Isotope Effects in Molecular Mechanics (MM2). Calculations on Deuterium Compounds

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Parameters have been derived so as to enable the inclusion of deuterium in the MM2 molecular mechanics force field. Several compounds were studied and the results are compared with experiment. The results are never qualitatively wrong, but the accuracy ranges from excellent to only fair. They are quite good for hydrocarbons, but less so for ketones.

An obuective that has occupied our attention for several years now has been the development of a molecular mechanics[1,2] calculational scheme (computer program) for dealing with problems of structure and energy that would meet three criteria. (a) It must be widely applicable, eventually to essentially all organic molecules; (b) it must give results with an accuracy competitive with high quality experimental measurements; and (c) it must require a minimum of computing time and power, consistent with objectives (a) and (b).

The MM2/MMP2 program sequence[3] has taken big steps toward solving these problems. (a) It is of modest generality, applicable to about 15 different classes of compounds in which a single functional group (or two or more reasonably distant functional groups) were present on a hydrocarbon (saturated, unsaturated, or conjugated) skeleton. (b) Molecular structures and heats of formation can indeed be calculated with an accuracy competitive with experiment in most cases, for the classes of compounds that can be dealt with. (c) The energy-minimization scheme developed uses a very efficient Newton–Raphson scheme, with effectively a block-diagonalization routine using analytically calculated first and second derivatives.[1,3] All competitive tests known to the authors to date[4] have shown that this program is faster for typical structures than competing computational schemes (full matrix Newton–Raphson, or pattern search methods) as incorporated in programs utilizing analytically or numerically calculated derivatives. Since the original

development of the MM2 program (1977),[3] it has been extended to cover a few additional items. One new item, deuterium compounds, will be discussed in this article. (These results are incorporated in MM2-82 and later versions of this program. They can be incorporated into earlier versions of the program by the user, utilizing the data in Table I as input.) Additional functional groups, and the general molecular mechanics treatment of polyfunctional molecules and their solvation, are complex problems discussed elsewhere.[5]

Isotope effects are generally classified as primary (those involving directly the isotope) or secondary (those involving other parts of the isotopically substituted molecule). To a good approximation, the potential well in which one isotope (deuterium) is found is identical with that for the other isotope (protium). The differences occur because of the mass difference between the isotopes. The heavier isotope lies lower in the potential well, and hence has a lower zero-point energy and vibrational frequency, and a smaller vibrational amplitude.[6] Because of the asymmetry of the potential well, bond lengths and bond angles involving the deuterium therefore are different than those involving hydrogen.

The MM2 force field is designed to represent a vibrationless model corresponding to an electron diffraction geometry.[1] How are the vibrational features that characterize the real molecule to be represented in the vibrationless model? Our conclusion was that the smaller amplitude of the C—D stretching and bending motion, relative to

Table I. Deuterium parameters for the MM2 force field.[a] Bending and torsion parameters, same as the analogous hydrogen parameters.

Bond	k_s	l_0
C—D	4.6	1.108
Van der Waals	r*	Epsilon
Deuterium	1.497	0.047
C/D	3.337 (sum r*	0.046
C—D	Reduction Factor	0.915

[a] Symbols and units have the same meaning as in ref. 3.

C—H, should be best accounted for with a smaller van der Waals radius for D than for H. Additionally, it is known that the C—D bond is shorter than the C—H[7] as a result of the anharmonicity of the bond stretching potential. The chemical effects of the difference between hydrogen and deuterium are fairly small, on the order of small calories per mol, and one might wonder if molecular mechanics can reproduce such small quantities. In an absolute sense, the answer would be no, but in a relative sense, which is the usual way the experiments are carried out, the answer is not obvious.

At this point in our considerations, Lee, Barth, and Djerassi, in the course of their studies of optical activity of deuterium compounds, published an article that included a description of force field calculations in which they independently decided to represent the D/H differences in terms of the bond length and van der Waals parameters.[8] They made reasonable estimates of the differences involved and showed that they accounted in an approximate way for the differences found experimentally in several cases. Our work has been aimed at finding optimum parameters for deuterium for the MM2 force field, and to examine a reasonable number of cases for which experimental data are available.

We began with ethane, for which good electron diffraction structures are available for both the perdeutero and the perhydro molecules.[7] These structures show that the C—D bond length is shorter than the C—H by 0.005 Å, and other effects are not significant. Accordingly, we set l_0 for C—D at 0.005 Å less than the C—H value. This left the van der Waals radius of the deuterium as the only parameter to be evaluated.

The conformational energy of the trideuteromethyl group on the cyclohexane ring, relative to that of the perhydro compound, has been measured in two different experiments, and the values obtained were in perfect agreement: 11.0 cal/mol,[9]

and 11.9 ± 1.5 cal/mol.[10] The —CD_3 group is "smaller" in each case (it prefers the congested axial position, relative to —CH_3). These values were taken as the ones to fit, and the van der Waals radius of D was adjusted downward from that of H until an acceptable value for the above energy difference was found. The value settled on was 1.497 Å for D (1.500 Å for H), and the CD radii sum was correspondingly taken as 3.337 (vs. 3.340 for CH). These values, together with the shorter C—D bond mentioned earlier, gave a calculated conformational energy difference between perdeutero- and perhydromethyl cyclohexanes of 11.3 cal/mol. There were then available several rather different pieces of experimental data on H/D isomers for which values could be calculated. These involved 1,1,3,3-tetramethylcyclohexane,[13,14] 9,10-dihydro-4,5-dimethylphenanthrene (I),[11] cyclopentanone,[12] and 2,2-dimethylcyclohexanone,[8] each of which will be considered in turn.

A study of 1,1,3,3-tetramethylcyclohexane, in which one —CH_3 group was replaced by a —CD_3 group has recently been reported.[13,14] The cyclohexane ring is in the chair form, and the —CD_3 group is in either an equatorial or an axial position. Since the —CD_3 group is smaller, it would be expected to preferentially occupy the axial position, and experimentally it does, with $\Delta G° = 24 ± 1$ cal/mol (at −100 °C in CS_2). The entropy change should be close to zero (both conformers are dl pairs with $\sigma = 1$). Our calculated energy (enthalpy) difference is 26 cal/mol, in good agreement with experiment.

9,10-Dihydro-4,5-dimethylphenanthrene and the corresponding molecule with trideuteromethyl groups exist in a nonplanar conformation with C_2 symmetry.[11]
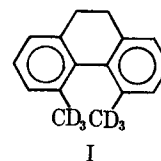
I

The planar (C_{2v}) conformation is at an energy barrier which separates the two (enantiomeric) C_2 conformations. The rate of racemization of I would be expected and has been found[11] to be faster in the deuterated compound than in the hydrogen analog, as the smaller —CD_3 groups can more easily pass each other. Can we calculate this barrier to racemization?

This is not necessarily as easy as it sounds. If one has the full force-constant matrix, and begins close to a transition state, application of the Newton–

Raphson method will lead one to the transition state (saddle point). However, the MM2 program does not ever calculate the full force-constant matrix. When our calculational scheme was devised, we were interested primarily in molecular ground states, and because the block-diagonal method is so much faster, that method was employed. The main reason why this method is faster is because one does not spend a lot of time calculating large numbers of off-diagonal elements which are near zero in the force-constant matrix. However, once committed to that method, one also has lost the best possibility for locating transition states. With the molecule at hand, there would appear to be quite a number of transition states possible, and of course the molecule will actually go through the one which is lower in energy. We have underway the addition of an option to MM2 which will calculate the full force-constant matrix and utilize it upon demand. However, this option is not available at present.

So how else might we calculate the transition state of geometry? The method which is most often used involves guessing what the transition state looks like, and then using the "driver" technique to force one (or more) dihedral angle of the molecule along what is hoped will approximate the reaction coordinate, until the transition state is reached and passed. One must first guess what the transition state of lowest energy will be. We first thought (naively) that the planar molecule would be the transition state. But, calculations showed it had an energy far too high above the ground state to correspond to the observed transition rate. We then tried to begin at the ground state and drive the molecule about the central (biphenyl) bond. But, the molecule refused to go through the transition state at all. The methyl groups held back, while the rest of the molecule continued past planarity and on to ever greater distortion. This result can be understood as a lack of correspondence between the angle being driven and the reaction coordinate desired.[15] Finally, we decided that at the transition state the Ar—CD$_3$ bonds and the biphenyl bond must be coplanar, but there was no reason why carbons 9 and 10 or the aromatic carbons to which they are attached needed to be coplanar at the same time. The barrier to the flipping of these atoms through the plane can occur before or after the transition state, and that energy is thus unnecessary at the transition state. Hence our next transition state model again went back to a planar (skeleton) molecule, except that

atoms 9 and 10 and the attached aromatic atoms were allowed to move above and below the plane. Indeed, this lowered the energy of the transition state significantly and it was now only slightly higher than the experimental value. We judged that this structure was then a reasonable model of the transition state. The calculated $\Delta H^{\ddagger}$ was 27.518 kcal/mol, while the reported experimental quantity was $E_{act} = 23.1$ kcal/mol (42 °C). The calculated $\Delta\Delta H^{\ddagger}(\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D)$ was 0.16 kcal/mol. The experimental values reported were 0.24 kcal/mol in benzene, and 0.19 kcal/mol in heptane, so the agreement is good.

One interesting observation made here concerns the relative orientations of the methyl groups in the transition state of I. Three extremes may be envisioned, (a)–(c):
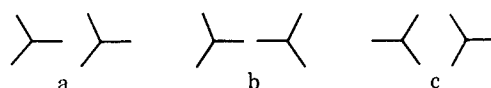
The methyl groups in cis-2-butene adopt conformation b in the ground state. There is an unfavorable repulsion between the nearest hydrogens, but the hydrogen eclipsing the double bond is the favored torsional arrangement, and that interaction wins out. But, in toluene the barrier for methyl rotation cannot have any components less of then sixfold because of symmetry, and the observed barrier is essentially zero. In this molecule, since the methyls interact, the ground state will have that geometry in which the methyl–methyl van der Waals repulsion is minimized. That proves to be geometry (c). The transition state to inversion is assumed to have these groups in an arrangement with approximate C_{2v} symmetry (the axis in between the groups and perpendicular to the plane of the paper). In the ground state one methyl shifts up, the other down, on the page, and the C_{2v} axis becomes a C_2 axis.

The hydrocarbon cases discussed above are well described by the MM2 force field with the specified parameters. In these cases the interaction with the C—D bond comes largely from the deuterium end of the bond (frontside). Now we will discuss several cases where the interactions are more from the backside, which happen to involve ketones.

2-Deuterocyclopentanone has been studied by circular dichroism.[12] Since molecular mechanics and spectroscopic studies have shown that the C_2 conformation corresponds to an energy minimum,[16] and the C_s to an energy maximum, the circular dichroism curve has been interpreted in terms of the following kind of equilibrium.
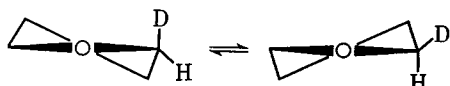
Using the optically active compound of known absolute configuration, and applying the octant rule, it was concluded that the equatorial deuterium was favored by 10 ± 2 cal/mol. Sundararaman, Barth, and Djerassi[12] noted that this equilibrium had a sign opposite to that expected, and said that their force field gave a sign as expected rather than as found, but they declined to speculate as to why this was true. The MM2 result is 1 cal/mol. While this calculated result is not qualitatively wrong, it is certainly not the kind of result we have come to expect from the MM2 program.

Finally, various possible n-deutero-1,1-dimethylcyclohexanones were studied. The equilibria are of the sort shown.
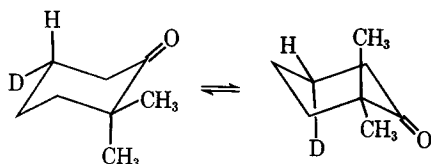
In each case the conformation with axial deuterium is favored.[8] The calculated and experimental[8] energy differences are given in Table II. The results here are qualitatively in agreement with experiment, but the quantitative agreement is poor. Of course we are talking about only a few small cal/mol, and we are looking at polar compounds that are known to solvate and dimerize,[17] and we are comparing experimental free energies with calculated (gas phase!) enthalpies, so there are many reasons why the agreement between calculation and experiment may not be perfect. It is possible that the experiment is not measuring quite what we are trying to measure. On the other hand, the calculations may be simply in error. The energy differences under consideration are, after all, pretty small. The accuracy or validity of a "vibrationless model" at this level is quite uncertain.

Conclusions. There are experimental and theoretical reasons for believing that a C—D bond is

Table II. Energy differences[a] $(E_e - E_a)$ for deuterated 2,2-Dimethylcyclohexanones (cal/mol).

D-Position	Calc.	Exp.[8]
3	2.3	9.5
4	9.6	4.2
5	1.8	2.7
6	5.1	…

[a] The calculated quantities are actually enthalpies, the experimental values are free energies.

shorter than the C—H analog, and that deuterium has a smaller van der Waals radius than hydrogen. For four examples of molecular hydrocarbon systems, where the interaction D/H or D/D is compared with H/H, it is found that a quantitative agreement between calculation and experiment of differences in steric interactions results from use of the known C—D bond length, a proper choice of the van der Waals radius of the deuterium. For several examples of ketones, in which various complicating factors are present, the calculations are in fair, but certainly not perfect, agreement with known experimental facts.

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