PERSPECTIVE

Understanding molecular structure from molecular mechanics

Norman L. Allinger

Abstract Molecular mechanics gives us a well known model of molecular structure. It is less widely recognized that valence bond theory gives us structures which offer a direct interpretation of molecular mechanics formulations and parameters. The electronic effects well-known in physical organic chemistry can be directly interpreted in terms of valence bond structures, and hence quantitatively calculated and understood. The basic theory is outlined in this paper, and examples of the effects, and their interpretation in illustrative examples is presented.

Keywords Molecular structure · Molecular mechanics · MM4 force field · Valence bond theory

Laws of nature

Ancient peoples knew something about natural laws thousands of years ago. The motions of the sun and moon, for example, were obviously considered to be important. They had to know when to plant crops, and so they developed accurate calendars.

On the other hand, there were many things that they did not understand, for example, the weather. So things like

Throughout this paper "quantum mechanical calculations", or (QM) means MP2/6-31G++(2p, 2d), unless otherwise stated. Geometric units are in Angstroms or Degrees, and Energies are in kcal/mol unless otherwise specified. The expression MM4O is used to mean the "Original" MM4 program before inclusion of the item under discussion.

N. L. Allinger (✉)
Department of Chemistry, Chemistry Annex, University of Georgia, Athens, GA 30602, USA
e-mail: allinger@chem.uga.edu

this were simply attributed to whims of the Gods. They tried to understand the latter, of course, and work with those whims as best they could.

Historians know much of the Egyptian civilization, in part because the Egyptians built a large number of buildings, and they tended to put profuse writings and artwork on the walls of those buildings. Other civilizations seemed to develop similar skills at about the same time and subsequently in several different places around the world. Many of these civilizations were quite skilled at engineering, as we can tell from buildings that have survived. Engineering requires a good understanding of much of mechanics. It is often stated that many of the buildings constructed by these early civilizations utilized immense stones so precisely fit together that one cannot slip a sheet of paper between them.

Some 95% of the universe is composed of dark matter/dark energy [1]. We have only rather recently learned of the existence of these items, and our knowledge of them is currently minimal. The problem is that they for the most part interact only feebly with ordinary matter, other than by gravity, which makes them quite difficult to even detect. The other 5% of the universe is made up of baryonic matter, and that we understand pretty well, relatively speaking. It seems fair to conclude that our overall knowledge of the universe must currently be judged as being quite poor.

Our understanding of the laws of nature as they affect daily life is considerably better than when we try to understand the universe as a whole. We want here to consider a few sets of rules or laws that impact us both as chemists, and as residents of the planet Earth, more directly. These would include Newtonian mechanics (1600s), quantum mechanics (early 1900s), thermodynamics (late 1800s). These three items are of immediate importance. In fact, they account for much of what we observe in nature and otherwise, apart from living organisms.

Molecular structure

From the viewpoint of a chemist, if we start with the smallest things, and work our way up to the largest, we have a chain that reads like this: Electrons plus nucleic → atoms → molecules → macroscopic assemblages. The boundary between chemistry and physics is indefinite at the lower end of this scale, which is why we have subjects called chemical physics, and physical chemistry. By common consent, the physicists pretty much leave molecules to the chemists. Atoms, and their constituent parts, are generally left to the physicists. Most of computational chemistry is directed at studies of molecules and molecular fragments. If these studies are quantum mechanical in nature, then molecules are necessarily considered as collections of nuclei and electrons. Now let's consider the three fundamental primary components of molecular structure studies, as we might divide up the subject:

> *Newtonian Mechanics*: Describes much of the behavior of inanimate objects that we see in daily life.
> *Quantum Mechanics (QM)*: Deals primarily with things that are very small. This includes especially electrons, but also much, some would say most, about what we are interested in regarding atoms and molecules. This subject is thus a fundamental part of chemistry.
> *Thermodynamics*: This subject has to do, literally, with the flow of heat (or energy). Molecular structure can be viewed as something separate from energy, but the two are so tightly intertwined, that normally they have to be considered together. An accurate molecular structure is always quantitatively related to the energy of the system.

For sure we can study molecules by QM. We can also, with some limitations, study them by Newtonian mechanics. The latter has some well-known disadvantages relative to the former, but it also has some advantages, not all of which are widely recognized.

Molecular models

There are two extremes in terms of accuracy when studying molecular structure from the viewpoint of an experimental chemist. At one extreme, the organic chemist may write a structure, say cholesterol (Structure 1) for example:

The structure as shown usually provides the necessary information about this molecule with the accuracy that the organic chemist may need for whatever problem is at hand.

The spectroscopist, on the one hand, might like to understand every line in the electromagnetic spectrum of a molecule. Beginning with the ultraviolet region, passing through the visible and infrared, and then the microwave region, one obtains considerable information about many
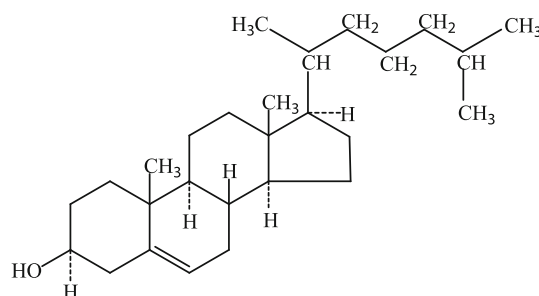
Structure 1

states of interest of the molecule. If one really understands the molecular structure in its entirety, then presumably one can relate the entire spectrum to the various states of the molecule. Such studies often lead to energy differences accurate to five or six decimal places.

Computational methods have advanced greatly since the 1950s due to the availability of computers. These have led to considerably greater accuracy in the structural information now available. And most spectroscopic and chemical problems are usually somewhere between the two extremes mentioned above, as far as an understanding of a particular molecular structure goes. "Chemical accuracy" has long meant an accuracy to 3–4 decimal places, and that is the accuracy that we will assume or strive for in this work, unless otherwise noted.

We know that quantum mechanics "works," in the sense that if we want to calculate just about anything concerning molecular structure we can do so in principle, to any desired degree of accuracy. Of course, in the real world we can't actually do this much of the time, because our computer power is insufficient. Density functional theory[1] [2, 3] offers an immensely faster method for carrying out such calculations than traditional or Schrödinger quantum mechanics. However, it does not at present "work" in a completely reliable general and accurate way. Computers are continuing to become faster, and better algorithms for calculating things are constantly being developed. Density functional theory is becoming more accurate, and may in the future have the accuracy that Schrödinger quantum mechanics now has.

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[1] The general problem with DFT methods, and in particular with B3LYP, is that, differing from Schrödinger methods, DFT methods cannot be systematically improved with increasing basis set size, and their accuracy in particular cases is often not known. In general, molecular structures are calculated less accurately by DFT methods than by Schrödinger methods. For energies, this may or may not be true, depending upon the case. There is a general error in B3LYP calculations, because the contribution of dispersion forces is omitted. This error may be small or large, depending upon the particular case, so one must be cautious about the use of such calculated values. There is a common tendency for users to overestimate the accuracy of B3LYP and related methods.

So if all of this can be done, or at least seems to be doable, why don't we go ahead and do it? Well, many people are involved in pursuing various aspects of that pathway in recent years, and with considerable success, although we aren't there yet.

There is also, however, another computational approach to molecular structure. This involves, to use the most general term, *molecular modeling* [4–6].

What we would like to do is apply classical mechanics to the study of molecular structure, where it is commonly called *molecular mechanics* [4a, 7]. Why do we want to do that? There are at least two reasons. One reason, which is widely appreciated, is that chemists have a continuing need for simple models of molecular structures. The hand-held Dreiding model has been and is widely used, to give chemists something to concentrate on and to point to when they discuss the subject. Molecular mechanics is in one respect a better Dreiding model. It can put on a quantitative basis the things that a Dreiding model can do on a qualitative basis.

The second reason for studying molecules with molecular mechanics is that it can teach us more about molecular structure. Lord Kelvin once said that if you cannot model something accurately, you probably do not understand it very well. The molecular mechanics model is highly correlated with the valence bond structures that are widely used by organic chemists to understand chemical structures and reactions, but this close correlation has not been widely appreciated nor exploited very much so far.

Perhaps it would be a good idea to ask at this point if there is a reasonable expectation that we can learn something useful by applying classical mechanics to a study of molecules. After all, we have known since the 1930s that quantum mechanics is the proper method for studying things that are very small, and this would certainly seem to include molecules. It turns out, however, that the use of classical mechanics for molecular studies is far more informative and useful, and also more accurate, than most chemists might have supposed.

It was known prior to 1930 that molecular mechanics "worked," in the limited sense that spectroscopists used it as a method to predict infrared spectra [8]. There were some definite limitations to the method, but it worked very well within certain areas. Nature was trying to tell us something here. We needed to look harder to understand better just what nature was doing. It turned out that molecular mechanics works a whole lot better than was appreciated at that time. It has proved to be useful not only for understanding infrared spectra, but more importantly, it can be used in a very general way in a predictive manner for studying molecular structures, and subsequently, related properties.

From a theoretical point of view, we need to first mention the Born–Oppenheimer surface. When chemists talk about a *molecular structure*, they commonly mean the relative coordinates of the atomic nuclei. Physicists may think of a molecular structure as a collection of nuclei, plus a collection of electrons, all close enough in space to be strongly interacting with one another. Quantum chemists normally divide a structure into two parts: the atomic nuclei are at certain positions, and the electrons are distributed about those nuclei in a certain way. If you have n nuclei, and m electrons, then you have what is sometimes called a $(n + m)$ body problem. Since the electrons have a very small mass compared to the nuclei, the problem is normally divided into two parts, the problem of the n nuclei, and the much larger and more complicated problem of the m electrons. The location of the n nuclei can be described with the aid of a (multi-dimensional) potential surface. The electrons are then distributed optimally about the fixed nuclei. This turns out to be quite a good approximation (the Born–Oppenheimer approximation) for most of what chemists are interested in, and greatly simplifies our understanding and solution of the problem.

In molecular mechanics we make one further simplification. We do not normally explicitly consider the m electrons at all. We consider only the n atoms (as opposed to n nuclei). This reduces the overall size of the problem by orders of magnitude from the size that it was when the electrons and nuclei are each considered separately.

Historically the first molecular models were of the ball-and-stick type. A. W. Hofmann, in the 1860s, made the first actual physical models of molecules, using croquet balls joined together by sticks which were constructed by cutting the mallet handles into convenient sizes, drilling holes in the croquet balls, and gluing the assemblage together. His models were quite similar to the ball-and-stick type models that are still sometimes used today, although in the 1860s chemistry was still two-dimensional, and so were his models.

After the work by van't Hoff and LeBel (1874), our understanding of molecules became three-dimensional. H. Sachse [9, 10] published drawings of ball-and-stick models of cyclohexane rings in the 1890s, with boat and chair conformations that looked very similar to ball and stick drawings of the same system that we might make today.

In the 1940s space-filling (hard sphere) mechanical models were developed to account approximately for van der Waals interactions between atoms. The hand-held Dreiding model was subsequently developed in the late 1950s. Both of these model types are made to scale, and they are quite useful for aiding in the visualization of more complicated molecules. These Dreiding and space-filling types of models and their descendants are still widely used.

Molecular mechanics models, principles [4–6]: an overview

Subsequent improvements in molecular models involve first going from the hard sphere to a soft sphere model for the atoms. The interaction potential between two non-bonded atoms can be represented by the interaction between two hard spheres, to a first approximation. But to a better approximation there are *van der Waals potentials*, or soft spheres, that need to be used. The soft sphere model would be prohibitively complex as an actual mechanical model, but it can easily be dealt with as a computational model.

While actual physical models of molecules were developed as outlined above, the computational models, or at least the forerunners of the computational models, also had to be devised. Actual structural information about molecules was quite limited before about 1900, but the branch of chemistry which we now refer to as *Stereochemistry* [11] was developing during that time. Methods had to be developed simultaneously for keeping track of this information, especially in the carbohydrate field. Accordingly, *Fischer Projections*, and later *Haworth Projections* were early structural methods for categorizing this information. In the 1930s, X-ray crystallography became seriously useful for determining the three-dimensional structures of organic molecules [12, 13], and the spring and weight model for vibrating systems was developed in order to understand infrared spectra [8]. By 1930, the possibility of developing what we now call molecular mechanics was well understood [8]. Then in the 1940s, Westheimer carried out actual quantitative force field calculations (by hand), and showed that this molecular mechanics model was capable of giving correct and reasonably accurate values for the rotational barriers in some hindered biphenyl compounds [14]. Ingold, in 1945 [15], discussed the steric effects of primary, secondary, and tertiary halides in S_N2 reactions. In the late 1950s and early 1960s, a number of attempts were made to understand various physical and chemical phenomena in the development of what became known as *Conformational Analysis* [16, 17]. These calculations were essentially molecular mechanics, without a computer. In 1961, Hendrickson began publishing a landmark series of computer calculations on the conformations of cyclic hydrocarbons [18], which were the first step in developing the molecular mechanics that we know today. Hendrickson made the approximation that since bond lengths were pretty rigid in these molecules, they could be taken as constant, while the bond angles and torsion angles were varied to let the molecule bend and undergo torsional motions. These angles were optimized to locate the energy minima. This work was an important advance because of the use of the computer, but also important was the fact that

this work showed that one could solve not only problems involving rather exotic compounds such as Westheimer had done, but one could study compounds as simple as cycloalkanes, which constitute a significant part of the nuts-and-bolts of organic chemistry. In 1965, Wiberg published his description of a generalized force field in which the atomic positions were specified using Cartesian coordinates [19]. Force field calculations were shortly thereafter carried out using computers by a number of workers on much of what was already known from conformational analysis by hand-calculated molecular mechanics. Over the next dozen years, molecular mechanics was further refined and applied to ever more generalized sets of organic molecules.

MM2 [20]

The MM [20] series of programs is descended from Wiberg's program [19], which was for hydrocarbons. Through a series of steps, improvements were made in the optimization scheme and the equations used in the force field, and parameters were developed to fit the common classes of organic molecules (alcohols, amines, carbonyl compounds, etc.). Electrostatics was also included once compounds more complicated than saturated hydrocarbons were studied, and considerable effort was required to deal with conjugated compounds. The first really general computer program that dealt with organic molecules was called MM2 [20]. The objective was to have a program that would do as much as possible, as accurately as useful, using the available theory, data, and computational hardware of the 1970s.

For convenience we can divide force fields into some general classes. A force field may be quite simple, or it may be complex, or anywhere in between. Hagler defined a class 1 force field as one in which the harmonic approximation was used and the force constant matrix was diagonal. The three basic equations describing stretching, bending, and torsion, respectively, are:

Stretching: $\quad E_s = \dfrac{k_s}{2}(1 - l_o)^2$

Bending: $\quad E_\theta \dfrac{k_\theta}{2}(\theta - \theta_o)^2$

Torsion: $\quad E_\omega \dfrac{V_3}{2}(1 - \cos 3\omega)$

where l_o and θ_o refer to the zero energy (strainless) positions of the bond lengths and angles, respectively, and the V_3 and 3ω terms are for saturated systems. These three types of equations can together rather well describe an ideal purely mechanical system (weights and springs). A description of a real molecule also requires a description of the internal van der Waals interactions of the molecule.

If one goes to molecules beyond hydrocarbons, one also needs to add electrostatics. To keep the discussion manageable here, we will only say that electrostatics constitutes an important part of a force field, but we will not discuss that subject here in any detail.

For more accuracy, it is necessary to add two different kinds of things. First we have to go beyond the harmonic approximation, so in general we would expand the first equation shown above to read

$$E_s = \frac{k_{sa}}{2}(1 - l_o)^2 + \frac{k_{sb}}{2}(1 - l_o)^3 + \cdots$$

The second of the above basic equations for bond angles would similarly be expanded into a power series, and the third equation, torsion angles, would be expanded in a Fourier series.

Then a second refinement would be to add cross-terms (off-diagonal elements) in the force constant matrix. That is, equations of the type

$$E_{s\theta} \frac{k_{s\theta}}{2}(1 - l_o)(\theta - \theta_o)$$

The MM2 force field was not exactly Class 1, but nearly so. Such force fields give reasonably good approximations for the structures and energies of a wide variety of molecules, particularly for those that are relatively strainless. Such calculations are of limited accuracy but this accuracy is sufficient for many purposes. They are widely used for very large molecules such as proteins which would otherwise be excessively computationally intensive.

MM4

A class 2 force field is anharmonic, and uses a full force constant matrix with all needed cross-terms. If the force constant matrix is very large, most of the terms will in fact be essentially zero, because distant parts of the molecule mostly have small to negligible interactions, apart from electrostatics.

We refer to a class 3 force field as one which explicitly includes "Special Effects" of organic chemistry in the force field. Thus the *anomeric effect*, *electronegativity effect*, *Bohlmann effect*, etc. are explicitly accounted for by equations that describe each of these effects. MM4[2] is a class 3 force field, which includes the effects known to be important in organic chemistry.

"Effects"—introduction

Organic chemists have known for generations that one can carefully plan and carry out an experiment, and if it is an experiment that has never been carried out before, there is at least a modest chance that the results will not be those anticipated. The product of a reaction is often obtained in lesser yield than expected, or it may not be obtained at all. A student is often told, not too seriously, "Perhaps you have discovered another 'effect' in organic chemistry."

Organic chemistry consists of, among other things, a hierarchy of rules which say that if you do thus and so, the result will be…, except in cases (a), (b), (c)…, and there are commonly many exceptions. The basic rules are learned by chemistry students early on, but understanding all of the exceptions takes much longer. (How much longer is hard to say, because the present author has not yet reached that point.) The reason for a particular exception to a rule, or to an exception of an exception is frequently ascribed to an "Effect."

These so-called "effects" are an important part of chemistry at the practical level. They impact chemical reactivity when they are present, and hence the outcome of many chemical reactions. They also impact many physical properties of molecules, particularly their spectra (of all kinds) and their structures. Needless to say, this is a vast subject, and we will here limit our discussion to a small selection of the impacts of these effects on the structures of organic molecules, and mention impacts on properties only as necessary to put things in context.

The major effects that are widely known and understood include the general classes of Electronegativity and of both positive Hyperconjugation and negative Hyperconjugation. These will be discussed in that order.

Beginning mostly in the 1920s, organic chemists have rationalized chemical reactions, and the corresponding molecular structures and properties, using structural formulas (pictures), which are also used in valence bond theory. Molecular mechanics is formulated to describe calculations which can be well represented by these same structures. Using molecular mechanics calculations as a basis, one can determine numerical values (parameters) for most of the structural consequences that result from these various Effects. Viewed in this way, molecular mechanics gives us a straightforward understanding of molecular structure (and much of the rest of organic chemistry which follows as well) in terms of the valence bond structures that are quite familiar to the organic chemist. Or, put another way, it gives us an accurate model.

Electronegativity effect [4e]

An electronegative group is a functional group which, when attached to a hydrocarbon molecule, tends to

withdraw electrons from the molecule to itself. Electropositive groups correspondingly repel electrons. (What follows here also applies to electropositive groups, where the sign of the effect is opposite.) Electronegativity effects in chemistry are ubiquitous, and the consequences are very diverse. Here we are only interested in the structural consequences of attaching an electronegative group into a molecule, and in particular, as a substituent on a hydrocarbon or a hydrocarbon portion of a molecule. It would be reasonable to assume, at least as an approximation, that any structural change induced into a hydrocarbon by a given functional group would result from the given force, which hopefully would be transferable in calculations from one molecule to a similar environment in a different molecule. This assumption proves to be a very good one.

Electronegativity is a relative property. Pauling [21] long ago assigned numerical values for electronegativities to different functional groups. Unfortunately, it's not as simple as one might like. That is, electronegativities generally tend to be qualitatively the same, no matter how they are determined, but they are not usually quantitatively the same. Thus fluorine is always the most electronegative element, oxygen and chlorine are quite electronegative, but less so than fluorine, while nitrogen and sulfur are still less electronegative, etc. The numerical values required to describe electronegativities in different contexts are generally similar but different, depending on the exact context [22]. Here we are concerned only with the geometric effects on molecular structure. And we can deduce a set of electronegativities that will enable us to predict quite accurately just what kind of distortion is induced into a structure by the presence of a given electronegative group.

How can we describe the physics involved here in a simple, numerically useful way? Early evidence for the electronegativity effect in experimental chemical properties was already known in the 1940s [23]. If we add an electronegative group to an aliphatic carboxylic acid, say a chlorine in the alpha position, the acid becomes stronger. We can understand this from elementary principles. If we add two chlorines in the alpha position, the acid becomes still stronger, but less than twice as strong. In other words there is a saturation effect with further additions. If we repeat the experiment using a different carboxylic acid, we find a similar result. So the electronegativity effect on acidity was found to be an accurately transferable property.

Then there are two variations of this effect in the above example that we should note. The one mentioned (multiple substitution) is similarly a transferable property. The other one is the fact that if we substitute the chlorine not in the alpha position, but in the beta position, we notice a qualitatively similar effect, but the magnitude is smaller. Generally, whatever the effect is from a single alpha substituent, a second alpha substituent has in addition about 0.6 times that effect. A beta substituent adds about 0.4 times as large an amount as the original alpha effect. Hence if we have multiple alpha and beta substituents, we can make a pretty good estimate of what the overall effect will be by assuming that these effects are additive when scaled appropriately. Presumably there is a gamma effect also, but it is ignored because it is quite small.

How do these electronegativity effects affect molecular structures [24, 25]? The methane molecule has four identical sp^3 bonds to hydrogen. If one of the bond angles is distorted in the direction of being smaller (toward 90°), those particular C–H bonds will become more p-like in character. We know that p bonds are not very strong compared to sp^3 hybrids, and p electrons generally lie in higher energy orbitals than s electrons, and are more polarizable. So as an H–C–H angle tends from tetrahedral toward a smaller value, those bonds will get weaker, and hence longer. In methane, if one bond angle gets smaller and the bonds get weaker, the remaining bond angles must accordingly open more, and those bonds consequently become more s in character, stronger, and hence shorter.

If we then look at methyl fluoride, the fluorine is withdrawing electrons from the system, and these will preferentially be p-electrons going into the C–F bond. Accordingly the C–H bonds are becoming more s in character, and becoming stronger. So is this effect large enough to be important, and if so, how do we take it into account in molecular mechanics?

The effect is certainly large enough to be significant. Table 1 gives some bond length changes induced by different common functional groups by changes in l_o for the C–H bond. The highly electronegative fluorine causes the C–H bonds on the carbon atom to shrink by 0.008 Å. The corresponding shrinkages observed for other groups

Table 1 MM3 electronegativity bond length corrections (Å) [48]

Bond type	Atom	Corr.
C–C	O	−.007
C–C	N	−.005
C–C	F	−.022
C–C	Cl	−.008
C–C	Br	−.012
C–C	I	−.005
C–C	S	−.001
C–C	Si	+.009
C–H	O	−.003
C–H	N	−.001
C–H	F	−.008
C–F	F	−.030

When an atom is attached to a particular type of bond (bond type), the value of l_o for that particular bond is changed by adding Corr. to l_o

are shown in the Table 1. It is seen that these generally are in the order one would expect from electronegativity effects, down to small values, and then the values become of opposite sign as we go to electropositive elements such as silicon. The H–C–H angle in methyl fluoride is opened to about 110°. The H–C–F angles are correspondingly closed to about 108.9°. And these kinds of numbers (δl_o and $\delta \theta_o$) are transferable from one molecule to another.

For a series of C–H bonds, as they get shorter, their vibrational potential wells get deeper and narrower, and the bond gets stronger. The (stretching) vibrational frequency is accordingly higher [26–28]. There is an inverse linear relationship between the frequency and the bond length. These frequencies are often easy to measure accurately, thus yielding accurate bond lengths.

As one would anticipate, if the C–H bonds are affected in a certain way by electronegative attachments, the C–C bonds should be affected similarly, although with different numerical constants, and this is what is found [29]. Not surprisingly, since the C–H bond is quite short and strong compared to other bonds, the electronegativity changes in bond length induced by a given functional group tend to be minimal with hydrogen, and they become larger with other atoms. Thus while a fluorine attached to the carbon causes the C–H bond to shrink by 0.008 Å, it causes a C–C bond to shrink by 0.022 Å.

Pursuing the idea that the force involved for a particular structural change should be similar, regardless of the rest of the molecular structure, this means that the θ_o and l_o values for the angle and length, respectively, should be changed by constant amounts when a given substituent is introduced into an arbitrary molecule. The actual observed change in the angle or length in question will then automatically be calculated by the program. It turns out that this approximation works quite well. In other words, these effects are "transferable."

This electronegativity effect is one of several "effects," which commonly occur in organic molecules, and which lead to experimentally significant structural differences. Classical mechanics takes these effects into account quite well, as does quantum mechanics. Thus the model reproduces experiment and quantum mechanics in a simple general way, to approximately within experimental error.

There is one thing about the Electronegativity Effect that sets it apart from other "effects" in organic chemistry. The other effects all involve changes in the force constant matrix. The electronegativity changes, on the other hand, come into the standard structure of the molecule, that is, the values for θ_o and l_o.

Hyperconjugation

Hyperconjugation was originally proposed by Mulliken [4b, 30, 31] in 1939, and is ubiquitous in organic molecules.
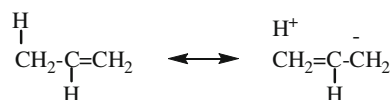
Structure 2

It can be divided into several cases, and it may be called *positive Hyperconjugation* to differentiate it from what is sometimes called *negative Hyperconjugation* (next section). It is a conjugative effect analogous to that in butadiene, but here it is between a sigma bond and an adjacent unsaturated carbon atom *p*-orbital, for example in propene (Structure 2).

In this case, the *p* component of one or two of the CH σ orbitals of the methyl group (depending on the rotational orientation of the methyl group) could overlap strongly with the *p* orbital of the *pi* system on the adjacent carbon, and this would lead to an effect similar to that of conjugation. But here the effect would be less pronounced for at least two reasons. First, the sp^3 orbital has a geometry such that it does not overlap with the adjacent *p* orbital as well as another *p* orbital would, and also, the electrons in a sigma orbital are generally much lower in energy, more stable and less easily delocalized, than pi electrons. Nonetheless, there should be at least a qualitative similarity. Mulliken called this weak conjugative effect *hyperconjugation*.

The effects of hyperconjugation are in fact similar to those observed in conjugation (in butadiene for example), but they are smaller. Propene is more reactive in electrophilic addition reactions than is ethylene (but much less so than butadiene), and it shows absorption in the ultraviolet analogous to the π–π* transition observed in ethylene but at a longer wavelength. The corresponding transition in butadiene is at an even longer wavelength.

Earlier we discussed electronegativity and how it affected bond lengths and angles in organic molecules. Here we wish to discuss the first example of a *stereoelectronic effect*, which in our model is fundamentally different from the electronegativity effect. The electronegativity effect is not conformationally dependent. (It might be slightly so in a better approximation.) On the other hand, hyperconjugation is a *stereoelectronic effect*, and it is conformationally dependent. These two classes of effects divide mathematically in a way that we want to note at this point. The electronegativity effect changes the values for structural constants (l_o and θ_o) that have to do with the atomic coordinates of a molecule. It does not appear directly in the **F** matrix. Hyperconjugative effects, on the other hand, instead occur in the **F** matrix, where they appear as off-diagonal elements.

In order to have hyperconjugation of the Mulliken type in propene, the CH bond on the methyl has to align itself properly with the *p* orbital on the sp^2 carbon to which the

Structure 3
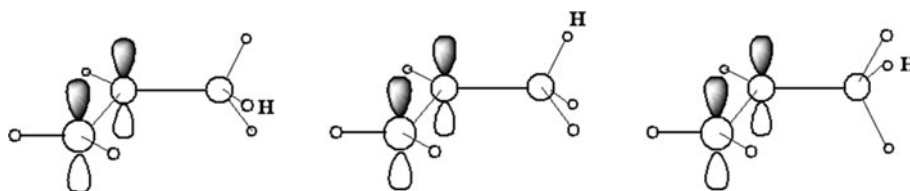
methyl group is attached. The most effective interaction between the C–H bond and the carbon p orbital will occur when the sigma bond is oriented at 90° relative to the plane of the double bond. In the ground state of propene, one hydrogen is eclipsing the double bond (with a dihedral angle of 0° with respect to the plane) as shown in the left structure in Structure 3. There would be no hyperconjugation between the double bond and that hydrogen, as the two do not overlap for symmetry reasons.

As the hydrogen indicated at the left in Structure 3 is rotated around from 0 to 180° (up and back with respect to the plane of the paper) hyperconjugation would begin, and it would increase to a maximum value at 90° (center structure), and then decrease as the rotation continued on to 180° (right structure). Thus a twofold cosine curve would describe this phenomenon. But since the geometries at 0° and 180° are different, we expect that "environmental effects" will also be present along with hyperconjugation. The phenomenon under examination will thus probably best be represented by a twofold cosine curve, superimposed upon a onefold cosine curve to allow for the cis–trans difference. And, of course, there are in fact three hydrogens to be concerned with. Some properties of the system are a function of these hydrogens one at a time (for example, the individual CH bond lengths), but other properties are a function of all three of them together (for example the C_{sp}^3–C_{sp}^2 bond length). So some properties will change with torsional rotation according to the above formulation, and others won't. That is the prediction that would come from examining Mulliken's proposal. What happens in the real world?

There are elementary predictions that can be made from the above model. These predictions involve, for example, the length of the CH bond on the methyl group as a function of torsion angle. This might in principle be studied experimentally, but in practice it would be quite difficult. It is hard to accurately measure CH bond lengths directly, because the hydrogen has such small values for whatever property one chooses to measure. It has a small mass (for microwave studies), it has a small electron density (for X-ray studies), and it has a small positive nuclear charge (for electron diffraction). It also has a large and anharmonic vibrational motion because of its small mass, making it hard to specify the location (vibrational average). Hydrogens are sometimes best located from neutron diffraction studies on crystals, but the accuracy

attainable here may be limited by the presence of the crystal lattice. But one can easily carry out accurate quantum mechanical studies on a molecule as simple as propene [32]. And they show that as one would expect from the earlier discussion, the CH bond length is at a minimum when the torsion angle with respect to the plane of the alkene is 0°, and there is no hyperconjugation, and it is similarly at another (somewhat different) minimum at 180°. It also reaches a maximum in between, near 90°, as implied by Structures 2 and 3, showing that hyperconjugation leads to a reduced C–H bond order, and hence to a longer bond length. The bond length variation here is sensitive to the basis set and the amount of electron correlation used in the quantum mechanical calculations, but only slightly so. The general result is really independent of those two things. So we may conclude that the Schrödinger equation tells us about this bond length variation with torsion angle of the CH bond in propene in accord with Mulliken's predictions. Figure 1 shows the results of a MP2/6-31G* calculation.[3] The bond length is a minimum at 180°. It lengthens by about 0.003 Å as the torsion angle is reduced to about 90°, and then shrinks back down to a somewhat higher minimum at 0°. (The maxima and minima in these and most similar curves are artificially displaced slightly from their "ideal" values because the structures were generated using a driver routine.) So hyperconjugation is real, but as far as the C–H bond length, the effect is small, about 0.003 Å.

The conclusion that one can draw from the above calculation is that hyperconjugation is a real effect, and it takes place in accordance with Mulliken's original suggestions. But it is a pretty small effect and it would be difficult to detect it experimentally by measuring the hydrogen position using microwave or diffraction methods. One might, however, devise experiments that would measure this phenomenon in any of several different indirect ways. For example, one interesting and very general experiment suggested by Pross, Radom, and Riggs [33] concerns measurement of the angle of tilt of the methyl group involved. This can be done with systems where the methyl is an electron donor (positive hyperconjugation to boron for example), or an electron acceptor (negative

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[3] Bond lengths such as these are somewhat basis set dependent for small basis sets, but the differences between such bond lengths are only slightly so for calculations of this level or higher.
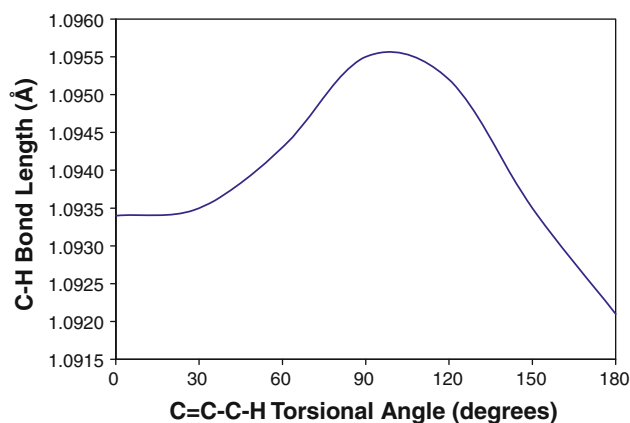
Fig. 1 The C_{sp3}–H bond length as a function of torsion angle in Propene
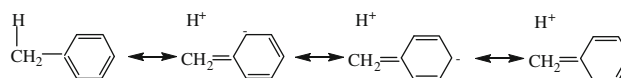

Structure 5

hyperconjugation from nitrogen for example, see later), where the magnitude and direction of the tilt (often several degrees) indicates which way the electrons have moved, and to what extent. It is very much easier and more reliable to calculate the magnitude of this effect than it would be to measure it experimentally, however.

Are there special cases where hypeconjugation might be still more important (and easier to measure)? Yes there are, and some of these have been studied. Again, the experiments would often be difficult to carry out, but one can easily do the calculation at a high enough level so that the conclusions are quite certain. Let's consider the molecule in which one of the methyl hydrogens of propene is replaced by a methyl group (to give 1-butene), and we rotate what is now the ethyl group relative to the double bond so that the dihedral angle that the ethyl makes with the alkene plane varies over the range of 0°–180°. If we reexamine Structure 2, we see that a proton is the detached fragment in the resonance form at the right. If we carry out the rotation shown in Structure 3 with 1-butene replacing propene, instead of a proton being the detached fragment, a methyl cation becomes the detached fragment (Structure 4).

And we can calculate the C–C bond length at various points throughout that rotation as we did for the propene case. Now instead of a hyperconjugative H^+ fragment, we will have CH_3^+. This was done, and in line with what one would expect from hyperconjugation, the ethyl C–C bond stretches as the bond goes from 0° to 90°, and then shrinks again back towards its original length as we continue from
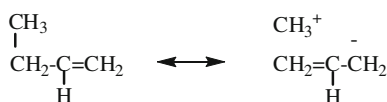
90° to 180°. Thus the methyl group C–C bond shows qualitatively the same hyperconjugative bond stretching that is shown by the C–H bond. When we look at the magnitude of the (MP2/6-31G*) stretching, the C–C bond stretches by 0.0078 Å, more than twice the distance by which the C–H bond stretches. The calculation evidently shows that hyperconjugation is not only important with C–C bonds, but that it is more important with C–C than C–H bonds, at least with respect to the bond stretching. But the stretching here is still not very large, 0.0078 Å. Can we imagine cases where it would be larger, and more accurately determined experimentally?

Well, suppose not just one double bond is hyperconjugating with the C–C bond that we are looking at, but suppose that we design a molecule such that two or more bonds hyperconjugate simultaneously. The cumulative stretching should be greater, and more readily determined.

Going back again to the propene molecule, we see that one thing happening due to hyperconjugation is that positive charge is being distributed onto one or more of the hydrogens of the methyl group, and negative charge is being distributed into the double bond. Is it possible to arrange a molecule such that the charges can be distributed (delocalized) still more widely, thus leading to a more stable molecule (more resonance forms)? Certainly, charge is distributed more widely in the toluene than in the propene case, just because there are more places to put the negative charge (Structure 5).

But we can go much further than this. Consider, for example, Structure 6a–c.

The hyperconjugative resonance forms that can be written for these structures indicate that certain bonds should be very long due to the hyperconjugation. These are the saturated C–C bonds that are aligned with the p orbitals of pi systems in such a way as to overlap with them. The bonds are numbered, 5–13 in a, 13–14 in b, and 1–7 in c. We can carry out the MM4 calculations, and see what sort of bond length is predicted for each of these when no hyperconjugation is included in the MM4 force field. (The MM4 program which does not include hyperconjugation is here referred to as MM4O.[4]) These structures are known

Structure 4

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[4] When MM4 is used to study structures, if we learn something useful we may wish to include it in the program. This means that when these studies are being carried out there are two versions of the program. One is the "original" version, called MM4O. The other version, after the improvements have been added, is called MM4 going forward.

Structure 6

a   b   c
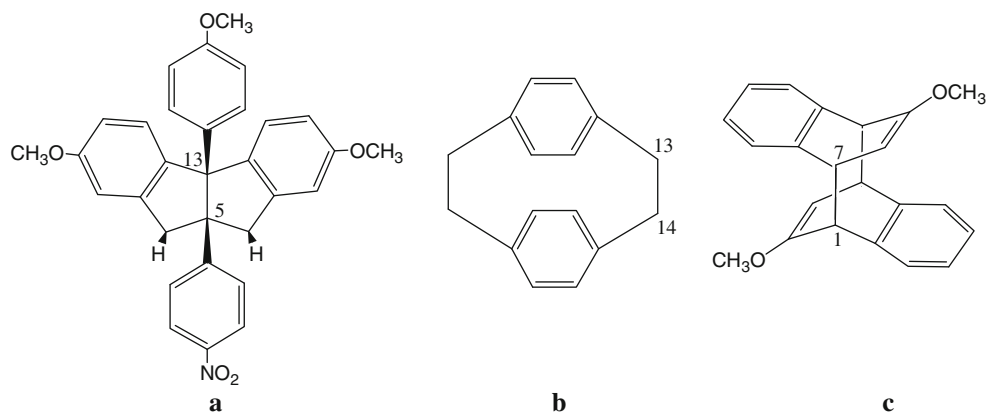
Table 2 Compounds showing long C–C bonds (Å) [32]

Compound	Bond	Expt.[a]	MM4O[b]/Δ	MM4[c]/Δ	Hyperconj. effect
a	C5–C13	1.621(2)	1.603/− 0.018	1.618/− 0.003	0.015
b	C13–C14	1.571	1.565/− 0.006	1.574/0.003	0.009
c	C1–C7	1.617(5)	1.589/− 0.028	1.623/0.006	0.034
		AVE[b]	−0.019	−0.003	
		RMS[b]	0.025	0.012	

Data are shown for three representative compounds (Structure 6). The actual study involved a total of twenty-five compounds. The overall errors quoted here are for all twenty-five

[a] X-ray values have been converted to r_g values. Additionally, 0.005 Å is added for the thermal libration correction

[b] Hyperconjugative effect excluded

[c] Hyperconjugative effect included

experimentally to varying degrees of accuracy from X-ray studies. The structural information is summarized in Table 2 [32]. When a comparison is made with each of the bonds mentioned, the MM4O value (not including hyperconjugation), in each case gives quite a long bond length for steric reasons (a, b, and c are 1.603, 1.565, and 1.589 Å, respectively). However, these are all shorter than the corresponding experimental bond lengths (by −0.018, −0.006 and −0.028 Å, respectively). Because the error here is systematic, it certainly suggests that these MM4O bonds are calculated too short. As a calibration, the remaining bonds in the molecule that are not expected to hyperconjugate have MM4 values that agree on average with those found by experiment.

When hyperconjugation was included in MM4, using the parameters developed from the data given earlier regarding propene and 1-butene, and this version of the program was used to calculate the structures of the same molecules, the structures were the same or very similar for the most part, but the specific bonds mentioned each stretched out further to give the values shown in the column labeled MM4. In each case the errors between MM4 and experiment were much reduced, and the hyperconjugative stretching effect in the three cases was calculated to

be 0.015, 0.009, and 0.034 Å. A much longer table of similarly related numbers was collected in the literature [32], but the above shows the important facts. Namely, if hyperconjugation is not included in the MM4 calculation, the calculated bond lengths are systematically too short, but they stretch out to the experimental values when hyperconjugation, based upon the small molecule parameterization mentioned earlier, is included. Note that these stretchings can be very substantial, up to 0.034 Å. Hence if our molecular mechanics model is to reproduce experiment (or ab initio calculations), this effect certainly needs to be included.

If we look again at the hyperconjugative structure of propene (Structure 2), we note that the hydrogen becomes positive and the bond from that hydrogen to carbon weakens as that resonance occurs. But notice also that the other carbon at the end of the chain becomes negative. Suppose instead of carbon, we substitute another atom there, one that will better accommodate negative charge? Should not the effect then be magnified?

Instead of propene, then, let us repeat the calculation of the C–H bond length for the rotating methyl group in acetaldehyde. The appropriate resonance forms are as shown in Structure 7:
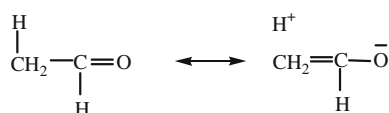
Structure 7

Evidently, the C–H bond should hyperconjugate more strongly in acetaldehyde than it does in propene, and the C–H bond length difference as we go from 0° to 90° in torsion angle should increase more. And that's what we find. The calculations show that in this case the C–H bond length increase in acetaldehyde is 0.0047 Å, versus 0.0030 Å in propene. This particular type of bond stretching has also been referred to in the literature as the *carbonyl effect* [34].

The weight of the above evidence, in the author's estimation, convincingly favors not only the existence of hyperconjugation, but also outlines part of its ubiquitous existence in organic chemistry. This is not a large effect in simple cases like propene, but it is clear and understandable, something that one expects should happen, and it does happen. And it can become a large effect in some cases. This effect is not observed in molecular mechanics calculations when a simple diagonal force constant matrix is used. So how, then, do we allow for this effect in molecular mechanics? How this is done is straightforward in principle, although somewhat complicated in detail. Look at, for example, acetaldehyde, Structure 7. The hyperconjugative resonance form is shown on the right. In this structure the C–H bond of the methyl group that is perpendicular to the plane of the double bond shows a maximum stretching, as in the propene example. The C=O bond also is stretched, while the C=C bond shrinks, in accordance with the resonance form. So we know qualitatively what happens. It can be represented in the force constant matrix by three cross-terms, one for each bond, which are torsion-stretch interactions. We know that the torsion part in each case will contain a V_3 term, because of the symmetry of the molecule. It may also contain a V_1 term (as in the propene example). We can choose these terms in order to fit the quantum mechanical bond lengths calculated for acetaldehyde. Thus in the molecular mechanics model, the torsion-stretch interactions are represented by the series of cross-terms. Similarly, torsion-bend interactions are represented by the appropriate cross-terms, and their signs and the symmetries are evident, since the resonance goes from a strictly sp^3–sp^2 type structure for the CH_2–C single bond, toward a structure that would be (in the limit) an sp^2–sp^2 hybridized structure for that bond.

We can then test how the MM4 model works for predicting the structures of a wide variety of compounds, and the abbreviated results shown in Table 2 are representative.

These cross-term parameters are transferable from one molecule to another just as the diagonal elements are.

The last fact is important. We can also obtain the total values for each of these off-diagonal matrix elements from quantum mechanical calculations, but there is no practical way available for breaking down these terms directly from the quantum mechanics into the familiar chemical effects of the organic chemist. The problem is that in the general case the matrix element contains not only the contribution from this effect, but also contributions from any other effects present, together with van der Waals and electrostatic contributions. But we know all of this from the MM4 model, because that is how we constructed the matrix element in the first place!

Negative hyperconjugation

Negative hyperconjugation can be subdivided into some special cases, of which we will mention specifically the Bohlmann effect [4c, 35, 36], and the anomeric effect [4d, 37–39]. Each of these is well known, and numerous papers including quite a few reviews have been written on them. Most of these above mentioned effects were discovered by experimentalists, or at least by people looking at experimental data. They can be divided into steric effects and electronic effects. More recently, each of them has been studied by methods of quantum chemistry. Hence we have a good overview of what each of these effects is all about. Each of the electronic effects involves a reasonably strong interaction by a substituent group on a molecule which causes a shift in electron density. This shift of electron density can be largely understood in terms of the electronegativities of the atoms or groups involved. These electronic effects can be subdivided into inductive and resonance effects. The geometrical consequences of those shifts can usually be rather easily rationalized in terms of molecular orbital theory. In a sense, this constitutes a solution to the problem of understanding these effects.

Bohlmann effect

This effect was observed and studied by Bohlmann in the infrared spectra of alkaloids in the 1950s [4c, 35, 36]. To start with the most simple example, consider methylamine, Structure 8. The lone pair on nitrogen in the ground state is anti to a hydrogen on the attached methyl, and gauche to the other two hydrogens. The C–H stretching frequency of the anti hydrogen is lowered about 150 cm^{-1} by the presence of the lone pair in the anti position. This moves that frequency out away from the other C–H frequencies (which in most molecules form a partially resolved envelope around 2,950 cm^{-1}), so that it is conspicuously obvious. The reason for this large frequency shift can be

Structure 8

gauche   anti
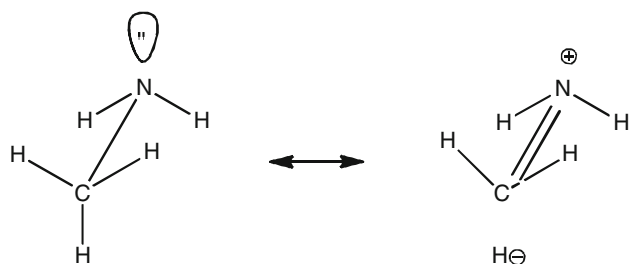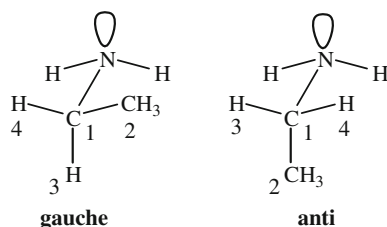
Structure 9

understood in terms of the resonance shown. The C–N bond becomes shorter and of higher bond order, and thus stronger than usual. The C–H bond indicated becomes correspondingly weaker, longer (by 0.007 Å relative to the other C–H bonds), and its stretching frequency is shifted lower. This conspicuous frequency shift identifies the stereochemistry of the hydrogen in question, and was of obvious use in natural product work.

If we next consider ethylamine Structure 9, the molecule has two conformations which are designated as gauche and anti (of the methyl with respect to the lone pair). The gauche conformation shows a large shift to lower frequency of the C–H hydrogen indicated as H_3 for the same reasons as described in the methylamine case. The anti conformation has the methyl group so located with respect to the lone pair. Correspondingly one would expect, and it is found, that the C_1–C_2 bond here similarly stretches, and its stretching frequency is reduced by some 38 cm^{-1} relative to the C_1–C_2 bond in the gauche conformation. Pertinent numerical data are given in Table 3. If we examine these data number by number, what we expect is indeed, at least pretty much, what we find.

The Bohlmann effect was first noted with the C–H stretching frequency in amines because the shift is dramatic, and it occurs into an otherwise almost vacant region of the spectrum. While the earliest case discovered involved C–H bonds on a carbon attached to nitrogen in amines, the effect is much more general than that. With a C–C bond properly oriented with respect to the lone pair there is a similar shift, but it is smaller, and it occurs in a much more crowded part of the spectrum and hence is less obvious [29]. But the result is similar. The changes in

geometry occur in a very general way when any sigma bond is anti to the lone pair on the nitrogen of an amine.

But there is more to it than that. Namely, the lone pair does not need to be on nitrogen. An oxygen or fluorine, for example, yields a similar effect. In those cases, however, the effect is less obvious, because the strong electronegativity of those elements induces substantial bond shortening of the C–H or analogous bond, which tends to cancel out the bond lengthening effect. However, we can and do account for these electronegativity effects separately in MM4. When all is properly taken into account, it is seen that a generalized Bohlmann effect occurs whenever the sigma bond is in an anti co-planar orientation with respect to a lone pair, regardless of the nature of the particular atoms involved [26–29]. In Table 4 are shown the distortions that occur in ethylamine, compared with those that occur in ethanol. (Note that because of the idiosyncrasies of organic nomenclature, it is the gauche form of ethanol that is analogous to the anti form of ethylamine.)

But the effect is still even more general than this. In the original Bohlmann effect the group which takes on the negative charge is a simple hydrogen atom (Structure 8). If this group is replaced by something that is more electronegative than hydrogen, then the effect becomes even stronger. A particularly well known example of this *generalized Bohlmann effect* has been long separately known,

Table 3 Geometries (r_e) of the ethylamine conformers (Geometric units Å and degrees. MM4 vibrational frequencies in cm^{-1} in parentheses)

Conformer	QM		MM4	
	Anti	Gauche	Anti	Gauche
C_1–C_2	1.526	1.519	1.527(849)	1.520(887)
C_1–H_3	1.094	1.099	1.095(2924)	1.104(2796)
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

QM, see footnote to manuscript title

Table 4 Bohlmann distortions for bonds (Å) and bond angles (°) in ethylamine and ethanol (r_e)

Bohlmann effect	Ethylamine[a]		Ethanol[b]	
	QM[c]	MM4	QM[c]	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 conformation minus gauche. The anti form has the lone pair anti to the methyl (Structure 9)

[b] Gauche conformation minus anti. The gauche form has a lone pair anti to the methyl

[c] See footnote to manuscript title

originally in carbohydrates, and later it was extended to many other classes of compounds. This one is called the *anomeric effect* [4d, 37–39].

Anomeric effect

In the original anomeric effect the lone pair is provided by oxygen instead of nitrogen, and the electronegative leaving group is also an oxygen, instead of a hydrogen. The two lone pairs on each oxygen both act as donors, and the two oxygens can both act as leaving groups, and all must be included in the full calculation. Originally the anomeric effect was calculated as an ordinary torsional effect (MM2) [40]. Later it was recognized that a better approach was the use of torsion-stretch/torsion-bend interactions in the force constant matrix [41]. Thus the anomeric effect is really just a special case of the *generalized Bohlmann effect*, or even more generally, of *negative hyperconjugation*.

In Structure 10 is shown again the methylamine hyperconjugation. This may be compared with the anomeric effect also shown. The analogy and the stereochemistry will be evident.

Additional effects also occur and must be taken into account in carbohydrate calculations [4f], but will not be detailed here (gauche effect, and delta-two effect).

The above is an overview of molecular mechanics as it exists today. With this material as a background, we would now like to discuss by examples two research studies that illustrate how molecular mechanics can improve our understanding of molecular structure, and of chemistry.

## Molecular mechanics examples

The structures of saturated hydrocarbon molecules can be described quite well by molecular mechanics by considering them as vibrating mechanical systems. The fact that this can be done was pretty well determined during the 1920s, and enabled Andrews to write his review [8] (1930) in which he outlined the subject that we today call Molecular Mechanics. He noted that while solution of the Schrödinger equation would tell us an immense amount about chemistry, it was computationally completely

impossible to solve it for most cases of interest. He also noted that if one used molecular mechanics equations instead, the computations would be enormously simplified. But they were still equally impossible to solve at a practical level at that time.

Andrews also noted that force constants were approximately transferable in many cases, which was early perceived as essential for the method to be useful. There are a few points of interest here. First, a hydrocarbon molecule is well approximated in general as a mechanical system. But the approximation is not expected to be perfect, nor is it. The major difference between the molecule and a purely mechanical system is that when the ideal mechanical system vibrates, Newtonian mechanics is expected to be directly applicable to springs and vibrating weights. But when the molecule vibrates, not only do the nuclei move, but the electronic system deforms to approximately follow that motion (orbital following). Depending on the circumstances, this will make a small or substantial difference between the actual case and the ideal case. In practice it is found that the difference between the two cases is often (not always) small, but we really want to look at this in some detail, and understand just how good this approximation is.

There are a number of differences between a quantum mechanical calculation of a molecular structure, and a similar molecular mechanical calculation. Some of these differences are clear enough. A particular difference that we will mention at this point is the following. When we carry out a quantum mechanical calculation, if we are going to compare the results with experiment there are a number of constants that we need to know. These include things like Planck's constant, the value of *pi*, etc. These things are constants of nature, and from the viewpoint of the chemist, they have generally been accurately determined and are well known. Similarly, if one wants to do a molecular mechanics calculation, there are constants that need to be known. These constants depend upon the force field, and different force fields in general require different constants. The problem is that these are not independently known. They are not just constants of nature, rather they are also constants of the force field. While we could determine a force field that would accurately describe a

Structure 10

Methylamine

Dimethoxymethane
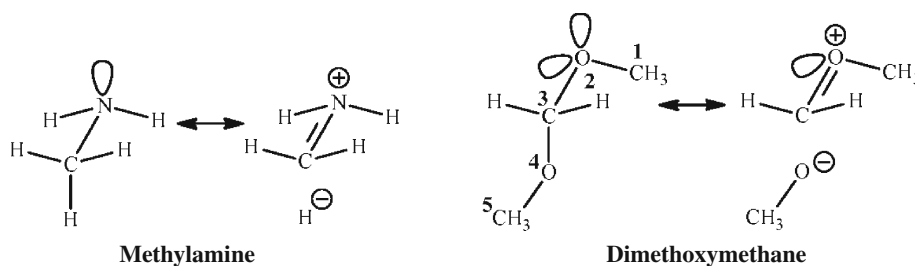
particular molecule, we have to already have an accurate description of that molecule in order to determine the constants required for the force field. While it is interesting that we can rather accurately describe a molecule with a classical mechanical molecule force field, it is not particularly useful, since we needed to already know at the outset the things that we can then calculate from the force field. For all of this to be really useful, the force field has to be "transferable" from one molecule to another. Then one can determine the needed constants from a limited set of small molecules, and subsequently use the force field to study molecules in general. As late as the 1970s there were many chemists, especially spectroscopists, who did not believe that really useful transferable force fields could be developed. They drew this conclusion by looking at the then currently available force fields, and how they frequently failed to accurately reproduce vibrational spectra for molecules, apart from those explicitly used to develop the force field. It turns out that the non-transferability conclusion was not exactly correct. It's not that it is impossible to develop an accurate general force field. It is impossible to develop an accurate *Class 1* (harmonic and diagonal) general force field. As it turns out, when the approximations are properly made, the degree of transferability of the force field is quite high. The result is that molecular mechanics is indeed a useful method, and generally can be developed to give results that are for the most part of chemical accuracy. But the devil is in the details of just how these approximations are made.

Electronic computers [4g] were unknown in the 1930s. To solve typical problems numerically by hand calculation, using the harmonic approximation is usually easier by an order of magnitude than it would be if one used a higher approximation. The difference in the work required here is so large that those who actually solved numerical problems did not ordinarily even think of higher approximations, beyond knowing somewhere in the back of their minds that such better approximations were in principle possible. As long as one deals with strainless molecules, the harmonic approximation does reasonably well for structural calculations. Those who looked at this method in work prior to the 1940s looked almost exclusively at vibrational spectra only. They could measure vibrational spectra down to an accuracy of about 1 cm^{-1}, for small molecules in favorable cases. This corresponds to a very tiny amount of energy (0.003 kcal/mol), which is far less than ordinary "chemical accuracy," (usually 0.1–0.5 kcal/mol in almost all cases except for spectroscopy). So the idea of the transferability of constants based on spectroscopy is misleading, when one is considering transferable constants used for structural chemistry. One does not need constants that are transferable to spectroscopic accuracy for most structural work. One only needs chemical accuracy.

Another point that was generally overlooked in the early work was that an actual *force constant* (that is, the matrix element in the force matrix) and the *force parameter* used in the equations given above (l_o, θ_o, etc.), are closely related, but they are not exactly the same quantity. Unfortunately, the practice was, and still is, to use the symbol k to represent both the stretching constant and the stretching parameter, for example. While the difference between the values of the two is typically small in many simple cases, it can become much larger, particularly in systems where electrostatics, and/or van der Waals repulsions come into play.

Class 1 force fields, when parameterized carefully, can be made reasonably accurate for molecules that are strainless, or at least of low strain energy. Force fields of this type are consequently used very often when one is dealing with very large calculations, such as dynamics problems involving proteins. This is a separate area of molecular mechanics from what will be discussed in the following. Here we wish to discuss problems involving ordinary (modest) sized molecules (say up to about 100 atoms or so), and we wish to be able to calculate properties of interest to "chemical accuracy." Can we do this? We usually cannot if we use a Class 1 force field. But if we use a Class 3 force field, we can in many, probably most, cases. So it is in practice useful to solve some problems using molecular mechanics in this way, but other problems are better solved by other methods. And importantly, one can usually tell by inspection which category of problem it is that one is looking at. The Class 3 force field is useful not only for obtaining numerical data, but it also can give these data *broken down into a context that is familiar to the organic chemist*. Hence it tells us not only what a structure is, but *it also tells us (rather accurately) why it is like that, in terms of the molecular mechanics model*.

We will give here some examples that illustrate specific effects which can be accounted for in molecular mechanics, and therefore can be understood not only in a qualitative sense, but also with useful numerical values. When organic molecules are being considered in a general way, it is common in a particular case to have several different steric and electronic effects operating at the same time. If they are all acting in the same direction, it is easy to make a qualitative prediction as to which way the result will move. But frequently they are interacting in different directions and even a qualitative result becomes unpredictable. A quantitative understanding of these effects can lead to a quantitative understanding of the molecular system, in familiar terms.

The applicability of molecular mechanics to the study of organic molecules is potentially vast. We will here outline just two applications to illustrate the usefulness of this approach.

α-Haloketones

The historically important example here was α-bromocyclohexanone, Structure 11.

The conformational structures of this and many related molecules have been studied and described in countless papers. The importance of steric effects in organic chemistry was recognized long ago (Newman [42]). But the importance of electrostatic effects in neutral molecules came somewhat later, beginning in part with a series of papers by Corey [43] where he stated that we knew a great deal about steric effects, and it was time to try to understand better how electrostatic effects impacted organic chemistry. At the time of his initial work electronic computers were not available, and experimental methods were basically those of the nineteenth century, with the availability of only a few more modern methods, particularly infrared spectroscopy. With these limited tools, Corey was able to learn a great deal about the effects of electrostatics on conformations in α-bromocyclohexanone, and subsequently in many related molecules. This work was briefly reviewed recently [4h].

To study a molecule as complicated as α-bromocyclohexanone by molecular mechanics, one must previously have studied a number of small molecules that constitute the component pieces of structure contained in the molecule of interest. Both alkyl bromides and ketones were classes of compounds that were well studied with early force fields and then with MM4 during the 1990s. Accordingly, to study α-bromocyclohexanone we already had most of the information required in the form of a transferable parameter set. The only remaining parameters required were those that involved both the ketone and bromine units at the same time. These were determined from quantum mechanical calculations on 3-bromo-2-butanone [4h].

Molecular mechanics calculations usually give us two different major kinds of information. First, they give us the total energies of the different conformations, broken down into component parts. These total conformational energies can be compared directly with experiment. The component parts of these energies are not directly available experimentally, but are useful as they lead to understanding. Second, they give us the structures of the different conformations, and in this case these show conspicuous and
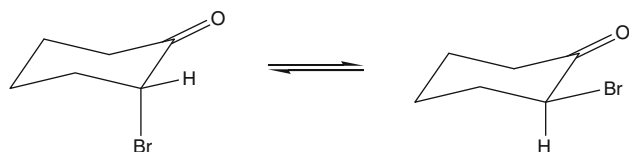
important differences. These structures are not accurately known experimentally, but they are known from quantum mechanical calculations, with which the MM4 calculations may also be compared. We can also compare the vibrational spectra from the MM4 and QM calculations with those from experiment.

First, we want to be sure that the structures obtained from the MM4 calculations adequately reproduce the quantum mechanical structures. From previous work we believe that the bond lengths obtained from the MM4 calculations are generally accurate to within about 0.003 Å. Vibrational frequencies are generally accurate to about 25 cm^{-1}. The quantum mechanical level used here (with some standard corrections for systematic basis set/correlation truncation errors [4i]) generally show about the same accuracy as the MM4 calculations. The MM4 calculations were found to be in reasonable agreement with both the QM calculations, and to the extent that it is available, the experimental information. The vibrational frequency comparisons between the MM4 and QM calculations are also noted. Finally, of particular interest is a comparison of the conformational energies calculated by MM4, both with respect to the QM energies, and also with respect to experiment.

In Fig. 2 are shown pertinent bond lengths for cyclohexanone and the conformers of α-bromocyclohexanone (left column of structures). These values were calculated by MM4, and also by QM (in parentheses). The agreement between the two sets of calculations is generally to
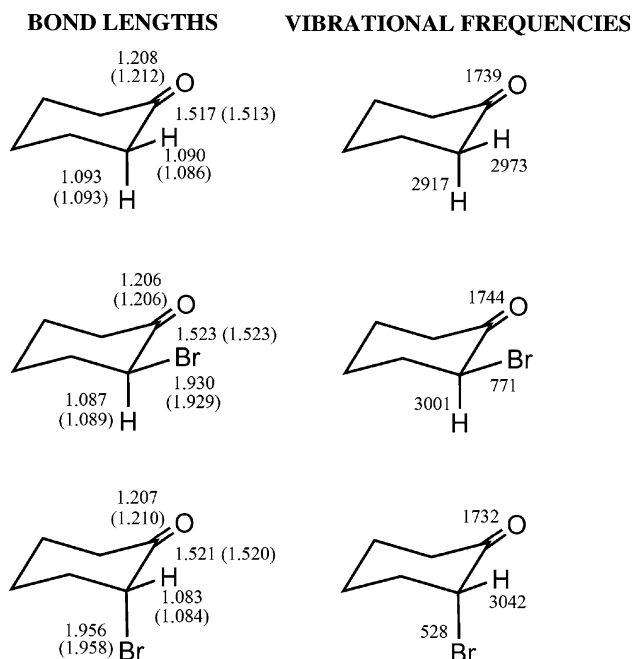
Structure 11

Fig. 2 MM4 (QM) bond lengths (Å) and stretching frequencies (cm^{-1}) for cyclohexanone and α-Bromo derivatives

about $\pm$ 0.003 Å, which we would refer to as "chemical accuracy."

We will first examine these structures in detail, and try to delineate the differences between them, mainly on the basis of some of these Chemical Effects. Subsequently we will examine the energetic consequences that accompany the structures.

There are three different Effects that are important here. These are (a) electronegativity effect; (b) carbonyl effect; and (c) what we will call "Corey resonance." The latter two effects are both examples of hyperconjugation. We will briefly summarize each of these effects.

Electronegativity Effect: This has been discussed previously. The bromine and the carbonyl group each induce electronegativity changes that lead to bond shortenings and angle bendings in their vicinities. These are accompanied by energetic changes and corresponding changes in the vibrational spectra.

Carbonyl Effect: A special case of simple hyperconjugation. It results when an alkene carbon is replaced by an oxygen as was discussed earlier for acetaldehyde (Structure 7).

Corey Resonance: This jargon simply means the hyperconjugative effect between the bromine-carbon single bond and the pi system, as shown in Structure 12.

Consider first the cyclohexanone molecule as our standard (Fig. 2, upper left). The C'=O and C–C' (where C' is used to represent the carbonyl carbon) bonds have the lengths shown. The hydrogens on the alpha carbon have bond lengths which are of interest. A resonance structure can be written for cyclohexanone itself involving hyperconjugation (the carbonyl effect) with the axial alpha hydrogen. The equatorial C–H bond and the carbonyl are essentially coplanar and hence do not show this resonance for symmetry reasons. The result is to make the C–H bond of the hydrogen in the axial position longer than that of the corresponding equatorial hydrogen. This is found both by MM4 and QM calculations.

When we add a bromine into the system, (lower two structures in the left column of Fig. 2), the bromine first of all exerts a powerful electronegativity effect, which causes all of the bonds at the alpha carbon to shorten considerably, and those at the beta carbon to shorten somewhat. So the alpha hydrogens on the carbon with the bromine are shorter in the *alpha*-bromocyclohexanone conformations than they
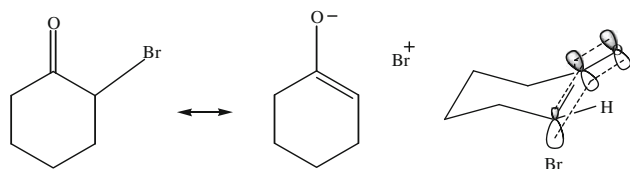
are in cyclohexanone itself. The *alpha* hydrogen in the equatorial bromo conformation is axial and can also undergo the carbonyl effect resonance, so it is longer than the corresponding equatorial hydrogen (1.087 vs. 1.083 Å). There is considerable van der Waals repulsion between the bromine and the rest of the molecule which causes the C–C' bond to stretch out in both of the bromo ketone conformations relative to cyclohexanone. But the axial bromo conformation undergoes Corey resonance, which causes the C–C' bond to shrink back again somewhat, so that the axial bromide ends up with that bond slightly shorter (1.521 Å) than the equatorial (1.523). All of these changes are small, but in the expected directions, and in agreement with those in the quantum mechanical structure.

There is one more thing that that is pertinent here. These are the vibrational stretching frequecies of the various bonds, which are shown in the right-hand column in Fig. 2. The cyclohexanone carbonyl frequency calculated by MM4 is 1,739 cm^{-1}. This number increases somewhat (to 1,744) for the equatorial bromine, and decreases somewhat for the axial bromine conformation (1,732).

The fact that the axial bromocyclohexanone has a lower carbonyl vibrational frequency than the equatorial was the critically useful diagnostic test that Corey had available for readily determining the conformations of these molecules in his studies. The explanation that he offered as to why this difference was found was straightforward. A ketone structure is often approximated as the sum of two resonance forms (Structure 13).

If there are two dipoles as here, they can be written as shown on the left in Structure 14.

The actual structure of the molecule is expected to be a combination of these two resonance forms, mainly the one at the left. But the C=O dipole in the right resonance form points in the same direction as the charge separation (another dipole) in the resonance form. Thus the importance of this resonance structure should be diminished in
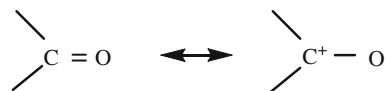
Structure 13
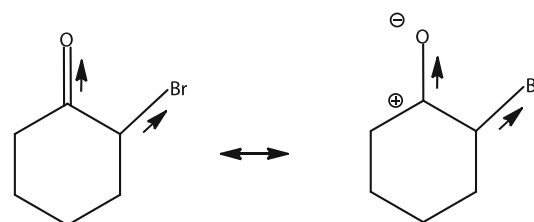
Structure 12

Structure 14

the equatorial conformation where the two dipoles are close together, relative to the axial where they are further apart and pointing more away from one another. This would increase the weighting of the resonance form on the left for the equatorial conformation in Structure 14 to reduce the electrostatic repulsion, making the C=O bond shorter, stronger, and raising its stretching frequency. This explanation was proposed by Corey, is straightforward, and was accepted for many years. But alas, it turns out not to be that simple. MM4 calculations show that modest changes in the magnitude of the dipole moment of the C=O bond do not cause detectable changes in the C=O bond lengths or in the stretching frequencies of the bromoketone conformers. So what really happens here? First, the electronegativity effect of the bromine shortens the C=O bond and makes it stronger, independently of conformation. This raises the stretching frequencies of both conformations. But the axial conformation also undergoes Corey resonance, which lengthens the C–O bond back out again, lowering the frequency back down. The carbonyl effect also lowers somewhat the C=O stretching frequency of the equatorial bromoketone. The combination of all of these effects yields the results shown. The equatorial frequency is raised by a small amount and the axial frequency is lowered a larger amount by both the MM4 calculation and experiment.

The C–H stretching frequencies are also shown (Fig. 2, right-hand column). As usual, the shorter bond has the higher stretching frequency. Looking at cyclohexanone itself, the shorter C–H bond should be the one that is not undergoing the carbonyl effect resonance, namely equatorial. The equatorial C–H frequency is indeed higher than the axial (2,973 vs. 2,917). If we look at the equatorial bromide, the hydrogen is axial. And the bromine raises the vibrational frequency still further from the electronegativity effect (up to 3,001 for that hydrogen). In the axial conformation (where the hydrogen is equatorial) it raises the C–H frequency all the way up to 3,042 cm^{-1}.

Finally, the C–Br stretching frequency is reduced because of the Corey resonance in the axial conformation relative to the equatorial (528 vs. 771 cm^{-1}). It may be mentioned that the frequency assignments for the C–Br bond are not as clear here as one would like. The problem is that the bromine does not really vibrate against the molecule as a hydrogen does, but rather the bromine pretty much sits still because of its high mass, and the molecule vibrates against the bromine. Hence there is much coupling of various frequencies where many things move at the same time. But the numbers do come out as shown.

We conclude from Fig. 2 that the MM4 model accurately calculates the structures of cyclohexanone and the two α-bromocyclohexanone conformers. It also calculates correctly the vibrational frequencies that are pertinent here. The interpretation as to why all of these things come out as

they do is straightforward, although tedious. But to really understand the structures of the bromo ketones, we have additionally to understand the energies of the two conformations. We know the difference between the energies of the conformations accurately, by both experiment and QM calculations. We want to be sure that MM4 reproduces that energy difference accurately. But MM4 can also tell us something that is not available either by experiment or from the QM calculations. Namely, it can tell us, in terms of the model, exactly why that energy difference comes out the way that it does. Corey's original conclusion was that that energy difference is predominantly due to electrostatics. The dipole–dipole repulsion in the equatorial conformation was much greater than in the axial conformation, and that determined the observed outcome, namely that the axial conformation was more stable.

The MM4 calculation gives us the energies of the two bromoketone conformations in terms of the sums of a number of component parts, namely stretching energy, bending energy, van der Waals energy, etc. To understand the energy difference between the two conformations, we can divide these component energies into two pieces, namely that involving the halo ketone fragment of the molecule, and that involving all of the rest of the molecule. Basically, the latter (the rest of the molecule) conformational energies just about cancel out. Things are twisted, bent, stretched, etc. but only a little bit in one conformation relative to the other. What we wish to examine are those few energies that involve the halo ketone part of the molecule, where there are real differences between the conformations. Inspection of the MM4 results shows us that there are six terms that we need to examine here. Of particular interest is the breakdown of the MM4 energies into the component pieces as are most readily understood by organic chemists. Table 5 shows these. Note that the total MM4 difference between the conformational energies in the gas phase is 1.30 kcal/mol, and the QM value is the same. Reading across Table 5 from the left, 0.54 kcal/mol of this energy comes from van der Waals repulsion. Contrary to what was believed when Corey did this work, although bromocyclohexane preferentially has the bromine rather strongly in the equatorial position because of van der Waals repulsions which are more serious when it is axial,

Table 5 MM4 component energies for bromocyclohexanones (kcal/mol) [4j]

	VDW	TORS	TOR/STR	TOR/BND	μ/μ	IND$_\mu$	E$_{TOT}$
Ax-2-Bromo	2.96	4.75	−0.38	−0.31	1.43	−1.30	7.15
Eq-2-Bromo	3.50	4.38	−0.09	−0.16	2.70	−1.88	8.45
Δ (E$_{eq}$ − E$_{ax}$)	+0.54	−0.37	+0.29	+0.15	+1.27	−0.58	+1.30

this is not true of bromocyclohexanone. In the equatorial conformer the bromine and oxygen have a particularly large repulsion between them (0.93 kcal/mol), which leads to the overall van der Waals interactions stabilizing the axial conformation by 0.54 kcal/mol. Corey noted that such a repulsion was a possibility, but he had no way to test this suggestion at the time. Corey's calculations correctly indicated that the dipole–dipole repulsion was more severe in the equatorial conformation, and he estimated this value at about 2.7 kcal/mol from hand calculations. MM4 indicates that indeed this repulsion is pretty serious (+1.27 kcal/mol) but much of this repulsion is canceled out by the induced dipoles in the molecule. Strong dipoles induce additional dipoles that oppose them when they are near to polarizable material. The hydrocarbon part of the molecule is somewhat polarizable, and the bromine is quite polarizable. The MM4 calculations say that the induced dipole energy difference is 0.58 kcal/mol, a little less than half of that of the direct interaction energies between the dipoles, and in the opposite direction. The net electrostatic repulsion is therefore 0.69 kcal/mol, favoring the axial (gas phase). So this number is only slightly larger than the van der Waals repulsion number, and in the same direction. Also note that the torsional energy is 0.37 kcal/mol, favoring the equatorial conformation.

Of special interest is the sum of the two numbers TOR/STR + TOR/BND. These are the energies of the stretching and bending distortions that are induced into the molecule by Corey resonance versus the carbonyl effect. They amount to 0.44 kcal/mol, which tends to stabilize the axial conformation. All together these energies reproduce the total energy difference calculated between the conformations quantum mechanically (1.30 kcal/mol). They also further say that if the dielectric constant of the medium around the molecule is increased, the equatorial conformation will be further stabilized, to a limit where the axial still remains more stable, but only by 0.59 kcal/mol. All of this is in good agreement with experiment, including the shift of the axial—equatorial equilibrium with the dielectric constant of the solvent [4k].

The detailed summation for the energy difference between conformations in the gas phase is given in Table 5. The total sum of the absolute values of these six energies is 3.20 kcal/mol, but they act in different directions, so that the net result is 1.30 kcal/mol favoring the axial. The MM4 model is thus in good agreement with the known energy information. This energy breakdown, we believe, tells the physical organic chemist what he really wants to do know with respect to the energetics of this α-bromocyclohexanone system. Similar experiments have been carried out for other α-halocyclohexanones (chloro [44] and fluoro [45]), and the conformational energy differences for them are also known experimentally.

These have not yet been studied in detail with MM4, but preliminary calculations indicate no reason to expect anything out of the ordinary will be found when such studies are carried out.

Potential surface for the cellobiose analog [46]

Cellobiose is a disaccharide which has an ordinary anomeric linkage between the anomeric carbon of one glucose molecule, and the C_4 carbon of a second glucose molecule. If we understand the potential surface of glucose methyl ether, then we might suppose that we would understand also the corresponding part of the cellobiose surface. This is a fairly large molecule computationally, containing eight hydroxyl groups. The latter add nothing of interest to the problem here, so for present purposes they have been deleted, and we will instead study the molecule that we refer to as the *cellobiose analog* (CBA), Structure 15 (hydrogens not shown).

The anomeric part of CBA which is of interest here is the $\Phi\Psi$ linkage. Quite a few, perhaps 40 or 50 molecules, having the CBA ring structure, but with various other substituents, have experimentally known crystal structures. We can construct a Ramanchandran plot for the $\Phi\Psi$ angles of the CBA potential surface as determined quantum mechanically (Fig. 3), and then for each of these experimentally known structures, we can include on the plot a mark for each of the geometries in question. What we see is that there is a single deep potential well centered approximately at Ψ −120°, Φ −70°, roughly oval in shape, and oriented north/south. There are also two other minima, about 3 and 4 kcal/mol higher in energy. The experimental points are located in the deepest potential well, and mostly within the 2.0 kcal contour. Perhaps two-thirds of them are within the 1.0 kcal contour. Considering the simplification of using only the CBA analog to generate the surface, and then fitting onto that surface this wide variety of structures, having only in common the CBA skeleton, the fit seems to be quite reasonable.

When this plot was originally prepared (2004), we thought that we understood the anomeric effect pretty well, and that the corresponding MM4O plot would be substantially the same. The MM4O plot is shown in Fig. 4.
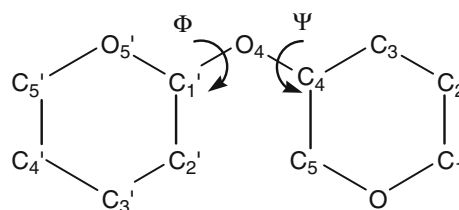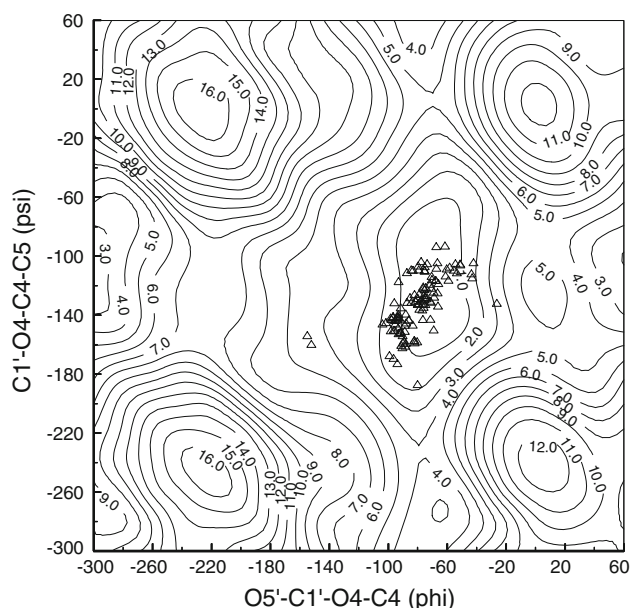

Structure 15

Fig. 3 Ramachandran plot of the CBA potential surface by (B3LYP/6-311++G(2d,2p)//B3LYP/6-31G*) calculations. The numbers on the contours are their energies relative to the minimum [46]
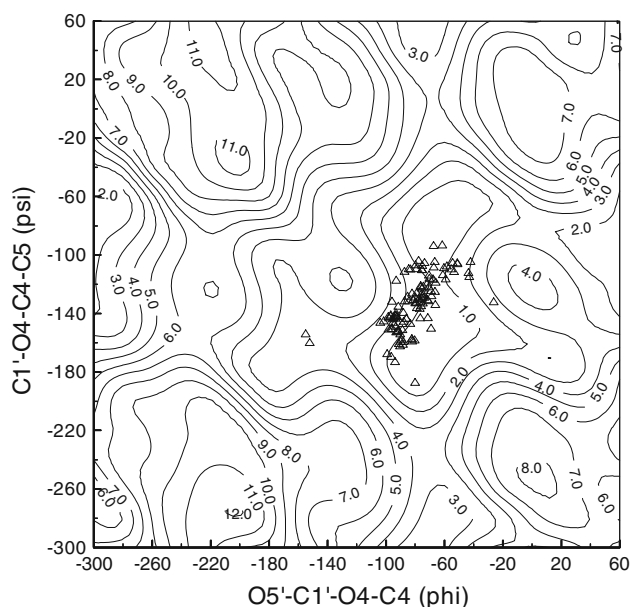

Fig. 4 Ramanchandran plot of the CBA potential surface by MM4O [46]

Indeed, there is a strong qualitative similarity. There is a single deep potential minimum (strongly bifurcated in the MM4O case), at the same place on the potential surface, and two more shallow minima, plus the four high mountains similar to those that are seen in Fig. 3. There is, however, a serious discrepancy regarding the way the experimental points fall into the MM4O minimum. Only about one-fourth of the points are actually below the

1.0 kcal contour, and about three-fourths of them are up on the side of the contour between the 1 and 3 kcal potential lines. It is also noted that the four mountains, which are from 11 to 16 kcals high in Fig. 3 (B3LYP), are in the 7.0–11.0 kcal range in Fig. 4 (MM4O).

Our conclusion was that the MM4O potential surface, while qualitatively OK, contained some hidden errors, and there was more to this problem than we originally thought.

There is one discrepancy between Figs. 3 and 4 here that is expected. Dispersion forces are not accounted for in a B3LYP calculation, and these tend to stabilize longer range van der Waals interactions. Hence the four "mountains" in the corners of Fig. 3 are expected to be somewhat too high, and they are indeed high relative to Fig. 4. But there is clearly a problem with the MM4O surface near the global energy minimum, which is of course the most important part of the surface. This is a case where molecular mechanics can be useful for teaching us things that we do not understand about chemistry.

The external anomeric torsional effect [46]

We had studied the anomeric effect itself in considerable detail over the years, and we thought that we understood it pretty well. But clearly something was left out of the MM4O calculation described by Fig. 4. The obvious place to look for a problem was not the internal part of the anomeric effect, but rather in the external part that had previously been studied in only a superficial manner.

In Structure 16 is shown the structure of dimethoxymethane, which is the usual starting structure that one examines when discussing the anomeric effect. The ordinary anomeric effect has to do with what happens between the two oxygens, but here we want to look at what happens outside of those two oxygens. All that we have outside of the two oxygens is a methyl group (twice over). Is that methyl group unusual in any way? It turns out that it is.

Suppose we compare the methyl group in methyl propyl ether with the methyl group in dimethoxymethane. (It is the methyl numbered C-5 in Structure 16.) Is the methyl group in the former compound affected when the further away oxygen (O-2) replaces the CH_2 group in the propyl part of the chain? In fact it is. The electronegativity effect of an oxygen is considerable when the oxygen is attached to an alpha carbon, but here it is attached to a beta carbon, and one might not expect that this effect would amount to much. However, one might expect that the torsion barrier for the rotation of the methyl group might be changed by the distant oxygen, and that this change in barrier height would be pretty small. It turns out this supposition is only partly correct. Thus the threefold rotational barrier of the methyl group in methyl propyl ether is calculated quantum
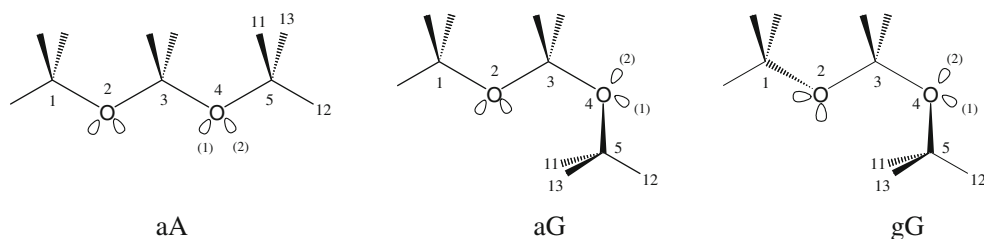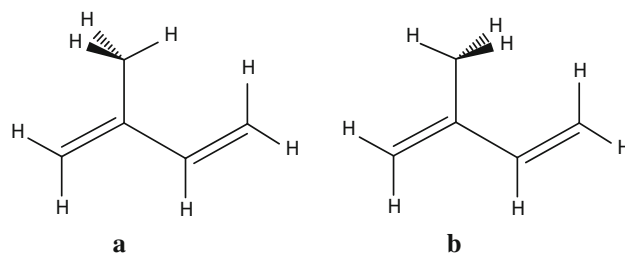
Structure 16

mechanically to be 2.32 kcal/mol compared to 2.22 kcal/mol for that in dimethoxymethane when both are in the aA conformation. But if one rotates the dimethoxymethane molecule about the C_3–O_4 bond to give the aG conformation, the methyl barrier (about the O_4–C_5 bond) drops to 1.52 kcal/mol (QM) while that in methyl propyl ether essentially remains constant. So what is really happening here?

As background for understanding the nature of the above problem, recall that in saturated compounds if a hydrogen eclipses another hydrogen (or carbon) on an adjacent carbon atom, this leads to (in effect) a repulsion, which results in a torsional barrier (the ethane barrier). On the other hand, in propene to take the most simple alkene example, when the methyl hydrogen eclipses the double bond, there is (relatively) an attraction rather than a repulsion, and the eclipsed form is the stable rotational form for that structure. If we generalize this, we find that for bonds of intermediate bond order (in between the bond orders of 1.0 and 2.0 in the previous examples), the lower energy always goes to eclipsing the bond with the higher bond order [47]. Thus propene has the double bond eclipsed. If we look at the molecule 2-methylbutadiene, Structure 17, we find that the ground state is the conformation in which the methyl group eclipses the double bond at the end of the chain, rather than the lower bond order double bond in the middle of the chain. Thus b is of lower energy than a.

Then in Structure 18, the bond order is higher about the 3,4 bond due to the presence of oxygen 2, as this makes possible the resonance shown. So the rotational barrier of hydrogen 6 about the 4,5 bond will be reduced from its usual value, as hydrogen 6 will have a greater tendency to eclipse the 3,4 bond. This rotational barrier will be lowered by about 1 kcal/mol (from QM calculations) which is the difference between the C_4–O_5 rotational barriers of methyl propyl ether and dimethoxymethane, brought about by the presence of oxygen 2 in a somewhat remote (β) position.

While this lowering of the 4–5 rotational barrier as in Structure 18 is easy to understand, what is happening here is really much more important that just that. As we know generally in hydrocarbons, if a C–H bond is induced to do something by an outside interaction, it is pretty sure that a corresponding C–C bond will also be similarly induced by
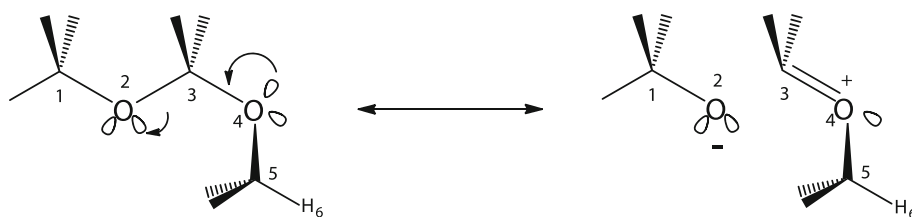

Structure 17

that same outside interaction. And that's what we find here. If we consider the rotational barrier in ethoxymethoxymethane (Structure 19), we note that what was the 3-4-5-H torsion in Structure 18 becomes 3–4–5–C in Structure 19. The 4,5 barrier is also significantly reduced. The height of this barrier comes into play in Figs. 3 and 4.

So if we go back to our small molecules, we have what we can call an *external anomeric torsional effect*, that we can represent in the force constant matrix by a torsion/torsion interacttion between the two torsion angles O_2–C_3–O_4–C_5 and C_3–O_4–C_5–C_6. To convert the MM4O program to MM4 then, we added this torsion-torsion term into the force constant matrix [46]. When we re-plotted the MM4O surface from Fig. 4 but this time using MM4 itself, we obtained the surface shown in Fig. 5. This is the correct molecular mechanics potential surface that should describe what was found quantum mechanically, and shown earlier in Fig. 3. When we compare Figs. 3 and 5, it is seen that they are much the same. The potential surface is a little more flat in the MM4 calculation than in the B3LYP calculation, and hence the MM4 1 kcal potential contour encompasses a slightly greater area, and indeed the fit of the experimental data by MM4 is noticeably better than the quantum mechanical fit, especially in the south-western corner of the minimum.

Now we can examine the difference between Figs. 5 and 4. This difference is shown in Fig. 6. This plot shows the energy of the external anomeric torsional effect plotted for the $\Phi\Psi$ change by itself, without all of the other things that happen in the molecule. Notice that there is a substantial hill right in the center of the diagram (in the crucial energy minimum region of the Ramanchandran plots). It has a
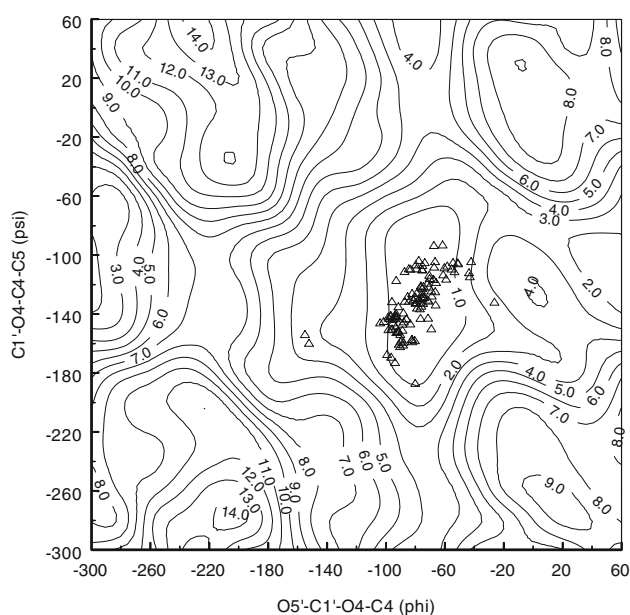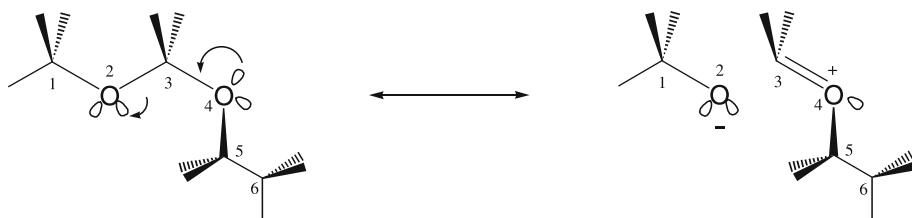
Structure 18

Structure 19

Fig. 5 Ramachandran plot of the CBA potential surface by MM4 [46]

Fig. 6 Ramanchandran difference plot of the CBA potential surface by (MM4O–MM4) [46]

height of 2.0 kcal/mol with the contour lines as shown in Fig. 6, but other parts of the surface have gone negative, and if we take the height of that hill relative to the zero energy of the surface (which is at −2.0 kcal/mol), the actual height of that hill is 4.0 kcal/mol! So in other words, although this effect is small in dimethoxymethane, when carried over to the more complicated CBA molecule it became quite a large number which severely distorts the potential surface. When this erroneous distortion is removed, the experimental data are fit even better than they were by the B3LYP surface.

Our conclusions here have wide implications in structural chemistry. Namely, molecular mechanics force fields, properly developed from small molecules so that they are transferable, can give good accuracy and considerable
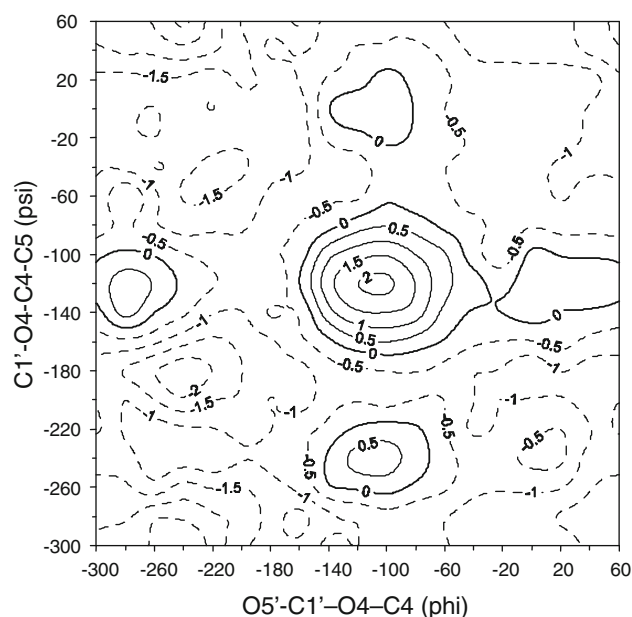
insight to why molecular structures are the way they are. We do not expect these force parameters to be transferable in an unlimited fashion, but what we have found over the course of many such studies is that they are more transferable than most chemists suspect, and the generation of such information can not only be useful in solving problems, but it relates those conclusions to easy-to-understand valence bond structures, as illustrated here.

Summary

Much of organic chemistry is most easily understood using valence bond structures and curved arrows. Molecular mechanics offers a quantitative basis for understanding

molecular structures from this viewpoint. A good (well developed, Class 3) molecular mechanics force field will usually give molecular structures that are approximately of chemical accuracy. When it fails to do so, there is a good chance that nature knows something that we don't.

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