Molecular Modelling

PRINCIPLES AND APPLICATIONS

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5.8 Applications of Energy Minimisation

Energy minimisation is very widely used in molecular modelling and is an integral part of techniques such as conformational search procedures (Chapter 9). Energy minimisation is also used to prepare a system for other types of calculation. For example, energy minimisation may be used prior to a molecular dynamics or Monte Carlo simulation in order to relieve any unfavourable interactions in the initial configuration of the system. This is especially recommended for simulations of complex systems such as macromolecules or large molecular assemblies. In the following sections we will discuss some techniques that are specifically associated with energy minimisation methods.

5.8.1 Normal Mode Analysis

The molecular mechanics or quantum mechanics energy at an energy minimum corresponds to a hypothetical, motionless state at 0K. Experimental measurements are made on molecules at a finite temperature when the molecules undergo translational, rotational and vibration motion. To compare the theoretical and experimental results it is
necessary to make appropriate corrections to allow for these motions. These corrections are calculated using standard statistical mechanics formulae. The internal energy $U(T)$ at a temperature $T$ is given by:

$$U(T) = U_{\text{trans}}(T) + U_{\text{rot}}(T) + U_{\text{vib}}(T) + U_{\text{vib}}(0)$$  \hspace{1cm} (5.26)

If all translational and rotational modes are fully accessible in accordance with the equipartition theorem, then $U_{\text{trans}}(T)$ and $U_{\text{rot}}(T)$ are both equal to $\frac{3}{2} k_B T$ per molecule (except that $U_{\text{rot}}(T)$ equals $k_B T$ for a linear molecule); $k_B$ is Boltzmann’s constant. However, the vibrational energy levels are often only partially excited at room temperature. The vibrational contribution to the internal energy at a temperature $T$ thus requires knowledge of the actual vibrational frequencies. The vibrational contribution equals the difference in the vibrational enthalpy at the temperature $T$ and at $0 \text{K}$ and is given by:

$$U_{\text{vib}}(T) = \sum_{i=1}^{N_{\text{nm}}} \left( \frac{\hbar \nu_i}{2} + \frac{\hbar \nu_i}{\exp[\hbar \nu_i / k_B T] + 1} \right)$$  \hspace{1cm} (5.27)

$N_{\text{nm}}$ is the number of normal vibrational modes for the system. Even the zero-point energy ($U_{\text{vib}}(0)$, obtained by summing $\frac{1}{2} \hbar \nu_i$ for each normal mode) can be quite substantial, amounting to about 100 kcal/mol for a six-carbon alkane. Other thermodynamic quantities such as entropies and free energies may also be calculated from the vibrational frequencies using the relevant statistical mechanics expressions.

Normal modes are useful because they correspond to collective motions of the atoms in a coupled system that can be individually excited. The three normal modes of water are schematically illustrated in Figure 5.15; a non-linear molecule with $N$ atoms has $3N - 6$ normal modes. The frequencies of the normal modes together with the displacements of the individual atoms may be calculated from a molecular mechanics force field or from the wavefunction using the Hessian matrix of second derivatives ($\nabla^2$). Of course, if we have used an appropriate minimisation algorithm then we already know the Hessian. The Hessian must first be converted to the equivalent force-constant matrix in mass-weighted coordinates ($F$), as follows:

$$F = M^{-1/2} \nabla^2 M^{-1/2}$$  \hspace{1cm} (5.28)

![Diagram of water molecule with normal modes](image)

**Fig. 5.15:** Normal modes of water. Experimental and (calculated) frequencies are shown. Theoretical frequencies calculated using a 6-31G* basis set.
\( M \) is a diagonal matrix of dimension \( 3N \times 3N \), containing the atomic masses. All elements of \( M \) are zero except those on the diagonal; \( M_{1,1} = m_1, \; M_{2,2} = m_2, \; M_{3,3} = m_3, \; M_{4,4} = m_4, \ldots, M_{3N-2,3N-2} = m_{N-1}, \; M_{3N-1,3N-1} = m_N, \; M_{3N,3N} = m_N \). Each non-zero element of \( M^{-1/2} \) is thus the inverse square root of the mass of the appropriate atom. The masses of the atoms must be taken into account because a force of a given magnitude will have a different effect upon a larger mass than a smaller one. For example, the force constant for a bond to a deuterium atom is, to a good approximation, the same as to a proton, yet the different mass of the deuteron gives a different motion and a different zero-point energy. The use of mass-weighted coordinates takes care of these problems.

We next solve the secular equation \([F - I] = 0\) to obtain the eigenvalues and eigenvectors of the matrix \( F \). This step is usually performed using matrix diagonalisation, as outlined in Section 1.10.3. If the Hessian is defined in terms of Cartesian coordinates then six of these eigenvalues will be zero as they correspond to translational and rotational motion of the entire system. The frequency of each normal mode is then calculated from the eigenvalues using the relationship:

\[
\nu_i = \frac{\sqrt{\lambda_i}}{2\pi} \tag{5.29}
\]

As a simple example of a normal mode calculation consider the linear triatomic system in Figure 5.16. We shall just consider motion along the long axis of the molecule. The displacements of the atoms from their equilibrium positions along this axis are denoted by \( \xi_i \). It is assumed that the displacements are small compared with the equilibrium values \( l_0 \) and the system obeys Hooke’s law with bond force constants \( k \). The potential energy is given by:

\[
\mathcal{V} = \frac{1}{2}k(\xi_1 - \xi_2)^2 + \frac{1}{2}k(\xi_2 - \xi_3)^2 \tag{5.30}
\]

We next calculate the first and then the second derivatives of the potential energy with respect to the three coordinates \( \xi_1, \xi_2 \) and \( \xi_3 \):

\[
\frac{\partial \mathcal{V}}{\partial \xi_1} = k(\xi_1 - \xi_2); \quad \frac{\partial \mathcal{V}}{\partial \xi_2} = -k(\xi_1 - \xi_2) + k(\xi_2 - \xi_3); \quad \frac{\partial \mathcal{V}}{\partial \xi_3} = -k(\xi_2 - \xi_3) \tag{5.31}
\]

![Diagram](image)

**Fig. 5.16:** Linear three-atom system with results of normal mode calculation.
The second derivatives are conveniently represented as a $3 \times 3$ matrix:

\[
\begin{vmatrix}
  k & -k & 0 \\
  -k & 2k & -k \\
  0 & -k & k \\
\end{vmatrix}
\]  

(5.32)

The mass-weighted matrix is

\[
\begin{vmatrix}
  m_1 & 0 & 0 \\
  0 & m_2 & 0 \\
  0 & 0 & m_3 \\
\end{vmatrix}
\]  

(5.33)

The secular equation to be solved is thus:

\[
\begin{vmatrix}
  \frac{k}{m_1} - \lambda & -\frac{k}{\sqrt{m_1m_2}} & 0 \\
  \frac{k}{\sqrt{m_1m_2}} & \frac{2k}{m_2} - \lambda & -\frac{k}{\sqrt{m_1m_2}} \\
  0 & \frac{k}{\sqrt{m_1m_2}} & \frac{k}{m_1} - \lambda \\
\end{vmatrix} = 0
\]  

(5.34)

This determinant leads to a cubic in $\lambda$ which has three roots ($\lambda_k$), each corresponding to a different mode of motion:

\[
\lambda = \frac{k}{m_1}, \quad \lambda = 0, \quad \lambda = k\frac{m_2 + 2m_1}{m_1m_2}
\]  

(5.35)

The corresponding frequencies can be obtained from Equation (5.29). The amplitudes ($A$) of each normal mode are given by the eigenvector solutions of the secular equation $FA = \lambda A$. If $A_1$, $A_2$ and $A_3$ are the amplitudes of each atom then the amplitudes obtained for each eigenvalue are:

\[
\lambda = \frac{k}{m_1}: \quad A_1 = -A_3; \quad A_2 = 0
\]  

(5.36)

\[
\lambda = 0: \quad A_1 = A_3; \quad A_2 = \sqrt{\frac{m_2}{m_1}}A_1
\]  

(5.37)

\[
\lambda = k\frac{m_2 + 2m_1}{m_1m_2}: \quad A_1 = A_3; \quad A_2 = -2\sqrt{\frac{m_1}{m_2}}A_1
\]  

(5.38)

These normal modes are schematically illustrated in Figure 5.16. They correspond to a symmetric stretch, a translation and an asymmetric stretch respectively.

We have already seen how the results of normal mode calculations can be used to calculate thermodynamic quantities. The frequencies themselves can also be compared with the results of spectroscopic experiments, information which can be used in the parametrisation of a force field. For example, the experimental frequencies for the normal modes of water are shown in Figure 5.15, together with the frequencies determined using a 6-31G* ab initio calculation. The calculated values clearly deviate from those obtained experimentally, but the ratio of the experimental and theoretical frequencies is