those at C1 and O1.

2.2.0 THE CHEMISTRY OF THE MONOSACCHARIDES IN SOLUTION

Since ß-anomers experience n-n interactions to a significantly greater degree than α-anomers, this model predicts that the ß-anomeric O1 will be a better nucleophile than the α-anomeric O1. Further, both anomeric oxygens will be better nucleophiles than any other oxygen in the sugar that does not experience these n-n interactions. These consequence of the n-n interactions have been demonstrated and will be discussed below.

THE EXPERIMENTAL EVIDENCE

THE GEOMETRY OF THE MONOSACCHARIDE MOLECULE

A COMMENT ON EXPERIMENTALLY DETERMINED BOND LENGTHS

Textbooks often state that the length of a particular type of bond will not vary by more than ±1% from the experimentally determined "mean length". From this we conclude, for example, that the length of the carbon-carbon single bond must always fall within the range 154 ±1.54 (152.46 to 155.54) pm. This generalization has created much confusion about the significance of the length of a bond. While it might be true for very simple molecules, the X-ray data of natural products show that more highly substituted molecules demand more flexibility in bond lengths and angles. A molecular graphics (lacking structure and energy minimization routines) program - STR3DI - was developed especially to facilitate the reviewing and manipulation of the X-ray crystallographic structural data of natural products and monosaccharides (ref. 15).

The program automatically portrays a molecule, determines bond orders and locates pi- and aromatic atoms, having been supplied only with the coordinates of the atoms and the atom types. In order to achieve this, an intimate appreciation of the experimentally determined bond lengths of a range of natural products was necessary.

During the development of the program, an algorithm was written which assembled on-

screen a three dimensional wire-frame structure of the molecule, but did not show bonds in the molecule which did not have lengths within a specified range, based on their "mean values". The examination of the X-ray data of several natural products using this algorithm showed that many of these compounds, in particular sugars, had bonds which did not fall within the expected narrow ±1% ranges.

In order to enable STR3DI to reproduce the complete structures of all of the molecules studied, the range of lengths allowed for any given type of bond, regardless of its environment, had to be increased to approximately ±7%. Some of the C-C bond lengths which tended towards the lower end of the range were those flanked by unsaturated systems and were formed between atoms in different oxidation/hybridization states. These short bond lengths were easily appreciated. However, there were other short C-C bonds, like those which had electron withdrawing groups attached to one or both tetrahedral carbon atoms, whose lengths could not be acceptably explained by hybridization phenomena. Here, the shortening of bonds by electronegativity effects offered a more suitable explantion (ref. 10). The bonds whose lengths tended towards the higher end of the range were bonds between tetrahedral carbon atoms which were highly substituted, or in strained situations. Again, a rationalization of the lengths of the bonds based on hybridization phenomena was unacceptable. Instead, the old explanation, based on the dynamic adjustment of the bond lengths to achieve a release of the strain, seemed much more plausible.

An almost identical profile was found for all of the different types of bonds reviewed, regardless of their multiplicities and constituent atoms. Interestingly, the ±7% ranges of bond lengths for single bonds and double bonds do not overlap, but approach each other quite closely. The range of bond lengths for double bonds and triple bonds overlap very slightly and suggests that there are alkenes whose shortened C=C double bonds do approach the lengths of the long alkyne bonds.

These findings dramatically illustrated the need for a flexible approach to the appreciation of "normal bond lengths", since there are bonds whose lengths are substantially different from the "mean lengths" that are often quoted in the literature. The geometrical features of any molecule, mediated by bonds and bond angles, change dynamically in order to accommodate the steric and other constraints in the molecule. Bonds and angles of "unusual" sizes are not necessarily the products of unusual stereo-electronic interactions operating on those bonds.

We routinely refer to the lengths of bonds by alluding to these lengths relative to

the classical single, double and triple bond lengths. For example a short C-C single bond "has bond order greater than 1", or "is intermediate in length between a single and a double bond", implying that the bond must have some of the features of a double bond. These allusions are often misleading. The lengths of the annular bonds of benzene do fall between those of ethane and ethene. However, these bonds fall within the ±7% range of the alkene bond length, but outside of the ±7% range of alkane bond lengths and - importantly - they possess similar chemical reactivity to alkenes, not alkanes. Thus, by considering the range of bond lengths within which these bonds fall, *and their chemistry*, we can assign the aromatic atoms to a certain category of hybridization.

Simple carboxylic esters provide another revealing example. The length of the bond which joins the carbonyl carbon to the alkyl oxygen is usually about 136 ±3 pm, shorter than the C-O bonds of an acetal group. The alkyl oxygen's lone pairs are apparently ideally suited for delocalization over the flanking carbonyl group. However, there is free rotation about this C-O bond and calculations using AM1 indicate that the lone pairs on the alkyl oxygen are about 94% localized on that oxygen. The short bond length is therefore a result of the "electronegativity" of the carbonyl carbon and not a result of extensive delocalization of the lone pairs of the oxygen over the carbonyl group. The "short" bond length is not an indication of a possible rehybridization of the alkyl oxygen and indeed the bond length does fall within the ±7% range of C-O single bond lengths.

The suggestion that a short alkane bond has π-character should also be borne out by the fact of its alkene-like behaviour. In the absence of greatly restricted free rotation and alkene-like chemical reactivity associated with this bond, then the causes of the shortening of the bond must be sought in areas other than a rehybridization of the component atoms.

THE BOND LENGTHS OF GLYCOPYRANOSYL COMPOUNDS

The X-ray data of several monosaccharide derivatives have been reviewed by Fuchs et al. (ref. 10), who statistically evaluated the lengths of the C-O bonds of the acetal moiety only. One of the limitations of this study is the comparison of bond lengths which have been obtained with different degrees of accuracy. As will be shown below, an experimental error of 1% to 2% in the determination of a bond length can make an enormous difference to the presumed significance of the bond length.

These considerations prompted a smaller study of the X-ray data of several glycopyranosidic compounds (ref. 15) which, in the same molecule, possessed either:

a) at least two acetal entities, the anomeric center and another simple acetal (like a benzylidene acetal, or a simple alkylidene acetal), or

b) at least two ester groups, one attached to the anomeric oxygen and the others attached elsewhere in the same molecule.

In this study, the X-ray data of each molecule had consistency for all of the structural units in that molecule and distances were measured with the same experimental error. Thus meaningful comparisons could be made regarding the relative bond lengths of key structural units. Space will only allow a discussion of the important trends observed, but the reader is encouraged to critically examine the lengths of each bond in the molecules chosen as representative examples. This data will dramatize many of the dangers inherent in the use of selected bond length data to lay the foundations of a theory, and will highlight the inconsistencies that have appeared in the literature concerning the relative lengths of the acetal bonds. The data will also show that focussing attention on the geometrical features of one site of a molecule, while pointedly ignoring similar features at other sites in the same molecule, is often misleading. The data cited are a sample taken from the large group reviewed, but do not constitute a unique group. There are many others molecules for which equally revealing X-ray data exist. The number of examples cited is relatively small, but identifying even a few exceptions to the postulates of a hypothesis invalidates that hypothesis.

OBSERVED TRENDS IN BOND LENGTHS

This review of the bond length data corroborated that done by Fuchs et al. (ref. 10). Ignoring biases due to the availability of data and sample sizes, one can state that the simple glycopyranosidic compounds have bond lengths usually in the following ranges (in pm):

	C1-O1	C1-O5	C-C	C-O-Acyl
α-anomer	138 - 142	138 - 145	148 - 159	142 - 145
β-anomer	137 - 141	139 - 145	148 - 159	142 - 145

The glycopyranoses and their derivatives, like other cyclic compounds, have their axial bonds usually slightly (about 1 pm) longer than similar equatorial bonds, regardless of the type of atoms forming the bond. The C-O bond lengths of ethers ranged from 140 to 145 pm. The alkyl oxygen bonds of benzoate, acetate and

pivalate esters rarely departed from the range 142 to 145 pm, regardless of the carbon to which the ester was attached, or its stereochemical orientation. The table shows that acetal bonds at the anomeric center covered the range 137 to 145 pm, 141 pm ±2.8%, regardless of the configuration. The C1-O1 bond is often, but not always, shorter than the C1-O5 bond. There are several α-glycopyranosides whose C1-O1 bonds are longer than the C1-O5 bonds. There are no examples of simple glycopyranoses in which the C1-OH bond is longer than the C1-O5 bond, regardless of whether the C1-O1 bond is axial, or equatorial.

The C1-O1 bonds of every anomeric pair studies differed only by 1 to 3 pm, 2% of the length of the C-O bond. There are no examples of pairs of anomers which have C1-O1 bond of the α-anomer about 10 pm longer than that of the β-anomer, as has often been stated in the literature. The range of length for a particular type of bond exists because each molecule has its own peculiar set of structural features which stimulate the dynamic adjustment of the molecule's geometry in order to accommodate these features. These dynamic processes must produce a range of bond lengths/angles for a group of similar molecules and could only be expected to produce a single set of values for nearly identical compounds.

Intermolecular hydrogen bonds and intermolecular dipole-dipole interactions can distort the features of a molecule. In particular, the β-anomer has a site, the O1-C1-O5 cluster of atoms, of high electron density which will often act as an electron donor/negatively charged site and the geometrical features at this site will frequently be distorted. These intermolecular events are not always obvious to the user of X-ray crystallographic data who usually obtains only the data for one molecule in the unit cell. The proximity and orientations of the surrounding molecules are important.

THE GLYCOPYRANOSIDES AND SIMPLE SUGARS

From electron diffraction studies, the acetal bonds of 1,3-dioxane (ref. 16a) and dimethoxymethane (ref. 16b) have been estimated to be 139.3 pm and 140.3 pm, respectively. Isopropylidene acetals, 4,6-O-benzylidene acetals and 4,6-O-alkylidene acetals of monosaccharides have C-O bonds which lie in the range 140 to 145 pm. As is expected, the more highly substituted molecules tend to have longer bonds. If n-σ* delocalizations do occur in these cyclic acetals, then their symmetry would foster the mutual cancellation of the structural consequences of these effects. Thus, the variations in the C-O bond lengths of cyclic acetals must

be due mainly to the geometrical adjustments of the total structure in order to minimize trans-annular and gauche interactions. The structural dimensions shown by these symmetrical cyclic acetals must therefore represent the true, stereo-electronically unperturbed norms for substituted acetals.

The range of bond lengths of the cyclic acetals (139 to 145 pm) overlaps that of the anomeric C-O bond lengths (137 to 145 pm) quite dramatically. Thus the C-O bonds of the structurally simpler acyclic acetals and of the pyranosidic compounds (particularly the C1-O5 bonds) do have normal, stereo-electronically unperturbed lengths.

The entire range of acetal C-O bond lengths covers an interval of 8 pm (5.6% of the mean - 141 pm), which is smaller than the 11 pm interval for the range of lengths of C-C bonds (7.1% of the mean - 153.5 pm). Within each group of anomers the range for the C1-O1, or C1-O5, bond lengths is about 4 to 6 pm (2.8% to 4.2% of the mean). The lengths of the C-O bonds of a particular pair of anomers differ only by 1 to 3 pm, or about 0.7% to 2.1% of the mean measured bond lengths and this range is smaller than the range of values within a particular group of anomers.

Thus, a ±2% error/uncertainty in measuring the acetal C-O bond lengths, which is smaller than the observed range of values for the particular bonds, can either support the n-σ* model, or negate it. If special stereo-electronic effects are needed to rationalize a 1 to 3 pm range of C-O bond lengths, then we have been negligent in ignoring the 11 pm range of bond lengths of the C-C bonds and the other larger ranges of bond length values mentioned above. It is clearly misleading to offer a single value for the "normal" length of any C-O bond and to assert that a ±2% variation in this length is unusual. A definitive assessment of whether the bonds to ß-anomeric glycosidic oxygens are always shorter than those to the analogous α-anomeric oxygens will only be properly and accurately revealed by examining molecules which have both anomeric groups in each molecule. In this way, data for the measurement of both sets of bonds will be obtained together, with the same experimental error.

THE GLYCOPYRANOSYL CARBOXYLIC ESTERS

Ester groups are much better leaving groups than ether groups. The σ* orbitals of ester C-O bonds must be closer in energy to lone pair orbitals than those σ* orbitals of ethers. The O-5 lone pair should therefore be more easily delocalized into the ester's C-O σ* orbital than into an ether's C-O σ* orbital.

The O1 of a glycopyranosyl ester must be a worse donor atom in a n-σ* delocalization process than the O1 of a simple glycoside, since one lone pair is partially delocalized over the ester carbonyl group, so bestowing a partial positive charge on the esterified O1. Thus, the strengthening of the C1-O1 bond by back donation by an O1 ether oxygen should be much greater than that by an esterified O1.

For the α-anomeric esters, one would therefore predict a strong O5 to C1-O1 n-σ* interaction, which would cause a significant lengthening of the C1-O1 bond. The X-ray data of the glycopyranosyl esters which have more than one ester group in the molecule, show that the length of the C1-O-acyl bond is fairly constant in value (covering a range of only 3 pm) regardless of the site, or stereochemical orientation, of the C-O bond in the molecule. Thus, there cannot be an important n-σ* delocalization (O5 to C1-O1 σ*) in the glycopyranosyl carboxylic esters. The absence of n-σ* interactions in these esters, which appeared to have been favourable host molecules for these effects, supports the conclusions that n-σ* interactions should not be normal features of the glycopyranosidic acetals, which are even worse candidates for these interactions.

THE BOND ANGLES OF THE GLYCOPYRANOSYL COMPOUNDS

Normally, X-ray crystallographic studies are unable to locate the hydrogens in a molecule with any degree of accuracy. Thus, we cannot comment on structural features at the anomeric center which involve the hydrogen at C1.

The bond angles at the potential donor atoms O1 and O5 have been regarded as important criteria and these bond angles have been scrutinized (ref. 10). However, any n-σ* phenomena involving the O5-C1, or the O1-C1, bonds must affect the magnitude of the O5-C1-C2, the O1-C1-O5 and the O1-C1-C2 bond angles in a definitive fashion, since the developing π-character will be seen either in the C1-O1 bond, or the C1-O5 bond. The magnitudes of each of these bond angles should also be important.

The unusually high electron density at the O1-C1-O5 site of β-anomers will make this site a very favourable one for intermolecular hydrogen bonding and dipole-dipole interactions. Both of these interactions will distort the O1-C1-O5 bond angle, resulting in a reduction of its size. This bond angle must therefore be examined with caution and significance attached to its magnitude only after it has been shown that the distortions mentioned have not occurred.

Haddon (ref. 17) has attempted to correlate bond angles with the state of hybridization at symmetrically substituted carbon atoms, with some degree of success. However, there are considerable problems involved in extrapolating those results to heteroatomic systems. For example, the carbonyl carbon of an ester group is sp2 hybridized and so one might assume that all of the bond angles at this atom will be about 120°. In fact, the X-ray data of several monosaccharide acetate and benzoate esters showed that the bond angles which flank the carbonyl oxygen were usually about 122-126°, while the bond angle which was opposite to the carbonyl oxygen was usually about 108-112°. This small bond angle (which was reproduced by AM1 calculations), which is identical to that found in saturated aliphatic systems, cannot be used by itself to assign the state of hybridization of, or degree of p-character possessed by, the ester's carbonyl carbon. The X-ray crystallographic data of a number of sugar derivatives have been reviewed, paying special attention to the sizes of the bond angles at all carbons. These bond angles frequently range from 103 to 115° in moieties which are undoubtedly aliphatic. Indeed, small bond angles (in the range 103° to 107°) frequently occur in acyclic groups such as the primary alcohol groups of sugars.

The O5-C1-C2, O1-C1-O5 and O1-C1-C2 bond angles of α-anomeric and β-anomeric compounds were reviewed and they fell well within the range (103° to 115°) found at the non-acetal sites of sugars. There are no examples of bond angles at the anomeric center which are larger and so warrant the presumption that the anomeric carbon has gained additional π character. A significant number of β-anomeric glycosides and glycosyl esters had their O1-C1-O5 bond angles in the range 106° to 108°, so showing evidence of the distortions mentioned above.

Fuchs et al. suggested (ref. 10) that the large (about 114°) bond angles seen at the O1 atom of β-anomers is indicative of a n-σ*, exo-anomeric effect. In fact, Brimacombe has produced (ref. 15k) some methyl 2,3-di-O-methylglucopyranosides whose bond angles at the O2 and O3 ether groups are larger than the bond angle at O1! Since O2 and O3 are not participating in n-σ* phenomena, then the similar, but smaller, bond angle at O1 cannot be diagnostic of the presence of the anomeric effects, or of the state of hybridization at this atom.

The variation of the H-C-H bond angle at C2 of propane, with the C-C-C bond angle, can be simulated by an algorithm which calculates the location of these hydrogens based on the following simple conditions.

a) The two C2-H bond lengths are equal.

b) The two C-C bond lengths are equal.

c) The C1-H2 and C3-H2 distances are equal.

This simple algorithm perfectly predicts what one would have expected from the widely accepted hybridization model. This algorithm was used in the program STR3DI to place hydrogens onto simple hydrocarbons and, provided that realistic bond lengths and C-C-C bond angles were used, the structures/energies of these model hydrocarbons were almost identical to those of a similar molecular models which had been subjected to a structure/energy minimization (MM2/MMX) routine. Thus, an algorithm which was driven by simple geometric requirements, allowed one to appreciate the dynamics of the structural features of an organic molecule, including the structural consequences of varying the bond angles within the molecule. Clearly, it is not necessary to invoke the rehybridization of an atom in order to rationalize the sizes of the bond angles at that atom.

THE CHEMISTRY OF THE MONOSACCHARIDES

THE RELATIVE NUCLEOPHILICITIES OF THE α- AND ß-ANOMERS

The X-ray data indicates that in both anomers the C1-O1 bond is usually shorter than the C1-O5 bond. The n-σ* hypothesis would therefore predict that the α-O1 ought to be a poor nucleophile, and the ß-O1 even worse. This predicted pattern of reactivity is inconsistent with the experimental facts and poses serious challenges to the validity of the n-σ* hypothesis. On the other hand, the n-n interaction model predicts with great reliability the actual reactivities of the anomers and imposes no constraints on the bond lengths at the acetal center.

A significant amount of experimental data has been generated which supports the fact that the anomeric hydroxyl groups of ß-glycopyranoses are much more nucleophilic than all of their other hydroxyl groups (refs. 4a and 18a-18c). Further, both anomeric oxygens are much better nucleophiles than the other secondary oxygen atoms of the simple glycopyranoses. This trend is evident in the chemistry of the glycopyranosides, where the ß-anomeric glycopyranosides react with electrophiles far more rapidly than the isomeric α-anomeric glycopyranosides, and both anomers react more readily than simple ethers (refs. 4a and 18d-18f). The enhanced nucleophilicities of the anomeric oxygens are primarily manifestations of the ß-effect.

Examples of the manifestation of the Γ-effect, which is also a consequence of n-n interactions, have been reported (refs. 4a and 18g) and have been exploited in our

laboratories (ref. 18h). The excellent nucleophilicity of the primary hydroxyl group of a simple monosaccharide, in comparison to the secondary hydroxyl groups, is a consequence of the greater steric hindrance encountered at the secondary anomeric hydroxyl groups, rather than a reduced availability of the nucleophilic electron pair (ref. 18i). Inclusion of the Γ-effect in assessments of the relative stabilities of anomers, or conformers, will clear up several ambiguities in current studies of the effects of solvent polarity on the magnitude of the anomeric effect (ref. 18j).

THE REACTIONS AT THE ANOMERIC CENTER

The n-σ* processes should be important in situations where a very good leaving group is attached to a carbon which is also bonded to a lone pair bearing atom, and the system is moving along the coordinates of an S_N1 reaction. As the S_N1 reaction proceeds towards the transition state, the developing positive charge on the reaction center will be stabilized by a n-σ* process. The n-σ* interaction ultimately becomes the n-p stabilization of the intermediate 'onium' ion formed in the S_N1 reaction (ref. 4b).

THE REVERSE ANOMERIC EFFECT

The "reverse anomeric effect" is shown by molecules, like the glycosyl pyridinium halides (ref. 12), which bear a positively charged atom/group (X) at C1, attached to C1 via a heteroatom. These molecules show the "normal" stereochemical biases of the cyclohexanes, and the β-anomers are more stable than the α-anomers. These compounds are usually quite reactive at C1, highlighting the favourable energetic relationship between their C1-X σ* orbitals and nucleophilic lone pair orbitals. Since the positively charged atom X will be a poor donor, the n-σ* model predicts no n-σ* interactions in the β-anomer, but a very strong interaction between the axial O5 lone pair and the axial C1-X σ* orbital of the α-anomer. This should contribute to a very strong anomeric effect. In the pyridinium salts, the relatively small steric requirements of the flat pyridinium group, which will be similar to that of a phenyl group (ref. 15j), should lead one to predict a normal anomeric effect, opposite to the observed trend.

An alternate view of the reverse anomeric effect, based on the lone pair interaction model, has been presented (ref. 4b) and suggests that this phenomenon is the result of the sum of:

a) an attractive, stabilizing interaction between the lone pairs of the O5 and the electron deficient σ*, or π*, orbitals of the glycosidic substituent, which occurs more readily in β-anomers than in α-anomers (the inverse β-effect),

b) the normal steric requirement of a substituent on the six-membered ring,

opposed by:

c) the n-σ* interactions, which are now very possible because of the favourable energetic and geometric relationship between the σ* orbital of the C1-hetero-atom bond and the axial O-5 lone pair.

The n-σ* interaction is clearly less important than the sum of the other two factors, so leading to the observed stereochemical bias.

THE S_N1 REACTIONS OF GLYCOPYRANOSIDES, GLYCOPYRANOSYL ESTERS AND HALIDES

The simple alkylglycopyranosides are very stable in neutral solutions in the presence of extremely potent nucleophiles. Anomerisations and substitutions at C1 only occur under the influence of acid catalysis (ref. 19). This stability and reluctance to participate in S_N1 reactions confirms the absence of strong n-σ* interactions in these molecules. Tvaroska has pointed out that the σ* orbital of a glycopyranosyl halide should be close in energy to a lone pair orbital and so allow some n-σ* interactions with the adjacent O5 lone pair (ref. 7a). Indeed, it is well known that the glycopyranosyl halides are very active in S_N1 processes and react with nucleophiles hundreds of times faster than simple alkyl halides. Notwithstanding their enhanced reactivities, glycopyranosyl halides often require Lewis acidic catalysis for preparatively acceptable reaction rates (ref. 20), as in the well known Koenigs-Knorr glycosidation reactions.

A comparison of the reactivities of the glycopyranosyl halides and the simple alkyl glycopyranosides clearly shows how the chemical reactivity of a molecule is affected by n-σ* interactions. This experimentally observable enhanced S_N1 reactivity ought to be one of our criteria for invoking the presence of n-σ* interactions in molecules.

The very strong anomeric effect shown by the glycopyranosyl halides must be due to significant contributions by both the n-n interactions and the n-σ* interactions. On the other hand, the moderate anomeric effect shown by the simple glycopyranosides and glycopyranosyl esters must be due mainly to the n-n interactions, with an insignificant contribution from any of the n-σ* interactions.

CONCLUSION

Notwithstanding the popularity of the n-σ* hypothesis, there is no clear experimental evidence for the dominant participation of n-σ* interactions in the anomeric effects, or in the chemistry shown by simple glycopyranosides, glycopyranosyl esters and glycopyranoses. Further, the chemistry predicted by the n-σ* model is not realized in the laboratory.

On the other hand, a model based on the dominant contribution of n-n interactions, plus a minor contribution from n-σ* interactions, does provide a satisfactory basis for the understanding of the chemistry and structural features of all the monosaccharides.

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Polyfunctional compounds :

ACALPA ACEGLL AOGAPY ATBRIB10 ATBXYL10 DIPTGP IPEPPL MABRHP MBDARP MBDRIP MBTCAP MEYGAL10 MTAGLV OBZXYP10 PACDGP TACRIB TALXYP TAXYLR TBZMAC

Simple glycopyranosides:

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