3 Molecular mechanics

3.1 Introduction

The calculations outlined in the previous chapter, while offering a rigorous description of the molecule from both a structural and electronic point of view, suffer as a result of their computer inaccessibility. The amount of computer time to do the conformational analysis, including minimization, or to define a potential surface even for a small molecule, can be prohibitive in terms of both time and memory. When these problems are considered in tandem with the explosion of structural data in both the biological and materials fields, it is obvious that a different representation is required. In addition, it should be borne in mind that for many applications the detailed information supplied by the quantum mechanical calculations is of little interest, especially if only a molecular geometry is required. At all times one should be pragmatic as to which method would be the best for a given application.

Just as the 1960s witnessed an explosion in the application of quantum mechanical methods, there was a complementary interest in so-called "force field" methods for conformational analysis. The origin of these methods lies in vibrational spectroscopy, where the information derived from detailed analyses of vibrational spectra required the development of potential functions to describe the overall molecular behavior. Two different approaches were considered. In the first, the Central Force Field (CFF) method, the molecular vibrations are fitted to a function which was a sum of pairwise interactions, without reference to the covalent structure of the molecule. The obvious disadvantage of this approach is that although such a description is correct in terms of a quantum mechanical model of the molecule, it lacks the intuitive link with structure which chemists are more happy.

The second method, the Valence Force Field (VFF), provides such a description in that the vibrational data is fitted to a potential function consisting of bond length and bond angle dependent terms. This is much more satisfactory and has the advantage of allowing comparisons between molecular alike the CFF potential functions which will be very facile dependent. The major criticism of the VFF method is that the force constants produced must attempt to incorporate intramolecular interactions such as dispersion forces which result from electron correlation, and therefore it is not a simplification of the intrinsic vibrational frequency.

These spectroscopic force fields provided the ideal starting point for what is now called molecular mechanics. By bringing together features from both the CFF and VFF methods, it proved possible to derive energy functions which were at once chemically intuitive while still retaining the concept of through-space attractions and repulsions.

The theoretical basis of the molecular mechanics method can be derived by taking an alternative approach to the Born-Oppenheimer approximation that considered in molecular orbital methods. In this case the molecular motion is considered while applying a fixed electron distribution associated with each atom. To this end a model has been developed whereby a molecule is represented as a collection of spheres (possibly deformable) joined by springs. The motion of these atoms can then be described by the laws of classical physics and simple potential energy functions can be used. This allows much larger chemical systems (of the order of thousands of atoms) to be investigated.

Although this method of calculation sounds simple, the following caveats must be kept in mind. First, as the method neglects explicit representation of electrons, it is restricted principally to the description of neutral ground states. This also disallows the investigation of reactions. Secondly, the whole stream will only be as good as the potential functions and parameters used, much of the potential surface defined by the force field has little validity, as typically, only external (stable conformations, rotational barriers etc.) are used in the parameterization procedure.

3.2 The energy calculation

The molecular representation introduced in the previous section was one which treated molecules as a set of vibrating spheres. The next step is to define an energy function which is consistent with this concept and allows accurate calculation of molecular properties. The force fields commonly encountered today have resulted from a number of generations of development. Typically, more structural and thermodynamic data have become available, coupled with considerable increases in computer power, allowing an extension of the functional form of the energy calculation. As more terms are included, the accuracy of the force field increases.

The energy of a molecule is calculated as a sum of the non-bonded interactions present. Therefore each bond length, angle and dihedral is treated individually while non-bonded interactions impose the influence of non-covalent forces.

\[ E_{\text{total}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}} + E_{\text{non-bonded}} \]  

(3.1)

Here, $E_{\text{bond}}$, $E_{\text{angle}}$ and $E_{\text{dihedral}}$ are respectively the total bond, angle, dihedral and non-bonded energies. This is shown pictorially in Fig. 3.1.

Bend-stretch

The typical vibrational behaviour of a bond is near harmonic so its equilibrium value lies between dissociation (a length bond lengths) and $\eta^2$. The most accurate description of the Morse function

\[ E_r = \sum D_j \left( 1 - \exp\left(-\frac{r}{\lambda}\right) \right) \left( 1 - \exp\left(-\frac{r}{\lambda}\right) \right)^2 \]  

(3.2)
where \( l_c \) is the equilibrium bond length, \( E_b \) the dissociation energy, and \( k_l \) a force constant. However, the exponential calculation is computationally expensive therefore most force fields have adopted a simple harmonic function

\[
E_l = \sum k_l (l - l_c)^2
\]

where \( l \) being the stretching force constant describing the deformation. The bond stretch is treated in the same fashion as a stretched spring. This equation has obvious limitations in that it only approximately describes the actual behavior of the bond. Figure 3 shows, for example, that the extended bond is much too loose (see Fig. 3.2), while it provides an acceptable description of a very large deformation. When discussing minimization of potential energy we will see that this can be an advantage as this function can allow "over extended bond to remain intact.

Other variation on Eq. (3.3) have been made to accommodate more accurate long distance behavior. Most commonly this takes the form of an additional quartic term

\[
E_l = \sum k_l (l - l_c)^2 + \sum l (l - l_c)^4
\]

but this suffers from the problem of inversion at long distances. Attempts have been made to remedy this by adding a quartic term which reverses the linear term.

Bead angles

Historically, bead angles have been treated in the same way as bond lengths and are usually described by a harmonic function.

\[
E_\theta = \sum \frac{1}{2} k_\theta (\theta - \theta_0)^2
\]

As before, \( k_\theta \) is a force constant and \( \theta_0 \) the equilibrium value for the bond angle. Again, this term is not ideal for the full range of values observed as higher order terms must be added. In a strained ring system, however, it is usually not possible to use the constraints derived for unsaturated and cyclic molecules so separate three- and four-membered ring constants have been developed.

Dihedral angles

In very "stiff" force fields it was thought that this term could be omitted; in-plane energy differences would be too small result from non-bonded interactions. This soon proved to be impossible task and dihedral angle terms were explicitly included. The functional form of this term is as a Fourier series

\[
E_\phi = \sum V_n \cos n \phi
\]

where \( V_n \) is the rotational barrier height, \( \phi \) the periodicity of rotation (e.g. in plane \( \phi = \pi \), in other \( \phi = 2\pi \) and \( \phi = \pi \) for staggered minima and \( \phi = 0 \) for eclipsed minima. Fig. 3.3 shows the \( \phi = \pi \), 2\( \pi \) and \( 3\pi \) curves.

In the simple molecules above, a single term, summed \( n \) to all permutations, would suffice, but as the symmetry across the nonbonds bonds breaks down, \( n \) complexity of the energyprofile increases. These can be corrected by the inclusion of other Fourier terms. Consider butane as 1,2- disubstituted. Obviously the eclipsing separation of the two methyl substituents will be higher in energy than that between one methyl and one hydrogen, or between two hydrogens. Increasing the size of the C-C-C-C

in Fig. 3.3 shows the \( \phi = \pi \), 2\( \pi \) and \( 3\pi \) curves. Non-bonded interactions

The interactions discussed in the previous sections can also be grouped together as the bonded interactions, in the sense that they are defined by the connectivity of the molecule. The non-bonded interactions, on the other hand, are distance-dependent and are calculated as the net effect over all atoms with a \( k_\phi \) or greater separation. It is usual to consider these interactions by dividing two components, van der Waals and electrostatics. The former can be

\[
E_\phi = \sum \left( \frac{1}{r} - \frac{1}{r^6} \right)
\]

while the latter provides a quantitative measurement of the influence of polarity on the energy gap structure.

Many different functional forms have been used for van der Waals interactions but the most common is the so-called 12-6 or Lennard-Jones potential

\[
V_{\text{LJ}} = \sum \left( \frac{1}{r} - \frac{1}{r^6} \right)
\]

while the latter provides a quantitative measurement of the influence of polarity on the energy gap structure.

Other forces have been proposed for the van der Waals interaction, principally because the \( r^{-6} \) term can be too steep for less than optimal distances. These short contacts are important when investigating structurally

\[
E_\phi = \sum \left( \frac{1}{r} - \frac{1}{r^6} \right)
\]

short distances the repulsive term dominates. The theoretical validity of this function is discussed in most physical chemistry textbooks.
interatomic distances the function inverts and goes $n \to \infty$, an obvious danger in poorly constrained model structures.

The choice of function has tended to be driven by competing equilibriums. For a small molecule the number of intramolecular interactions is relatively small and the close range behaviour is crucial. In this situation the overhead involved in calculating $e_1$ as opposed to $e_2$ and the exponential is not too high. For a protein the number of interactions is considerably higher, but the contacts are likely to be close to equilibrium values. Using the Lennard-Jones function avoids the calculation of large numbers of square root and exponential (see 8.5) can be calculated from $e_2$. The 8–12 function also has the added advantage of equating fewer parameters.

The second component of the non-bonded potential is the electrostatic term. This is usually calculated using partial charges $q_{i}$ on the atom centres with the energy calculated using Coulomb’s Law

$$E_{el} = \sum q_{i} q_{j} / r_{ij},$$

with the dielectric constant $D$ taking a value appropriate to a given solvent or made proportional to the distance $r_{ij}$ between the charges. The electrostatic contribution is one of the most controversial in molecular mechanics and will be discussed further in part of the parameterisation procedure.

Other terms

The five terms outlined above constitute the core of almost all molecular mechanics force fields. In some cases the entire energy function. In many situations, however, it is necessary for additional terms to be included.

For systems where hydrogen bonding is vital for stability, e.g. biological molecules, it has been common to include an additional, explicit hydrogen bond energy function to ensure correct geometries. In certain protein force fields this takes the form

$$E_{HB} = \sum (E_{ij} + E_{ji})$$

where $E_{ij}$ is the force constant and $x$ the height above the plane. A modified version of this type of function can also be used as a chirality constraint.

Thus far, all of the potential functions have been concerned with isolated features of molecules. If any structural changes are correlated then, in this type of force field, they must result from a combination of appropriate features. If only structural and thermodynamic data are required to be reproduced, this form of the force field (so-called second generation) is adequate. However, to fit, in addition, vibrational frequencies, the coupling between geometric features must be explicitly included in the representation of the molecule.

If one considers the structure of butane (Fig. 5.3) it is clear that in the conformation changes from and to the there is a change in the C=C bond length and an opening of the C-C=C-C bond angles. The best way to incorporate this kind of feature into the force field is via a stretch-bend interaction. This has the effect of restraining distortion of the angle through compensatory bond stretches. A potential term of this type allows greater flexibility in the non-bonded angle terms which, if fitted to butane data, would otherwise give poor ethanol geometries.

Other commonly used cross terms include bend-bend and torsion-bend. The functional forms are as follows:

stretch-bend

$$E_{sb} = \sum k_{bb} (\theta_{ij} - \theta_{ij}^0)$$

bend-bend

$$E_{bb} = \sum k_{bb} (\theta_{ij} - \theta_{ij}^0)(\theta_{ij} - \theta_{ij}^0)$$

torsion-bend

$$E_{tb} = \sum k_{tb} (\phi_{ij} - \phi_{ij}^0)(\phi_{ij} - \phi_{ij}^0)$$

where $\theta_{ij}$ and $\phi_{ij}$ are the angles in the dihedral and torsion link.

A force field including all of the valence, non-bonded and cross terms can be parameterised to give very close agreement with experiment for a large number of properties. Problems may occur, however, when highly polyatomic groups or ions are present. In this situation the static charge distribution assumed in the electronic term is no longer realistic and an adequate additional parameterisation will be required. Also, the van der Waals potential assumed must pairwise interactions but more complex, many-body terms might also come into play. Attempts to include these effects are still at an experimental stage and no simple representation can be prescribed.

The final situation to be considered is the presence of delocalised $\pi$ systems. This does not have any bearing on protein and other biological systems as the $H$ systems are isolated from other unsaturated regions, e.g. aromatic amine-amides and DNA bases. This allows the use of large twofold twistor constants which will resist deformation out of the plane without stiffening with the conformational mobility of other regions of the molecule. For many small, saturated molecules, and systems based upon pyrrolines, this is not possible, unless one creates a new set of atom types for every instance. Here, some account must be taken of the degree of partial
3.3 Energy minimization

If one has generated a model using molecular graphics, based upon standard molecular fragments, or from a z-matrix of typical internal coordinates, the energy obtained from the molecular mechanics calculation is likely to be high and not representative of the actual structure. To obtain more reliable geometries and energies one must attempt to minimize the energy of the system. This problem can be approached in two ways: either one can vary the actual internal coordinates to find their optimum value, or, as is more common, work in Cartesian coordinate space and optimize the atomic positions subject to the restraining forces generated by the molecular force field. Since most minimization methods require first, and sometimes second, derivatives of the energy the latter method is more convenient and the potential functions are easily differentiated.

A second issue which must be addressed is local versus global minimization. Given that there are three degrees of freedom per atom, for a molecule of N atoms there are 3N·6 variables to be minimized (subtracting those due to rotation and translation). A multi-dimensional problem of this nature is further complicated by the presence of many local energy troughs on the potential surface which are minima in a mathematical sense, however, they are higher in energy than the lowest energy state, or global minimum. This situation manifests itself even in the simple rotational potential for a 1,2-di-substituted ethane (Fig. 3.6). Clearly the gauche (ga = 60°) conformation is stable but the molecule's preference would be for the trans conformation. This atomic trivial example highlights perhaps one of the most difficult problems in computational chemistry: how does one find the global minimum (and how can one be certain that it is, in fact, the lowest energy structure)?

Many of the minimization programs currently in use today are based upon the mathematical principles of the Newton-Raphson method. This requires first and second derivative information about the energy surface, but a family of algorithms exist which use different approximations to the second derivative matrix (the Hessian). An important property of the functions used for force field calculations is that they are continuous and differentiable. From simple calculus we know that the condition for a minimum on a curve, the point \( x^* \), is that the first derivative equals zero, i.e.

\[ f'(x^*) = 0 \]  

(3.13)

Since our starting point is \( x \) and not the minimum \( x^* \) we can write

\[ x^* = x + x \delta x \]  

(3.18)

where \( \delta x \) represents the changes which \( x \) must undergo to reach the minimum value. The condition for the minimum can therefore be written in terms of \( \delta x \)

\[ f(x + \delta x) = 0 \]  

(3.17)

and expanded as a Taylor series

\[ f(x + \delta x) = f(x) + f'(x)\delta x + \frac{1}{2} f''(x)(\delta x)^2 + \ldots \]  

(3.18)

which is also set equal to zero. Tayloring the Taylor series after the second order term gives

\[ f(x + \delta x) = 0 \]  

(3.19)

Rearranging Eqs. 3.19 gives the expression for the change which must be made to \( x \) to reach the minimum

\[ \delta x = -f'(x)^{-1}f''(x) \]  

(3.20)

which can be substituted back into 3.16 to give

\[ x^* = x - f(x)^{-1}f''(x) \]  

(3.21)

This is the simple one dimensional case. When considering molecules, each atom has three degrees of freedom - \( x, y, z \) and the term \( f''(x) \) must be replaced by a \( 3N \times 3N \) matrix \( H \) containing terms \( H_{ij} \), the derivatives of the potential energy \( V \) with respect to a change in coordinate \( i \). The corresponding second derivative matrix is constructed using all the cross-derivative terms \( H_{ij} \), involving each coordinate. Since matrices have replaced the single values in Eqs. 3.21, it is no longer possible to carry out the simple division. Fortunately standard computational procedures exist to derive the inverse of the Hessian matrix and the second term in Eq. 3.21 can be replaced by \( H^{-1}F \) hence \( H^\dag \) represents the inverse of the Hessian.

It should be noted that by truncating the Taylor series the assumption is made that the minimum is exactly quadratic in behaviour. For a complex surface this will not hold true far from the minimum but will be a better approximation as it moves closer. This limits the calculation to be carried out in a successive, iterative fashion, rather than reaching the minimum first time.

When working with small molecules (\( \leq 30 \) atoms) this approach is efficient and will converge after relatively few steps. As the number of atoms is increased, the number of matrix elements in the Hessian goes up rapidly.
making the calculation much slower. Additional problems with computer
memory requirements for the storage of the Hessian may also be a severe
limitation. This has necessitated the application of less efficient, but more
practical algorithms, usually through an approximation of the Hessian.
These include neglecting off-diagonal interactions between atoms (block
diagonal Newton-Raphson), and the diagonal Newton-Raphson method which only
calculates diagonal values, neglecting correlation between the three
degrees of freedom for a given atom.

A much more severe approximation is the Hessian to consider it as a
constant. This produces the steepest descent method which is driven purely
by force gradients along the potential surface. If one imagines the energy
surface as being rather like a bumpy landscape then the most reliable way to
find a valley, or energy well, is to follow the gradient downhill. As the
gradient method has no information about the local curvature of the energy
surface, minimization by this method slows considerably as the gradient
decreases. Close to the bottom of the potential well the energy
differences can be rather small, however, the forces acting on the molecule
can still be relatively large compared to those observed by a less approximate
method. The principal advantage of the steepest descent method is that it is
very efficient when very large forces are present, far from a minimum,
making it a robust choice to tidy up model geometries prior to further
refinement by another method.

It is possible to exert more control in first derivative methods by including
some kind of history of the minimization path. In pattern search methods
the previous step is used to accelerate movement if the gradient is in the same
direction as before. If the gradient changes, the pattern is abandoned and a
new one set up.

A more elegant improvement to this method is to use conjugate gradients
which, like pattern search, uses information from previous steps to modify
the move in the next step. Unlike pattern search, it does not abandon the
history if the direction changes. In the first step, where the gradient vector is
\( \mathbf{g}_0 \), the move is given by

\[
\mathbf{x}_1 = \mathbf{x}_0 - \beta_0 \mathbf{g}_0
\]

(3.22)
The new direction from this step takes into account the previous gradient and
follows the search direction

\[
\mathbf{g}_1 = \mathbf{g}_0 - \beta_0 \mathbf{g}_0
\]

(3.23)
where \( \beta_0 \) is the search direction from the previous step and \( \beta_0 \) is a scaling
factor given by

\[
\beta_0 = \frac{\mathbf{g}_0 \cdot \mathbf{g}_1}{\mathbf{g}_0 \cdot \mathbf{g}_0}
\]

The effect of the second term in Eq. 3.27 is to release the constraint that
the \( n+1 \) gradient must be orthogonal to the \( n \) gradient. Hence, better search
directions are usually obtained by this method than by steepest descents and
a far better convergence properties (Fig. 3.7).

In addition to its speed and memory requirements, the conjugate gradient
method has the additional advantage that it is unlikely to maximize rather
than minimize. This is one of the shortcomings of the Newton-Raphson
method. The conjugate gradient family of methods use only derivative information to search for
stationary points: this could be either a maximum or a minimum. If a maximum on the energy surface is close to the starting point it is likely that a
will be found, and a transition state structure will be obtained rather than a
stable ground state.

In conclusion, the choice of minimizer should be tempered by the state of
the starting structure: if it is a model, far from a minimum, then a method
such as steepest descents should be applied. Once a low energy has been
obtained it is advisable to switch to a method with better convergence
properties – some variant of the Newton-Raphson method or conjugate
gradients – which will have greater success in actually finding the minimum.

Applying Newton-Raphson methods to poor structures could lead to
catastrophic results, including maximized structures.

3.4 Force field parameterization

It is obvious that the quality of a given force field depends crucially on the
parameters which are derived as constants in the potential function. Just as a
given application can dictate which functional form is the most appropriate,
the parameterization procedure must include this data when developing force
constants and equilibrium values, in order to be valid. This can be both a
strength and weakness of the force field method; the predictive ability of
the method cannot easily extend beyond certain well-determined bounds, while
within those limits the results can be very good indeed.

When discussing the different terms incorporated into the energy function,
force fields were referred to as second or third generation. This reflects both
the functional form of the potential equation and the scope of the data used in
the fitting procedure. Available computer power must be considered as a
vital factor in this historical division, obviously some kind of balance must be
measured between accuracy of calculation and time taken. Another
characterization is the types of application of the force field. In the 1970s
the principal interest was structure, which can be quite well described by the
simple potential forms. More recently, interest has shifted to the dynamic
behaviour of molecules. No longer is one interested restricted to the minima
on the energy surface and this requires better defined descriptions between
the extrema. Only by using complex energy functions which incorporate
interaction between internal coordinates has this improvement been achieved.

A parameterization can be approached from two directions. One can
attempt to automate the procedure and use least-squares optimization
methods to obtain a simultaneous best fit of calculated results to
experimental data. Like all multi-dimensional problems, local minimization
is a hazard leading to mathematical solutions which have little physical
significance. Optimization in this way must be closely watched to avoid excessive bias towards parameters of the opposite of errors.

Alternatively, a trial and error procedure can be used. Here the user makes small changes to the parameters in an attempt to achieve the best possible fit. One advantage of this contrast intervention is that a greater feel is obtained for the interrelationships between parameters. In combination with a least squares optimization better results should be possible than by the currently automated method.

As stated earlier, the data to be fitted should reflect the kind of applications for which the program will be used. For small molecules the most reliable source of data on geometries is gas phase structural studies, usually microwave or electron diffraction. The use of solution phase or crystal geometries is to be avoided if the influence of the environment is an unknown factor. Spectroscopic data also provide information on rotational barriers and vibrational frequencies. Thermodynamic data such as heats of formation may also be included, but group contributions to such must also be derived. Data from ab initio molecular orbital calculations can also provide target values if new experimental data are available. More recently, the latter method has been extended. Ab initio molecular orbital surfaces are calculated for typical molecules using basic sets of solvable quantities. Rather than using equilibrium geometries, these surfaces and their first and second derivatives have been evaluated for a collection of geometries distorted along the normal modes of vibration. These surfaces now describe not just minimum energy positions but give a more accurate representation of the complete potential energy surface. By fitting a potential energy function and its derivatives to such a set of data one can be sure that energies of non-minimum energy structures are considered in "real" behavior. The obvious limitation of this approach is that the surface is only as good as the ab initio calculations used to derive it, but with enough computer time one could do a problem. The main problem remaining is that the gas-phase part of the van der Waals function is not amenable to calculations at the Hartree-Fock level.

The next issue is the origin of the scaling values for each of the parameters. The important thing which must be remembered is that the resulting geometries come from the total interactions of the force field and not simply the force constants and equilibrium values for a given internal coordinate. This has the serious disadvantage that it is not strictly correct to place physical significance on the components of a force field alone. However, this allows greater flexibility in fitting the experimental data as the equilibrium values (E, dih, etc.) become additional variable parameters. A reasonable starting point for the bond-irreps and angle-bond force constants would be a consensus value from all the available in the spectroscopic literature. Standard equilibrium values for bond lengths and angles must also be taken. For dihedral angles it should be remembered that there is an additional contribution from the non-bonded energy terms in the rotational potential. This may be subtracted before fitting $V_{\phi}$ values.

Finding suitable values for van der Waals parameters presents one of the greatest problems in force field development. Although the close-picked geometry of a crystal would provide details about intramolecular parameters, a simple decomposition into static contributions is not easy; the close approach of hydrogen in an alkane crystal is modeled not just by H-H interactions but by C-C and C-H pairs. The resultant intermolecular arrangement is a balance over all the interactions at the far range. Using heat of sublimation data, however, the crystal energies can be calculated as a test of the parameters. Typically, however, the van der Waals radii are used as "soft" parameters that is to say, the exact values have less influence upon the final geometry than the high force constants bond-stretching and angle-bending terms. Therefore, these parameters can be used to fine tune the potential.

The ab initio approach is useful in that the charge densities will be different for a given atom type across a range of compounds. One must either assign genetic values to an atom type and make the assumption that the atom's contribution to the overall electronic energy is modulated by these other charges, or one can be consistent with the calculated values. Only charges calculated by this method will be compatible with the given force field.

Unlike dealing with near-zero systems, the charges on a molecule will have less influence on the final geometry (since the electronic force falls off as $r^{-7}$ than as the energy of a system. This allows one to think in terms of molecular charge distributions rather than absolute values. In some applications (free energy calculations — Chapter 4, molecular stability — Chapter 6) net improvements have been found when using better quality charge distributions.

The charges themselves can be calculated by a number of methods. Empirical charge schemes, which have usually been parameterized to give close agreement with experimental atomic moment values, provide a fast way of generating charges. These are currently suitable for electronic calculations and large systems. Some force fields have been parameterized using charges obtained from molecular electrostatic potentials (see Chapter 2) and this procedure should be followed when applying the program to unknown molecules. Although there can be a tendency to use the best possible charges, one must always bear in mind that the absolute value will be to the application. There is little point in wasting computer time on expensive ab initio calculations when all one wishes is to do they as the strengthening of a model structure.

A different approach to generating new shaped parameters is to fit them to data on liquid properties, the Monte Carlo method can be used for this (Chapter 4). This method can be used to derive parameters for a wide range of molecular liquids involving that it is a reliable procedure.

3.5 Conformational analysis

One of the most useful aspects of molecular mechanics calculations is that they allow rapid determination of molecular energies. This makes them very
suitable for problems of conformational analysis. Since the energies calculated are relative, in the sense that they depend entirely on the connectivity of the molecule, they cannot be compared between molecules. However, when investigating conformational space this does not arise; only internal coordinates will be changed, not connectivities.

The simplest way to carry out conformational analysis is to derive the complete energy surface which results from changing a particular rotational variable. Making the approximation that only conformations close to the minima and maxima of the rotational potential will be observed, rotations about a saturated C=C bond can be reduced to six points. For a small molecule with, say, three rotatable bonds this does not present much of a problem as only $6^3$ (216) conformations will be generated. If a large molecule, containing six rotatable bonds, is of interest the number of $\omega_{\text{virtual}}$ increases dramatically to $6^6$ (46,656) and this is still a very small molecule. Obviously this kind of density grid scan must be modified for general use. Above, if more than two variables are used it is difficult to visualise the energy surface being $\omega_{\text{virtual}}$.

Most of the solutions to the combined $\omega_{\text{virtual}}$ of them of conformational search rely on methods to filter out poor conformations in order to save time. Possible reducing the number of values per rotatable bond is an obvious answer but immediately it should be recognised that one runs the risk of overlooking potentially interesting structures. In the case of amine acids, each residue can be calculated to be considered a pair of interdependent variables, with only certain minima from the conformational energy map (Ramachandran map) accessible. By reducing the number of points to either minima, or minima within a threshold of the global minimum, one can reduce interconverting conformations space to a very few points, of the order of 5-10 per residue. Similar restrictions can be applied to any pair of dihedral angles. A conformational search procedure can then proceed by considering combinations of the minima along the given chain.

A second method of increasing the efficiency of a conformational search is to use a two-search. Here, the search starts out as a complete grid search but as individual conformations are being generated checks are carried out to eliminate unstable structures before completion. Typical tests would include checking for adverse non-bonded contacts. Since many large systems contain cyclic regions, ring closures is a particularly good criterion. As a conformation is being generated it should be possible to tell whether it will ever be capable of cyclizing, based on the maximum length of a unit in the chain (Fig. 3.39).

Usually the conformations generated by any of the above methods will have high energies. Hence, minimization will be required to produce more realistic structures. If only minima are required then one can proceed as in Section 3.3.4, however, one is instead in mapping out a complete surface, and barrier heights and isomerization pathways are of interest, means must be found to hold abridges at particular values while minimizing all other variables. The simplest way to do this is to modify the rotational potential of the fixed dihedral by applying an offset $\omega_2$ to the minimum value and using a very large rotational barrier constant $\beta_2$.

$$E = \omega_2(1 + \cos(\alpha_2 + \omega_2))$$

(3.25)

Following minimization the energy must be recalculated using the correct potential constant. Great care must be taken when applying this method, especially when investigating cyclic molecules as the pathway across a surface may depend upon the starting point and the location of other stationary points on the energy surface.

Having obtained a potential energy surface, or conformational reaction coordinate, by one of the above methods, it is tempting to place an interpretation on the different contributions to the barrier height etc. This must be approached cautiously as it should be remembered that only features such as total energy, geometry and vibrational frequencies can be considered to have any physical meaning.

In the next chapter we will see that Monte Carlo and molecular dynamics methods, which allow molecules to traverse energy barriers, are more useful for larger systems.

3.6 Summary

Force field methods of the type outlined in this chapter are finding increasing application in many areas of structural chemistry. The principal advantage of these methods is that they rapidly provide potential energy functions less computationally expensive than quantum mechanical methods, allowing systems of the order of thousands of atoms to be considered. A large body of data now exists validating the functional forms and the various parameters used so far, as long as one is aware of the limitations associated with a given force field, reliable results may be obtained. Many of the older force fields will be valid only for structures whose thermodynamic data can be calculated from second generation force fields such as MM2. If one wants to know more about vibrational frequencies, a force field containing force terms in the energy function must be applied. Typically, this type of force field will be more reliable between stationary points on the energy surface.

Minimization of structures is usually required to remove strain from poorly defined geometries. When far from a minimum, simple gradient techniques, and a less complex force field expression are the methods of choice. But, as one approaches the minimum, more sophisticated methods such as conjugate gradients are recommended; these converge much more quickly. It is also important that the parameters used are consistent with the rest of the force field. Since the parameters arise from a fitting procedure they can have little physical significance. A "mix and match" approach is to be avoided. Conformational search procedures often utilize molecular mechanics calculations but one must be careful that the methods used do not introduce bias into the calculation otherwise a true representation of the energy surface will not be obtained, or low energy conformers will be omitted.