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Alcohols, Ethers, Carbohydrates, and Related Compounds Part V.[2] The Bohlmann Torsional Effect[†]

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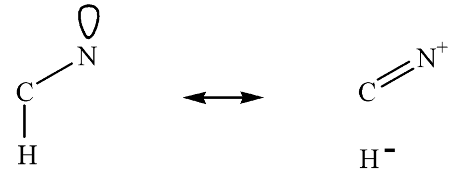
The Bohlmann effect, in its original context, occurred when, on a carbon attached to an amine nitrogen, there was a C−H bond anti−coplanar to the nitrogen lone pair. A negative hyperconjugation between the lone pair and that C−H bond (a transfer of electron density from the lone pair into the C−H σ^* orbital) led to the bond becoming weaker, stretching, and having its stretching frequency in the infrared shifted lower by 100−150 cm^{-1}. In the *generalized Bohlmann effect*, one does not need specifically a hydrogen, but an alkyl group (for example) will serve as well. Quantum mechanical calculations (at any level) show this effect clearly, both for the hydrogen case and for the sp^3 carbon as the attached electron-accepting atom. The C−H bond stretches by about 0.005 Å, and a C−C bond similarly stretches by about 0.007 Å. If one replaces the amine nitrogen with an ether (or alcohol) oxygen, a similar effect is noted. The bond (C−H or C−C) anti to a lone pair on oxygen stretches, and its stretching frequency is reduced. The reduction of the stretching frequency in the ether or alcohol case is partly compensated by the increase in stretching frequency resulting from the electronegativity of the attached oxygen, so the spectroscopic effect is less dramatic in ethers than in amines. A similar effect can be shown to occur in fluorides, but it has no stereochemical consequences. An *exo-Bohlmann torsional effect* was also uncovered in this work. An alkyl group on the oxygen or nitrogen atom, on the other side away from the area where the Bohlmann effect is occurring, suffers a reduction in the size of its torsional barrier. This is still one further example of the *"effects"* that complicate organic chemistry, which must be taken into account if molecular mechanics is to give a good representation of molecular structural behavior.

Introduction

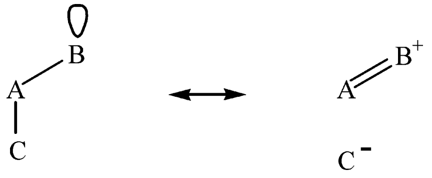
The Bohlmann Effect. It was noted by Bohlmann in the 1950s that some alkaloids showed C−H stretching frequencies in the infrared that were about 100−150 cm^{-1} lower than normal C−H frequencies.[2] These bands (subsequently known as *Bohlmann Bands*) were intense, and in a normally vacant part of the spectrum, and hence were quite conspicuous. It was discovered in time that such frequencies arose when there was a C−H bond anti−coplanar to an amino nitrogen lone pair of electrons.[3] This unusual spectral shift proved to be of diagnostic value in elucidating the stereochemistry of alkaloids. In the valence-bond formulation, what we have called the *Bohlmann effect* of which the above is an example, occurs because one has the following resonance (Scheme 1).

SCHEME 1



The Generalized Bohlmann Effect. This effect has also been called the *trans lone-pair effect* or *negative hyperconjugation*.[3] In molecular-orbital terms, electron density is transferred from the lone pair into the C−H antibonding orbital. This Bohlmann effect does not explicitly require either a nitrogen atom or a C−H bond. What we might call the generalized *Bohlmann effect*[4] would be represented as shown in Scheme 2:

SCHEME 2



Comparison of Scheme 2 with Scheme 1 correctly suggests that the Bohlmann effect is a special case of something that is much more general. The Bohlmann effect was discovered because the appearance of C−H stretching frequencies in an unusual place in the infrared was quite evident to the chemists of the time. But one should ask, "what is really required in a molecule for this effect to occur?" Well, it is clear that a lone pair of electrons is needed so that organic molecules containing first-row atoms to the right of carbon in the periodic table should all show an effect qualitatively similar to the Bohlmann effect. In fact, the same resonance does occur with such compounds, but the nitrogen lone pair is held less tightly to the nitrogen atom than are the lone pairs of oxygen or fluorine, and hence the nitrogen lone pair delocalizes more easily, leading to a greater spectral shift. Additionally, the electronegativity of the nitrogen, or other atom, tends to cause a spectral shift in the opposite direction (to higher frequency), in proportion to the electronegativity of the atom. Since nitrogen is not very electronegative, it induces a large Bohlmann shift and a small

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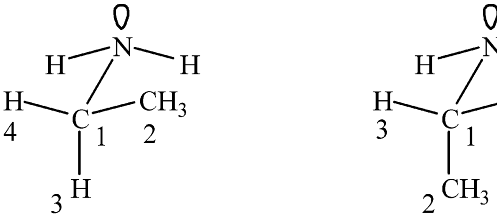
CHART 1



gauche **anti**

electronegativity shift. With oxygen and fluorine, these two shifts are more equally balanced so that, experimentally, one does not see for oxygen and fluorine compounds the large conspicuous shifts of the C−H stretching frequencies that are observed with amines. It is not that the Bohlmann effect does not occur with these compounds, it's just that the result of that effect, in terms of spectral shifts, is largely masked by other details of the system.[4]

Results and Discussion

Looking further at the Bohlmann effect, it would seem that the hydrogen atom is not explicitly required as the acceptor of negative charge. An electronegative atom should show the effect more strongly than a more electropositive atom, but in principle, any atom in that location would do. (If that atom is oxygen, we have the *anomeric effect*. Thus the anomeric effect is just a special case of the more general Bohlmann effect.) Let us specifically consider the case where there is a carbon atom (an alkyl group) located in the position that is anti−coplanar to the lone pair on nitrogen. By analogy with the normal Bohlmann effect, we would expect to see the C−C stretching frequency for such a structure lowered, relative to what the C−C stretching frequency would be when the bond was oriented in a position gauche to the lone pair. The other consequences of the Bohlmann effect should also be evident. As the structure shown in Scheme 2 indicates, the C−C bond (A−C in Scheme 2) is partly broken by the effect (its bond order is reduced), and hence that particular C−C bond should be longer than the gauche counterpart would be. These things are all readily verified by quantum mechanical calculations on appropriate model compounds, and they can also be found to be true by examining appropriate experimental data.

The *generalized Bohlmann effect*, which hereafter we will refer to as just the *Bohlmann effect*, that occurs when an alkyl group is the electron acceptor in place of a hydrogen, can lead to conspicuous changes in geometries, energies, and other properties of a molecule. Consider as a simple example the two conformations of ethylamine, where one of them has the methyl group anti to the lone pair, and the other one is gauche (Chart 1).

The ordinary Bohlmann resonance will tend to lengthen the C_1-H_3 bond in the gauche conformation, relative to the C_1-H_4 bond or relative to the C_1-H_3 and C_1-H_4 bonds in the anti conformation. And the C_1-C_2 bond in the anti conformation will also stretch out, relative to the same bond in the gauche conformation. This latter stretching will also cause carbon 1 to flatten in the anti conformation, and it will change the bond angles accordingly. These effects are quite evident in the results of the quantum mechanical calculations. In Table 1 are given the ethylamine data, calculated by the MP2/BC method (where the notation for MP2/6311++G(2d,2p) is B for big basis set and C for the inclusion of bond length corrections to r_e for basis set/electron correlation truncation errors).[5,11a] It should be noted that this effect is evident with small or large basis sets and with or without DFT or MP2 correlation. The numbers change somewhat, but the presence of the effect is independent of the level of the calculation.

TABLE 1: Geometries (r_e) of the Ethylamine Conformers[a]

	MP2/BC		MM4[5]	
conformer	anti	gauche	anti	gauche
C_1-C_2	1.526	1.519	1.527	1.520
C_1-H_3	1.094	1.099	1.095	1.104
C_1-H_4	1.094	1.093	1.095	1.096
C_2-C_1-N	115.4	109.7	114.2	109.5

[a] The MM4 values are equilibrium bond lengths (r_e) here and elsewhere in this paper. The appropriate corrections for the MP2/BC calculations (for basis set and electron correlation) have also been made so as to yield r_e geometries.[5,11a]

The Bohlmann Effect in MM4. Note that the quantum mechanical calculations show that, indeed, the changes that would be predicted from the above considerations are found as predicted. And these changes are fairly large. The C−C bond length increases by 0.007 Å and the CCN angle by 4.7° on going from the gauche to the anti conformation. For molecular mechanics to be competitive with experiment (or quantum mechanics) in structural chemistry, this Bohlmann effect must be somehow included in the force field.

Our MM4 (molecular mechanics) program as previously described in the literature,[6a−f] apart from additions to the program made herein, has been used in this work. Some of the details of this program and force field evolved from our earlier MM3 program,[6g−i] as we found that the accuracy of the latter is insufficient in certain cases. In the MM4 program,[6a−i] torsion-stretch and torsion-bend interactions[7] have been included so as to reproduce what is predicted by quantum mechanics (Table 1). The torsional potential of the system is also changed by this effect, and that is similarly taken into account. Note that the force constant for stretching the C−C bond is effectively changed by this effect, so that particular force constant is effectively not a constant but is a function of the torsion angle. As ethylamine undergoes a torsional rotation from the gauche to the anti conformation, the resonance shown in Scheme 2 affects the molecular geometry as discussed above. The longer (weaker) bond leads to a smaller effective stretching force constant and to shifts of the corresponding bands in the vibrational spectrum. (In MM4, the effective force constant is weakened by the torsion-stretch interaction.) These shifts are very large and apparent in the classical Bohlmann effect involving a C−H bond (100−150 cm^{-1}). Here for C−C bond, the changes are smaller but still quite noticeable. When the vibrational spectrum of ethylamine was calculated at the B3LYP/6-31G* level using Pulay's frequency-scaling method,[8] the C−C stretching frequency was found to be 883 cm^{-1} for the gauche conformation, and this value was reduced to 842 cm^{-1} in the anti conformation. The corresponding values calculated with MM4 are 887 and 849 cm^{-1}, respectively. So the Bohlmann effect on the vibrational spectrum is quite clear. Although the effect is smaller in terms of the actual spectral shifts with C−C than with C−H bonds, it is still obvious in ethylamine. In more complicated molecules, it is expected that the coupling of the C−C stretching with other similar frequencies may render this shift less clear.

In Table 1 are also included the structural results from the MM4 calculation, for comparison with the quantum mechanical results. The MM4 results appear to mimic the quantum mechanical results adequately in all respects. The Bohlmann effect is expected to occur whenever we have a lone pair of

CHART 2

gauche **anti**

TABLE 2: Geometries (r_e) of the Ethanol Conformers

	MP2/BC		MM4	
conformer	anti	gauche	anti	gauche
C_1-C_2	1.511	1.517	1.517	1.522
C_1-H_3	1.096	1.097	1.098	1.098
C_1-H_4	1.096	1.091	1.098	1.093
C_2-C_1-O	107.2	112.3	107.1	111.5

electrons that can significantly delocalize into an attached alkyl group. This will clearly be anticipated not only in amines but also in alcohols, ethers, and fluorides. Its importance with second-row elements has also been previously noted.[7,9]

In Chart 2 are shown the two conformers of ethyl alcohol, and pertinent structural data are given in Table 2. Note that the conformational nomenclature is different (in fact reversed) in the alcohol from that in the amines. In the amines, trans means *trans to the lone pair*, whereas in the alcohol, trans means *trans to the hydroxyl hydrogen* (and hence not trans to a lone pair). So in the amine, it is the trans group that shows the Bohlmann effect, but in the alcohol, it is the gauche.

If we compare Table 2 with Table 1, we see that the Bohlmann effect in the alcohols is (allowing for the difference in nomenclature) quite similar in the two cases. Normally the bond that is trans to the lone pair stretches, be it carbon or hydrogen, and the bond angle bends, opening to a much large value. The only really noticeable difference in the two cases is that while the amine numbers match quite closely when MP2/BC is compared with MM4, in the case of the alcohols there is a systematic discrepancy in the C_1-C_2 bond lengths in the two calculations. The C−H bond lengths and the bond angles match quite well. The bond-length discrepancy is that the MM4 C−C bonds are about 0.005 Å longer than the MP2/BC bonds. The difference between anti and gauche is similar in both calculations. The reason for the systematic discrepancy is uncertain. The absolute values in MM4 were fit to moment of inertia data (which are accurate and reliable) for both the alcohols and amines. We therefore suspect that the MP2/BC calculations are showing a systematic error in bond length, but it could be that the corrections of the r_g bond lengths in MM4 to the r_e values shown in the table contributes to part of this discrepancy.

We expect that the C−C stretching frequency should be reduced in the gauche form, relative to the trans form of ethanol. The vibrational spectrum of the trans form is known experimentally,[10] but that for the gauche is not. Accordingly, we calculated the spectra for both isomers, using both Pulay's method[8] and also with MM4. The shift from the trans to the gauche C−C stretching frequency by Pulay's method was 17 wavenumbers (877 to 860 cm^{-1}). A similar shift (11 cm^{-1}) in the same direction was calculated by MM4 (885 to 874 cm^{-1}). The experimental value for the trans isomer is 885 cm^{-1}.

TABLE 3: Distortions for Bonds and Bond Angles in Ethylamine and Ethanol (r_e)

	ethylamine[a]		ethanol[b]	
Bohlmann effect	MP2/BC	MM4	MP2/BC	MM4
ΔCC	+0.007	+0.006	+0.006	+0.005
ΔCH	−0.005	−0.009	−0.005	−0.005
ΔCCX	+5.7°	+4.7°	+5.1°	+4.4°

[a] Anti minus gauche. The anti form has the lone pair anti to the methyl (Chart 1). [b] Gauche minus anti. The gauche form has a lone pair anti to the methyl (Chart 2).

Although the fluoride is expected to show the Bohlmann effect in the same way that the alcohol and amine do. Since the lone pairs on the fluorine are indistinguishable and there is no attached group, there are no conformational aspects to the Bohlmann effect. With the fluoride, the effect simply has the result of increasing a C−C or C−H bond length that is in the α position. But the electronegativity effect of the fluorine is simultaneously reducing those bond lengths. We cannot individually determine the magnitudes of these effects directly; we can only determine their sum. We can determine them individually indirectly, however, in the following way.[4] The Bohlmann effect is specific for the α bonds, whereas the electronegativity effect (an inductive effect) is large for the α bonds but smaller (and nonzero) for the β bonds. Hence if we optimize separately the bond lengths for the α and β bonds, in principle we can obtain unique values for both the Bohlmann and electronegativity effects in those compounds, and this was done earlier.[4,6g−i]

What we anticipate would be that the lone pairs on oxygen would tend to delocalize less effectively than those on nitrogen so that the shifts observed as a result of the Bohlmann effect would be similar to those in amines but smaller. (There are two lone pairs on oxygen and only one on nitrogen, but as we go between the two conformations gauche and anti, in the amine there is a single lone pair in the gauche or anti position, and in the alcohol there is one lone pair in either the gauche or the anti position, and the other lone pair is gauche in both cases. Thus the effect of the other lone pair should be minimal on the difference between the two positions.) The lone pairs on fluorine would be expected (and were found)[4,6] to delocalize even less, leading to still smaller shifts in that case.

We believe that the case for the Bohlmann effect, both in amines and alcohols (as well as sulfides[7] and phosphines)[9] is unequivocally clear from the many lines of evidence outlined above. It results from the delocalization of a lone pair of electrons on any of the heteroatoms mentioned into an adjacent C−C or C−H bond, with clear and well-understood geometric consequences. In each case the bond in question is lengthened when the lone pair and the bond are in an anti−coplanar arrangement relative to a gauche or other conformation. It seems to make little difference as to the nature of the donor atom in terms of the bond-angle deformations, although it makes some small difference in terms of the bond-length deformations. For nitrogen and oxygen, the anti−coplanar bonds stretch by approximately 0.005−0.007 Å, and the number is similar for C−H and C−C bonds. The C−C−X bond angle opens out about 5 or 6° more in the lone-pair anti form than in the gauche. In Table 3 these geometric shifts are summarized as they occur in ethylamine and in ethanol, both according to MP2/BC calculations and as reproduced by MM4. The bond angle deformation is similar in both the first- and second-row elements. The bond length deformations are perhaps smaller with the second row atoms. The resulting shifts in the stretching frequencies are quite large in the amines when a C−H bond is involved. But they are relatively small for a C−C bond, or for C−H or C−C with any heteroatom other than nitrogen. These effects should be pervasive throughout much of the periodic table, and while only a few scattered examples have so far been

TABLE 4: Methyl Rotational Barrier (kcal/mol)[a]

configuration	DFT/B	MP2/B	MM4O	MM4	comments
		$CH_3CH_2CH_2CH_2-CH_3$			
anti, anti	2.82	3.10	2.82	2.82	
anti, gauche	2.63	2.83	2.72	2.72	
barrier reduced	−0.19	−0.27	−0.10	−0.10	from H/H vdw
		$CH_3CH_2CH_2O-CH_3$			
anti, anti	2.32	2.54	2.70	2.40	
anti, gauche	1.68	1.79	2.49	1.71	
barrier reduced	−0.64	−0.75	−0.21	−0.69	from H/H vdw + BH
		$CH_3CH_2CH_2NH-CH_3$			
anti, anti	2.82	3.03	2.97	2.82	
anti, gauche	2.33	2.50	2.90	2.43	
barrier reduced	−0.49	−0.53	−0.07	−0.49	from H/H vdw + BH

[a] The barriers are calculated as the differences between eclipsed forms (H−C−X−C = 0.0°; where X = C, O, or N) and stable conformations, which normally have dihedral angles near 60°. BH signifies Bohlmann effect.

studied, one would certainly expect that, in any compound bearing a delocalizable lone pair of electrons, the effect should occur. The only question is whether the effect is small or large in a particular case. Thus we might for example expect to see this effect in such diverse structures as oximes, hydrazines or azo compounds.

The Bohlmann Torsional Effect. *The Methyl Group.* We have been aware of the importance of the Bohlmann effect insofar as the way it changes geometries and properties of C−H bonds for a long time,[4,7] and we have also been aware of the geometric changes that can result when C−C bonds are involved.[4,7] There is in addition, however, one further aspect to the Bohlmann effect that has not been previously recognized or discussed in the literature to our knowledge. This further complication has to do with torsional barriers about bonds that are adjacent to atoms that are involved in the Bohlmann effect. Let us consider as a simple example the molecule methyl propyl ether. The rotational barrier of the methyl group in that compound, when the molecule is in the anti−anti conformation, is 2.32 kcal/mol by DFT/B (B3LYP/6-311++G(2d,2p)) calculations, 2.54 kcal/mol by MP2/B (MP2/6-311++G(2d,2p) calculations, and 2.70 kcal/mol by the earlier MM4 calculations. (The version of MM4 used in the earlier calculations, paper I,[11a] will be called MM4O (for old) here.) These values are regarded as indistinguishable (2.50 ± 0.20). The value is not known experimentally. The designation MM4 will be used to indicate the program after the torsional Bohlmann effect has been taken into account. This information is summarized in Table 4, in the second entry.

These numbers are in reasonable agreement for the anti−anti form, and nothing exceptional is noted here (see Figure 1). However, if the methyl conformation relative to the chain is changed from anti to gauche (CCOC 75°), the rotational barrier of the methyl group is noticeably decreased, by approximately 0.70 kcal/mol, according to the quantum mechanical calculations (see Figures 2 and 3 and Table 4). No experimental value for that quantity is available, and MM4 calculations in their original form (listed in the columns MM4O in Table 4) do not show such a decrease. In the original (MM4O) calculation, the barrier is somewhat smaller (0.21 kcal/mol) in the gauche than in the anti conformation. The reason for the 0.21-kcal/mol barrier reduction in the latter case is that the hydrogen on the methyl, which is nearest to carbon 2 of the propyl group in the gauche conformation, is closer to the latter than the sum of the van der Waals radii of the nearest hydrogens. This leads to a repulsion between those two hydrogens in the gauche conformation, which is relieved when the methyl rotates into the transition state. Since the ground state is strained and the transition state is not, this steric effect reduces the barrier in the gauche conformation of methyl propyl ether by 0.21 kcal/mol, according to MM4O. There is a similar reduction of the methyl barrier height in *n*-pentane as one goes from the anti to the gauche form (entry 1 in Table 4). The energy difference is a little smaller in the hydrocarbon (0.10 kcal) because the C−C bond lengths are slightly longer than the C−O lengths. But the actual reduction of the barrier in the ether is 0.64 kcal/mol by DFT/B calculations or 0.75 kcal/mol by MP2/B calculations. This extra reduction in the barrier height as revealed by quantum mechanics is not very large (about 0.5 kcal/mol for gauche relative to anti), but it turns out to be quite real and not just an incidental artifact. If we look at conformations where the torsion angle is allowed to increase from gauche (60°) to 120° or to decrease to 0°, the reduction in barrier height becomes much greater (Figures 3, 4, and 5). How and why does this extra barrier reduction arise? If we wish the accuracy of our molecular mechanics calculations to be competitive with those from quantum mechanics, we have to understand the nature of this barrier reduction and how to include it in the molecular mechanics calculations. It is a relatively small number in this present case, but it can become much larger and more significant in other cases, so we need to understand this barrier reduction and properly account for it.

We have mentioned from time to time that one of the important uses of molecular mechanics is that it enables us to understand chemistry. If we include everything we know in a molecular mechanics calculation and cannot reproduce the facts correctly, then nature knows something that we do not, and what we are discussing here has until now been such a case.

A rotational barrier of a methyl group attached to a saturated carbon (as in ethane) is quite important in chemistry, and it is well known and understood (although the resulting discussion involving the "cause" of the barrier has continued endlessly since the 1930s).[12] The barrier involved when a methyl group is attached to an unsaturated carbon (as in propene) is also pretty well known and understood.[6,12] The two barriers are qualitatively different, in the following sense. In the ethane case, the eclipsed form H−C−C−H corresponds to the energy maximum, and the staggered form corresponds to the energy minimum. In propene, a C═C−C−H eclipsed form is the stable conformation, and the staggered form is the transition state for the rotational barrier. The barriers vary somewhat in simple cases from a height of about 3 kcal/mol in the saturated case (ethane type) to a height of about 1.5 kcal/mol (with a negative sign) in the unsaturated case (propene type). The sizes of these barriers are, of course, affected by any steric effects that may be present in the ground or transition states of the molecules involved. But even in simple compounds where such effects are minimal, the barriers can also be affected by the bond order of the (double) bond being eclipsed (which we would take to be 1 in ethane and 2 in propene). If the bond order is changed, the rotational barrier is changed. While alkanes and alkenes are usually considered to have bond orders of 1 and 2, respectively, if we look at a molecule such as butadiene and consider a methyl group on carbon 2, the bond order in the direction toward the end of the chain is something like 0.9, while in the other direction it is something like 0.3. And the bond orders lead to the methyl group strongly preferring to eclipse the bond with the higher bond order (toward the end of the chain in the butadiene case). Various conjugated molecules have different bond orders in different bonds, and the rotational barriers of the methyl groups vary accordingly.[13]

Now let us look at the methyl propyl ether example shown in Scheme 3.

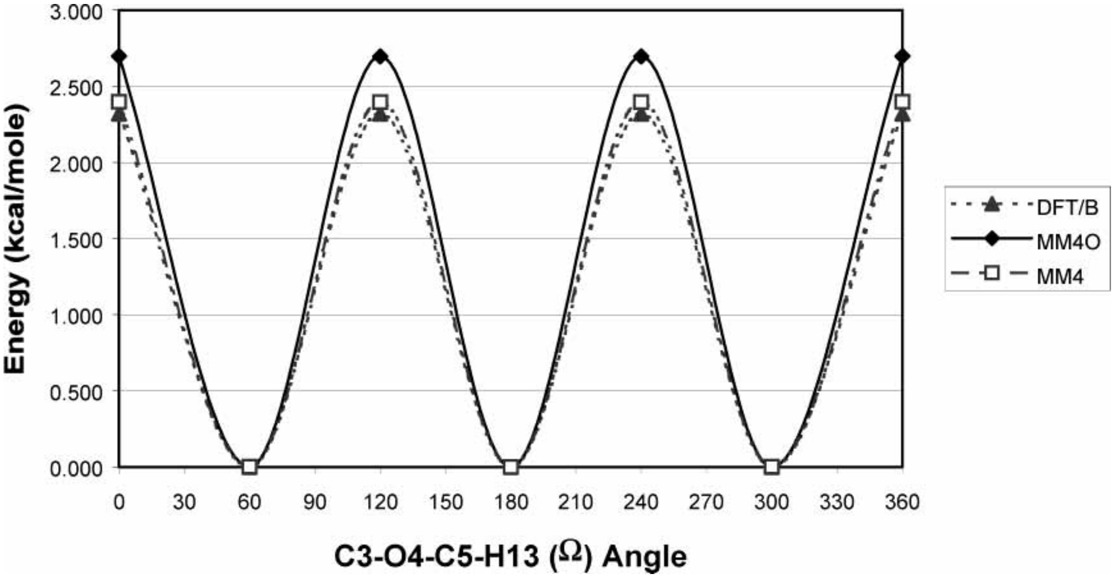


Figure 1. The torsional potential for rotation of a methyl group in methyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180°.

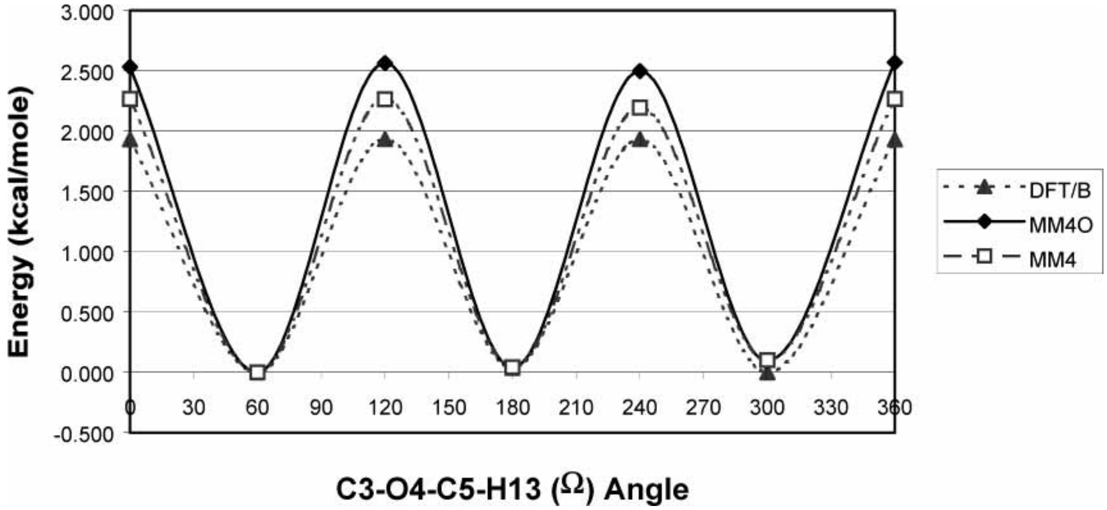


Figure 2. The torsional potential for rotation of a methyl group in methyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 60°, respectively.

To the extent that the Bohlmann effect occurs in the tG conformation, the O−Pr bond that was nominally single increases its bond order and hence should show a decreased rotational barrier for a methyl group (or an alkyl group) attached to it. When the O-methyl group is in the anti position, any Bohlmann effect is minimal (Table 4). But when the methyl is rotated into a gauche position, the Bohlmann resonance occurs as indicated in Scheme 3. And the consequence of this should be that the barrier to the rotation of the methyl group is reduced. This is an electronic effect (a consequence of the Bohlmann effect) that is separate from any steric effect that may occur in the molecule. By examination of Table 4, we see that this effect must amount to about 0.50 kcal/mol (0.70 kcal/mol total effect, less about 0.2 for the steric effect) so that it is small but not negligible.

The next point would be how, exactly, should we formulate this effect in molecular mechanics? We want to consider two cases. The first is the methyl case, where the rotating group has the structure C−O−C−H, and then separately we want to consider the ethyl (or larger) group, where the rotating structure contains the moiety C−O−C−C, in place of one or more of the C−O−C−H interactions of the methyl.

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 torsional effect. The new parameters of C−O−C−H (Ω) and C−O−C−C (Ψ) are not constants but are functions of the adjacent C−C−O−C (Φ) torsional angle.

For C−O−C−H (Ω), the Bohlmann torsional effect changes the torsional constant from V_3 (Ω), 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)

$$V'_1(\Psi) = V_1(\Psi) + (K_4/2)(1 - \cos(2\Phi)) \quad (2)$$

$$V'_2(\Psi) = V_2(\Psi) + (K_5/2)(1 - \cos(2\Phi)) \quad (3)$$

$$V'_3(\Psi) = V_3(\Psi) + (K_6/2)(1 - \cos(2\Phi)) \quad (4)$$

where K_1, K_2, K_3, K_4, K_5, and K_6 are adjustable parameters.

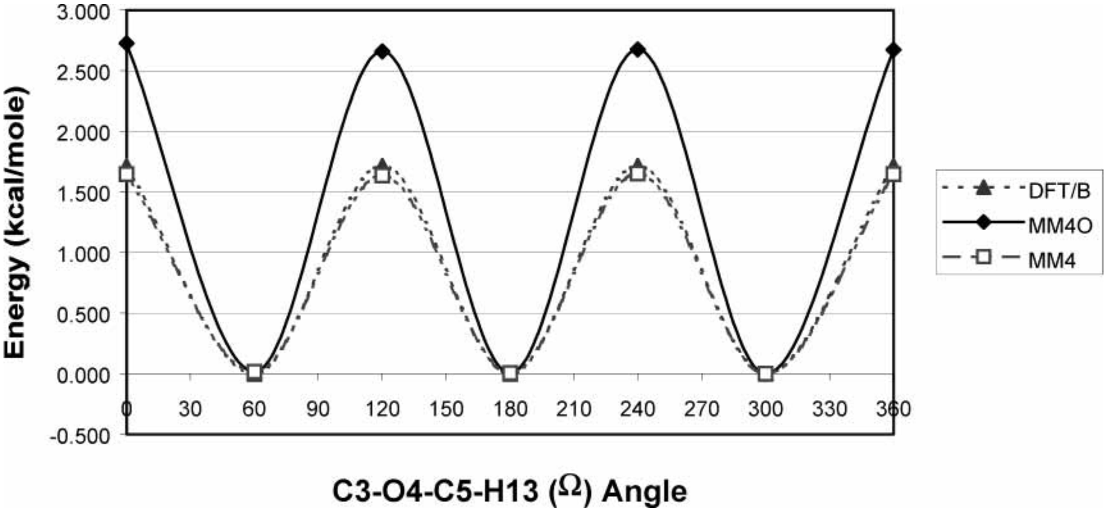
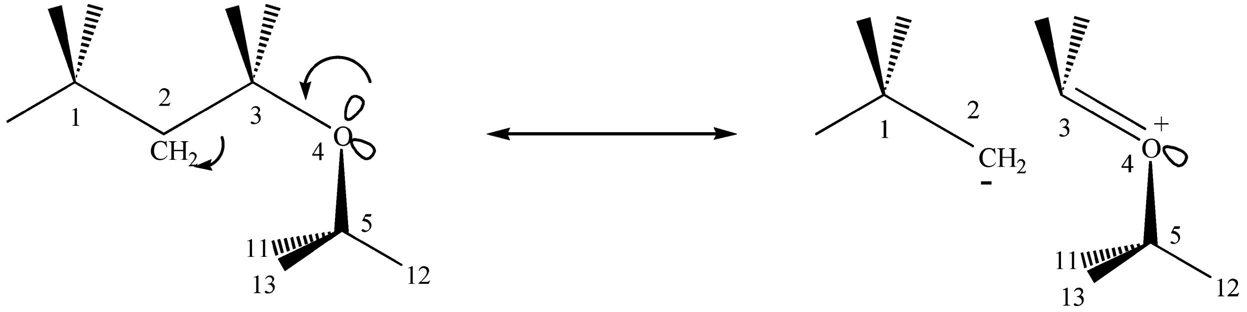


Figure 3. The torsional potential for rotation of a methyl group in methyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 90°, respectively.

SCHEME 3: The Bohlmann Effect in the tG Conformation of Methyl Propyl Ether



MM4 calculations with the new procedure were carried out for the model compounds methyl propyl ether and ethyl propyl ether, and the values of K_1-K_6 were optimized by fitting their MM4 torsional profiles to the QM results. MM4 calculations were also carried out for the heats of formation of ether compounds in general, to make sure that these changes did not introduce any unexpected errors. The best values for K_1-K_6 were established (Table 5) and are incorporated in MM4 (not in MM4O), and their effects are shown in Figures 1−9.

We recently published a series of four papers that described MM4 calculations on simple alcohols and ethers and also on more complicated alcohols and ethers, including carbohydrates.[1,11] At that time, we thought that our carbohydrate calculations were complete and accurate, as the force field used contained everything we knew to be important for molecular mechanics calculations on these molecules. The Bohlmann effect for alkyl groups was largely, but not completely, included in that work. We were aware of the importance of the torsion-stretch interaction, and especially the torsion-bend interaction, and included those approximately in the original papers. (They must be included, at least approximately, or the moments of inertia of the molecules could not have been adequately fit.) However, much of the work described in those papers was carried out about 10 years ago, and at that time we were restricted to quantum mechanical calculations only up to about the MP2/6-31G* level. We did not have great confidence in the accuracy of those calculations and relied mainly upon experimental information at that time. Now we can carry out much larger quantum calculations, and these have been in part carried through a focal point analysis to show their accuracy,[14] and we have more confidence in the accuracy of the results. We therefore looked again at simple alcohols and the Bohlmann bond stretching for alkyl groups, which we have now improved very slightly from the way it was presented in paper I. More importantly, we have now included the Bohlmann torsional barrier effect in the current study, and in this paper, reference to MM4 means the version of MM4 under discussion here that includes the Bohlmann torsional effect. This effect was previously unknown, and in fact unsuspected, as we had never carried out calculations on the right conformations of the right molecules (nor have the appropriate experiments ever been published) in order to detect it. The effect probably occurs in all other molecules that contain lone pairs of electrons in suitable locations. While these barrier lowerings are not very large in the case of simple alcohols and ethers, they may become larger in other cases, particularly in medium rings, anomeric compounds, and when multiple heteroatoms are present. The anomeric case will form the basis for a subsequent publication.[15]

The Alkyl Group. Of course, if there is a reduction in a methyl group rotational barrier, one expects a corresponding reduction in the similar barrier that results from an ethyl or higher alkyl group. The reduction in the latter cases will normally be mixed in with more or less serious steric effects, which in molecular mechanics will be accounted for separately and need not concern us here. However, the ethyl barrier may be different in magnitude from the methyl barrier for electronic reasons, and that needs to be explicitly accounted for.

In Figure 6, the torsional energy profile is shown for rotation of the ethyl group of ethyl propyl ether in the tT conformation. In Figure 7, the torsional energy profile is given for ethyl propyl ether, when the propyl group is fixed in an anti conformation, and the C−C−O−C torsion angle is fixed at 60° (tG conformation). The rotation of the ethyl group with respect to the propoxy group may then be examined (Figure 7). Note that in this case

TABLE 5: Parameters for Alcohols and Ethers to Account for the Bohlmann Effect[a]

Torsional Parameters (kcal/mol)

torsional angle	V_1	V_2	V_3	V_4	V_6	BTB[b]
5−1−1−6	−0.593	0.554	0.474	0.000	0.045	−0.10
1−1−6−1	1.900	−0.500	1.250	0.000	0.000	0.00
1−1−6−21	0.100	0.640	0.000	0.000	0.093	−0.09
5−1−6−21	0.000	0.000	0.336	0.000	0.035	−0.06

Bond Stretching Parameters

bond	K_s, mdyn/Å	l_o, Å
1−6	4.90	1.4200

Electronegativity Bond-Length Correction Parameters (Å)

bond	end atom	attached atom type	primary correction	secondary correction (%)
1−6	6	21	0.0136	20

Torsion-Stretch Parameters (kcal/Å mol)

	left bond (type2)			central bond (type 1)			right bond (type2)		
	K_{ts1}	K_{ts2}	K_{ts3}	$K_{ts1'}$	$K_{ts2'}$	$K_{ts3'}$	$K_{ts1''}$	$K_{ts2''}$	$K_{ts3''}$
5−1−6−21	2.900	5.550	0.000	0.000	0.000	1.559	0.000	0.000	0.000
1−1−6−21	0.000	3.550	0.000	0.000	0.000	1.559	0.000	0.000	0.000
1−1−6−1	0.500	1.000	2.000	−5.500	1.000	2.459	0.000	2.000	0.000
1−1−1−6	0.750	−1.000	0.000	3.500	−3.000	2.160	0.500	2.200	0.750

Torsion-Bend Parameters (mdyn Å/rad)

	left angle			right angle		
	K_{TB1}	K_{TB2}	K_{TB3}	$K_{TB1'}$	$K_{TB2'}$	$K_{TB3'}$
5−1−1−6	0.006	−0.006	0.000	0.008	−0.010	0.000
1−1−6−1	−0.043	−0.013	−0.002	−0.015	−0.017	−0.014
1−1−6−21	−0.028	−0.022	0.000	0.025	−0.018	−0.003
5−1−6−21	−0.013	−0.020	−0.004	0.015	−0.015	0.000

Electronegativity Bond-Angle Correction Parameters (deg)

angle	attached atom	correction	type
1−1−1	6	1.10	2

Coefficients for Equations 1−4

K_1	K_2	K_3	K_4	K_5	K_6
−0.10	−0.19	−0.30	0.60	−0.30	0.05

[a] These are to be added to, or to replace, parameters in the older version of MM4 (ref 11). [b] Bend-Torsion-Bend (BTB) parameters are in units of mydn Å/rad^2.

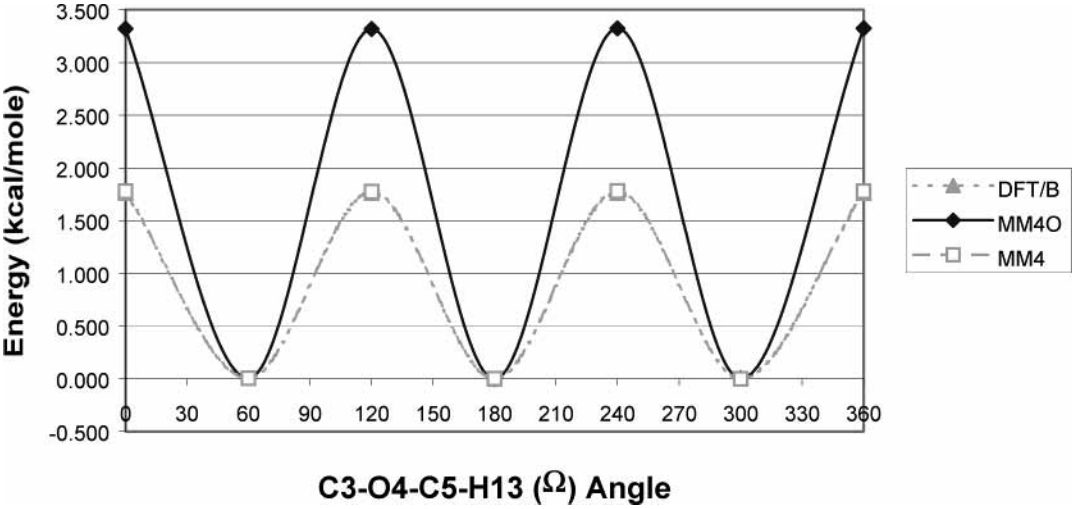


Figure 4. The torsional potential for rotation of a methyl group in methyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 120°, respectively. (The DFT/B and MM4 curves are superimposed.)

the curve is unsymmetrical due to steric effects. The DFT/B calculations show two minima, but the third minimum (near 300°) has disappeared. If we fix 60° as our reference point (Figure 7), the conformational energy minimum for the gauche conformation by DFT/B is about 1.2 kcal/mol, while that for MM4 is slightly higher and at a slightly lower torsion angle. In

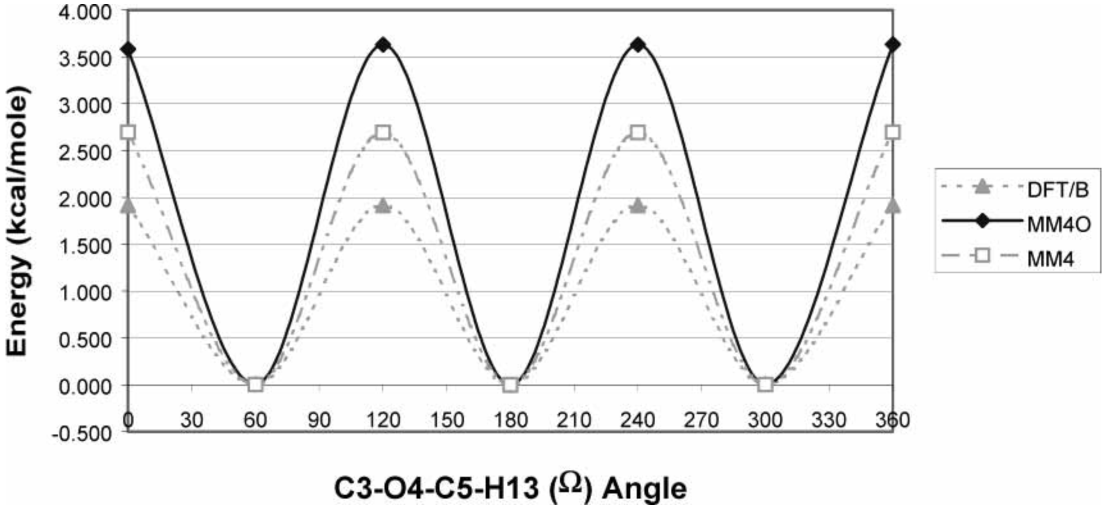


Figure 5. The torsional potential for rotation of a methyl group in methyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 0°, respectively.

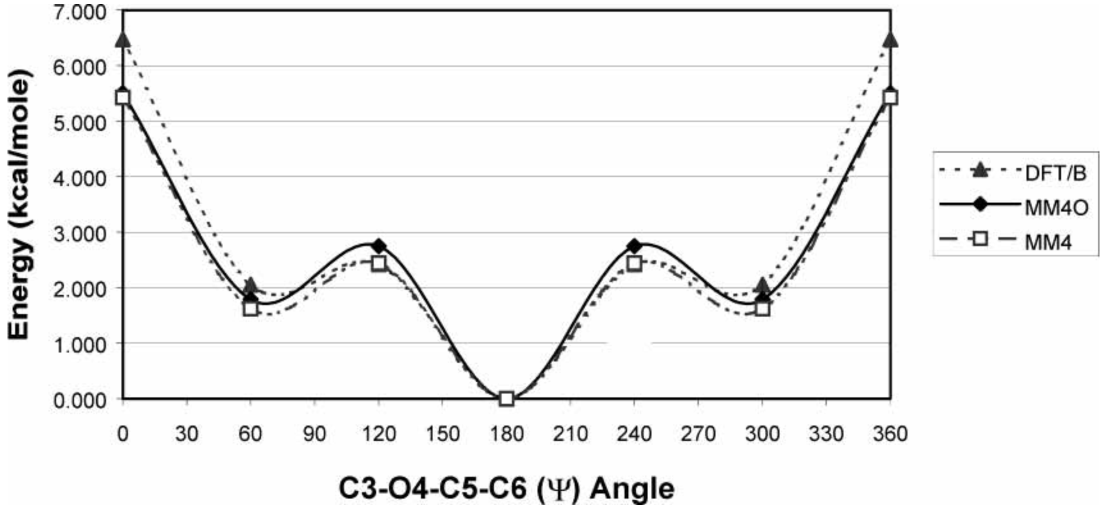


Figure 6. The torsional potential for rotation of the ethyl group in ethyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180°.

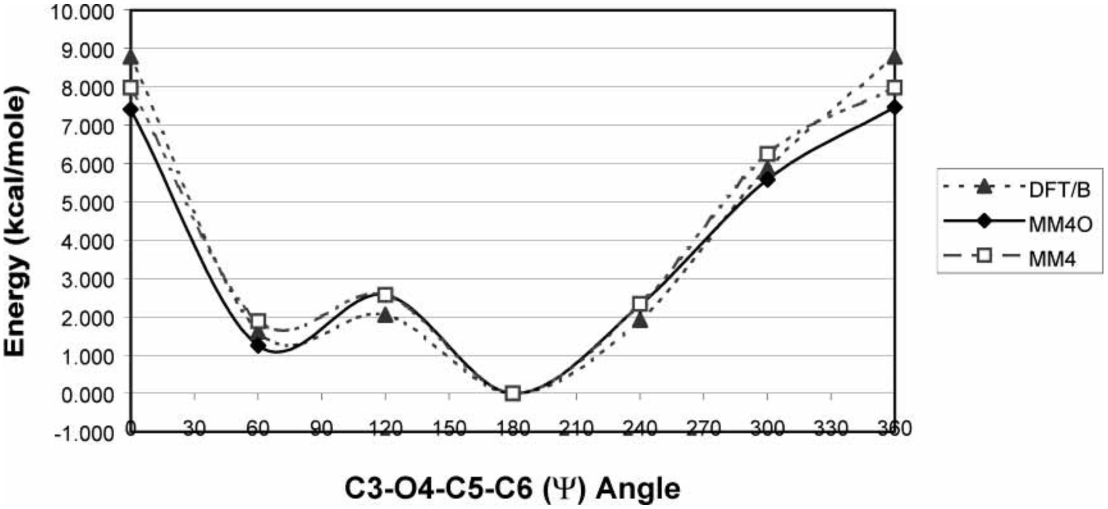


Figure 7. The torsional potential for rotation of the ethyl group in ethyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 60°, respectively.

the MM4 calculations, the shape of the potential matches that of the DFT/B calculation better, and the energy is somewhat higher than in the earlier calculations. Again, if one gets away from the fixed torsion angle of 60° for the C−C−O−C dihedral angle and goes to higher or lower values, the old MM4 energies are too high, and the new MM4 values have been reduced to better match the DFT/B values (Figures 8 and 9).

Inclusion of the Bohlmann effect, and the Bohlmann torsional effect, in the MM4 program leads to small changes relative to the results of the earlier calculations on alcohols, ethers, and

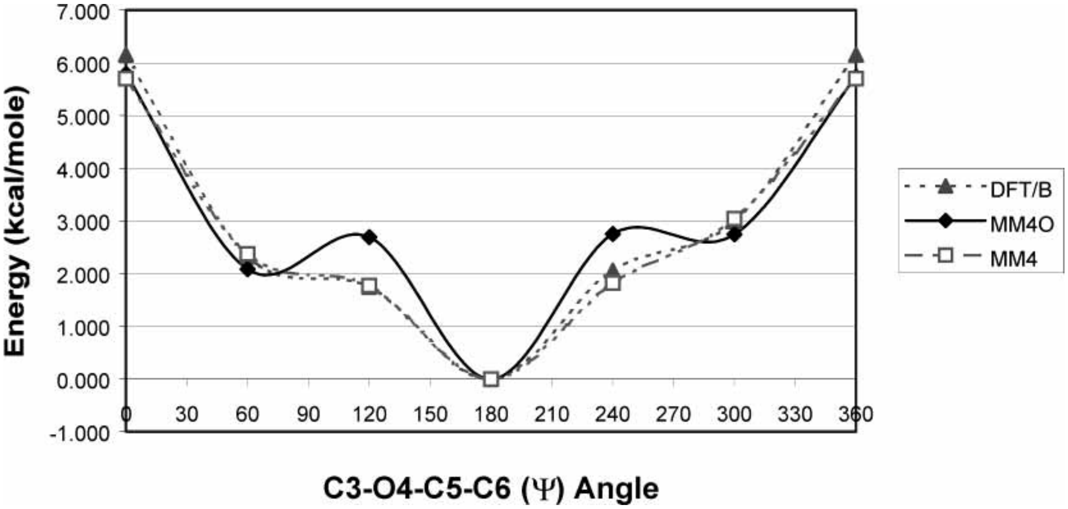


Figure 8. The torsional potential for rotation of the ethyl group in ethyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 90°, respectively.

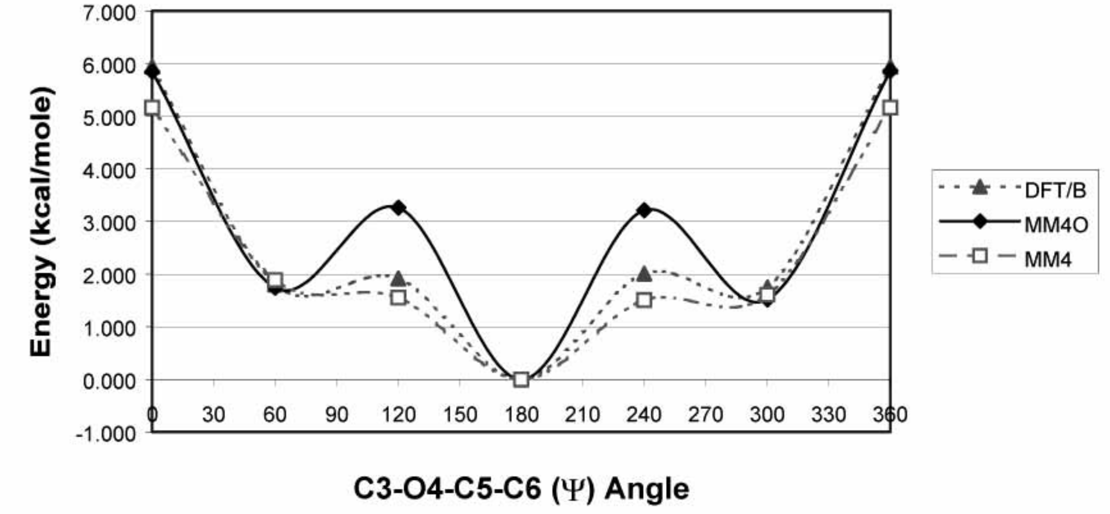


Figure 9. The torsional potential for rotation of the ethyl group in ethyl propyl ether with the $C_1-C_2-C_3-O_4$ and $C_2-C_3-O_4-C_5$ (Φ) angles fixed at 180 and 120°, respectively.

related compounds.[1,11] As a consequence of these changes, some of the numbers now show small changes from those published in our four earlier manuscripts (usually only in the last decimal place). We do not intend to publish all of this revised material, which would be essentially a duplication of papers I−IV. But we want to alert the reader that many of the numbers in those papers will not be exactly reproduced by the publicly available versions of MM4, which will also include details from this and a later[15] paper. A few vibrational frequencies have been changed as a result of changing the barrier heights. Normally these changes are only of the order of 2 wavenumbers or less, many are zero, and the largest was 5 wavenumbers. Thus it will not be possible to reproduce exactly all of the calculations in those earlier papers, but they can be reproduced with what we might call "chemical accuracy," that is, to within an accuracy that is better than the accuracy of typical experimental measurements.

To summarize briefly the small size of these changes, we might note the following. In our original paper on alcohols and ethers (paper I), important summaries were given in Tables 27 and 30, which are, respectively, the moments of inertia (39 moments) and the heats of formation (32 compounds). The overall RMS errors for those tables were 0.25% and 0.27 kcal/mol, respectively, in paper I. With the changes and additions reported in the present work, the same root-mean-square errors now have values of 0.27% and 0.26 kcal/mol, respectively.

The MM4 parameters derived from this work are listed in Table 5.

Summary

The Bohlmann effect has previously been recognized to result from a negative hyperconjugation which leads to geometric changes in molecules in which a C−H bond is anti−coplanar to a lone pair of electrons. It is not so widely recognized, but is equally true, that a C−C bond is affected similarly to a C−H bond in terms of structural changes, although the shift of the vibrational frequencies is smaller (of the order of 120 cm^{-1} for C−H and 40 cm^{-1} for C−C). Nor has it been previously recognized that torsional barriers about bonds that extend in the opposite direction from the atom donating the lone pair in the Bohlmann effect are reduced by about 0.5 kcal/mol in the case of alcohols and ethers (and also in amines, which will be discussed in detail in a subsequent paper).[5] The change in barrier height occurs in all molecules that contain ether (or alcohol) oxygen, or amine nitrogen, and is expected to occur more generally. With alcohols and ethers, the reduction in barrier height is approximately 0.5 kcal/mol. While this value is not large, it is pervasive, and consequently in molecules such as carbohydrates, it may be expected to have significant consequences.

References and Notes

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(6) (a) It is intended to make the MM4 program available shortly. The UNIX and LINUX versions will be available from Tripos, Inc. (1699 South Hanley Road, St. Louis, MO 63144), and a Windows version will be available from Wavefunction (18401 Von Karmen, Suite 370, Irvine, CA 92715). Interested persons should contact the appropriate distributor directly. (b) Allinger, N. L.; Chen, K.; Lii, J.-H. *J. Comput. Chem.* **1996**, *17*, 642. (c) Nevins, N.; Chen, K.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 669. (d) Nevins, N.; Lii, J.-H.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 695. (e) Nevins N.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 730. (f) Allinger, N. L.; Chen, K.; Katzenellenbogen, J. A.; Wilson, S. R.; Anstead, G. M. *J. Comput. Chem.* **1996**, *17*, 747. (g) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (h) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566. (i) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576.

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(8) Baker, J.; Pulay, P. *J. Comput. Chem.* **1998**, *19*, 1187. The general scaling factors reported in this paper (ref 8) were used to scale the Hessian matrix (actually, the square roots of the numbers given in Table 2 in ref 8), where the same numbers are used for oxygen as are given for fluorine. The ref 9 given in ref 8 was unpublished when our calculations were carried out, but Professor Pulay confirmed to us (personal communication) that this was the proper procedure.

(9) Parametrization of Molecular Mechanics (MM4) for Large Biological Systems: Small Peptides—Emphasis on Protein Modeling Alkylphosphines—Emphasis on DNA Structure, by Patricia Metthe Todebush, a dissertation submitted to the Graduate Faculty of the University of Georgia in partial fulfillment of the requirements for the degree Doctor of Philosophy, Athens, GA, December 7, 2000.

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