Ab Initio Prediction of Possible Crystal Structures for General Organic Molecules

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The performance of a new crystal packing procedure for the *ab initio* prediction of possible molecular crystal structures is presented. The method is based upon only molecular information, i.e., no unit cell parameters are assumed to be known. The search for the global crystal energy minimum and all local minima inside an energy window is derived from Monte Carlo simulated annealing methods and has been applied to various organic molecules containing heteroatoms and polar groups. A systematic evaluation of the search method and of the quality of the potential energy function has been established. It is demonstrated that the packing of general organic molecules is possible even with standard force fields like CHARMM provided that the charges defining the electrostatic interactions are based upon physical models rather than transferable empirical parameters. Concepts of crystal packing that were based till now upon assumptions and speculations could be proved or disproved by solving directly the extended global optimization problem related to crystal packing. Crystal structures of molecules as complex as those treated in this article have not been, till now, predicted by a computational approach. In one case, a disagreement between the predicted and experimental structure was evident and, based upon the computations, we suspect that the published structure is the wrong one. © 1992 by John Wiley & Sons, Inc.

INTRODUCTION

Theoretical solid-state physics and chemistry have achieved during the last decades a high degree of sophistication and are well recognized as explanatory tools for various phenomena.[1] A precise knowledge of the crystal structure is, however, essential for the application of these theories. These theories, at least in the field of organic molecular solids, are still of little practical use because of their limited potentiality as tools for designing new materials composed of, as yet, unsynthesized molecules. The key to a rational design of crystalline organic materials is the solution of the packing problem that consists in predicting the stable crystal modifications of a given molecular structure in the absence of any unit cell information.

Computational methods dealing with crystal geometry optimization and crystal dynamics are well developed,[2] but they do not tackle the packing problem itself because they invariably rely upon the existence of a reasonable starting structure. However, these computational methods are indispensable in the later stages of a packing procedure after solving the problem of establishing reasonable starting structures.

We are not going into the details of the heated discussion[3] whether it is possible to predict the structure of crystals from first principle or not. The state of the art in the field of crystals is that implementations of generally applicable methods do not exist. Since the basic work of Kitaigorodzky[4] in the 1970s, two main approaches toward a solution of the packing problem evolved.[5] The first, the data base approach, is based upon the statistical analysis of the "Cambridge Structural Database,"[6] where molecular descriptors are tentatively correlated to crystal parameters. The nasty facts that minor structural changes in the molecular structure may cause large changes in the packing and that a molecular descriptor like the dipole moment is often irrelevant in the packing of medium-sized molecules[7] present a serious obstacle to the general applicability of this approach as a reliable predictive tool. Nonetheless, the statistically significant facts about the prevailing geometric motifs associated with certain interactions present valuable information to guide the organic crystal engineer.

The second approach toward a solution of the packing problem is the physical one.[4,5] Two things are necessary for this approach: a reliable potential function and a reliable search methodology to locate the lowest minima of the potential function. The underlying assumption is that the crystal structures corresponding to these lowest minima represent the possible crystal modifications. Classic poten-

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tial functions based upon transferable force field parameters[8] are at present applied to packing studies of organic molecules. The reliability of such force fields is questionable and the sensitivity of the packing with respect to some force field parameters is low.[9] Successful packings have thus been achieved mainly with hydrocarbons,[4,10] which are neither the most representative nor the most chemically useful compounds. A common approach to the global search of crystal structures is to extrapolate molecular cluster results to crystals and use them as reasonable starting crystal structures for further investigations. Researchers at Hitachi Ltd.[11] used this method for designing nonlinear optical materials. By analyzing the features of bimolecular complexes, they focused their interest on the question of whether the crystal modifications of an organic molecule will be centrosymmetric or not. Till now, the broadest scope of searching the energy hypersurface of organic crystals has been published by Gavezzotti.[10] His method consists of building multimolecular clusters using appropriate symmetry operators and then extending the most promising clusters in three directions in space. One drawback, mentioned by Gavezzotti himself, is that the decision for performing a translational search (i.e., generating the full crystal) must be taken on the basis of the cluster energies where the periodic boundary conditions are not yet taken into account. For some semiconductor and metal solids, it has been recently shown[12] that the initially formed small clusters have no resemblance to the final crystal structures. For hydrocarbons, Gavezzotti's results are impressive. To the best of our knowledge, no results for organic molecules containing heteroatoms have yet been published.

Recently, one of the authors[13] proposed a generally applicable packing method based upon a modified Monte Carlo simulated annealing[14] method with impressive results for some hydrocarbons (hexamethyl benzene as P-1, $Z = 1$ and ethylene as P1, $Z = 2$). The implemented search method uses, from the very beginning, periodic boundary conditions (i.e., a crystal and not a cluster approach). Publications that claim the predictions of crystal structures by simulated annealing are known[15] but a closer inspection reveals that they do not tackle the real packing problem because the values of the unit cell parameters are assumed to be known.

In the subsequent sections, we give a comprehensive overview of the method and evaluate the predictions for a broad class of molecules including polar and H bonding species.

DEFINITIONS AND PROBLEM FORMULATION

The mathematical formulation of the packing problem for crystals built of one molecular entity is:

Given (1) a molecular structure, (2) Z = the number of molecules in the unit cell, (3) the space group, and (4) a potential function of the degrees of freedom of the molecular crystal, find the global minimum energy and all the low-energy minima (i.e., all energies inside a given "energy window") of this function. We will refer to this problem, where the complete low-energy spectrum is requested, as the "extended global optimization problem."

The fact that a space group must always be specified is by no means restrictive because we can always refer to the simplest space group, P1, with a sufficiently large Z. If the molecule favors a space group containing additional symmetry elements, a successful packing should reproduce these symmetries automatically.

The complete set of degrees of freedom for the molecular crystal consists, in the case of one molecule per asymmetric unit, of:

(a) The internal degrees of freedom of the molecule.
(b) The unit cell constants (depending upon the crystal system), e.g., in the triclinic case the six unit cell constants a, b, c, α, β, and γ.
(c) The three rotations of the molecule θ_1, θ_2, and θ_3 inside the asymmetric unit, i.e., the Eulerian angles.
(d) Depending upon the space group, up to three translations inside the asymmetric unit, e.g., for space group P1 there will be no translations, for space group P2 there will be two translations, etc.

For each additional molecule in the asymmetric unit, the internal degrees of freedom, three translations, and three rotations of that molecule must be added.

To make the point clear: No information except molecular structure information is needed and because bond length and angles are fairly constant the principal unknowns for which we seek for solutions are the main intramolecular torsions and the variables uniquely defining the crystal, i.e., those mentioned in (b)–(d) above.

METHOD AND IMPLEMENTATION

Outline

It is obvious that the extended global optimization problem is by far too complex to be solved in the whole configuration space (i.e., the space defined by the whole set of degrees of freedom). The usual way to overcome this difficulty is to split the solution procedure into several sequential stages. An outline of our packing procedure that consists of three such stages is:

Stage 1. The first stage consists of a search for reasonable crystal structures using the Monte Carlo simulated annealing method in a low-dimensional space

resulting from freezing internal degrees of freedom like bond length and bond angles. No knowledge of unit cell parameters is required. As will be shown below, a key feature of the method is that some of the degrees of freedom must be made dependent upon the others to prevent an "evaporation" of the crystal (this will be discussed later in a more comprehensive manner).

Stage 2. The first stage above will generate a large number of crude crystal structures in the search space. However, the number of structures is still too large and not all of them can be optimized with respect to all degrees of freedom. The second stage consists of a mathematical procedure termed cluster analysis,[16] i.e., "similar" crystal structures are grouped and only the lowest energy structure in such a group will be chosen for a subsequent full lattice optimization.

"Similarity" between two reduced crystal structures (i and j) belonging to the same space group is defined as in ref. 13 by means of their rms, the square root of

$$MS_{ij} = 1/3[(\mathbf{a}_i - \mathbf{a}_j)^2 + (\mathbf{b}_i - \mathbf{b}_j)^2 + (\mathbf{c}_i - \mathbf{c}_j)^2] + 1/N\Sigma_n[(x_n^i - x_n^j)^2 + (y_n^i - y_n^j)^2 + (z_n^i - z_n^j)^2] \quad (1)$$

where N is the number of atoms in the asymmetric unit and x_n^i etc. are the coordinates of the nth atom in the ith crystal.

Stage 3. The modest number of cluster representatives from the second stage (the number will depend mainly upon the computer resources at hand) is submitted to a crystal optimization where all degrees of freedom are taken into account. The resulting low-energy structures (after the elimination of duplicate structures) laying inside the predefined energy window are considered the solution to the extended global optimization problem.

Suppression of Crystal Evaporation

Let us now explain the first stage in more detail. A Monte Carlo simulation[17] consists of the generation of a sequence of points (or trajectory) in some space for which a potential function is defined, according to the simple Metropolis et al. algorithm.[18] For the sake of completeness, we give a short outline of this algorithm: Assume that $\mathbf{X}_n$ is the last point (i.e., a vector containing the degrees of freedom in the search space) in the sequence where the potential function has the value E_n. Generate a trial point $\mathbf{X}^* = \mathbf{X}_n + \Delta\mathbf{X}$ with $\Delta\mathbf{X}$ being some random vector. Let ΔE be the potential difference between this trial point and the last point $\mathbf{X}_n$. If ΔE is negative (i.e., the trial point has a lower energy) $\mathbf{X}^*$ is accepted as the new point $\mathbf{X}_{n+1}$ of the sequence; otherwise, $\mathbf{X}^*$ will be accepted as the new point with a probability given by $\exp(-\beta\Delta E)$, β being proportional to the reciprocal "temperature."

We assume first that the independent variables defining the search space consist of the lattice parameters, the rotations and translations of the molecules in the asymmetric unit, and the main torsions in the case of flexible molecules. The simulated annealing protocol[19] could be described as follows: Starting with a sufficiently high "temperature" necessary to overcome energy barriers, the temperature value is lowered slowly until the system has "frozen." In practice additional features like the control of the step size etc. must be taken into account.[13]

However, it turns out, that frequently the system continues to stay as a "gas," i.e., at least one of the values a, b, or c remains so large that there is no contact between the molecules in the corresponding direction.

The crystal evaporation has been suppressed in our method by excluding the degrees of freedom that determine the spatial extensions of the crystal (i.e., the unit cell length and some translations) from the search space. The independent variables are all the angular degrees of freedom. Let $\mathbf{\Phi} = (\alpha, \beta, \gamma, \ldots)$ be these angular variables and let $\mathbf{S} = (a, b, c, \ldots)$ be the variables determining the spatial extensions of the crystal. The original search space in which evaporation occurred was $\mathbf{X} = (\mathbf{\Phi}, \mathbf{S})$, where both $\mathbf{\Phi}$ and $\mathbf{S}$ were varied independently. The new search space consists only of $\mathbf{\Phi}$. The variables in $\mathbf{S}$ are now dependent upon $\mathbf{\Phi}$, i.e., $\mathbf{S} = \mathbf{S}(\mathbf{\Phi}) = [a(\mathbf{\Phi}), b(\mathbf{\Phi}), c(\mathbf{\Phi}), \ldots]$. For a set of angular variables (i.e., a point in the search space), these dependent variables, $\mathbf{S}$, are computed by an additional process. This process consists of minimizing the crystal energy with respect to **only** these few variables determining the spatial extension of the crystal.

As an example, consider the case of a rigid ethylene molecule in the P1 space group with $Z = 2$ (i.e., two molecules in the asymmetric unit). The variables that define the spatial extensions of the crystal are the lattice parameters a, b, c, and the three components of the translation vector of the second ethylene molecule. It is possible to express the translation vector in polar coordinates so that actually only the distance between the centers of the molecules, d, will affect, in addition, the spatial extensions of the crystal. The independent angular variables are the three lattice angles α, β, γ, the three Eulerian angles of the first molecule, θ_1, θ_2, θ_3, the three Eulerian angles of the second molecule, τ_1, τ_2, τ_3, and the two polar angles of the translation vector, φ and ϕ, i.e., $\mathbf{\Phi} = (\alpha, \beta, \gamma, \theta_1, \theta_2, \theta_3, \tau_1, \tau_2, \tau_3, \varphi, \phi)$. We have thus 11 independent angular variables defining the Monte Carlo search space. The dependent variables, in this example, $\mathbf{S} = (a, b, c, d)$, are determined for a given set of independent variables, $\mathbf{\Phi}$, as follows: In a first step, the a, b, c, and d values are altered by an interval method so that the bad contacts (i.e., interpenetrations of atoms under the van der Waals limits) are just relieved. In a second step, the crystal

energy is minimized keeping all the variables except a, b, c, and d fixed. To summarize, each Monte Carlo step consists of choosing a set of independent angular variables with a subsequent optimization of the energy only with respect to the few variables affecting the spatial extensions of the crystal.

Force Field

We used the CHARMM[20,21]* program for implementing all the described methods. The CHARMM program has a user interface that enables the programmer to link his or her own routines to this program. Thus, all the operations dealing with the crystal building, lattice energy calculations, derivative calculations, and crystal optimization with respect to all degrees of freedom were performed by the CHARMM program under the control of the user. With the exception of the atomic point charges, which will be discussed in detail below, the CHARMM "full-atom" force field has been used without introducing any modifications to the existing parameters. Missing bond and angle parameters were estimated roughly and turned out to be noncritical in the examples presented below.

A copy of the force field parameter file in CHARMM format (about 60 pp.) is available from the authors upon request.

Evaluation Method

Our crystal packing procedure depends upon both the quality of the force field and the reliability of the search method. When a predicted crystal structure does not agree with an experimental one, the main question is: Is the mismatch caused by a wrong force field or by errors in the search method?

To answer this question, evaluations were performed as shown in the scheme given in Figure 1. A molecule with published crystal data was built independently, supplied with force field parameters, optimized by a gas phase calculation, then submitted to the described packing procedure that delivered a set of crystal structures inside an energy window. This comprises the right hand part of Figure 1. The known crystal structure of the molecule is submitted to a full crystal minimization using the same force field parameters as for the packing procedure. Five different cases are conceivable for the resulting minimized experimental structure:

Case 1. The experimental structure corresponds to the global minimum found by the packing procedure.
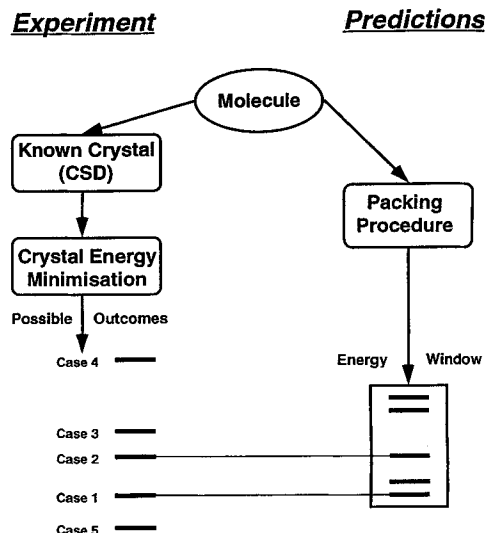
Figure 1. Systematic evaluation scheme for analyzing the performance of the packing procedure with respect to the minimized experimental crystal structure. The "energy window" is some arbitrarily specified energy cutoff relative to the located global minimum.

This is obviously the best case, i.e., both the force field and the search method seem to be correct.

Case 2. The energy of the minimized experimental structure lies inside the energy window and the packing procedure located a corresponding structure. In this case, the search method succeeded but it is unclear whether the force field is imprecise or whether other effects (e.g., entropy effects) are responsible for favoring the experimental structure. Because force fields are reasonable but not perfect, we expect this situation frequently.

Case 3. As in case 2 but without locating a corresponding structure by the packing procedure. In addition to the statements of the previous case, the search method shows some deficiencies in solving the extended global optimization problem. Because the Monte Carlo simulated annealing search is strongly biased toward the lower part of the energy window, we also expect this situation frequently.

Case 4. The energy of the minimized experimental structure is outside and above the energy window. Here, either the force field is completely useless or the experimental crystal structure is derived from wrong experiments (i.e., the published structure is simply wrong!). As will be shown below, this case is in particular interesting because the outcome can be used for correcting the force field or detecting experimental errors.

Case 5. The minimized experimental structure has a lower energy than the lowest energy located by the packing procedure. In this case, the packing method failed. Reasons for the failure could be either an insufficient search or the ill-conditioned nature of the potential function (e.g., a "noisy" potential function).

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*The CHARMM version we used was CHARMm 21.3, supplied by Polygen, Inc.

APPLICATIONS AND RESULTS

In the following, the main results of extensive crystal packing calculations will be given. One of the major problems in reporting the results of such extensive computations is the reproducibility and verification of these results. For obvious reasons, it is impossible to specify the fractional coordinates and atom types for each outcome. Supplementary material for the most important results marked with an asterisk in the following tables is available from the authors upon request. It consists of the fractional coordinates in common crystallographic file format and the atomic charges and the CHARMM atom types (condensed to 19 pp.).

Results for AZIBYD

Our first example will deal with the azo-bis (isobutironitrile) molecule (Fig. 2). Crystal data derived from neutron diffraction studies for the triclinic form are available (P1; $Z = 1$).[22a] We will refer to the molecules by their Cambridge reference code, in this case AZIBYD. The true space group of AZIBYD is P − 1 with half a molecule in the asymmetric unit. The assumed P1 space group is due to the fact that we can only deal with complete molecules in the asymmetric unit ignoring any intrinsic molecular symmetry.

Parametrization. Atomic charges were computed by the Gasteiger[22b] method and are given in parentheses in Figure 2.
Crystal minimization options. All crystal minimizations were done with an image cutoff of 20 Å for the electrostatic interactions. The dielectric constant was 1.
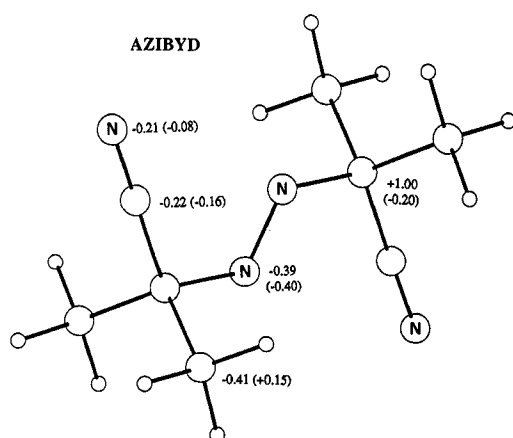
Figure 2. AZIBYD molecule with scaled MOPAC-ESP and Gasteiger (in parentheses) charges. Unnamed atoms are either carbons or hydrogens. The Gasteiger hydrogen charges are all equal to 0.084 e and the precise MOPAC-ESP charges of all atoms are delivered upon request as supplementary material.

Packing procedure. A conformational analysis revealed that the conformation with the two cyano groups in *trans* orientation is by far the most stable. Hence, this molecule was submitted as a rigid molecule to the packing procedure assuming P1, $Z = 1$. During the Monte Carlo simulated annealing procedure, the range of interactions taken into account for the lattice energy estimation was 1 (i.e., the interactions between the unit cell and its 26 neighbors were computed and periodic boundary conditions were kept throughout the whole calculations. The "range number" n defines a chemical system consisting of the molecules in the asymmetric unit and all symmetry images of these molecules that belong to the unit cells with translations $-n \leq i, j, k \leq n$. For efficiency reasons, images that do not possess an inverse image are ignored).

The results are given in Table I. Because this table format will be used also for all the other results, its entries and columns will be explained at this point in greater detail. The first entries (i.e., Exp.) are the experimental lattice constants as published in the Cambridge Data Base. The second entry (i.e., Min.) contains the results of the minimized experimental structure. Because the choice of unit cell constants is rather arbitrary, we present the same crystal in the Niggli-reduced[23] form in the third entry of the table (i.e., Min. red.) to enable an easier comparison with the predicted crystal structures. Each subsequent entry contains a predicted crystal structure in ascending energy order (i.e., entry 4 contains the global minimum etc.). Entries marked with an asterisk will be supplied as supplemental material. The columns contain the following information: Tot. E contains the total crystal energy per asymmetric unit in kcal/mol; the values of the lattice constants follow (Å and degrees). Next comes the volume of the unit cell, then the van der Waals image energies (i.e., the intermolecular van der Waals energy per asymmetric unit, and last comes the electrostatic image energies (i.e., the intermolecular electrostatic interaction energy per asymmetric unit). What can be seen from Table I? First, rather large changes occurred during the minimization of the experimental structure (compare entry 1 with entry 2). Second, the minimum of the experimental energy is far above the energy window (i.e., it is more than 7 kcal/mol above the globel energy). In other words, case 4 (see previous section) occurred, which means (if we exclude the possibility of a wrong experimental structure) that the force field is completely inadequate for this kind of packing problems. However, a glance at the last column reveals that something with the electrostatics must be wrong.

A second run was performed as above with electrostatic potential derived charges.[24] The geometry of AZIBYD was first optimized with MOPAC[25] using the AM1 Hamiltonian[26] and then the atomic charges

Table I. Packing results for AZIBYD using Gasteiger charges (outcome corresponds to evaluation case 4).

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. $(\text{Å})^3$	vdW (kcal/mol)	Electrostatic.
Exp.		7.86	5.55	6.20	71.3	78.0	79.2	248.4		
Min.	−73.14	7.15	5.81	5.60	84.3	96.4	84.4	228.5	−18.13	−16.38
Min. red.		5.60	5.81	7.15	95.6	96.4	95.7			
1	−80.19	5.40	5.40	8.41	72.2	72.2	88.3	222.3	−17.29	−24.92
2	−80.17	5.40	5.41	8.50	106.	109.	91.6	222.4	−17.29	−24.87
3	−76.00	5.30	6.05	8.24	95.5	104.	113.	229.1	−17.01	−20.83
4	−75.86	5.30	6.23	8.74	64.3	84.6	62.7	229.0	−17.03	−20.66

Table II. Packing results for AZIBYD using scaled MNDO electrostatic potential fitted charges (outcome corresponds to evaluation case 1).[a]

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. $(\text{Å})^3$	vdW (kcal/mol)	Electrostatic.
Exp.		7.86	5.55	6.20	71.3	78.0	79.2	248.4		
Min.*	−91.63	7.32	5.42	6.20	74.8	78.5	84.6	232.3	−19.25	−5.20
Min. red.		5.42	6.20	7.32	78.5	84.6	74.8			
1*	−91.67	5.43	6.17	7.37	78.2	84.7	74.5	232.3	−19.17	−5.27
2*	−91.63	5.66	5.83	7.16	92.1	97.7	91.1	233.9	−18.79	−5.50
3*	−91.33	5.34	5.88	7.23	89.4	81.3	88.4	237.1	−18.33	−5.65
4*	−90.12	5.67	5.77	8.17	75.1	76.8	72.0	242.5	−17.79	−4.92
5	−90.00	5.64	5.64	8.55	78.0	70.0	73.1	242.9	−17.68	−4.99

[a]Entries with an asterisk are available as supplementary material.

were fitted to the electrostatic potential (on about 3000 points) derived from the MNDO electron density (MOPAC-ESP).[27] These charges are given in Figure 1. The standard charge scaling of MOPAC-ESP has been used in this and all subsequent examples.

The results of the second run are given in Table II and a dramatically different picture emerges now! The minimized experimental structure and the global minimum produced by the packing procedure are identical (although the predicted second-best structure has practically the same energy). Referring to our evaluation terminology the most favorable case, i.e., case 1 (see Fig. 1) occurred by this simple force field adjustment. The results in Table II also indicate that the packing forces are dominated in all the reported AZIBYD crystals by van der Waals forces and the closest packing concept[4] applies as well.

In any discussion we had, the question of electrostatic cutoffs and the necessity of an Ewald summation[28] arose. Table III summarizes the results of a series of runs using different cutoff distances for the interaction of a unit cell with its images. Complete molecules are always taken into account such that electroneutrality is always ensured. The energies are not comparable to the previous run because we used here a distance-dependent dielectric constant. The results in Table III indicate that our standard image cutoff distance of 20 Å is adequate in the case of the AZIBYD molecule provided that the neutral sphere requirement[29] is preserved. The differences in the total energies between the cutoff of 20 and 32 Å are small and the energy differences between the energy levels for each cutoff are prac-

tically identical. Here, we just mention that the outcome of the packing with $\epsilon = 1/r$ seems to improve the results by increasing the energy gap between the global and the next to the global minimum in favor of the experimental crystal structure.

The following CPU consumption refers to a Silicon Graphics 4D/25 although later runs were performed on an IBM-RS-6000/550, which is about an order of magnitude faster. During the Monte Carlo simulated annealing procedure, about 2000 crystal structures were generated, of which about 1000 were accepted, and the whole run consumed about five CPU h. The clustering procedure had been requested to deliver

Table III. Two lowest crystal energies in the energy window of AZIBYD at different image cutoff distances (calculations with distance-dependent dielectric constant).

	Image cutoff (Å)			
	20	24	28	32
1. Energy	−38.297	−38.295	−38.361	−38.348
a	5.42	5.42	5.42	5.42
b	6.18	6.18	6.18	6.18
c	7.35	7.34	7.35	7.36
α	78.6	79.1	78.6	78.5
β	85.1	85.1	85.2	85.2
γ	74.8	74.6	75.0	74.9
2. Energy	−38.055	−38.082	−38.115	−38.124
a	5.63	5.61	5.64	5.64
b	5.85	5.86	5.84	5.84
c	7.21	7.22	7.20	7.20
α	92.6	92.6	92.6	92.7
β	97.1	96.9	97.1	97.1
γ	91.9	92.1	91.8	91.8
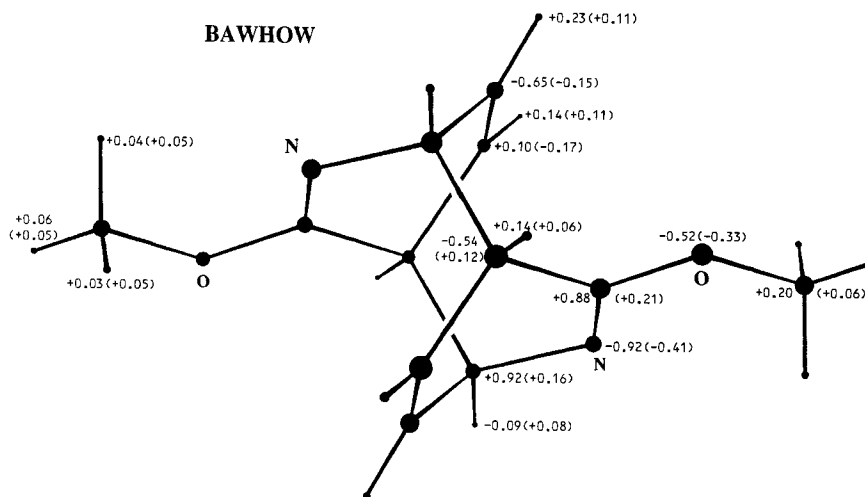
BAWHOW

Figure 3. BAWHOW molecule with scaled MOPAC-ESP and Gasteiger (in parentheses) charges. Precise MOPAC-ESP charges of all atoms are delivered upon request as supplementary material. The small terminal circles are hydrogen atoms.

50 structures with a minimum rms difference of 0.6 Å (for more details, see ref. 13). These 50 structures were minimized with respect to all degrees of freedom. One such minimization consumed between 20 and 30 min when a cutoff distance of 20 Å was in use, i.e., the whole packing procedure for P1, $Z = 1$ consumed about 2 days on the 4D/25 (or less than 5 h on the RS-6000/550). The most time-consuming part was the manual inspection and analysis of the results. AZIBYD is a symmetric molecule and simple rms comparisons will usually deliver each structure twice.

Results for BAWHOW

The second polar test molecule was 4,8-dimethoxy-3,7-diazatricyclo (4.2.2.2-2,5-) dodeca-3,7,9,11-tetraene (or simply BAWHOW) and is depicted in Figure 3. The figures in parentheses are Gasteiger charges and the other figures are MNDO-electrostatic potential fitted charges (settings were, more or less, as for AZIBYD).

This molecule is a bit more complex than AZIBYD, contains nitrogen and oxygen heteroatoms, and its crystal structure[30] is available from the Cambridge

Data Base (P1, $Z = 1$ although the true space group is, due to the molecular inversion center, P-1).

The first run was performed with Gasteiger charges and the results are reported in Table IV. The minimized experimental structure corresponds to the third-best crystal structure located by the packing procedure. The energy difference between the global minimum and the experimental minimum is about 0.7 kcal/mol and, above all, the packing procedure succeeded in locating this local minimum, i.e., case 2 in our evaluation terminology.

The results for the next run on BAWHOW with the quantum chemically derived charges are reported in Table V. There is again a dramatic improvement in the results. The outcome corresponds to case 1 in our evaluation terminology and this time the difference between the global minimum energy and the next minimum energy is already about 0.3 kcal/mol.

What else could be seen from Table V? We see that although the packing forces in all BAWHOW crystals are dominated by van der Waals forces the smaller electrostatic contribution and not the van der Waals forces determine the most stable structure. The concept of closest packing fails here as well (e.g., compare the volume of structure 4 to that

Table IV. Packing results for BAWHOW using Gasteiger charges (outcome corresponds to evaluation case 2).

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. (Å)^3	vdW (kcal/mol)	Electrostatic.
Exp.		6.37	7.16	6.35	100.0	106.0	73.5	264.9		
Min.	26.95	6.29	7.02	6.69	103.0	109.0	75.3	267.5	−27.18	−3.96
Min. red.		6.29	6.69	7.02	77.3	75.3	71.1			
1	26.22	6.36	6.61	7.03	66.7	77.0	74.1	258.8	−28.96	−3.53
2	26.74	5.94	7.11	7.20	64.2	74.7	78.7	262.7	−27.82	−4.18
3	26.95	6.29	6.70	7.01	77.4	75.2	71.2	267.5	−27.18	−3.95
4	27.06	6.06	6.94	6.96	78.0	73.1	70.3	261.6	−28.37	−2.76

Table V. Packing results for BAWHOW using scaled MNDO electrostatic potential fitted charges (outcome corresponds to evaluation case 1).[a]

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. (Å)³	vdW (kcal/mol)	Electrostatic.
Exp.		6.37	7.16	6.35	100.	106.	73.5	264.9		
Min.	86.49	6.56	7.05	6.50	102.	108.	72.0	270.2	-26.13	-6.86
Min.* red.		6.50	6.56	7.05	72.0	78.1	72.4			
1*	86.52	6.50	6.56	7.05	72.0	78.0	72.4	270.2	-26.08	-6.87
2*	86.81	6.21	6.31	7.96	89.5	74.2	64.0	267.6	-27.33	-5.76
3	86.87	6.21	6.31	8.66	72.2	62.1	64.0	267.6	-27.28	-5.76
4	86.92	5.89	7.09	8.10	105.	120.	101.	262.9	-27.55	-5.76

[a]Entries with an asterisk are available as supplementary material.

of the global minimum). This finding deviates, to some extent, from assumptions upon which packing theories rely.

Because of the present and subsequent success with electrostatic potential derived charges, (with MOPAC 6.0-ESP[27] or with PDM88[32] in conjunction with Gaussian 86[32]), these charges are now used exclusively. The empirical charges derived from the methods of Gasteiger or DelRe (as implemented in the program MACROMODEL[32]) and also Mulliken charges derived from quantum mechanical calculation gave inferior results and will not be mentioned further.
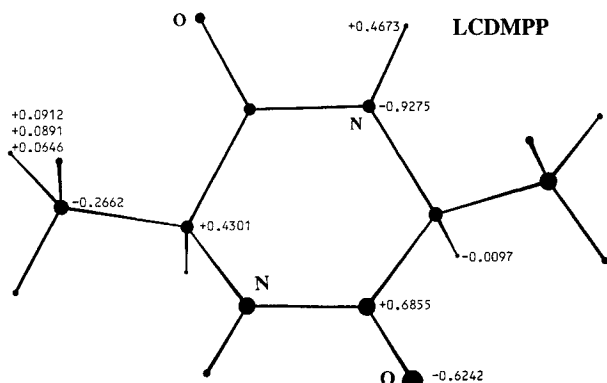
Results for LCDMPP

The next test example deals with the particularly interesting case of a crystal containing a strongly hydrogen bonding molecule, cyclo-L-alanyl-L-alanyl (or simply LCDMPP),[33] shown in Figure 4 together with the MNDO electrostatic potential fitted charges. The MNDO dipole moment of LCDMPP is below 1 Debye so that no serious electrostatic cutoff problems are to be expected.

Although the binding motifs in such crystals are quite obvious, the search method does not take these facts into account. It turned out that searching for

Figure 4. LCDMPP molecule with scaled MOPAC-ESP charges. The molecule has a 2 symmetry in the AM1-optimized geometry.

the global minimum for this kind of structure is more difficult than for those of the previous examples. The system freezes at a rather high temperature and the rate of cooling had to be set to a low value (i.e., the parameter T_{cool} had to be set to a value very close to 1, in this example to 0.998–0.999). The consequence of such settings is that more points had to be sampled (about 4000) and more clusters had to be fully minimized (about 80) to obtain reliable results.

In the first run, a dielectric constant of 1.0 was used and the results are reported in Table VI. The global minimum located by the packing procedure was not identical with the minimized experimental structure, which is practically identical with the third-lowest minimum (the geometric precision by which minima are located will be discussed later). This corresponds to case 2 in our evaluation terminology with a difference of about 0.25 kcal/mol between the global and experimental minimum. A closer inspection of Table VI reveals that the optimized experimental crystal and the global minimum located by the packing procedure belong to different cell types (types II and I, respectively), which is an invariant of the primitive cell.[23] A graphic comparison between the minimized experimental structure and the global minimum confirmed the great similarity between the two structures. This fact is not unexpected because the values of a, b, c, and the image energies are similar.

We tried to improve the description of the electrostatic interactions by introducing lone-pair pseudoatoms.[24] This was tedious work because the code of MOPAC-ESP had to be altered to include lone-pair pseudoatoms and a whole set of new force field constants had to be added to the CHARMM force field. Eight lone-pair pseudoatoms had been introduced into the LCDMPP molecule (two in the plane of each amide oxygen and two perpendicular to the amide plane, below and above the nitrogen atoms). The improvement was, however, not too dramatic (the energy difference between the minimized experimental and global minimum was about 0.15 kcal/mol instead of 0.25 kcal/mol without lone-pair pseudoatoms).

Table VI. Packing results for LCDMPP using a dielectric constant $\epsilon = 1.0$ (outcome corresponds to evaluation case 2).

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. $(\text{Å})^3$	vdW (kcal/mol)	Electrostatic.
Exp.		8.01	6.08	5.16	132.0	82.4	107.0	180.4		
Min.	−97.39	7.52	6.08	5.20	131.0	84.3	107.0	169.2	−18.29	−19.96
Min. red.		4.73	5.20	7.52	95.7	106.0	105.0			
1	−97.70	4.73	5.20	7.71	75.6	69.8	75.3	169.4	−18.05	−20.50
2	−97.51	4.73	5.20	8.15	114.	100.0	105.0	169.4	−18.10	−20.25
3	−97.45	4.74	5.19	7.52	95.7	106.0	105.0	169.4	−18.16	−20.13
4	−96.34	6.09	6.38	6.39	60.2	61.2	89.9	179.2	−15.86	−20.53
5	−96.32	6.09	6.36	6.40	92.6	119.0	118.0	179.2	−15.88	−20.49

Turning back to the H bonding problem, from simulations done on water clusters[34] it is known that polarization forces must be taken into account when strong H bonding dominates the intermolecular interactions. The crudest way for taking polarization into account is to use a distance-dependent dielectric constant. The results for a similar run on LCDMPP using the dielectric "constant" $1/r$ are reported in Table VII. The difference between the global minimum energy located by the packing procedure and the minimized experimental energy (identical to the second located minimum) is only 0.04–0.05 kcal/mol and corresponds to the noise encountered in the minimizations. The differences between the relative orientations of the molecules are now almost negligible. To summarize, this last run indicates the importance of the polarization in the case of H-bonded crystals and it would be worth investing more efforts in that direction.[35]

Results for Additional P1, $Z = 1$ Molecules

The successful packing of hexamethylbenzene has been published elsewhere.[13] It is worth mentioning here that attempts to pack this molecule in the united atom approximation (i.e., considering the methyl groups as a single pseudoatom) failed. We tried to pack five additional molecules (from the Cambridge Data Base) containing heteroatoms, some of them flexible (KINTIN, DADLAV, AMFPDO, KAJHIM, and DADLEZ), but all ended up in case 4 of our evaluation terminology (i.e., the minimized experimental structure lies above the energy window). A closer inspection revealed, however, that the failure was

due to wrong crystal data. These crystals, with the reported P1, $Z = 1$ space group and cell constants, contain large empty spaces. Because this fact is noticeable upon a simple crystal minimization that is accompanied by a shrinkage of more than 50%, we will not attribute this "detection" to our packing procedure. What can be learned from these last mentioned examples is that trying to pack a molecule by minimizing an arbitrary starting crystal geometry has a low chance of success.

Results for the P21 Space Group

Application of the packing procedure to ethylene has already been described[13] and will not be repeated in detail here. The charges were computed with the PDM88 program (using Gaussian 86 with a 6-31G** basis). The most remarkable outcome is that, without making any symmetry assumption, i.e., by assuming P1 and $Z = 2$, the packing procedure produced the experimental structure as the global minimum.

Our next molecule is isoiridomyrmecin (or simply ISIRIN), shown in Figure 5 with the MNDO-ESP charges. The crystal structure of this molecule was published in 1961[36] and looks reasonable (i.e., no abnormal shrinkage on crystal energy minimization). It is of particular interest because we suspect, on the basis of our computational approach, that the published structure is wrong. We believe that it will be a convincing argument in favor of the method should the published structure turn out to be wrong and our predicted structure to be true.

Table VII. Packing results for LCDMPP using a distance-dependent dielectric constant (outcome corresponds to evaluation case 2).[a]

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. $(\text{Å})^3$	vdW (kcal/mol)	Electrostatic.
Exp.		8.01	6.08	5.16	132.	82.4	107.0	180.4		
Min.	−48.21	7.56	6.07	5.18	131.	84.0	108.0	169.8	−16.23	−22.92
Min.* red.		4.75	5.18	7.56	95.7	106.0	105.0			
1*	−48.26	4.75	5.18	8.13	113.	99.5	105.0	169.8	−15.93	−23.27
2*	−48.20	4.75	5.18	7.56	96.0	106.0	105.0	169.8	−16.22	−22.92
3	−48.19	4.75	5.18	7.74	75.0	69.9	75.2	169.8	−16.20	−22.92

[a]Entries with an asterisk are available as supplementary material.
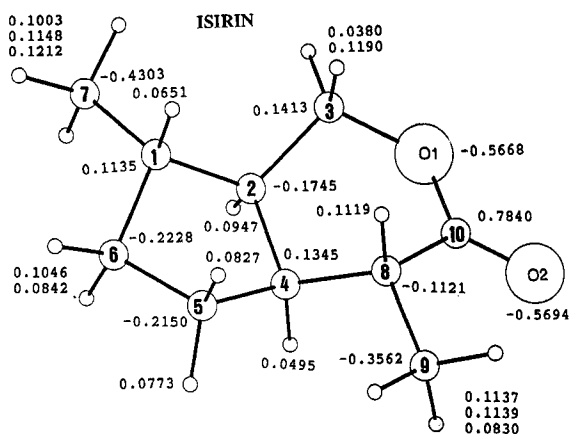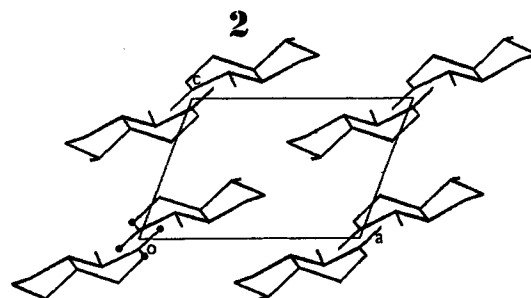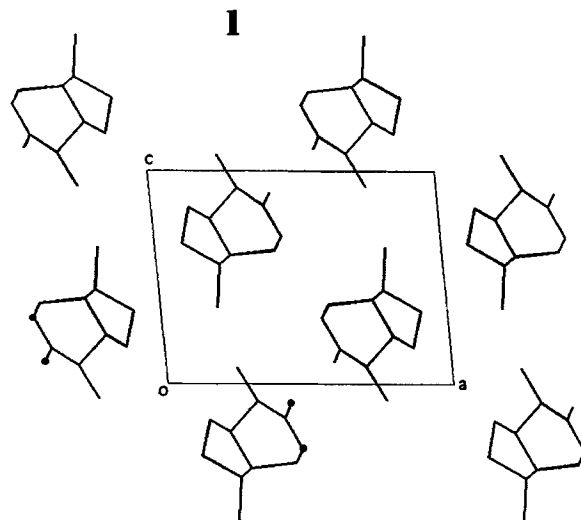
Figure 5. ISIRIN molecule with scaled MOPAC-ESP charges. The carbon atoms are numbered in this controversial molecule as in the supplementary material.

Figure 6. View along the unique axis of the ISIRIN P21, Z = 2 crystals. (1) (upper part), published experimental crystal; (2) (lower part), best predicted crystal. (○), origin of the unit cell; (●), oxygen atoms of two ISIRIN molecules related by the screw axis.

Two runs were performed on ISIRIN, the first assuming a P21, Z = 1 space group, the second assuming a simple P1, Z = 1 space group (which does not exist in the Cambridge Data Base). The results are reported in Table VIII.

The results for the first run indicate that the minimized experimental structure lies outside the energy window and its energy is about 3 kcal/mol above the located global minimum. This is an astonishing result because the original ISIRIN molecule from the Cambridge Data Base and the gas phase-minimized molecule do not deviate significantly from each other (i.e., an indication that the force field is reasonable) and because our present experience with charges for such a "simple" molecule (i.e., no H bonds and no torsions) can hardly explain a force field error as high as 3 kcal/mol.

The computed dipole moment of ISIRIN (Gaussian 90 at the 6-31G** level) is about 5.6 Debye. The packing calculations were repeated with different image cutoff distances and charges (i.e., 6-31G** electrostatic potential fitted charges) but no essential change in the results occurred despite the nonvanishing dipole moment. At present, we have no other explanation for this large discrepancy except the

possibility of a wrong interpretation of the diffraction data. In Figure 6, a view along the unique screw axis of the published and predicted crystals is shown. This view underlines the large difference in the crystal packings of these structures.

In a second run, the best P1, Z = 1 crystal modification (bottom of Table VIII) is predicted to be about 3 kcal/mol less stable than the best P21 mod-

Table VIII. Packing results for ISIRIN in two different space groups using an ε = 1.0 (outcome for the first space group corresponds to evaluation case 4).[a]

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. (Å)³	vdW (kcal/mol)	Electrostatic.
P21, Z = 2										
Exp.		10.1	6.41	7.50	90.0	96.4	90.0	482.1		
Min.* red.	−15.97	7.36	6.42	10.1	90.0	94.6	90.0	473.8	−21.80	−2.82
1*	−18.95	5.27	12.4	7.77	90.0	69.1	90.0	474.5	−21.73	−5.82
2*	−17.88	7.11	7.35	9.63	90.0	81.0	90.0	497.0	−20.59	−6.22
3*	−17.79	6.53	7.88	9.72	90.0	105.	90.0	482.4	−21.24	−5.40
4	−17.77	6.36	9.02	8.29	90.0	96.9	90.0	471.9	−22.62	−3.98
P1, Z = 1										
1*	−15.99	5.33	7.02	8.00	69.0	69.8	62.0	241.1	−21.53	−3.20
2	−15.00	5.36	7.05	8.54	60.6	86.2	61.8	241.7	−21.33	−2.45

[a]Entries with an asterisk are available as supplementary material.
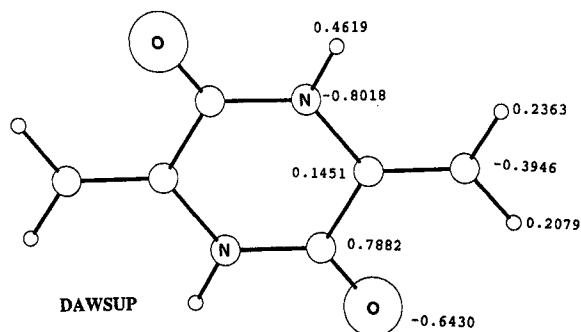
Figure 7. DAWSUP molecule with scaled MOPAC-ESP charges.

ification, which at least confirms the observation that this modification of ISIRIN is unknown.

Our last example consists of rather preliminary results on a P21, $Z = 2$ crystal with extensive H bonding motifs. We mention these calculations because they show some difficulties and deficiencies of our present implementation where the translational degrees of freedom are not yet expressed in terms of polar coordinates. The molecule to be packed was the centrosymmetric 3,6-dimethylene-piperazine-2,5-dione (or simply DAWSUP,[37] shown in Figure 7, which is closely related to the LCDMPP molecule discussed above (Fig. 4), where we already encountered some difficulties (e.g., sudden freezing and force field deficiencies due to polarization forces). Here, we have in addition to deal with a larger search space and more dependent variables (in the present implementation two additional translations in the P21, $Z = 2$ case and three additional translations in the P1, $Z = 2$ case). In the two runs, a distance-dependent dielectric constant, a cooling rate, T_{cool}, of 0.999 and an interaction range of 2 (i.e., the interaction with 124 images) were used. Some of the results are reported in Table IX and it is apparent that the search procedure failed, i.e., the outcome corresponds to case 5 in our evaluation terminology. The predicted global minima are 0.2 and 0.25 kcal/mol above the minimized experimental en-

ergy. At present, we are analyzing the reasons for this failure, a task that is not simple due to the prohibitive CPU consumption and the many error sources.

DISCUSSION

One feature common with all examples is the noisy nature of the crystal potential function. The energy levels inside the generated energy window lay close to each other and although the rms between the structures are 0.6–0.8 Å many of them seem to get stuck on the way to the same minimum. This fact of noisy minima in high dimensions is well known from proteins[38] and therefore it is not astonishing that in the case of a "protein-like" structure such as DAWSUP crystals (last example) this phenomenon is most pronounced. The packing procedure failed apparently to locate the minimized experimental structure. However, a careful analysis of the many local minima reveals that the structures 7 and 8 in Table IX (upper part) are already similar to the experimental structure although the energy difference is as high as 0.6 kcal/mol. The great similarity between structure 8 (Table IX) and the experimental crystal structure is shown in Figure 8. The proper way to overcome this problem of noisy minima would be, in analogy to the treatment of bimolecular systems, the use of molecular dynamics starting from the located minima.

Even if we represent similar minima belonging to the same basin of attraction by one structure, the energy differences are still small (of the order of a fraction of 1 kcal/mol, a fact inherent to the problem and reflected in the tendency of organic molecule toward polymorphism) and hence the necessity of a high-quality force field. We have shown that packing problems can be solved in some cases using a standard force field such as CHARMM provided the charges are determined independently by quantum chemical methods. This is in contrast to a common and widespread opinion[4c,39] that charges are force

Table IX. Packing results for DAWSUP in two different space groups using an $\epsilon = 1/r$ (outcome for the first space group corresponds to evaluation case 5).[a]

	Tot. E (kcal/mol)	a	b	c	α	β	γ	Vol. $(\text{Å})^3$	vdW (kcal/mol)	Electrostatic.
P21, $Z = 2$										
Exp.		5.26	13.6	4.57	90.0	105.0	90.0	316.8		
Min.* red.	−53.81	4.88	12.1	5.36	90.0	107.0	90.0	302.9	−14.27	−25.00
1*	−53.61	6.93	4.14	10.6	90.0	83.0	90.0	303.3	−13.57	−26.22
2	−53.61	7.43	5.20	7.50	90.0	84.6	90.0	288.4	−15.36	−24.17
7	−53.23	4.94	12.0	5.36	90.0	107.0	90.0	302.3	−14.32	−25.01
8*	−53.21	4.87	12.1	5.36	90.0	107.0	90.0	302.7	−14.32	−25.04
P1, $Z = 2$										
1*	−53.60	6.03	7.37	7.51	96.0	100.0	116.	289.1	−15.44	−22.69
2*	−53.60	5.20	7.43	7.49	84.8	90.0	90.0	288.4	−14.31	−24.22

[a]Entries with an asterisk are available as supplementary material.
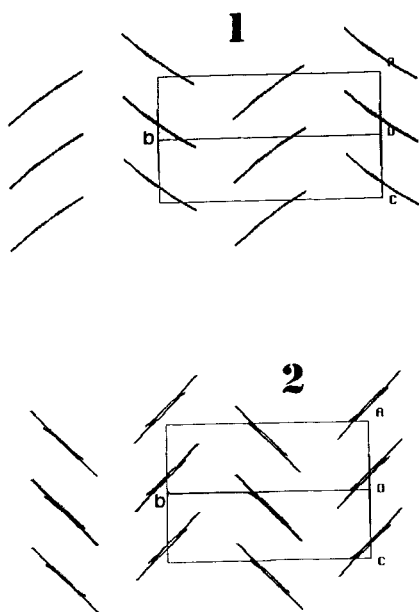
Figure 8. View through the DAWSUP P21, $Z = 2$ crystals. (1) upper part, original DAWSUP crystal (Cambridge Data Base, first entry in Table IX); (2) lower part, structure 8 of Table IX, which is structurally identical to the minimized experimental structure but has still an energy of 0.6 kcal/mol above the minimized experimental one.

field parameters that should be fitted simultaneously with the other parameters of that particular force field and that no physical significance should be attached to the various terms in the energy expression. Of equal importance is the proper treatment of the electrostatic interaction in the crystal. In the version of the CHARMM program at our disposal, the Ewald summation was not yet implemented so reliable results for unit cells with large dipole moments cannot be expected although some ideas about reasonable packing possibilities should be feasible.

Solving the packing problem is closely related to the establishment of force fields: Nobody can claim that his or her force field is "good" unless he or she has solved the extended global optimization problem! The common force field evaluation procedures[41] consist in taking an experimental structure and then optimizing the experimental geometry. If the resulting optimized geometry does not deviate significantly from the experimental one, the force field under evaluation is considered "good." However, good agreement between experimental and optimized geometries is necessary but not sufficient for qualifying a force field as good. A sufficient condition is given if the force field evaluator can show that there exists no additional structure with an energy lower than that of the minimized experimental structure (provided that the energy is indeed the major factor). This is a global rather than a local optimization problem. Thus, the solution of the packing problem not only allows us to predict crystal

structures, but also to evaluate and develop good force fields.

A more important question arises at this point: Do we need transferable force fields for solving the packing problem at all? The fact that we must perform a precise quantum chemical calculation to derive the electrostatic potential fitted charges makes it natural to derive from that calculation the remaining force field parameters. It requires little additional computational effort. Methods to do this are now emerging[40] so that, perhaps apart from the van der Waals parameters, nothing needs to be transferable.

The small energy differences between the low-energy minima have another implication that severely limits the reliability of any search procedure in a lower-dimensional space: The minima located by the search procedure refer to structures with frozen degrees of freedom. A subsequent minimization of such a structure with respect to all degrees of freedom is always accompanied by some lowering in the value of the energy. If the energy lowering, compared to the differences between the different energy minima, is large (say, more than an order of magnitude), then the reliability of the search procedure becomes questionable. A typical example is given by the DAWSUP, P1, $Z = 2$, results (last example).

We have not mentioned examples with flexible molecules although we are working intensively in that direction. In view of the precision requirements posed upon the potential function, our present experience allows us to predict that just allowing the torsions to vary while keeping bond lengths and bond angles fixed will be sufficient for packing. Although the coupling between torsion and bond angles have relatively small effects on the overall geometry, they influence the energy significantly. The approach we are adopting now is to define multidimensional tables with torsion values (also values not matching energy minima) and corresponding (relaxed) intramolecular energies and use such tables during the Monte Carlo simulated annealing search process.

The only other published global search method for packing organic molecules is that of Gavezzotti.[10] A direct comparison between our and his search method is at present not possible because he has not yet applied his method to molecules containing heteroatoms where the periodic boundary conditions might be too important to be ignored at the beginning of the search.

SUMMARY AND CONCLUSIONS

It has been shown that the *ab initio* packing of general organic molecules with the present computational technology is possible in a global sense. The

performances of a global search procedure based upon a Monte Carlo simulated annealing method in a low-dimensional space that prohibits evaporation has been reported for some examples with small Z values. No reference to diffraction data such as unit cell parameters is used. The formulation of the problem as an extended global minimization problem allowed us to establish a systematic evaluation procedure on known crystal structures from the Cambridge Data Base, and in addition it awarded us with the ability to prove rather than assume or speculate about basic concepts dealing with the nature of crystal packing. No molecule with a complexity comparable to those reported in this article has ever been packed. The presented results are not just reports of success but contain valuable details that will allow other researchers in that area to proceed toward their solution of the packing problem for general organic molecules.

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