ORIGINAL PAPER

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The role of lone pair and dipolar interactions in the non-planarity of 1,3-dioxolane and 1,3-dioxole

Abstract 1,3-Dioxole has been shown to be non-planar by infrared and Raman spectroscopy. An MM3 study of this molecule enabled the investigators to suggest that this non-planarity was due to the anomeric effect. Subsequently, an ab initio theoretical study of this molecule was performed, which also concluded that the non-planarity of 1,3-dioxole was due to the anomeric effect and not to dipole–dipole interactions. Neither study used rigorous methods for assessing the role of dipolar interactions in the geometry of 1,3-dioxole. A new study of 1,3-dioxole, 1,3-dioxolane, tetrahydrofuran, cyclopentane, and some related molecules using the new QVBMM (molecular mechanics) force field shows conclusively that the non-planarity of 1,3-dioxole and 1,3-dioxolane is due primarily to torsional and dipolar effects, and not secondary molecular orbital overlap interactions.

Keywords 1,3-Dioxole · Tetrahydrofuran · QVBMM · Molecular mechanics · Dipolar interactions · Lone pair interactions · Anomeric effect

Introduction

The anomeric effect is normally shown by acetals and most molecules that possess two or more lone-pair-bearing heteroatoms geminally bonded to carbon. [1, 2, 3, 4, 5, 6] In the 2-alkoxypyrans, the axial 2-alkoxypyrans are usually more stable than their equatorial conformers. In the similarly substituted cyclohexanes the equatorial conformers are normally more stable. Thus, the stereochemical preference for alkoxyl substituents of the 2-alkoxypyrans is the reverse of that expected for similarly substituted cyclohexanes. This phenomenon has become

the stereochemical hallmark of the anomeric effect. The *gauche* relationship between heteroatomic substituents geminally bonded to carbon has also been observed in acyclic systems. [1, 2, 3, 4, 5, 6]

Two models are widely recognized for the rationalization of the anomeric effect. [2, 5, 6] In the 2-alkoxypyrans, the n–σ* model suggests that the dominant delocalization of the axial-like O-1 lone pair into the C-2–OR σ* orbital stabilizes this conformer, thus leading to the observed geometry. This model, shown in Scheme 1, has also been called the "double bond–no bond resonance" model and is the basis of the molecular orbital based ab initio calculations that seek to rationalize the anomeric effect. The n–σ* model uses a σ, π pair of orbitals for the oxygen lone pairs, and it is the π-type lone pair that is implicated in the n–σ* interaction, since it has the correct symmetry requirements[1]. In Scheme 1, the equivalent sp^3-like orbitals are shown for convenience.

The dipolar, lone pair interaction model [1, 6] suggests that the axial 2-alkoxypyrans are more stable than their equatorial conformers because the axial conformers have fewer repulsive n–n interactions and more stabilizing C–H hydrogen bonding interactions. This model suggests that the anomeric effect is a significantly destabilizing interaction, and so the less destabilized conformer is more stable. The dipolar, lone pair interaction model assumes that the oxygen's lone pairs are in sp^3-like orbitals, consistent with the principles of VSEPR theory. This model is shown in Scheme 2.

If the anomeric effect is a stabilizing interaction, as is suggested by the n–σ* model, then in the absence of other stereoelectronic factors, all conformations of acetals that do not experience the anomeric effect should be higher in energy than those that do. Stated otherwise, the n–σ* model leads us to conclude that the most stable conformation of an acetal should experience the anomeric effect.

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[1] While there is still controversy about the nature of the lone pair orbitals on oxygen, many theoreticians acknowledge that the σ, π pair are essentially equivalent to the sp^3 pair of orbitals, see [2].
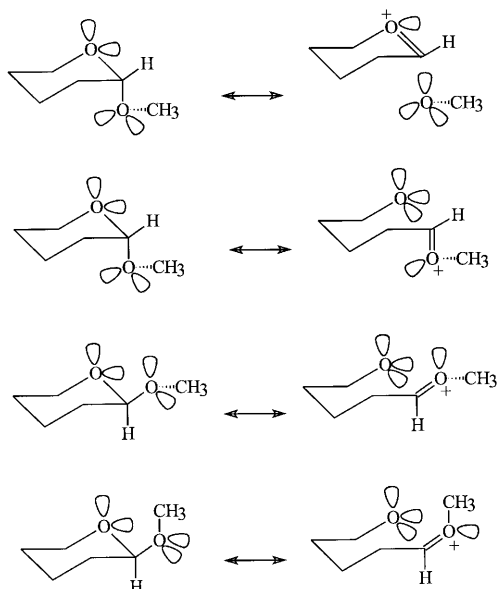
Scheme 1 Double bond–no bond resonance model
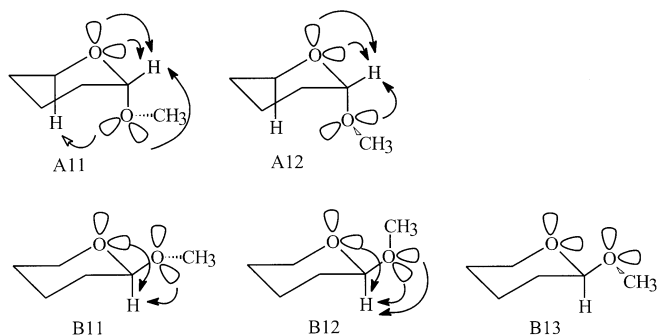
Scheme 2 The dipolar, lone pair interaction model. Curved arrows link lone pairs and hydrogen in C–H hydrogen bonds. Shaded lone pairs are coplanar and interact with repulsion

On the other hand, since the dipolar, lone pair interaction model [1, 6] suggests that the anomeric effect is due to combinations of unfavorable repulsive n–n interactions and reduced opportunities for C–H hydrogen bonding, then the most stable conformation of an acetal should not experience n–n interactions and should benefit from significant C–H hydrogen bonding. The dipolar, lone pair interaction model suggests that conformations that do not experience the anomeric effect are more stable.

There are obviously going to be many acetals whose stable conformations cannot experience n–n repulsions. Many will also be geometrically incapable of attaining geometries in which n–σ* interactions can occur. In these cases, where the stability of one conformer over the others is not due to reduced n–n interactions coupled with increased favorable C–H hydrogen bonding and dipolar interactions, or this most stable conformer cannot experience more effective n–σ* interactions than the others, then these acetals should clearly be identified as not

experiencing the anomeric effect. The stabilities of the conformers of these acetals must be attributed to differences in their dipolar interactions and C–H hydrogen bonding only.

1,3-dioxole and the anomeric effect

Laane et al. [7] have determined that the 1,3-dioxole ring is not coplanar by using IR and Raman spectroscopy, and they estimated the "bending angle" of the ring to be about 24°. They attributed the non-planarity of the 1,3-dioxole ring to the anomeric effect, wherein the molecule had assumed a geometry best suited to the manifestation of the anomeric effect. This conclusion arose from the MM3 prediction of a planar structure for the 1,3-dioxole ring. Thus, the puckered conformation would be "unusual", so showing that it was stabilized by some stereoelectronic effect, and they suggested the anomeric effect. They successfully reparameterized the MM3 program – by adjusting the size of the 2-fold torsional potential energy term V2 – and hence obtained good agreement between experiment and their MM3 molecular mechanics calculations. [7]

Suarez et al. [8] performed MP4/6-31G**//MP2/6-31G** calculations and NBO analyses on 1,3-dioxole and concluded that the distortion of this system was due to n–σ* delocalizations involving the oxygen lone pair and the flanking C–O bond, the anomeric effect. They also performed a "careful" analysis of the dipole–dipole interactions in 1,3-dioxole and concluded that "the 4electrostatic theory does not help to rationalize the experimentally observed puckered-ring conformation of 1,3-dioxole". [8] Thus, they concluded that the geometry of 1,3-dioxole was due entirely to the stereochemical influence of the anomeric effect.

However, as will be seen in the discussion below, neither of these groups possessed, or were able to use, a molecular modeling method that would have allowed them to exclude the roles of dipolar interactions in the determination of the conformational features of these molecules reliably. Thus, these carefully done studies obviously needed further corroboration that was not available at the time of their work. The newly developed quantized valence bonds' molecular mechanics (QVBMM) force field has offered us an opportunity to contribute in this area, because of the thoroughness with which it assesses lone pair and dipolar interactions

The QVBMM force field

Molecular mechanics, semiempirical, and molecular orbital based theoretical calculations have become very widely used in organic chemistry. However, none of these methods was designed to render a true assessment of the dipolar interactions within a molecule. Most glaringly, interactions involving lone pairs of electrons are not estimated by any of these methods, and the lone pair

effects are parameterized into these methods. Thus, theoretical chemistry has lacked a calculation method that would perform a detailed and thorough assessment of all of the lone pair and dipolar interactions in a molecule, and hence enable one to estimate the role that these interactions played in the determination of the structural and chemical properties of that molecule.

The newly developed QVBMM force field [9] was designed to be a quantitative implementation of the valance shell electron pair repulsion (VSEPR) theoretical model [10, 11] for the prediction of the structures of organic molecules. The QVBMM force field intimately incorporates lone pairs and their interactions into the fabric of the molecular mechanics calculations to a degree that no previous molecular mechanics program has. The QVBMM force field also considers all dipole–dipole interactions (even C–H bond polarization in alkanes) in the molecule being studied, and the interactions of these dipoles with lone pairs present in the system. The QVBMM force field will simulate delocalized and non-delocalized π-systems, as directed based on the starting structure of the molecular model whose structure energy it will minimize, and integrates the interactions of these π-electrons into the molecular mechanics calculations.

The QVBMM force field was parameterized using a few simple molecules (primarily ethane, ethene, propyne, butane, butadiene, the methylcyclohexanes, 1,2-dimethoxyethane, benzene, acetone, acetaldehyde, and ethyl acetate). Since any given basic stereoelectronic interaction must have the same origins in any molecule in which this interaction is found, then the magnitude of this interaction in a given molecule must only depend on the influence of other local factors. For example, torsional (σ–σ repulsions) interactions must have the same origins in all molecules that experience them, and will vary in magnitude only with variations in the electron density distribution and dihedral geometry for a particular pair of bonds. Thus, the parameterization of the force constants of the QVBMM force field for σ–σ repulsions, using ethane, must be valid for all molecules provided that local electron density distributions and dihedral geometries are subsequently taken into account.

Interestingly, the parameterization of the QVBMM force field using these simple molecules was shown to be valid for all of the first row elements and only one generalized adjustment was needed for polarizable heteroatoms (those with atomic radii greater than 1.1 Å). The ability of the minimally parameterized QVBMM force field to simulate accurately the structures of a very wide range of molecular types completely supported the validity of the approach taken in the design and construction of the QVBMM force field.

This theoretical approach has proven to be remarkably successful, and the molecular simulation data generated by the QVBMM force field have proven to be congruent with the known experimental data for a very wide range of organic molecules, of varying sizes and functional group complexity. Thus, while the QVBMM force field has not been specifically parameterized for any particular complex stereoelectronic effects, like the anomeric effects shown by acetals, the force field has successfully simulated such effects, thus suggesting that they are simply aggregates of the basic/fundamental stereoelectronic effects.

The QVBMM force field has been very successful in predicting and rationalizing the anomeric effects in a wide variety of acetals. [6, 9] It has not only been used to study the simple pyrans, but also to study complete monosaccharides, and in all cases the data generated from the QVBMM force field were congruent with the available experimental data. The QVBMM force field is also very successful in the rationalization of the anomeric effects observed in the 1,3-dithianes and other related molecules.

Indeed, the QVBMM force field has successfully tackled other problems that have not yet been undertaken successfully by the other molecular modeling methods, like the prediction of the preferred site of nucleophilic reactivity in the 4,6-*O*-ethylidineglycopyranosides. [12] The QVBMM force field has greatly assisted in the identification of non-planar peptide linkages in proteins and in the development of a new insight into enzymatic peptide cleavage mechanisms. [13] The QVBMM force field has also been used to provide a completely new evaluation of the stereoelectronic factors that influence the reverse anomeric effect shown by the glycosylamines and the glycosylated nitrogen heterocycles. [14]

These achievements clearly show that the QVBMM force field is currently the most capable molecular mechanics force field for use in the assessment of dipolar interactions in heteroatom-containing molecules. It is therefore very suitable for use in examining the stereoelectronic effects in 1,3-dioxole and 1,3-dioxolane, particularly from the point of view of evaluating the dipolar interactions in these molecules, and the roles of these dipolar interactions in determining the stabilities of the their conformers.

Molecular orbital effects versus dipolar interactions

Before the advent of the QVBMM force field, one of the major problems in theoretical chemistry was the absence of a theoretical method that could accomplish a detailed and reliable analysis of a molecule for its dipolar interactions, especially those involving the lone pairs of electrons. Further, since the molecular orbital based calculations, and the other currently available molecular mechanics programs, do not explicitly handle n–n, n–σ, and n–π repulsions, then theoretical molecular orbital chemists have been unable to decide unequivocally whether molecular structural effects were due to lone pair and/or dipolar interaction phenomena rather than to secondary molecular orbital phenomena, or vice versa.

The QVBMM force field performs an extremely detailed analysis of the stereoelectronic effects in any molecule, and completely involves the lone pairs present in that molecule in the calculations. Thus, if it fails to rationalize the known structural features of any molecule then

we can confidently assert that those structural features must be due primarily to secondary molecular orbital effects. On the other hand, if the QVBMM force field fully rationalizes the structural features of a molecule, then we must conclude that those features are due primarily to dipolar (and lone pair, if present) effects, rather than to secondary molecular orbital effects. There must also be situations in which both secondary molecular effects and dipolar interactions will contribute significantly to a molecule's structural and chemical properties, and these situations will clearly require a joint analysis of these molecules by the QVBMM and the molecular orbital based methods.

Thus, we suggest that structural phenomena that can be fully rationalized by the QVBMM force field should best be treated as dipolar based phenomena, and those that cannot should be treated as being wholly, or partly, due to secondary molecular orbital interactions. This QVBMM study of 1,3-dioxole, 1,3-dioxolane and related molecules should therefore be seen as a theoretical approach to enable us to decide whether the structural features of these molecules are primarily the consequences of secondary molecular orbital interactions, or of dipolar interactions.

Conformational energy barriers

In order to measure a conformational energy barrier one must either "capture" the molecular model, during a structure energy minimization run, at that energy maximum, or "assemble" the atoms of the molecular model in the geometry that one thinks exists at the energy maximum. Then a measurement of the static energy of the molecular model will yield the desired quantity.

However, "assembling" a molecule in its geometry at the energy maximum must obviously be fraught with problems. Then, you will invariably get what you want, rather than an assessment of the truth, since the geometry imparted to the molecule is of your own selection. Further, "fixing" the positions of some of the atoms of a molecular model in a predetermined relative arrangement and then minimizing the energy of that structure, while not allowing the "fixed" atoms to move, must also lead to an artificial result that cannot be accepted without great reservations.

The STR3DI32.EXE molecular modeler cannot easily "capture" a molecule at a conformational energy maximum. With the expenditure of a lot of effort, one can "capture" the molecular model when it is close to the conformational energy maximum, but then there is still considerable uncertainty about the projected energy at the maximum. Thus, the QVBMM force field cannot give reliable, reproducible results on transitional conformations that lie between local energy minima. While we shall not comment on the sizes of conformational energy barriers, we shall report the energies of metastable conformations (high energy local minima), and often the data for these conformations shed some light on the conformational characteristics of the system.

Discussion

The molecules examined

Since the oxacyclopentane rings will obviously be smaller than cyclopentane (C–O bonds are significantly shorter than C–C bonds), they will be less flexible than cyclopentane and experience more pronounced torsional interactions. Cyclopentenes were therefore included in this study as more suitable analogues of the oxacyclopentanes whose structures we wished to examine.

The QVBMM force field was used, without reparameterization, to simulate the minimum energy structures of the molecules shown above, in Scheme 3. The force field is quite susceptible to detecting local minima. We therefore initially created several conformations of each molecule, each more slightly puckered than the others, and then allowed the QVBMM force field to minimize the structure energies of the set. Thus, we determined the minimum energy conformation for each molecule and some of the higher energy conformations whose local minima were close to the minimum energy system. It is quite possible that we could have failed to simulate/detect some conformations whose local minima were "shallow" energy wells, thus allowing the force field to push these structures out of these shallow minima and into more stable states.

The dihedral angles between ring atoms that could best indicate the degree of non-planarity in that ring were measured, and are listed in Table 1. Note that we have used a "non-standard" numbering of the non-furanoid molecules (as is shown in Scheme 3 above) in order to give these molecules a numbering that would make their geometrical features directly comparable to those of tetrahydrofuran and 4,5-dihydrofuran. This allowed us to compare similar dihedral angles directly, across the range of structures studied, more easily.

Cyclopentane

The QVBMM force field predicted dihedral angles for the minimum energy conformation of cyclopentane, corresponding to those shown in Table 1, demonstrating that cyclopentane was not only the most highly puckered
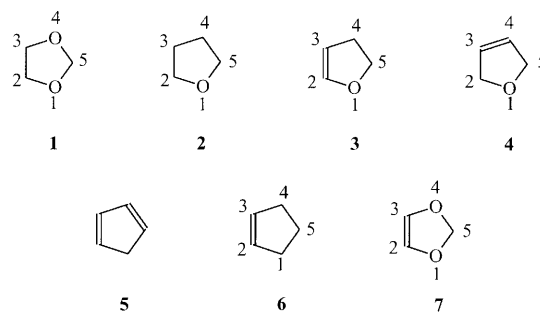
Scheme 3 Molecules calculated with QVBMM

Table 1 Some QVBMM calculated enthalpies and dihedral angles in the molecules **1–7**

Molecule	Enthalpy (kcal mol⁻¹)	Dihedral angles in minimum energy conformation (degrees)				
		1, 2, 3, 4	1, 5, 4, 3	2, 3, 4, 5	2, 1, 5, 4	5, 1, 2, 3
1	10.517	23.36	15.46	4.91	31.04	32.80
	12.260	5.89	3.70	1.35	7.55	8.05
2	11.199	18.43	18.10	0.19	30.73	30.83
	11.710	26.42	30.87	33.62	14.99	7.47
	14.762	3.16	5.22	4.90	3.36	0.09
3	19.105	0.05	4.55	2.78	4.55	2.95
	19.123	0.04	4.48	2.69	4.52	3.01
	19.938	0.12	25.56	15.39	25.69	17.01
4	17.153	9.44	9.41	0.02	15.24	15.24
	17.253	0.23	0.34	0.07	0.49	0.45
	17.701	16.31	16.37	0.04	26.43	26.41
5		0.00	0.00	0.00	0.00	0.00
6		0.00	17.76	11.52	17.74	11.50
7	32.437	0.02	4.77	2.83	4.79	2.87
	33.102	0.05	15.66	9.27	15.69	9.35
	33.159	0.01	16.26	9.66	16.25	9.65

molecule, but also the most irregular. Thus, depending on which atom was labeled "1", the dihedral angles covered a range from 10.6° to 38.0°.

The QVBMM force field predicted that the lowest energy conformation of cyclopentane was a significantly twisted envelope conformation. This conformation clearly allowed the most effective minimization of torsional strain in the cyclopentane molecule. Cyclopentane can only experience torsional and dipolar interactions, and so the twisted low energy conformations of cyclopentane are "normal", in the sense that their geometries are not due to the influence of any complex stereochemical interaction.

We should therefore expect that puckering is normal in molecules analogous to cyclopentane, and that torsional and dipolar interactions will contribute significantly to their structures. The molecules (**2**, **3**, **4**, and **6**), none of which can experience an anomeric effect, were also found to be puckered in their minimum energy conformations, so providing support for the significant roles of dipolar interactions and σ–σ, n–σ, and σ–π torsional effects in the determination of the structures of these molecules.

Cyclopentadiene

The QVBMM force field predicted that cyclopentadiene (**5**) was planar.

The furanoid molecules

Tetrahydrofuran (**2**) was predicted to be in a twisted envelope conformation, as is shown by the dihedral angles in Table 1, and to have dihedrals quite similar to those of cyclopentane. The largest predicted dihedral angle in

the minimum energy conformation, 30.8°, is quite similar to the experimentally observed value of 35.0°. [12] However, a slightly higher energy conformer (by 0.51 kcal mol⁻¹) had its largest dihedral angle at 33.6°. The similarities in the degree of puckering of tetrahydrofuran and cyclopentane should not be very surprising since the n–σ and σ–σ torsional interactions should be similar in magnitude.

The enol ether (**3**) was predicted to be substantially puckered, whether one assumed that it had a delocalized π-system, or a not. It is important to note that analyses of bond length data from X-ray crystallographic studies clearly suggest that simple dienes and simple enol ethers do not generate delocalized π-systems. [15, 16] The QVBMM generated data presented here are for the corresponding non-delocalized molecular models.

The largest dihedral angle predicted by the QVBMM force field for the minimum energy conformation of the enol ether (**3**) was only 4.6°, smaller than the 19.4° cited by Suarez et al. [8] However we found that this molecule had another low energy conformation (only about 0.83 kcal mol⁻¹ less stable that the minimum energy conformation) that had its largest dihedral angle at 25.7°. Thus, only a small amount of energy is required to change the geometrical features of this molecule quite significantly. We were unable to find the conformation that had its largest dihedral angle at about 19°, which suggests that this conformer, intermediate in energy between the two we have mentioned, might not be at a local energy minimum.

The 2,5-dihydrofuran (**4**) presented the most interesting data. The QVBMM force field found three low energy conformations whose energies were within 0.54 kcal mol⁻¹ of each other. Two of these conformations differed in energy by only 0.1 kcal mol⁻¹. Each of these conformations had a very different structure from the other two. The lowest energy conformation was pre-

dicted to be puckered, but less so than the larger molecules (**1** and **2**), while the next higher energy conformation, by only 0.1 kcal mol^{-1}, was planar. The 2,5-dihydrofuran (**4**) molecule's minimum energy conformation was predicted to have its largest dihedral angle at 15.2°. The next, higher energy, conformation was predicted to have its largest dihedral angle at 0.5°. It was remarkable that two conformations, so close in energies, were so different in geometries. The highest energy conformation of the three, which was only 0.55 kcal mol^{-1} higher in energy than the minimum, had its largest dihedral angle at 26.4°.

Once again we see that a significant change in the geometry of the molecule (**4**) should only require a small amount of energy. It should also be quite difficult to suggest unequivocally which of this molecule's low energy conformations would be most populated in solution, or in the solid phase, since solvation energies and crystal packing forces can provide enough energy to alter the conformation from the minimum to any of the other two low energy ones discussed. The experimental data support the prevalence of the planar conformation.

Notice that the puckering predicted for the minimum energy conformations of these molecules decreases in the order: cyclopentane and **2**>**4**>**3**, consistent with trend of decreasing puckering with decreasing ring size. Notice too that the puckering predicted for the enol ether (**3**) was less than that predicted for the molecule **4**, whether or not delocalization was assumed to occur between the lone pair and the π-bond.

It must now be obvious that comparing data gathered from different types of molecular modeling tools could lead to great confusion. These molecules, especially 2,5-dihydrofuran (**4**), have quite simple structures, but can easily assume a range of bond and dihedral angles without incurring very serious energy penalties. The QVBMM prediction that energetically similar conformations can show significant structural differences must warn us of the possibility that investigators will report different dihedral angles for these molecules. Indeed, we have also found a conformation of the enol ether (**3**) that is only about 0.02 kcal mol^{-1} higher in energy than the minimum, but which appears to be flatter than the minimum energy conformation.

1,3-Dioxolane

Tetrahydrofuran (**2**) was predicted to be in a significantly twisted envelope conformation, as is shown by the dihedral angles in Table 1. The smaller molecule 1,3-dioxolane (**1**) was predicted to be just as puckered as tetrahydrofuran (**2**) and be in a significantly twisted envelope conformation, also shown by the dihedral angles in Table 1. Since the 1,3-dioxolane ring (**1**) is smaller than the tetrahydrofuran ring (**2**), one might have predicted the opposite trend in the relative degree of puckering in these rings. This result shows that the additional lone pairs do play very significant roles in the determination of the geometry of the 1,3-dioxolane ring.

The non-planarity of the 1,3-dioxolane molecule (**1**) is predicted by the QVBMM force field even though this force field considered only torsional, lone pair, and dipolar interactions. The QVBMM data showed that the structure of this molecule was as highly influenced by torsional, lone pair, and dipolar interactions as were the structures of cyclopentane, cyclopentene, and the furanoids. This result casts considerable doubt on the need to invoke n–σ* effects as the sole origins of the puckering of 1,3-dioxolane, and suggests that any n–σ* effects present must play only a very small role.

It is also very important to recognize that the QVBMM predicted puckered geometry of 1,3-dioxolane (**1**) does not allow the π-type lone pair of either of its oxygens to approach coplanarity with a flanking C–O bond, a necessary condition for us to invoke the intervention of a significant n–σ* anomeric effect. The lone pairs of 1,3-dioxolane (**1**) also do not approach each other closely enough to cause n–n repulsions in any of its stable conformations. These data suggest that 1,3-dioxolane (**1**) cannot experience an anomeric effect.

In order to enable us to better understand the QVBMM structural predictions for 1,3-dioxolane (**1**), we examined the most planar metastable conformations (as predicted by the QVBMM force field) of tetrahydrofuran and 1,3-dioxolane, in an effort to reveal the sizes of their stereoelectronic effects. These data are shown in Table 2.

Contributions from torsional strain obviously dominate the stereoelectronic profiles of these molecules and the smaller ring will obviously experience larger torsional interactions. The flattened cyclopentanoid molecule must not only have more torsional strain than the puckered molecule, but also the heterocyclic lone pairs will be coplanar with the vicinal C–H bonds, thus leading to stronger, stabilizing, lone pair–C-H dipole interactions in the flattened molecule. The flattened molecule (**1**) did not show any n–n repulsions as these lone pairs were too far from each other.

Table 2 shows quite clearly that there is no need to invoke "unusual" or "complex" stereoelectronic interactions in either tetrahydrofuran or 1,3-dioxolane in order to rationalize their structural features. The puckering of these heterocyclic molecules, like the puckering in cyclopentane, was simply due to "normal" stereoelectronic and dipolar interactions, and certainly did not involve to exotic factors such as the anomeric effect. Indeed, as was stated above, no conformation of the 1,3-dioxolane mol-

Table 2 QVBMM calculated enthalpies and stereoelectronic interactions (kcal mol^{-1}). (Negative energy values represent stabilizations due to favorable lone pair -dipolar interactions)

Molecule	**1**	Flattened **1**	**2**	Flattened **2**
Enthalpy	10.517	12.260	11.199	14.762
Bond length strain	0.051	0.032	0.053	0.082
Angle strain	2.190	0.793	2.001	1.421
Steric and dipolar	–0.027	0.431	–0.132	0.797
Torsional	12.824	18.195	11.295	16.005
Lone pair	–4.521	–7.192	–2.018	–3.544

ecule either showed the n–n repulsions that are hallmarks of the anomeric effect in acetals, or had a geometry suitable for any strong n–σ* interactions.

The anomeric effect usually manifests itself by causing a molecule to adopt a conformation that would not normally be adopted by its carbocyclic analogue. Thus, the anomeric effect displays itself in the 2-methoxypyran by causing the axially substituted conformer to be more stable than the equatorially substituted conformer, a result that is opposite to that expected in the analogous methoxycyclohexane. Since cyclopentane is not flat, and indeed is predicted to show the largest puckering of all of the cyclopentanoids studied, it cannot be argued that the puckered conformations of tetrahydrofuran and 1,3-dioxolane are "not what would have been predicted", based on the known conformational features of cyclopentane. It might be argued that the size/degree of puckering of the molecule might suggest the presence of exotic stereoelectronic effects in the heterocycles, but note that the puckering predicted for tetrahydrofuran and 1,3-dioxolane is quite similar to that found in cyclopentane – a molecule that cannot show anomeric effects. The puckering of 1,3-dioxolane is therefore not indicative of the presence of the anomeric effect in this molecule.

It has been also suggested that any conformation of a molecule that has a lower dipole moment should be more stable (than one that has a higher dipole moment). Hence, if puckering produces the higher dipole moment conformer, then this conformer should "normally" be the less stable conformer, unless some exotic stereoelectronic effect intervenes. [7, 8] However, we must remember that an incomplete analysis of the conformational populations of any molecule can lead to erroneous judgments. This was seen in the case of 1,2-dimethoxyethane whose *gauche* conformers are more highly populated than the *anti–anti–anti* conformer, even though the *gauche* conformers have larger dipole moments. [6, 9]

1,3-Dioxole

Having fully analyzed the stereoelectronic milieu of 1,3-dioxolane (**1**), we can now begin to understand that of 1,3-dioxole (**7**), as was predicted in the QVBMM simulation of this molecule. Table 1 shows that the QVBMM force field predicts that the minimum energy conformation of the non-delocalized structure of 1,3-dioxole (**7**) is puckered. Interestingly, if this molecule is assumed to be a delocalized enol ether, then it ought to be flat, as is the case with cyclopentadiene. The experimental observation of puckering in this molecule is, indeed, strong evidence against delocalizaions in enol ethers and enediol ethers as we have previously suggested. [15, 16]

The puckering predicted for 1,3-dioxole (**7**) is smaller than those of the other heterocycles examined – the largest predicted dihedral angle is only 4.8° – and this is as one would predict for the heterocycle with the smallest

ring and the most restrained conformational opportunities. Indeed, the enol ether (**3**) was predicted to be similarly puckered and had its largest predicted dihedral angle of 4.6°. Consistent with the trend shown by the other heterocycles of the ease of distortion of the ring by a small increase in the conformational energy of the ring, we found two conformers of the 1,3-dioxole molecule that had energies 0.67 and 0.72 kcal mol^{-1} higher than that of the minimum. The largest predicted dihedrals in these two higher energy conformations were 15.7° and 16.3° respectively.

The small pucker predicted for minimum energy conformation of 1,3-dioxole (**7**) also emphasizes that the π-type lone pairs of the oxygens are not suitably oriented with respect to the flanking C–O bond for any meaningful n–σ* interactions to occur. Further, as in the 1,3-dioxolane molecule, there is no stable conformation of 1,3-dioxole that would have permitted n–n repulsions to occur.

The puckering of 1,3-dioxole is therefore due only to dipolar interactions within that molecule, especially to the torsional repulsions between the n and π orbitals. Since no conformation of 1,3-dioxole or 1,3-dioxolane either showed the n–n repulsions that are hallmarks of the anomeric effect in acetals, or had a geometry suitable for even modest n–σ* interactions, then we must conclude that 1,3-dioxolane and 1,3-dioxole do not experience the anomeric effect. Indeed, since the structural features of these molecules can be effectively simulated by the QVBMM force field – a force field that only considers lone pair and dipolar interactions – then one must conclude that n–σ* molecular orbital (bonding) interactions are not important in the determination of the structural features of these molecules.

Some molecular geometries

The geometrical features of the molecules **2**, **3**, and **7** are presented in Table 3, where the data in the columns AI, QVBMM, and X-ray correspond to data from the ab initio studies performed by Suarez et al., [8] data from the QVBMM studies, and data from X-ray studies performed by Lugar and Buschmann, [17] respectively.

Note the close correspondence between the QVBMM predicted data and the X-ray crystallographic data for tetrahydrofuran (**2**) and, in particular, note the correspondence between the bond lengths for the O-1–C-5 bonds. Note also the correspondence between the bond lengths predicted by the ab initio methods and the QVBMM force field for the O-1–C-5 bonds in the molecules **3** and **7**.

The ab initio predicted lengths of the C-2–C-3 bonds of the molecules **3** and **7** are greater than those predicted by the QVBMM force field, presumably because the ab initio methods invoke a delocalization of the π oxygen lone pair electron density into these flanking π-bonds (resonance). The QVBMM force field calculations do not normally invoke resonance in enol ethers because

Table 3 Geometrical features of molecules **2**, **3**, and **7** (AI – ab initio predicted, QVBMM predicted, and X-ray crystallographically determined data respectively)

	2		3		7	
	X-ray	QVBMM	AI[a]	QVBMM	AI[a]	QVBMM
Bonds						
1,2	1.429	1.420	1.372 (1.375)	1.375	1.391 (1.393)	1.367
2,3	1.517	1.533	1.337 (1.347)	1.319	1.335 (1.346)	1.313
3,4			1.507 (1.517)	1.491		
4,5			1.533 (1.543)	1.541		
5,1			1.452 (1.456)	1.427	1.426 (1.430)	1.425
Angles						
1,2,3	107.4	107.2	115.1 (115.1)	117.6	110.2 (110.0)	112.9
2,3,4	102.0	104.4	107.9 (108.0)	107.3		
3,4,5			100.5 (100.6)	101.6	102.4 (102.7)	100.2
4,5,1			106.6 (106.8)	108.6	107.3 (107.1)	113.2
5,1,2	108.2	107.2	105.6 (105.5)	104.3		

[a] Ab initio data (AI) – MP2(FULL)/6-31G** (Dunning–Huzinaga double ζ polarization basis set results in parenthesis)

X-ray crystallographic data have suggested that enol ethers do not experience resonance. [15, 16]

Conclusion

The QVBMM force field predicts that 1,3-dioxolane, 1,3-dioxole, cyclopentane, and tetrahydrofuran are significantly puckered molecules because of their lone pair (where applicable), torsional, and dipolar interactions. The QVBMM data are also congruent with the experimental data. The QVBMM predicted minimum energy geometries of 1,3-dioxolane and 1,3-dioxole do not seem to be suitable for anomeric n–σ* interactions, nor do any of their conformations experience direct n–n repulsions. Thus, the QVBMM calculated data suggest that 1,3-dioxolane and 1,3-dioxole cannot, and should not, experience the anomeric effect, regardless of which of the currently held theoretical views of the origins of the anomeric effect is applied.

We have seen that the secondary molecular orbital effects considered in the molecular orbital based ab initio methods seem to be able to rationalize the structures of 1,3-dioxolane and 1,3-dioxole. [7, 8] We now see that a consideration of lone pair and dipolar interactions can also rationalize the structures of 1,3-dioxolane and 1,3-dioxole. This study has identified one of those ambiguous situations that will obviously not be easily resolved by theoretical discussions. It might be that a resolution of this problem must await suitable definitive experimental evidence. However, this study must force us to examine other theoretical explorations that seek to link significant structural features of molecules only to their secondary molecular orbital interactions, without a suitable proper investigation of the roles of dipolar interactions in these molecules critically.

This study was not done with the intent to challenge the integrity or validity of the molecular orbital based calculations, or to bring molecular orbital based calculations into disrepute. Rather, we hope that the results of this study will draw the attention of molecular orbital theoreticians to the possible use of the QVBMM force field as a complimentary tool to assess the roles of dipolar effects in molecules they intend to study[2] In this way, their subsequently performed molecular orbital calculations can address the structural issues in question with greater focus and precision.

References

1. Box VGS (1982) Heterocycles 19:1939
2. Tvaroska I, Bleha I, Bleha T (1989) Adv Carbohydr Chem Biochem 47:45
3. Box VGS (1990) Heterocycles 31:1157
4. Box VGS (1991) Heterocycles 32:795
5. Juaristi E, Cuevas G (1992) Tetrahedron 48:5019
6. Box VGS (1998) Heterocycles 48:2389
7. Laane J, Cortez E, Verastegui R, Villarreal J (1993) J Am Chem Soc 115:12132
8. Suarez D, Sordo TL, Sordo JA (1996) J Am Chem Soc 118:9850 and references cited therein
9. Box VGS (1997) J Mol Model 3:124
10. Gillespie RJ, Hargittai I (1991) The VSEPR model of molecular geometry. Allyn and Bacon, Boston, Mass., and references cited therein
11. Gillespie RJ (1992) Chem Soc Rev 59 and references cited therein
12. Box VGS, Evans-Lora, T (2000) J Mol Struct 516:203
13. Box VGS, Smith W (2000) J Mol Struct 520:229
14. Box VGS (2000) J Mol Struct 522:522
15. Box VGS (1991) Heterocycles 32:2023
16. Box VGS (1992) Heterocycles 34:1631
17. Lugar P, Buschmann J (1983) Angew Chem Int Ed Engl 22:410 and references cited therein

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[2] The molecular modeling program, STR3DI32.EXE, that uses the QVBMM force field to perform structure energy minimizations can be obtained from Exorga, Inc., P. O. Box 56, Colonia, N.J. 07067, U.S.A. A 30-atom demo version, suitable for performing the theoretical experiments described above, can also be downloaded from Exorga's internet website at: http://ourworld.compuserve.com/homepages/exorga.