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The Role of Coulomb Forces in the Crystal Packing of Amides. A Study Based on Experimental Electron Densities

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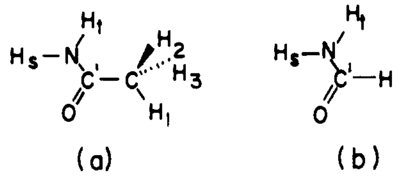
Abstract: Atomic multipole moments of acetamide and formamide were derived from low-temperature X-ray diffraction data. These atomic moments comprised net atomic charges, dipoles, and quadrupoles. The derived molecular dipole moment of formamide compares well with that as obtained from other experiments. These atomic moments were used to calculate the Coulomb energies of various hydrogen-bonding motifs found in the crystals of primary amides and of cis and trans secondary amides, demonstrating how Coulomb forces determine hydrogen bond arrangements. For the most common hydrogen-bonding motifs the dominant contributions to the intermolecular Coulomb energy are charge–charge and charge–dipole terms. Comparisons of commonly and rarely observed hydrogen-bonding motifs demonstrate that Coulomb forces generally favor the former. The linearity of the N—H···O bond, the N—(H)···O=C angle, the degree of nonplanarity of the N—H···O=C< system and the distinct stacking motifs of primary amides were each examined in terms of Coulomb forces. In some cases van der Waals interactions were calculated from known atom–atom potential parameters to emphasize the role of Coulomb interactions in determining packing arrangements.

1. Introduction

The significant contribution of Coulomb energy to the crystal energy of polar molecules has been established.[1,2] The electrostatic properties used in those studies were obtained from theoretical charge distributions[1] and, for the crystalline amides, by a force field derived from experimental structure, heats of sublimation, and molecular dipole moments.[2]

In recent years accurate experimental charge distributions have been obtained from X-ray and neutron diffraction data.[3] The aim of this work is to exploit such charge distributions for the calculation of intermolecular Coulomb energies of amide systems to account for the characteristic features of their molecular packing in the solid. We shall not calculate lattice energies of entire crystals but for some exceptions. Rather, we shall make use of acetamide (**1a**) and formamide (**1b**) as model molecules (Table I) for insertion into a variety of one-, two-, and three-dimensional packing motifs of cis and trans secondary amides **2a** and **2b** and primary amides **2c** to demonstrate the critical role played by Coulomb forces in determining hydrogen bond arrangement as well as overall packing. We shall discuss the results for amides **2a**, **2b**, and **2c** in turn.


(a) (b)

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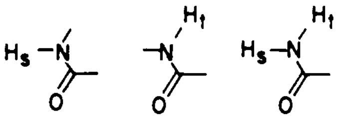
(a) (b) (c)

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2. Parameters for Energy Calculations

The intermolecular potential energy for a pair of atoms i and j separated by a distance r_{ij} can be represented in the form

$$V = -Ar_{ij}^{-6} + Be^{-\alpha r_{ij}} + \int \frac{\rho_i(\mathbf{r})\rho_j(\mathbf{r})\, dv_i dv_j}{r_{ij}}$$

Table I. Atomic Coordinates (Å) of Formamide and Acetamide in Two Convenient Orthonormal LMN Coordinate Systems ($\mathbf{r} = l\mathbf{L} + m\mathbf{M} + n\mathbf{N}$)[a]

	a			b		
atom	l	m	n	l	m	n
O	−0.6963	0.0038	0.0	1.5638	1.1300	0.0
N	1.2257	−1.1323	0.0	1.3745	−1.0946	0.0
C′	0.5547	−0.0003	0.0	2.1029	0.0012	0.0
C	1.3332	1.2910	0.0	3.6040	−0.1400	0.0
H_s(N)	0.7686	−2.0216	0.0	0.3747	−1.0688	0.0
H_t(N)	2.2250	−1.1582	0.0	1.7851	−2.0062	0.0
H_1	2.400	1.100	0.0	3.847	−1.196	0.0
H_2	1.050	1.900	+0.850	4.024	0.351	0.850
H_3	1.050	1.900	−0.850	4.024	0.351	−0.850
H	1.071	0.856	0.0	3.100	−0.100	0.0

[a] Atom labeling is shown in Figure 2.

The first two terms are van der Waals interactions, and the third term is the Coulomb energy, where $\rho_i(\mathbf{r})$ and $\rho_j(\mathbf{r})$ are the atomic charge distributions and $\mathbf{r}$ is measured from the nucleus. It is convenient to work with the atomic deformation density $\delta\rho(\mathbf{r})$ which is the electron density of the bonded atom minus that of the free atom.[4] Then the Coulomb energy is given by $\int \delta\rho_i(\mathbf{r})\delta\rho_j(\mathbf{r})\, dv_i dv_j / r_{ij}$. This integral can be evaluated via the multipole moments[5] of $\delta\rho(\mathbf{r})$. It is sufficient for this work to employ only the first three moments (see section 6), namely, the atomic net charge and the dipole and quadrupole moments.

2.1. Electrostatic Parameters. The electrostatic properties of acetamide were calculated from the deformation density distribution of acetamide in its molecular complex with allenedicarboxylic acid[6] derived from X-ray diffraction data measured at −150 °C. The atomic multipole moments of the acetamide molecules were determined from the molecular deformation density distribution by using an atomic partitioning scheme introduced by Hirshfeld.[4] This method yields atomic moments which appear to be transferable from one molecule to another of similar character. We made use of these transferability properties to derive multipole moments of formamide because no accurate low-temperature X-ray diffraction study of formamide had been reported at the time this work was undertaken.

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(1) P. H. Smit and J. L. Derissen, *J. Chem. Phys.*, **67**, 274 (1977), and references therein.

(2) (a) A. T. Hagler, E. Huler, and S. Lifson, *J. Am. Chem. Soc.*, **96**, 5319 (1974); (b) A. T. Hagler and S. Lifson, *ibid.*, **96**, 5327 (1974).

(3) P. Coppens and E. D. Stevens, *Adv. Quantum Chem.*, **10**, 1 (1977).

(4) F. L. Hirshfeld, *Theor. Chim. Acta*, **44**, 129 (1977).

(5) (a) The electrostatic energy of interaction between two charge distributions, represented by two sets of multipoles, was calculated according to the Coulomb law. The equations used were derived from an expression describing the potential energy of a charge distribution in an external electric field.[5b] (b) J. C. Slater and N. H. Frank, "Electromagnetism", McGraw-Hill, New York, 1947, p 227.

(6) Z. Berkovitch-Yellin, L. Leiserowitz, and F. Nader, *Acta Crystallogr., Sect. B*, **B33**, 3670 (1977).

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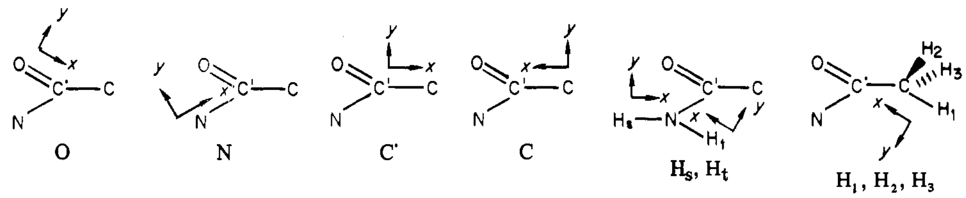
Table II. Electrostatic Properties and van der Waals Potential Parameters

a. Net Atomic Charges ($\times 10^4$) and Dipole and Quadrupole Moments ($\times 10^4$) of Acetamide in Local Cartesian Coordinate Systems x, y, z Centered on Each Atom



atom	charge,[a] e q	dipole moment,[a] e Å d_x	d_y	d_z	quadrupole moment,[a] e Å^2 μ_{xx}	μ_{yy}	μ_{zz}	μ_{xy}	μ_{yz}	μ_{xz}
O	−3900	669	−89	−8	−392	−840	−583	−46	1	0
N	−777	−477	73	10	656	814	695	33	7	−21
C'	1298	−222	−304	7	96	185	1377	42	3	−8
C(methyl)	−2776	−295	−59	13	361	−162	−163	−72	8	10
H_s,H_t[b]	1154	−475	−63	−11	265	513	421	−40	−5	0
H_1,H_2,H_3[b]	1282	−860	−33	3	256	345	128	−15	−5	6

b. Atom-Atom van der Waals Potential Parameters A, B, and α[c]

atom pair	A, kcal/(mol Å^6)	B, kcal/mol	α, Å^{-1}
H…H	29	4 900	4.29
H…C	118	18 600	3.94
H…N	91	14 300	4.00
H…O	87	19 300	4.23
C…C	421	71 600	3.68
C…N	332	55 500	3.73
C…O	335	74 800	3.91
N…N	259	42 000	3.78
N…O	261	57 500	3.97
O…O	259	78 000	4.18

[a] The net charge for atom i, $q_i = -\int \delta\rho_i(\mathrm{r})\,dv$, where $\delta\rho_i(\mathrm{r})$ is the atom deformation density and r is measured from the nucleus of atom i; the negative sign obeys the convention that electrons are negatively charged. The atomic dipole moment $d_{i,x} = -\int x\rho_i(\mathrm{r})\,dv$, where x is the component of vector r. Similar expressions apply to $d_{i,y}$ and $d_{i,z}$. The quadrupole moment tensor of $\delta\rho_i(\mathrm{r})$ has six independent components, $\mu_{i,xx}$, $\mu_{i,yy}$, $\mu_{i,zz}$, $\mu_{i,xy}$, etc. $\mu_{i,xy} = -\int xy\delta\rho_i(\mathrm{r})\,dv$. [b] The atomic moments were averaged for atoms H_s and H_t, and for atoms H_1, H_2,H_3. [c] $V = -Ar^{-6} + B\exp(-\alpha r)$.

The amide hydrogen atoms are labeled H_s and H_t to denote the cis and trans configurations of the N–H_s and N–H_t bonds, respectively. The atomic moments of acetamide are listed in Table IIa. The electrostatic properties of formamide were obtained as follows. The $CONH_2$ group of formamide was assumed to have an electron density distribution sufficiently similar to that of acetamide to be assigned the same atomic moments; the remaining formamide hydrogen atom H was taken to be sufficiently similar to a methyl hydrogen atom of acetamide and so was assigned the same moments.[7]

2.2. van der Waals Parameters. We shall provide estimates for the van der Waals energies in some cases to emphasize the role of the Coulomb interactions. The van der Waals energies were calculated from atom–atom potential parameters derived by Kitaigorodskii, Mirskaya, and Nauchitel,[8a] which are listed in Table IIb. The parameters for hydrogen, derived from hydrocarbon crystal data, were used both for hydrogen bonded to carbon and hydrogen bonded to nitrogen. We were aware of the inadequacy of this choice particularly because Hagler, Huler, and Lifson found in their derivation of a force field from amide crystals[2] that the amide hydrogen atom has no effective van der Waals radius (i.e., the parameters A and B, in Table IIb, would be zero). However, we refrained from using their van der Waals parameters because of the large diffference between the electrostatic terms in their model and ours[8b] and the obvious correlation between the atomic charges and the van der Waals parameters derived by energy minimization.

Table III. Calculated Dipole Moments (1 D = 4.808 e Å) of Formamide and Acetamide Referred to the Molecular Coordinate System **L**, **M**, **N**, Given in Table Ia.

	D = d_lL + d_mM + d_nN d_l	d_m	d_n	D
formamide	4.298	−1.200	0.015	4.5
acetamide	4.950	−0.327	0.012	5.0

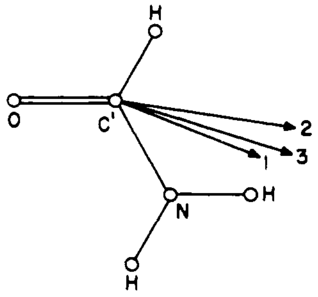


Figure 1. The dipole moment of formamide as derived by various experimental methods. The molecular l,m coordinates are given in Table Ia: (1) microwave measurement,[9a] μ = 3.71 D; (2) Low-temperature X-ray diffraction study of formamide,[9b] μ = 4.4 D; (3) present study, μ = 4.5 D.

2.3. Dipole Moments of Acetamide and Formamide. The molecular dipole moments of acetamide and formamide, derived from their atomic moments, are given in Table III. The dipole moment of formamide is compared in Figure 1 with those obtained from microwave measurements[9a] and from a low-temperature

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[7] The net charge on this formamide H atom was reduced from 0.13 e (i.e., the charge on the methyl H atom) to 0.11 e in order that the derived formamide molecule be neutral, i.e., the sum of the net atomic charges $\sum q_i$ = 0.

[8] (a) A. I. Kitaigorodskii, K. V. Mirskaya, and V. V. Nauchitel, *Sov. Phys.-Crystallogr.* (*Engl. Transl.*), **14**, 769 (1970); K. V. Mirskaya and V. V. Nauchitel, *ibid.*, **17**, 56 (1972); K. Mirsky, *Acta Crystallogr., Sect. A*, **A32**, 199 (1976). (b) Hagler, Huler, and Lifson[2] derived a charge of 0.4 e on the amide hydrogen atom compared with our value of 0.12 e. They used a charge of −0.8 e on the N as against our value of −0.08 e.

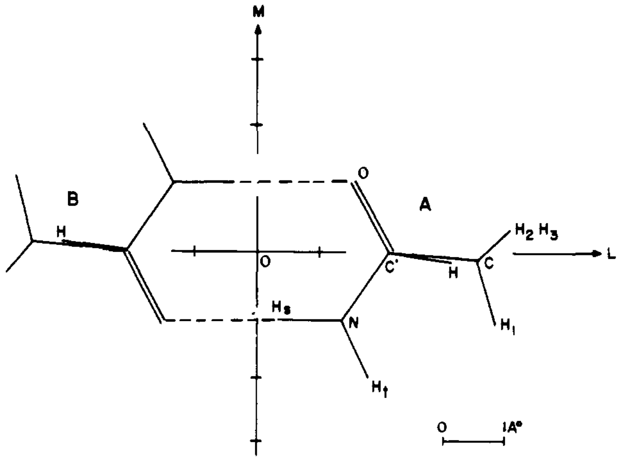
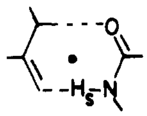


Figure 2. Hydrogen-bonded dimers of acetamide and of formamide, superimposed on each other. The coordinates of the atoms, expressed in the orthonormal L, M, N system, are given in Table Ib.

X-ray diffraction study of formamide.[9b] The agreement between the two dipole moments derived from X-ray diffraction is excellent, providing a measure of the accuracy of the atomic moments. The match with the dipole moment of the gas-phase molecule is encouraging considering the differences in both technique and medium.

3. The N—H_s···O Hydrogen Bond

The N—H_s···O bond in cis amides generally appears in either the cyclic dimer (**3**) or the chain (**4**), which we examine in turn.



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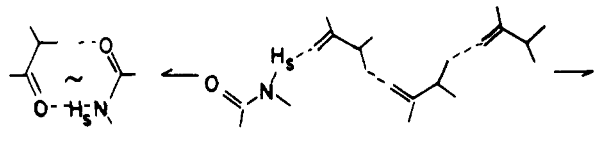

(a) view along the 2_1-axis (b) view perpendicular to the 2_1-axis

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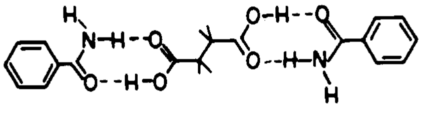
3.1. The Cyclic Dimer. Variation in Coulomb energy of the cyclic dimer (**3**) was computed as a function of relative displacement of the two molecules. The initial position of the dimer, consisting of molecules A and B, is shown in Figure 2. A and B are related by a center of symmetry, are coplanar, and are interlinked by a linear N—H_s···O bond of length[10] 2.94 Å. The displacement of B relative to A was made in three ways. (i) Molecule B was moved along the directions **L** and **M** (see Figure 2) so that the dimer was kept coplanar and centrosymmetric. (ii) Molecule B was moved essentially along the direction **N**, which is perpendicular to the plane of molecule A. (iii) The center of symmetry was relaxed and displacement took the form of a variation of the dihedral angle between the planes of A and B about the **L** axis, which is almost parallel to the C(amide)···C(amide) line.

Movement of type i measures the effect of N—H_s···O separation and N—H_s···O angle on the energy of the coplanar dimer. The contour lines of the Coulomb energy for formamide (Figure 3a) are symmetrically disposed about the **L** axis corresponding to the linear N—H_s···O bond. Making the N—H_s···O bond nonlinear by displacing molecule B from its initial position, but keeping the N—H···O distance at 2.94 Å, results in an increase of energy (Figure 4a), from its initial value of −10.7 kcal/mol. The Coulomb energy can be maintained at −10.7 kcal/mol by moving B, from its initial position, along the contour of constant Coulomb energy. However, this movement brings the two amide groups A and B together, which would be unfavorable because of repulsive van der Waals forces. Already at the initial position for which the N—H···O distance is 2.9 Å, the computed van der Waals forces between the N-H_s group and the oxygen atom are repulsive as we shall observe; consequently the most favorable structure of the formamide cyclic dimer with the given Coulomb energy is that in which the two amide groups are furtherest apart. This arrangement corresponds to a linear N—H_s···O bond. To elucidate the role of the van der Waals forces, we computed the corresponding energy map for the formamide dimer (Figure 3b). At the N—H_s···O distance of 2.94 Å the net van der Waals energy is positive. Of relevance is the relatively shallow variation in this energy along the **M** direction (which is almost perpendicular to the linear N—H_s···O vector), indicating that the linearity of the N—H_s···O bond is determined primarily by Coulomb forces. The combined Coulomb plus van der Waals energy map (Figure 3c) has a minimum $l = -0.4$, $m = 0.1$ Å which corresponds to an almost linear N—H_s···O bond of length 3.3 Å and of energy −7.2 kcal/mol. This N—H_s···O distance is 0.4 Å longer than the observed average value of 2.9 Å, suggesting an inadequacy of the atom–atom potential parameters, most probably those of the H atom bonded to N.

Displacement ii involves the separation of the planes of molecules A and B along the direction **N** by a distance Δ, keeping the H_s···O distance at 1.94 Å. The resulting rise in Coulomb energy of the formamide dimer is only 0.3 kcal/mol for Δ = 0.5 Å which corresponds to an angle N—H···O = 165°, and as large as 1 kcal/mol for Δ = 1 Å corresponding to an N—H···O angle of 150.5°. These results are consistent with the observation that although there is a tendency for coplanarity in primary amide structures, deviations up to 0.5 Å are not uncommon, but a separation as large as 1 Å was not observed.[10b]

A deviation from N—H···O linearity is less costly in energy by molecular displacement of type ii than type i. For example, the loss in Coulomb energy for an N—H···O angle of 165° is 0.3 and 0.8 kcal/mol for types ii and i, respectively.

Displacement iii involves the relative rotation of the two amide planes. When the N—H_s···O distance[11] is maintained at 2.94 Å, rotations of 0, 10, 20, and 30° yield energies of −10.7, −10.5, −9.9, and −8.9 kcal/mol, respectively. Such angular distortion has not yet been encountered in amide crystal structures, although an analogous distortion due to packing forces is found in the crystal structure of the benzamide–succinic acid complex[12] (**5**), where the angle between the planes of the amide and carboxyl groups is 20°.



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The rise in Coulomb energy of almost 1 kcal/mol caused by a twist of 20° easily accounts for the absence of such a distortion in amide dimers. However, the total absence of twist in the amide dimer in the solid can hardly be attributed to loss of Coulomb energy since a rotation of 10° induces a calculated loss of only 0.2 kcal/mol. This absence must be due to overall packing factors

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(9) (a) R. J. Kurland and E. B. Wilson, *J. Chem. Phys.*, **27**, 585 (1957). (b) P. Coppens, T. N. Guru Row, H. K. Hansen, P. Leung, and E. D. Stevens, *Acta Crystallogr., Sect A*, **A34**, S 26 (1978).

(10) (a) The average length of the N—H···O bond in primary amides is 2.94 Å.[10b] (b) L. Leiserowitz and G. M. J. Schmidt, *J. Chem. Soc. A*, 2372 (1969).

(11) Here and elsewhere in this paper we have maintained the N—H···O distance at 2.94 Å when Coulomb energy comparisons are made as the motif is varied.

(12) (a) C. M. Huang, L. Leiserowitz, and G. M. J. Schmidt, *J. Chem. Soc., Perkin Trans. 2*, 503 (1973); (b) L. Leiserowitz and F. Nader, *Acta Crystallogr., Sect. B*, **B33**, 2719 (1977).

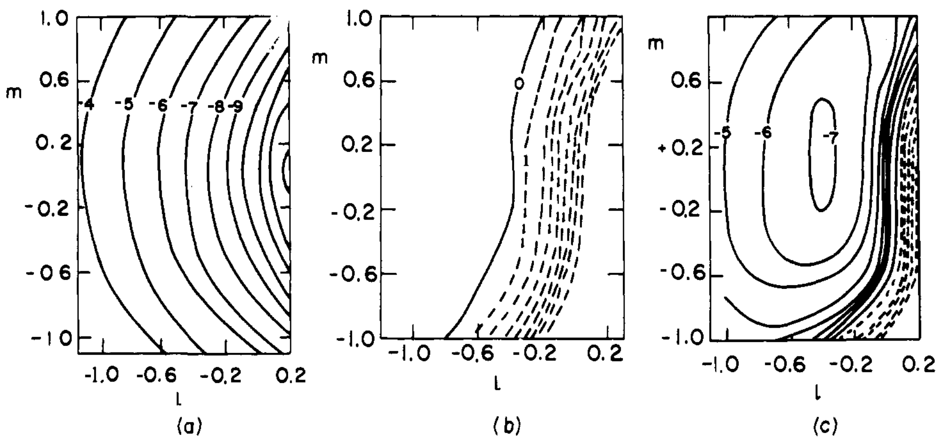

Figure 3. Energy (kcal/mol) contour maps for the formamide dimer (see section 3.1). The *l*,*m* coordinates (Å) describe the displacement of molecule B relative to its zero position in Figure 2: (a) Coulomb energy, (b) van der Waals energy, (c) sum of Coulomb plus van der Waals energy. Contour interval is 1 kcal/mol. Broken lines denote positive energy.

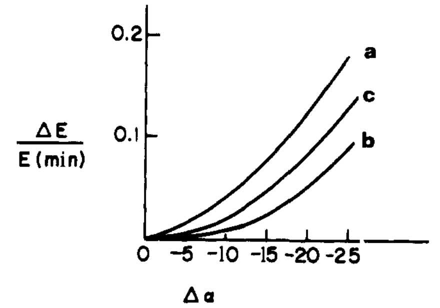

Figure 4. Variation of "normalized" Coulomb energy $\Delta E/E(\mathrm{min})$, as a function of the N—H···O angle, α say, in three different motifs containing formamide. E(min) is the minimum energy of the motif. The angle $\alpha = \alpha_0 + \Delta\alpha$, where α_0 is the initial position of α (deg) in the three different motifs. (a) The centrosymmetric cyclic dimer (**3**). α_0 is 180°; namely, the initial position corresponds to a linear N—H$_s$···O bond. E(min) = −10.7 kcal/mol (see section 3.1). (b) Two formamide molecules related by 5-Å translation as in motif **6**. α_0 = 180°, corresponding to a linear N—H$_t$···O bond. E(min) = −6.4 kcal/mol (see section 4.1). (c) Two formamide dimers related by translation as in motif **18**. The N—H$_t$···O angle is varied. α_0 = 161°, which does not correspond to a linear N—H$_t$···O bond. E(min) = −8.1 kcal/mol dimer (see section 7.1).

Table IV. Lengths of the Twofold-Screw Axis in the Amide Crystals Containing the Helical Motif (4)

compd	axial length, Å	compd	axial length, Å
formamide–formic acid[14]	3.6	2-oxazolidinone[20]	5.7
6-azauracil[15]	4.9, 5.0	*cyclo*-L-Ala-D-Ala[21]	6.2
hydroxyurea[16]	4.9	uric acid[22]	6.3
parabanic acid[17]	5.0	cyclopropanecarboxamide[23]	6.8
isohydroxyurea[18]	5.7	glutarimide[24]	7.4
α-pyridone[19]	5.7		

because the twisted dimer can be generated in the crystal symmetry only via a twofold axis, a symmetry element which cannot produce as good an overall packing as a center of inversion.[13]

3.2. The Helical Motif. An alternative mode (**4**) of forming N—H$_s$···O bonds is by a 2_1 axis. The trace of the atoms O=C—N—H$_s$ interlinked by the hydrogen bond along the 2_1 axis describes a helix. The observed lengths of this 2_1 axis in both secondary and primary amides (Table IV) range from 4.9 to 7.4 Å. Some of these hydrogen-bonding arrangements are depicted in Figure 5a. Although this motif is not uncommon in secondary amides, it has been found in only three primary amides. The motif also occurs in the formamide–formic acid complex[14] with a short

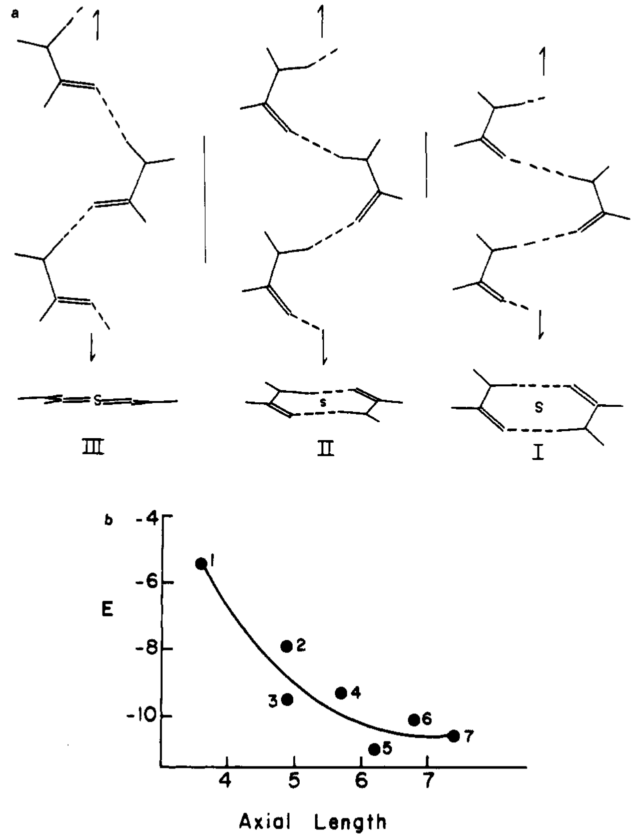

Figure 5. (a) Formamide inserted into the helical motif (**4**) in the arrangements of (i) 6-azauracil, (ii) *cyclo*-L-Ala-D-Ala, and (iii) glutarimide. Views are given both parallel and perpendicular to the 2_1 axis. (b) Coulomb energy (kcal/mol) of helical chain of formamide molecules as a function of axial repeat (Å). The points correspond to motifs found in the crystals of (1) formamide:formic acid, (2) hydroxyurea, (3) 6-azauracil, (4) isohydroxyurea, (5) *cyclo*-L-Ala-D-Ala, (6) cyclopropanecarboxamide, and (7) glutarimide.

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(13) A. I. Kitaigorodskii, "Organic Chemical Crystallography", Consultants Bureau, New York, p 65.

(14) I. Nahringbauer and G. Larsson, *Ark. Kemi*, **30**, 91 (1969).

(15) P. Singh and H. J. Hodgson, *Acta Crystallogr., Sect. B*, **B30**, 1430 (1974).

(16) I. K. Larsen and B. Jerslev, *Acta Chem. Scand.*, **20**, 983 (1966).

(17) D. R. Davies and J. J. Blum, *Acta Crystallogr.*, **8**, 129 (1955).

(18) I. K. Larsen, *Acta Chem. Scand.*, **22**, 843 (1968).

(19) B. R. Penfold, *Acta Crystallogr.*, **6**, 591 (1953).

(20) J. W. Turley, *Acta Crystallogr., Sect. B*, **B28**, 140 (1972).

(21) E. Sletten, *J. Am. Chem. Soc.*, **92**, 172 (1970).

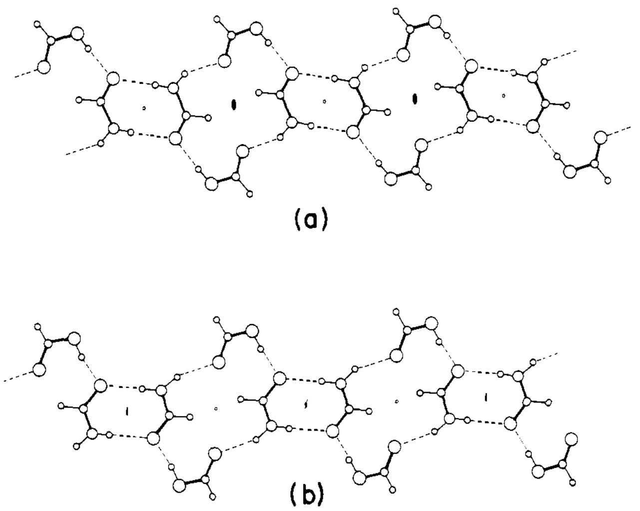

Figure 6. The two hydrogen bonding motifs of formamide:formic acid, as viewed along the unique 3.6-Å b axis, incorporating (a) the cyclic amide dimer and (b) the helical motif.

b axis of 3.6 Å. The lengths of the helical axes cluster between 5 and 7 Å. To establish whether this preferred range arises from Coulomb forces between amide groups, we computed the Coulomb energy of formamide as inserted into seven different helices[25] which appear in the crystal structures listed in Table IV. These energies are plotted against the length of the 2_1 axis in Figure 5b. The energy variation is compatible with the observed axial length cluster between 5 and 7 Å. In addition the figure demonstrates that an axial length as short as 3.6 Å is unfavorable. Only formamide, in its complex with formic acid, has such a short axis, probably imposed upon by the overall packing requirements of the complex in which the 3.6-Å axis also serves to generate a stack of formamide cyclic dimers (Figure 6). We note from a smooth curve that may be drawn through the points of Figure 5b that the helical motifs of the three primary amides hydroxyurea, isohydroxyurea, and cyclopropanecarboxamide all have energies higher than specified by the curve. We tentatively correlate this observation with the fact that these primary amides participate in at least four hydrogen bonds per molecule in their crystal structures so that these amide groups are less free to adopt the most favorable helical motif than the secondary amides.

3.3. Comparison between the Cyclic Dimer and the Helical Motif. The Coulomb energy of the helical motif (**4**), which is an infinite one-dimensional array, cannot be reliably compared with that of the cyclic dimer unless the latter is also inserted into a one-dimensional array. Consequently we constructed a stack of cyclic dimers related by translation, which is a common way of packing amide dimers, so as to include interactions between cyclic dimers.

The Coulomb energy was calculated (Figure 7) for a stack of amide dimers whose planes were kept separated by the usual distance of 3.5 Å but with the amide dimers allowed to move within their planes. The variation in energy is comparatively large. According to this energy contour map there is a wide range of ways in which cyclic dimers may be stacked with an overall Coulomb energy lower by approximately 1 kcal/mol than the best helical arrangement. (Amide stacking is discussed in detail in section 8.1.)

This comparison serves to illustrate one significant advantage of the cyclic dimer over the helical motif: the dimers are freer to adopt a more satisfactory stack than the molecules related by translation in the helical motif, which are constrained by the $\mathrm{N{-}H_s\cdots O}$ bond to adopt a more fixed arrangement.

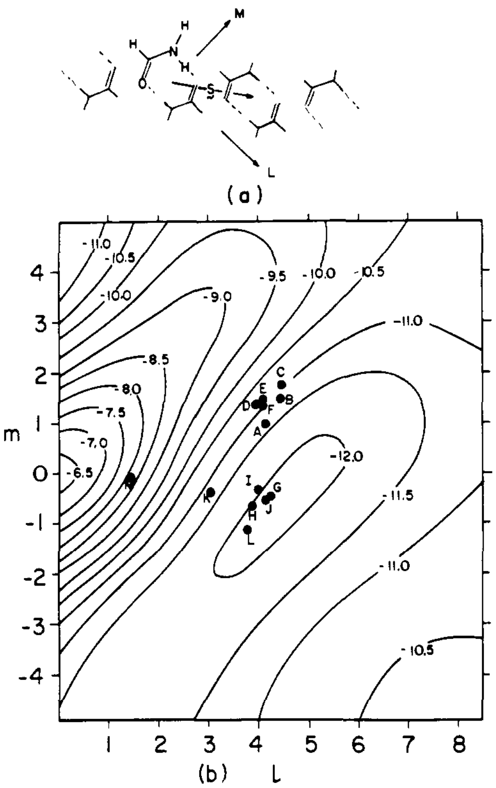

Figure 7. (a) A stack of formamide dimers, related by translation axis $\mathbf{S} = l\mathbf{L} + m\mathbf{M} + 3.5\mathbf{N}$, where 3.5 Å is the interplanar distance between the dimers. The stack is viewed along the N axis. The atomic coordinates are given in Table Ib and Figure 2. (b) Coulomb energy (kcal/mol) of the stack as a function of the coordinates l and m (Å) of axis S, keeping the n coordinate fixed at 3.5 Å. The observed l,m coordinates of the stack axis in several amide compounds, listed in Table VI and discussed in section 8.1, are shown: A = fluoroacetamide, B = acrylamide, C = furylacrylamide, D = δ-pyrazinecarboxamide, E = sebacamide, F = decanamide, G = benzamide, H = *p*-iodobenzamide, I = terephthalamide, J = *m*-fluorobenzamide, K = *m*-bromobenzamide, L = glutaramide, M = β-pyrazinecarboxamide.

A full understanding why a given molecule adopts its actual hydrogen-bonding motif requires overall packing to be taken into consideration. For example, enantiomeric *cyclo*-L-Ala-L-Ala[21] forms cyclic dimers, whereas *cyclo*-L-Ala-D-Ala[21] adopts the helical motif. It is possible to explain on steric grounds why *cyclo*-L-Ala-L-Ala, with its given molecular conformation in the crystal, cannot be inserted into the helical motif of *cyclo*-L-Ala-D-Ala. However *cyclo*-L-Ala-D-Ala can easily form cyclic hydrogen-bonded dimers so generating infinite hydrogen-bonded chains. To account for the observed crystal structure of *cyclo*-L-Ala-D-Ala, it would therefore be necessary to generate all possible crystal structures comprising these chains, for which recipes are available,[26] and to compare their lattice energies with that of the observed crystal structure.

4. The $\mathrm{N{-}H_t\cdots O}$ Bond

We now focus on the $\mathrm{N{-}H_t\cdots O}$ bond in trans amides $\mathrm{R_c{-}CONH{-}R_N}$, where $\mathrm{R_c}$ and $\mathrm{R_N}$ are residue groups. These amides form $\mathrm{N{-}H_t\cdots O}$ bonds in various motifs. The most common are translation (**6**), the glide and 2_1 axis (**7**), and the 4_1 axis (**8**).

According to a classification of the packing characteristics of trans amides[27] the intermolecular arrangement of the hydrogen-bonding system is determined mainly by the nature of the residues $\mathrm{R_c}$ and $\mathrm{R_N}$. As to preferred hydrogen bond geometry, the $\mathrm{N{-}H_t\cdots O}$ bonds tend to be linear and the $\mathrm{N{-}H_t\cdots O{=}C<}$ system tends to be coplanar, but evidence is marginal for a preferred

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(22) H. Ringertz, *Acta Crystallogr.*, **20**, 397 (1966).

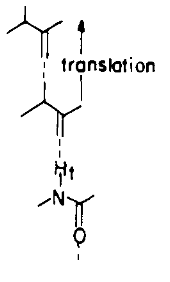
(23) R. E. Long, H. Maddox, and K. N. Trueblood, *Acta Crystallogr., Sect. B*, **B25**, 2083 (1969).

(24) C. S. Peterson, *Acta Chem. Scand.*, **25**, 379 (1971).

(25) These arrays were at least 30 Å in length. Throughout this work the lengths of the one-, two-, and three-dimensional arrays were chosen such that extension thereof had an insignificant effect on their energies.

(26) L. Leiserowitz and A. T. Hagler, to be submitted for publication.

(27) L. Leiserowitz and M. Tuval, *Acta Crystallogr., Sect. B*, **B34**, 1230 (1978).



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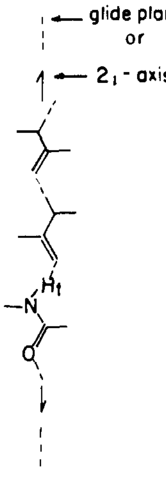
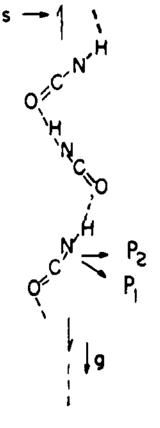
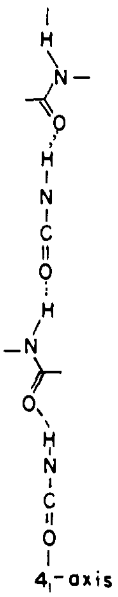


7a



7b

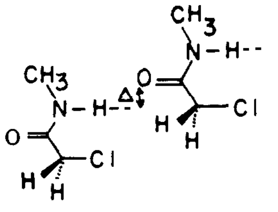


8

C=O···(H)N angle in the range 130–180°. These observations raise questions as to the role played by Coulomb interactions in determining the arrangements between amide groups.

4.1. The Translation Motif. The Coulomb energy maps for two coplanar formamide molecules related by translation (Figure 8a) is shown in Figure 8b. The energy is −6.4 kcal/mol for a collinear $N-H_t\cdots O=C$ system in which the $N-H_t\cdots O$ distance is 2.94 Å. The contour lines in Figure 8b are symmetrically disposed about the line at m = 1.1 Å, which corresponds to a collinear $N-H_t\cdots O=C$ bond. The sum of the Coulomb and van der Waals energies (Figure 8c) yields a minimum at an N—H···O distance of 3.3 Å. The shape of this minimum is extended along the direction perpendicular to that of the collinear $N-H_t\cdots O=C$ bond, which suggests that the strength of the N—H···O bond is not critically dependent on the N—H···O angle. This conclusion is supported by Figure 4b which describes the Coulomb energy change in making the $N-H_t\cdots O$ bond nonlinear, keeping the N—H···O distance at 2.94 Å. The distortion from a linear N—H···O bond in this system does not result in as significant a Coulomb energy rise as was found for the cyclic dimer (Figure 4a). For example, an offset between the N—H and O=C bonds of 0.5 Å, corresponding to an N—H···O angle of 165°, leads to an energy loss of 0.2 kcal/mol which is significantly less than for a comparable N—H···O angle in the cyclic dimer (cf. parts a and b of Figure 4). This result would seem to indicate that the linearity of the N—H···O bond in trans amides is easily distorted, certainly more so than in cyclic dimers.

To throw experimental light on this question, we consider three hydrogen-bonding structures. In the crystal structure of N-methyl-α-chloroacetamide[28] (**9**) the in-plane offset Δ between the N—H and C=O bonds is ≃1 Å. Aligning the translation-related molecules to form a collinear N—H···O=C bond would be possible with a change in conformation involving a twist of the Cl substituent about the C—C bond, otherwise too close an O···Cl distance would be incurred.



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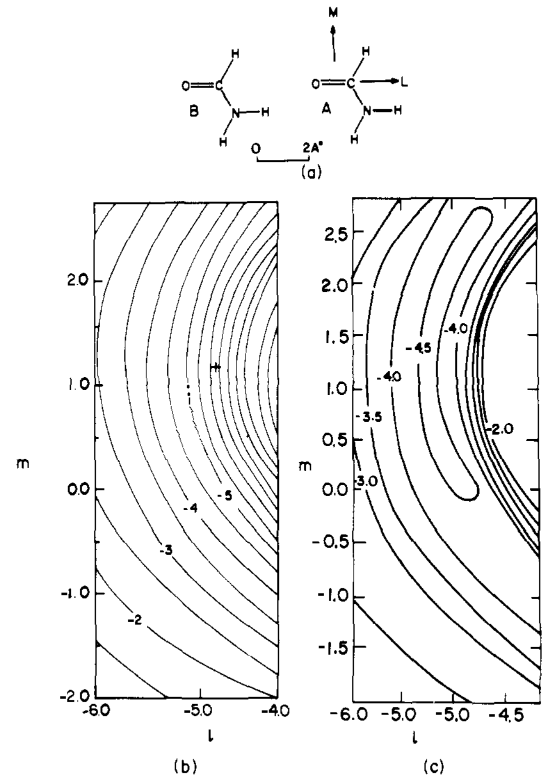
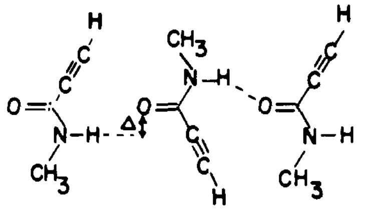


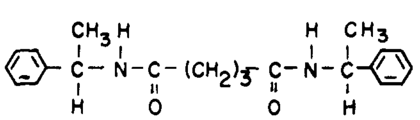
Figure 8. (a) Two formamide molecules A and B related by translation. The atomic coordinates of molecule A are listed in Table Ia. (b) Coulomb energy (kcal/mol) map for the two formamide molecules A and B where the l,m coordinates (Å) describe the displacement of B relative to A. (c) Coulomb plus van der Waals energy.

In the crystal structure of N-methyltetrolamide[27] the amide groups are interlinked by a 2_1 axis, as shown in **10**, yet the hydrogen-bonded N—H and O=C bonds are parallel as in the translation motif. The in-plane offset Δ between the N—H and O=C bonds in N-methyltetrolamide is 0.5 Å. There are no obvious steric forces between molecules within the hydrogen-bonded chain (10) which could preclude a collinear N—H···O=C bond. This offset is compatible with the Coulomb energy map (Figure 4b) according to which the energy loss for an in-plane offset between N—H and O=C bonds of 0.5 Å is 0.2 kcal/mol.



10

We determined the crystal structure of (R,R)-N,N'-(α-phenylethyl)glutarodiamide[29a] (**11**) to provide direct evidence how



$$C_6H_5-\underset{H}{\overset{CH_3}{C}}-\overset{H}{N}-\underset{O}{\overset{}{C}}-(CH_2)_3-\underset{O}{C}-\overset{H}{N}-\underset{H}{\overset{CH_3}{C}}-C_6H_5$$

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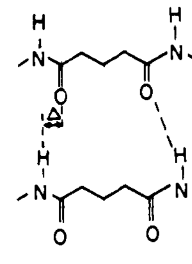
[28] Y. Koyama and T. Shimanouchi, *Acta Crystallogr., Sect. B*, **B27**, 940 (1971).

[29] (a) Z. Berkovitch-Yellin, L. Leiserowitz, and C. P. Tang, to be submitted for publication. (b) The molecules H bond along a 5-Å axis. The cell constants are a = 19.2 Å, b = 5.1 Å, c = 21.3 Å, and β = 113° with Z = 4 for space group $C2$. (c) E. Benedetti, M. R. Ciajolo, and P. Corradini, *Eur. Polym. J.*, **10**, 1201 (1974). (d) A precise measure of the linearity of these N—H···O bonds cannot be unambiguously established here since the atomic positions of the hydrogen atoms were not located.

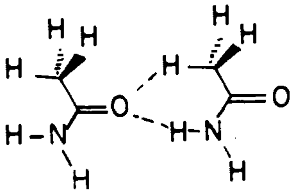
a molecule may adjust its conformation to form linear N—H···O bonds. Were the molecule to form a hydrogen-bonded chain (**12**) along its 5-Å axis[29b] such that the central moiety $CHNOC_5ONHC$ is coplanar with reasonable bond lengths and angles, the offset between the N—H and C═O bonds forming the hydrogen bond would be as large as 1 Å. In the observed crystal structure (Figure 9) the two N—H···O bonds tend to be linear ($N_1—H_1···O_1 = 171°$, $N_2—H_2···O_2 = 175°$), achieved by an appropriate conformation of the central carbon chain. *N,N'*-Bis(*β*-chloroethyl)glutaramide[29c] provides a similar example of how the molecule adjusts its conformation, tending to form nearly linear N—H···O bonds. The two amide groups of the molecule form N—H···O bonds by translation along two different 5-Å axes.[29d]



12

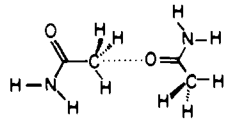
Deviation from collinearity of the $N—H_t···O═C$ system can also be made by an out-of-plane displacement between the translation-related molecules. Separating the planes along the N direction of two translation-related formamide molecules interlinked by an $N—H_t···O$ bond of 2.94 Å leads to a Coulomb energy increase of 0.2 and 0.7 kcal/mol for displacements of 0.5 and 1.0 Å, respectively. In crystal structures such as oxamide, *N*-methylsorbamide, and *N*-methyldipropylacetamide the offset is less than 0.02 Å.[10b,27] There are crystal structures such as benzamide in which the offset is 1 Å; the bulky phenyl group precludes a smaller offset.[10b] That an offset up to 0.5 Å results in a negligible loss of hydrogen bond energy is exemplified by the crystal structures of fluoroacetamide and suberamide. Their offsets are 0.5 and 0.4 Å, respectively,[10b] despite the fact that the sizes of their residue groups would not hinder coplanar hydrogen-bonded systems.

The Coulomb energy map (Figure 10) for two coplanar acetamide molecules related by translation shows almost parallel contour lines at right angles to the O═C bond direction. This map suggests a "bifurcated" N—H···O and C—H···O hydrogen bond (**13**) but seems to overestimate the acidic properties of the C—H bond relative to the N—H bond. Nevertheless this C—H···O interaction is indirectly supported by comparing the crystal structures of urea–barbital[30a] and acetamide–barbital[30b] where urea is isomorphously replaced by acetamide. Urea forms a bifurcated bond (2.95, 3.16 Å) with an oxygen atom of barbital (Figure 11a). Acetamide makes similar contacts in which an acetamide C—H···O distance of 3.45 Å replaces a urea N—H···O bond (Figure 11b). To further substantiate this C—H···O interaction, we calculated a Coulomb energy of −2.2 kcal/mol for motif **14** in which the $C(H_3)$ and O atoms are separated by 3.3 Å, which is a reasonable van der Waals C···O distance.



13

4.2. The Glide Motif. Various arrangements of the glide motif (**7**) have been observed, depending on the orientation of the amide group with respect to the glide plane. Two distinct arrangements are shown in **7a** and **7b**. In **7a** the normal $\mathbf{P}_1$ to the amide plane is perpendicular to both the glide axis **g** and to $\mathbf{P}_2$ which is the normal to the glide plane. This geometry ensures a coplanar hydrogen-bonded system in which the one variable for a linear $N—H_t···O$ bond is the $C═O···(H_t)N$ angle θ depicted in **15**. In motif **7b** the normal $\mathbf{P}_1$ makes an angle $90 - \phi$ with $\mathbf{P}_2$ in such a way that $\mathbf{P}_1$ lies within the plane defined by $\mathbf{P}_2$ and the glide axis **g**. In this motif the $N—H_t···O═C<$ system is nonplanar where ϕ is the dihedral angle between the N—H bond and the amide plane as illustrated in **16**.



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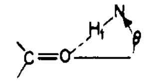

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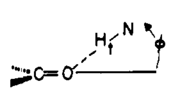

16

A measure of the variation in Coulomb energy for the two motifs (**15** and **16**) may be obtained from the electrostatic potential energy surface about the oxygen atom for a unit positive charge placed 2 Å from the oxygen atom (Figure 12). The minimum lies at $\phi = 0°$ and $\theta = 20°$. There is a significant energy loss (of 30%) as ϕ increases from 0 to 90° at $\theta = 0°$, which in motif **16** corresponds to a change from a collinear $N—H_t···O═C$ bond to one where $N—H_t$ is perpendicular to the carbonyl system O═C<. The energy rise is ≃10% for a change in θ from 0 to +60°, whereas a change in θ from 0 to −60° results in an energy increase ≃30%. This potential surface provides only a crude description of the variation in energy as a function of ϕ and θ for motifs **15** and **16**. A more detailed analysis is given below.

4.2.1. The Coplanar Glide Motif. The Coulomb energy was computed for two coplanar formamide molecules related by a glide and interlinked by a linear $N—H_t···O$ bond of 2.94 Å. The angle θ was allowed to vary[31] from −5° to +55° (Figure 13a). The energy minimum of −6.35 kcal/mol occurs at $\theta = 15°$. The maximum variation in energy is as low as 0.4 kcal/mol within the θ range examined, which is compatible with the observation that there appears to be no preferred θ angle in the glide motif (**7a**).[27]

We compare the Coulomb energy of this glide motif with that of the translation motif (**6**) by generating chains of formamide molecules in both motifs with linear $N—H_t···O$ bonds; the angle θ for the glide motif was set at the optimum value of 15°. Their Coulomb energies are almost equal at −14.4 and −14.5 kcal/mol, respectively, which is consistent with the observation that the mode of interlinking secondary trans amides $R_c—CONH—R_N$ is determined mainly by the residues R_c and R_N.[27]

4.2.2. The Nonplanar Glide Motif. Several amide crystal structures embody the N—H···O bond in which the $N—H_t$ vector makes an angle ϕ with the amide plane which differs appreciably from zero, as shown in **16**. These include *N*-methylpropiolamide[27] ($\phi = 26°$), (*RS*)-*N*-acetyl((1-naphthyl)ethyl)amine[32] ($\phi \simeq 50°$), urea[33] ($\phi \simeq 118°$), and the urea–barbital and acetamide–barbital

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(30) (a) G. L. Gartland and B. M. Craven, *Acta Crystallogr., Sect B*, **B30**, 980 (1974). (b) I. Hsu and B. M. Craven, *ibid.*, **B30**, 974 (1974).

(31) There is sufficient evidence[27] that the glide motif (**7a**) is precluded, on steric grounds, if the angle θ is appreciably less than −5°.

(32) S. Weinstein and L. Leiserowitz, *Acta Crystallogr., Sect. B*, **B36**, 1406 (1980).

(33) J. E. Worsham and H. A. Levy, *Acta Crystallogr.*, **10**, 319 (1957).

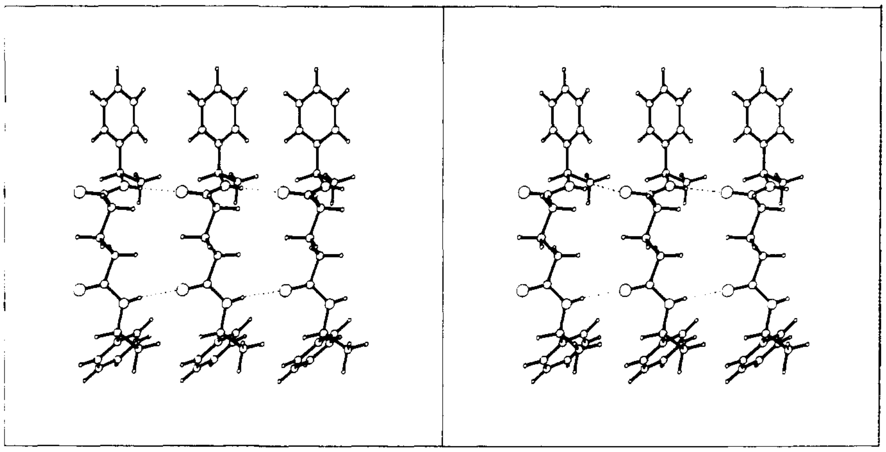


Figure 9. Stereoview of the hydrogen bond motif of (*R*,*R*)-*N*,*N'*-(α-phenylethyl)glutarodiamide.

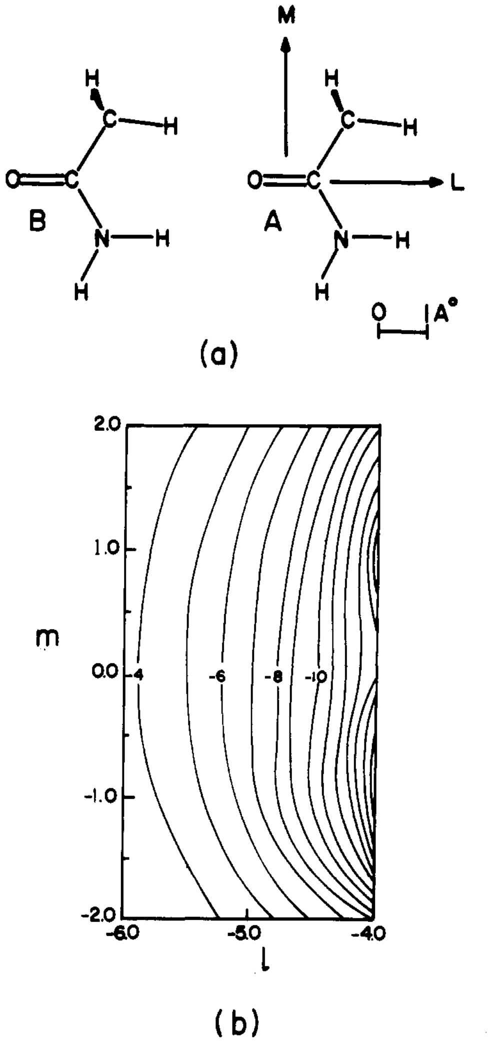


Figure 10. (a) Two acetamide molecules A and B related by translation. The *l*,*m*,*n*, atomic coordinates of molecule A are listed in Table Ia. (b) Coulomb energy map (kcal/mol) obtained by moving molecule B relative to A in the *l*,*m* coordinate system (Å).

complexes.[30] The Coulomb energy, shown in Figure 13b, is for two formamide molecules related by the glide motif (**7b**) and interlinked by a linear N—H$_t$···O bond of 2.94 Å, in which ϕ was allowed to vary from 0 to 90°. There is a rise in energy that increases with increasing ϕ. At $\phi = 50°$ the loss in energy is 0.6 kcal/mol, whereas at $\phi = 90°$ the loss is 2 kcal/mol. This loss at $\phi = 50°$ is sufficiently low that we may infer that in the crystal structure of (*RS*)-*N*-acetyl((1-naphthyl)ethyl)amine, for which $\phi \simeq 50°$, molecular packing forces could easily compensate for this energy loss. This argument is supported by the crystal structure of the enantiomeric form of *N*-acetyl((1-naphthyl)ethyl)amine[32] in which the amide groups are hydrogen bonded along a 5-Å translation axis with an approximately collinear N—H···O=C bond. It is instructive that no secondary amide crystal structure has been observed with a ϕ angle larger than 50°, consistent with the energy variation in Figure 13b.

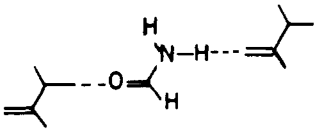
In the crystal structure of urea, the motif (**16**) is generated by $\bar{4}$ symmetry. The pertinent hydrogen bond is formed by atom H$_s$ and not H$_t$. We calculated the Coulomb energy of a model arrangement similar to that of urea, comprising two formamide, or two acetamide, molecules related by $\bar{4}$ symmetry (Figure 14a). The N–H$_s$···O distance was kept at the observed value of 3.03 Å and the N—H$_s$···O angle was varied. The energy minima (Figure 14b) occur at angles of 166° and 155° for formamide and acetamide, respectively, in good agreement with the observed value of 167.5° for urea. The energy minimum of –5.9 kcal/mol is almost as low as that computed for two formamide molecules interlinked by a N—H$_t$···O bond by 5-Å translation (–6.4 kcal/mol), suggesting that the motif, found only in urea, is precluded for primary amides and secondary cis amides probably because of the disadvantages of $\bar{4}$ crystal symmetry and not because of unfavorable Coulomb energy.

5. The N—H···O Distances in Cis and Trans Amides

The average N—H$_s$···O and N—H$_t$···O bond lengths, for cis and trans secondary amides, respectively,[27] are the same and equal to 2.85 Å. Therefore a reliable calculation of the N—H$_s$···O and N—H$_t$···O distances corresponding respectively to the energy minima of the two commonly occurring motifs **3** and **6** should reproduce those observations. We cannot make a reliable comparison because of the deficiencies of the van der Waals parameters, especially those for the amido hydrogen atom.

6. Atom and Multipole Moment Contributions to the Coulomb Energy of the H Bond

Here we present the various contributions to the Coulomb energies of two common motifs which involve N—H$_s$···O and N—H$_t$···O bonds, respectively, namely the cyclic dimer (**3**) and the 5-Å translation motif (**6**). For simplicity we do not consider a stack of molecules as in motif **6** but rather a trimer (**17**), so limiting the interactions to those between the central molecule and its two neighbors. We have used formamide as the model molecule for the calculation. In both motifs the N—H···O=C< system is coplanar and the N—H···O bond length is 2.94 Å.



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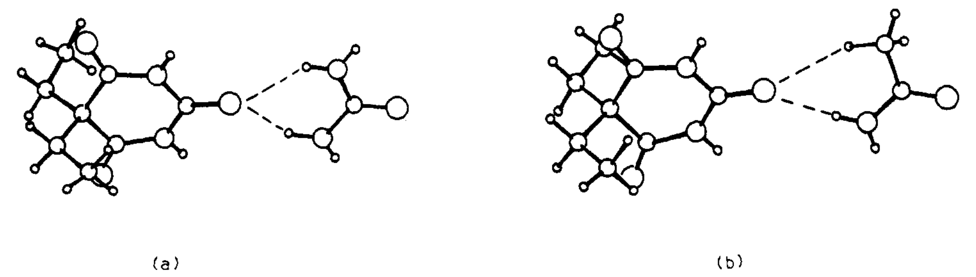

(a) (b)

Figure 11. Hydrogen bond motifs of (a) barbital and urea and (b) barbital and acetamide.

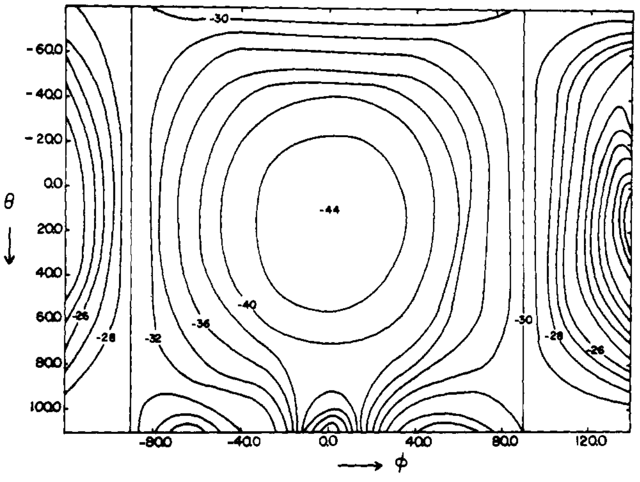


Figure 12. Potential energy surface (kcal/mol) about the oxygen atom of acetamide. The angles ϕ and θ (deg) are defined in **15** and **16**.

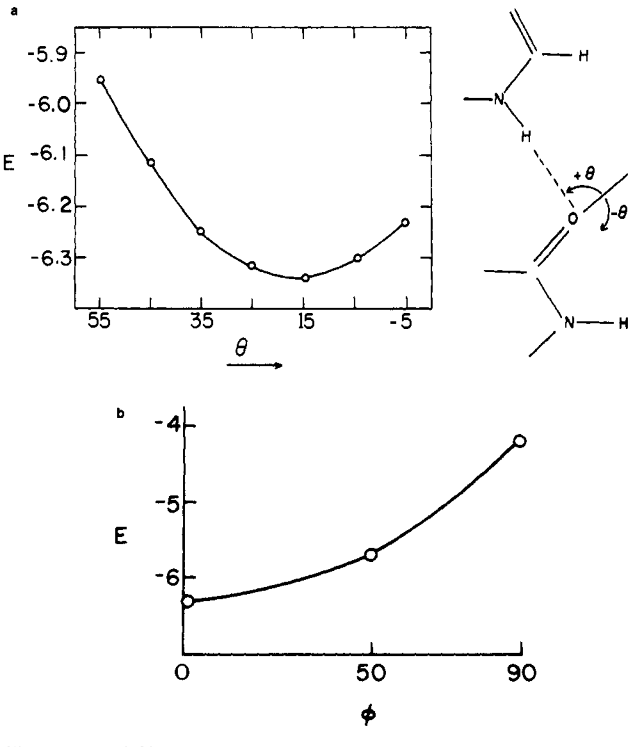


Figure 13. (a) Variation in Coulomb energy (kcal/mol) of two coplanar formamide molecules related by a glide (motif **7a**) as a function of the angle θ (deg). (b) Coulomb energy (kcal/mol) of two glide-related formamide molecules appearing in motif **7b** in which the angle ϕ, defined in **16**, was varied from 0 to 90°.

Table V lists energy sums over the complete molecule for each of the contributing interactions between the multipole moments, as well as the net interaction energies of each atom with all atoms of the neighboring hydrogen-bonded molecules.

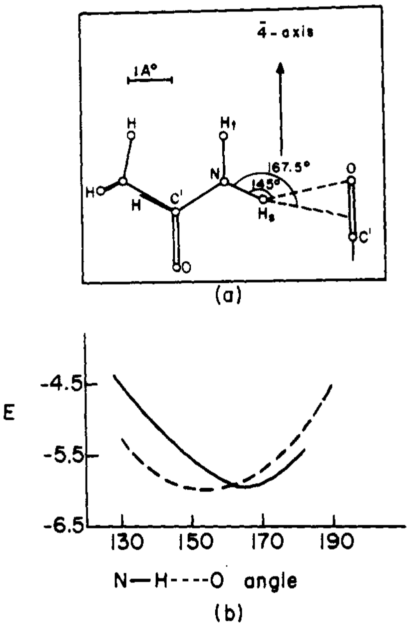


Figure 14. (a) Two formamide, or two acetamide, molecules related by $\bar{4}$ symmetry, as in urea. The arrangement is drawn for an N—H_s···O angle of 145°. The angle observed in the crystal structure of urea is 167.5°. (b) Variation in Coulomb energy (kcal/mol) for formamide (full line) and acetamide (broken line) as a function of the N—H_s···O angle (deg).

The sums of the atomic charge–charge (i.e., q–q) and the charge–dipole (q–d) energy terms in Table Va constitute the major contributions of the net energies in both motifs. The dipole–dipole and charge–quadrupole terms each make up 5% of the net energies. Dipole–quadrupole and quadrupole–quadrupole contributions are insignificant. According to Table Vb the intermolecular interactions involving the oxygen and hydrogen atoms of the reference molecule participating in the N—H···O bonds and all atoms of the neighboring molecules contribute 90% to the total energy. However, the sums of the contributions involving these oxygen and hydrogen atoms only (i.e., O···O, H···H, and O···H) are −3.7 and +1.1 kcal/mol in motifs **3** and **17**, respectively. Consequently, we may infer from the energy contributions of the charge–dipole terms and the contributions of atoms other than oxygen and hydrogen that the total Coulomb energy depends not only on the length of the hydrogen bond but also on the relative orientations of the amide groups.

7. Primary Amides

We now consider the hydrogen-bonding modes of primary amides which incorporate both N—H_s···O and N—H_t···O bonds. For these molecules the N—H_s···O bond is generally achieved via the cyclic dimer (**3**) and only very rarely by a 2_1-axis, unlike secondary cis amides. A common way of interlinking the cyclic dimers via N—H_t···O bonds is by translation along a 5-Å axis resulting in motif **18**. The 5-Å translation axis also serves to interlink primary amide molecules by N—H_t···O bonds about a 2_1 axis as depicted in **19**. This motif has been observed only in

Table V. Contributions to the Coulomb Energy (kcal/mol) of Formamide in the Cyclic Dimer (3) and the 5-Å Translation Motif (17)

a. The Energy Contributions of the Various Multipoles Involving All Atoms *i* of One Formamide Molecule and All Atoms *j* of Its Hydrogen-Bonded Neighbors[a]

multipolar terms[a] summed over all atoms *i* and *j*	energy for cyclic dimer motif 3	Energy for 5-Å translation motif 17
$\sum_{ij} q_i q_j$	-6.00	-7.73
$\sum q_i d_j$	-4.33	-5.15
$\sum q_i \mu_j$	0.34	0.82
$\sum d_i d_j$	-0.61	-0.89
$\sum d_i \mu_j$	-0.17	0.36
$\sum \mu_i \mu_j$	0.13	-0.07
total energy, E	-10.6	-12.7

b. The Coulomb Energy E_i for Atom *i* of the Reference Formamide Molecule and All Atoms *j* of Neighboring Molecule(s)

atom *i*	E_i motif 3	E_i motif 17
O	-4.75	-6.04
N	0.38	0.69
C'	-0.32	-0.57
H_s	-4.48	-0.58
H_t	-1.37	-5.41
H	-0.11	-0.79
total energy, E	-10.6	-12.7

[a] The multipolar contributions are labeled: charge-charge = q_i, q_j; charge-dipole = q_i, d_j; charge-quadrupole = q_i, μ_j.

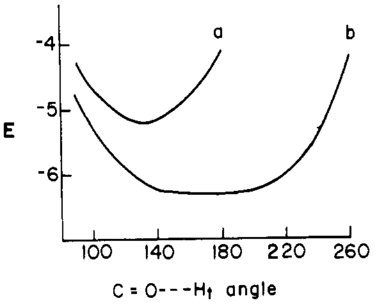
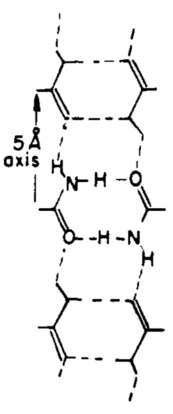


Figure 15. Coulomb energy (kcal/mol) as a function of the C=O···H_t angle (deg): (a) motif **22**, which contains two N—H···O bonds; (b) motif **23**, which contains one N—H_t···O bond.

the crystal structures of adipamide,[34] *p*-aminobenzamide,[35] and *o*-chlorobenzamide.[36]



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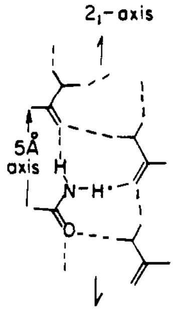
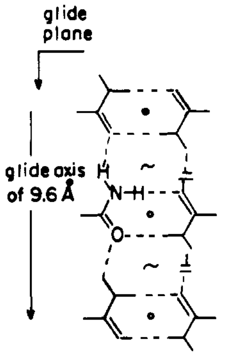
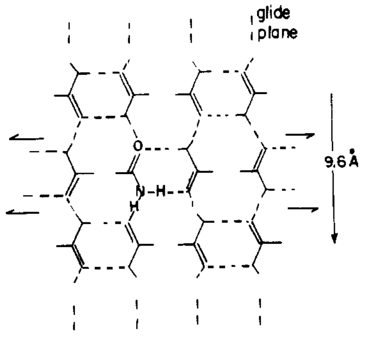


19

Another common way of interlinking the cyclic dimers is by a glide of axial length 9.6 ± 0.3 Å. If the angle between the glide and amide planes is between 30 and 70°, a layer structure (**20a**), labeled the "shallow"-glide motif,[10b] is generated. This motif does not impose severe constraints on the size of the residue R_c and is often encountered. If the angle between the glide and amide planes is close to 90°, an amide sheet structure (**20b**) is generated, designated as a "steep"-glide motif.[10b] This motif imposes severe constraints on the size of the residue R_c in monoamides R_c—$CONH_2$ and diamides H_2NOC—R_c—$CONH_2$.

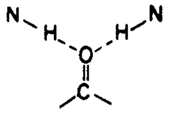


20a



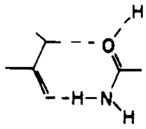
20b

It had been shown that amide molecules tend to crystallize in the steep-glide motif (**20b**) if the constraints on R_c are satisfied.[10b] Only in this molecular arrangement, with the possible exception of the hexameric crown motif of rhombohedral acetamide,[37] can a geometry about the oxygen atom be achieved in which the hydrogen bonding system (**21**) is coplanar, the N—H···O bonds



21

are linear, and the C=O···H angles are ≃120°. Therefore it was concluded that motif **21** is the preferred hydrogen bond system for a carbonyl oxygen atom which participates in two hydrogen bonds.[10b] We tested the validity of this deduction by computing the Coulomb energy of interaction between a formamide cyclic dimer and an isolated hydrogen "atom" H_t placed 1.94 Å from the oxygen atom as shown in motif **22**. The electrostatic properties



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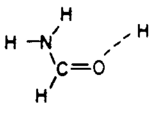

23

of H_t were represented by its charge and its dipole moment which, being almost parallel to the N-H_t bond (see Table IIa), was set parallel to the line O···H_t so as to simulate a linear N—H_t···O bond. The energy minimum (Figure 15a) occurs at a C=O···H_t angle of 130° which is in agreement with a preference for the hydrogen bonding system (**21**). This energy minimum is much sharper than that (Figure 15b) obtained from an analogous motif (**23**) comprising only one formamide molecule and a H_t "atom" so forming only *one* N—H···O bond. This comparison is compatible with the observation that the geometrical requirements for preferred N—H···O geometry in a motif comprising a primary amide oxygen atom involved in an N—H_t···O and an N—H_s···O bond are more stringent than for a secondary trans amide whose oxygen atom participates only in an N—H_t···O bond.[27]

There is a third glide motif (**24**), in which the N—H_s···O bond is generated, not about a center of inversion as in motif **20a**, but

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(34) M. Hospital and J. Housty, *Acta Crystallogr.*, **20**, 626 (1966).

(35) M. Alleaume, Thesis, University of Bordeaux, 1967.

(36) Y. Kato, Y. Takaki, and K. Sakurai, *Acta Crystallogr., Sect. B*, **B30**, 2683 (1974).

(37) W. A. Denne and R. W. H. Small, *Acta Crystallogr., Sect. B*, **B27**, 1094 (1971).

(38) L. Leiserowitz and D. Rabinovich, *J. Chem. Soc. A*, 2367 (1969).

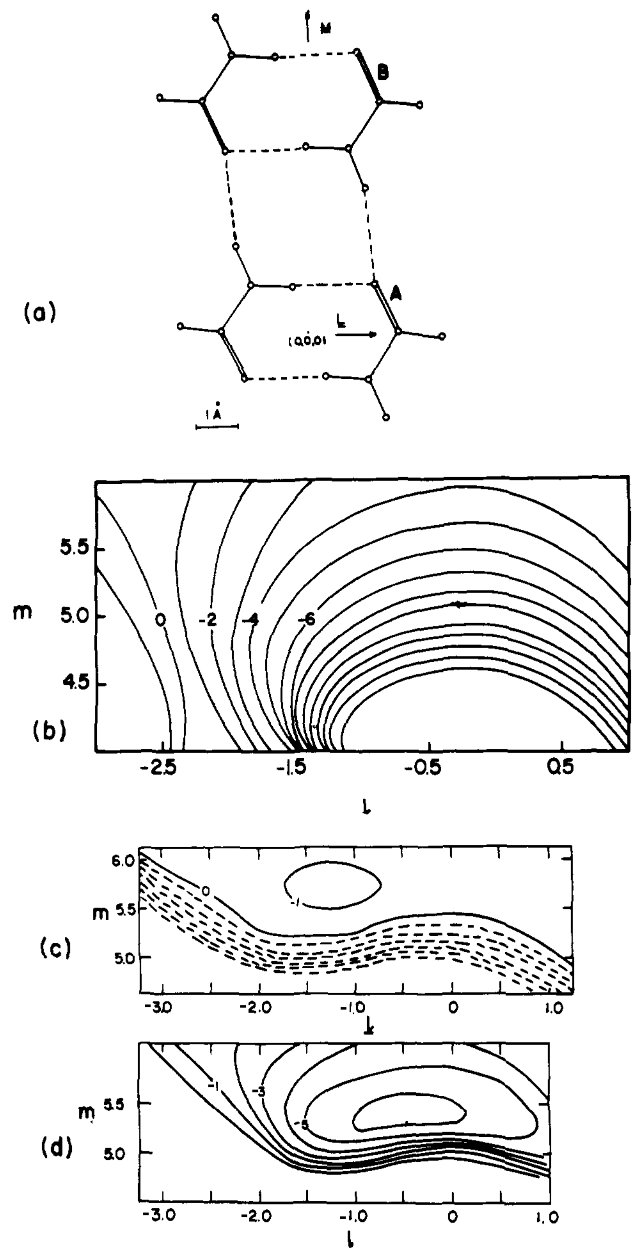
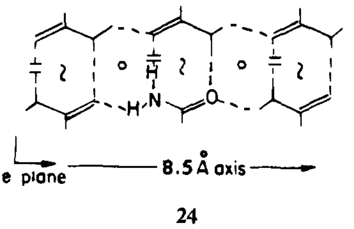


Figure 16. (a) Two formamide dimers A and B related by translation. The atomic coordinates of A are given in Table Ib. Parts b, c, and d depict the energy variation of the A, B pair as a function of the l,m coordinates (Å) of the dimer B relative to A: (b) Coulomb energy, (c) van der Waals energy, (d) Coulomb plus van der Waals energy.

about a 2_1 axis of length 5.8 ± 1.0 Å. Thus this motif incorporates the helical chain (**4**) found in secondary cis amides (see section 3.2). The helices are joined by N—H_t···O bonds along a glide axis of 8.5 ± 0.5 Å forming a layer. This motif occurs rarely and so we refer to it as the rare-glide motif.



24

We shall compare by Coulomb energy calculations the ribbon motifs (**18** and **19**) and the layer motifs (**20a** and **24**). A meaningful comparison between the ribbon and layers motifs would require the construction of various layers from the former motif, which was not undertaken.

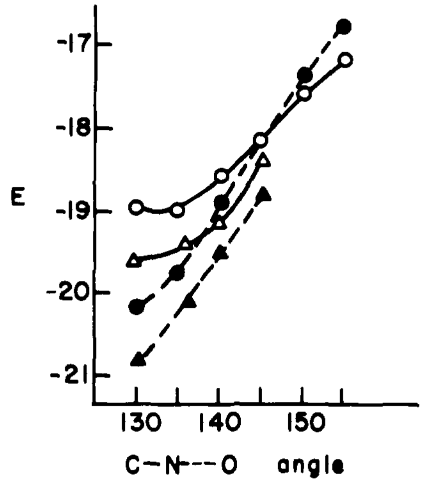


Figure 17. The Coulomb energies (kcal/mol) of formamide (full lines) and of acetamide (broken lines), for each molecule inserted into motifs **18** and **19**. The C—N(H_t)···O angle (deg) between atoms of molecules related by 5-Å translation was varied: motif **18**, triangles; motif **19**, circles.

7.1. Cyclic Dimers Interlinked by 5-Å Translation. The Coulomb energy of interaction between the two formamide dimers related by translation in a coplanar system is shown in Figure 16b. The contour lines in this map are symmetrically disposed about a line parallel to vector **M** at l = −0.2 Å. The variation in Coulomb energy of this system keeping the N—H_t···O distance between the two dimers fixed at 2.94 Å (Figure 4c) yields an energy minimum of −8.1 kcal/mol dimer at l = −0.2, m = 5.14 Å. In this arrangement the C=O···(H_t)N and C—N(H_t)···O angles are 161 and 137°, respectively, and compare well with the average values of 158 and 139° obtained from a number of primary amide crystal structures,[10b] indicating that these hydrogen-bonding angles are determined primarily by Coulomb forces. A van der Waals energy map (Figure 16c) shows contour lines almost parallel to **L** in the region l = −0.2, m = 5.14 Å. The combined Coulomb plus van der Waals energy map (Figure 16d) shows a minimum energy of −6.3 kcal/mol dimer at l = −0.5, m = 5.35 Å corresponding to an N—H_t···O distance of 3.2 Å. The C=O···N and C—N···O angles are 165 and 135°, respectively.

7.2. The 2_1 Axis Motif. As mentioned earlier, the hydrogen-bonded chain (**19**) formed by both a 5-Å translation axis and a 2_1 axis is rarely found. So we compare it with the commonly occurring motif (**18**) in which cyclic dimers are interlinked by 5-Å translation. Their Coulomb energies were computed for coplanar arrays of formamide (and of acetamide) molecules in which the angular geometry of the N—H_t···O hydrogen bond was varied, and the N—H···O distances kept fixed at 2.94 Å. The energy curves (Figure 17) show that the rare 2_1 axis motif (**19**) is less stable than the usual motif (**18**) by about 0.6 kcal/mol for a C—N(H_t)···O angular range of 130–145°, in which most structures lie. These results complement atom–atom potential calculations carried out on adipamide which appears in the rare motif (**19**). It was found[39] that the overall packing energy of the observed crystal structure of adipamide is lower by at least 0.5 kcal/mol than the energies of numerous hypothetical crystal arrangements containing the usual hydrogen-bonding dimer (**3**) to more than compensate for the loss in hydrogen-bonding energy in the actual structure.

7.3. The Glide Motifs. We now compare the Coulomb energies of the shallow-glide motif (**20a**) and the rare-glide motif (**24**). Whereas the former is commonly observed, the latter has been found only in the crystal structures of hydroxyurea[16] and isohydroxyurea[18] and, to an extent, in cyclopropanecarboxamide.[23] In the two hydroxyurea structures the helical chains (**4**) are interlinked not only by N—H_t···O bonds along the glide axis but

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(39) A. T. Hagler and L. Leiserowitz, *J. Am. Chem. Soc.*, **100**, 5879 (1978).

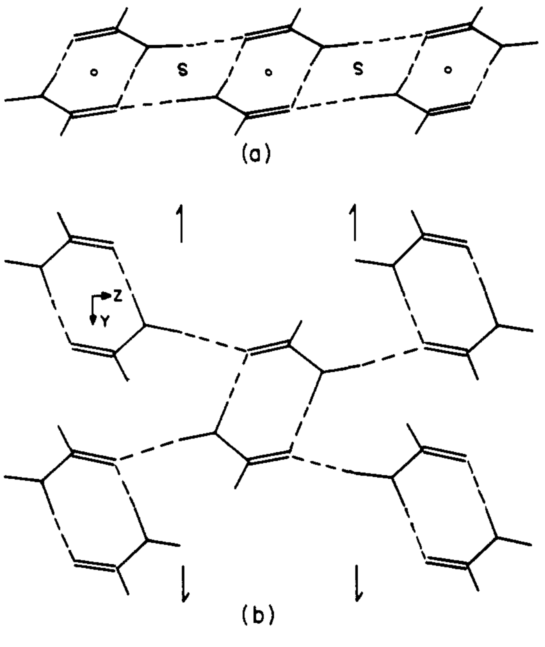

Figure 18. Formamide inserted into the shallow-glide motif of furylacrylamide: (a) view along the *b* axis of the hydrogen-bonding layer; (b) view perpendicular to the *bc* layer. The axial lengths are *b* = 5.9 Å and *c* = 9.9 Å.

also by other hydrogen bonds, a fact that seems to imply that its glide motif (**24**) is stabilized by these additional interactions.

As a representative arrangement of the shallow-glide motif (**20a**), the hydrogen-bonding layer of furylacrylamide[38] was chosen. Thus formamide was inserted into the hydrogen-bonding layer structures of furylacrylamide, hydroxyurea, isohydroxyurea, and cyclopropanecarboxamide, as shown in Figures 18 and 19. The molecules were adjusted so that all N—H···O bonds equalled 2.94 Å. Only intralayer energies were computed.

The energies of these four layers are −19.9, −19.5, −19.3, and −19.4 kcal/mol, respectively. It is uncertain whether the lower energy of the shallow-glide motif (**20a**) of 0.5 kcal/mol is sufficient to account for the rare occurrence of the glide motif (**24**), and so we infer that the relative packing properties of the amide residues in the glide motifs (**20a** and **24**) may be a determining factor in favor of the former. This argument is buttressed by the observation that in the shallow-glide motif the arrangement of cyclic amide dimers **3** stacked along the *b* axis is certainly more flexible than the amide helices (**4**) formed along the *b* axis in the rare-glide motif (**24**). We invoke this kind of reasoning to explain the absence of the hydroxyurea and isohydroxyurea type layer structures for other primary amides. The unit cell *b* × *c* areas of the four layers are 58, 41, 48, and 60 Å^2, respectively (see Figures 18 and 19). The areas of hydroxyurea and isohydroxyurea (41 and 48 Å^2) are significantly less than those of furylacrylamide and cyclopropanecarboxamide, as well as the aliphatic monoamides[40] CH_3—$(CH_2)_n$—$CONH_2$ ($n \geq 1$) which appear in the shallow-glide motif with a corresponding area of 56 Å^2. Therefore it appears that the *b* × *c* areas of hydroxyurea and isohydroxyurea would be too low to accommodate amide residues larger in cross section than even a $-CH_2$—CH_2 group of an extended aliphatic chain.

8. Coulomb Forces and Overall Packing

8.1. Stacking of Amide Dimers. Hydrogen-bonded dimers of primary amides $RCONH_2$ and of carboxylic acids RCO_2H form distinctive stacking arrangements[41] for a variety of R groups.

Table VI. *l*, *m*, *n* Coordinates (Å) of the Stack Axis Relating Cyclic Dimers of Primary Amides as Referred to the Molecular Axial System Given in Table Ib[a]

compd	*l*	*m*	*n*	axial length, Å	H-bond motif[b]
	Cluster a				
furylacrylamide[38]	4.4	1.8	3.5	5.9	G
fluoroacetamide[42]	4.1	1.0	3.2	5.3	T
acrylamide[43]	4.4	1.5	3.5	5.8	G
δ-pyrazinecarboxamide[44]	3.9	1.4	3.1	5.2	T
sebacamide[45]	4.0	1.5	3.8	5.7	G
decanamide[46]	4.0	1.4	3.7	5.6	G
av for cluster a	4.1	1.4	3.5	5.6	
	Cluster b				
benzamide[47]	4.2	−0.4	3.7	5.6	T
p-Iodobenzamide[48]	3.8	−0.6	3.7	5.3	T
terephthalamide[49]	3.9	−0.3	3.6	5.3	T
m-fluorobenzamide[50]	4.1	−0.5	3.7	5.5	T
m-bromobenzamide[51]	3.0	−0.4	3.8	4.8	G
β-pyrazinecarboxamide[52]	1.5	−1.0	3.2	3.7	G
glutaramide[53]	3.7	−1.1	3.4	5.1	T
av[c] for cluster b	3.8	−0.6	3.6	5.3	

[a] The axial components fall into two clusters a and b, whose average coordinates are given. [b] T denotes the 5-Å translation motif (18) and G the shallow-glide motif (20b). [c] β-pyrazinecarboxamide was excluded from the averaging.

These results imply that Coulomb forces play a definite role in determining overall molecular packing of amides and acids.

The stack arrangements of thirteen amide dimers (Table VI) demonstrate that the axial vectors of these stacks cluster in two regions. The averages of the axial vectors in each of these two clusters are $\mathbf{S}_1 = 4.1\mathbf{L} + 1.4\mathbf{M} + 3.5\mathbf{N}$ and $\mathbf{S}_2 = 3.8\mathbf{L} - 0.6\mathbf{M} + 3.6\mathbf{N}$. Thus adjacent amide pairs in these stacks overlap in two distinct motifs (Figure 20) where the *l*,*m* coordinates (4.1, 1.4 Å; 3.8, −0.6 Å) describe the offset between adjacent amide pairs, and the *n* coordinate (3.5, 3.6 Å) describes the plane-to-plane separation between amide pairs. The lengths of $\mathbf{S}_1$ and $\mathbf{S}_2$ are 5.6 and 5.3 Å, respectively. The amide dimers, in these two stacking motifs, form links with adjacent stacks by N—H_t···O hydrogen bonds either along the 5-Å translation axis or via the shallow glide of axial length 9.6 ± 0.3 Å (Table VI). The interstack arrangements of these two hydrogen-bonding motifs are decidely different. Moreover the geometry of the interstack N—H_t···O bond in the shallow-glide motif (**20a**) depends on the length and direction of the stack axis **S** which is perpendicular to the glide axis, whereas in the 5-Å translation motif (**18**) this dependence does not hold. Yet both stacking arrangements occur in each of the two hydrogen-bonding motifs (**18** and **20b**). We have avoided an analysis of the interdependence of the intrastack packing and the interstack N—H_t···O bond geometry present in the shallow-glide motif by examining intrastack interactions on one hand and only the interstack interactions in which the stacks are interlinked by N—H_t···O bonds along a 5-Å axis, namely, motif **18**. We considered stacks comprising formamide dimers **3** sep-

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(40) J. D. Turner and E. C. Lingafelter, *Acta Crystallogr.*, **8**, 549 (1955).

(41) (a) R. S. Miller, D. Y. Curtin, and I. C. Paul, *J. Am. Chem. Soc.*, **96**, 6340 (1974); (b) L. Leiserowitz, *Acta Crystallogr., Sect. B*, **B32**, 775 (1976).

(42) D. O. Hughes and R. W. H. Small, *Acta Crystallogr.*, **15**, 933 (1962).

(43) I. V. Isakov, *Zh. Strukt. Khim.*, **7**, 898 (1966).

(44) G. Rø and H. Sørum, *Acta Crystallogr., Sect. B*, **B28**, 1677 (1972).

(45) J. Heraud, M. Hospital, and J. Housty, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **263**, 1126 (1966).

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(47) C. C. F. Blake and R. W. H. Small, *Acta Crystallogr., Sect. B*, **B28**, 2201 (1972).

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(51) Y. Kato, T. Taniguchi, Y. Takaki and K. Sakata, *Mem. Osaka Kyoiku Univ.*, **16**, 45 (1967); **14**, 56 (1965).

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

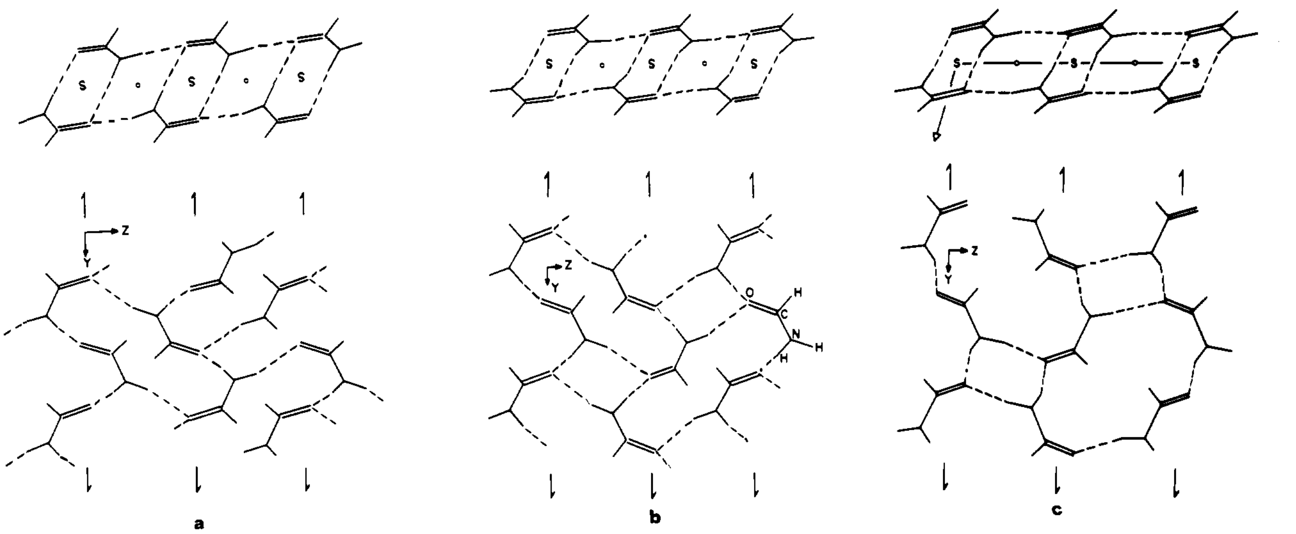

Figure 19. Formamide inserted into the three observed arrangements of the layer motif (**24**) as viewed along the *b* axis (top) and perpendicular to the *bc* layer (bottom): (a) hydroxyurea ($b = 4.9$ Å, $c = 8.4$ Å), (b) isohydroxyurea ($b = 5.7$ Å, $c = 8.3$ Å), (c) cyclopropanecarboxamide ($b = 6.8$ Å, $c = 8.8$ Å).

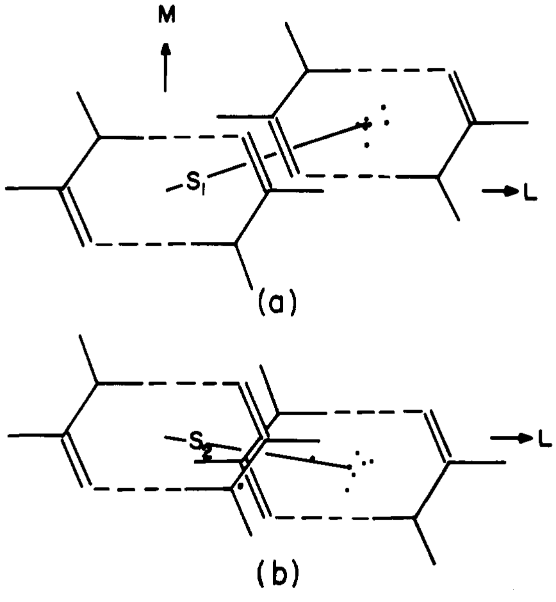

Figure 20. Two types of observed stacking arrangements in primary amides. The *l*,*m* coordinates of the axes of the several compounds, as listed in Table VI, are represented by dots. The axes appear in two clusters, as displayed in a and b, respectively. The axes S_1 and S_2, whose coordinates are given in Table VI, are the averages for these two clusters.

arated by 3.5 Å. The Coulomb energy was varied as a function of the *l* and *m* components of the stack axis $S = lL + mM + 3.5N$.

The energy map (Figure 7b) for the isolated stack (Figure 7a) has been presented earlier. It shows a maximum variation of −6.5 to −12.1 kcal/mol. The *l*,*m* coordinates of axis S_1, and particularly S_2, lie close to the lowest energy contour of −12 kcal/mol, revealing the role played by Coulomb forces in fixing the stacking motif. The Coulomb energy of the formamide dimer is −10.7 kcal/mol so that the maximum stacking energy is −1.4 kcal/mol.

The Coulomb energy map for the two-dimensional array (Figure 21a) comprising formamide stacks interlinked by $N-H_t\cdots O$ bonds along a 5-Å axis is shown in Figure 21b. The total energy variation is −17.7 to −20.1 kcal/mol. Within the two-dimensional array the hydrogen-bonded ribbon, comprising amide dimers interlinked by $N-H_t\cdots O$ bonds along the 5-Å axis, contributes a fixed Coulomb energy of −19.1 kcal/mol. Therefore the maximum stacking energy is −1 kcal/mol. The *l*,*m* coordinates of the six amide structures listed in Table VI, which appear in the 5-Å translation motif, fall close to the minimum energy contour of −20 kcal/mol. The energy minimum has some bearing on possible

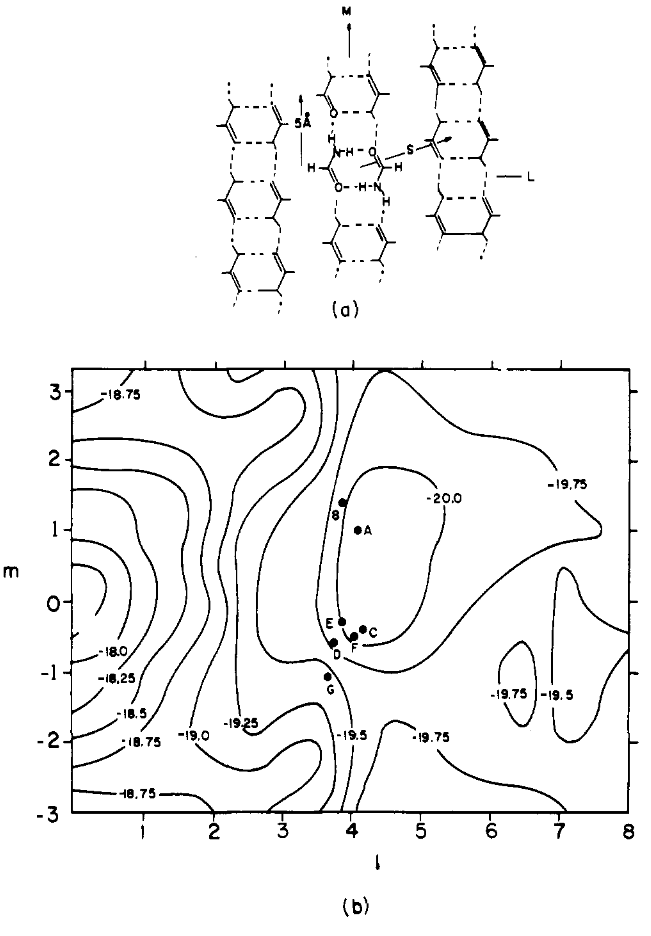

Figure 21. (a) Hydrogen-bonded chains of formamide dimers interrelated by a stack axis $S = lL + mM + 3.5N$, where 3.5 Å is the interplanar distance between the dimers. Atomic coordinates are given in Table Ib. The 5-Å axis = $-0.2L + 5.14M + 0N$ (see section 7.1). (b) Coulomb energy (kcal/mol) of the above motif as a function of the coordinates *l* and *m* (in Å) of the stack axis S. The *l*,*m* coordinates of the stack axis in seven compounds which appear in the 5-Å translation motif (see Table VI) are shown: A = fluoroacetamide, B = δ-pyrazinecarboxamide, C = benzamide, D = *p*-iodobenzamide, E = terephthalamide, F = *m*-fluorobenzamide, G = glutaramide.

crystal symmetry in terms of the angle between the 5-Å axis ($=-0.2L + 5.14M + 0N$, see Figure 21) and the stack axis. This angle for axis S_2 lies close to 90°, as would be required in an

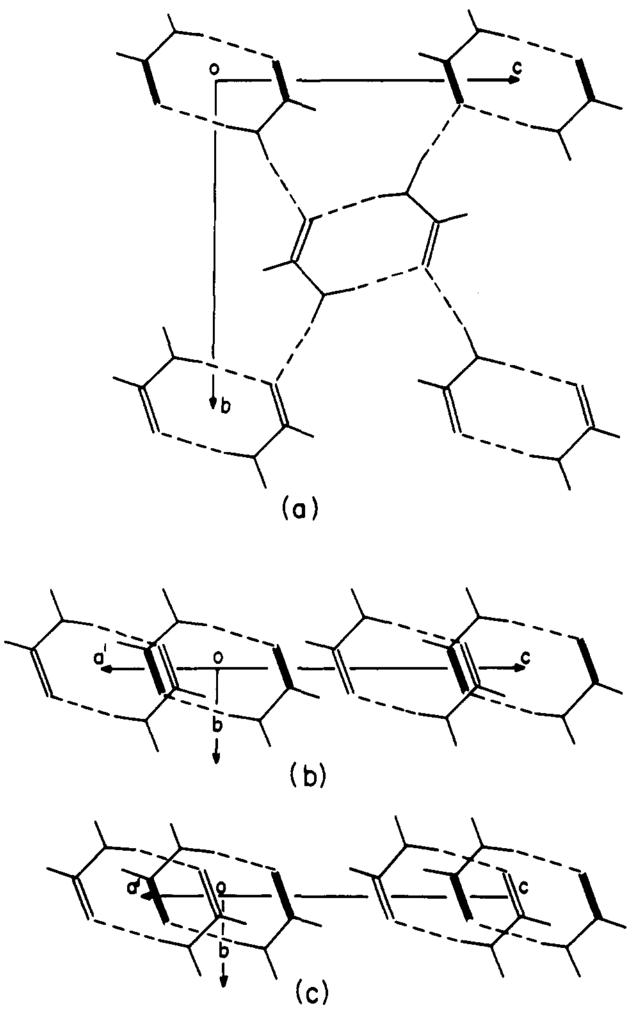

Figure 22. (a) The observed *bc* layer of formamide, seen perpendicular to the layer. (The C=O bonds at the top of the layer are filled.) (b) The interlayer arrangement of formamide corresponding to the minimum Coulomb energy. *a'*, of length 3.2 Å, is the projection of the *a* axis onto the *bc* plane and is equal to the offset between adjacent layers. Only the top of the layer is shown. (c) The interlayer arrangement as observed in the crystal and according to the minimum Coulomb plus van der Waals energy. The projection $a' = -2.1$ Å.

orthorhombic crystal and also in a monoclinic crystal with the qualification that either the 5-Å axis or the **S** axis be the unique monoclinic axis.

8.2. Interlayer Contact in Formamide. We now examine how Coulomb forces determine the interlayer arrangement in the crystal structure of formamide,[54] with cell constants $a = 3.6$ Å, $b = 9.1$ Å, $c = 8.4$ Å, and $\beta = 125°$ ($P2_1/c$), where the molecules within the layer (Figure 22a) are hydrogen bonded in a manner akin to the steep-glide motif (**20a**).

The Coulomb energy of a hypothetical crystal was calculated (Figure 23), maintaining the structure of the observed hydrogen-bonded *bc* layer and the interlayer separation of 2.94 Å ($=a \sin \beta$) but varying the offset ($=a \cos \beta$) between adjacent layers. The Coulomb energy variation shows a maximum difference of 6 kcal/mol with the minimum energy occurring at an offset of −3.2 Å, which corresponds to axis $a = (2.94^2 + 3.2^2)^{1/2} = 4.35$ Å and a β angle of 137°. In the actual structure the offset between layers is −2.1 Å (=3.6 cos 125°), so the difference in layer offset between the observed and the calculated structure is 1 Å. The corresponding energy difference is 1.5 kcal/mol. It is clear from Figure 22b, which shows the interlayer arrangement corresponding to an offset of −3.2 Å, that the atomic overlap is pronounced, so that the van der Waals interactions between layers must be unfavorable. We therefore calculated the van der Waals energy. The energy minimum was obtained with a layer offset of −2.2 Å, almost equal to that observed. The corresponding interlayer arrangement is depicted in Figure 22c. The calculated values of a and β are 3.77 Å and 127°, respectively.

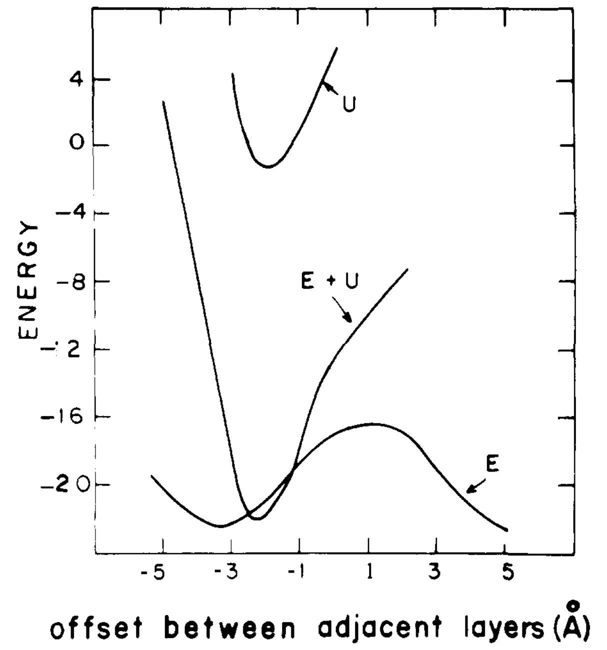

Figure 23. Variation in energy (kcal/mol) as a function of changing the offset (in Å) between observed hydrogen-bonded *bc* layers of formamide: E, Coulomb energy curve; U, van der Waals energy; E + U, Coulomb plus van der Waals energy.

8.3. Comparison of the Rhombohedral and Orthorhombic Forms of Acetamide. Acetamide exists in a stable rhombohedral form[37] and a metastable orthorhombic form.[55] The Coulomb energies of these two modifications[56] are −19.5 and −19.1 kcal/mol, respectively. These calculations are compatible with the relative stabilities of the two crystal forms.

Conclusion

The information contained in electron density distributions of polar molecules derived from diffraction measurements can be used for the calculations of Coulomb interaction energies, between molecules, and consequently the determination of possible and preferred molecular packing modes.

To date it has been difficult to differentiate between the van der Waals and Coulomb terms contributing to crystal energy. Consequently the atom–atom potential parameters suffer from such a correlation. Therefore using given experimentally derived atomic moments, one may obtain more reliable estimates of the van der Waals atom–atom potential parameters.

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(55) W. C. Hamilton, *Acta Crystallogr.*, **18**, 866 (1965).

(56) We were not able to locate the hydrogen atoms of the orthorhombic form from electron density difference maps by using the published structure factors. Consequently we inserted the two hydrogen atoms attached to nitrogen and the three methyl hydrogen atoms by assuming the usual synplanar H—C—C—N conformation.[57]

(57) A. T. Hagler, L. Leiserowitz, and M. Tuval, *J. Am. Chem. Soc.*, **98**, 4600 (1976).