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The external-anomeric torsional effect[☆]

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Dedicated to Professor David A. Brant

Abstract—The rotational barrier for a methyl group at the end of an anomeric system is sometimes lower than we might have anticipated. Thus, in the *trans–trans* conformation of dimethoxymethane, the barrier to methyl rotation is calculated (B3LYP/6-311++G(2d,2p)) to be 2.22 kcal/mol, just slightly smaller than the corresponding barrier to rotation of the methyl group in methyl propyl ether of 2.32 kcal/mol. However, if the methyl being rotated in dimethoxymethane is placed into a *gauche* conformation, that rotational barrier is reduced to 1.52 kcal/mol. This substantial (0.80 kcal/mol relative to methyl propyl ether) reduction in barrier height in the latter case is attributed mainly to the change in the bond order of the C–O bond to which the methyl is attached, as a function of conformation, which in turn is a result of the anomeric effect. We have called this barrier lowering the *external-anomeric torsional effect*. This effect is apparently widespread in carbohydrates, and it results in the changing of conformational energies by up to about 2 kcal/mol. If polysaccharide potential surfaces are to be accurately mapped by molecular mechanics, this effect clearly needs to be accounted for.

Keywords: External-anomeric torsional effect; MM4; Ab initio; Dimethoxymethane; 2,4-Dioxahexane; Disaccharide; Conformation

1. Introduction

In computerized molecular modeling, forces acting on the atoms can be calculated with empirical equations for bond stretching, angle bending, and so forth. Alternatively, the model can be based on electronic structure theory. Empirical force field equations are often referred to as 'molecular mechanics' and electronic structure theory methods are called 'quantum mechanics' or just QM. Authors of molecular mechanics software strive to incorporate enough relevant knowledge into their software so that reasonably correct results can be obtained rapidly. Quantum chemistry software, on the other hand, depends on fundamental principles that can be encoded in increasingly complete ways. With more complete theory, results should be more accurate. At present, however, QM methods of sufficient accuracy for general use are too time-consuming for large molecules, and molecular mechanics representations are expected to be useful for many years to come.

A major limitation to molecular mechanics modeling is the need to incorporate all of the relevant facts for the systems to be studied. Much of this knowledge has come from laboratory experiments such as spectroscopy and diffraction. To fill in missing information, the important forces in molecules can be calculated with QM for small molecules. Then, empirical parameters and equations can be developed so that the resulting models duplicate the behavior of QM models. In the past decade or so, several workers have developed general empirical force field systems that are based extensively on QM studies of fragment molecules.[1–3]

[☆] Part VI of the series: Alcohols, ethers, carbohydrates, and related compounds.

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Other workers have employed QM to parameterize general purpose empirical force fields for specific kinds of molecules when experiments did not agree with calculations.

For carbohydrates, the positions and energies of atoms near the anomeric centers have been critical questions.[4,5] In the early 1970s, QM studies of small relevant molecules established a foundation for further progress.[6–8] More recently, several authors have focused on QM energy profiles for rotations about the glycosidic bond to improve energies for conformational analyses of disaccharides.[9–13] At least one paper has calculated QM torsional energies of methoxyl groups attached at nonglycosidic positions on tetrahydropyran to represent the aglycon bonds.[14]

When we wrote our four manuscripts on the molecular mechanics (MM4[15]) of alcohols, ethers, and carbohydrates,[16–19] we thought that we had accounted fairly well for the structural characteristics of carbohydrates in terms of the related characteristics of the simpler component molecules, plus explicit effects that occur in sugars and related compounds. These effects include hydrogen bonding, the anomeric effect,[17] and also the delta-2 effect.[19] We subsequently found that another known effect, called the Bohlmann effect, which is of some importance even in simple alcohols and ethers,[20] was accounted for only partially in the earlier work. Now we see another effect that is important and previously unrecognized. It causes changes to the calculated potential energy surfaces of many carbohydrate molecules in certain areas by up to about 2 kcal/mol. This effect, which we designate as the '*external-anomeric torsional effect*,'[†] occurs only in systems that show the anomeric effect. It is a special case of the more general *Bohlmann Torsional Effect*, which was discussed in detail earlier in another paper.[20] The Bohlmann Torsional Effect is quite widespread, apparently occurring in all molecules that contain an atom with a lone pair of electrons attached to an alkyl group. Here we will specifically discuss the external-anomeric torsional effect.

2. Physical basis and formulation of the new effect

The new effect was discovered while tracking down discrepancies between a carefully parameterized empirical force field (MM4) and observations from crystallography or calculations with QM.[21] The present work reflects a progression of the development of the MM4 method to more accurately reproduce what was found by QM calculations, especially for the smaller molecules, and by experiment.

For the small molecules dimethyl ether, dimethoxymethane, and ethoxymethoxymethane (2,4 dioxahexane), we used a particular basis set for QM calculations (6-311++G(2d,2p)). The reasons for this choice were given earlier.[22] We have generally done the calculations with two different correlation treatments. These are MP2 and B3LYP. We informally refer to this basis set as *Big*, and so we represent these two kinds of calculations by the shorthand MP2/B, or DFT/B. We have generally found (K.-H. Chen, unpublished) that MP2/B gives better geometries,[23] but we are uncertain about the energies, and hence usually use both calculations. In the present case, there are usually small or negligible differences between the results from the two methods.

We will use the expression *MM4O* to represent the 'old' version of MM4 (without the anomeric or Bohlmann torsional effects) as described in our earlier carbohydrate papers.[16–19] We will use *MM4* to represent the version developed herein with the effects included. The predictive utility of the various methods is assessed by comparing with crystalline conformations of molecules that contain a cellobiose analog (CBA). That analog has two tetrahydropyran rings, linked analogously to cellobiose. QM calculations on the larger CBA molecule were done at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level. Geometries of small-molecule crystals[24] were from the Cambridge Structural Database.[25] Crystalline complexes of proteins and cellodextrins also furnish data on CBA conformation, and those were gained from the Protein Databank.[26] Conformations from protein–lactose complexes were not included in the present work.

The *external-anomeric torsional effect* in its most simple form may be illustrated by the rotational barrier of a methyl group in dimethoxymethane. This barrier proves to have a height that depends on the conformation of the anomeric part of the molecule. The important conformations of this molecule are shown in Scheme 1. (Throughout this manuscript, a capital *T* or *G* is used to indicate a *trans* or *gauche* conformation in the part of the molecule under discussion, and small letters are used to indicate other parts of the molecule.)

As shown in Table 1, if the molecule is in the *tT* conformation, the barrier heights for rotation of a methyl group by DFT/B or MP2/B calculations are quite simi-

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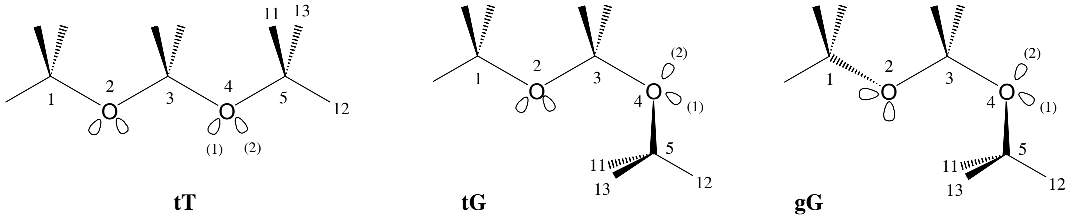
[†] The name of the effect was chosen only after considerable discussion. Using methyl glucoside as an example, the new effect applies to the energy barriers encountered during rotation of the methyl group about its bond to O-1. Our initial name (J.-H. Lii, K.-H. Chen, G. P. Johnson, A. D. French, and N. L. Allinger, was the 'New *exo*-anomeric torsional effect.' Abstract CARB025, ACS National Meeting, Anaheim, 2004.), The *exo-anomeric torsional effect* was chosen because it refers to atomic positions affected by the geometry of the anomeric sequence but that are outside that sequence. Another candidate name, the Ψ effect, made sense because it is important in calculations of energies for the Ψ coordinate (using accepted conventions) of Φ,Ψ energy surfaces for conformational studies of disaccharides. However, the '*exo*-anomeric torsional effect' is too close to the widely used, if somewhat obsolete, '*exo*-anomeric effect', and the Ψ effect is felt to be insufficiently descriptive. A referee has suggested the aglycon effect.



Scheme 1. Conformers of dimethoxymethane.

Table 1. Methyl rotational barriers in dimethoxymethane

Conformation	Calculation			
	DFT/B	MP2/B	MM4O[a]	MM4[b]
tT	2.22	2.39	2.60	2.24
tG	1.52	1.66	2.57	1.52

[a] Without the external-anomeric or Bohlmann torsional effects.

[b] With the external-anomeric and Bohlmann torsional effects.

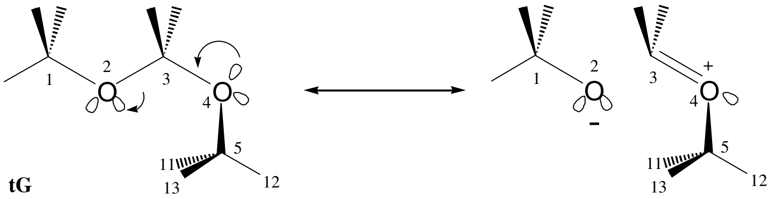
lar (2.22 and 2.39 kcal/mol). With the MM4O force field, that barrier was calculated a little bit high (2.60 kcal/mol). We have reduced this barrier slightly, and with MM4 the value is calculated to be 2.24 kcal/mol.

Interestingly, when the molecule is put into the *tG* conformation (which is more stable than the *tT* conformation), these barriers are reduced by approximately 0.7 kcal/mol, to heights of 1.52 and 1.66 kcal/mol by DFT/B and MP2/B calculations, respectively. Because there is a negligible steric effect involved here, the MM4O calculations gave a barrier height of 2.57 kcal/mol, insignificantly different from that of the *tT* conformation. Compared to the QM calculations, however, this barrier height is too high by about 1.0 kcal/mol, which is a significant error. The reason for this error is that in the anomeric system there are stereoelectronic effects, not properly included in the MM4O calculation. Those need to be included if one is to obtain the correct barrier height.

Let us first examine the *tG* conformation of dimethoxymethane. The methyl numbered 5 (Scheme 2) is being rotated. The resonance that occurs in the anomeric effect tends to increase the bond order of the 3–4 C–O bond, and reduce the bond order of the adjacent 2–3 C–O bond. The particular valence bond structure that is important in this case is shown in Scheme 2.

Thus, the bond order about the C–O (3–4) bond is higher (more double bond character) than it would be if the other oxygen (O-2) were not present in the *gauche* conformation (since a lone pair on O-4 must be *anti* to the 2–3 bond for effective resonance). Rotational barriers in saturated molecules (sp^3–sp^3, for example, the methyl group in propane), are normally oriented such that the staggered conformation is the energy minimum, and the eclipsed conformation the energy maximum. But in sp^2–sp^3 systems such as propene, the double bond is normally eclipsed by a methyl hydrogen in the ground state. Also, previous studies have shown that the height of the rotational barrier of a methyl group attached to a normal double bond varies with the precise bond order of that double bond.[27,28] If the double bond has a high bond order as in propene, the eclipsed structure is more stable by a relatively large amount (about 1.5 kcal/mol). This amount is reduced as the bond order of the double bond is reduced, and would presumably become negative at a sufficiently low bond order, that is, the previous energy minimum would become, or at least tend toward, an energy maximum.

Applied to the case at hand, if we look at the principle resonance form of dimethoxymethane (on the left in Scheme 2), the 3–4 C–O bond vicinal to the rotating methyl is single, and if we call that a bond order of one (or nearly so), that would be a reference point. But to the extent that the resonance indicated in Scheme 2 occurs (structure on the right), that bond becomes more double, of higher bond order, and therefore the hydrogen on the methyl eclipsing that bond (at the top of the barrier) is in a more stabilized conformation. Thus, the rotational barrier of the methyl group goes down as expected, and this will happen in the *gauche* (but not the *anti*) conformation. Hence, we have the physical basis of *external-anomeric torsional effect*.



Scheme 2. The external-anomeric torsional effect in the *tG* conformation of dimethoxymethane.

The rotational barrier of the methyl group on dimethoxymethane goes down considerably (to 1.66 kcal/mol, MP2/B) when that methoxyl group is *gauche* to the rest of the system, compared to 2.39 kcal/mol if it is *anti*. It makes a negligible difference whether the methoxyl group on the other end of the system is *gauche* or *anti* (C-1–O-2–C-3–O-4 = 66° or 180°), as suggested by the valence bond pictures, and as confirmed by MP2/B calculations. However, if the methoxyl were to be *gauche* (C-1–O-2–C-3–O-4 = −66°), there would be an additional large steric effect between the two ends of the system, and that would be a separate matter.

Hence, we conclude that this effect is dependent upon a lone pair delocalization, as illustrated in the valence bond pictures shown in Scheme 2. The effect would be near a maximum when that methoxyl is *gauche* to the rest of the system, and it amounts to about 0.7 kcal/mol in the case of a methyl substituent.

To some extent the anomeric resonance shown also occurs in the *trans–trans* conformation. For the anomeric resonance to be most effective, the lone pair on oxygen, which is being donated into the σ*-orbital (forming the double bond in the valence bond picture) needs to be *anti* (180°) to the leaving group (the other oxygen). If the angle were to be 90°, there would be no resonance effect. The two lone pairs on oxygen can never be oriented so that both of them are simultaneously 90° with respect to the leaving group, so the effect can never go to zero. What is usually referred to as the *anomeric effect* is the energy difference between the *anti* and *gauche* conformations.

We might now ask, is it really all that important that the rotational barrier of a methyl group is reduced by 0.7 kcal/mol? The answer might appear to be ‘probably not’ for the case of methyl itself, but whatever happens for the methyl group would presumably happen (in a qualitative sense) for an alkyl group as well. In the latter case this effect could lead to significant conformational consequences when appropriate structures occur in larger molecules. Such structures turn out to be plentiful in the carbohydrate field, so the effect has a greater significance than might have been evident at first sight.

The next point would be how, exactly, should we formulate this effect? We want to consider two cases. The first is the methyl case, where the rotating group has the structural segment C–O–C–H, and then separately we want to consider the ethyl (or larger) group, where the rotating structure contains the segment C–O–C–C, in place of, or in addition to, the C–O–C–H. (The isopropyl and *tert*-butyl groups are just combinations of the above two terms in molecular mechanics.)

The MM4 torsional parameters of C–O–C–H (Ω) and C–O–C–C (Ψ) were modified using the equations below to account for this effect. Note that the torsional elements being considered here (Ω and Ψ) are not for these units in isolation, but only when they are external to the anomeric system so that we have the arrangement, O-1–C-2–O-3–C-4–H-5 (where 2–3 is Φ, and 3–4 is Ω, or O-1–C-2–O-3–C-4–C-5 where 2–3 is Φ and 3–4 is Ψ). The new parameters for torsional angles of C–O–C–H (Ω) and C–O–C–C (Ψ), are not constants, but are functions of the adjacent O–C–O–C (Φ) torsional angle.

For C–O–C–H (Ω), the external-anomeric torsional effect changes the torsional constant from $V_3(\Omega)$, the earlier MM4O value, to $V_3'(\Omega)$:

$$V_3'(\Omega) = V_3(\Omega) + K_1/2 * (1 - \cos(\Phi)) + K_2/2 * (1 - \cos(2\Phi)) + K_3/2 * (1 + \cos(3\Phi)) \quad (1)$$

and similarly,

For C–O–C–C (Ψ)

$$V_1'(\Psi) = V_1(\Psi) + K_4/2 * (1 - \cos(2\Phi)) + K_7 \quad (2)$$

$$V_2'(\Psi) = V_2(\Psi) + K_5/2 * (1 - \cos(2\Phi)) + K_8 \quad (3)$$

$$V_3'(\Psi) = V_3(\Psi) + K_6/2 * (1 - \cos(2\Phi)) + K_9 \quad (4)$$

where K_1–K_9 are adjustable parameters.

The MM4 calculations with the new procedure were carried out for the model compounds dimethoxymethane and ethoxymethoxymethane, and the values of K_1–K_9 were optimized for the external-anomeric case by fitting their MM4 torsional profiles to the QM results. The best values for K_1–K_9 are −0.13, −0.40, −0.27, 0.68, −0.30, −0.40, 0.33, 0.10, and 0.0, respectively.

3. Results and discussion

3.1. Small model systems

The general nature of the problem can perhaps best be understood by first examining Figures 1 and 2. If we consider dimethoxymethane, and begin with the *trans–trans* conformation (Fig. 1), we can consider what happens to the energy of the system as we rotate one of the methyl groups. A plot of the energy (DFT/B) is shown, as is the corresponding MM4O plot. They show the expected 3-fold symmetry, and the MM4O plot shows barriers that are slightly higher. Lowering the V_3 term in the MM4O function yields the MM4 function, which now agrees with the DFT calculations. But if we now rotate the methoxyl stepwise around into a *gauche* conformation, changing the Φ torsion angle of the methoxyl from 180° to 120°, and then to 90°, then to the *gauche* conformation (Fig. 2), we find that the MM4O barriers change in height considerably, from about 2.6 kcal in Figure 1, up to 3.5 kcal at 120°, and then back down to 3.0 kcal at 90°, and 2.6 kcal in Figure 2. (The figures for Φ = 120° and 90° are in the Supplementary material.) The reason

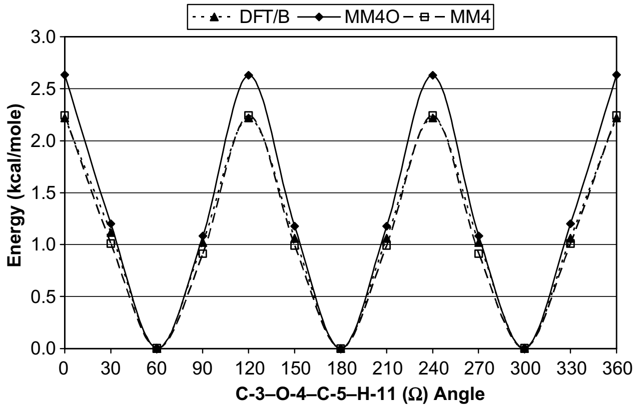


Figure 1. The torsional potential for rotation of a methyl group in dimethoxymethane with the C-1–O-2–C-3–O-4 and O-2–C-3–O-4–C-5 (*Φ*) angles fixed at 180°. Note that this figure (and some of those that follow, 2–8) sometimes show a lack of symmetry relative to what might have been expected. These are artifacts of the driver method that was used to generate these figures (Ref. 29).

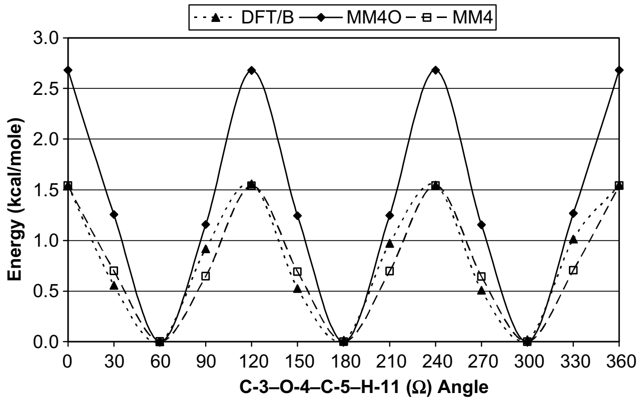


Figure 2. The torsional potential for rotation of a methyl group in dimethoxymethane with the C-1–O-2–C-3–O-4 and O-2–C-3–O-4–C-5 (*Φ*) angles fixed at 180° and 66.3°, respectively.

for these changes is mainly a steric effect in the MM4O calculations. At *Φ* equals 120°, the rotating methyl carbon eclipses a C–H bond from C-3, and hence the MM4O energy of the barrier to methyl rotation is very high (3.5 kcal). But the DFT/B values are quite different. Here the energy barrier is only about 1.3 kcal/mol at *Φ* angles of 120° and 90°, and then is slightly higher, about 1.5 kcal/mol, at 66.3° (the *gauche* conformation, Fig. 2). The MM4O barrier heights consequently are slightly too high for the *trans–trans* conformation, but much too high for all of the other conformations. Correcting these original MM4O values using Eqs. 1–4 with the parameter values given in the previous section, MM4 gave the curves as shown in Figures 1 and 2 (open squares labeled MM4). It may be seen that compared with the earlier MM4O values, these energies are now in reasonable agreement with the DFT/B values. These corrections amount to more than 2 kcal/mol at some geometries, so they can be quite substantial.

A more important case results when instead of dimethoxymethane we consider the molecule ethoxymethoxymethane, which has an ethyl group replacing one of the methyls of the original system. (The methyl is to some extent a special case. The ethyl is a better representation of an alkyl group.) Here we wish to rotate the ethyl group with respect to the rest of the anomeric system. The structure and numbering system is shown in Scheme 3.

Again, starting with the anomeric system at a dihedral angle (*Φ*: O-2–C-3–O-4–C-5) of 180°, and rotating the ethyl group through dihedral angles (*Ψ*: C-3–O-4–C-5–C-6) of 0° to 360° (Fig. 3), and then repeating the calculation for *Φ* dihedral angles sequentially of 120°, 90°, and 60° (the 60° case is shown in Figure 4, and the others in the Supplementary material), we obtained profiles

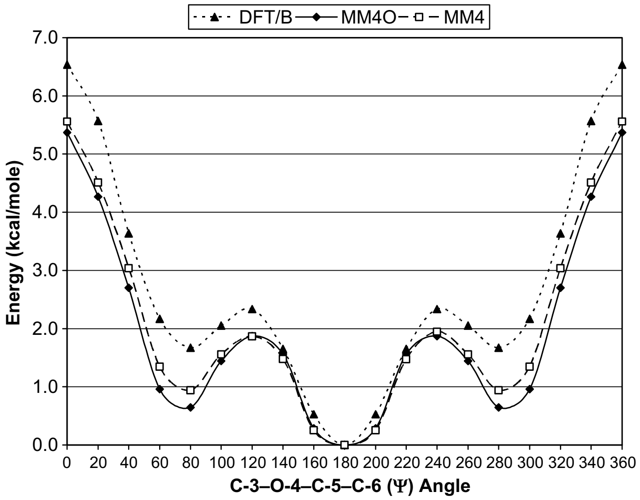
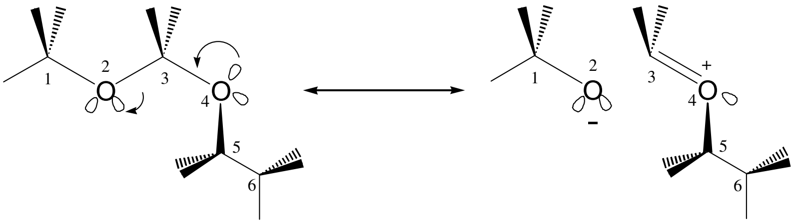


Figure 3. The torsional potential for rotation of the ethyl group in ethoxymethoxymethane with the C-1–O-2–C-3–O-4 and O-2–C-3–O-4–C-5 (*Φ*) angles fixed at 180°.



Scheme 3. The external-anomeric torsional effect in the *tG* conformation of ethoxymethoxymethane.

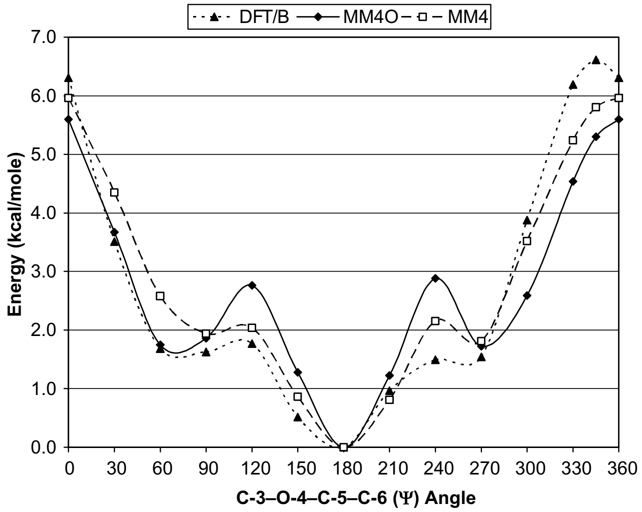
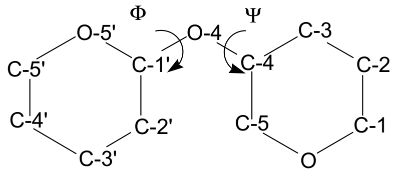


Figure 4. The torsional potential for rotation of the ethyl group in ethoxymethoxymethane with the C-1–O-2–C-3–O-4 and O-2–C-3–O-4–C-5 (Φ) angles fixed at 180° and 60°, respectively.



Scheme 4. The structure and numbering for the cellobiose analog (CBA).

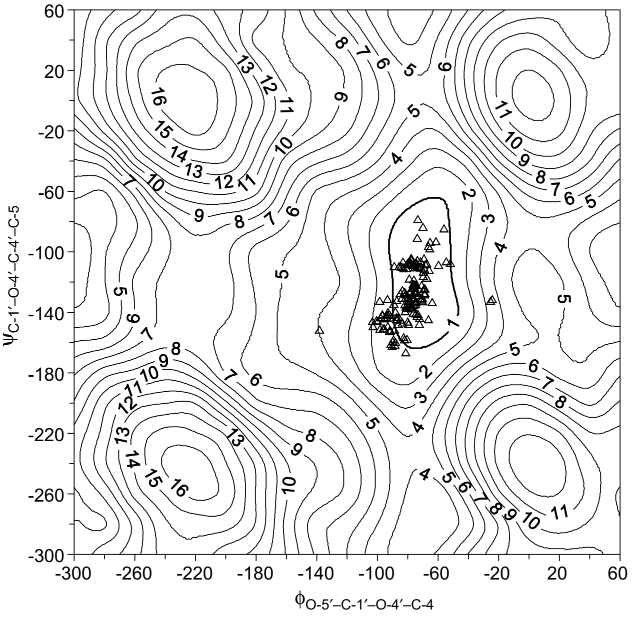


Figure 5. Ramachandran plot of the CBA potential surface by QM (B3LYP/6-311++G(d,p)//B3LYP/6-31G(d)) calculations. The numbers on the contours are their energies relative to the minimum at about Φ −70°, Ψ −120°. Conformations observed in experimental crystal structures are shown as triangles.

that are roughly analogous to those with the methyl group, but distorted somewhat by the presence of the ethyl. Note that in Figure 3 the MM4O and MM4 calculations show rather small differences in the heights of the barriers. But for the *gauche* conformation (Fig. 4), as the angle (Φ) decreases, the DFT/B values are rather different from the MM4O values, and the MM4 values have been adjusted to fit better to the DFT/B values. The fits of the MM4 values to the DFT values as shown in Figures 3 and 4 could obviously be further improved, but this was not done as other items discussed later would then have been more poorly fit.

3.2. Carbohydrate systems

We now wish to examine what happens in carbohydrate molecules of interest, where this external-anomeric torsional effect comes into play. This can be presented by discussing a study of the *cellobiose analog* (CBA), which is a disaccharide ring system with all the *exo*-cyclic groups removed (Scheme 4). Cellobiose is in turn a model for the important common polysaccharide, cellulose. A comprehensive approach to the study of CBA conformations was to calculate the QM energy surface for Φ,Ψ space shown in Figure 5. To carry out this calculation by molecular mechanics, we need the force field and parameters as presented earlier (Eqs. 1–4, and constants K_1–K_9).

There can be seen in the central region of the surface in Figure 5 just a single potential minimum, at Φ,Ψ approximately −70°/−120°. The minimum energy area for CBA (Fig. 5) is more or less oval shaped and oriented north-south. There are also four large ‘mountains,’ near the corners of the map. These are quite high, in the 11–16 kcal range, according to DFT calculations. Such DFT calculations tend to significantly overestimate the energies in places where there are high van der Waals repulsions,[30] so these mountains are expected to actually be smaller than indicated in Figure 5 (but still large). On the corresponding CBA MM4O contour map (Fig. 6), there are two main minima rather than the oval shape in Figure 5. The four mountains are still in place, although substantially lower (in the range of 8–13 kcal/mol) than on the DFT map, and we believe that the MM4O values for these are more accurate. There are many cellobiose derivatives (disaccharides containing the CBA ring system) that have known crystal structures. We have placed points on these contour maps corresponding to the experimental linkage conformations. On Figure 6, they form a pattern that is roughly centered on the saddlepoint between the two 1-kcal/mol contours, a little bit to the west (left) and spilling over the 1.0 and 2.0 kcal contours further to the west. The experimental pattern is not circular, but elliptical, with the major axis pointing roughly north-south (or perhaps

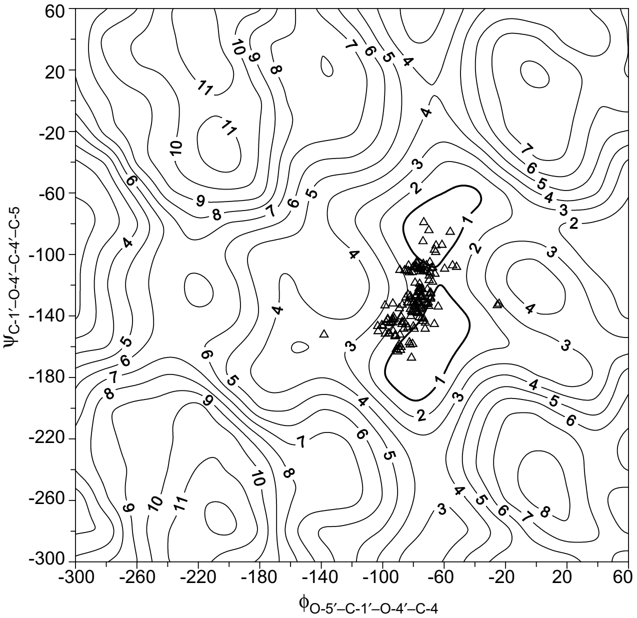


Figure 6. Ramachandran plot of the CBA potential surface by MM4O (without the external-anomeric torsional effect). Crystal structures are shown.

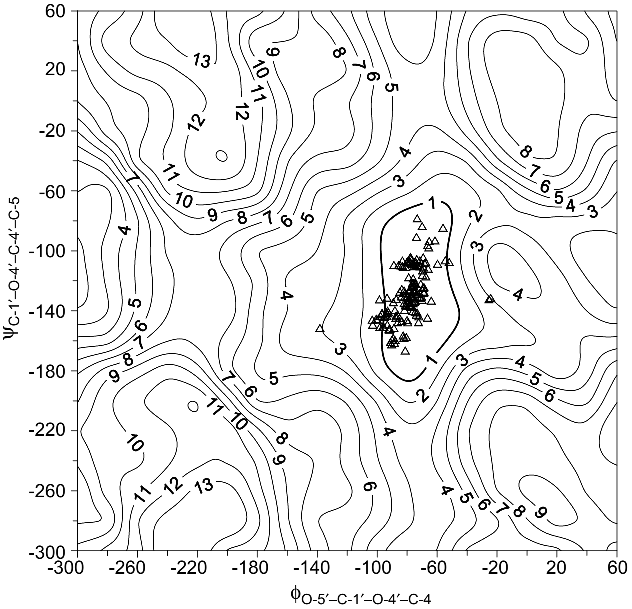


Figure 7. Ramachandran plot of the CBA potential surface by MM4 (with the external-anomeric torsional effect included). Crystal structures are shown.

northeast-southwest). If we compare the location of the experimental data points in Figure 6 with the energy minimum in Figure 5, the points and the QM plot are in agreement. There is a major disagreement between the MM4O plot (Fig. 6) and both the experimental values and the QM plot, however. The presence of the saddlepoint in the MM4O calculations is clearly inconsistent with quantum mechanics and experiment.

In Figure 7, the MM4 plot is shown as is shown in Figure 6 for MM4O. We note that the saddlepoint between the two minima in Figure 6 has largely disappeared. Many more of the experimental points (most of them) now lie within the 1.0-kcal contour than was observed with the original MM4O map (Fig. 6). In Figure 7, the minimum is located at about −80°/−125°, similar to that from the quantum mechanical calculations in Figure 5 (−70°/−120°).

It is instructive to note the differences between MM4O and MM4 as shown by Ramachandran maps. The (MM4O − MM4) difference map is shown in Figure 8. There is a substantial broad peak almost in the center of the map (at Φ/Ψ about −100°/−120°), that is, 2 kcal/mol above the zero reference. There are four smaller peaks (N, S, E, and W), each 0–0.5 kcal/mol high. These are all relative to a general surface at a value of about −0.5 or −1.0 kcal/mol. Thus, the MM4O surface relative to the better MM4 surface is best thought of as consisting of one broad, large peak 2.5–3 kcal high, and four smaller ones about 0.5–1.0 kcal high.

Finally, we may examine Figure 9, which compares MM4 to the QM calculations. The 2 kcal/mol mountain shown in Figure 8 is gone, and a large portion of the surface is now surrounded by contours labeled 0 or 0.5. There are four mountains in the corners, corresponding to the locations of the peaks on Figures 5–7 and these are now fairly low, 3.5–5.5 kcal/mol being the highest energy difference contours on the map. According to MM4 (Fig. 7), these mountains have actual energies relative to the minimum in the 8–14 kcal/mol range, so the

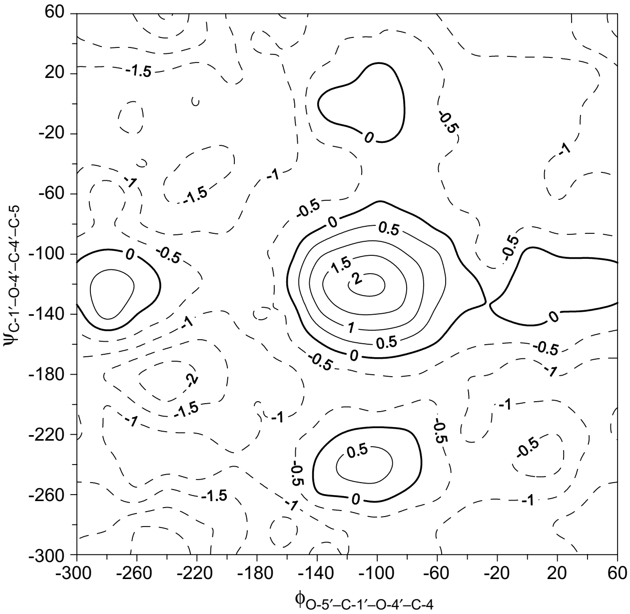


Figure 8. Ramachandran difference plot of the CBA potential surface (MM4O − MM4).

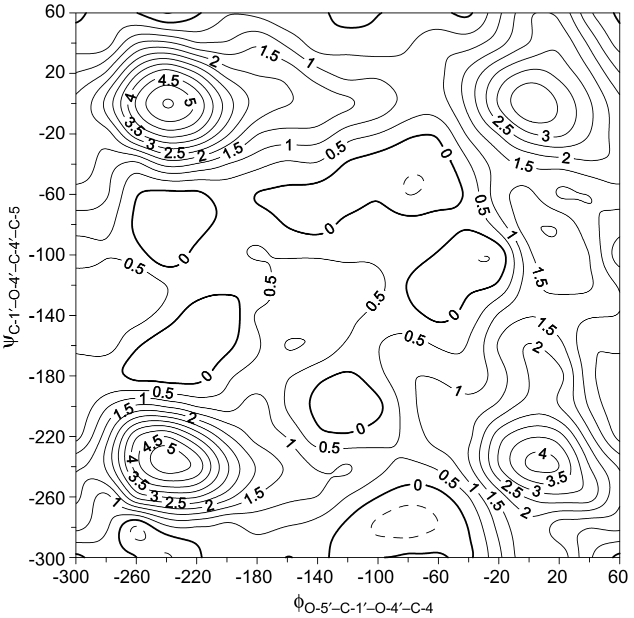


Figure 9. Ramachandran difference plot of the CBA potential surface (QM − MM4).

discrepancies in Figure 9 between MM4 and QM are probably due in large part to the inaccurate representation of the dispersion energies by the DFT method. The discrepancies in Figure 9 are smaller where the peaks in Figures 5–7 are smaller.

Our older and widely used MM3 program[31] does not include the external-anomeric torsional effect, and hence an MM3 plot (Supplementary material) that corresponds to Figures 5–7 shows this same kind of bifurcated minimum defect as seen in the corresponding original MM4O plot (Fig. 6).

One of the principles of molecular-mechanics development is that parameters are determined from a study of small molecules. They are not whimsically adjusted in larger molecules, but are transferred from the small model systems. This procedure has been followed in the present case. No parameters have been specifically adjusted to fit the carbohydrate data. If that had been the approach, the resulting force field would have been less universal in its application, and an understanding of the actual stereochemistry would not have been forthcoming. One might have initially assumed that one could transfer parameters from simple alcohols and ethers to carbohydrates. However, stereoelectronic effects are well known in organic chemistry.[32] In the present case, dimethoxymethane represents the smallest model system that contains the stereoelectronics in question. And hence, in addition to the simple alcohols and ethers themselves, it has to be used as the basis from which we must work. A present limitation in molecular mechanics, which is probably more widespread than is generally recognized, is that model compounds cannot be chosen from the smallest available systems containing the proper individual bonds, but must be constructed from the *smallest stereoelectronically complete systems that contain the necessary bond combinations*. It is not certain that all of the stereoelectronic systems necessary for use in molecular mechanics have been identified, and it is even less certain that all of the *effects* shown by such systems have been recognized (the external-anomeric torsional effect being a case in point).

The changes in the MM4 force field described herein might also be expected to have greater or lesser effects on the energies and properties of various other compounds that show the anomeric effect. The nature of molecular mechanics is such that parameters for the

Table 2. Torsional parameters (kcal/mol) for alcohols and ethers to account for the external-anomeric torsional effect[a]

	Torsional angle					
	V_1	V_2	V_3	V_4	V_6	BTB[b]
6–1–6–1	−1.850	−1.300	0.100	0.503	0.000	−0.150

	Torsion–bend parameters (mdyn Å/rad)					
	Left angle			Right angle		
	K_{TB1}	K_{TB2}	K_{TB3}	$K_{TB1'}$	$K_{TB2'}$	$K_{TB3'}$
6–1–6–1	0.030	−0.040	0.009	−0.003	0.000	0.000

	Torsion–torsion parameters (kcal/mol)			
	K_{TT1}	K_{TT2}	K_{TT3}	Type
6–1–6–1–6	−0.25	0.04	0.12	1
1–1–1–6–1–1	0.00	−0.08	0.00	2
1–6–1–6–1–1	−0.14	−0.23	0.00	2

Coefficients for Eqs. 1–4 (kcal/mol)

K_1	K_2	K_3	K_4	K_5	K_6	K_7	K_8	K_9
−0.13	−0.40	−0.27	0.68	−0.30	−0.40	0.33	0.10	0.00

[a] These are to be added to, or to replace parameters in the older version of MM4 (Refs. 16–19).

[b] Bend–torsion–bend (BTB) parameters are in units of mdyn Å/rad^2.

equations are chosen to fit the available data as well as possible. In the present work, a new effect has been uncovered, that can properly be allowed for as discussed above. But if this set of changes alone were simply added into the MM4 force field, many other things would no longer fit very well. The reason is that the parameters used for those other things were chosen so as to optimize the *overall results* in the absence of explicit inclusion of this new effect. If we are now going to explicitly include the new effect, then we must derive a new set of MM4 parameters that will be based on that effect being explicitly included, rather than simply averaged out insofar as possible by parameter adjustment.

The only way to have MM4 give other results as they were previously in MM4O was to go back and reparameterize anomeric systems, so that was done. The full parameter set arrived at is given in Table 2. We then repeated calculations of all of the anomeric compounds previously studied in paper II[17] and the results differ in only trivial ways. They are given in full in the Supplementary material. Because of these differences, however, versions of MM4 dated 2004 or later will generally give slightly different results than did the earlier versions.

4. Conclusions

Still one more effect that complicates organic chemistry, and which we have chosen to call the *external-anomeric torsional effect* has been recognized. The result of this effect is the substantial lowering of potential energy barriers to rotation in certain anomeric systems. These lowerings were found to lead to changes in model compound potential surfaces that indicate corresponding changes in the energy surfaces of di- and poly-saccharides of 1–2 kcal/mol are to be expected. The roles of the various anomeric effects in the conformational analysis of disaccharides (or CBA) are as follows: The *anomeric effect* describes the anomeric form at the linkage (an *endo*-ring torsion), but this is already determined in a given disaccharide. The *exo-anomeric effect* contributes substantially to the energy for rotation about the glycosidic bond (the Φ torsion angle). The *external-anomeric torsional effect* contributes substantially to the energy for rotation about the bond to the aglycon (the Ψ torsion angle.) This *external-anomeric torsional effect* has now been formulated and included in MM4, so that calculations on carbohydrates and related molecules will automatically have the effect taken into account.

An important use of the molecular-mechanics model is to reproduce results that are known from experiment, and/or from ab initio calculations. When the model fails to correctly reproduce something, it is always possible that some previously unrecognized 'effect' is responsible for the discrepancy. Hence molecular mechanics can be a powerful tool for *understanding* chemistry, as well as for generating numerical information.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2005.01.032.

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