$\partial \ln B_0 = 1.34$, and $\partial a_x/\partial \ln q_0 = -0.99$. The corresponding elements of the Z matrix for the lattice energy of succinamide are $\partial V_L/\partial \ln A_0 = -13.57$, $\partial V_L/\partial \ln B_0 = 9.24$, and $\partial V_L/\partial \ln q_0 = -30.3$.

(4) The Hydrogen Bond. The energy functions derived through the CFF method to describe the amide hydrogen bond are seen to differ in no way from other interatomic interaction potentials. This raises a semantic question; is there such a thing as a hydrogen bond energy of the system $C=O\cdots H-N$? If such energy could be defined exclusively as the extra energy, say due to charge transfer, which should exist over and above the various nonbonded interactions, then our results could not confirm its significance. It is more appropriate to consider the hydrogen bond as the sum of all interactions which make the system $C=O\cdots H-N$ particularly stable. In this connection it is worth noting that the most general and useful definitions of hydrogen bonds are geometric.

In fact, the energy and geometric dependence of the $C=O\cdots H-N$ system as given by these potential functions are, not surprisingly, very similar to those which have long been assigned to the hydrogen bond.[8] The minimum energy of this interaction is -2.4 kcal and occurs at an $O\cdots H$ distance of 2.1 Å. This feature along with the angular dependence of this interaction will be discussed in detail elsewhere.[58]

(58) A. T. Hagler, E. Huler, and S. Lifson, Proceedings of the Rehovot Symposium on Polyamino Acids, Polypeptides and Proteins, and their Biological Implications, 1974.

III. Summary

A force field for amides has been derived by a least-squares fit to the unit cell parameters, crystal energy, and dipole moments of amides. It was found that no explicit function need be included to represent the hydrogen bond, in order to fit the properties of these crystals. Instead the qualitative features of the hydrogen bond were seen to be natural outcomes of the usual nonbonded and electrostatic energy functions. What makes the hydrogen bond interaction particular is the negligible radius of the amide hydrogen, which allows a short contact distance between the NH and the CO groups, resulting in a strong electrostatic interaction. The nonbonded van der Waals radii, r^*, as derived by the least squares, with no *a priori* assumptions as to minimum energy distances, are larger than those currently used for conformational calculations. This is the result of taking full account of the effect of compression due to intermolecular forces on the observed contact distances. The charges as derived here are in general agreement with those commonly used in conformational calculations of peptides as derived from the amide dipole moment. The charges on the NH_2 group as derived here are in better agreement with those obtained by *ab initio* calculations of formamide than with those obtained from CNDO/2 and Del Re method calculations on the same molecule.

Energy Functions for Peptides and Proteins. II. The Amide Hydrogen Bond and Calculation of Amide Crystal Properties

A. T. Hagler* and S. Lifson

Contribution from the Chemical Physics Department, Weizmann Institute of Science, Rehovot, Israel. Received December 27, 1973

Abstract: The potential functions derived in the previous paper are tested by minimization of ten amide crystals (oxamide, malonamide, succinamide, glutaramide, adipamide, urea, formamide, diketopiperazine, LL-3,6-dimethyl-2,5-piperazinedione, and cyclopropanecarboxamide). The structures of these crystals are calculated by minimizing the energy with respect to all crystalline degrees of freedom with no constraints except for the experimentally determined number of molecules per unit cell. The potentials were found to account satisfactorily for the structure, including the symmetry which was derived and not imposed, and the energy of these crystals. An analysis was made of the deviations between the calculated and experimental crystal structures in some compounds in terms of their structural features and in terms of possible weaknesses in the potential functions. Deviations in formamide, along with other compounds, indicated that inclusion of the effect of the lone pair orbitals of oxygen may possibly give a better description of the hydrogen bond energy.

In the previous paper[1] (hereafter referred to as I) a force field for intermolecular interactions in amides was derived through a least-squares fit to experimental structure and heat of sublimation of amide crystals and to dipole moments of some amides. This force field is intended to be part of a general force field for use on biological macromolecules, as well as on other systems. The hydrogen bond was found to be adequately rep-

(1) A. T. Hagler, E. Huler, and S. Lifson, *J. Amer. Chem. Soc.*, **96**, 5319 (1974).

resented by partial charges placed on the atoms C', O, H_N, and N and nonbonded parameters of the Lennard-Jones type between atom C', O, and N. The nonbonded parameters for the amide hydrogen H_N were found to be negligible.

In the present work we shall examine how well the force field derived in I fits experimental properties of amide crystals, beyond those used for the optimization in I. To this end, the energies of ten amide crystals were minimized with respect to all degrees of freedom

available to the crystal as determined by the number of molecules per unit cell. In this way the symmetries of these crystals, rather than being imposed, were derived.

We shall see that the force field fits the properties rather well in most cases and discuss the possible sources of discrepancies where they occur. In particular, deviations in crystal structure are analyzed in terms of the particular interactions responsible for the deviations, and possible improvements to the potential functions are suggested.

I. Calculation of Crystal Properties

(A) Coordinates Used in Minimizing Crystal Energy. A true *a priori* calculation of crystal structure would involve mapping of all possible periodic crystal structures without restrictions of any kind. The number (s) of molecules per unit cell, the crystallographic symmetry, as well as the quantitative derivation of all $6(s - 1) + 9$ degrees of freedom of the crystal geometry would all be derived by finding the structure of minimum energy.

Such a calculation has never been attempted. Not only the number of molecules per unit cell but also the crystallographic symmetry, and often even the unit cell vectors and other experimental constraints, have been taken from experiment by previous authors.[2-5] Only two or three degrees of freedom are usually considered. Inasmuch as the purpose of the calculation is to help determine the packing arrangement of a crystal, given the symmetry and unit cell vectors, such calculations may certainly be useful.[2] However, the calculated structure, minimized under such restricted conditions, need not necessarily be a true minimum. Thus, for purposes of deriving and testing potential functions, it is desirable to allow as many degrees of freedom as possible to vary, so as to provide the best possible test.

Here we calculate the structures of the eight amide crystals which were considered in I (for references to experimental structures and energies see I) as well as glutaramide[6] and cyclopropanecarboxamide[7] (CPC) with just one constraint, namely the number of molecules per unit cell. Crystal symmetry is derived and not assumed, and the minimization is carried out with respect to the unit cell vectors and rotational and translational degrees of freedom of the molecules within the unit cell. Since optimization[1] involved only the unit cell vectors of the eight molecules treated in I, the calculation of their crystal structure constitutes a further test of the potential functions.

The $6(s - 1) + 9$ degrees of freedom of each crystal were chosen as follows. A Cartesian coordinate system was constructed, with the x axis along the experimental unit cell vector **a** and the y axis in the **ab** plane. One molecule was arbitrarily fixed in this coordinate system. Parallel Cartesian axes were attached to all other $s - 1$ molecules in the unit cell. All nine components of the three unit cell vectors were allowed to vary in the

minimization, as were the remaining degrees of freedom of these molecules, the $3(s - 1)$ translations and the $3(s - 1)$ rotations about the z, x, and y axes, respectively, of these coordinate systems. Cartesian rotations were chosen rather than Eulerian angles, because in the latter system a small rotation may require large rotations in Eulerian angles (*e.g.*, to perform an infinitesimal rotation $\delta\beta$ around the y axis requires the Eulerian rotations (90°, $\delta\beta$, $-90°$) around the z, x', and z'' axes as they are usually defined[8]).

(B) Lattice Energy. The lattice energy of the calculated structure and the nonbonded and electrostatic contributions to it are given in Table I for both the

Table I. Results of Minimization of Ten Crystals (6–12 and 6–9 Potentials) (12 Å Cut Off)

| | Lattice energy | | | |
	Initial[a]	Final	Nonbond	Electro-static
(a) 6–12 Potential				
Oxamide	-25.6^b	-27.5^b	-12.9	-14.7
Malonamide	-31.5	-31.7	-12.5	-19.2
Succinamide	-33.1	-33.5	-15.3	-18.2
Glutaramide	-34.9	-36.0	-16.2	-19.8
Adipamide	-38.1	-38.3	-19.6	-18.7
Urea	-22.8	-23.0	-6.3	-16.7
Formamide	-16.3	-16.5	-6.3	-10.2
Diketopiperazine	-26.4	-27.7	-18.6	-9.1
LL-DMDKP	-26.4	-27.4	-19.6	-7.8
Cyclopropane-carboxamide	-21.0	-21.4	-10.3	-11.1
(b) 6–9 Potential				
Oxamide	-24.7	-25.4	-8.2	-17.2
Malonamide	-30.8	-31.0	-8.5	-22.5
Succinamide	-34.2	-34.3	-12.2	-22.1
Glutaramide	-36.0	-36.9	-12.9	-24.0
Adipamide	-38.7	-38.8	-16.6	-22.2
Urea	-23.0	-23.4	-4.1	-19.3
Formamide	-15.3	-15.7	-3.2	-12.5
Diketopiperazine	-26.2	-27.0	-16.4	-10.6
LL-DMDKP	-26.1	-27.3	-18.0	-9.3
Cyclopropane-carboxamide	-23.2	-23.7	-10.2	-13.5

[a] Note, differences between these initial results and lattice energies quoted in I arise from the use of a smaller cut off in the minimization. The energy can be more negative with the smaller cut off, indicating that the electrostatic interactions at long distances may result in a positive contribution to the energy, as is the case in urea. [b] This minimization was carried out with a total of $9^3 = 729$ unit cells and a 14 Å cut off. As in I the difference amounted to 0.4 kcal.

6–9 and 6–12 potential, along with the initial energy at the experimentally observed coordinates. The minimization was carried out with lattice sums extended over two unit cells on each side of the central unit cell, *i.e.*, a total of 125 unit cells, and with a 12-Å cut-off rule between molecules as described in I. (Both the cut off and use of 125 unit cells were tested in the case of oxamide and formamide and found to be sufficient in that neither energy nor geometry changes significantly on increasing cut off; see also ref 9 for further quantitative results for different cut-off distances.) This cut-off distance corresponds to the interaction of more than 100 molecules with each molecule in the central unit

(2) D. E. Williams, *Acta Crystallogr., Sect. A*, **25**, 464 (1969).

(3) V. M. Coiro, E. Giglio, and C. Quagliata, *Acta Crystallogr., Sect. B*, **28**, 3601 (1972).

(4) N. A. Ahmed, A. I. Kitaigorodsky, and K. V. Mirskaya, *Acta Crystallogr., Sect. B*, **27**, 867 (1971).

(5) H. A. Scheraga, Nobel Symposium 11 on "Symmetry and Function of Biological Systems at the Macromolecular Level," A. Engstrom and B. Strandberg, Ed., Almgvistand Wiksell, Stockholm, 1969, p 43.

(6) M. Hospital and J. Housty, *Acta Crystallogr.*, **21**, 413 (1966).

(7) R. E. Long, H. Maddox, and K. Trueblood, *Acta Crystallogr., Sect. B*, **25**, 2083 (1969).

(8) H. Margenau and G. M. Murphy, "The Mathematics of Chemistry and Physics," Vol. 1, 2nd ed, Van Nostrand, New York, N. Y., 1956, p 287.

(9) A. T. Hagler and S. Lifson, *Acta Crystallogr., Sect. B*, 619 (1974).

cell, for the crystals considered here. The minimization was terminated when all derivatives were less than 10^{-5} kcal/(mol Å) or 10^{-5} kcal/(mol deg) except for that of CPC for which the derivatives were of the order of 10^{-2} at termination. In all cases the decrease in energy per iteration was less than 0.01% at convergence.

As can be seen from Table Ia for the 6–12 potential, the energies of most of the calculated and experimental structures do not differ by more than a few tenths of a kilocalorie per mole. The minimum energy of oxamide is 2 kcal lower than that at the experimental structure, while those of glutaramide, diketopiperazine (DKP), and LL-3,6-dimethyl-2,5-piperazinedione (LL-DMDKP) are about 1 kcal lower. The electrostatic contribution accounts for 50% or more of the total energy for the primary amides and approximately 33% for DKP and LL-DMDKP. In this regard it is interesting to note that the force field accounts for the sublimation energy of urea in which the electrostatic energy is more than two thirds of the total, as well as for formamide which has the same nonbonded energy but 6 kcal less electrostatic energy. In urea, the strange situation of four hydrogens bonding to the same oxygen obtains, and yet the lattice energy is predicted well (see I), with no added assumptions being needed to account for this. The sublimation energy of DKP, where the electrostatic is only one third of the total, is also well accounted[1] for by the force field.

The electrostatic energy of the crystals of the homologous series $CONH_2(CH_2)_nCONH_2$ (oxamide through adipamide) is essentially constant except for oxamide. The reason for the relatively small electrostatic energy of oxamide in terms of its crystal structure[10] can be seen from Figure 1. Because there are no aliphatic groups between the two amide units in the molecule, the amide units of neighboring molecules which are not hydrogen bonded to each other are relatively close, and the dipoles of the carbonyl and NH_2 groups of these amides are in unfavorable orientations. The resulting rather large electrostatic repulsion leads to the relatively small negative energy. The distances and energies of some of these interacting groups are given in Figure 1. Malonamide has only one (CH_2) group, and therefore might be expected to have a slightly smaller electrostatic contribution then it does. However, here the amide groups in the molecule are twisted by almost 90° with respect to each other,[11] so the hydrogen bonded groups on each side of the molecules are not close.

The energies of the crystals as obtained from minimization using the 6–9 potential are given in Table Ib. They exhibit the same trends as discussed for the 6–12 potential, except for the relative contributions of the nonbonded and electrostatic contributions. In all cases the electrostatic contribution is approximately 20% greater for the 6–9 than for the 6–12 and the nonbonded contribution correspondingly smaller.

(C) Crystal Structure. The discussion of the calculated crystal structures will be divided into two parts. In the first part we present the results and compare the calculated and experimental structures. Problems involved in the comparison are discussed, along with possible solutions. In the second part we shall focus attention on some of the discrepancies that occur be-

(10) E. M. Ayerst and J. R. C. Duke, *Acta Crystallogr.*, 7, 588 (1954).
(11) P. C. Chieh, E. Subramanian, and J. Trotter, *J. Chem. Soc. A*, 179 (1970).
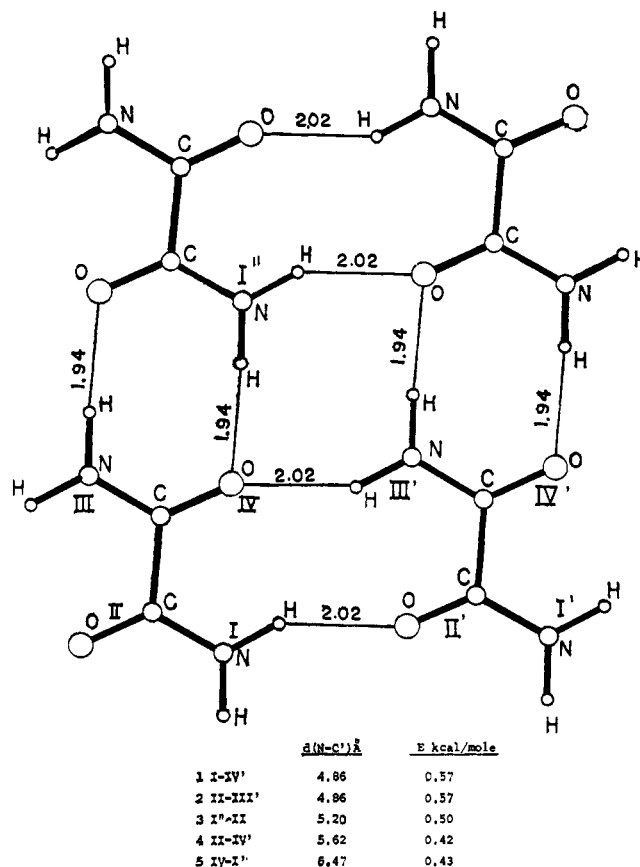
Figure 1. Planar structure of the oxamide crystal showing unfavorable electrostatic interactions which arise because of the absence of the aliphatic chain in the molecule. The roman numerals correspond to either C=O (carbonyl) or NH_2 groups. The distances given are between the nitrogen or carbon atoms of the corresponding groups.

		$d(N-C')$ Å	E kcal/mole
1	I-IV'	4.86	0.57
2	II-III'	4.86	0.57
3	I"-II	5.20	0.50
4	II-IV'	5.62	0.42
5	IV-I"	6.47	0.43

tween calculated and experimental structures and analyze the deviations in terms of possible improvements of the potential.

(1) Comparison of Calculated and Experimental Structures. Table II gives the six unit cell parameters (a, b, c, α, β, γ), the three angles between the experimental and calculated unit cell vectors $\mathbf{a}$, $\mathbf{b}$, and $\mathbf{c}$ and the $6(s - 1)$ translations and rotations of the $s - 1$ molecules in the unit cell. (Note that the experimental values of the translation and rotation are by definition zero.) The experimental and calculated unit cell volumes have also been included.

The first nine parameters are given rather than the nine Cartesian components of the three unit cell vectors (which were the ones actually used in the minimization), because comparison with experiment is more meaningful this way.

The agreement with experiment is seen from Table II to be in general quite satisfactory for most crystals. In fact, the agreement is even better than it appears from this table, for the following reason. There are many ways of determining the set of degrees of freedom, or variables, to describe the crystal geometry. As the $6(s - 1) + 9$ degrees of freedom are defined here, one of the molecules in the unit cell is arbitrarily fixed in space, for computational convenience, and the three unit cell vectors and the positions and orientations of the rest of the molecules are allowed to vary in the minimization process. The energy of the crystal depends only on the

Table II. Results of Minimization-Crystal Structure (6–12 Potential) (Distances in Å, Angles in Degrees)

	Exptl	Calcd		2	3	4	5	6	7	8
							Molecule			
							5	6	7	8
					Oxamide					
a	3.63	3.90 (0.27)								
b	5.19	5.13 (−0.06)								
c	5.66	5.67 (0.01)								
α	83.7	82.3 (−1.4)								
β	114.1	112.4 (−1.7)								
γ	115.1	120.1 (5.0)								
V	87.7	90.4								
$\angle a_{exptl} - a_{calcd}$		2.5								
$\angle b_{exptl} - b_{calcd}$		3.9								
$\angle c_{exptl} - c_{calcd}$		2.2								
					Malonamide					
a	13.07	12.94 (−0.13)	Δx	−0.05	0.14	0.19	0.07	0.13	−0.02	−0.02
b	9.45	9.59 (0.14)	Δy	0.03	−0.05	−0.09	0.09	0.04	−0.22	−0.17
c	8.04	8.02 (−0.02)	Δz	0.16	−0.12	−0.28	0.24	0.09	−0.16	0.02
α	90	90.0 (0.0)	θ_z	0.1	0.2	0.2	0.5	0.3	0.3	0.4
β	73	72.2 (−0.8)	θ_x	−0.2	0.2	−0.3	2.8	3.5	3.2	3.2
γ	90	90.0 (0.0)	θ_y	−0.2	0.1	−0.3	0.1	−0.2	−0.2	−0.3
V	950	949								
$\angle a_{exptl} - a_{calcd}$		0.6								
$\angle b_{exptl} - b_{calcd}$		1.6								
$\angle c_{exptl} - c_{calcd}$		1.4								
					Succinamide					
a	6.93	7.05 (0.13)	Δx	−0.08	−0.34	−0.24				
b	7.99	7.98 (−0.01)	Δy	−0.02	−0.02	−0.02				
c	9.88	9.89 (0.01)	Δz	−0.18	−0.24	−0.06				
α	90.0	90.0 (0.0)	θ_z	0	0.6	0.6				
β	102.5	102.4 (−0.1)	θ_x	0	0.2	0.2				
γ	90.0	90.0 (0.0)	θ_y	0	−0.0	0.0				
V	534	545								
$\angle a_{exptl} - a_{calcd}$		3.1								
$\angle b_{exptl} - b_{calcd}$		0.3								
$\angle c_{exptl} - c_{calcd}$		2.9								
					Glutaramide					
a	6.19	5.50 (−0.69)	Δx	−0.04	−0.44	−0.40				
b	8.26	8.67 (0.41)	Δy	0.19	0.44	0.22				
c	17.46	17.63 (0.17)	Δz	0.08	0.18	0.10				
α	90.0	90.0 (0)	θ_z	0.9	0.0	0.9				
β	130.8	128.3 (−2.5)	θ_x	−0.9	0.0	−0.9				
γ	90.0	90.0 (0)	θ_y	0.0	0.0	0.0				
V	675	660								
$\angle a_{exptl} - a_{calcd}$		2.7								
$\angle b_{exptl} - b_{calcd}$		0.6								
$\angle c_{exptl} - c_{calcd}$		0.1								
					Adipamide					
a	6.89	6.93 (0.04)	Δx	0.09						
b	5.15	5.12 (−0.03)	Δy	0.06						
c	10.67	10.76 (0.11)	Δz	0.08						
α	90.0	90.0 (0)	θ_z	−0.9						
β	111.0	110.0 (−1)	θ_x	0.1						
γ	90.0	90.0 (0)	θ_y	0						
V	354	359								
$\angle a_{exptl} - a_{calcd}$		0.6								
$\angle b_{exptl} - b_{calcd}$		0.4								
$\angle c_{exptl} - c_{calcd}$		0.6								
					Urea					
a	5.66	5.58 (−0.08)	Δx	−0.03						
b	5.66	5.58 (−0.08)	Δy	0.05						
c	4.71	4.74 (0.03)	Δz	−0.14						
α	90	90.02 (0.02)	θ_z	0.0						
β	90	89.94 (−0.06)	θ_x	−0.2						
γ	90	89.99 (−0.01)	θ_y	0.0						
V	151	148								
$\angle a_{exptl} - a_{calcd}$		0.2								
$\angle b_{exptl} - b_{calcd}$		0.2								
$\angle c_{exptl} - c_{calcd}$		0.1								
					Formamide					
a	3.69	3.73 (0.04)	Δx	0.26	−0.78	−0.05				
b	9.18	9.59 (0.41)	Δy	−0.47	0.03	0.42				
c	6.87	6.40 (−0.47)	Δz	0.22	−0.20	−0.34				
α	90.0	90.0 (0)	θ_z	−0.4	19.0	19.4				
β	98.0	95.9 (−2.1)	θ_x	0.1	−1.7	−1.9				

Table II (*Continued*)

| | Exptl | Calcd | | Molecule | | | | | | |
				2	3	4	5	6	7	8
γ	90.0	90.0 (0)	θ_y	1.4	0.3	0.7				
V	230	228								
$\angle a_{exptl} - a_{calcd}$	9.8									
$\angle b_{exptl} - b_{calcd}$	9.5									
$\angle c_{exptl} - c_{calcd}$	4.5									

Diketopiperazine

	Exptl	Calcd								
a	5.23	5.31 (0.08)	Δx	0.03						
b	11.55	11.54 (−0.01)	Δy	−0.02						
c	3.98	4.13 (0.15)	Δz	−0.29						
α	90.0	90.0 (0.0)	θ_z	0.0						
β	98.0	97.8 (−0.2)	θ_x	−5.4						
γ	90.0	90.0 (0.0)	θ_y	0.0						
V	238	251								
$\angle a_{exptl} - a_{calcd}$	2.5									
$\angle b_{exptl} - b_{calcd}$	2.7									
$\angle c_{exptl} - c_{calcd}$	3.6									

LL-3,6-Dimethyl-2,5-piperazinedione

	Exptl	Calcd								
a	8.06	7.75 (−0.31)								
b	6.08	6.23 (0.15)								
c	5.16	5.28 (0.13)								
α	131.7	131.6 (−0.1)								
β	−82.4	82.0 (−0.4)								
γ	106.6	108.5 (1.9)								
V	180	180								
$\angle a_{exptl} - a_{calcd}$	1.6									
$\angle b_{exptl} - b_{calcd}$	2.1									
$\angle c_{exptl} - c_{calcd}$	2.2									

Cyclopropanecarboxamide

	Exptl	Calcd		2	3	4	5	6	7	8
a	6.92	6.90 (−0.02)	Δx	−0.25	0.27	0.51	−0.22	−0.05	0.48	0.32
b	8.27	8.21 (−0.06)	Δy	−0.23	0.24	0.46	−0.29	0.19	0.51	0.05
c	16.31	16.48 (0.16)	Δz	−0.22	0.44	0.67	0.26	0.85	0.18	−0.39
α	90.0	89.9 (−0.1)	θ_z	−0.4	0.3	−0.4	−1.7	−1.0	−1.7	−1.02
β	90.2	90.7 (0.5)	θ_x	−5.1	0.6	−5.0	−8.1	−2.0	−7.9	−1.6
γ	90	90.0 (0)	θ_y	8.0	−0.6	8.0	−0.9	8.0	−0.9	8.0
V	934	933								
$\angle a_{exptl} - a_{calcd}$	4.1									
$\angle b_{exptl} - b_{calcd}$	3.6									
$\angle c_{exptl} - c_{calcd}$	5.0									

relative positions of the molecules in the crystal. By fixing one molecule the other molecules have to move further from their experimental positions than might be the case if that molecule were free to move as well. Therefore, one can translate and rotate the calculated crystal as a whole after minimization in such a way as to bring all molecules in the crystal as near as possible to their corresponding experimental positions. Such a transformation would affect the three angles between corresponding experimental and calculated unit cell vectors as well as translations and rotations of the molecules in the unit cell in the direction of showing a better fit than that which appears in Table II, although obviously there is no change in the crystal structure. In order to demonstrate this effect we present in Figure 2 the results of minimizing the energy of formamide with respect to the variables as described above. Figure 3 represents the results after the calculated crystal structure as a whole was shifted in such a way as to minimize the sum of squares of distances between the corresponding atoms in the calculated and experimental structures. It is clearly seen that Figure 3 *appears* to present a much better fit, and this of course would be reflected in the coordinates of the shifted structure. In order to get around this problem, another measure of the fit between the experimental and crystal structure is given in Table III. It includes the mean of the absolute differences, $|r_{exptl} - r_{calcd}|$, between the interatomic distances

of less than 4 Å in the experimental structure, denoted in brief as r_{exptl}, and the corresponding interatomic distances in the calculated structures, r_{calcd}. These measures involve over 100 distances in the case of oxamide with one molecule per unit cell and up to 940 distances in the case of malonamide. Also presented in Table III are the mean of the absolute differences between experimental and calculated O···H distances, N–H···O angles, and H···O=C angles in hydrogen bonds. All these quantities are, like internal coordinates, independent of the translations and rotations of the crystal as a whole, as well as the coordinate system used to describe the structure.

It can be seen from Table III that apparent large deviations in the coordinates presented in Table II do not necessarily lead to large changes in the relative positions of the molecules as measured by changes in interatomic distances. Thus although both formamide and glutaramide have fairly large deviations in some of the coordinates presented in Table II, the changes in the interatomic distances of formamide (Table III) are reasonable, while glutaramide is fit poorly by all criteria.

It is interesting to note, however, that the hydrogen bond geometry is fit very well in all crystals, even where the overall structure changes considerably, as for example in glutaramide.
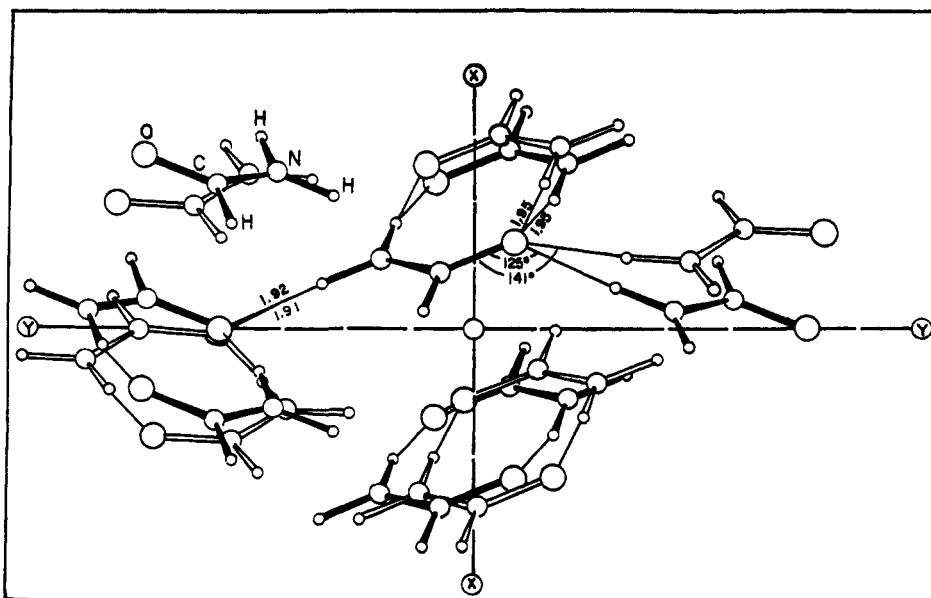
(2) **Analysis of Discrepancies. Formamide.** A

Figure 2. A comparison of the observed and calculated crystal structures of formamide. The molecules in the observed structure have solid bonds, while the bonds of the molecules in the minimized structure are open. Hydrogen bonds are shown by single lines.

Table III. Average Absolute Differences between Experimental[a] and Calculated Interatomic Distances ($d \leq 4$ Å), Hydrogen Bond Distances (r_{OH}), and Angles (N—H$\cdots$O) and (H$\cdots$O=C)

	6–12 potential				6–9 potential			
	$\|\Delta d\|$	$\|\Delta r_{OH}\|$	$\|\Delta\theta_{NHO}\|$	$\|\Delta\theta_{HOC}\|$	$\|\Delta d\|$	$\|\Delta r_{OH}\|$	$\|\Delta\theta_{NHO}\|$	$\|\Delta\theta_{HOC}\|$
Oxamide	0.16	0.03	4.3	6.8	0.10	0.01	2.8	6.6
Malonamide	0.06	0.04	1.4	1.6	0.05	0.04	1.1	1.5
Succinamide	0.07	0.01	2.3	0.5	0.04	0.01	1.1	0.3
Glutaramide	0.18	0.02	6.7	8.3	0.17	0.03	5.7	8.1
Adipamide	0.04	0.02	0.5	0.5	0.04	0.02	1.8	1.5
Urea	0.07	0.04	1.1	1.5	0.08	0.08	2.0	2.0
Formamide	0.13	0.00	6.4	8.1	0.16	0.02	5.3	9.9
DKP	0.11	0.09	11.9	8.1	0.10	0.11	9.4	8.6
LL-DMDKP	0.14	0.08	4.7	6.6	0.17	0.10	4.5	7.7
Cyclopropanecarboxamide	0.10	0.04	1.8	4.6	0.15	0.06	3.5	3.3

[a] The locations of the hydrogens, which were not seen by X-rays, were determined by minimizing the intramolecular energy.

comparison of the minimized crystal structure of formamide with the observed is given in Figures 2 and 3. From these figures it can be seen that the structure of the centrosymmetric rings has not changed by much in the minimization. The cause for the fairly large change in coordinates as reported in Table II would seem to be due to the change in the H$\cdots$O=C angle in the hydrogen bond between adjacent centrosymmetric rings. This angle has opened up from approximately 125° in the observed structure to 141° in the minimized structure. In terms of this picture we can also see why the relatively large changes in coordinates give rise to a relatively small change in both interatomic distances and energy (Tables III and I). The latter two are of course highly correlated, and as given in Table I, the entire change in structure in formamide corresponds to a difference in energy of only 0.2 kcal. Thus, the change in all these coordinates might be thought of as roughly analogous to a change in one "normal coordinate" (out of a total of $6(s - 1) + 9 = 27$) in the formamide crystal corresponding to the "inter-ring" H$\cdots$O=C angle. The energy is rather insensitive to the H$\cdots$O=C angle and, since the other "normal coordinates" do not change by much, the change in structure gives rise to only a change of 0.2 kcal.

The location of the minimum energy as a function of the H$\cdots$O=C angle is a subject of controversy, and functions with minima both at 180 and 120° have been used in conformational analysis. The latter corresponds to the assumed direction of the lone pair orbital. The results discussed above, and shown in Figures 2 and 3, indicate that the lone pairs may indeed be important and that the reason for the discrepancy in formamide may be due to the omission of the effect of these orbitals from the force field.

A summary of the changes in some of the H$\cdots$O=C and N–H$\cdots$O angles on minimization is given in Table IV. The trend in H$\cdots$O=C angles for all the molecules agrees with the hypothesis based on the analysis of formamide that the orbital position may indeed correspond to the energy minima with respect to the H$\cdots$O=C angles. It is significant that the deviation in angle is essentially independent of whether the 6–12 or 6–9 potential is used. From this we are inclined to infer that it is not an artifact inherent in one of the force fields but is rather due to a shortcoming common to both potentials such as the neglect of the lone pair orbitals. This brings out one of the advantages of analyzing conformational properties by more than one force field in that it reduces the danger of drawing
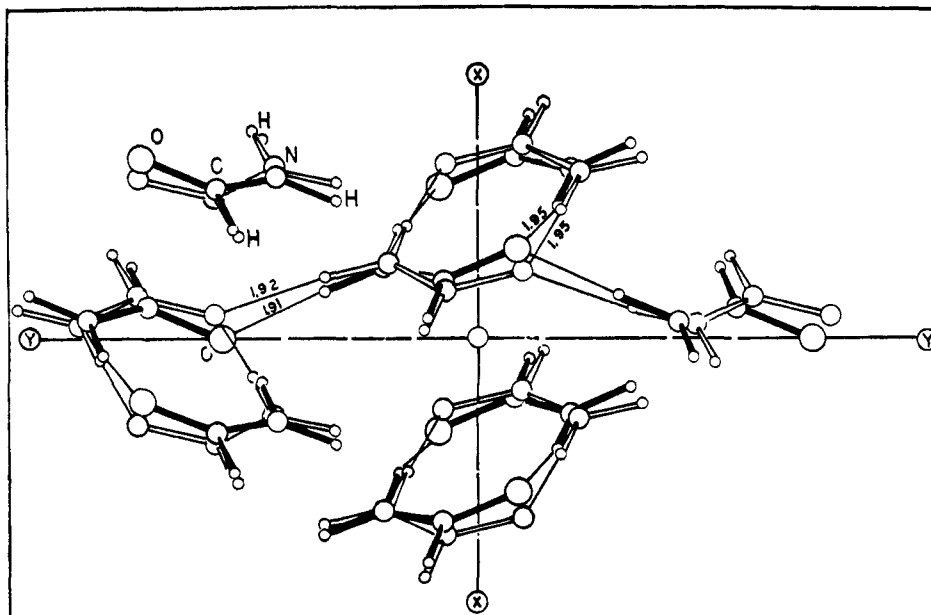
Figure 3. A comparison of the observed and calculated crystal structure of formamide. In this figure the calculated structure, obtained by energy minimization as described in the text, has been rotated and translated as a whole so as to best superpose the two structures (see the text for further discussion).

Table IV. Some Experimental and Calculated Hydrogen Bonded HOC and NHO Angles in the Amide Crystals

Crystal	—H···O=C angle—			—N—H···O angle—		
		Minimized			Minimized	
	Exptl	6–12	6–9	Exptl	6–12	6–9
Oxamide	155	163	162	29	20	21
	119	114	114	4	4	2
Malonamide	144	147	145	29	29	28
Succinamide	138	137	137	3	6	4
Glutaramide	151	162	163	28	17	17
	121	114	115	11	14	11
Adipamide	146	147	148	35	34	33
Urea	106	102	103	12	17	16
Formamide	125	141	142	19	16	13
DKP	123	131	132	4	16	13
LL-DMDKP	123	130	130	13	19	16
CPC	136	128	129	19	22	17
	115	115	118	10	6	4

conclusions which might be based on artifacts inherent in one of the potentials. The effect of inclusion of lone pair orbitals on the properties of these crystals is under investigation.

Oxamide. Oxamide is a planar molecule and to a good approximation the molecules lie in the b–c plane, forming hydrogen bonded sheets.[10] The interplanar distance of 3.0 Å is rather short (compare for example with the 3.4-Å separation in succinamide[12]) and the molecules in the parallel sheets are packed such that each oxygen atom lies between the two C' atoms of a molecule in a neighboring sheet. This gives rise to relatively short nonbonded C'–O distances of 3.1 and 3.16 Å.[10] From Table VII of I we see that $r_{C'O}*$ is approximately 3.6 Å, and thus these distances are well within the repulsive region of the nonbonded potential.

As can be seen from Table II the deviation in the crystal structure of oxamide is mainly in the vector a. Thus the calculated structure deviates from the experimental mainly in the interplanar distance, which is

larger in the calculated structure. This can also be seen clearly if the average absolute deviation of 0.16 Å (Table III) is separated into its intraplanar (0.09 Å) and interplanar (0.19 Å) contributions. In fact the C'···O distances have increased to 3.36 and 3.39 Å, respectively, in the minimized structure.

The fit of the crystal structure is better in the case of the 6–9 potential, although the same behavior is observed. Here the unit cell vector a increased by only 0.06 Å and the average absolute deviation as given in Table III is only 0.10 Å. The better fit to the interplanar distance here is due to the fact that the repulsive region of the 6–9 potential is of course much softer than the 6–12. Therefore the short C'–O contact does not result in as large a force, and the subsequent expansion of the crystal (increase in a) is smaller when calculated assuming the ninth power repulsion.

This effect may also be related to the need to take into account oxygen orbitals, though in a less direct way than the deviation of the H···O=C angles as discussed above. The oxygen atom was taken in our force field as isotropic, but if we consider the possible effects of lone pair orbitals it would clearly be anisotropic. That is, it may well have an effectively larger diameter in the plane of the lone pairs than in the direction perpendicular to the lone pairs. Although this hypothesis obviously could account for the deviation in the calculated structure (and the short C'–O non-bonded distance), it is still speculative, and its confirmation awaits the results of work in progress on the effects of inclusion of orbitals.

Glutaramide. In glutaramide the large deviations in a and b are correlated in such a way as to keep the translation axis (a + b) corresponding to the 5 Å hydrogen bonding translation axis[13] essentially constant. This accounts for the relatively small changes in the hydrogen bonding structure accompanying these rather large changes in unit cell vectors. The net result

(12) R. Davies and R. A. Pasternak, *Acta Crystallogr.*, **20**, 626 (1966).

(13) L. Leiserowitz and G. M. J. Schmidt, *J. Chem. Soc. A*, 2372 (1969).

of these changes is to decrease the distance between the planes of the aliphatic chains (decrease in **a**), while increasing the offset between the molecules in the adjacent planes containing the aliphatic chains (increase in **b**). This results in a smaller distance between the aliphatic chains in the two molecules and as seen in Table II a slight decrease in the volume of the unit cell. It is interesting to note that these changes in the structure of glutaramide were obtained not only with the 6–9 and 6–12 potentials reported here but also with the Morse potential and with other potentials considered in the intermediate stages of I.

LL-DMDKP. The largest deviation in LL-DMDKP occurs in the calculated unit cell vector **a** which is 0.31 Å shorter than the experimental vector. The deviation is even larger for the 6–9 potential where the vector **a** is 0.43 Å shorter than the experimental one. Such a deviation, although high, is well within the accuracy obtained by potential energy calculations at this time.[14–17] It is, however, certainly significant and deserves a careful analysis. The important interaction along the **a** axis is the interaction of the methyl groups of two neighboring molecules which come in contact along this direction.[18]

The problem here is the opposite of that observed in oxamide, how to account for a calculated unit cell vector **a** which is significantly shorter than the experimental one. Computer experiments on optimizing the LL-DMDKP crystal structure alone show that optimization with respect to the nine amide parameters does not solve the difficulty. Optimization with respect to C or H of the CH bond leads to a repulsive distance which is significantly larger than that of alkanes in general and is therefore unacceptable. The solution must therefore lie in the particular structure of LL-DMDKP. The methyl hydrogens are not observed by the X-ray diffraction, so we placed them at the staggered position. A 20° rotation of one methyl of the molecule in the crystal, keeping all other atoms fixed, decreases the nearest intermolecular H···H distance from 2.36 to 2.10 Å, and further rotation would reduce it to 1.96 Å. Thus if the methyl hydrogens are not located where we assumed them to be, a longer unit cell in the expected direction would be obtained. We believe that this is what actually happens, perhaps due to the librational or rotational motion of the methyls in the LL-DMDKP crystal. In this molecule it affects the **a** vector only, increasing its length significantly, while in other molecules the effect of such motion is spread over the three unit cell vectors, affecting each vector to a lesser extent.

(D) Symmetry. As discussed above no symmetry was imposed on the system except for taking the number of molecules per unit cell from experiment. In all cases the symmetry was derived to a high degree of accuracy with these potential functions. Thus, for example, in formamide the maximum deviation from the center of symmetry after minimization was 0.005 Å. In some cases the symmetry elements moved with respect to each other, but again by the same order of magnitude as the deviations from symmetry. Strictly speaking, if it is desired to prove that the symmetry is derived, the starting conformation should be perturbed in such a way as to destroy the original symmetry. In fact, this perturbation is automatically accomplished by not considering an infinite crystal. However, to further test this, the initial conformation of succinamide was changed by rotating the molecules by different amounts up to 3° and translating them by up to 0.5 Å. The resulting minimum energy structure was the same as arrived at by starting with the experimental coordinates.

II. Concluding Remarks

(A) Comparison with Other Calculations. There have been a number of calculations of crystal structures and energies involving molecules related to those considered here. Scheraga[5] has reported on calculations in which various amide and carboxylic acid crysals were minimized with respect to the lattice constants, a, b, and c. Overall agreement with observed lattice parameters was better in the amides (maximum deviation being 0.23 Å in these variables) than for the acids (maximum deviation being 0.36 Å). The deviation in sublimation energies was large, amounting to as much as 8 to 10 kcal. Revised calculations involving crystal calculations similar to these are being carried out by Scheraga at the present time.[19] Giacomello and Giglio[14] have calculated the energy of diketopiperazine as a function of three rotational degrees of freedom of one of the molecules in the unit cell (the other being generated by symmetry). In this study the unit cell vectors were kept fixed, and the 14 nearest neighbor molecules were included.

In a more recent paper, Dentini, et al.,[15] who studied the packing of N-methylacetamide (NMA), concluded that the Stockmayer potential as used by Giacomello and Giglio,[14] and themselves, was inadequate to account for the packing of this molecule. Dentini, et al., kept the unit cell vectors fixed and imposed the observed symmetry on the calculations. They then calculated the energy as a function of two translations and a rotation of the independent molecule including all interactions up to 7 Å. The dipole potential used by these workers (energy of −5 kcal/mol for linear N–H···O=C) produced considerable deviations from the experimental crystal structure (in fact N–H···O=C became collinear in the calculated structure). It was then found that the structure could be fit if the dipole on the carbonyl was directed along the orbital positions of the oxygen rather than along the C=O bond, at a distance of 0.12 Å from the oxygen. Here again, however, the hydrogen bond potential seems to have imposed the N–H dipole direction to be collinear. Although this fits NMA it is not expected to fit a wide variety of crystals where, as we have seen, the hydrogen bond geometry varies considerably.

Ramachandran, et al.,[16] have also considered the packing of NMA. Molecules within 10 Å were con-

(14) P. Giacomello and E. Giglio, *Acta Crystallogr.*, *Sect. A*, **26**, 324 (1970).

(15) M. Dentini, P. De Santis, S. Morosetti, and P. Piantanide, *Z. Kristallogr.*, *Kristallgeometric*, *Kristallphys.*, *Kristallchem.*, **136**, 305 (1972).

(16) G. N. Ramachandran, K. P. Sarathy, and A. S. Kolaskar, *Z. Naturforsch. A*, **28**, 643 (1973).

(17) D. Ferro and J. J. Hermans in "Liquid Crystals and Ordered Fluids," J. F. Johnson and R. S. Porter, Ed., Plenum Press, New York, N. Y., 1970, p 259.

(18) E. Benedetti, P. Corradini, and C. Pedone, *Biopolymers*, **7**, 751 (1969).

(19) H. A. Scheraga, *Chem. Rev.*, **71**, 195 (1971).

sidered, and the energy was also calculated as a function of two translations and a rotation. They also found NMA difficult to fit, the largest deviation from experiment being 0.6 Å for the C-methyl carbon.

From these results it can be seen that the force fields derived in I and used here give as good if not better agreement with crystal properties of amides than achieved previously. This, in spite of the fact that the force fields in I are for the most part simpler, in that no special function is invoked to account for the hydrogen bond. Furthermore, a stricter test of these force fields has been imposed, in that ten crystals were examined simultaneously and that the energy was minimized with respect to all degrees of freedom (consistent with the number of molecules per unit cell), thus avoiding the danger of apparent minima.

(B) Summary. The potential functions (6–9 and 6–12) derived in I have been used to minimize the energy of ten amide crystals. It was noted that a true *a priori* calculation of crystal structure would involve the derivation of the number of molecules per unit cell, the symmetry, as well as all remaining rotational and translational degrees of freedom of the molecules within the unit cell by finding the structure of minimum energy. Although such a calculation is not computationally feasible at the present time, the ten amide crystals treated here were minimized with respect to all degrees of freedom but the number of molecules per unit cell. It was seen that the energy at the calculated structure was at most only 2 kcal/mol lower than at the experimental structure (oxamide) and for most of the crystals the difference amounted to only a few tenths of a kilocalories per mole (for both the 6–9 and 6–12 potentials). The electrostatic contribution varies from $^1/_3$ to $^2/_3$ of the total energy for the ten crystals for the 6–12 potential and is roughly 20% greater for the 6–9. The experimental lattice energies of crystals having very different proportions of nonbonded and electrostatic energies (*e.g.*, oxamide, urea, formamide, and diketopiperazine) were well accounted for by both the 6–9 and 6–12 potential.

Most of the crystal structures were also fit satisfactorily, as judged by deviations between the experimental and calculated coordinates used to minimize the crystal, with the notable exceptions of formamide and glutaramide. It was shown, however, that since these coordinates are not internal coordinates, they do not provide a unique description of the crystal and can give exaggerated apparent deviations. Thus another measure of fit was also introduced, the mean deviation of the absolute value of the difference in interatomic distances between the calculated and experimental crystals.

An analysis of the deviations between calculated and experimental structures given by these two measures in formamide indicated that the lone pair orbitals on the oxygen may play a role in determining the structure of amide crystals and should be taken into account in the potential. It was hypothesized that the inclusion of the effect of the lone pairs could also account for the positive deviation in the calculated interplanar spacing in oxamide in terms of the resultant anisotropy of the oxygen atom. The deviations in the calculated and experimental crystal structures of glutaramide and LL-DMDKP were also discussed. The latter was shown to be due to an inadequacy in the treatment of the methyl–methyl interaction, possibly due to neglect of the librational motion of the methyl groups.

The resultant symmetry of the ten crystals was also calculated, not imposed, and was shown to be reproduced to within approximately 0.005 Å in all cases. Finally previous calculations on similar systems were discussed, and the results derived from the force fields used here were shown to compare favorably with these calculations.