The amide hydrogen bond and the anomalous packing of adipamide

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the structural and thermodynamic features of ternary and binary cycloamylose complexes. A further understanding of the factors involved in aqueous Cy complex formations and, in particular, selectivity in these reactions, appears central to the role of cycloamyloses as models for biological complexations.

Experimental Section

Lithium and sodium salts of *p*-methylcinnamic acid were prepared by treatment of portions of the parent acid, obtained from the Aldrich Chemicals Co., with an excess of Li_2CO_3 or NaOH in hot aqueous solution. The crude salt was collected after cooling and was twice recrystallized from boiling water. Portions of the sodium salt were analyzed by titration with standard HCl and were employed for all ^{13}C NMR measurements. Solutions of the lithium salt were employed for conductance measurements after appropriate analysis with standard HCl. In both cases, the precipitation of *p*-methylcinnamic acid during titration with HCl precluded the usual analysis of the titration data obtained before or near the equivalence point. The end points were determined by a suitable Gran plot method.

Cyclohexaamylose was obtained from the Aldrich Chemicals Co. and was used without further purification. Subsequent ^{13}C NMR experiments gave resonances which could only be ascribed to cyclohexaamylose. No additional signals above the normal noise level could be detected under high signal/noise conditions.

^{13}C NMR experiments employed a Varian CFT-20 spectrometer equipped with a 10-mm sample tube maintained at 30 ± 2 °C. In a typical series of experiments, spectra were recorded after each addition of a microweighed portion of sodium *p*-methylcinnamate to an 8.00-mL aliquot of α-cyclodextrin solution contained in the sample tube. Instrument settings were as follows: 30° tip angle; 2-s delay time; 1-s acquisition time. A spectral width of 4000 Hz was employed with accumulation of 8192 data points so that the resolution was 0.02 ppm throughout. Several thousand cycles were acquired for each spectrum. Proton-decoupled ^{13}C chemical shifts were measured in parts per million downfield from external Me_4Si.

Conductance measurements employed a General Radio 1608A impedance bridge equipped with dip-type conductance cell. The experiments involved addition of weighed portions of α-cyclodextrin to a sample solution contained in a vessel thermostated at 30 ± 0.1 °C. The conductance was measured upon each addition after allowing appropriate time for equilibration.

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On the Amide Hydrogen Bond and the Anomalous Packing of Adipamide

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Abstract: A methodology for the study of the role of hydrogen bonding and other energetic factors in determining the symmetry and secondary and tertiary structures of hydrogen-bonded crystals is presented. Lattice energy minimization techniques are extended to the study of "hypothetical" crystal packing modes in order to carry out this analysis. The comparison of these hypothetical crystal structures with observed structures is also proposed as a useful tool for testing the validity of potential functions. The model system chosen for this initial study is adipamide. The observed packing mode of adipamide is anomalous with respect to the family of primary amides in that it does not involve hydrogen-bonded rings. The hydrogen-bonding structure of adipamide appears to be less stable than the standard packing motif. A total of 16 hypothetical crystals, comprising various space groups, were constructed. These include the three typical modes of hydrogen-bonded networks (secondary structures) related by various symmetries to form structures common to the family of primary amides. The observed structure is calculated to be more stable than all hypothetical structures considered. Analysis of intra- and interlayer energies indicates that adipamide, by foregoing the most favorable hydrogen-bonding arrangement, achieves a better interlayer packing which more than compensates for the poorer hydrogen bonding. Several hypothetical structures are found to be within a kilocalorie or two of the experimental structure. This result is related to the tendency to form the maximum number of hydrogen bonds and polymorphism in crystals. Finally, the results are discussed in terms of symmetry considerations, both with regard to the experimental observation that amides rarely pack in orthorhombic and higher symmetries, and the need to relax symmetry constraints when studying hypothetical models.

Introduction

There have been many studies of the lattice energetics of organic molecules carried out in the past few years.[2-8] These have been mainly directed towards using the precise information available in the crystalline state to determine and test intermolecular potential functions. In these studies the common practice has been to minimize the crystal energy with respect to some subset of the crystalline degrees of freedom in

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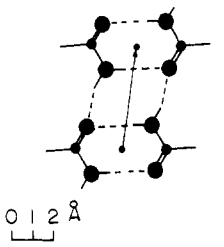


Figure 1. Schematic representation of the packing of amide dimers along a translation axis.

order to reproduce the experimentally observed crystal structures.

The work presented here has several objectives, all of which are related to the analysis and understanding of the crystalline state and intermolecular forces in organic crystals. A methodology for the study of the underlying factors determining the symmetry and secondary and tertiary structure of hydrogen-bonded crystals is developed. By secondary structure we refer to the topology of the hydrogen-bonded network, while by tertiary structure we refer to the way in which these hydrogen-bonded networks pack in the crystal.[9] This is accomplished by extending the usual lattic energy minimization techniques to the study of "hypothetical" crystal structures, in which the molecule of interest is packed in its alternate packing modes and space groups. This extension is combined with an analysis of the possible packing modes of the molecule of interest, which in the case of amides led to a classification, into several distinct classes, of the possible secondary and tertiary structures in which molecules containing this functional group can pack.[9] The final step in this methodology is the development of techniques for the "construction" of (hypothetical) crystals of a given molecule in the appropriate symmetries and packing arrays.

We have chosen adipamide as our model system for this study for several reasons. The main reason is that it packs in an apparently anomalous motif with a secondary structure that is only rarely observed among the primary amides.[9,10] The hydrogen bonding in this structure is distorted, and apparently less favorable than the secondary structures commonly observed in primary amides. The reason for this anomalous packing has not been explained to date. Secondly, this system provides a further test of the intermolecular potential functions recently derived for amides and peptides.[2,11] This aspect comprises a general objective of the work as well. Thus by considering alternate symmetries we provide a second potentially important method for the evaluation of potential functions being derived from crystal properties. This is over and above the "fitting" of the experimental structure starting with the experimental symmetry. This test may be especially useful in systems such as adipamide, where the packing mode is unusual (with respect to other molecules in the family), and thus the potential functions must account for the (sometimes subtle) factors stabilizing this structure over the "hypothetical" standard packing modes which are not observed for the molecule. Thirdly, we should gain insight into the nature of the amide hydrogen bond and its geometric dependence by studying this system, since as noted above the hydrogen-bonded network is significantly distorted in the adipamide structure. The results of this study, along with those on other systems,[12] as well as results obtained in a recent study of the effect of crystal forces on molecular conformation,[13] indicate that it is becoming possible to understand the nature of the forces underlying the stability of a given crystal form. Lastly, this study provides an example of the application of the principles developed for the derivation of the crystal coordinates of molecules in theoretical packing modes. It should be stressed

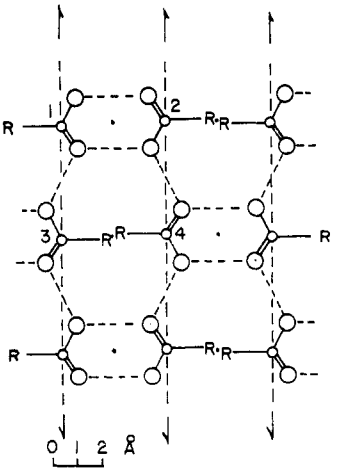
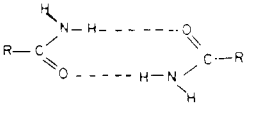


Figure 2. Schematic representation of the packing arrangement of amide dimers related by a glide plane. The dashed line (--) represents the glide and the arrows (—) represent the twofold screw axes.

that the "building" of these "hypothetical" crystals is not trivial. The unit cell vectors and orientation of the asymmetric unit with respect to these vectors (and symmetry elements) in the unit cell must be derived from a consideration of the desired secondary and tertiary structure.

In this study we consider the energetics of adipamide in the three secondary structures typical of amides, packed in several observed tertiary structures of each.[9] A total of 16 crystal structures comprising various space groups are considered. As noted above, the study of the lattice energetics of these theoretical forms not only serves as a further test of intermolecular potential functions, but would seem to be a necessary step if we are to understand *why* a crystal packs as it does, instead of in some alternate packing mode. Finally, it brings us one step closer to the prediction of the packing modes of organic crystals and to the engineering or rational design of crystal structures.

Anomalous Secondary Structure of Adipamide. In the crystalline state, primary amides, $RCONH_2$, form cyclic hydrogen-bonded dimers (I) with very few exceptions.[14] There



I

are three ways in which these cyclic *dimers* may be interlinked to form a hydrogen-bonded secondary structure, either by a translation axis (Figure 1), a glide plane (Figure 2), or a twofold screw axis.[14] (If the amide and R group are coplanar the latter two are identical and thus we give only one figure. If the R group is not in the amide plane, they differ in that glide-related R groups are on the same side of the amide planes while "screw"-related R groups are on alternate sides of the amide planes in Figure 2.)

The crystal structure of adipamide is a rare exception,[9,14] which does not form any of these cylic dimer hydrogen-bonded secondary structures (I). Rather the amide groups in adipamide are hydrogen bonded along a twofold screw axis as shown in Figure 3. As seen in this figure, this results in the amide group of a single adipamide molecule being hydrogen bonded to two other molecules across the screw axis. The resulting secondary structure is distorted owing to the incompatibility in intra- and intermolecular geometry. Thus, as depicted in the figure the *intra*molecular N···O distance is 2.3 Å, while the translation-produced intermolecular N···O distance is 2.95 Å leading to N···O hydrogen bonds across the twofold axis which

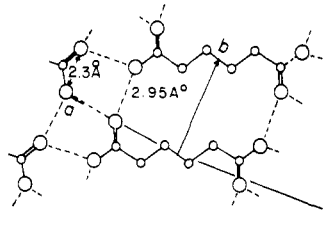


Figure 3. Schematic representation of adipamide packing arrangement in which the amide groups do not form dimers, but rather hydrogen bond along a twofold screw axis.

Table I. Hydrogen Bond Geometry in Observed and Hypothetical Crystal[a] Structure of Adipamide

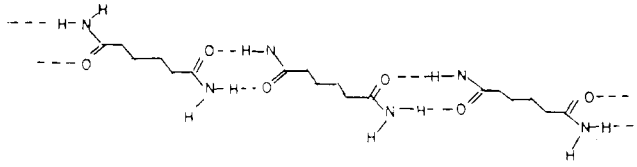
	distance, Å of H···O	angles, deg 180° − N-H···O	angles, deg H···O=C
observed[b]	1.98	18	127
	2.06	35	146
model I[a]	1.94	5	118
	1.95	25	156
model II[a]	1.95	9	119
	1.98	29	151

[a] After minimization (6-12 potential). [b] The hydrogens in the observed structure were obtained by an energy minimization.[2a]

are not parallel and splayed open (Figure 3). The puzzle of the adipamide packing can then be stated as "why does adipamide choose to crystallize in this anomalous packing mode in which there is obvious distortion of the hydrogen-bonded network as opposed to one of the more usual secondary structures containing cyclic hydrogen-bonded dimers, observed in almost all other amide crystals?"

Method

Construction of Hypothetical Crystal Structures. Initially we constructed two triclinic structures containing the centrosymmetric cyclic dimer I. The cyclic dimers at each end of the diamide result in chains of adipamide molecules II, containing



II

the centrosymmetric rings linked by N—H···O bonds. The line joining the centers of symmetry corresponds to one of the crystal axes, arbitrarily taken as *a*. Its length must be ~10.3 Å which follows from the length of the adipamide molecule, and the N···O distance of 2.9 Å in the amide hydrogen bond.[9,14] The second unit cell vector is determined by the requirement of creating the "5 Å" translation related hydrogen-bonding secondary structure. In this secondary structure the hydrogen bond between the free N—H group and the carbonyl of a second molecule is generated by a 5 Å translation. This translation axis (*b*) is then constructed in the plane of the amide groups at an angle (γ) close to 90° from *a*, with a length of 5 Å. This then generates the secondary structure, a hydrogen-bonded layer network, here an "*ab*" layer, and the next step is to construct the interlayer arrangement which completes the crystal structure. For the triclinic ($P\bar{1}$) case, the layers are related by translation. It should be noted at this point that the final structure of the crystal will be determined by energy minimization, and here we only require a "correct" overall structure. We have constructed two models, as shown in Figures 4 and 5 in which the chains (II) interleave each other in different ways. The ~3.4-Å separation between amide hydrogen-bonded layers and the interleaving pattern determine the length of the unit cell vector **c** and the angles α and β. The triclinic structures, in which the secondary structure is generated by translation, are of course the most straightforward to generate. Nevertheless they serve to demonstrate the principles by which the crystal structures are built. In addition to the two triclinic structures we have generated another 14 structures of both monoclinic and orthorhombic symmetry. These contain the remaining secondary and tertiary structures characteristic of amides.[9] The geometric and symmetry considerations involved in the construction of these crystal structures are described in detail elsewhere.[9]

The distortion of the hydrogen-bonded secondary structure in the observed structure[10] and a comparison with the hydrogen bond geometry in the two minimized triclinic structures are given in Table I.

Potential Functions and Energetic Analysis. The energy of each hypothetical crystal structure is minimized with respect to all crystalline degrees of freedom, the only constraint being the number of molecules per unit cell.[2b] In practice this is accomplished by minimizing with respect to the nine cartesian components of the unit cell vectors, as well as the three translations and three rotational degrees of freedom of all molecules but one in the basic unit cell (the degree of freedom of the last molecule would correspond to rotation and translation of the whole crystal). The triclinic crystals were minimized with both 6-9 and 6-12 potentials derived in a previous study of amide crystals.[2] Two potential functions were used to avoid drawing "potential-dependent" conclusions. It should be emphasized that *no* changes were made in these potentials for this application; they were simply *transferred* from the previous study.[2] The form of the potential function and the constants used are given in ref 2a.

Complete analyses of the energetics of the triclinic structures as well as the experimental packing were carried out to determine the factors stabilizing the "anomalous" observed mode. This included a partitioning of the energy into the intralayer (secondary structure) contribution and interlayer (tertiary structure) contribution. These contributions were themselves partitioned into their electrostatic and "van der

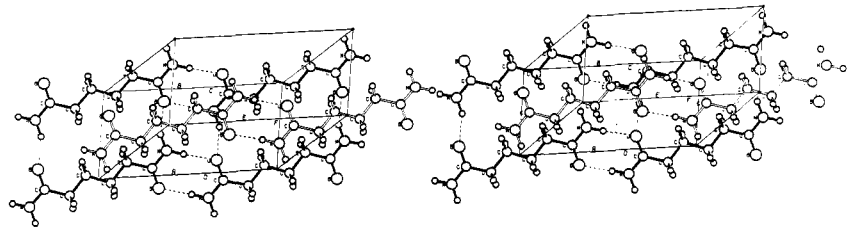


Figure 4. Stereoview of the hypothetical packing arrangement of adipamide, model I. This is the minimum energy structure of model I as calculated with 6-12 potential (see text). The molecules with open bonds lie above the approximate plane formed by four molecules with filled bonds. Hydrogen bonds are indicated by dotted lines.

Table II. Energies of Experimental and Minimized Hypothetical Structures of Adipamide[a]

	6-12 potential			6-9 potential		
	exptl[b]	model I	model II	exptl[b]	model I	model II
van der Waals	−19.75 (−.19.66)	−17.81	−18.61	−16.90 (−16.60)	−15.05	−15.57
electrostatic	−18.34 (−18.63)	−19.50	−18.87	−21.85 (−22.22)	−23.23	−22.95
total	−38.09 (−38.29)	−37.31	−37.48	−38.75 (−38.82)	−38.29	−38.52

[a] In kilocalories/mole. [b] Energies of experimental structure after minimization[2b] are given in parentheses.

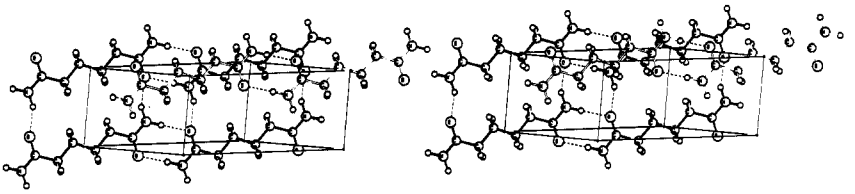


Figure 5. Stereoview of the hypothetical packing arrangement of adipamide, model II. This is the minimum energy structure of model II as calculated with 6-12 potential (see text). The molecules with open bonds lie above the approximate plane formed by four molecules with filled bonds. Hydrogen bonds are indicated by dotted lines.

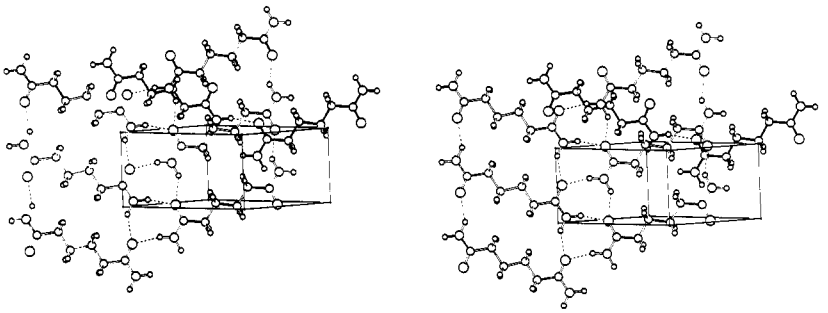


Figure 6. Observed crystal structure of adipamide showing interplanar packing. Molecules with filled bonds lie below the plane formed by molecules with open bonds. The hydrogen bonds are indicated by dotted lines.

Waals" (Lennard-Jones) components. Finally, a further 14 monoclinic and orthorhombic structures were minimized with the 6-12 potential, and their total energy, and van der Waals and electrostatic components determined. A cutoff distance of 12 Å was used for all minimizations.[2b] If any atom of a molecule is within 12 Å of a given molecule in the basic unit cell, the *whole molecule* is included in the minimization. (This is done to avoid the creation of spurious charges or dipoles.) Thus the effective cutoff is much larger than 12 Å. The cutoff is applied to the initial structure and the molecules included in the minimization process determined at that time. No changes are made in the system being minimized during the course of the minimization (this procedure is followed both for efficiency and for ensuring the stability of the minimization algorithm).[15] All minimizations were carried out using the quadratically convergent algorithm VA09A, available from the Harwell subroutine library.

Results and Discussion

The minimum energies of the two hypothetical triclinic structures as well as the initial and final energy of the observed structure are given for both the 6-9 and 6-12 potentials in Table II. The corresponding minimized[2b] and observed[10] quantities for the experimental structure are also given for comparison. The resulting lattice parameters, as well as the crystal coordinates and unit cell volumes resulting from the minimization of the two model structures, are given in Table III. The three-dimensional packing arrangements of the two triclinic structures are shown in Figures 4 and 5, and the observed packing is shown in stereo in Figure 6.

Models I and II show essentially the same hydrogen-bonded secondary structure, forming approximate layer structures. The primary difference between the two models is manifested in their tertiary structure (their interlayer arrangements). As can be seen in Figure 4, the interlayer arrangement in model I is such that a molecule in one layer is interleaved between two molecules in the adjacent layer along the 5-Å axis, *b* (molecule "E" is interleaved between molecules A and B). In addition the interleaved molecule forms a "stacking arrangement" with another molecule in this plane, consisting of pairs of antiparallel amide groups (molecules E and C).

The interlayer arrangement of the second triclinic structure is quite different from that of model I. The molecules in adjacent layers are not interleaved, but rather they are arranged such that two of the methylene groups lie in the "holes" formed by the hydrogen-bonding network, while the carbonyl groups form antiparallel pairs (features similar to the experimental structure). As discussed above the hydrogen-bonded secondary structure of adipamide (Figure 6) is very different from that of the two model structures, the one common feature being the N—H···O translation motif along the 5-Å axis *b*. In the observed interlayer structure the methylene chain $-CH_2-CH_2-CH_2-CH_2-$ lies in a position such that two of the methylene groups lie below the holes of the hydrogen-bonded network while the other two methylene groups lie below the gap between the two molecules related by the 5-Å axis. The C=O bonds form antiparallel pairs as in model II.

Assessment of Potential Functions. The differences in the secondary and tertiary structures of these crystals are reflected in the difference in lattice energies as given in Table II. As can be seen from this table the energy of the experimental structure is more negative (favorable) than the energy of either of the model structures, for both the "6-9" and the "6-12" potentials. Thus these potentials account for the stability of the observed structure over the models. This holds in spite of the fact that, as hypothesized, the "hydrogen-bonding energy", as reflected

Table III. Lattice Constants, Crystal Coordinates, and Unit Cell Volumes of Minimized Hypothetical Structures of Adipamide[a]

A. 6-12 potential

	unit cell vectors					
	model I, $P\bar{1}$			model II, $P\bar{1}$		
	a = 10.192 Å, α = 56.6°			a = 10.276 Å, α = 90.5°		
	b = 5.092 Å, β = 48.7°			b = 5.064 Å, β = 30.5°		
	c = 6.156 Å, γ = 83.4°			c = 7.142 Å, γ = 83.5°		
	V = 186 Å^3			V = 183 Å^3		
	crystal coordinates					
atom	x	y	z	x	y	z
N	0.3674	0.2750	0.0160	0.3303	0.2961	0.0708
H	0.4603	0.2199	0.0259	0.4227	0.2476	0.0778
H	0.3297	0.4637	0.0155	0.2777	0.4882	0.0949
C	0.2969	0.0874	0.0027	0.2816	0.0944	0.0273
O	0.3418	−0.1457	0.0005	0.3459	−0.1448	−0.0059
C	0.1603	0.1818	−0.0166	0.1460	0.1763	0.0135
H	0.0538	0.2060	0.2025	−0.0269	0.3496	0.2531
H	0.2394	0.4396	−0.2929	0.2858	0.2518	−0.2507
C	0.0618	−0.0669	0.0264	0.0579	−0.0496	0.0222
H	−0.0231	−0.3227	0.3065	−0.0888	−0.1207	0.2907
H	0.1681	−0.0991	−0.1860	0.2294	−0.2265	−0.2110

B. 6-9 potential

	unit cell vectors					
	model I			model II		
	a = 10.320 Å, α = 62.1°			a = 10.305 Å, α = 92,1°		
	b = 5.066 Å, β = 48.0°			b = 5.045 Å, β = 29.8°		
	c = 5.603 Å, γ = 84.7°			c = 7.178 Å, γ = 84.6°		
	V = 181 Å^3			V = 180 Å^3		
	crystal coordinates					
atom	x	y	z	x	y	z
N	0.3751	0.2762	0.0051	0.3397	0.2892	0.0606
H	0.4666	0.2199	0.0168	0.4310	0.2388	0.0678
H	0.3428	0.4688	−0.0023	0.2920	0.4821	0.0810
C	0.2991	0.0845	−0.0012	0.2855	0.0885	0.0219
O	0.3372	−0.1538	0.0050	0.3437	−0.1519	−0.0065
C	0.1648	0.1802	−0.0238	0.1518	0.1727	0.0076
H	0.0648	0.2368	0.1956	−0.0213	0.3535	0.2493
H	0.2441	0.4032	−0.3108	0.2994	0.2401	−0.2650
C	0.0605	−0.0655	0.0288	0.0564	−0.0503	0.0232
H	−0.0244	−0.2858	0.3196	−0.0982	−0.1130	0.3000
H	0.1604	−0.1293	−0.1836	0.2278	−0.2345	−0.2121

[a] Experimental:[10] a = 6.89, b = 5.15, c = 10.67 Å; β = 111°; V = 353 Å^3.

by the electrostatic energy, favors both model structures over the experimental structure (for both potentials). This result then serves as a further indication of the reliability of these potential functions, both for the present application and for the representation of the intermolecular forces between amides. The success of the potential functions in accounting for the stability of the experimental structure depends strongly on the nature of the representation of the amide hydrogen bond and, in particular on its "shallowness", with respect to both distance and angular dependence. Thus a potential in which the hydrogen-bonding or electrostatic contribution is exaggerated with respect to the distance and angular dependence (i.e., is too steep) would lead to the prediction that the hypothetical structures are more stable. This tendency is reflected in Table II where it is seen that the "6-9" potential, which has a slightly larger electrostatic component than the "6-12",[2] yields energies for the model structures closer to the experimental than the "6-12", although still less favorable.

As a further demonstration, we minimized the energy of these crystals using a Morse potential to represent explicitly the hydrogen bond potential. This potential has the form

$$V_{HB} = D^*(1 - e^{-\alpha(r-r_{OH})^2})e^{-(\theta/\theta_0)^2}$$

For this experiment D^*, the depth of the potential, was taken as 3 kcal/mol, r_{OH}, the unperturbed OH distance as 2 Å, and α as 5. The last term corresponds to an attenuation of the hydrogen bond energy with deviation of linearity of the NHO angle (θ = 180° − ∠NHO), and θ_0 was taken as 30°. This representation is the initial trial function used by Hagler et al.[2a] in their derivation of an amide force field. It was concluded there that the inclusion of the Morse potential was unnecessary to fit the properties of amide crystals, and in fact no *explicit* function over and above the electrostatic term was needed. The energy of the model structures when calculated with this potential was 5 kcal/mol more stable than the experimental structure. These results demonstrate the ability of the procedure used here to test the validity of potential functions and further support the conclusion that no explicit function is needed to represent the hydrogen bond.

The Energetic Basis of the Anomalous Packing of Adipamide. A partition of the lattice energy into its secondary (intraplanar) and tertiary (interplanar) components is given in Table IV for both triclinic forms as well as for the observed structure. The underlying cause for the stability of the anomalous packing becomes apparent from a consideration of these contributions and those given in Table II. As noted above, the

Table IV. Inter- and Intralayer Energies in the Experimental and Hypothetical Structures of Adipamide[a]

	exptl		model I		model II	
	intralayer	interlayer	intralayer	interlayer	intralayer	interlayer
		A. 6-12 potential				
van der Waals	−3.91 (−3.53)	−15.84 (−16.13	−3.17	−14.63	−3.43	−15.18
electrostatic	−17.06 (−17.41)	−1.28 (−1.22)	−18.71	−0.79	−18.07	−0.79
total	−20.97 (−20.94)	−17.12 (−17.35)	−21.88	−15.42	−21.51	−15.97
		B. 6-9 potential				
van der Waals	−1.23 (−0.79)	−15.67 (−15.81)	−0.26	−14.79	−0.31	−15.26
electrostatic	−20.15 (−20.67)	−1.70 (−1.55)	−22.53	−0.70	−22.25	−0.70
total	−21.38 (−21.46)	−17.37 (−17.35)	−22.79	−15.49	−22.56	−15.96

[a] In kilocalories/mole.

electrostatic interactions in the observed crystal are less favorable than in the hypothetical models owing to the distortion of the hydrogen-bonded network. The nonbonded interactions, however, favor the experimental structure and more than compensate for the relatively unfavorable electrostatic contribution. Thus the total energy favors the experimentally observed structure.

It appears from the partition of the total energy that the packing of adipamide in the experimentally observed structure is due to a compromise between the best intralayer hydrogen-bonded structure, and the best interlayer packing arrangement. By foregoing the optimum intralayer, hydrogen-bonded arrangement, adipamide has been able to achieve a significantly more favorable interplanar packing. This is verified in Table IV where it is seen that essentially all the electrostatic energy in the crystal arises from the intralayer interactions, while most of the nonbonded energy comes from the interlayer, tertiary structure interactions. The total interlayer energy is ~1.5 kcal/mol more favorable for the experimental structure than for the model structures, and more than compensates for the less favorable intralayer energy as was reflected in the total energy.

Both the interlayer electrostatic energies as well as the intralayer nonbonded energy, although quite small in absolute magnitude (between 3 and 10% of the total energy), favor the experimental structure over the hypothetical structures. It can be seen, from the contributions discussed above and given in Table IV, that in the experimental structure both the inter- and intralayer packing as generated by the twofold screw axis is more efficient with respect to the van der Waals energy than the translation-generated packing. This is also reflected in the smaller volume of the experimental structure is also reflected in the smaller volume of the experimental structure (177 Å^3/molecule) as compared with the volumes of the hypothetical structures given in Table III. These factors all combine to overcome the decrement in the hydrogen-bonding energy of the experimental structure, with respect to the model compounds.

It is worth noting that the differences in energy between the various structures is small, of the order of a kilocalorie or less. This result is to be expected and has ramifications both with respect to hydrogen bonding in crystals and the existence of polymorphism. These facets will be discussed at more length below. Nevertheless, the question arises as to whether these small differences are significant. Clearly the absolute energies calculated with these potentials are *not* accurate to within 0.5 kilocalorie. This in fact can be seen immediately by comparing the lattice energies obtained with the 6-9 and 6-12 potentials, which differ by about a kilocalorie. Nevertheless *both* potentials give the *same* relative stabilities for the three different structures. Similar results were obtained recently in studies of the relative stabilities of various dichlorobenzylideneaniline polymorphs and discussed in some detail there.[13] From these preliminary results it would appear that, if the functional form is approximately correct, the *differences* in energy do indeed reflect the differences in the geometry of packing.[13] This conclusion is subjected to still further tests below.

Energetics of Adipamide in Crystals of Higher Symmetry Containing Other Secondary and Tertiary Structures. To further understand the energetics of amide crystals, test the potential functions, and further substantiate the validity of the packing analysis presented above, an additional 14 crystal structures of adipamide were constructed and minimized. Hypothetical crystals of adipamide were generated in both monoclinic and orthorhombic space groups following the principles outlined in the Method section for the generation of the triclinic crystals.[9] The results of the minimization of these crystal structures are given in Table V. Column 2 specifies the plane in which the molecule lies and the direction of the molecular axis. The packing of two of the monoclinic forms, $A2/a$ and $P2_1/a$ are given in stereo in Figures 7 and 8.

Several interesting observations arise from consideration of the results of the minimization of the energy in these additional space groups. The first observation to be made is simply that *none* of the additional 14 hypothetical structures has a lower calculated lattice energy than the observed structure. The source of the relative stability of the experimental structure over these crystals varies depending on the space group. Several structures have comparable electrostatic contributions to the experimental, but, as in the case of the triclinic structures, they do not pack as efficiently leading to a much smaller dispersion stabilization. In other space groups ($P2_1/a$ (3), $P2/a$ (7) and $A2/a$ (9)), the hydrogen-bonding network is strained, but good packing is achieved. In all cases the potential functions account for the stability of the experimental structure.

Comment on Hydrogen Bonding in Crystals. Ubiquity of Hydrogen Bonds and Polymorphism. A fundamental principle of the packing of molecules with functional groups capable of forming hydrogen bonds is that all hydrogen bonds that can potentially be formed are formed.[9] This principle is perhaps exemplified best by the crystal of urea ($(NH_2)_2CO$) which has four donor hydrogens and only one carbonyl oxygen bonds.[16] Part of the reason for this ubiquity of hydrogen bonds is demonstrated by the results in Tables II and V. There are at least five alternate packing modes which have calculated energies within 1 kcal of the experimental structure and nine within 2 kcal. It appears that hydrogen-bonded secondary structures may be accommodated in a variety of space groups and alternate tertiary structures, all reasonably close in energy. This would appear to be a general rule and thus, if a particular secondary or tertiary structure is ruled out because of steric interactions, another in which the hydrogen bonding is satisfied of comparable energy is available and will be "chosen", rather than leaving a potential hydrogen bond (~2-3 kcal) unformed.

Polymorphism. These results not only account for the ubi-

Table V. Lattice Constants and Energies of Hypothetical Monoclinic and Orthorhombic Crystal Structures of Adipamide[a]

	space[b] group	molecular[c] plane/axis	lattice constants						energy		
			a	*b*	*c*	α	β	γ	nonbonded	elect	total
1	$P2_1/c$	*ac* plane	5.10	7.00	10.30	90.0	96.0	90.0	−14.5	−19.0	−33.5
		c axis	5.098	7.64	10.31	76.2	97.4	78.2	−18.6	−18.2	−36.8
2	$P2_1/a$	*ac* plane	5.10	7.00	10.30	90.0	96.0	90.0	7.53	−17.51	−9.98
		c axis	5.03	7.55	10.37	92.7	92.6	76.1	−18.35	−16.99	−35.34
3	$P2_1/a$	*bc* plane	13.6	5.10	10.30	90.0	150.0	90.0	−7.75	−18.4	−26.2
		c axis	10.5	5.00	10.43	89.7	137.7	92.1	−19.8	−17.6	−37.4
4	$P2_1/a$	*bc* plane	7.9	5.10	10.30	90.0	120.0	90.0	−1.4	−18.2	−19.6
		c axis	9.1	4.98	10.40	89.6	127.1	94.7	−18.9	−18.0	−36.
5	$P2_1/a$	$b + c$, a	9.50	4.50	9.30	90.0	95.0	90.0	−13.5	−19.7	−33.2
		$b + c$	9.80	4.13	9.50	90.0	87.0	90.0	−17.6	−18.3	−36.0
6	$P2_1/n$	*ac* plane	5.10	7.00	10.30	90.0	96.0	90.0	−10.3	−19.8	−30.1
		c axis	5.12	7.28	10.30	90.0	96.9	90.0	−17.9	−18.7	−36.6
7	$P2/a$	*bc* plane	13.6	5.10	10.30	90.0	150.0	90.0	−5.1	−17.8	−22.9
		$b + c$ axis	11.3	5.00	10.41	89.36	133.2	68.5	−19.7	−17.8	−37.5
8	$P2/a$	*bc* plane	7.85	5.10	10.30	90.0	120.0	90.0	18.3	−17.0	1.31
		c axis	8.30	5.15	10.30	75.6	116.0	90.1	−18.6	−16.3	−34.9
9	$A2/a$	*bc* plane	14.4	5.10	20.0	90.0	150.0	90.0	−1.61	−15.2	−16.8
		c axis	13.5	5.20	19.9	90.0	148.3	90.0	−19.6	−17.6	−37.2
10	*Pban*	*ac* plane	20.6	7.60	5.10	90.0	90.0	90.0	−14.5	−16.9	−31.4
		a axis center 0,0,0	19.0	8.91	4.93	66.5	90.3	91.3	−17.9	−18.0	−35.9
11	*Pban*	*ac* plane	20.6	7.60	5.10	90.0	90.0	90.0	−10.7	−16.9	−27.6
		a axis center ¼, 0,0	20.8	9.28	4.95	60.0	90.2	69.1	−18.6	−18.3	−36.9
12	*Pnna*	*bc* plane	7.60	20.6	5.10	90.0	90.0	90.0	17.0	−6.7	10.3
		$b + c$	7.97	19.6	4.95	90.0	90.0	90.0	−18.6	−12.5	−31.1
13	*Pnna*	*ab* plane	20.6	5.10	7.60	90.0	90.0	90.0	−3.40	−17.0	−20.4
		a axis	19.6	4.93	8.24	81.4	77.1	88.5	−17.9	−17.9	−35.8
14	*Pmna*	*bc* plane	7.6	10.30	5.10	90.0	90.0	90.0	−14.0	−17.2	−31.2
		b axis	7.6	10.37	4.93	90.2	83.1	96.5	−17.6	−18.0	−35.6

[a] The first line gives the lattice constants and energy of the initial structure (as constructed) while the second line gives the corresponding values after minimization. [b] This is the space group of the initial structure. As can be seen from the final values of the angles (α, β, and γ), and discussed in the text, symmetry is often "lost" when minimizing these hypothetical structures. [c] The molecular plane indicates the (approximate) plane in which the molecule lies, while the axis indicates the direction of the long axis of the molecule.

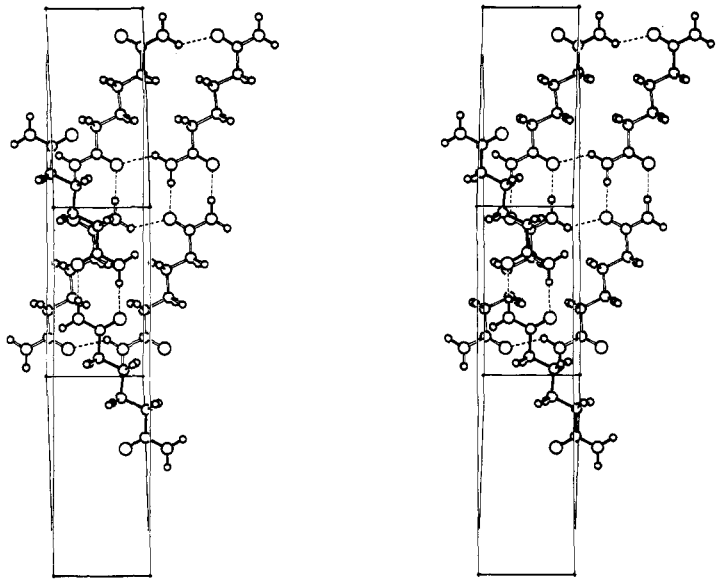


Figure 7. Stereoview of hypothetical adipamide crystal containing a translation secondary structure packed in monoclinic symmetry ($A2/a$) ($E = -37.2$ kcal/mol).

quity of the hydrogen bond, but they appear to be the first quantitative rationalization of the widespread observation of polymorphism. Kitaigorodskii[17] has pointed out that the majority of organic substances are capable of crystallizing in several different structures. Polymorphism among the amides as in other families is common.[9,18] Two examples are acetamide (CH_3CONH_2) which crystallizes in two forms, orthorhombic ($Pccn$)[19] and rhombohedral ($R3c$),[20] and, perhaps more relevant, *o*-chlorobenzamide which crystallizes in four forms,[21,22] the β form of which ($P2_12_12_1$)[21] contains the same hydrogen-bonding secondary structure as adipamide. (The α form ($P2_1/n$)[21] forms the usual hydrogen-bonded cyclic dimers, which in turn hydrogen bond by translation to form extended chains.[9]) It is clear that the energy differences between different polymorphic forms cannot be more than the difference of 1-2 kcal obtained here for several of the hypothetical

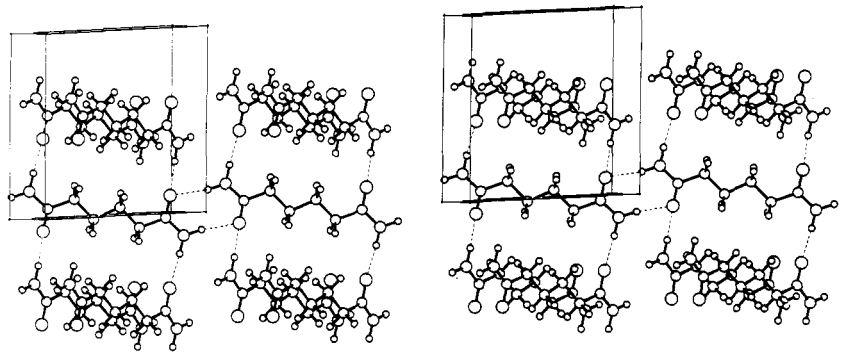


Figure 8. Stereoview of hypothetical adipamide crystal consisting of "shallow-glide" secondary structure packed in monoclinic space group $P2_1/a$ (E = −36.0 kcal/mol).

polymorphs as compared with the experimental structure.[17] For example, values for the energy difference between α and β-oxalic acid of 1.2 kcal/mol,[23a] and more recently 0.3 kcal/mol,[23b] have been reported. Values of the order of 1 kcal/mol have also recently been obtained for the differences in the lattice energies of several benzylideneanilines[13] which exhibit conformational polymorphism. Thus the picture which emerges is that a given molecule can generally pack in any one of several alternate structures, all of which are within a kilocalories or two. If the free-energy surfaces of these forms cross at some temperature, or crystallization from different solvents favors one over another, polymorphism is observed. Otherwise the alternate structures are never obtained. It should be noted in this connection that many polymorphic forms may exist which simply have not been found yet, since the proper conditions for the crystallization did not obtain.[24] In this regard it is interesting to note that the γ and δ forms of *o*-chlorobenzamide were obtained "by accident" and could not be obtained again.[22]

Symmetry. Finally, it is of interest to consider the results from the point of view of symmetry. Orthorhombic space groups often impose severe constraints on the tertiary structure of amide systems and, as a consequence, often lead to "bad" contacts, which destabilize these structures. It is for this reasons that amides are only rarely observed to pack in these space groups.[9,14] This is reflected in the energies of the orthorhombic structures which are higher for the most part than those in the monoclinic or triclinic space groups.

A second aspect of these results related to symmetry is worthy of comment. This concerns the "destruction" of the symmetry upon minimization of the lattice energy of most of the hypothetical crystals. As noted in the method, in the minimization procedure that we use here, symmetry is not imposed but derived. In theory, if one starts with a symmetric structure the symmetry must be maintained, as the derivatives with respect to the breaking of any symmetry element must be zero by virtue of its being a symmetry element. However, in practice, because of the finite computational accuracy, these derivatives are nonzero. Thus, if the extremum in the direction corresponding to the breaking of symmetry is a maximum rather than a minimum, the symmetry will be lost. In previous applications, where the initial structure corresponds to the observed structure and the object has been simply to investigate the fit to experiment, the derivation of symmetry is generally not required, as for any reasonable potential the observed space group will constitute at least a local minimum.[2b] Thus the general practice of assuming symmetry as a constraint is valid for these applications. However, we see that, if one considers hypothetical packing modes, it is necessary to consider the degrees of freedom corresponding to relaxation of symmetry. This is especially true if space groups are considered in which the secondary or tertiary structure is severely distorted because of symmetry considerations, as is the case with adiplamide in several of the monoclinic and orthorhombic space groups considered here.

Summary

The energetics of 16 hypothetical adipamide crystals of space groups and packing modes typical of amides were studied and compared with the observed packing mode. In this way it was shown that we can obtain an understanding of the factors determining the symmetry and packing modes of organic crystals. In particular we have accounted for the (previously unexplained) anomalous packing of adipamide, which contains a distorted and energetically unfavorable hydrogen-bonded network. It was shown that the adipamide molecule, by foregoing the most favorable hydrogen-bonding secondary structure available to it, attains a better interlayer packing which compensates for the better hydrogen-bonding energies achieved in several of the hypothetical crystals. The presence of all possible hydrogen bonds in crystals which contain functional groups which potentially can form hydrogen bonds, the scarcity of orthorhombic amide crystals (and space groups of higher symmetry) and the widespread occurrence of polymorphism were also discussed in light of these results. Finally, it was proposed that the use of hypothetical crystals, typical of the packing of crystals containing a given functional group, provides another, potentially sensitive test of intermolecular energy functions.

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(24) Prompted by the results of this study, we have carried out several preliminary attempts to obtain polymorphs of adipamide (presumably containing the usual cyclic dimer as in *o*-chlorobenzamide) by varying the solvent. So far these attempts have been unsuccessful, but we are continuing to use varying conditions of solvent and temperature.

Nucleophilic Ion Pairs. 5. Facile Cleavage of Amide Substrates by a Hydroxamate Anion in Aprotic Solvents. Efficient Inhibition by Minute Amounts of Water[1]

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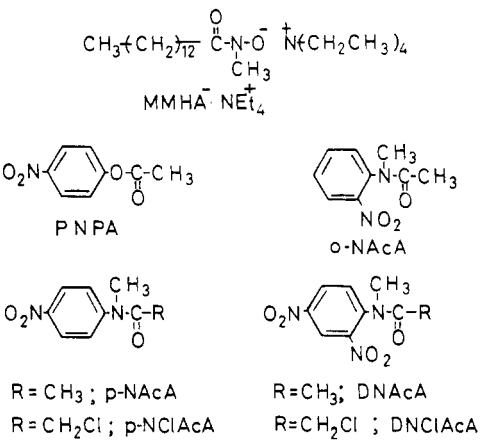
Abstract: A quaternary ammonium salt of the hydroxamate anion was found to cleave several *N*-methylanilide substrates very readily at room temperature in dry, aprotic media. In contrast, the reaction was very slow in protic media and, for example, a rate difference of $>10^5$ was observed between dimethylformamide and formamide media for the reaction of *N*-methyl-*p*-nitroacetanilide and tetraethylammonium *N*-methylmyristohydroxamate. The reaction was efficiently suppressed by minute amounts of water and a kinetic isitope effect (k_{H_2O}/k_{D_2O}) of 1.3–1.5 was observed for some substrates. These results indicate that both the nucleophilic attack and the proton transfer to the tetrahedral intermediate were facilitated in dry, aprotic media. The reaction of the hydroxamate and *p*-nitrophenyl acetate was facilitated in dry, aprotic media and in aqueous cationic micelles. Thus, the complete suppression of the amide cleavage in the cationic micelle was attributed to the inefficient proton transfer to the tetrahedral intermediate.

In model studies of the hydrolytic enzyme, most of the research has been carried out with activated substrates such as phenyl esters. Similar studies with amides and aliphatic esters have been relatively fruitless, because of the much smaller reactivities of these substrates. For instance, a highly activated amide like trifluoroacetanilide is hydrolyzed by imidazole catalysts at very slow rates.[2,3]

Recently, a variety of anionic nucleophiles including hydroxamates was found to be remarkably activated in the presence of cationic micelles and cationic polymer micelles. We believe that the large rate enhancement is mainly derived from formation of the hydrophobic ion pair between the anionic nucleophile and the quaternary ammonium group in the hydrophobic region of the micelles.[4] If this concept is valid, such ion pairs should also be highly reactive in organic media. Thus, we prepared tetraethylammonium *N*-methylmyristohydroxamate ($MMHA^-NEt_4^+$) and studied its reaction with several amide and ester substrates. This study shows for the first time that amide substrates are cleaved quite readily at ambient conditions, and that a small water concentration can considerably affect the reactivity of the hydroxamate anion in contradiction to the commonly accepted notion that the last trace of water hardly changes the anion reactivity in dipolar aprotic solvents.[5-7]

The enhanced reactivity of these ion pairs in the proton abstraction reaction has been published.[8]



Experimental Section

Materials. The preparation of $MMHA^-NEt_4^+$ was reported previously.[8] *o*-Nitro-*N*-methylacetanilide (*o*-NAcA) was prepared by methylation of *o*-nitroacetanilide (mp 88–90 °C, lit.[10] 93 °C). *o*-Nitroacetanilide (3.1 g, 0.017 mol) was dissolved in 30 mL of anhydrous tetrahydrofuran (THF) and 1 g (0.04 mol) of NaH as a suspension in 30 mL of THF was added dropwise with stirring over 30 min. After hydrogen evolution ceased, 2 mL (0.032 mol) of CH_3I was added and the reaction mixture was stirred for 3 h at room temperature. Then it was neutralized with acetic acid, solvent was evaporated, and the residue was recrystallized from benzene and cyclohexane to give slightly yellow needles, mp 68–70 °C (lit.[10] 71.2–71.4 °C).

p-Nitro-*N*-methylacetanilide (*p*-NAcA) was similarly prepared by methylation of *p*-nitroacetanilide and recrystallized from benzene and hexane, to give slightly yellow needles, mp 150–152 °C (lit.[11] 153–154 °C). *p*-Nitro-*N*-methylchloroacetanilide (*p*-NClAcA) was obtained from *p*-nitro-*N*-methylaniline (mp 150–153 °C, lit.[12] 150–157 °C) by reaction with 0.5 equiv of chloroacetyl chloride in refluxing benzene. The aniline hydrochloride was filtered and the solution was evaporated to dryness. Recrystallization of the residue from benzene and ligroin gave slightly yellow plates, mp 109–111 °C (lit.[13] 109–110 °C).

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