Investigation and Parametrization of a Molecular Dielectric Function

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Abstract: The necessity for a dielectric function at the molecular level is investigated by energy minimization of amino acid crystals. A step function description of the dielectric function is developed and tested using several species of amino acid crystals, including two containing water of crystallization. Different sets of published parameters for the Lennard-Jones potential function are also compared. The necessity for a molecular dielectric function is discussed and comparisons are made between results obtained in the crystalline state and in previously reported solution studies.

Introduction

The macroscopic dielectric constant is related to the dielectric permeability of the medium and reflects a diminution of charge interaction resulting from permanent or inducible multipole moments between the interacting charges. In studying the conformation of biological molecules by use of semiempirical potential functions, it has been common practice to approximate the dielectric effect by either a constant or a function dependent on r_{ij}, the distance between interacting species. It is necessary to take account of dielectric phenomena when computing the conformation of molecules such as peptides and proteins, especially when attempting to account for the role of solvent in the calculation of the conformation of molecules in aqueous solution. In instances where a dielectric constant has been used, values ranging between 1 and 5 have been proposed, although use of these values has not been satisfactorily justified. There is even evidence that the use of a dielectric constant at the molecular level is inadequate for the calculation of the entropy or free energy of even simple ions, let alone solution conformation of more complex species.[1,2] The case for a dielectric function has been insufficiently investigated.

A paper by Ralston and Samorjai[3] proposed a dielectric function which the authors use to investigate the effect of dielectric screening on the folding of a peptide. Similarly, a paper by Kumbar and Sankar[4] investigates the effect of different dielectric constants on the conformation of tryptamine and seratonin. As interesting as these studies are, they both deal with the conformation of a single molecule in a dynamic system. They give little insight into the interactions which give rise to the dielectric effect at the molecular level.

A recent paper by Momany[5] reports an attempt to use a molecular dielectric function in crystals. However, the justification for the form of the function used is unclear and there is a problem in the methodology used (see below under Discussion).

In order to investigate the effects on structure of dielectric phenomena, we chose to try to predict the structure of amino acid crystals using empirically determined dielectric functions. Amino acid crystals provide an excellent object for such an investigation because (1) all amino acids are in the zwitterionic form in the crystal, emphasizing the electrostatic interactions; (2) the nonbonded potential functions have been parametrized for the atom types found in amino acids; (3) amino acid crystal structures derived by neutron diffraction are available in which the positions of the hydrogen atoms have been experimentally determined. In addition, computation of the structure of amino acid crystals constitutes a further test of the uses of semiempirical potential functions in predicting conformation.

Computations

Energy Parameters. The contributions to the total energy of the crystal were assumed to come only from nonbonded and electrostatic energy. Studies in the literature have shown that there is little difference between the forms of the nonbonded potential functions. Therefore, the Lennard-Jones potential function was chosen because of its computational simplicity. Except where noted, the constants used for the nonbonded potential function were those of Hagler, Huler, and Lifson.[6] The hydrogen bond model proposed by these authors was also used (see also ref 7). Other sets of parameters were also used as described in the text.

Del Re's data[8] for the partial charges on the zwitterionic amino acids were used. Where appropriate, the correction proposed by Poland and Scheraga[9] for including the π contribution to the partial charge on an atom were included.

Atom coordinates were supplied by Dr. T. F. Koetzle or were from ref 24.

Variables. All six parameters of the crystallographic unit cell (a, b, c, α, β, γ) were varied. The six positional parameters of the central molecule (translations parallel to the x, y, and z axes and three Euler rotation angles ϕ, ψ, and θ) and the torsion angles (or angles of rotation) around single bonds were also varied. The molecules of the crystal were generated from the central or "input" molecule via the symmetry relations. Each variation in the central molecule was therefore reflected in the other molecules of the crystal.[10] A more realistic approach would be to allow each of the molecules in the central unit cell to vary its positional parameters independently of the others, but the computational demands for most crystals studied are prohibitive. (In the studies reported here, computer runs usually took between 60 and 90 computer minutes on the IBM 360/65.) No differences in results were obtained when the positional parameters for each molecule were varied in the glycine crystal.

Powell's minimization procedure as modified by Zangwill was used.[11] Each minimization was carried out twice, the second starting from the minimized position reached by the first. The second minimization always produced negligible changes in the position reached by the first. In these cases where the minimization had still not converged after 700 crystal energy calculations, the run was terminated. The run usually converged within 300-400 energy calculations (including both minimizations). All calculations were done on a PDP-12 with a floating point processor or on an IBM 360/65. The programs were written in FORTRAN except for some inner loops which were hand coded in assembly language for efficiency.

Crystal Size. Care must be exercised in generating the atom

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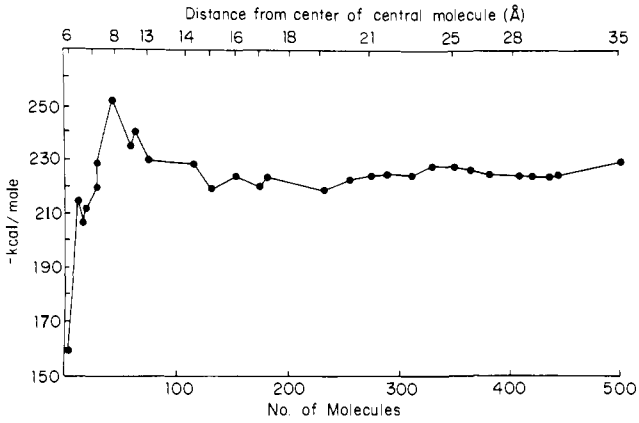


Figure 1. Energy of the alanine crystal as a function of the number of molecules in the crystal.

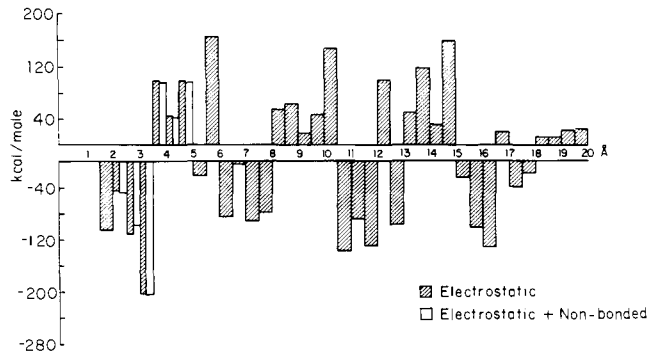


Figure 2. Energy profile for the alanine crystal with the dielectric constant equal to unity. Experimentally determined structure.

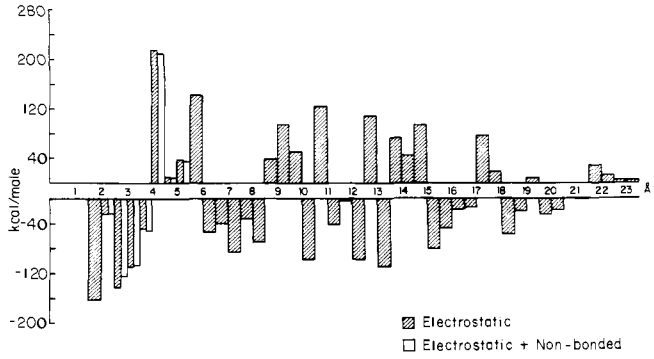


Figure 3. Energy profile for the alanine crystal. Semi-minimized structure.

coordinates of the crystal upon which the calculations are to be performed. Since the molecules of all amino acids are in the zwitterionic form, the molecules are electrically neutral but have a strong ionic character. Therefore, only whole molecules should be considered in the computations. Unlike the nonbonded energy, which has an r^{-6} dependence, the electrostatic energy, with an r^{-1} dependence on the distance between the interacting species, does not converge. At large distances, however, the interactions are essentially dipole-dipole in nature. In order to keep the number of molecules (and therefore the computational requirements) as low as possible, the optimum crystal size was determined by computing the crystal energy as a function of the number of molecules in the crystal. Successive shells of molecules were added to the crystal, and the effect of the next layer of molecules on the total energy was determined. The "next shell" was added in the following manner: the distance from the center of the central molecule to the center of another molecule in the crystal was computed; if that distance was less than some preselected distance, then that molecule was counted as one of the surrounding molecules. By doing successive energy calculations in which the cutoff distance was increased, one added successive shells to the crystal. The result of such a calculation can be seen in Figure 1. A cutoff distance of 16 Å was chosen as that which came closest to duplicating the large crystal energy but keeps the number of computations low. For the alanine crystal, 16 Å produces a crystal of 153 molecules. In order to test the assumption that results obtained on the smaller crystal represent a valid approximation to the larger one, an energy minimization using the larger crystal of 500 molecules was performed for alanine. The same changes in the variables occurred in the large crystal as in the smaller one.

Result of Minimization

Upon minimizing the energy of the alanine crystal with the dielectric constant equal to unity, the variables differed from the experimental x-ray values significantly. The changes from crystal structure are given in Table I. The changes from the experimental values listed represent the lowest energy position reached before the limiting number of crystal energy calculations was reached and does not represent a minimum. Since the lowest energy calculated structure already differed significantly from the experimental structure, the minimization was not continued.

By analyzing the changes in crystal structure, factors causing the changes may be determined. To examine the interactions in the crystal, the energy of the crystal was broken down into "shells" or radial distribution plots for the crystal structure and semi-minimized structure. Comparison led to a hypothesis explaining the divergence of the calculated structure from the experimental one.

The energy profile for the crystal structure and the semi-minimized structure are presented in Figures 2 and 3. The decline in energy of the first "destabilizing" (or positive energy) section (4.0-6.0 Å) is striking. The electrostatic energy of this destabilizing section went from 389 to 361 kcal/mol (a 28 kcal/mol *decrease* in destabilizing energy). Simultaneously, the electrostatic energy of the first "stabilizing" section (0.0-3.5 Å) went from −470 to −445 kcal/mol. Clearly, the decrease in crystal energy which results from minimization is the result not of an increase in stabilization energy, but of a relative decrease in destabilizing energy. The absolute value of the electrostatic energy of the entire crystal decreased in the course of minimization. All of the stabilizing contributions to the x-ray determined structure sum to −1534 kcal/mol, while the sum for the semi-minimized structure is −1432 kcal/mol. Likewise, the positive destabilizing energy goes from +1315 to 1197 kcal/mol. Since the absolute value of energy computed in the calculations reported here is solely an inverse function of distance, the distances between molecules must be increasing. Furthermore, the changes in the crystal structure that occurred during the minimization caused "flattening" of the unit cell and an increase of the unit cell volume and, therefore, increased distances between molecules (see Figure 4).

To cause the distances between molecules to increase, there must be a positive, or destabilizing, contribution to the energy that is pushing the molecules apart. Positive contributions to the energy come from the nonbonded repulsive contribution and the interaction of like electric charges. The energy profile indicates that there are no strongly positive contributions to the energy from the nonbonded component. Therefore, the destabilizing positive contribution to the energy must come from the electrostatic interactions. Also, the direction of the change in crystal structure appears to be toward reducing the

Table I[a]

	ΔV, Å^3	Δa, Å	Δb, Å	Δc, Å	$\Delta\alpha$, deg	$\Delta\beta$, deg	$\Delta\gamma$, deg	Δx, Å	Δy, Å	Δz, Å	Φ, deg	Ψ, deg	θ, deg	χ_1, deg	χ_2, deg	χ_3, deg,	χ_4, deg	χ_5, deg	χ_6, deg
Alanine ϵ = 1	19.62	0.195	1.253	−0.256	−15.71	0.63	−1.58	0.299	0.130	0.967	2.99	4.09	8.24	−27.00	0.0	8.47			
Alanine ϵ = 2	13.19	0.028	0.574	−0.012	10.70	−0.42	1.59	0.141	−0.051	−0.496	−2.90	2.00	−0.40	−22.7	0.2	4.8			
Alanine ϵ = step function	−2.42	−0.033	0.0	0.0	0.19	−0.10	−0.01	−0.003	−0.003	−0.022	0.25	0.0	0.14	−0.31	0.49	−2.14			
Glycine ϵ = step function	−2.13	0.478	0.010	−0.117	−0.03	0.36	0.23	−0.371		0.040	0.42	0.0	0.0	−0.03	−6.88				
Serine ϵ = step function	−3.39	−0.019	0.235	−0.149	0.04	−0.04	0.01	0.01	0.010	−0.005	0.11	−1.10	0.22	5.72	−4.81	0.0	1.60		
Proline ϵ = step function	3.99	0.002	0.052	0.007	0.01	−0.10	0.14	−0.015	−0.025	−0.007	0.0	0.32	0.0	0.0					
Threonine ϵ = step function	−14.35	−0.552	0.262	−0.096	0.24	0.11	0.03	−0.013	0.064	−0.087	0.0	1.49	0.0	6.40	0.54	29.19	5.81	2.50	
Glutamic acid ϵ = step function Charges ref 8	39.95	0.330	0.092	−0.003	−0.39	−0.01	−0.21	0.011	−0.190	0.019	0.4	−2.6	0.7	1.3	−0.6	−0.2	0.4	−0.9	−16.2
Glutamic acid ϵ = step function Charges ref 9	10.22	0.018	−0.168	0.160	−0.35	−0.08	0.18	−0.051	−0.043	0.001	8.5	−4.3	−0.9	1.1	−0.1	3.0	4.2	−17.0	8.3
Asn·H_2O ϵ = 1 Charges ref 8	13.8	0.032	0.700	0.662	−0.44	7.27	1.34	−0.235	−0.320	0.110	3.28	4.65	−0.32	19.28	30.10	0.89	50.16	0.87	
	H_2O molecule movement							0.283	−0.531	0.448	−8.95	1.05	1.52						
Asn·H_2O ϵ = step function Charges ref 9	23.18	0.192	−0.003	0.020	0.13	0.31	0.12	−0.159	−0.008	0.035	−0.69	6.92	0.0	1.60	−4.06	10.69	5.79	0.72	
	H_2O molecule movement							0.374	0.090	0.051	−0.53	3.72	−0.43						
Asn·H_2O ϵ = step function Charges ref 8	17.14	0.195	−0.043	0.035	0.12	0.80	0.56	−0.165	−0.018	0.030	0.73	6.43	−0.58	2.75	−8.27	7.56	6.73	0.24	
	H_2O molecule movement							0.051	0.095	0.047	3.02	1.00	−2.29						
Serine·H_2O ϵ = step function	−8.16	−0.097	−0.040	0.006	−0.06	0.08	−0.02	−0.008	0.003	0.007	−4.98	0.0	0.0	−8.02	0.17	0.57	−3.25		
	H_2O molecule movement																		
Alanine Constants and H-bond ref 17 ϵ = 1	−76.37	−0.627	−0.104	−0.388	7.05	0.25	−0.75	−0.591	−0.071	−0.154	0.0	3.17	1.25	−3.9	−0.70	−20.80			
Alanine ϵ = 1 Constants and H-bond ref 14	−62.91	−0.698	−0.054	−0.228	0.58	0.18	−0.76	−0.034	0.007	0.025	0.80	0.34	0.93	0.0	11.83	61.36			
Alanine ϵ = 1 Constants ref 15 H-bond ref 9	−66.56	−0.49	−0.070	−0.373	1.14	0.27	−1.26	−0.015	−0.003	−0.007	0.29	4.58	1.20	1.20	−0.97	−20.28			

[a] ΔV, change in unit cell volume; a, b, c, α, β, γ, unit cell parameters; x, y, z, Φ, ψ, θ, positional parameters of central molecule; χ_n, angle of rotation around bonds.

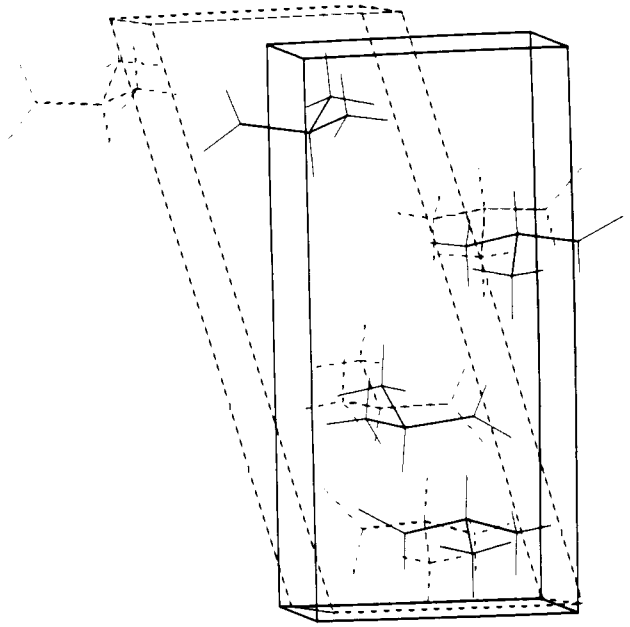


Figure 4. Appearance of the unit cell of alanine after semi-minimization with $\epsilon = 1$. Solid line, experimentally determined structure. Dotted line, semi-minimized structure.

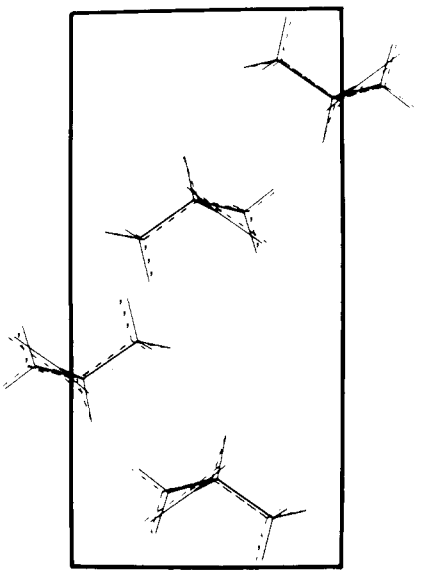


Figure 5. Appearance of unit cell of alanine with ϵ = step function.

effect of the positive electrostatic contributions to the energy, especially the first "destabilizing" shell between 4.0 and 6.0 Å.

A reasonable hypothesis is that the effect of the longer range interactions needed to be diminished by use of a dielectric constant. However, using a dielectric constant of 2 for all interactions produced results very similar to those produced by a dielectric constant of 1. Since one might expect the close-range interactions to be screened less than the longer range ones, a dielectric function that varies with distance was examined. As a first approximation a step function was chosen, such that the dielectric factor would be 1 for interactions involving distances less than some cutoff distance, and 2 for distances greater than that. A cutoff distance of 3.5 Å was chosen to emphasize the close-range stabilizing interactions and deemphasize the first destabilizing section. The results are presented in Figure 5. As can be seen, the changes from the x-ray determined positions are small. Setting the cutoff distance at either 3.0 or 4.0 Å produced substantial deviation from the experimental structure.[12] Armed with the step dielectric function, the energy of other nonhydrated amino acid crystals was minimized. Among the crystals tested, in addition to alanine, were glycine, proline, serine, threonine,[21] and glutamic acid. All the calculated structures closely agreed with the observed x-ray structures (see Table I). (See Table II for a summary of the energy changes on minimization.)

Of the nonhydrated amino acids used in these studies, none of the side chains has any π character except glutamic acid. The Del Re data for the partial charges[8] assume the existence only of σ bonds. Poland and Scheraga[9] have calculated the additional charge needed to take account of π bonds in the charge distribution. When Scheraga's partial charge data was used in the minimization, agreement was again good. The same was done for Asn·H_2O. The data would indicate that the minimization is relatively insensitive to small variations in charge.

Two amino acid crystals containing water of crystallization were energy minimized: serine monohydrate and asparagine monohydrate. The dielectric step function was used in the minimization. The water molecules were allowed to translate and rotate independently of the amino acid molecule. Both crystals minimized with the experimental and theoretical positions showing good agreement.

In order to test further the hypothesis that the electrostatic interactions involving atoms separated by more than 3.5 Å should be shielded, the energy of the asparagine monohydrate crystal was minimized assuming a dielectric constant equal to one. The asparagine monohydrate crystal was chosen because an energy profile showed that there existed a strong attractive region between 3.5 and 4.0 Å. Unlike the alanine crystal, which had a destabilizing region after 3.5 Å and which showed a decrease in the absolute value of the electrostatic energy of the entire crystal on minimization with $\epsilon = 1$, it was anticipated that minimization of the Asn·H_2O crystal would produce an *increase* in the absolute value of the crystal energy because the attractive component between 3.5 and 4.0 Å would cause de-

Table II. Summary of Energy Changes on Minimization (kcal/mol)

	Start				Finish				
	Total energy	Non-bonded	Electro-static	Intra-molecular	Total	Non-bonded	Electro-static	Intra-molecular	Dielectric
Alanine	−224	−5	−219	−81	−234	+3	−237	−81	$\epsilon = 1$
Alanine	−349	−5	−344	−48	−357	−6	−351	−48	$\epsilon(r)$ = step function
Proline	−321	−4	−317	−88	−323	−5	−317	−88	$\epsilon(r)$ = step function
DL-Serine	−343	+11	−354	−31	−389	+8	−397	−34	$\epsilon(r)$ = step function
Glycine	−286	+20	−306	−35	−352	+34	−386	−36	$\epsilon(r)$ = step function
Glutamic	−323	−11	−312	−68	−454	−1	−453	−81	$\epsilon(r)$ = step function
Threonine	−231	+46	−277	−34	−351	+57	−408	−32	$\epsilon(r)$ = step function
Serine H_2O	−333	+3	−336	−49	−424	+9	−433	−47	$\epsilon(r)$ = step function
Asparagine H_2O	−284	−3	−281	−112	−473	+2	−475	−111	$\epsilon(r)$ = step function
Asparagine H_2O	−306	−3	−303	−141	−333	0	−333	−146	$\epsilon = 1$

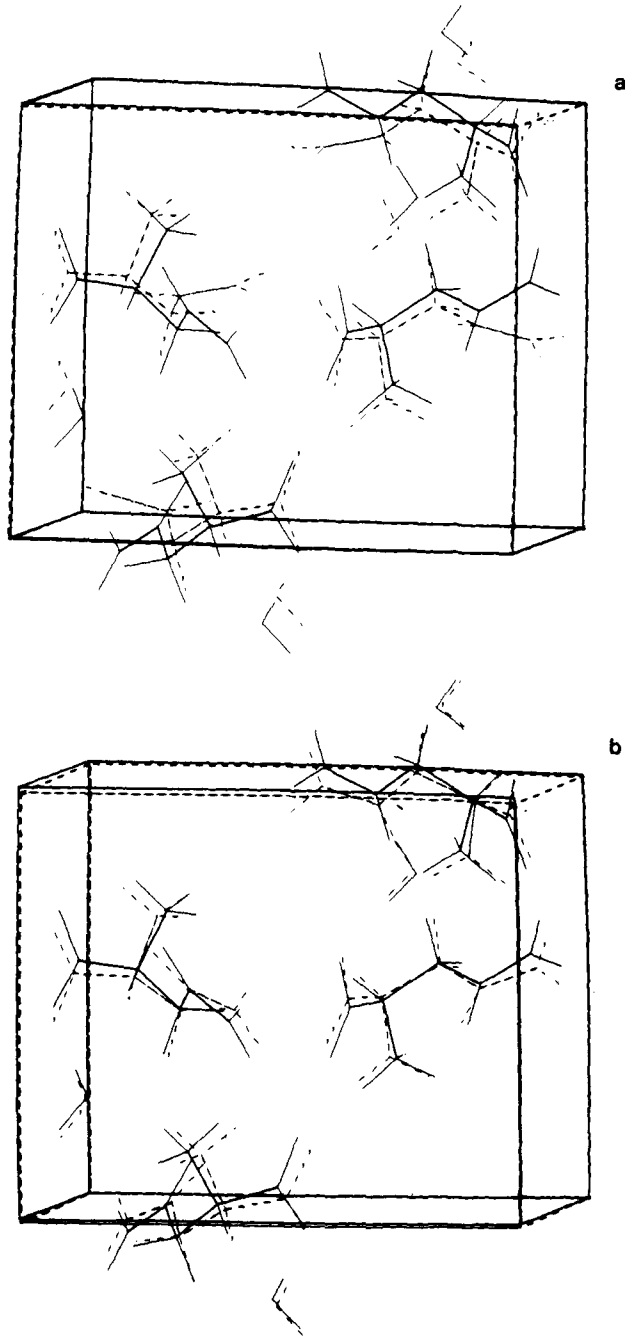


Figure 6. (a) Asparagine monohydrate crystal semi-minimized with $\epsilon = 1$; (b) asparagine monohydrate crystal minimized with ϵ = step function.

creasing interatomic distances. Such a prediction was made because the very strong region of negative energy between 3.5 and 4.0 Å would be expected to cause a contraction of the crystal structure in a way analogous but opposite to the alanine crystal's expansion with $\epsilon = 1$. The results bore out the prediction (see Figure 6). On minimization with $\epsilon = 1$, the total electrostatic stabilizing energy of the crystal went from −2031 to −2746 kcal/mol. Examination of only the first stabilizing (0–4 Å) and destabilizing regions (4–6 Å) shows that the energy of the former went from −583 to −706 kcal/mol and the latter from 404 to 593 kcal/mol.

As noted, the nonbonded constants used in the above calculations are those derived by Hagler et al.[6] This set of constants was chosen for several reasons: (1) they provided a reasonable and easily implemented description of the hydrogen bond; (2) the constants and H-bond description were derived using amide crystals, the molecules of which form hydrogen bonds; (3) the constants were checked by minimizing amide crystals. Most other nonbonded constants were not derived in a similar way. The nonbonded constants of Ferro et al.,[13,23] for example, were derived by investigating the interactions of atoms in hydrocarbon and non-hydrogen-bonding nitrogen and oxygen-containing crystals. In order to be able to apply the constants thus derived to hydrogen-bonding crystals, the above cited authors used the hydrogen bonding model of Poland and Scheraga.[9]

When applied to the amino acid crystals, the constants and hydrogen bonding models used by most other authors gave poor results (the dielectric constant was set equal to unity for these calculations). Unlike the results obtained using the constants of Hagler et al., results using Ferro's constants caused the distances between molecules to decrease, as indicated by the large drop in unit cell volumes. Also again unlike the constants of Hagler et al., an energy profile revealed that in none of the interaction shells was there a positive nonbonded energy contribution. At no point was the attractive electrostatic in the very important first stabilizing section (0.0–3.5 Å) offset by a repulsive component. Constants reported by Hopfinger,[14] as well as a scheme for generating a description of the hydrogen bond reported by him, and constants reported by Scheraga[15] together with the Poland and Scheraga hydrogen bond[9] were also tried, but failed to produce agreement with experimental observations (see Table I).[22]

Discussion

Other Nonbonded Constants. It has long been understood that the repulsion part of the potential function is of primary importance in determining the structure of a crystal.[16,17] The repulsion portion of the potential function determines how close together two atoms can approach—hence, the success of the hard-sphere model in the prediction of crystal symmetry, based on packing considerations alone.[17] Such a generalization appears also to be true for systems in which charged interactions contribute significantly to the energy.

A clue to the failure of the other potential function constants can be gleaned by looking at the van der Waals contact distances determined by the various constants. Such a comparison is made in Table III. The constants of Hagler, Huler, and Lifson usually predict contact distances significantly greater than the predictions made by the constants of other authors. At least part of the reason for this is the description of the hydrogen bond used. Hagler et al. originally assumed a Morse potential function as a description of the hydrogen bond, but found that the parameters of the functions were smaller than the standard deviations. They therefore set the parameters of the Morse function to zero. In the resulting scheme, the repulsion comes from the nitrogen to which the hydrogen-bonded hydrogen is attached, not the hydrogen itself. As a result, the atoms must have a greater apparent diameter, as determined by the van der Waals distance. However, merely adjusting the van der Waals distance cannot be expected to adequately offset the role that the dielectric function has in these calculations. Whereas the parameters of Hagler et al. for the nonbonded potential function might be said to have predicted a minimum energy distance which was "too large" in the case of alanine (since the unit cell volume was seen to increase with $\epsilon = 1$), the opposite was true in the case of the asparagine monohydrate crystal.

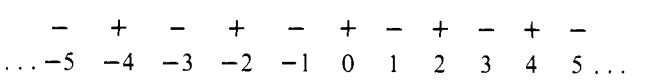
Molecular Dielectric Function. There is some doubt about the necessity for including a dielectric of any kind at a molecular level when dealing with a crystal. In crystals of molecules such as amino acids, the macroscopic dielectric constant is thought to arise almost exclusively from the polarization of electrons in response to the applied electric field since there is no orientational freedom allowed the molecules in the crystal.

In the presence of only the charges inherent in the molecules of the crystal, the situation is less clear. The electrons on the atoms presumably interact with the field produced by all the charges in the crystal, but exactly what form this interaction takes when there is molecular asymmetry is unknown.

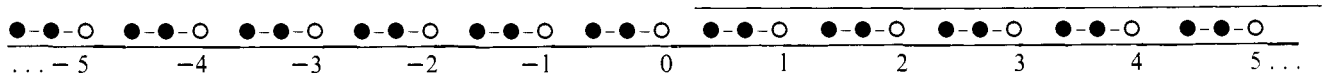
In the case of a simple, highly symmetric crystal such as sodium chloride the field at a point in the crystal due to all the charges in the crystal is zero. If the assumptions usually made when calculating conformation by the semiempirical method are used, then the field at a point (j) due to surrounding charges can be computed by

$$F_j = \sum_i \frac{e_i r_{ij}}{r_{ij}}$$

where e_i is a charge located at a distance r_{ij} from point j. If we look at a one-dimensional sodium chloride crystal as follows



it is apparent that the electrostatic field at point 0 will be zero because each term in the sum will be canceled by an exactly equal term of opposite sign. (The situation in the three-dimensional case is exactly analogous.) When one explores the situation in a crystal whose molecules are polyatomic and therefore do not occupy only lattice points, and also have inherent asymmetry, the result is different. If we viewed the arrangement of atoms in a one-dimensional crystal of asymmetric molecules (or the projection on one axis of a three-dimensional crystal) we might get the following picture. (Assume that the molecules are electrically neutral but each atom has a partial charge):



Clearly, there are some distances between the atoms of the central molecule and the atoms of other molecules that are not canceled as was the case in the sodium chloride crystal. Nor can one "build" a crystal so that the terms of the sum cancel. At best, one can get the field at one of the atoms of the central molecule to be in a zero electrostatic field, but one then forces the fields that the other two atoms are in to be nonzero. Since we deal with three-dimensional crystals, it is possible that the charge, the component of the distance in the numerator, and the cube of the distance in the denominator produce a number which exactly cancel other terms of the sum, but such an occurrence would have to be considered fortuitous (a brief computer experiment using alanine bears this out). In addition, if one considers the field at an atom due to other atoms within the same molecule, it is virtually impossible to have a zero electrostatic field unless the molecule is symmetric.

This existence of a different electrostatic field at each atom in the molecule would lend theoretical justification to the concept of a dielectric function at the molecular level in some crystals. An alternative to invoking a dielectric function might be to say that the electrostatic field at each atom induces dipoles on those atoms in response to the field. Whether such an alternative will succeed in predicting crystal structure with the same accuracy as our model dielectric function remains to be determined and is under investigation.

Hagler, Huler, and Lifson[6] had no need to assume the existence of a dielectric function when deriving their constants for hydrogen bonded amide crystals. Any dielectric function would probably have been incorporated into the parameters of the potential function during the least-squares fit. In the system we used, the contribution of the electrostatic energy to the total energy of the amino acid crystal was far greater than in the amide system. In the amide crystals considered by Hagler et al., the nonbonded energy contributed approximately 25-75% of the total energy of the crystal. In amino acids, the nonbonded energy seldom contributed more than 2%. In addition, the calculated energy of the amino acid crystals was more than an order of magnitude higher than the energy calculated for the amide crystals. (One might expect such a finding since, unlike the amide crystals, the amino acid crystals decompose before they sublimate, indicating very strong intermolecular forces.) Clearly, the electrostatic interactions play a much greater role in the energy of amino acid crystals than in amide crystals. As a result, one would also expect to see the effect of a dielectric function in amino acids and not necessarily in the amide system.

Table III. Comparison of Minimum Energy Distance for the Nonbonded Potential Function Constants

	Hagler et al. (6)	Ferro et al. (10)	Hopfinger (14)	Scheraga (15)
C···C	4.35	4.31	2.95	3.40
N···N	3.93	3.52	3.17	3.10
O···O	3.21	3.15	3.04	3.04
H···H	2.75	2.79	2.40	2.40

The results from the hydrated amino acid crystals would indicate that no "special" interaction need be included in any solution model to account for solute-solvent interaction. Furthermore, the demonstration of a dielectric function at the molecular level and verification in crystals fills a gap in our understanding of how to apply the semiempirical potential function method to large molecules as well as solutions.

The only other attempt to fit crystals of charged molecules is reported by Momany et al.[18,19] However, there are several difficulties in interpreting the results of this work: (1) The nonbonded constants used were derived by varying only the independent lattice variables instead of allowing the crystal structure to change and the molecules in the unit cell to vary independently of each other as was done by Hagler et al.[6] (2) Studies in our laboratory have shown that unless more variables are included, one does not adequately test the potential functions and, at times, almost any set of potential function constants will produce agreement with the experimental values. If, for example, one only varied the one independent lattice parameter in a cubic lattice,[18] one would change the distance between molecules but not other relationships. One must let the crystal structure change, at least to a limited extent, to adequately test the potential functions. We tested the potential function constants, partial charges, and hydrogen bond function of Momany et al. Upon energy minimization, using only the variables that the above authors employed, our results agreed closely with theirs. However, when the full number of variables was allowed to change in the minimization, the crystal structure diverged greatly. We also tested other sets of potential functions using only the limited number of variables used by Momany et al. While their constants and partial charges gave the smallest deviations from the experimental structure, the others were close enough to make the choice of potential functions equivocal. (3) The lattice energies calculated for amino acids are too low. It seems unlikely that substances that decompose before melting or subliming would have lattice energies below substances which have measurable sublimation energies. In later work[5] where the same nonbonded constants are used to investigate the acetic acid and formic acid crystals, a dielectric function is used in the energy calculation (how the form of the dielectric function was chosen is not discussed). That a dielectric function would be necessary in

the calculation of the lattice energy of uncharged molecules and not necessary for charged molecules such as amino acids is not credible. Work in our laboratory (Greenberg, in preparation) on the energy of peptide crystals shows, as expected, that where the lattice energy is primarily determined by the nonbonded constants, the dielectric function makes no difference in the predicted crystal structure.

There is evidence from solution studies favoring the distance of 3.5 Å at which the step in the step function occurs and the discontinuous nature of the step itself. Theoretical studies on the free energy and entropy of hydration of ions in solution indicate that there is a discontinuity in ϵ at the edge of the first layer of water molecules surrounding an ion.[20] Furthermore, there is some evidence that the dielectric constant is the bulk value at distances from a hydrated ion of on the order of only 3 Å, depending on the size of the ion.[20] Other theoretical studies,[20] on the salting out behavior of ions, show that assuming a sharp cutoff after the primary hydration shell produces much better agreement with experiment than do continuum models (see also the review by Conway[1]).

The above cited studies offer compelling corroboration of the present work. Despite the differing assumptions and approaches, these investigations revealed a sharp change in the dielectric constant at a critical distance related to the ion-water contact radius, results which exactly parallel the present findings in the crystalline state.

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Basis Set Dependence of Spatial Electron Distribution. Implications for Calculated Conformational Equilibria

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Abstract: The effect of deficiencies in the description of the spatial electron densities as calculated with minimal basis sets on conformational equilibria are described. Total electron density maps of *N*-methylacetamide for both minimal and extended basis sets and difference maps (extended minus minimal) are presented to demonstrate the difference in "atomic sizes" in the two basis sets. It is concluded that the "steric" effect, which is of major importance in determining conformation, is inadequately represented with minimal basis sets. A partitioning of the total energy supports these conclusions as well as further demonstrating that the main contribution to the barrier about the N–C$^{\alpha}$ bond (ϕ) is the syn-planar H···O steric repulsion.

In recent years there has been an ever-increasing number of molecular orbital calculations of molecular properties. Many of these calculations are directed toward the investigation of molecular structure and conformation.[1,2] Conformation is of special interest in the case of biological molecules (or model compounds) because of the relation between conformation and activity of these molecules.[2c,3] In addition to the direct calculation of molecular conformation, several studies have recently appeared which propose the use of molecular orbital theory to obtain information about the (Born–Oppenheimer) energy surface of molecular systems for use in the development of analytical expressions for this energy surface.[4] The latter ap-

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