

3.3. MOLECULAR MODELLING AND GRAPHICS

It may happen that $B_1^T M_2 B_1$ is itself singular because there are insufficient data in the vector t_2 to control the structure and the parametric shifts contained in θ_2 fully. In this event the same process may be applied again, basing the solution for θ_2 on

$$\begin{pmatrix} A_2^T \\ B_2^T \end{pmatrix} B_1^T M_2 B_1 (A_2 B_2)$$

so that the vectors in B_2 represent the degrees of freedom which remain uncommitted. This method of application of constraints by subspace sectioning may be nested to any depth and is completely general.

A valid matrix A_1 may be found from M_1 by using the fact that the columns of M_1 are all linear combinations of the columns of E_λ and are void of any contribution from E_0 . It follows that A_1 may be found by using the columns of M_1 as priming vectors in the Gram–Schmidt process [Section 3.3.1.2.3 (i)] until the normalizing step involves division by zero. A_1 is then complete if all the columns of M_1 have been tried. $(A_1 B_1)$ may then be completed by using arbitrary vectors as primers.

Manipulation of a ring of n atoms may be achieved by treating it as a chain of $(n + 2)$ atoms [having $(n + 1)$ bond lengths, n bond angles and $(n - 1)$ dihedral angles] in which atom 1 is required to coincide with atom $(n + 1)$ and atom 2 with $(n + 2)$. t_1 then contains two vectors, namely the lack-of-closure vectors at these points, and is typically zero. A_1 is then found to have five columns corresponding to the five degrees of freedom of two points of fixed separation; θ_1 contains only zeros if the ring is initially closed, and contains ring-closure corrections if, through non-linearity or otherwise, the ring has opened. B_1 contains $(p - 5)$ columns if the chain of $(n + 2)$ points has p variable parameters. It follows, if bond lengths and bond angles are treated as constants, that the seven-membered ring is the smallest ring which is flexible, that the six-membered ring (if it can be closed with the given bond angles) has no flexibility (though it may have discrete alternatives) and that it may be impossible to close a five-membered ring. Therefore some variation of bond angles and/or bond lengths is essential for the modelling of flexible five- and six-membered rings. Treating the ring as a chain of $(n + 1)$ atoms is less satisfactory as there is then no control over the bond angle at the point of ring closure.

A useful concept for the modelling of flexible five-membered rings with near-constant bond angles is the concept of the pseudorotation angle P , and amplitude θ_m , for which the j th dihedral angle is given by

$$\theta_j = \theta_m \cos\left(P + \frac{4\pi j}{5}\right).$$

This formulation has the property $\sum_{j=0}^4 \theta_j = 0$, which is not exactly true; nevertheless, θ_j values measured from observed conformations comply with this formulation within a degree or so (Altona & Sundaralingam, 1972).

Software specialized to the handling of condensed ring systems has been developed by van der Lieth *et al.* (1984) (Section 3.3.3.3.1) and by Cohen *et al.* (1981) (Section 3.3.3.3.2).

3.3.2.2.2. Methods based on positional coordinates

Modelling methods in which atomic coordinates are the independent variables are mathematically simpler than those using angular variables especially if the function to be minimized is a quadratic function of interatomic distances or of distances between atoms and fixed points. The method of Dodson *et al.* (1976) is representative of this class and it may be outlined as follows. If \mathbf{d} is a column vector containing ideal values of the scalar distances from atoms to fixed target points or to other atoms, and if \mathbf{l}

is a column vector containing the prevailing values of these quantities obtained from the model, then

$$\mathbf{d} = \mathbf{l} + D\delta\mathbf{x} + \boldsymbol{\varepsilon}$$

in which the column matrix $\delta\mathbf{x}$ contains alterations to the atomic coordinates, $\boldsymbol{\varepsilon}$ contains residual discrepancies and D is a large sparse rectangular matrix containing values of $\partial l/\partial x$, of which there are not more than six non-zero values on any row, consisting of direction cosines of the line of which \mathbf{l} is the length. $\boldsymbol{\varepsilon}^T W \boldsymbol{\varepsilon}$ is then minimized by setting

$$D^T W (\mathbf{d} - \mathbf{l}) = D^T W D \delta\mathbf{x},$$

which they solve by the method of conjugate gradients without searches. This places reliance on the linearity of the observational equations (Diamond, 1984*b*). It also works entirely with the sparse matrix $W^{1/2} D$, the dense matrix $D^T W D$, and its inverse, being never calculated.

The method is extremely efficient in annealing a model structure for which an initial position for every atom is available, especially if the required shifts are within the quasi-linear region, but is less effective when large dihedral-angle changes are involved or when many atoms are to be placed purely by interpolation between a few others for which target positions are available. Interbond angles are controlled by assigning d values to second-nearest-neighbour distances; this is effective except for bond angles near 180° so that, in particular, planar groups require an out-of-plane dummy atom to be included which has no target position of its own but does have target values of distances between itself and atoms in the planar group. The method requires a d value to be supplied for every type of nearest- and next-nearest-neighbour distance in the structure, of which there are many, together with W values which are the inverse variances of the distances concerned as assessed by surveys of the corresponding distances in small-molecule structures, or from estimates of their accuracy, or from estimates of accuracy of the target positions.

Hermans & McQueen (1974) published a similar method which differs in that it moves only one atom at a time, in the environment of its neighbours, these being considered fixed while the central atom is under consideration. This is inefficient in the sense that in any one cycle one atom moves only a small fraction ($\sim 3\%$) of the distance it will ultimately be required to move, but individual atom cycles are so cheap and simple that many cycles can be afforded. The method was selected for inclusion in *Frodo* by Jones (1978) (Section 3.3.3.2.7) and is an integral part of the *GRIP* system (Tsernoglou *et al.*, 1977; Girling *et al.*, 1980) (Section 3.3.3.2.2) for which it was designed.

3.3.2.2.3. Approaches to the problem of multiple minima

Modelling methods which operate by minimizing an objective function of the coordinates (whether conformational or positional) suffer from the fact that any realistic objective function representing the potential energy of the structure is likely to have many minima in the space of the variables for any but the simplest problems. No general system has yet been devised that can ensure that the global minimum is always found in such cases, but we indicate here two approaches to this problem.

The first approach uses dynamics to escape from potential-energy minima. Molecular-mechanics simulations allow each atom to possess momentum as well as position and integrate the equations of motion, conserving the total energy. By progressively removing energy from the simulation by scaling down the momentum vectors some potential-energy minimum may be found. Conversely, a minimization of potential energy which has led to a minimum thought not to be the global minimum may be continued by introducing atomic momenta sufficient to overcome potential-