THE ANOMERIC EFFECT OF MONOSACCHARIDES AND THEIR DERIVATIVES. INSIGHTS FROM THE NEW QVBMM MOLECULAR MECHANICS FORCE FIELD

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Abstract - The new force field, Quantized Valence Bonds' Molecular Mechanics, QVBMM, was designed to embrace most of the concepts in Valence Shell Electron Pair Repulsion (VSEPR) theory and to uniquely integrate lone pairs into molecular mechanics. This force field is executed in the molecular modeling program STR3DI.EXE and is particularly useful in the molecular modeling studies of molecules that possess lone-pair-bearing heteroatoms. This force field was used to study the stereo-electronic effects found in the simple derivatives of tetrahydropyran, and hence to investigate the Anomeric Effect of monosaccharides.

INTRODUCTION

The QVBMM force field has recently been described.[1] The QVBMM force field intimately, and uniquely, integrates the lone pairs of electrons on heteroatoms into the total appreciation and implementation of the molecular mechanics of organic molecules.[1] The QVBMM force field also polarizes all bonds between dissimilar atoms, based on their relative electronegativities, and integrates these dipoles into the implementation of the molecular mechanics of organic molecules.[1] This new design embraced some of the energy potentials traditionally used in molecular mechanics, but was also innovatively based on the premise of the quantization of the properties of chemical bonds, new energy potentials for torsional interactions and bond length dynamics, and the application of VSEPR theory[2] to intramolecular interactions in this context of quantized valence bonds.[3] The QVBMM force field has produced excellent simulations of the molecular geometries, and properties, of a wide variety of organic molecules, with and without heteroatomic components.[1] The geometric features of the molecular models generated by the QVBMM force fields were very similar to those generated by MM2 and MMX, for every kind of molecule examined in a comparative exercise.

Carbohydrate chemists are aware of the continuing discussions on the origins of the Anomeric Effects,[4] and several publications,[4] among many others too numerous to cite here, summarize not only the wealth of experimental data that has been gathered, but also the significant theoretical contributions to this matter. However, notwithstanding all of the effort that has been expended, the only true consensus reached in these discussions to date, is that the Anomeric Effects owe their existence to the lone pairs of electrons that are borne by the participating (anomeric) heteroatoms.

Most molecular mechanics force fields are not designed to incorporate the lone pairs of electrons on heteroatoms into their calculations, nor are they designed to explicitly use the polarizations of bonds between all dissimilar atoms. Instead, these force fields are often carefully parameterized to accommodate some of the stereo-electronic effects due to lone pairs and dipolar interactions, and these force fields usually required special parameterization for each molecular type. These force fields do not always reproduce accurately, or simulate, the Anomeric Effects, and have not been reliable sources of information on the possible origins of these stereo-electronic effects. Indeed, the majority of theoretical attempts to rationalize the Anomeric Effects have used the Molecular Orbital based (*ab initio* and semi-empirical) methods. These studies have provided many insights into the stereo-electronic effects which might be responsible for the Anomeric Effects, and have added great depth to these discussions.[4]

Since the QVBMM force field uses heteroatomic lone pairs and bond dipoles in ways that were never implemented in MM2 or MM3, and since the QVBMM force field has been shown to be a reliable source of structural and strain energy (enthalpy) data,[1] it was therefore quite appropriate that a detailed examination of the Anomeric Effects be undertaken using this new force field.

The Anomeric Effect was very briefly mentioned in the work describing the parameterization of the QVBMM force field for acetals and 2-halotetrahydropyrans,[1] but that discussion was focused on parameterization of the force field and did not attempt to reveal insights, concerning the general features of the Anomeric Effect, that had been obtained. This work will specifically relate a careful study of the Anomeric Effects using the QVBMM force field, and will draw attention to the many stereo-electronic interactions that contribute to these Anomeric Effect. The manuscript will concentrate on pyranoid acetals and their derivatives that have a heteroatom bonded to C-1, structures traditionally associated with the Anomeric Effect.

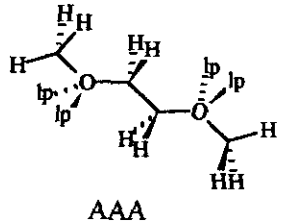
THE MOLECULAR MECHANICS OF ETHERS, AMINES, ALCOHOLS AND HALIDES

The simple monosaccharides are usually hosts for the ether, alcohol, halide and aminoid functional groups. Thus, it is useful to precede the discussion of the molecular mechanics of the pyranosidic molecules with some of the results that the QVBMM force field has generated from simple molecules that possess these functional groups. Indeed, the congruence of the data produced by the QVBMM force field for these simple molecules with the experimental data and with those data produced by other molecular mechanics force fields, should help to reassure us of the appropriateness of the use of the QVBMM force field in this study.

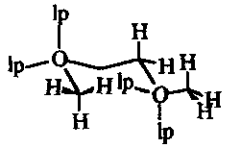
Polyethers and Polyols

Most molecular mechanics programs do not consider the roles of the lone pairs of heteroatoms in the *conformational* stabilities of molecules. They usually treat lone pair bearing atoms simplistically as the negative ends of dipoles, and the energies of their dipole - dipole attractions, or repulsions, are included the overall potential energy analyses. Unfortunately, these simplifications are sometimes fatal, as in the erroneous prediction by MM2 and MMX that the enthalpy of the anti-anti-anti-(AAA) conformation of 1,2-dimethoxyethane should be about 2.04 kcal/mol less (more stable) than that of the gauche-gauche-anti-(+G-GA) conformation). The *ab initio* studies[5a, 5b] have assessed this enthalpy difference at about 0.5 kcal/mol.

Dimethoxyethane



AAA



GGA

Studies[5a, 5b, 6] of 1,2-dimethoxyethane suggested that it exists in the conformational populations shown in Table 1.

While the anti conformation of 1,2-dimethoxyethane, AAA, is the conformer with the lowest enthalpy, those conformations in which the central CH2-CH2 bond is gauche are more highly populated (totaling

79%) than conformations in which this bond is *anti* (totaling 21%).[5a, 5b, 6] Thus, entropy factors are responsible for the overall greater stability of the gauche conformers. The gauche conformers have larger dipole moments than the anti conformers, and so the observed conformational preference cannot be explained in terms of dipole - dipole interactions.

Table 1.

Conformational Population Distribution for Dimethoxyethane[5a, 5b, 6]

Rotamer	Population (%)	
AAA	13	
AAG	3	
GAG	5	subtotal 21%
GGG	3	
AGA	23	
GGA	53	subtotal 79%

	100%	

The electronegativities of hydrogen, carbon and oxygen are 2.20, 2.55 and 3.44 respectively. The hydrogen in an R-O-C-H moiety must experience a cascading negative inductive effect, R-O-<-C-<-H, giving this hydrogen a significant partial positive charge, significantly greater than that on a hydrogen of a simple hydrocarbon. Interestingly, the structure energy minimized molecular model of the +G-GA conformation of 1,2-dimethoxyethane (either by QVBMM, or by *ab initio* methods[5]) has a geometry that places a methyl group's hydrogen quite closely to an oxygen atom, as is shown in the diagram. The distance between the hydrogen and the oxygen is ideal for the interposition of a lone pair. This clearly indicates the presence of a strong attraction between the oxygen's lone pair and the positive end of the -O-C-H dipole, which is very similar to the "hydrogen bond" found in alcohols.[5] These interactions must also occur between the oxygen's lone pair and the gauche or syn C-H bonds of the carbon to which the oxygen is bonded. The structure energy minimized molecular model of the +G-GA conformation of 1,2-dimethoxyethane also showed that the distance of closest approach of any pair of its non-geminal lone pairs was greater than 3.0 Angstroms, so allowing n - n interactions to be ignored. Thus, this minimum energy structure confirmed that the "C-H ..... :-O" hydrogen bond was indeed the dominant feature which

conferred stability on the +G-GA conformation. This "C - H" hydrogen bond will be seen to be of critical importance in understanding the Anomeric Effect.

The experimental fact of the greater stability of the gauche conformations of 1,2-dimethoxyethane over the *anti conformations* illustrated the need for a new approach to the molecular mechanics of heteroatoms. The approach adopted for the total integration of heteroatoms and their lone pairs into the QVBMM force field involved replacing dipole - dipole interactions with a linear combination of all of the interactions of the neighbouring atomic point charges, and including the n - n, n - σ and n - π interactions generated by its lone pairs.[3] This approach has been successful and the QVBMM force field calculated the enthalpy difference between the +G-GA and the AAA conformations, of 1,2-dimethoxyethane, to be about 0.51 kcals/mol, similar to the *ab initio* determined value.

Halocyclohexanes and Aminocyclohexanes

Table 2.

Experimental Conformational Free Energies of Heteroatom Substiutuents on Cyclohexane

	Experimental (kcal/mol)[7,8]
Substituent	Conformational Free Energy
-OH	0.3 to 1.5
$-OCH_3$	0.4 to 0.74
-OAc	0.36 to 1.60
$-NH_2$	1.23 to 1.7
$-NHCH_3$	1.29
-SH	1.21
$-SCH_3$	1.04
-F	0.25 to 0.42
-Cl	0.53 to 0.64
-Br	0.48 to 0.67
-I	0.47 to 0.61

Once the critically important concept of the "C - H" hydrogen bond had been parameterized into the QVBMM force field, the force field produced excellent simulations of most organic molecules

containing the first row elements, and was easily parameterized for the other halogens. The experimentally determined conformational free energies, and the QVBMM calculated conformational enthalpies, for some simple derivatives of cyclohexane are shown in Tables 2 and 3 respectively.

Table 3.

QVBMM Calculated Enthalpies of Heteroatom Substituents of Cyclohexane[1]

Molecule	QVBMM Calculated Enthalpy (kcal/mol)	Enthalpy Difference
eq-Cyclohexanol	8.071	
"	9.012	
ax-Cyclohexanol	9.054	
"	9.375	0.98
Methoxycyclohexane		0.74
eq-Cyclohexylamine	6.437	
"	6.897	
ax-Cyclohexylamine	7.495	
"	7.900	1.05
N-Methylcyclohexylamine		0.90
Thiocyclohexanol		0.68
Fluorocyclohexane		0.39
Chlorocyclohexane		0.43
Bromocyclohexane		0.66
Iodocyclohexane		0.59

The QVBMM force field does not explicitly consider the effects of solvation on the energies of the molecules being modeled. This force field assumes that the molecular models are in the gas phase, or are in a non-polar hydrocarbon solvent. Thus, the energies calculated by the QVBMM force field are enthalpies, and are not free energies. In fact, these QVBMM calculated energies are really stereo-electronic strain energies. In order to compare the QVBMM calculated numbers with the experimental free energies, one must have access to reliable entropy data, particularly entropies of solvation. In the discussion below, on the Anomeric Effects, we must remember that the experimental data are usually conformational free energies. The QVBMM calculated enthalpy data will be seen to match the trends

established by the experimental data, but will not produce data directly comparable to these experimentally determined free energies.

THE ANOMERIC EFFECT[4]

The Anomeric Effects have bewildered and confused carbohydrate chemists for decades. Many plausible rationalizations have been proposed for the origins of the Anomeric Effect, and the Anomeric Effect has been the subject of many investigations.[4] Acetals are among the most widespread, simplest, and yet most important organic molecules that can show significant n - n interactions, and these molecules have been widely studied in order to quantify these interactions. Currently, the conformational enthalpy associated with the Anomeric Effect of simple alkoxyl groups is thought to be between 2.0 to 4.0 kcal/mol.[4c] Acetals were therefore the obvious models to employ in the parameterization of the QVBMM force field for n - n interactions. Indeed, one of the goals of the development of the QVBMM force field was to address and quantify several aspects of the geometrical features of acetals, and to see if these data would shed more light on the Anomeric Effect.

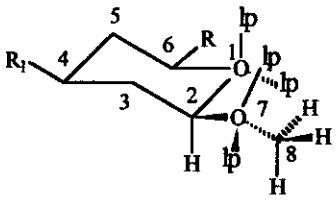
This study initially performed a molecular mechanical analysis of the simple 2-substituted tetrahydropyrans and their Anomeric Effects. Then, a hydrogen on C-3 was replaced by a hydroxyl or methoxyl group and the analysis repeated. By sequentially replacing hydrogens on the other, consecutive, rings atoms (4 to 5) by hydroxyl groups and performing the molecular mechanical analysis, we eventually arrived at the common pentapyranosidic molecules and the molecular mechanical analyses of the stereo-electronic features of every member in that series. This allowed us to monitor the trends in the Anomeric Effects that develop as we went from the simple tetrahydropyrans to the common pentapyranosidic molecules.

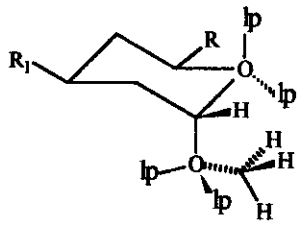
The 2-Methoxytetrahydropyrans

Before the QVBMM force field was parameterized for n - n interactions, the force field was completely parameterized using molecules which could not possibly experience n - n interactions, like simple monosubstituted compounds and 1,2-dimethoxyethane. Then the force field was used to model the isomers of 2-methoxytetrahydropyran (**1** and **2**) in order to establish a framework for the later inclusion of a potential to assess the n - n interactions. This exercise, in which the lone pair n - n interaction was ignored, immediately highlighted the tremendous roles of the "C - H" hydrogen bonds because the conformers that possessed these hydrogen bonds were more stable than the others. These conformers are shown in the diagram, and are obviously the most stable conformers for the anomers. Thus, the "C - H"

hydrogen bonds are responsible, in large part, for the "exo-anomeric" conformers being the most stable for the α–anomers.

The 2-methoxytetrahydropyrans





1 R = R_1 = H
3 R_1 = H, R = CH_3
5 R = H, R_1 = CH_3

2 R = R_1 = H
4 R_1 = H, R = CH_3
6 R = H, R_1 = CH_3

An examination of a model of 2-methoxytetrahydropyran showed that the "C - H" hydrogen bonding interactions between the lone pairs of O-1 and the hydrogens of C-6, and between the lone pairs of O-7 and the methyl hydrogens (C-8) were features common to both anomers and so were not instrumental in determining the relative stabilities of the anomers. However, the number of the lone pair interactions with the H-2 (on the acetallic carbon), and between the lone pairs of O-7 pair and H-6, are dependent on the orientation of the anomeric group and so these interactions were also very important in determining the relative stabilities of the anomers.

The acetal's carbon is attached to two oxygens and so experiences considerable negative inductive effects. The sole hydrogen attached to this acetallic carbon, H-2, must therefore also experience a considerable, cascading, negative inductive effect and must therefore bear a significant partial positive charge. The H-2 can participate in a favourable n - dipole interaction with the oxygen's lone pairs with which it is gauche or *syn*, but will not be significantly affected by the *trans*-diaxial lone pairs. There are usually only two such stabilizing n - dipole interactions in the β–anomers of the 2-methoxytetrahydropyrans, but there are usually three such interactions in the α–anomers. These n - dipole interactions are very important contributors to the Anomeric Effect.

The axial hydrogen at C-6 can only interact with an axial α-anomeric atom's lone pairs. Thus, while α–anomers will experience this stabilization, β–anomers will not. There is also severely restricted rotation

about the C-2 - O-7 bond which causes the aglycone unit to seldom occupy the highly unfavourable position over/under the pyran ring(one of the contributors to the "Exo Anomeric Effect"). This conformational restraint in the α–anomers ensures the prolonged existence of the n - dipole interaction between a lone pair on O-7 and the axial H-6.

The hydrogen on C-3 can also engage in n - dipole interactions with the anomeric atom's lone pairs, but, since these will depend on the nature, and the orientation, of the substituent at C-3, and on the conformation adopted about the C-2 - O-7 bond, it is best to treat these on a case by case basis. If C-3 is not substituted, then the inductive effects experienced by H-3 will be smaller than those experienced by either H-2 or H-6, and so the H-3 partial charge will be smaller, resulting in weaker n - dipole interactions.

Indeed, having become more aware of the ubiquity and considerable influence of these n - dipole interactions, it was clear that these interactions must be identified and considered in any attempt to establish the relative stabilities of the anomers. Thus, the lone pairs of the α–anomer are involved in significant "C - H" hydrogen bonding between O-1 and H-8; O-1 and H-2 (one for each lone pair); O-7 and H-2; and O-7 and axial H-6. The β–anomer had similar interactions between O-1 and H-2, O7 and H-2, and O-1 and H-8. Thus, there were a larger number of strongly stabilizing, attractive, "C - H" hydrogen bonding interactions in the α–anomer than in the β–anomer.

As the lone pair, n - n, interactions were introduced (the potential was activated in the computer program) and increased in size it became clear that the geometry of the α–anomer changed simultaneously in order to minimize the possible n - n interactions. Thus, even if the conformation was changed to place two lone pairs within interaction distance, during the subsequent structure energy minimization process, the rotation of the C-2 - O-7 bond occurred to minimize this interaction. Similarly, when the starting geometry of the β–anomer allowed n - n interactions between the O-1 and the O-7 lone pairs, this geometry of the β–anomer changed during the structure energy minimization process, by rotation about the C2-O7 bond, to separate the axial lone pairs and so mollify the n - n interaction, while preserving the C-8 - H hydrogen bond with O-1. The geometries and energies of these systems were therefore significantly influenced by the n - n interactions, the "C - H" hydrogen bonds and the conformational flexibility of the anomers.

The experimentally measured[4c, 4h, 4k] conformational equilibrium between the anomeric 2-methoxytetrahydropyrans (**1** and **2**) favoured the axial α–anomeric isomer, by approximately a 4:1 ratio. Therefore, the n - n interactions in the QVBMM force field were parameterized to make the β–anomeric 2-methoxytetrahydropyran 0.97 kcal/mol less stable than the isomeric α–anomeric acetal.[1]

Interestingly, halving the value of the force constant, K_{n-n}, associated with the potential used in the calculation of the n - n interactions[1] did not significantly change the conformational enthalpy difference between the anomeric 2-methoxytetrahydropyrans. Thus, these anomers were able to mollify the destabilizing n - n interactions by conformational changes that adjusted the sizes of the gauche interactions and the stabilizing "C - H" hydrogen bonding. This interesting ability of these "glycosides" to minimize the n - n interactions is not found in all pyranosidic derivatives. Indeed, QVBMM studies of the 2-halotetrahydropyrans and the alkoxides of the 2-hydroxytetrahydropyrans show that these molecules are dramatically affected by n - n repulsions, and varying the value of the force constant, K_{n-n}, associated with this n - n interaction potential had a significant effect of the relative stabilities of the anomers.

The 2-Methoxy-6-methyltetrahydropyrans and the 2-Methoxy-4-methyltetrahydropyrans

The published experimental data[4c, 4h, 4k] on the 2-substituted tetrahydropyrans tends to include data on the 6-methyl- and the 4-methyl-2-substituted tetrahydropyrans (compounds **3** to **6** respectively). This implicitly assumes that these methyl substituents should not affect the sizes of the Anomeric Effects in the tetrahydropyrans. However, the QVBMM calculated enthalpies of the anomeric 2-substituted 6-methyltetrahydropyrans were consistently larger than those of the corresponding 2-substituted tetrahydropyrans, or the 2-substituted 4-methyltetrahydropyrans. This effect was independent of the type of anomeric atom or group.

The 4-methyl group is quite far from the anomeric center and should have little , or no, influence on the Anomeric Effect. Indeed, the QVBMM calculated data for these molecules were almost identical to those of the simple 2-substituted tetrahydropyrans. On the other hand, the equatorial 6-methyl group can interact directly with O-1, but not with O-7 or the aglycone. Thus, the effect of the 6-methyl group must be mediated by O-1. It seemed very likely that the 6-methyl group exerted a "buttressing" effect[7] on the lone pairs of O-1, so preventing them from distorting away from the anomeric interactions with the anomeric atom (O-7) and its substituents. This buttressing effect must be more significant in the β–anomers which have the equatorial anomeric atom, the ring oxygen and the equatorial 6-methyl group,

almost in the same plane. The axial orientation of the anomeric atom of the α–anomer would allow this atom to attain its maximum distance from the ring oxygen's lone pairs.

Thus, the location of the alkyl substituent on the tetrahydropyran ring was critical to its influence on the interactions between the ring oxygen and the anomeric atom, and we must be more concerned about the roles of "simple" alkyl substituents in the evaluation of the Anomeric Effect. Similarly, we should be more aware of the possible influences of other groups at C-6 on the relative stabilities of the anomers, and the experimental data do support this point.[4c, 4h, 4k]

Solvation

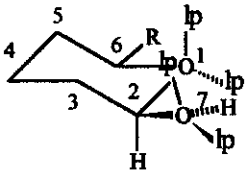
It is also well known that the nature of the solvent dramatically affects the percentage of the axial β–anomer of the 2-substituted tetrahydropyrans present at equilibrium.[4c, 4h, 4k] In the case of the 2-methoxyltetrahydropyrans, the equilibrium distribution of the axial β–anomer ranged from a high of 82% in carbon tetrachloride to a low of 52% in water. Thus, either the stabilities of the β–anomers increased in polar solvents, or the stabilities of the α–anomers decreased in these polar solvents. The net effect, however, was the reduction of the sizes of the Anomeric Effect in polar solvents, and the enhancement of sizes of the Anomeric Effect in non-polar solvents.

The QVBMM force field does not directly take solvation into consideration, but rather factors the effects of solvation into the calculation of electrostatic interactions. In this context, therefore, the enthalpy values calculated by the QVBMM force field for the simple 2-substituted tetrahydropyrans best match those expected from equilibria studied in solvents like chloroform and acetone, whereas the data calculated for the 6-methyltetrahydropyrans best match those observed in a wider range of relatively non-polar solvents.

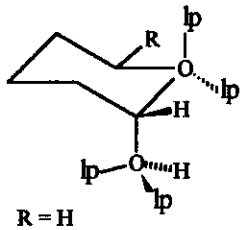
The 2-Hydroxytetrahydropyrans

The 2-hydroxytetrahydropyrans (**7** and **8**) are very intriguing test molecules for programs which seek to model the Anomeric Effect since the experimental data for these anomers show that they have approximately equal conformational stabilities. Indeed, the percentage of the α–anomer, at equilibrium, is 47% in carbon tetrachloride, 55% in chloroform, and 47% in dimethyl sulfoxide. Solvation and entropic effects must play significant roles in the determination of the relative stabilities of these anomers.

The 2-hydroxytetrahydropyrans



7 R = H
9 R = CH_3



8 R = H
10 R = CH_3

The QVBMM force field calculated the conformational enthalpy difference for the 2-hydroxytetrahydropyrans anomers to be 0.33 kcal/mol. This value is small, and close enough to zero, to allow the effects of solvation and entropy to be the deciding factors. The QVBMM calculated enthalpy difference for these molecules was therefore quite consistent with the experimental data.

The QVBMM calculations also showed that protonation of the anomers at the 2-hydroxyl group reversed their stabilities, resulting in the β–anomer being more stable by 0.22 kcal/mol. This is obviously an example of the "reverse" Anomeric Effect. The protonated β–anomer had no n - n interaction, but instead had each hydrogen on O-2 in a 1,3-*syn*-coplanar relationship with a lone pair on O-1, as if a "double" hydrogen bond existed between O-7 and O-1. The α–anomer had only one such hydrogen bond. The extreme polarization of these O-7 - H-7 bonds, due to the positive charge on O-7, cause these n - dipole interactions to be unusually large and stabilizing.

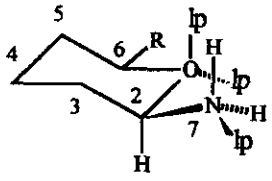
The anomers of the 6-methyl-2-hydroxytetrahydropyrans (**9** and **10**) were calculated to have a conformational enthalpy difference of 1.00 kcal/mol. The protonated anomers were calculated to have a conformational enthalpy difference of 0.47 kcal/mol, with the marked reduction in the conformational enthaply being due to the "reverse" Anomeric Effect.

The 2-Aminotetrahydropyrans

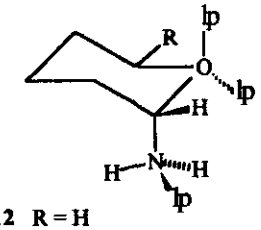
Whereas the 2-hydroxytetrahydropyrans were almost equal in conformational enthalpies, the 2-aminotetrahydropyrans (**11** and **12**), which are iso-electronic with the protonated 2-hydroxytetrahydropyrans, predictably showed a conformational enthalpy difference of - 0.90 kcal/mol (the β–anomer was the more stable anomer). The 6-methyl-2-aminotetrahydropyrans (**13** and **14**)

showed a smaller enthalpy difference of - 0.24 kcal/mol, but the β–anomer was still the more stable anomer. These instances of the "reverse" Anomeric Effect were obviously also due to the very favourable "double" hydrogen bond in the β–anomers, even though these interactions will be much weaker than those in the charged iso-electronic hydroxyl analogues.

The 2-aminotetrahydropyrans



11 R = H
13 R = CH_3



12 R = H
14 R = CH_3

The origins and existence of the "reverse" Anomeric Effect have been controversial subjects. However, the data obtained for the 2-aminotetrahydropyrans and the 2-hydroxytetrahydropyrans clearly supported the notion that the "reverse" Anomeric Effect shown by these tetrahydropyrans was due solely to hydrogen bonding. Obviously, compounds that have acidic hydrogens bonded to their anomeric atoms (O-7) should show this "reverse" Anomeric Effect more strongly that their less acidic analogues. The QVBMM force field calculations were therefore complementary with the experimental data and support the existence and the origin of the "reverse" Anomeric Effect. This paper will not deal with the Anomeric Effects of the pyridinium or the imidazolium glycosylamines, whose "reverse" Anomeric Effects will be discussed in a forthcoming paper.

The *Influence of* Ring Substituents on the Anomeric Effect

The nature of the interactions of ring substituents with the anomeric moiety, and with each of their other neighbouring substituents, must be understood in order to predict the reactivities of the functional groups of the pyranoside. However, most of the theoretical examinations of the Anomeric Effect have carefully avoided investigations of the influence of the ring substituents on the size of the Anomeric Effect. In part, this must be due to the much greater complexity of the calculations involved.

Therefore, the QVBMM force field was used to calculate the relative stabilities of some 2-methoxytetrahydropyrans that had one or more oxygen substituents on the ring atoms. In this way, the sequence of compounds, from the 2-methoxytetrahydropyrans to the methyl pentapyranosides, were studied in order to identify trends in their stability and the structural features responsible for these trends. The detailed analysis of the structural features and stereo-electronic interactions present in each molecule would occupy many pages and cannot be presented in this paper. Thus, only the trends in overall stability, along with a very brief identification of the major contributing stereo-electronic factors involved, are presented here.

The tetrahydropyrans studied have intentionally been described by their structural similarities to the more widely known glycohexopyranosides, since the Anomeric Effect is most widely discussed in reference to these molecules. Thus, the axial 3-hydroxytetrahydropyran will be referred to as a "manno-like" compound.

The Dimethoxytetrahydropyrans

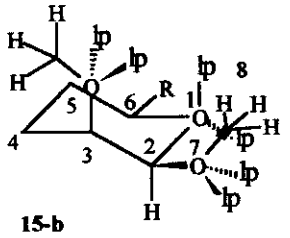
The QVBMM force field was used to calculate the enthalpies of the 6-methyl-2-methoxytetrahydropyrans which had one additional methoxyl group, in an axial or equatorial orientation, on the ring, but not at C-6. This data is shown in Table 4, along with the enthalpy differences between the anomers. Note that the 6-methyl group increased the energies of the β–anomers relative to those of the α–anomers, as was discussed above.

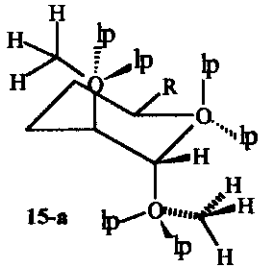
Both the axial and the equatorial 3-methoxyl substituent of compounds (**15**) and (**16**) destabilized their β–anomers much more than their α–anomers. This was especially evident for the 3-equatorial substituent. The C-3 - H-3 bond was highly polarized by the 3-methoxyl group and this could allowed very small, but favorable, n - dipole interactions to occur between H-3 and some of the anomeric lone pairs, if these were properly oriented. The equatorial C-H bond of compound (**15**) enabled both its anomers to engage in n - dipole interactions between one of the lone pairs of O-7 and H-3, but no interactions could occur with the remote lone pairs of O-1. In fact, the n - dipole interaction between H-3 and a lone pair of the α–anomeric O-7 was shown to be quite significant in compound (**15-a**).

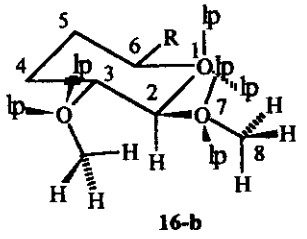
In contrast, the minimum energy structures of the most favourable conformations of the molecules (**16**) showed no interactions between H-3 and the lone pairs of O-7 and O-1 because these entities were far enough apart to ensure that the n - dipole interactions were almost nil.

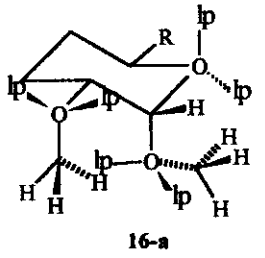
Thus, the 3 -axially substituted, "manno-like", compounds (**15**) showed greater overall stabilities, and a slightly smaller Anomeric Effect than the 3-equatorially substituted, "gluco-like", analogues (**16**). This was a surprising result, since the mannopyranosides usually show greater Anomeric Effects than analogous glucopyranosides, and this has been attributed to the mannopyranoside's axial O-2.

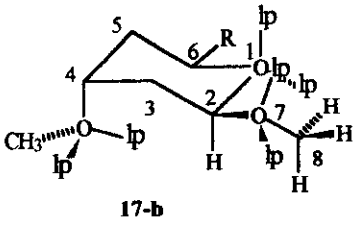
The dimethoxytetrahydropyrans

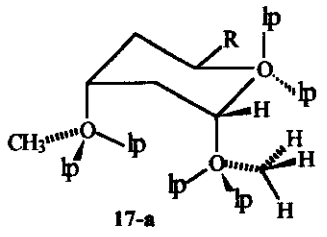












However, we shall see below that the "manno-like" 3-hydroxy compounds do show a greater Anomeric Effect than the analogous "gluco-like" molecules, indicating that the substituent attached to the O-3 (the mannopyranoside's axial O-2) does play a significant role in determining the relative stabilities of these molecules. Thus, we must always be cautious when indulging in generalizations concerning the

influence of the pyran ring substituents on the Anomeric Effect, and especially cautious concerning those generalizations that ignore the stereo-electronic features of these substituents.

Table 4

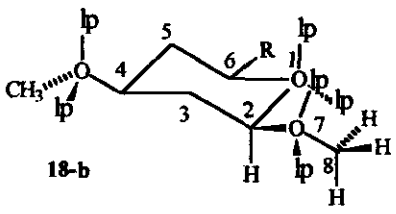
QVBMM Calculated Enthalpies of the Dimethoxytetrahydropyrans

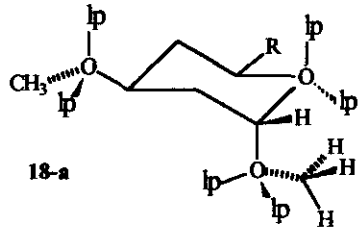
Substituent Site and Orientation	β–Anomer Enthalpy	α–Anomer Enthalpy	Anomeric Enthalpy
3-axial (**15**)	34.960	30.146	4.81
3-equatorial (**16**)	35.975	30.996	4.97
4-axial (**17**)	30.973	35.963	- 5.02
4-equatorial (**18**)	30.670	28.494	2.17
5-axial (**19**)	35.594	33.339	2.25
5-equatorial (**20**)	33.315	31.512	1.80

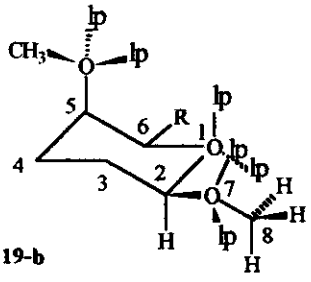
The 4-methoxyl groups (axial and equatorial) had relatively little influence on their β–anomers, which differed in enthalpy by only 0.26 kcal/mol. The oxygens (O-7 and O-1) of the β–anomer, and their lone pairs, were too distant to interact with C-4 and its substituents. However, the α–anomers of the compounds (**17**) and (**18**) were both highly influenced by the 4-methoxyl group. The 1,3-diaxial repulsion between the lone pairs of the axial 4-methoxyl group and the "*endo*" lone pair of the axial α–anomeric methoxyl group in the "allo-like" compounds (**17**) resulted in the "reversed" anomeric stabilities normally seen in these anomers. On the other hand, the 4-equatorial "gluco-like" compound (**18**) had the most stable α–anomer because of the favourable n - dipole interaction of the "endo" anomeric lone pair (of O-7) with the axial, highly polarized C-4 - H-4 bond. We shall see below that replacing the axial 4-methoxyl group with an axial 4-hydroxyl group restored the greater stability of the α–anomer of the "allo-like" compounds by the formation of a very favourable 1,3-diaxial hydrogen bond between O-7 and the 4-hydroxy group.

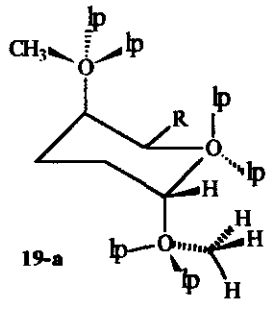
The axial 5-methoxyl group of compound (**19**) destabilized both its anomers because of the n - n interactions between one of its lone pairs and the axial lone pair of O-1, across the top of the ring. In contrast, the equatorial 5-methoxyl group of compound (**20**) caused the polarized, axial C-5 - H-5 bond to show a very small (almost zero), but favorable, n - dipole interaction between this hydrogen and the axial

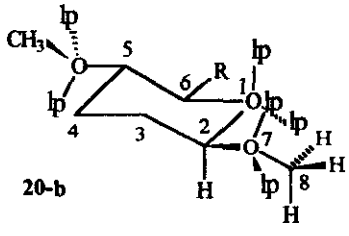
lone pair of O-1. The greater anomeric instabilities of the 5-axial, "galacto-like", compounds over the 5-equatorial, "gluco-like", compounds are known and result in the greater reactivity of the β–galactopyranosides over the corresponding β–glucopyranosides.[4a]

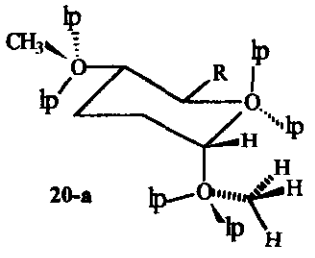












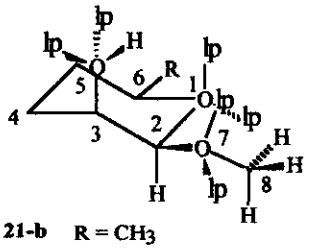
This study of the dimethoxytetrahydropyrans clearly demonstrated that the relative stabilities of anomeric pairs cannot be rationalized by narrowly focusing attention at C-1 and C-2 of the glycopyranosides. *Indeed, the nature and orientation of substituents at each and every other atom on the pyranosidic ring* can influence the magnitude of the Anomeric Effect. Thus, efforts to rationalize the origins of the Anomeric Effect in the monosaccharides, that have neglected the effects of the substituents on the pyranosidic ring that were thought to be "remote" from the anomeric center, have been severely flawed.

The Hydroxy-2-methoxytetrahydropyrans

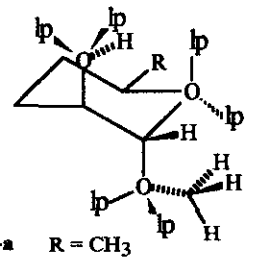
The "gluco-like" and "manno-like" 3-hydroxy-2-methoxytetrahydropyrans could have strong intramolecular hydrogen bonding of the hydroxyl group to the anomeric atom (O-7) and/or to O-1. Their

data are shown in the Table 5, below, for the 3-hydroxy-2-methoxytetrahydropyrans. The data for the 6-methyl-3-hydroxy-2-methoxytetrahydropyrans is also presented in order to highlight the effect to the 6-methyl groups on the molecular enthpalies.

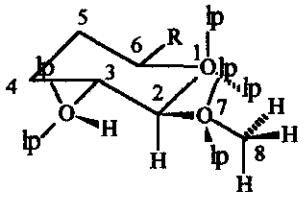
The hydroxy-2-methoxytetrahydropyrans



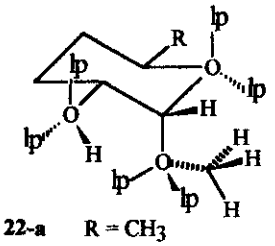
21-b R = CH_3
23-b R = H



21-a R = CH_3
23-a R = H



22-b R = CH_3
24-b R = H



22-a R = CH_3
24-a R = H

While the α–anomers of the the "manno-like" compounds (**21**) and the "gluco-like" compounds (**22**) have very similar energies, the enthalpies of their β–anomers differed by about 1 kcal/mol. An examination of the higher energied "manno-like" compound (**21-b**) showed that any hydrogen bond between the axial hydroxyl group on C-3 and an axial lone pair on O-1 or O-7 was accompanied by a lone pair repulsion between the unhydrogen bonded axial lone pair of O-1 or O-7 and one of the lone pairs of the axial hydroxyl group on C-3. Placing the β–anomeric methoxyl group in a conformation similar to that shown in compound (**15-b**) caused an increase in the enthalpy of that anomer. Thus, the QVBMM force field calculations showed that these "manno-like" 2-hydroxy compounds do show a greater Anomeric Effect than the "gluco-like" compounds, unlike their 3-methoxy analogues above. Notice however, that the conformations and interactions in the 3-methoxy compounds discussed above were quite different from those in the these 3-hydroxy compounds.

Table 5

QVBMM Calculated Enthalpies of the Hydroxy-2-methoxytetrahydropyrans

Substituent Site and Orientation	β–Anomer Enthalpy	α–Anomer Enthalpy	Anomeric Enthalpy
6-Methyl-3-hydroxy-2-methoxytetrahydropyrans			
3-axial (**21**)	28.043	23.247	4.97
3-equatorial (**22**)	26.950	23.320	3.63
3-Hydroxy-2-methoxytetrahydropyrans			
3-axial (**23**)	24.053	20.508	3.54
3-equatorial (**24**)	22.963	20.151	2.81

These results also show that the nature of the substituent attached to the oxygen at C-3 was important in determining the relative stabilities of the "gluco-like" and "manno-like" anomers. However, glucopyranosides and mannopyranosides are much more complex molecules and the influences of their other substituents cannot be ignored while focusing attention solely on the O-3 group. Indeed, the studies, below, on the di- and trihydroxy compounds will support this conclusion.

The Dihydroxy-2-methoxytetrahydropyrans

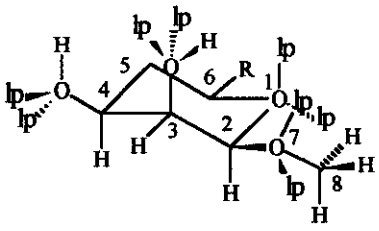
Table 6

QVBMM Calculated Enthalpies of the Dihydroxy-2-methoxytetrahydropyrans

Substituent Site and Orientation	β–Anomer Enthalpy	α–Anomer Enthalpy	Anomeric Enthalpy
6-Methyl-3,4-dihydroxy-2-methoxytetrahydropyrans			
3-ax, 4-eq (**25**)	29.253	23.817	5.43
3-eq, 4-eq (**26**)	27.322	23.860	3.46
3-eq, 4-ax (**27**)	27.072	21.830	5.24
3,4-Dihydroxy-2-methoxytetrahydropyrans			
3-ax, 4-eq (**28**)	25.014	20.605	4.40
3-eq, 4-eq (**29**)	23.154	20.523	2.63
3-eq, 4-ax (**30**)	23.685	18.572	5.11

The "inverted" Anomeric Effect of the previously discussed "allo-like", 4-axial-methoxy compounds (**17**) was noteworthy. However, the "normal" Anomeric Effect shown by the analogous "allo-like" 3-equatorial-4-axial-dihydroxy compounds (**27**) and (**30**) show that the data obtained for the compounds (**17**) cannot form the basis of a generalization on "allo-like" systems. The α–anomers of the 4-hydroxy compounds (**27**) and (**30**) were now much more stable than their β–anomers, because the α–anomers were stabilized by very favorable 1,3-diaxial hydrogen bonds. The β–anomers of the "gluco-like" and the "allo-like" 4-hydroxy compounds [(**26**) and (**27**), and (**29**) and (**30**) respectively] had similar enthalpies showing that these β–anomeric atoms were too far from the 4-hydroxyl groups to be influenced by them.

The dihydroxy-2-methoxytetrahydropyrans



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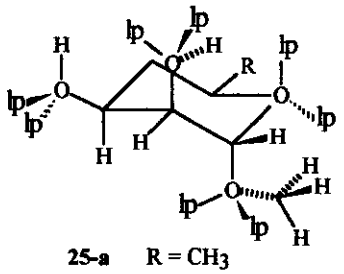
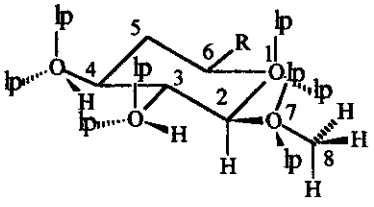
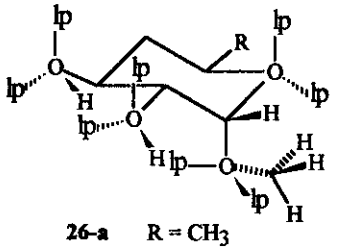
28-b R = H



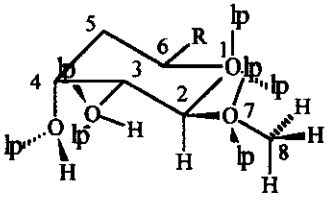
25-a R = CH_3
28-a R = H



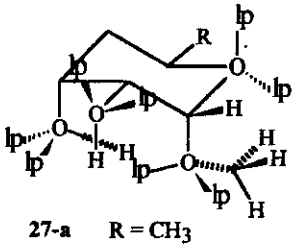
26-b R = CH_3
29-b R = H



26-a R = CH_3
29-a R = H



27-b R = CH_3
30-b R = H



27-a R = CH_3
30-a R = H

The "manno-like" 3-axial, 4-equatorial compounds (**25**) and (**28**) still had the larger Anomeric Effects than the "gluco-like" compounds (**26**) and (**29**). Interestingly, the Anomeric Effects of the "allo-like" 3-equatorial, 4-axial compounds (**27**) and (**30**) were very large and similar to those of the "manno-like" compound.

The Trihydroxy-2-methoxytetrahydropyrans

These molecules are the methyl pentapyranosides whose names, for consistency and rapid appreciation of the previously presented data, have been related to their corresponding tetrahydropyrans. Thus, the 3-ax, 4-eq, 5-eq tetrahydropyran (**35**) is the lyxopyranoside; the 3-eq, 4-eq, 5-eq tetrahydropyran (**36**) is the xylopyranoside; the 3-eq, 4-ax, 5-eq tetrahydropyran **37** is the ribopyranoside; and the 3-eq, 4-eq, 5-ax tetrahydropyran (**38**) is the arabinopyranoside.

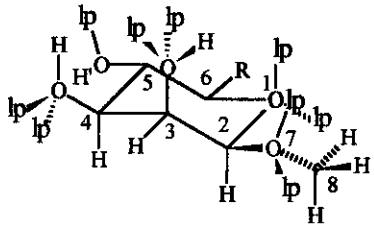
Table 7
QVBMM Calculated Enthalpies of the Trihydroxy-2-methoxytetrahydropyrans

Substituent Site and Orientation	β–Anomer Enthalpy	α–Anomer Enthalpy	Anomeric Enthalpy
6-Methyl-3,4,5-trihydroxy-2-methoxytetrahydropyrans			
3-ax, 4-eq, 5-eq (**31**)	29.933	24.565	5.36
3-eq, 4-eq, 5-eq (**32**)	29.247	25.576	3.67
3-eq, 4-ax, 5-eq (**33**)	28.984	25.130	3.85
3-eq, 4-eq, 5-ax (**34**)	33.039	28.392	4.64
3,4,5-Trihydroxy-2-methoxytetrahydropyrans			
3-ax, 4-eq, 5-eq (**35**)	25.600	21.215	4.38
3-eq, 4-eq, 5-eq (**36**)	24.086	21.512	2.57
3-eq, 4-ax, 5-eq (**37**)	24.032	20.191	3.84
3-eq, 4-eq, 5-ax (**38**)	27.693	23.750	3.94

"Adding" a 5-equatorial hydroxyl group to the compounds (**25**) and (**28**), had little effect on the Anomeric Effect of the resulting "manno-like" compounds (**31**) and (**35**), and these Anomeric Effects were the largest in their groups. However, the "additional" 5-equatorial hydroxyl group of the "gluco-like"

compounds (**32**) and (**36**) caused an increase in their Anomeric Effects over those of the compounds (**26**) and (**29**).

The trihydroxy-2-methoxytetrahydropyrans



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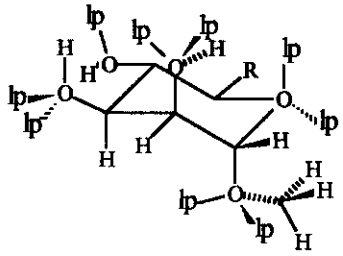
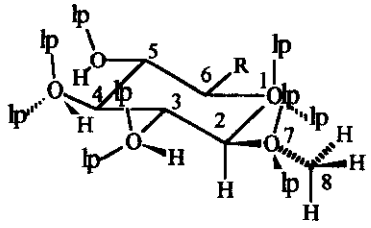
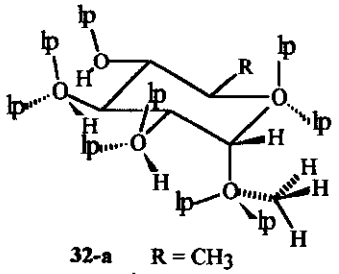
35-b R = H



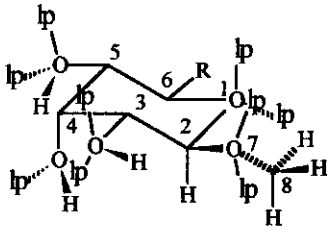
31-a R = CH_3
35-a R = H



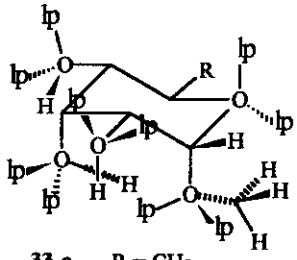
32-b R = CH_3
36-b R = H



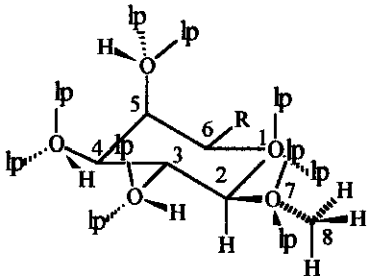
32-a R = CH_3
36-a R = H



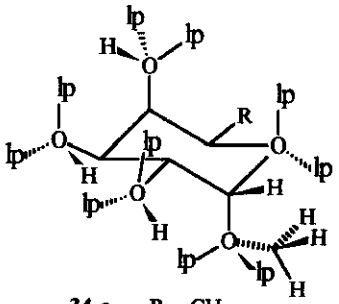
33-b R = CH_3
37-b R = H



33-a R = CH_3
37-a R = H



34-b R = CH_3
38-b R = H



34-a R = CH_3
38-a R = H

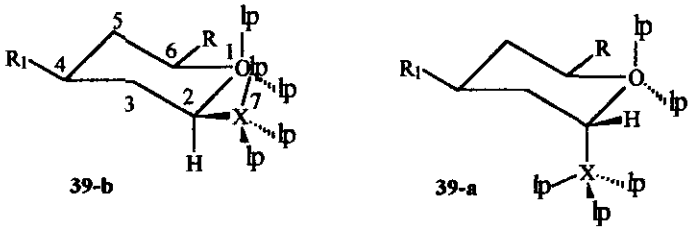
Once again, the β–anomers of the "gluco-like" compound (**36**) and "allo-like" compound (**37**) had very similar enthalpies, showing that the hydroxyl group at C-5 had little effect on the stability of their β–anomers. Notice also that the 6-methyl group increased the Anomeric Effect in going from the compound (**38**) to compound (**34**) by increasing the enthalpy of the β–anomer of compound (**34**) to a *greater extent than that of the α–anomer.*

The Glycosyl Halides

The importance of the Anomeric Effect in the glycosyl halides is very well known, and their Anomeric Effects are among the largest observed in stable pyranosides.[4a, 4c, 4h, 4k] The glycosyl halides are iso-electronic with the glycosyl alkoxides. These compounds have 5 anomeric lone pairs (on O-1 and O-7) in comparison to the 4 anomeric lone pairs of the glycosides. Thus the glycosyl halides and alkoxides will have more n-n interactions, and more interactions of the lone pairs with the H-2 and H-6, than the glycosides, but will obviously lack the stabilising C-H hydrogen bonding features involving the aglycones of the glycosides.

The experimentally measured[4c, 4h, 4k] conformational preference for the axial, α–anomeric, isomer of the 2-bromotetrahydropyrans and the 2-chlorotetrahydropyrans were about 96% in each case, and this value was also found for the 2-halo-4-methytetrahydropyrans. These equilibria were measured in carbon tetrachloride, in which the sizes of the Anomeric Effects of the 2-halotetrahydropyrans should be maximal, since the Anomeric Effects normally increases with decreasing solvent polarity, as found for the glycosides. These axial/equatorial ratios indicate conformational free energy differences of about 1.8 kcal/mol for these anomeric 2-halotetrahydropyrans. In the absence of definitive estimates of the entropies for these molecules it is difficult to estimate their enthalpies, which are the quantities to be compared with the QVBMM data.

The glycosyl halides



The QVBMM force field calculated the conformational enthalpy difference between the anomeric 2-chloro-6-methyltetrahydropyrans to be 1.54 kcal/mol, and that between the 2-bromo-6-methyltetrahydropyrans to be 1.74 kcal/mol, consistent with the experimental data. Once again the 6-methyl group exerted a considerable influence in these molecules because the calculated conformational enthalpy difference between the anomeric 2-chlorotetrahydropyrans was 0.73 kcal/mol, the anomeric 2-chloro-4-methytetrahydropyrans was 0.72 kcal/mol, the anomeric 2-bromotetrahydropyrans was 0.72 kcal/mol, and the anomeric 2-bromo-4-methytetrahydropyrans was also 0.72 kcal/mol.

The experimentally measured conformational enthalpy differences between the simple 2-fluorotetrahydropyrans seems not to have been reported. The QVBMM force field calculated the conformational enthalpy difference between the anomers of 2-fluoro-6-methyltetrahydropyran to be 2.30 kcal/mol, the anomers of 2-fluoro-4-methyltetrahydropyran to be 1.10 kcal/mol and the anomers of 2-fluorotetrahydropyran to be 1.29 kcal/mol.

The discussion of the methyl pyranosides, above, revealed that ring substituents, particularly axial substituents at C-3, C-4 and C-5, exerted significant influence on the Anomeric Effects in their host molecules. A similar situation was encountered in the glycosyl halides. Thus, while the Anomeric Effects calculated for the simple 2-halotetrahydropyrans were smaller than those calculated for the more highly substituted glycopyranosyl halides, the Anomeric Effects calculated for the 3-methoxy-2-halotetrahydropyrans were quite large and comparable to those seen in the glycopyranosyl halides. For example, the calculated conformational enthalpy differences between the anomers of the "manno-like" 3-methoxy-2-fluorotetrahydropyran was 3.95 kcal/mol, and that of the analogous "gluco-like" molecules was 3.28 kcal/mol.

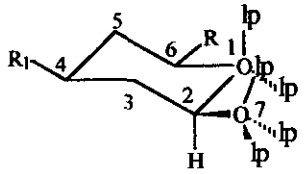
In general, the trends reported above for the 2-methoxytetrahydropyrans were seen in the 2-halotetrahydropyrans. A forthcoming paper will discuss the variation of the Anomeric Effect of the glycosyl halides with the ring substitution.

The Glycosyl Alkoxides

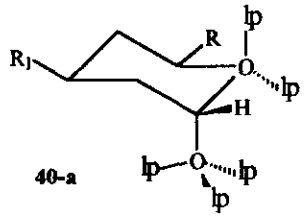
The alkoxide of the anomeric hydroxyl group of any given sugar is isoelectronic with that sugar's glycosyl fluoride. However, while experimental data on the Anomeric Effect is available for some of the glycosyl halides, this experimental data does not seem to be available for anomeric alkoxides. Among the 2-halotetrahydrofurans, the sizes of the Anomeric Effect seem to increase with the electronegativity of the

halogen.[4c, 4h, 4k] This trend should logical place the Anomeric Effect due to the anomeric alkoxide closer to that of chlorine, because the full negative charge on the oxygen should reduce its electronegativity. On the other hand, the alkoxide's negative charge, and its larger size than fluorine, should increase the sizes of n - n interactions, and the dipolar interactions. Thus, it was not clear whether the Anomeric Effect would be greater in the glycosyl alkoxide or in the glycosyl fluoride.

The glycosyl alkoxides



40-b



40-a

Our work on the acylations of glucose and 2,3,4,6-tetrabenzylglucose with acyl chlorides under alkaline, phase-transfer, reaction conditions had allowed us[10a] to study the known dominant nucleophilicity of the β–anomeric alkoxides over the corresponding α–anomeric alkoxides.[4a] Our studies consistently produced yields of β–anomeric esters that were at least 97% of the total produced esters, and the reaction profile varied only very slightly with acyl chloride structure (acetyl, benzoyl, pivaloyl)[9a] after allowance had been made for the consequences of ester migration.

Simple equatorial cyclohexanols are known to undergo acylation 6 times faster than their axial isomers[9b] presumably because of the greater activation energy required for acylation of the axial hydroxyl group, due to the greater steric congestion in that transition state, as compared to the transition state for the acylation of the equatorial hydroxyl group. The higher ground state energy of the axial alcohol should reduce this activation energy difference somewhat. Thus, if we ignored the Anomeric Effect, the axial α–anomeric alkoxides should also require a greater activation energy for their acylations than the corresponding equatorial β–anomeric alkoxides. However, the Anomeric Effects causes the β–anomeric alkoxides to have higher ground state energies than their α–anomers, and this factor should reduce the activation energy for the acylation of the β–anomeric alkoxide relative to that for the α–anomer. Qualitatively, one can understand why the β–anomeric alkoxide should be acylated much more rapidly than the α–anomer, if these two species possessed similar nucleophilic characteristics. However, a

further consequence of the Anomeric Effect is the prediction that the lone pairs of the β–anomeric alkoxides should be at higher energies than those of the α–anomers, and these more energetic lone pairs should be more nucleophilic.[4a, 4c, 4h, 4k] Taken all together, these trends are supported by the acylation experimental data we have obtained.

Our acylation data also indicated that the rates of equilibration of the anomeric alkoxides far exceeded those of their acylation, a necessary condition for the application of the Curtin-Hammett principle[10]. Thus, our acylation data did not reveal the conformational enthalpy difference between the "ground states" of the anomeric alkoxides, which would also have been the size of the implicated conformational and kinetic Anomeric Effects, and at best might only be correlatable to the difference in the activation energies for these acylations.

In any event, the QVBMM force field calculated the β–anomeric alkoxide of 2-hydroxytetrahydropyran to be 1.49 kcal/mol less stable than the isomeric α–anomeric alkoxide, while the calculated enthalpy difference between the anomeric 2-fluorotetrahydropyrans was 1.29 kcal/mol. The calculated enthalpy difference between the anomeric 2-fluoro-6-methyltetrahydropyrans was 2.30 kcal/mol and that between the alkoxides of the anomeric 2-hydroxy-6-methyltetrahydropyrans was 2.61 kcal/mol. Thus, the QVBMM force field predicted that the Anomeric Effect will be greater in the tetrahydropyranyl alkoxides than in the analogous fluorides. A discussion of the variation of the Anomeric Effect of the glycosyl alkoxides and halides with the ring substitution will be presented in a forthcoming paper.

CONCLUSION

We should now be able to recognize the folly of assigning a fixed value to the Anomeric Effect that we can apply to all monosaccharides. The magnitude of the Anomeric Effect will vary with the structural features of the monosaccharide and with the substitution, or derivatization, of the monosaccharide. While this paper only examined the very simplest monosaccharides for the origins of their Anomeric Effects, a forthcoming manuscript will show that the Anomeric Effects found in simple monosaccharide acetates follow similar, and now predictable, patterns.

The successes of the QVBMM force field in simulating the structures and enthalpies of the tetrahydropyrans, using only the well known steric and dipolar interactions, indicate that this molecular mechanics force field will be a useful addition to the molecular modeling methods available to organic chemists. Indeed, we shall show in a forthcoming publication that the QVBMM force field accurately

Molecular Geometry About the Anomeric Center of Some Selected Pyrans

	Bond Lengths		Bond Angles				Exo-Anomeric
Molecule	O-1 - C-2	C-2 - A-2	O-1 to C-2 to C-3	O-1 to C-2 to A-2	C-3 to C-2 to A-2	C-2 to A-2 to C-7	Dihedral Angle
QVBMM Data							
1	1.4264	1.4245	111.51	115.24	108.09	112.99	60.24
2	1.4240	1.4238	111.12	114.37	111.44	112.70	66.07
7	1.4248	1.4192	112.67	113.86	108.71		46.18
8	1.4231	1.4194	112.65	113.23	111.35		50.41
11	1.4243	1.4772	112.98	111.11	109.31		
12	1.4227	1.4785	112.62	113.4	111.92		
23-b	1.4263	1.4243	113.17	115.36	109.41	113.69	55.66
23-a	1.4237	1.4236	111.2	114.16	111.01	112.83	66.69
24-b	1.4269	1.4254	111.6	114.49	109.61	113.19	62.41
24-a	1.4241	1.4245	109.44	113.83	112.89	112.6	68.49
28-b	1.4263	1.4243	113.19	115.4	109.54	113.77	55.71
28-a	1.4241	1.4229	111.14	114.58	110.27	112.86	65.53
29-b	1.4267	1.4252	111.56	114.27	110.35	113.25	62.69
29-a	1.4233	1.4243	109.78	113.8	112.12	112.67	68.09
30-b	1.4271	1.4251	110.48	114.37	110.57	113.07	63.32
30-a	1.4235	1.4236	109.4	114.51	112.82	113.04	63.38
35-a	1.4238	1.4229	110.01	114.72	110.68	112.87	65.76
35-b	1.4257	1.4243	110.2	114.72	111.62	112.61	67.06
36-a	1.4227	1.4234	109.45	113.95	112.03	112.47	68.8
36-b	1.4261	1.4252	110.28	114.14	110.97	113.09	63.54
37-a	1.4236	1.4232	109.24	114.41	112.8	112.94	63.71
37-b	1.4267	1.4238	110.89	114.42	109.37	112.93	63.04
38-b	1.4269	1.4257	113.62	114.49	110.15	113.49	59.66
38-a	1.4236	1.424	110.63	112.91	111.82	112.92	68.22
39-b	1.4269	1.3808	112.49	115.61	108.19		
39-a	1.4241	1.3791	111.67	115.15	110.7		
40-b	1.4272	1.4219	112.68	115.76	107.67		
40-a	1.4237	1.4191	111.47	114.31	111.45		
MMX Data							
1	1.4303	1.4301	109.47	111.25	107.75	112.52	70.12
2	1.4295	1.4297	110.33	113.58	109.55	112.85	69.63
21-b	1.4306	1.4307	110.11	111.99	107.67	112.67	67.82
21-a	1.4299	1.4303	110.1	113.56	109.57	112.87	69.6
22-b	1.431	1.4309	109.42	110.94	107.34	112.57	71.5
22-a	1.4305	1.4304	109.91	113.18	109.5	112.87	70.71

The external (non-ring) anomeric atom is labelled "A", and can be oxygen, nitrogen or fluorine. The atom type is ascertainable by consulting the structure diagram indicated.

predicts the relative reactivities of the hydroxyl groups of the monosaccharides, and other areas of monosaccharide chemistry, while several authors have contended that the data provided by the application of the currently used *ab initio* M.O. theoretical methods to monosaccharides do not always concur with the experimental data for these molecules.[3b, 4k]

A table showing the molecular geometry about the anomeric centers of some of the tetrahydropyrans discussed above is also presented herein. The table also shows some data from the MMX calculations of some of these molecules, for comparative purposes.

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