Intra- and Intermolecular Interactions in Crystals of Polar Molecules. A Study by the Mixed Quantum Mechanical/Molecular Mechanical SCMP-NDDO Method

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ABSTRACT: Stabilization energies of crystals of polar molecules were calculated with the recently developed NDDO-SCMP method that determines the wave function of a subunit embedded in the symmetrical environment constituted by the copies of the subunit. The total stabilization energies were decomposed into four components. The deformation energy is the difference between the energy of the molecule in the geometries adopted in the crystal on one hand, and in vacuo, on the other hand. Further energy components are derived from the molecular geometry found in the crystal phase. The electrostatic component is the interaction energy of the molecule with the crystal field, corresponding to the charge distribution obtained in vacuo. The polarization component is the energy lowering resulted in the self-consistent optimization of the wave function in the crystal field. The rest of the stabilization energy is attributed to the dispersion–repulsion component, and is calculated from an empirical potential function. The major novelty of this decomposition scheme is the introduction of the deformation energy. It requires the optimization of the structural parameters, including the molecular geometry, the intermolecular coordinates, and the cell parameters of the crystal. The optimization is performed using the recently implemented forces in the SCMP-NDDO method, and this new feature is discussed in detail. The calculation of the deformation energy is particularly important to obtain stabilization energies for crystals in which the

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molecular geometry differs considerably from that corresponding to the energy minimum of the isolated molecule. As an example, crystals of diastereoisomeric salts are investigated. © 2001 John Wiley & Sons, Inc. J Comput Chem 22: 1679–1690, 2001

Keywords: molecular crystal; crystal stabilization energy calculation; energy decomposition; mixed QM/MM; crystal structure prediction

Introduction

The complexity of the interactions governing the structure and properties of molecular crystals renders their theoretical treatment difficult. Classical force fields are able to describe crystals of apolar and moderately polar molecules by transferable parameters. On the other hand, Coulomb interactions play an essential role in crystals of polar molecules, and they cannot be accounted for by transferable parameters. A fully quantum chemical approach can be, in principle, used to treat such cases; however, the computational requirements of the *ab initio* periodic Hartree–Fock method becomes soon prohibitive as the size of the asymmetric unit of the crystal increases.

The complexity of the description and the computational requirements is well balanced in approaches that use an empirical force field complemented by appropriately derived atomic charges and possibly higher rank multipole moments. Charges derived from the electrostatic potentials of isolated molecules as first proposed for crystals by Cox and Williams and applied by Williams and coworkers represent a significant step towards the correct description of electrostatic interactions. An alternative approach invokes distributed multipole analysis (DMA) to derive appropriate multipoles. Both electrostatic potential and DMA derived multipoles are able to correctly account for electrostatic effects. On the other hand, charge density deformations caused by the crystal field and associated with polarization (induction) effects are missing in descriptions based on multipoles (charges) of isolated molecules.

We have recently proposed the SCMP-NDDO method which combines the semiempirical quantum mechanical determination of electrostatic and polarization interactions with the classical description of dispersion and short-range repulsion effects. As discussed in the forthcoming sections, this approach makes it possible to optimize the wave function and thus to take into account the charge density deformation caused by the crystal environment.

Another, so far unexploited, feature of the SCMP-NDDO method is that structural parameters of crystals can be optimized. The optimization includes both inter- and intramolecular interactions, and thus it becomes possible to investigate structural changes of molecules as caused by the crystal formation.

The subject of the present article is the implementation and application of structure optimizations in the SCMP-NDDO method. A brief overview of the SCMP-NDDO method is presented in the next section. Then the implementation of forces is discussed, followed by applications including crystal structure optimizations and stabilization energy calculations. A specific example, the structure and energetics of a pair of diastereoisomeric crystals, is presented in more details. Finally, the conclusions are summarized.

Method

The SCMP-NDDO method has been described in detail in ref. 18. Here, the main characteristics of the method are briefly recapitulated and then, the new feature, the calculation of deformation energy by optimization of the cell parameters and the molecular geometry is presented.

The SCMP-NDDO method calculates the wave function of the subunit, typically the molecule in the asymmetric unit, in the field of its copies, the latter are represented by atomic point multipoles consistent with the molecular wave function. The semiempirical AM1 Hamiltonian has been chosen because it is economical and is known to describe electrostatic effects reasonably. The resulting intermolecular potential was shown to be greatly superior to semiempirical AM1 potentials. The SCMP-NDDO method is able to reproduce experimental sublimation enthalpies of a series of molecular crystals.

The computational procedure of the SCMP-NDDO method without geometry optimization
starts with the determination of the molecular wave function in the geometry found in the crystal. Then this wave function is used to calculate the crystal field and the interaction energy of the molecule with the field. This way the electrostatic interaction energy, $\Delta E^{el}$, is obtained. Then the wave function is optimized variationally by minimizing the stabilization energy of the crystal. The consistency of the subunit wave functions and the crystal field is maintained in the course of the optimization. The resulting energy lowering is the polarization energy, $\Delta E^{pol}$. The total crystal stabilization energy is obtained as the sum of the electrostatic and polarization energies together with the classically calculated dispersion–repulsion energy, $\Delta E^{DR}$. We emphasize that this computational scheme would yield the correct stabilization energies if the molecular geometries did not deform in the course of crystal formation. However, molecular subunits usually adopt a higher energy molecular geometry and/or conformation in the crystal than in isolation, and the excess internal energy is compensated by increased intermolecular attractions. There are, for instance, polymorphic molecular crystals, where the conformation of the subunits are radically different.27

To calculate stabilization energies of crystals containing molecules deformed with respect to their lowest energy geometry, this excess deformation energy of the molecule has to be taken into account. Because the geometry of the isolated molecule and the geometry of the molecule in the crystal correspond to minima on their respective potential energy surfaces they can be obtained from energy minimizations. The other impetus to implement full geometry optimization in crystal calculations is to obtain a predictive method, which—as a final goal—may contribute to the prediction of crystal structures on the basis of the constitution of molecules.28 Although crystal energy minimization is a prerequisite for achieving such a goal, experience shows that due to the large number of minima on the potential energy surface and to other factors, like kinetic effects, the ab initio prediction of crystal structures is a fairly difficult task.

The calculation of the stabilization energy with parameter optimization is performed with the SCMP-NDDO method as follows. First, the crystal structure including the molecular geometry and the cell parameters is optimized. The geometry of the isolated molecule is also optimized, and its deformation energy is calculated as the difference between molecular energy taken at its optimal (in vacuo) geometry and that calculated at the geometry adopted in the crystal. Having the wave function of the isolated molecule in the geometry within the crystal, the procedure applied in the SCMP-NDDO method without geometry optimization is followed. First, the electrostatic then the polarization energies are calculated, and they are complemented with the dispersion–repulsion energy as it is described above.

**SCMP Energy and Derivatives**

In the SCMP-NDDO method interactions within a subunit are treated quantum mechanically, and therefore, the subunit is often referred to as quantum motif. The smallest possible quantum motif comprises the asymmetric unit, but it may be chosen to contain a larger fraction of a unit cell or even a whole or several unit cells. However, a reasonable choice of the quantum motif always comprises whole molecule(s), even if the asymmetric unit contains only a fragment of a molecule.

**ENERGY EXPRESSION**

The total energy per quantum motif is given as

$$E^{SCMP} = E^{\text{intra}} + E^{\text{EE}} + E^{\text{EN}} + E^{\text{NN}} + E^{\text{DR}} \quad (1)$$

The meaning of the terms appearing in the above equation is the following. $E^{\text{intra}}$ is the internal energy of the molecule(s) in the quantum motif. $E^{\text{EE}}$ is the interaction energy of the electrons of the molecule(s) in the quantum motif and the electrons in the environment. $E^{\text{EN}}$ comprises the interaction energy of the electrons in the quantum motif and the nuclei in the environment together with the interaction energy of the nuclei in the quantum motif and the electrons in the environment. $E^{\text{NN}}$ is the interaction energy of the nuclei in the quantum motif and the nuclei of the environment. $E^{\text{DR}}$ is the dispersion–repulsion interaction energy of the atoms in the quantum motif and the atoms in the environment.

Detailed expressions of the terms on the right-hand side of eq. (1) are given below.

\begin{align*}
E^{\text{intra}} &= \frac{1}{2} \sum_{\mu \nu} P_{\mu \nu} (F_{\mu \nu}^0 + h_{\mu \nu}^0) \\
&\quad + \frac{1}{2} \sum_i \sum_j Z_i Z_j |R_i - R_j|^{-1} \quad (2) \\
E^{\text{EE}} &= \frac{1}{2} \sum_{\mu \nu} \sum_{\lambda \sigma} P_{\mu \nu} P_{\lambda \sigma} (\mu \nu |G^{\text{MAD}}(\mathbf{r}, \mathbf{r})|_{\lambda \sigma}) \quad (3) \\
E^{\text{EN}} &= -\sum_{\mu \nu} P_{\mu \nu} \sum_i (\mu |Z_i G^{\text{MAD}}(\mathbf{r}, \mathbf{R}_i)|_{\nu}) \quad (4)
\end{align*}
\[
E_{\text{NN}}^{\text{MAD}} = \frac{1}{2} \sum_{i} \sum_{j} Q_i Q_j G^{\text{MAD}}(R_i, R_j) \tag{5}
\]

Here, \(G^{\text{MAD}}\) is the Madelung kernel as given in ref. 18, and other symbols have the usual meaning. The dispersion–repulsion energy is

\[
E^{\text{DR}} = \frac{1}{2} \sum_{n} \sum_{l} E_{\text{0nl}}^{\text{MM}} \tag{6}
\]

where \(E_{\text{0nl}}^{\text{MM}}\) is the dispersion–repulsion interaction between the quantum motif and its copy obtained by the \(l\) translation and \(Q^n\) symmetry operation. The prime in the above equation indicates that the term belonging to the \(\hat{l} = \hat{Q}^n = \hat{I}\) (identity) operator is missing, i.e., only intermotif interaction appear in \(E^{\text{DR}}\). Further decomposition of \(E_{\text{0nl}}^{\text{MM}}\) is given in ref. 18.

The terms \(E^{\text{INTRA}}\) and \(E^{\text{DR}}\) will not be explained in more details in the forthcoming discussion, while \(E^{\text{EE}}\) will be transformed to clearly show some specific features of the SCMP-NDDO method. In the NDDO approximation only products of orbitals centered on the same atom are different from zero. Then \(E^{\text{EE}}\) of eq. (3) can be written as

\[
E^{\text{MAD}}_{\text{EE}} = \frac{1}{2} \sum_{\mu \nu \in I} \sum_{\lambda \sigma \in J} \sum_{i} \sum_{j} P_{\mu \nu} P_{\lambda \sigma} \langle \mu \nu | G^{\text{MAD}}(r_i, r_j) | \lambda \sigma \rangle \tag{7}
\]

where \(i\) and \(j\) run through the atoms in the quantum motif and through all atoms generated by the symmetry operations of the space group, respectively. Equation (7) can be transformed to

\[
E^{\text{MAD}}_{\text{EE}} = \frac{1}{2} \sum_{\mu \nu \in I} \sum_{\lambda \sigma \in J} \sum_{\lambda \sigma \in J} \sum_{n} \sum_{n} P_{\mu \nu} P_{\lambda \sigma} \times \hat{Q}_n^{\mu} \langle \mu \nu | G^{\text{MAD}}(r_i, r_j) | \lambda \sigma \rangle \tag{8}
\]

where both \(i\) and \(j\) run through the atoms in the quantum motif and \(n\) runs through the symmetry operations of the space group. In addition, it is explicitly marked that the integral \(\mu \nu | G^{\text{MAD}}(r_i, r_j) | \lambda \sigma \rangle\) is subject to the transformation \(\hat{Q}_n\). This symmetry transformation generates the center of the orbitals \(\lambda\) and \(\sigma\) (atom \(j\)) from a center in the asymmetric unit. To use the same \(P_{\lambda \sigma}\) for a molecule in the asymmetric unit and for a molecule generated by the symmetry operation \(\hat{Q}_n\), the integrals have to be transformed as it is shown in the equation.

Finally, an alternative form of eq. (8) is eq. (9).

\[
E^{\text{MAD}}_{\text{EE}} = \frac{1}{2} \sum_{i} \sum_{j} \sum_{\mu \nu \in I} \sum_{\lambda \sigma \in J} \left(1 - \frac{1}{2} \delta_{ij}\right) P_{\mu \nu} P_{\lambda \sigma} \times \hat{Q}_n^{\mu} \langle \mu \nu | G^{\text{MAD}}(r_i, r_j) | \lambda \sigma \rangle \tag{9}
\]

Expressions in eqs. (4)–(5) can be transformed in an analogous manner.

Note, that the crystal stabilization energy is obtained as the difference between \(E^{\text{SCMP}}\) and the energy of the isolated molecule. The latter is clearly independent of the crystal structure, and is not the subject of the forthcoming discussion.

**ENERGY DERIVATIVES**

We choose the fractional coordinates of the quantum motif and the strain matrix as the set of independent variables to describe the deformation of the crystal. The fractional atomic coordinates, \(\mathbf{R}_p\), are related to the Cartesian ones by the matrix \(\mathbf{X}\), of the cell vectors:

\[
\mathbf{R}_p = \mathbf{X} \mathbf{\tilde{R}}_p \tag{10}
\]

(Here, and later on, a tilde on a vector indicates that coordinates refer to the fractional coordinate space.)

The strain matrix, \(\epsilon\), that describes the deformation of the unit cell, is defined as a symmetric matrix transforming any vector in the lattice as

\[
\begin{pmatrix}
R_1 \\
R_2 \\
R_3
\end{pmatrix} =
\begin{pmatrix}
\epsilon_{11} & \epsilon_{12} & \epsilon_{13} \\
\epsilon_{12} & \epsilon_{22} & \epsilon_{23} \\
\epsilon_{13} & \epsilon_{23} & \epsilon_{33}
\end{pmatrix}
\begin{pmatrix}
R'_1 \\
R'_2 \\
R'_3
\end{pmatrix} \tag{11}
\]

In what follows, we refer to the strain matrix as \(\epsilon\), and to its elements either with one subscript (\(\epsilon_{ip}\)) as in the above equation or with two subscripts (\(\epsilon_{ij}\)), where \(i\) and \(j\) are the row and column indices of the matrix \(\epsilon\).

The energy expressions (3)–(5) depend on the intermotif electron–electron, electron–nuclear, and nuclear–nuclear interaction tensors. In the present approximation these tensors represent the interaction of point multipole and thus they are formed as the Cartesian derivatives of \(|\mathbf{R}_p|^p\). \(|\mathbf{R}_p|^p\) is a Cartesian vector pointing from atom \(i\) in the quantum motif to atom \(j\) in the motif generated by the symmetry operation \(\hat{Q}_n\) and the \(l\)-th lattice translation vector.) The highest rank tensor is of rank 4, and describes the interaction of two quadrupoles representing the products of two \(p\) orbitals.

These interaction tensors are calculated as Ewald sums. Neither their forms nor their derivatives will be given here (see, e.g., in ref. 29), but it is noted that they depend on atomic fractional coordinates, \(\mathbf{R}_p\), and the strain matrix, \(\epsilon\), through the interatomic separation vectors, \(\mathbf{R}_p^a\), on the reciprocal lattice vectors, \(\mathbf{K}_a\), as well as on the volume \(V\) of the unit cell.
Fractional Coordinate Derivatives

The derivative of an energy term (\(E_{\text{XX}}^{\text{MAD}}\)) with respect to the \(\omega\)-th component of the fractional coordinate of the \(k\)-th atom (\(\bar{R}_{k}\)) can be written as

\[
\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial \bar{R}_{k}} = \sum_{ij} \sum_{\omega} \sum_{n} \frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}} \frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}
\]  
(12)

where \(R_{ij}^{\text{nl}}\) is the \(\omega\)-th Cartesian coordinate of the internuclear separation vector, \(\bar{R}_{ij}\).

The explicit expression for \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\) is not given here but certain aspects of its calculation is briefly discussed. The term \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\) involves the derivative of an Ewald sum. Both its direct and reciprocal space parts depend on \(R_{ij}^{\text{nl}}\). However, because according to eq. (15) \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}\) is independent of both the direct and reciprocal space lattice vectors the terms appearing in the derivative of \(E_{\text{XX}}^{\text{MAD}}\) can be summed up first and then multiplied by \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}\). As the interaction tensors are Cartesian derivatives of \(|\bar{R}_{ij}|^{-1}\), the derivative of a rank \(n\) tensor appearing in eq. (12) is a rank \(n+1\) tensor.

Equation (12) shows that we need to evaluate \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}\). To calculate \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}\), we need the relation between \(R_{ij}^{\text{nl}}\) and \(\bar{R}_{k}\), given by the following two equations

\[
R_{ij}^{\text{nl}} = (I + \epsilon)X\bar{R}_{ij}^{\text{nl}}
\]  
(13)

\[
\bar{R}_{ij}^{\text{nl}} = Q_{ij}^{\text{n}}\bar{R}_{ij} + \sigma_{n} + \bar{t}_{i} - \bar{R}_{k}
\]  
(14)

In eq. (13) \(I\) is the unit matrix, \(X\) transforms fractional coordinates to orthogonal ones, and \(\bar{R}_{ij}^{\text{nl}}\) is an interatomic separation vector in fractional coordinates. \(\bar{R}_{ij}^{\text{nl}}\) is defined in terms of a reference unit cell whose deformation is described by the strain matrix \(\epsilon\) defined in eq. (11). In eq. (14) \(Q_{ij}^{\text{n}}\) is the matrix of the rotation/reflection part and the \(\sigma_{n}\) vector is the translation part of the \(Q_{ij}^{\text{n}}\) symmetry operator. \(\bar{R}_{ij}\) is the vector pointing to the \(j\)-th nuclei and \(\bar{t}_{i}\) is a lattice translation vector.

The term \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}}\) can be obtained from eqs. (13)–(14)

\[
\frac{\partial R_{ij}^{\text{nl}}}{\partial \bar{R}_{k}} = [(I + \epsilon)X(Q_{ij}^{\text{n}}\delta_{jk} - I\delta_{ik})]_{\omega,o}
\]  
(15)

where \([\_]_{\omega,o}\) is the \(\omega'\)-th element of the matrix in square brackets.

Strain Derivatives

The Ewald sum, appearing in the interaction tensors, involves interatomic separation vectors, reciprocal lattice vectors, and the lattice volume, which all vary with the lattice strain. (However, the product of a direct space vector and a reciprocal lattice vector is independent of strain.) Thus the strain derivatives of the energy can be written as

\[
\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial \epsilon_{p}} = \sum_{ij} \sum_{\omega} \sum_{n} \frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}} \frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}} + \frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial V} \frac{\partial V}{\partial \epsilon_{p}}
\]  
(16)

The explicit forms of the partial derivatives of \(E_{\text{XX}}^{\text{MAD}}\) are not given, but some notes regarding their evaluations are made.

The partial derivatives \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\), in eq. (16) are the ones appearing in eq. (12). The important difference between eq. (12) and eq. (16) is that in the latter the partial derivatives \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\) are multiplied by an \(l\) (summation index in the lattice sum)-dependent term, \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}}\). This is in contrast to eq. (12), where the lattice sum involved in \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\) can be performed first and then multiplied by \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}}\) in eq. (16), a new type of lattice sum appears, in which each term of \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial R_{ij}^{\text{nl}}}\) is multiplied by \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}}\) as it is given in eq. (17).

Note, that the reciprocal space part of the Ewald sum contains \(R_{ij}^{\text{nl}}\) only in the product \(K_{ij}^{\text{n}}R_{ij}^{\text{nl}}\), which is independent of strain. Thus, only the direct space sum has to be considered in these strain derivatives.

Because the reciprocal lattice vectors enter only in the reciprocal space sum and not in the direct space sum, only the former has to be considered in the calculation of \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial \epsilon_{p}}\). Similarly, the direct space sum does not contain \(V\), and only the reciprocal space sum has to be considered, when calculating \(\frac{\partial E_{\text{XX}}^{\text{MAD}}}{\partial V}\).

The second part of the terms in eq. (16) will be discussed below. Let us first consider \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}}\). From eq. (13) the \(\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}}\) derivative can be written as

\[
\frac{\partial R_{ij}^{\text{nl}}}{\partial \epsilon_{p}} = \frac{\partial \epsilon}{\partial \epsilon_{p}} X\bar{R}_{ij}^{\text{nl}}
\]  
(17)

with

\[
\frac{\partial \epsilon_{\alpha\beta}}{\partial \epsilon_{p}} = \begin{cases} 
\delta_{\alpha p} & p = 1, 2, 3 \\
\frac{1}{2} (\delta_{\alpha 2} \delta_{p 3} + \delta_{\alpha 3} \delta_{p 2}) & p = 4 \\
\frac{1}{3} (\delta_{\alpha 1} \delta_{p 3} + \delta_{\alpha 3} \delta_{p 1}) & p = 5 \\
\frac{1}{6} (\delta_{\alpha 1} \delta_{p 2} + \delta_{\alpha 2} \delta_{p 1}) & p = 6 
\end{cases}
\]  
(18)

eq. (18) comes from eq. (11).

Let us now consider \(\frac{\partial K_{ij}}{\partial \epsilon_{p}}\) appearing in eq. (16). Because \(K_{ij}^{\text{n}}\) is independent of strain, we...
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can write
\[
\frac{\partial K^+}{\partial \epsilon_p} \mathbf{R} + K^+ \frac{\partial \mathbf{R}}{\partial \epsilon_p} = 0
\]
Using eqs. (13) and (17) it can be written as
\[
\frac{\partial K^+}{\partial \epsilon_p} (\mathbb{I} + \epsilon) \mathbf{X} \mathbf{R} + K^+ \frac{\partial \epsilon}{\partial \epsilon_p} \mathbf{X} \mathbf{R} \mathbf{A} = 0
\]
from which we obtain the derivative
\[
\frac{\partial \mathbf{K}}{\partial \epsilon_p} = -(\mathbb{I} + \epsilon)^{-1} \frac{\partial \epsilon}{\partial \epsilon_p} \mathbf{K}
\]  
(19)

Finally, we need an explicit formula for \( \partial V/\partial \epsilon_p \). The lattice volume varies with strain as
\[
V = \left| \mathbb{I} + \epsilon \right| V^0
\]
where \( \left| \mathbb{I} + \epsilon \right| \) is the determinant of the matrix \( \mathbb{I} + \epsilon \) and \( V^0 \) is the volume at zero strain. Then
\[
\frac{\partial V}{\partial \epsilon_p} = \frac{\partial \left| \mathbb{I} + \epsilon \right|}{\partial \epsilon_p} V^0
\]  
(20)
and
\[
\frac{\partial \left| \mathbb{I} + \epsilon \right|}{\partial \epsilon_p} = \begin{cases} 
(1 + \epsilon_2)(1 + \epsilon_3) - \frac{1}{4} \epsilon_4^2 & p = 1 \\
(1 + \epsilon_1)(1 + \epsilon_3) - \frac{1}{4} \epsilon_5^2 & p = 2 \\
(1 + \epsilon_1)(1 + \epsilon_2) - \frac{1}{4} \epsilon_6^2 & p = 3 \\
-\frac{1}{2}(1 + \epsilon_1)\epsilon_4 + \frac{1}{4} \epsilon_5 \epsilon_6 & p = 4 \\
-\frac{1}{2}(1 + \epsilon_2)\epsilon_4 + \frac{1}{4} \epsilon_4 \epsilon_6 & p = 5 \\
-\frac{1}{2}(1 + \epsilon_3)\epsilon_4 + \frac{1}{4} \epsilon_4 \epsilon_5 & p = 6 
\end{cases}
\]  
(21)

GEOMETRY OPTIMIZATION METHOD

The geometry optimizations were performed by the BFGS Hessian update using the L-BFGS-B code.\(^{30}\) The structures were considered as converged as far as the gradient norm became lower than the threshold of 0.0005 eV (~0.05 kJ/mol). (Note, that the variables are dimensionless.)

Results and Discussion

Molecular geometries and cell parameters were optimized for a series of molecular crystals (Fig. 1 and Table I). Parameters of the experimental structures were used as starting values. Two sets of calculations were performed; in the first, space group symmetry was maintained in the course of optimization while in the second, symmetry change was allowed. The differences between the cell parameters and atomic positions between the experimental and optimized structures are presented in Table II. Changes resulted in symmetry-restrained optimizations are fairly small in most cases. The largest differences are found for a cell edge of CYAMPD03 and for the cell angles FORMAM, TATNBZ, and ECARBM01. Among them, the deviations in the cell angles of TATNBZ are substantial. Here we note that the static structure optimiza-

\[\text{TABLE I.} \]

<table>
<thead>
<tr>
<th>Molecule</th>
<th>CSD Coden</th>
<th>Space Group</th>
<th>Z(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidazor(^{43})</td>
<td>IMAZOL13</td>
<td>P(_2_1/c)</td>
<td>4</td>
</tr>
<tr>
<td>Benzimidazor(^{44})</td>
<td>BZDMAZ</td>
<td>P(_2_1)nb</td>
<td>4</td>
</tr>
<tr>
<td>Formamide(^{45})</td>
<td>FORMAM</td>
<td>P(_2_1/c)</td>
<td>4</td>
</tr>
<tr>
<td>Gytosine(^{46})</td>
<td>CYTSIN01</td>
<td>P(_2_1)(_2)(_1)</td>
<td>4</td>
</tr>
<tr>
<td>1,3,5-Triamino-2,4,6-trinitrobenzene(^{33})</td>
<td>TATNBZ</td>
<td>P(_\bar{1})</td>
<td>2</td>
</tr>
<tr>
<td>Uracil(^{47})</td>
<td>URACIL</td>
<td>P(_2_1)(_a)</td>
<td>4</td>
</tr>
<tr>
<td>Maleic anhydride(^{48})</td>
<td>MLEICA</td>
<td>P(_2_1)(_2)(_1)</td>
<td>4</td>
</tr>
<tr>
<td>Succinic anhydride(^{49})</td>
<td>SUCANH</td>
<td>P(_2_1)(_2)(_1)</td>
<td>4</td>
</tr>
<tr>
<td>Urethane(^{50})</td>
<td>ECARBM01</td>
<td>P(_\bar{1})</td>
<td>2</td>
</tr>
<tr>
<td>Dicyanodiamide(^{51})</td>
<td>CYAMPD03</td>
<td>C(_2/c)</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Number of symmetry related molecules in the unit cell.
TABLE II.
Differences between Optimized and Experimental Crystal Structures.

<table>
<thead>
<tr>
<th>Coden</th>
<th>Cell Edges</th>
<th>Cell angles</th>
<th>Atomic Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental Structures</td>
<td>Errors in Calculated Structures</td>
<td>Experimental Structures</td>
</tr>
<tr>
<td></td>
<td>Symm. d</td>
<td>Unsymm. e</td>
<td>Symm. d</td>
</tr>
<tr>
<td>IMAZOL13</td>
<td>7.732</td>
<td>-0.086</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>5.458</td>
<td>0.108</td>
<td>0.100</td>
</tr>
<tr>
<td></td>
<td>9.779</td>
<td>0.181</td>
<td>0.184</td>
</tr>
<tr>
<td>BZDMAZ</td>
<td>6.940</td>
<td>0.109</td>
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<td></td>
<td>13.498</td>
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<td>-0.372</td>
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<td></td>
<td>6.808</td>
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<td>-0.087</td>
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<tr>
<td>FORMAM</td>
<td>3.613</td>
<td>0.086</td>
<td>0.191</td>
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<tr>
<td></td>
<td>9.053</td>
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<td></td>
<td>8.419</td>
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<td>-0.256</td>
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<td>CYTSIN01</td>
<td>13.044</td>
<td>0.146</td>
<td>0.455</td>
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<td></td>
<td>9.496</td>
<td>0.058</td>
<td>-0.035</td>
</tr>
<tr>
<td></td>
<td>3.814</td>
<td>0.073</td>
<td>0.033</td>
</tr>
<tr>
<td>TATNBZf</td>
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<td>0.034</td>
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<td></td>
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<td>6.812</td>
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<td>0.414</td>
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<tr>
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<td>11.938</td>
<td>0.398</td>
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<td></td>
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<td>0.243</td>
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</tr>
<tr>
<td></td>
<td>3.655</td>
<td>-0.026</td>
<td>-0.024</td>
</tr>
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<td>MLEICA</td>
<td>7.180</td>
<td>-0.012</td>
<td>-0.128</td>
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<td></td>
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<td>0.291</td>
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<td>5.390</td>
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<td></td>
<td>5.402</td>
<td>0.133</td>
<td>0.105</td>
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<td>ECARBM01</td>
<td>5.051</td>
<td>-0.071</td>
<td>-0.116</td>
</tr>
<tr>
<td></td>
<td>7.011</td>
<td>0.011</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>7.543</td>
<td>0.107</td>
<td>0.066</td>
</tr>
<tr>
<td>CYAMPD03</td>
<td>14.879</td>
<td>0.814</td>
<td>0.544</td>
</tr>
<tr>
<td></td>
<td>4.424</td>
<td>-0.333</td>
<td>-0.234</td>
</tr>
<tr>
<td></td>
<td>10.538</td>
<td>0.306</td>
<td>0.306</td>
</tr>
</tbody>
</table>

a Cell edges and their errors are given in the order a, b, and c.
b Cell angles and their errors are given in the order α, β, and γ. Only symmetry-independent values are given.
c Root-mean-square difference of all atomic coordinates.
d Calculated with symmetry restraints.
e Calculated without any symmetry restraint.
f Optimized with ring torsions constrained to experimental values (see text).

It is worth noting, however, that the prediction in ref. 13, though using a dispersion–repulsion potential fitted with an explicit electrostatic term also resulted in considerable errors for the same parameters.

Releasing symmetry restraints in the optimization generally yields small changes in the resulted structures. Table II shows that cell angles defined by symmetry typically change some hundredth of degrees, while atomic positions change some hundredth of Ångstroms. Changes upon relaxation of
symmetry restraints affect primarily those cell parameters that are not restrained by the symmetry, for example, the $\beta$ angle the monoclinic FORMAM and CYAMPD03 crystals and the angles of the triclinic systems TATNBZ and ECARBM01. Thus, it is found that crystal systems have not been changed when symmetry restraints released.

The calculation for TATNBZ was performed in a way different from other structures. This was necessitated by the following findings. It was formerly shown that semiempirical methods predict boat conformation for the 1,3,5-triamino-2,4,6-trinitrobenzene molecule, while the ring is planar at $ab\ initio$ 6-31G(D) level. The TATNBZ crystal contains a molecule whose ring is nearly planar. In these circumstances it is unjustified to use the semiempirical AM1 Hamiltonian for optimizing intramolecular geometrical parameters. For this reason calculations for TATNBZ were performed so that the torsion angles specifying the ring conformation were kept fixed at the values obtained from X-ray data for the crystal.

The constrained optimization of TATNBZ is not possible in the strain+fractional space discussed in detail in the previous section and used for full optimization of all other structures. The coordinate set applied for TATNBZ included the strain matrix elements, the internal coordinates of the molecule, and three further coordinates describing the orientation of the molecule in the unit cell. Such a choice of coordinates makes it possible to perform full-structure optimization just as with the strain+fractional coordinate variables, and it also makes it possible to fix some of the internal coordinates of the molecules.

It is to be noted that the structure of TATNBZ is not without controversy. X-ray structure determination gave a P$\bar{1}$ space group, while the crystal shows nonlinear optical activity that is incompatible with nonpolar structures. There have been several attempts to reconcile this apparent discrepancy between experiments. The conspicuous deviation between experimental structures and optimized SCMP-NDDO cell parameters, especially that found in the calculation without symmetry restraints, also suggest that a noncentrosymmetric arrangement of layers results in a favorable packing of TATNBZ.

The good agreement between optimized and experimental structures provides further evidence for the good quality of the SCMP-NDDO intermolecular potential, which, in an earlier study, has been proven to be superior to the semiempirical AM1 potential and that of the optimized isolated monomer is satisfactory for the description of molecular crystals.

It is important to stress that the present SCMP-NDDO crystal structure optimizations take into account intramolecular interactions by the semiempirical AM1 Hamiltonian. The agreement between calculated and experimental structures suggests that intramolecular interactions are also reasonably described. (Note, however, the exception of TATNBZ as discussed above.) It is concluded then that the SCMP-NDDO potential, composed of an AM1 intramolecular and an intermolecular component, including empirical dispersion–repulsion potential and electrostatic and polarization effects described by the AM1 wave function, is satisfactory for the description of molecular crystals.

To obtain crystal stabilization energies, the difference between the energy of the optimized crystal and that of the optimized isolated monomer is formed. The latter calculation is equivalent with the AM1 minimization of the energy of the molecule (or of the molecules) in the quantum motif. The starting geometries for this minimization were those observed in the crystal. Although, in general a more complete exploration may be necessary to obtain the global minimum of the potential energy surface of the intramolecular degrees of freedom, the molecules studied are fairly rigid, which justifies the present approach.

Calculated stabilization energies and experimental crystal sublimation enthalpies are compiled in Table III. The first column contains energies obtained with crystal optimizations in which crystals are constrained to preserve the experimentally found space group. The second column reports the energies obtained without any constraint, allowing the crystals to form lower energy structures. As it was already discussed in connection with structural parameters, the release of symmetry constraints results in some relaxation of the structures with slight changes in the cell parameters, but without altering crystal systems. In line with the small change in cell parameters and atomic positions the change in the stabilization energies is also small, being typically some tenths of a kJ/mol. The largest deviations are obtained for CYTSIN01 and TATNBZ. As it is discussed later, these systems undergo notable intramolecular deformations upon optimization without symmetry restraints. Moreover, as it was discussed previously, TATNBZ is able to adopt a packing arrangement qualitatively different from that coming from the X-ray structure determination of ref. 33.

The third column of Table III presents stabilization energies obtained at the experimental crystal geometries, i.e., without any geometry opti-
TABLE III.
Calculated and Experimental Lattice Energies (kJ/mol).

<table>
<thead>
<tr>
<th>Coden</th>
<th>Optimized with Symmetry Constraint</th>
<th>Optimized</th>
<th>Not Optimized(^a)</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMAZOL13</td>
<td>−79.9</td>
<td>−79.9</td>
<td>−82.6</td>
<td>−83.0(^b,c)</td>
</tr>
<tr>
<td>BZDMAZ</td>
<td>−95.9</td>
<td>−96.2</td>
<td>−94.7</td>
<td>−102.2(^d)</td>
</tr>
<tr>
<td>FORMAM</td>
<td>−63.7</td>
<td>−64.4</td>
<td>−68.3</td>
<td>−71.7(^b,e)</td>
</tr>
<tr>
<td>CYTSINO1</td>
<td>−141.3</td>
<td>−143.2</td>
<td>−145.7</td>
<td>−155.0(^b)</td>
</tr>
<tr>
<td>TATNBZ</td>
<td>−165.6(^g)</td>
<td>−178.6(^g)</td>
<td>−177.5</td>
<td>−168.2(^b)</td>
</tr>
<tr>
<td>URACIL</td>
<td>−112.8</td>
<td>−113.1</td>
<td>−107.6</td>
<td>−131.0(^b)</td>
</tr>
<tr>
<td>MLEICA</td>
<td>−72.8</td>
<td>−73.2</td>
<td>−67.9</td>
<td>−68.1(^f)</td>
</tr>
<tr>
<td>SUCAHN</td>
<td>−80.1</td>
<td>−81.1</td>
<td>−73.8</td>
<td>−82.3(^f)</td>
</tr>
<tr>
<td>ECARBM01</td>
<td>−76.5</td>
<td>−76.7</td>
<td>−71.2</td>
<td>−80.1(^f)</td>
</tr>
<tr>
<td>CYAMPD03</td>
<td>−124.5</td>
<td>−125.5</td>
<td>−137.7</td>
<td>−129.3(^f)</td>
</tr>
</tbody>
</table>

\(^a\)Ref. 18.
\(^b\)Ref. 52.
\(^c\)Other available value: −83.1.\(^53\)
\(^d\)Ref. 53.
\(^e\)Other available value: −73.9.\(^54\)
\(^f\)Ref. 54.
\(^g\)Optimized with ring torsions constrained to experimental values (see text).

These energies do not depend on the ability of the AM1 potential to predict intramolecular geometrical parameters and associated energies. On the other hand, they do not correspond to a minimum on the intermolecular potential surface, either.

Note that when stabilization energies are calculated with optimized structures, then the zero level is the energy of the relaxed isolated monomer. This is in contrast to the energy calculation with experimental structures in which case the zero level is the energy of the isolated molecule in the geometry found in the crystal. The energy of such a molecule cannot be lower than the energy of the relaxed isolated monomer. Due to the difference in the zero levels the stabilization energies obtained with optimized structures can be both larger and smaller than those obtained without optimizations.

The last column shows experimental sublimation enthalpies. Calculated crystal stabilization energies agree reasonably well with these experimental values. It is interesting to see that energies calculated without geometry optimization overestimate the experimental values in two cases (TATNBZ, CYAMPD03). After structure optimization, these stabilization energies decrease. Thus, the general trend is that stabilization energies calculated with geometry optimizations slightly underestimate experimental sublimation enthalpies. Nevertheless, two points should be emphasized. First, experimental sublimation enthalpies are not equivalent with crystal stabilization energies, and a difference of 8–9 kJ/mol is considered to be acceptable between these two quantities.\(^37\) Second, the parameters of the SCMP-NDDO potentials were not directly fitted to reproduce experimental results. In particular, it is expected that fitting the parameters of the dispersion–repulsion potential to experimental results like cell parameters and possibly to sublimation enthalpies would allow an even better reproduction of these experimental values.

The decomposition of calculated crystal stabilization energies is presented in Table IV. It differs from former decompositions based on the SCMP-NDDO method\(^18,27\) by the appearance of the deformation energy. This is the energy difference of the molecular energy in the geometry adopted in the crystal at the one hand, and in the \textit{in vacuo} geometry, on the other hand. As it has already been mentioned, the crystals studied here are built from fairly rigid molecules, and thus no considerable deformation upon crystal formation is expected. Indeed, they are less than 4 kJ/mol in 7 out of 10 cases. The largest deformation energies are nearly 10 kJ/mol for CYTSINO1 and TATNBZ and slightly above 10 kJ/mol for CYAMPD03. Larger deformation energies for these molecules are obtained because the optimization of the isolated monomers resulted in considerable en-
Crystals as Calculated by the SCMP-NDDO Method.

TABLE IV. Decomposition of the Stabilization Energy, $E^\text{tot}$, of Crystals as Calculated by the SCMP-NDDO Method.

<table>
<thead>
<tr>
<th>Crystal Code</th>
<th>$E^\text{def}$</th>
<th>$E^\text{ele}$</th>
<th>$E^\text{pol}$</th>
<th>$E^\text{DR}$</th>
<th>$E^\text{tot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMAZOL13</td>
<td>1.5</td>
<td>-41.3</td>
<td>-15.0</td>
<td>-24.9</td>
<td>-79.9</td>
</tr>
<tr>
<td>BZDMAZ</td>
<td>2.7</td>
<td>-37.2</td>
<td>-12.4</td>
<td>-49.2</td>
<td>-95.9</td>
</tr>
<tr>
<td>FORMAM</td>
<td>3.9</td>
<td>-43.7</td>
<td>-16.0</td>
<td>-8.0</td>
<td>-63.7</td>
</tr>
<tr>
<td>CYTSIN01</td>
<td>8.3</td>
<td>-83.4</td>
<td>-28.6</td>
<td>-37.6</td>
<td>-141.3</td>
</tr>
<tr>
<td>TATNBZa</td>
<td>9.6</td>
<td>-77.2</td>
<td>-10.0</td>
<td>-88.1</td>
<td>-165.6</td>
</tr>
<tr>
<td>URACIL</td>
<td>3.5</td>
<td>-60.1</td>
<td>-19.1</td>
<td>-37.3</td>
<td>-112.8</td>
</tr>
<tr>
<td>MLEICA</td>
<td>1.1</td>
<td>-32.4</td>
<td>-8.1</td>
<td>-33.4</td>
<td>-72.8</td>
</tr>
<tr>
<td>SUCANH</td>
<td>0.9</td>
<td>-37.9</td>
<td>-9.1</td>
<td>-34.0</td>
<td>-80.1</td>
</tr>
<tr>
<td>ECARBM01</td>
<td>2.8</td>
<td>-42.9</td>
<td>-11.5</td>
<td>-24.9</td>
<td>-76.5</td>
</tr>
<tr>
<td>CYMPD03</td>
<td>11.8</td>
<td>-79.8</td>
<td>-26.4</td>
<td>-30.1</td>
<td>-124.5</td>
</tr>
</tbody>
</table>

All energies are in kJ/mol.

\( ^a \) Optimized with ring torsions constrained to experimental values (see text).

Energy lowering. This decreased zero point is also reflected in decreased crystal stabilization energies with respect to values obtained without optimization. The electrostatic, polarization, and dispersion–repulsion components are slightly different from those found without optimizations, but their relative importance is similar. Data presented in Table IV confirms that polarization is a significant component of the stabilization energy of crystals, and it has to be taken into account for a quantitative reproduction of experimental values.

It is worth noting here that the largest energy difference between structures optimized with and without symmetry restraints were obtained for the molecules with the largest deformation energies (CYTSIN01, TATNBZ and CYMPD03; cf. Tables III and IV). According to the semiempirical AM1 potential these molecules adopt a strained geometry in the crystal and the release of symmetry restraints allows some intramolecular relaxation that is accompanied with an energy decrease.

(R)- AND (S)-N-METHYLAMPHETAMINE BITARTARATE.

The crystal structures of (R)- and (S)-N-methylamphetamine bitartrates (RMERTA and SMERTA) were reported in ref. 38. These diastereoisomeric crystals are similar regarding both their cell dimensions and the conformations of the ions. There are small differences, however, which results in slightly higher density (1.331 vs. 1.292 g/cm$^3$), higher melting point (164 vs. 115$^\circ$C) and lower solubility (0.10 vs. 4.10 g/100 g ethanol). Fogassy et al. suggest that the higher number of C–H…O contacts in RMERTA contributes to its higher stability. A theoretical study based on Cyclic Cluster Model proposed that the stability difference between the diastereoisomeric salts cannot be solely attributed to the O–H…O contacts.

An analysis of the interactions in RMERTA and SMERTA has been performed by the SCMP-NDDO method. The crystal structures were optimized using the experimental data as starting values. The determination of the geometry and the energy of the isolated molecules started with the conformational analyses of N-methylamphetamine and tartaric acid that were performed with the “randomsearch” option of the SYBYL program using MMFF94 force field. Conformers with energies within 10 kJ/mol from the lowest energy conformer were optimized by the semiempirical AM1 Hamiltonian as implemented in the SCMP-NDDO method. The sum of the energies of the lowest energy structures of N-methylamphetamine and tartaric acid was accepted as the energy of the isolated molecules.

Stabilization energies and their components for the two diastereoisomeric crystals are shown in Table V. We note that the deformation energy of the molecules is high and even the difference between them is over 15 kJ/mol. Clearly, the crystal stabilization energies could not be obtained correctly without taking into account these values. This deformation energy is considerably higher in RMERTA but intermolecular interactions counterbalance the excess energy. In particular, electrostatic interaction strongly favors RMERTA over SMERTA. Interestingly, polarization contributions, although important regarding their magnitude, are fairly similar in the two crystals.

Although no experimental sublimation enthalpies are available for the RMERTA and SMERTA crystals, physiochemical data in ref. 38, cited above, prove the higher stability of RMERTA. The NDDO-SCMP method predicts an energy difference of 4–5 kJ/mol. Similar small differences were found.

TABLE V. Decomposition of the Stabilization Energy of (R)- and (S)-N-Methylamphetamine Bitartrates (RMERTA and SMERTA).

<table>
<thead>
<tr>
<th>Molecule</th>
<th>$E^\text{def}$</th>
<th>$E^\text{ele}$</th>
<th>$E^\text{pol}$</th>
<th>$E^\text{DR}$</th>
<th>$E^\text{tot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMERTA</td>
<td>+141.3</td>
<td>-222.1</td>
<td>-52.0</td>
<td>-51.1</td>
<td>-183.9</td>
</tr>
<tr>
<td>SMERTA</td>
<td>+124.7</td>
<td>-206.9</td>
<td>-51.6</td>
<td>-45.7</td>
<td>-179.4</td>
</tr>
</tbody>
</table>

All energies are in kJ/mol.
earlier for polymorphic modifications\textsuperscript{18, 41, 42} and refer to delicate differences in the interactions. Our energy decomposition scheme does not assign energy components directly to structural features, and thus it is not straightforward to check the validity of the proposal\textsuperscript{38} that it is the extra C–H...O contact that is primarily responsible for the higher stability of RMERTA. (However, we note that the SCMP-NDDO energy can be decomposed into one- and two-particle contributions, and thus such an analysis is, in principle, possible.) Our present energy decomposition scheme shows that the small difference in the stabilization energies is an interplay of various interactions in which the unfavorable geometry of RMERTA is counterbalanced by increased electrostatic and dispersion–repulsion interactions.

**Conclusion**

The optimization of crystal structures with the SCMP-NDDO method results in structural parameters and stabilization energies close to the experimental values. The method offers a decomposition scheme for the total crystal stabilization energy. The energy components include deformation, electrostatic, polarization, and dispersion–repulsion contributions. The introduction of the deformation energy became possible by the implementation of forces into the SCMP-NDDO method. This deformation energy is attributed to the distortion of the molecular structure upon crystal formation. The polarization contribution is due to the deformation of the charge density in the crystal environment, and its importance is clearly pointed out by the results. The usefulness of the method in analyzing interactions in crystals of large polar molecules is exemplified by a study of a pair of diastereoisomeric salt crystals. The SCMP-NDDO method selects the lower energy isomer in accordance with pieces of experimental evidence. In this isomer the strained geometry of the molecules is accompanied by favorable electrostatic and dispersion–repulsion interactions, thus leading to a relative stabilization with respect to the other isomer.

**Acknowledgments**

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**References**

40. SYBYL 6.5; Tripos Inc., 1699 South Hanley Rd., St. Louis, MO, 63144; USA.