

A Procedure for Obtaining Energy Parameters from Crystal Packing

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An efficient method for deriving energy parameters from crystal packing is described. The Newton-Raphson approximation is used in a least-squares procedure to obtain the energy parameters. Lattice sums of the energy, first derivatives, and second derivatives are calculated only once for the experimental crystal structure. Thus their recalculation, which is a very time-consuming operation, is avoided. The method is tested on six amide crystals, and results are given. It is also shown to be applicable to other fields of conformational analysis. A method of energy minimization involving lattice sums of third derivatives, which is an extension of the Newton-Raphson approximation, is also presented.

Introduction

In theoretical conformational analysis a set of energy functions is chosen from which the equilibrium coordinates of molecules are calculated by solving the set of equations

$$\partial V_{\text{mol}}/\partial r_s = 0 \quad (1)$$

where V_{mol} is the total molecular energy, and r_s are atomic (or internal) coordinates. Similarly, equilibrium structures of crystals are obtained by solving the set of equations

$$g_\alpha = \partial V_{\text{cryst}}/\partial a_\alpha = 0 \quad (2)$$

where V_{cryst} is the energy of the crystal lattice and a_α are the components of the vector \mathbf{a} , representing the unit-cell parameters and molecular coordinates necessary completely to describe the crystal structure. The solution of (2) is of interest in connexion with the calculation of molecular packing, by minimization of the potential energy of the crystal. This possibility, and the success of such calculations, are of obvious importance to the study both of intermolecular forces and the crystalline state. It is the subject of increasing attention, although most of the recent studies have been carried out by mapping the potential surface in one or two variables, rather than using minimization techniques to solve (2) in general (Coiro, Giglio & Quagliata, 1972; Ahmed, Kitaigorodsky & Mirskaya, 1971; Giglio, 1970; Dentini, De Santis, Morosetti & Piantanida, 1972).

The choice of energy parameters for crystal-structure calculations is often based on a least-squares fit of the calculated and experimental properties. However, the calculation of $\mathbf{a}_{\text{eq,calc}}$, the calculated equilibrium value of \mathbf{a} , is a lengthy numerical process involving a repeated calculation of the lattice sums,* which enter into the expression for the energy and its derivatives. This whole process must be repeated iteratively in the least-

squares optimization of the energy parameters to yield

$$\sum_{\alpha} (a_{\text{calc}} - a_{\text{exp}})^2 = \text{minimum} \quad (3)$$

The lattice sums are time-consuming and constitute the major part of the computing time of the calculation of $\mathbf{a}_{\text{eq,calc}}$. Optimization in this way is therefore a much too expensive computer operation. In order to avoid repeated calculations of lattice sums, the common practice (Williams, 1966; Momany, Vanderkooi & Scheraga, 1968; Minicozzi & Stroot, 1970) has been to optimize the energy parameters so as to minimize the squares of the calculated forces g_α at the experimental equilibrium structure. In other words, one seeks a set of energy parameters for which

$$\sum_{\alpha} [g_{\text{calc}}(\mathbf{a}_{\text{exp}}) - g_{\text{exp}}]^2 = \sum_{\alpha} [g_{\text{calc}}(\mathbf{a}_{\text{exp}})]^2 = \text{minimum} \quad (4)$$

(g_{exp} are by definition zero).

This method avoids solving (2) and has the great advantage that the repeated evaluation of lattice sums for the energy and derivatives at the calculated crystal structure is avoided. Instead, the derivatives are evaluated for the experimental crystal structure only.

A second major advantage is related to certain forms of the potential, for which only a single evaluation of the lattice sums is necessary for any number of iterations in a least-squares optimization. This may best be seen by looking at an example. The potential Williams (1966) uses to describe the energy of hydrocarbons is

$$2V_{\text{cryst}} = A_{\text{CC}} \sum r_{\text{CC}}^{-6} + B_{\text{CC}} \sum \exp(-C_{\text{CC}}r_{\text{CC}}) + A_{\text{CH}} \sum r_{\text{CH}}^{-6} + B_{\text{CH}} \sum \exp(-C_{\text{CH}}r_{\text{CH}}) + A_{\text{HH}} \sum r_{\text{HH}}^{-6} + B_{\text{HH}} \sum \exp(-C_{\text{HH}}r_{\text{HH}}) \quad (5)$$

where A_{ij} , B_{ij} and C_{ij} are energy parameters belonging to the two atoms i and j , and r_{ij} is the interatomic distance. For each iteration of a non-linear least-squares optimization, one needs to calculate the observables (in this case V and certain g_α), and the derivatives of the observables with respect to the energy

* We use the term lattice sum to mean a summation over all the atoms in the crystal lattice of some function of the distance between atoms.

parameters. Since the energy parameters A_{ij} and B_{ij} are outside the summation, the change in energy for a change in any one of these parameters does not necessitate a recalculation of the lattice sums. The derivatives of the energy with respect to the crystal coordinates, g_α , involve similar sums. Thus in a least-squares optimization, the values of the observables and their derivatives with respect to A_{ij} and B_{ij} may be calculated for any values of these parameters without a recalculation of the lattice sums.* Note that this condition does not hold for the constants C_{ij} , and for this reason these constants had to be obtained in a different way (Williams, 1966).

There is, however, a disadvantage with this method. This is in the implicit assumption that optimizing over the derivatives is equivalent to optimizing over the crystal structure itself. In fact it is obvious that if the potential is very shallow, the derivatives can be very small, even though the distance from the minimum may be large.

We tried to apply this method to amide crystals. We used (4) to obtain a set of optimized energy parameters, and then used these parameters to determine the calculated crystal structure $\mathbf{a}_{\text{eq,calc}}$ by minimizing the crystal energy, *i.e.* solving (2). We found that the deviations between calculated and experimental \mathbf{a}_{eq} were often rather large. It thus became apparent that the optimized derivatives did not lead to an optimized crystal structure for these crystals. This problem was recognized by Warshel & Lifson (1970) who actually solved for $\mathbf{a}_{\text{zcalc}}$ in (3) by a Newton-Raphson minimization for hexane. They obtained the Z matrix (the derivatives of $\mathbf{a}_{\text{zcalc}}$ with respect to the parameters) for the least-squares optimization of (3) by a lattice-sums technique, and recalculated the lattice sums only every three to five iterations. The recalculation of lattice sums and the solution of (3) is too time-consuming for larger systems or when many crystals with more than one molecule per unit cell are being treated. Thus we were led to a modification of the previous methods. We follow Warshel & Lifson (1970) in abandoning (4) as a criterion for the set of energy parameters. Instead, we incorporate the crystal structure itself as a basis for optimization into a lattice-sums technique. In this way we obtain all the advantages of (4) while at the same time optimizing over the crystal structure and not the derivatives; minimization of energy is avoided therefore and lattice sums are calculated only once for the experimental crystal geometry.

Application of Newton-Raphson method with lattice sums

A set of linear equations may be obtained for $(\mathbf{a}_{\text{zcalc}} - \mathbf{a}_{\text{zexp}})$, the quantity which appears in (3), by expanding

* This is true even when the A 's and B 's are inter-related non-linearly, *e.g.* when it is desired to test the correlation $A_{\text{CH}}^2 = A_{\text{CC}}A_{\text{HH}}$, by an iterative linearized least-squares (see *e.g.* Hamilton, 1964).

the gradient at the calculated minimum energy $\nabla_{\mathbf{a}}V(\mathbf{a}_{\text{calc}}) = \{\partial V/\partial a_\alpha\}$, in a Taylor series about the experimental coordinates

$$\nabla_{\mathbf{a}}V(\mathbf{a}_{\text{calc}}) = \nabla_{\mathbf{a}}V(\mathbf{a}_{\text{exp}}) + \mathbf{F}(\mathbf{a}_{\text{exp}})(\mathbf{a}_{\text{calc}} - \mathbf{a}_{\text{exp}}) + \dots \quad (6)$$

where $\mathbf{F}(\mathbf{a}_{\text{exp}})$ is the matrix of second derivatives

$$\mathbf{F}(\mathbf{a}_{\text{exp}}) = (\partial^2 V/\partial a_\alpha \partial a_\beta) \text{ at } \mathbf{a}_{\text{exp}}. \quad (7)$$

The distance to the minimum is then obtained approximately by noting that $\nabla_{\mathbf{a}}V(\mathbf{a}_{\text{calc}}) = 0$ and solving the equation

$$\Delta \mathbf{a}_{\text{NR}} \equiv (\mathbf{a}_{\text{calc}} - \mathbf{a}_{\text{exp}}) = -\mathbf{F}^{-1}(\mathbf{a}_{\text{exp}})\nabla_{\mathbf{a}}V(\mathbf{a}_{\text{exp}}). \quad (8)$$

Thus $\Delta \mathbf{a}_{\text{NR}}$ gives the Newton-Raphson approximation to the difference between the observed coordinates \mathbf{a}_{exp} , and the calculated minimum energy coordinates \mathbf{a}_{calc} . It is exact only for a quadratic function but is a good approximation in the more general case, insofar as the Taylor series of (6) may be truncated after the second term, namely when the calculated minimum is sufficiently close to the experimental coordinates.

Thus our proposed optimization procedure is to estimate $\mathbf{a}_{\text{calc}} - \mathbf{a}_{\text{exp}}$ in (3) by (8), and solve for the energy parameters which satisfy the condition

$$|\mathbf{F}^{-1}(\mathbf{a}_{\text{exp}})\nabla_{\mathbf{a}}V(\mathbf{a}_{\text{exp}})|^2 = \text{minimum}. \quad (9)$$

Test of the proposed optimization procedure

In order to test the two measures of the differences between calculated and experimental crystal structure [*i.e.* derivatives at minimum as in (4) or (9)] we have minimized the energy of six amide crystals (oxamide, succinamide, urea, formamide, diketopiperazine and *L-cis*-3,6-dimethyl-2,5-piperazinedione) with respect to the nine Cartesian components of the unit-cell vectors. That is, we have tested these procedures with respect to how unit cells pack. This was done for the potential (Warshel & Lifson, 1970):

$$V_{\text{cryst}} = \frac{1}{2} \sum_{ij} \{ \epsilon_{ij} [2(r_{ij}^*/r_{ij})^9 - 3(r_{ij}^*/r_{ij})^6] + q_i q_j / r_{ij} \} \quad (10)$$

where $r_{ij}^* = \frac{1}{2}(r_i^* + r_j^*)$, $\epsilon_{ij} = (\epsilon_i \epsilon_j)^{1/2}$ and ϵ_i and r_i^* are constants defined for atoms of type i having the di-

Table 1. Parameters for test potential functions

	r^* (Å)	ϵ (kcal mole ⁻¹)	q (electrons)‡
H _C †	3.55	0.0025	0.108
O	4.08	0.0195	-0.505
N	4.06	0.0974	
C	3.62	0.184	
H _N †	1.74	0.00568	0.329, 0.395

† H_C and H_N represent the hydrogen on carbon and on nitrogen, respectively.

‡ The following groups were defined as neutral: C=O, N-H, N-H₂, and CH_n; the charges for H_N refer to H in N-H, and in NH₂ respectively. The charges given along with the neutrality condition thus determine all the charges in these molecules.

Table 2. Comparison of different measures of true distance from observed to calculated minimum-energy unit-cell parameters

	$\frac{\partial V}{\partial a_{ij}}$ kcal mole ⁻¹ Å ⁻¹	Δa_{true}			
		Δa_{NR}	50 Å cut-off	12 Å cut-off	8 Å cut-off
Oxamide					
a_{1x} *	-2.59	0.079	0.118	0.120	0.127
a_{1y}	-0.63	0.114	0.093	0.085	0.143
a_{1z}	-1.09	0.016	0.012	0.012	-0.048
a_{2x}	-0.23	-0.085	-0.120	-0.114	-0.186
a_{2y}	2.44	-0.167	-0.157	-0.155	-0.171
a_{2z}	-1.28	0.207	0.176	0.176	0.189
a_{3x}	-0.97	0.075	0.091	0.088	0.134
a_{3y}	0.28	-0.125	-0.119	-0.119	-0.046
a_{3z}	0.98	-0.009	-0.002	-0.003	0.024
Succinamide					
a_{1x}	1.39	-0.076	-0.084	-0.090	-0.054
a_{1y}	0.00	0.000	0.000	0.000	0.000
a_{1z}	-0.62	0.257	0.327	0.376	0.244
a_{2x}	-0.00	0.000	0.000	0.000	0.000
a_{2y}	10.85	-0.067	-0.056	-0.056	-0.054
a_{2z}	0.01	-0.000	-0.000	-0.000	-0.000
a_{3x}	0.33	-0.102	-0.105	-0.102	-0.130
a_{3y}	0.00	-0.000	-0.000	-0.000	-0.000
a_{3z}	6.10	-0.096	-0.088	-0.084	-0.095
Urea					
a_{1x}	2.85	-0.181	-0.106	-0.112	-0.117
a_{1y}	-0.02	-0.055	-0.029	-0.031	-0.031
a_{1z}	-2.14	0.172	0.129	0.128	0.123
a_{2x}	0.05	-0.080	-0.059	-0.061	-0.062
a_{2y}	2.81	-0.154	-0.075	-0.081	-0.085
a_{2z}	2.16	-0.173	-0.123	-0.127	-0.121
a_{3x}	-0.00	-0.020	-0.022	-0.022	-0.024
a_{3y}	0.06	0.017	-0.019	0.019	-0.019
a_{3z}	3.07	-0.052	-0.057	-0.065	-0.055
Formamide					
a_{1x}	-1.07	0.045	0.054	0.051	0.065
a_{1y}	0.01	0.016	0.011	0.011	0.011
a_{1z}	3.29	0.027	0.030	0.023	0.029
a_{2x}	-0.11	-0.103	-0.100	-0.094	-0.091
a_{2y}	-0.22	0.110	0.090	0.090	0.082
a_{2z}	-0.04	0.180	0.146	0.144	0.124
a_{3x}	-0.42	0.106	0.090	0.095	0.066
a_{3y}	0.01	-0.103	-0.085	-0.082	-0.076
a_{3z}	3.86	-0.285	-0.232	-0.222	-0.200
Diketopiperazine					
a_{1x}	-1.15	0.016	0.036	0.040	0.060
a_{1y}	0.00	-0.065	-0.056	-0.055	-0.053
a_{1z}	-3.06	0.252	0.236	0.238	0.243
a_{2x}	-0.04	0.067	0.052	0.047	0.020
a_{2y}	-0.40	0.085	0.075	0.075	0.074
a_{2z}	-0.00	-0.198	-0.187	-0.185	-0.186
a_{3x}	1.08	-0.161	-0.179	-0.183	-0.200
a_{3y}	0.00	0.056	0.048	0.047	0.046
a_{3z}	-5.70	-0.029	-0.030	-0.033	-0.038
L-cis-3,6-Dimethyl-2,5-piperazinedione					
a_{1x}	1.32	-1.034	-0.335	-0.329	-0.300
a_{1y}	0.36	0.196	0.074	0.064	0.085
a_{1z}	-0.64	1.097	0.270	0.256	0.253
a_{2x}	3.38	-0.378	-0.372	-0.369	-0.368
a_{2y}	1.90	-0.042	-0.038	-0.037	-0.083
a_{2z}	-1.43	-0.005	-0.054	0.069	0.060
a_{3x}	-0.17	-0.068	-0.011	0.005	0.027
a_{3y}	0.00	-0.017	-0.030	-0.044	-0.031
a_{3z}	0.11	0.015	-0.011	-0.021	-0.020

* a_{ax} is the x component of unit-cell vector a_a and similarly for a_{ay} and a_{az} .

mension of energy and distance respectively, q_i is the partial charge on atom i , r_{ij} is the distance between atoms i and j , and i runs over all atoms in a central unit cell, j over all the atoms in the crystal (except the atoms of the molecule to which atom i belongs). The parameters used in this test are given in Table 1.*

The lattice sums were performed over 5 unit cells in each direction (*i.e.* the central unit cell interacted with a total of 124 other unit cells).

Since the unit cells in some of these crystals were quite large we introduced a cut-off rule: the interaction between any two molecules is neglected if no experimental distance r_{ij} between an atom i of one molecule and an atom j of the other is smaller than a predetermined cut-off distance.

The results of the test are presented in Table 2. The first column represents the derivatives of the energy with respect to the components of the unit-cell vector, g_a , calculated at the experimental geometry. In the second column of Table 2 the approximate distances to the minimum $\Delta a_{\text{NR}} = -\mathbf{F}^{-1}\nabla V$ are given, as calculated by (8). The third column represents the true difference Δa_{true} between the calculated and experimental crystal structures. The calculated structures were obtained by a Fletcher-Powell (1963) iterative solution of (2). The cut-off for the lattice sums was taken as 50 Å. The criterion for a minimum was that all derivatives, $\partial V_{\text{cryst}}/\partial a_a$, were smaller than 10^{-5} kcal mole⁻¹ Å⁻¹.

As can be seen from Table 1, the values obtained from the Newton-Raphson formula approximately parallel the true deviations, while there is no such correlation between the derivatives and the true deviations. For example, the derivative $\partial V/\partial a_{2y}$ is equal to 10.85 in succinamide while the corresponding distance to the minimum from the experimental value $\Delta a_{2y} (= a_{2y\text{calc}} - a_{2y\text{exp}})$ is only -0.067 Å, while on the other hand the derivative in the direction a_{1z} in succinamide is only $\partial V/\partial a_{1z} = -0.062$ while Δa_{1z} is 0.257. Thus if one were trying to find energy parameters to fit the crystal structure of succinamide by optimizing over derivatives with (4), one would erroneously change the parameters to reduce the derivatives in the direction a_{2y} , even though the minimum geometry in this direction is not far from the experimental (-0.067 Å). At the same time, the a_{1z} direction would be largely discounted by the least-squares, since the derivative is small, and here the calculated geometry is off by 0.257 Å. Many other examples of this type can be seen in Table 2.

We may summarize the discussion as follows.

(a) As stated in the Introduction, (4), which optimizes the the crystal forces, does not yield an optimum crystal structure.

(b) As seen from Table 2, the reason for (a) is that

* These parameters were obtained from a least-squares solution of (9). They were derived in the initial stages of a study on hydrogen bonding (Hagler, Huler & Lifson, 1974), and do not represent the final results of that study.

the calculated forces (column 1) do not correlate well with the crystal structure (column 3).

(c) The Newton–Raphson approximation (column 2) does correlate well with the crystal structure and therefore serves as an appropriate basis for the optimization of the energy parameters of intermolecular interactions in crystals. The details of the use of this procedure are given in the Appendix.

Some comments on the use of this procedure

Although (8) does not hold for large deviations $\mathbf{a}_{\text{calc}} - \mathbf{a}_{\text{exp}}$ which might prevail initially for an arbitrary set of starting parameters, in practice this does not cause trouble. The least-squares procedure is convergent, and as the parameters become better, the deviations become smaller and (8) is valid.*

The process is fast, since once the lattice sums have been stored, each iteration of the least-squares requires only the evaluation of (8) and the derivatives of $\mathbf{F}^{-1} \nabla V$ with respect to the parameters. These, as can be seen in the Appendix, involve nothing more than some multiplications, and the inversion of a small matrix. A typical iteration in which 14 parameters were optimized with the lattice constants of 11 molecules as observables took approximately 15 s on an IBM 370-165.

The calculation of the lattice sums themselves took approximately 20 min for 10 molecules, with a 50 Å cut-off. Although this is a considerable amount of time, this calculation has only to be done once for a molecule. This is true even if it is desired to study various potentials along with these non-bond and electrostatic potentials. An example would be the study of various hydrogen-bond potentials with these crystals as observables. The potential could be expressed as

$$V_{\text{crys}} = V_{\text{nonbond}} + V_{\text{elec}} + V_{\text{Hbond}} \quad (11)$$

where $V_{\text{nonbond}} + V_{\text{elec}}$ are the same as in (10). For this case the whole procedure would be the same, namely (9) would be solved to determine the energy parameters. However, the derivatives of V_{Hbond} would be added to those of V_{nonbond} and V_{elec} to obtain ∇V_{crys} , and similarly with the second derivatives to obtain \mathbf{F} . The derivatives of V_{nonbond} and V_{elec} could still be obtained from the lattice sums. The important point is that even if the various hydrogen-bond potentials to be investigated were not of the correct form to be written in terms of lattice sums, they are short-range potentials, and thus would not take long to calculate.

* It may be noticed that the difference between $\Delta \mathbf{a}_{\text{NR}}$ and $\Delta \mathbf{a}_{\text{true}}$ is quite large for the last molecule even for the final parameters. This structure could not be fitted with the parameters being optimized in this run. Even though they are far from the minimum, the values of $\Delta \mathbf{a}_{\text{NR}}$ still reflect the true values $\Delta \mathbf{a}_{\text{true}}$ in that both are large, and of the same order of magnitude (unlike the derivatives).

Use of different cut-off distances

The question of what cut-off distance to use in packing analysis of crystals and conformational analysis of macromolecules is often raised. The 50 Å used in the minimization here is an extreme, taken to ensure that no errors were introduced from the cut-off, for the sake of the tests performed. We have also minimized the energy with 8 and 12 Å cut-offs and the results are presented in Table 2 columns 4 and 5. It can be seen that with an 8 Å cutoff the results differ by 0.05–0.08 Å in many cases. The results for the 12 Å cut-off seem satisfactory. It should be noted that we are minimizing with respect to only 9 variables and if more degrees of freedom (such as rotation and translation of the molecules within the unit cell) are included the effect of a small cut-off can be larger. Thus 12 Å would seem to be a minimum cut-off distance in calculations involving polar molecules.

Extension of Newton–Raphson to include third derivatives

We have seen that \mathbf{a}_{true} , the calculated equilibrium unit-cell parameters obtained by solving (2) iteratively, are in general quite well approximated by \mathbf{a}_{NR} . In other words, both deviations from the experimental unit-cell parameters, $\Delta \mathbf{a}_{\text{true}}$ and $\Delta \mathbf{a}_{\text{NR}}$, are in general close to each other. However, dimethylpiperazinedione constitutes an exception. Here the calculated crystal structure deviates considerably from the experimental one, *i.e.* some components of $\Delta \mathbf{a}_{\text{true}}$ are large, *e.g.* 0.34, 0.27 and 0.37 Å for a_{1x} , a_{1z} and a_{2x} respectively. Therefore the Taylor expansion of $\nabla V(\mathbf{a}_{\text{calc}})$ as written in (6) should not be expected to converge as fast as in the other cases. Consequently, $\Delta \mathbf{a}_{\text{NR}}$ as given by (8) may not be expected to give a good approximation to $\Delta \mathbf{a}_{\text{true}}$. This expectation is substantiated in Table 2.

A better approximation for $\Delta \mathbf{a}_{\text{true}}$ should be obtained by including the third derivatives in the Taylor series of (6),

$$\begin{aligned} \partial V(\mathbf{a})/\partial a_\alpha = \partial V(\mathbf{a}_{\text{exp}})/\partial a_\alpha + \sum_{\beta} F_{\alpha\beta}(\mathbf{a}_{\text{exp}}) \Delta a_\beta \\ + \frac{1}{2} \sum_{\beta\gamma} G_{\alpha\beta\gamma}(\mathbf{a}_{\text{exp}}) \Delta a_\beta \Delta a_\gamma = 0 \end{aligned} \quad (12)$$

where $G_{\alpha\beta\gamma} = \partial^3 V / \partial a_\alpha \partial a_\beta \partial a_\gamma$. This equation can be solved iteratively for $\Delta \mathbf{a}$ by writing the *i*th iteration as

$$\begin{aligned} \Delta \mathbf{a}^i = - |F_{\alpha\beta}(\mathbf{a}_{\text{exp}}) \\ + \frac{1}{2} \sum_{\gamma} G_{\alpha\beta\gamma}(\mathbf{a}_{\text{exp}}) \Delta a_\gamma^{i-1}|^{-1} \nabla_{\alpha} V(\mathbf{a}_{\text{exp}}) \end{aligned} \quad (13)$$

In the first iteration $\Delta \mathbf{a}^0 = 0$, which corresponds to (8). This process converges quickly, taking 12 iterations in dimethylpiperazinedione, and 8 iterations for oxamide.

The results of this calculation are given in Table 3, where it is denoted by $\Delta \mathbf{a}_{\text{TD}}$. All calculations were carried out with a cut-off of 50 Å, and the third deriv-

Table 3. Application of third derivatives

	$\Delta a_{\text{true}} (\text{\AA})$	$\Delta a_{\text{true}} - \Delta a_{\text{NR}}$	$\Delta a_{\text{true}} - \Delta a_{\text{TD}}$
Oxamide			
a_{1x}	0.118	0.039	-0.015
a_{1y}	0.093	-0.021	0.025
a_{1z}	0.012	-0.004	-0.012
a_{2x}	-0.120	-0.035	-0.015
a_{2y}	-0.157	0.010	-0.008
a_{2z}	0.176	-0.031	-0.002
a_{3z}	0.091	0.016	0.012
a_{3y}	-0.119	0.006	0.004
a_{3z}	-0.002	0.007	0.004
L-cis-3,6-Dimethyl-2,5-piperazinedione			
a_{1x}	-0.335	0.699	0.124
a_{1y}	0.074	-0.122	-0.038
a_{1z}	0.270	-0.827	-0.127
a_{2x}	-0.372	0.006	0.036
a_{2y}	-0.038	0.004	-0.005
a_{2z}	0.054	0.060	0.014
a_{3x}	-0.011	0.057	0.009
a_{3y}	-0.030	-0.014	-0.005
a_{3z}	-0.011	-0.025	-0.014

atives were obtained numerically from the analytical second derivatives.

The first column of Table 3 gives the exact distance to the minimum as obtained by minimization, and is the same as column 3 of Table 2. The second column is the difference between the true distance to the minimum in column 1 and the Newton-Raphson approximation. The third gives the difference between the distance to the minimum as obtained from (12), Δa_{TD} , and the true value. The differences for dimethylpiperazinedione have been reduced from as much as 0.69 and 0.83 Å for the Newton-Raphson approximation to 0.13 Å by the use of (12). In the case of oxamide the difference between the predicted and the true distance to the minimum has been reduced to less than 0.02 Å in all but one direction. Equation (13) predicts the deviation so well that it appears to be a reliable minimization procedure if the Δa_{NR} components are smaller than ~ 0.3 Å. Thus it seems* that the benefits of the experimental lattice-sum technique can be applied to minimization as well. This gives considerable savings in time, though at the expense of space requirement for the storage of the many lattice sums involved in the third derivatives. The quantity Δa_{TD} , obviously, may also be used in the least-squares procedure instead of Δa_{NR} if for some reason the process does not converge with Δa_{NR} . Although in our experience this problem has not occurred it is not inconceivable, and the use of Δa_{TD} provides a viable alternative.

Applicability to molecular conformational analysis

In molecular conformational analysis (see review by Williams, Stang & Schleyer, 1968) potential functions

* We have only tested this procedure on the two examples cited here and further experience is necessary before it can be accepted as a standard technique.

are sought which can be used to predict the equilibrium conformations of single molecules. The optimization of the energy parameters of these functions is best derived, as in crystal packing analysis, by least-squares techniques. It is easily seen that the method presented here is directly applicable in conformational analysis as well.

The molecular energy, like the crystal energy in (5), is given as a sum of terms representing bond stretching, bond-angle bending, torsional twisting, *etc.* Consider for example the contribution of bond stretching, represented usually by $\frac{1}{2} \sum_b K_b \sum_i (b_i - b_0)^2$. K_b and b_0 are constants characteristic of a given bond type b , while b_i are the various bond lengths of that type. In optimizing the parameters K_b , one may introduce 'bond sums' like $\sum b_i^2$, $\sum b_i$, where b_i are chosen to be the experimental values and optimization is obtained by expressions of the type (9). In order to include b_0 also in the optimization, it is sufficient to expand the expression $(b_i - b_0)^2$ and treat the terms separately. Similar considerations are applicable to energy functions of bond angles, torsions *etc.*, to the extent that the energy parameters may be taken out of the 'angle sums', 'torsion sums' *etc.*, which is usually the case.

APPENDIX

Use of Newton-Raphson method in least-squares procedure

The solution of (9), to determine energy function parameters, is almost as simple as that of (4). An example is given for the potential of (10), where the observables are the 9 Cartesian coordinates of the unit-cell vectors of several amides, and the parameters we wish to adjust are those given in Table 1. The energy must be written in the form of (5),

$$\begin{aligned}
 2V_{\text{cryst}} = & A_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} r_{ij}^{-9} - B_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} r_{ij}^{-6} + Q_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} r_{ij}^{-1} \\
 & + A_{\text{HC}} \sum_{\substack{i=\text{H,C} \\ j=\text{C,H}}} r_{ij}^{-9} - B_{\text{HC}} \sum_{\substack{i=\text{H,C} \\ j=\text{C,H}}} r_{ij}^{-6} + Q_{\text{HC}} \sum_{\substack{i=\text{H,C} \\ j=\text{C,H}}} r_{ij}^{-1} \\
 & + \dots + Q_{\text{HNHN}} \sum_{\substack{i=\text{HN} \\ j=\text{HN}}} r_{ij}^{-1}
 \end{aligned} \quad (\text{A1})$$

where

$$A_{ij} = 2\epsilon_{ij} r_{ij}^{*9}, \quad B_{ij} = 3\epsilon_{ij} r_{ij}^{*6} \quad \text{and} \quad Q_{ij} = q_i q_j.$$

The derivatives can be written in a similar way by noting that

$$\frac{\partial V_{\text{cryst}}}{\partial a_{\alpha\beta}} = \sum_{ij} \frac{\partial V_{\text{cryst}}}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial a_{\alpha\beta}}. \quad (\text{A2})$$

To simplify the notation we focus on a specific unit-cell vector, \mathbf{a}_1 (the formula can be easily generalized). Since the derivatives with respect to the unit-cell vectors are not affected by interactions within the central unit cell, we can take the index i as going over atoms in

the central unit cell, and j as going over the surrounding unit cells, for the sums in (A2). Noting that r_{ij} varies with a_{1x} only through $x_j - x_i$, and that $x_j = x_j^0 + l_1 a_x + l_2 a_{2x} + l_3 a_{3x}$, one gets

$$\begin{aligned} \frac{\partial V_{\text{crys}}}{\partial a_{1x}} = & -A_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{9l_1(x_j - x_i)}{r_{ij}^{11}} \\ & + B_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{6l_1(x_j - x_i)}{r_{ij}^8} - Q_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{l_1(x_j - x_i)}{r_{ij}^3} \\ & - A_{\text{HC}} \sum_{\substack{i=\text{H,C} \\ j=\text{C,H}}} \frac{9l_1(x_j - x_i)}{r_{ij}^{11}} + \dots \\ & - Q_{\text{HNN}} \sum_{\substack{i=\text{HN} \\ j=\text{HN}}} \frac{l_1(x_j - x_i)}{r_{ij}^3}. \end{aligned} \quad (\text{A3})$$

The second derivatives can be written similarly as

$$\begin{aligned} \frac{\partial^2 V_{\text{crys}}}{\partial a_{1x} \partial a_{2y}} = & A_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{11 \cdot 9 \times l_1 l_2 (x_j - x_i) (y_j - y_i)}{r_{ij}^{13}} \\ & - B_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{8 \cdot 6 \times l_1 l_2 (x_j - x_i) (y_j - y_i)}{r_{ij}^{10}} \\ & + Q_{\text{HH}} \sum_{\substack{i=\text{H} \\ j=\text{H}}} \frac{3 \times l_1 l_2 (x_j - x_i) (y_j - y_i)}{r_{ij}^5} \\ & + A_{\text{HC}} \sum_{\substack{i=\text{H,C} \\ j=\text{C,H}}} \frac{11 \cdot 9 \times l_1 l_2 (x_j - x_i) (y_j - y_i)}{r_{ij}^{13}} \dots \end{aligned} \quad (\text{A4})$$

The important equations are of course (A1), (A3) and (A4) which give the energy, first derivatives, and second derivatives in the form of constants containing the energy parameters to be optimized, multiplied by lattice sums. The sums in the three equations (actually 9 equations for the derivatives and 45 for the second derivatives) are calculated for the experimental crystal geometry, and stored according to atom pairs. The gradient, $\nabla_a V$ and second derivative matrix F are obtained for an initial set of parameters, \mathbf{p}^0 , by multi-

plying the corresponding sums by the appropriate constants. Equation (8) is then solved for the unit cells of all crystals included as observables in the least-squares calculation. In order to solve the least-squares problem, one also needs the matrix of the derivatives of the deviations with respect to the parameters, $\mathbf{Z} = \partial(\mathbf{F}^{-1} \nabla V) / \partial \mathbf{p}$. These we obtained numerically. The iterative, linearized least-squares solution (Hamilton, 1964) is given for the i th iteration, $\delta \mathbf{p}^i = \mathbf{p}^i - \mathbf{p}^{i-1}$, by

$$\delta \mathbf{p}^i = -[(\mathbf{Z}'\mathbf{Z})^{-1} \mathbf{Z}' \Delta y]^i \quad (\text{A5})$$

where the \mathbf{Z} matrix has been defined above, and Δy is the vector of deviations between the experimental and calculated unit-cell vectors. Our proposed least-squares procedure, using the Newton-Raphson approximation and (A5) to solve (9), then becomes

$$\delta \mathbf{p}^i = [(\mathbf{Z}'\mathbf{Z})^{-1} \mathbf{Z}' (\mathbf{F}^{-1} \nabla V)]^i \quad (\text{A6})$$

and all the quantities involved in (A6) may be calculated from lattice sums as described above.

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