

## Prediction of Solid Solution Formation in a Family of Diastereomeric Salts. A Molecular Modeling Study

Claire Gervais,<sup>\*,†,||</sup> Reinier F. P. Grimbergen,<sup>†</sup> Imre Markovits,<sup>§</sup> Gerry J. A. Ariaans,<sup>§</sup> Bernard Kaptein,<sup>\*,‡</sup> Alle Bruggink,<sup>‡</sup> and Quirinus B. Broxterman<sup>‡</sup>

Contribution from DSM Research, ACES – Center for Particle Technology, and DSM Pharma Chemicals, Advanced Synthesis and Catalysis, DSM Research, P.O. Box 18, 6160 MD Geleen, The Netherlands, and Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

Received June 12, 2003; E-mail: bernard.kaptein@dsm.com

**Abstract:** The possibility of solid solution behavior of diastereomeric salts, containing multiple resolving agents of the same family (Dutch Resolution), is predicted by molecular modeling. Super-cells containing different ratios of resolving agents in the diastereomeric salt are constructed and optimized, and their lattice energy is computed. The energy difference between these “simulated solid solutions” and the native structures is related in an understandable fashion to the probability of solid solution formation. This procedure is applied to a family of diastereomeric salts of ephedrine and cyclic phosphoric acids, for which the ternary diagrams have been determined experimentally at 25 °C in ethanol. Good agreement between experimental and computational results indicates that this relatively simple and fast method could predict the stable character of solid solution behavior in binary systems.

### Introduction

Although the development of methods for the prediction of new crystalline phases for a given compound led to an abundant amount of literature in the past several decades, there have been few attempts to predict solid solution formation between two organic compounds. The complexity of the task is doubtlessly the main reason for this lack of publications. The increasing development of computational power now allows enhanced numbers of degrees of freedom to be taken into account during the computation, so that prediction of crystal structures of semiflexible molecules is no longer an unrealistic goal.<sup>1,2</sup> However, it is not sufficient to predict crystal packings that exhibit many degrees of freedom,<sup>3</sup> which is the case for crystal structures with an asymmetric unit containing more than one molecule, hydrates or solvates, and solid solutions between two organic compounds.

Kitaigorodsky<sup>4</sup> attempted to give some conditions for formation of solid solutions by using a geometrical approach and

defined the rule of solubility: “The molecule A dissolves in the crystal B only if the coefficient of the geometrical similarity of the molecule exceeds 0.8 and if a replacement of the molecule A by the molecule B does not disturb significantly the molecular packing.” The author concluded that the main questions were to define what is a significant disturbance and how it can be quantified.

In this paper, an attempt is made to answer these questions by setting up a simple procedure for the prediction of solid solution formation. Solid solution behavior is a generally observed phenomenon in the crystallization induced resolution of racemates by diastereomeric salt formation with a family of resolving agents.<sup>5</sup> With this so-called Dutch Resolution procedure, the possibility of success in finding an efficient resolution is highly increased in comparison with a classical resolution where single resolving agents are used.<sup>6</sup> Most of the families used nowadays consist of a mixture of two or more homochiral resolving agents varying in the substituents on the aromatic group, as, for example, the Cyphos system in Figure 1. Solid solution formation also allows the simultaneous resolution of two racemic derivatives using a single resolving agent.<sup>7</sup> In this case, a racemate having a low resolution efficiency with a given resolving agent can be co-resolved in an efficient resolution of a related racemate.

<sup>†</sup> ACES – Center for Particle Technology, DSM Research.

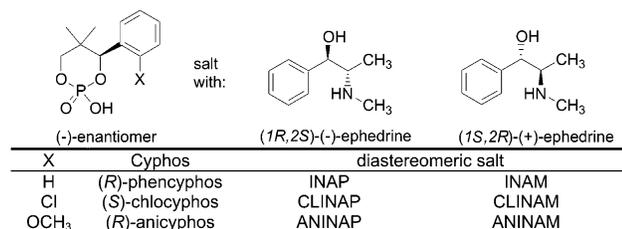
<sup>‡</sup> DSM Pharma Chemicals, DSM Research.

<sup>§</sup> University of Nijmegen.

<sup>||</sup> Current address: Department for Chemistry and Biochemistry, University of Bern, Switzerland.

- (1) van Eijck, B. P.; Mooij, W. T. M.; Kroon, J. *J. Phys. Chem. B* **2001**, *105*, 10573. Pillardy, J.; Arnautova, Y. A.; Czaplowski, C.; Gibson, K. D.; Scheraga, H. A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 12351. Mooij, W. T. M.; van Eijck, B. P.; Kroon, J. *J. Am. Chem. Soc.* **2000**, *122*, 3500.
- (2) Leusen, F. J. J. *Cryst. Growth Des.* **2003**, *2*, 189–192.
- (3) Motherwell, W. D.; Ammon, H. L.; Dunitz, J. D.; Dzyabchenko, A.; Erk, P.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Lommerse, J. P. M.; Mooij, W. T. M.; Price, S. L.; Scheraga, H.; Schweizer, B.; Schmidt, M. U.; van Eijck, B. P.; Verwer, P.; Williams, D. E. *Acta Crystallogr., Sect. B* **2002**, *58*, 647.
- (4) Kitaigorodsky, A. I. *Mixed Crystals*; Springer-Verlag: Berlin, 1984 (ISBN: 3-540-10922-6).

- (5) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2349.
- (6) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981.
- (7) Kaptein, B.; Elsenberg, H.; Grimbergen, R. F. P.; Broxterman, Q. B.; Hulshof, L. A.; Pouwer, K. L.; Vries, T. R. *Tetrahedron: Asymmetry* **2000**, *11*, 1343.



**Figure 1.** Description of the Cyphos system studied. The cyclophosphoric acids are denoted by the common abbreviation cyphos with a prefix. The names of the diastereomeric salts are composed of the general code INA, followed by P or M, indicating the two pairs of diastereomers, P-salt, (–,–) or (+,+), and M-salt, (+,–) or (–,+), respectively. The prefix refers to the aromatic substituent of the cyclophosphoric acid.

Although the exact origin of the Dutch Resolution effect is not clear, solid solution behavior might offer a viable thermodynamic explanation. In addition to this solid solution behavior, nucleation inhibition by one of the family members has recently been described as a possible explanation for the improved Dutch Resolution results.<sup>8</sup>

To obtain better insight into the nature of the Dutch Resolution effect, molecular modeling tools are employed to simulate solid solutions between different derivatives of a series of ephedrine-cyclophosphoric acid salts<sup>9</sup> (Cyphos system) in different ratios.

In the first part of this paper, the procedure for the construction of these solid solutions is described. The conditions for optimization and lattice energy calculation of these phases are then set, by studying the influence of different parameters such as the charge set or the value of the dielectric constant. Finally, the ability of the procedure to predict solid solution formation between different pairs of diastereomeric salts is tested by comparing the computational results to experimental data, depicted by ternary phase diagrams established in ethanol. The results are discussed and proposals are made for the most important factors responsible for the formation of solid solutions.

### Presentation of the Cyphos System

The diastereomeric salts studied are composed of (+)- or (–)-ephedrine associated with one of the three substituted (–)-cyclophosphoric acids (Figure 1).

Relevant details of the crystal structures of these salts are summarized in Table 1. Note that the conformations of both ephedrine and cyclophosphoric acid derivatives are identical in all of the structures. CLINAM crystallizes in two polymorphic forms, CLINAM-1 being the most stable form at room temperature.<sup>10</sup>

In this series of diastereomeric salts, all of the structures are composed of H-bond ribbons running along the *b* axis. On the

**Table 1.** Structural Data for the Different Salts Studied (See Ref 11)<sup>a</sup>

salt	class	space group (Z-value)	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	$\beta$ (deg)
INAM	I <sub>m</sub>	<i>P</i> 2 <sub>1</sub> (2)	13.842	7.804	10.168	92.95
INAP	I <sub>p</sub>	<i>P</i> 2 <sub>1</sub> (2)	14.004	8.095	9.709	98.9
CLINAM-1	III	<i>P</i> 2 <sub>1</sub> (2)	19.659	7.208	7.921	100.73
CLINAM-2	I <sub>m</sub>	<i>P</i> 2 <sub>1</sub> (2)	13.414	8.079	10.334	91.67
CLINAP	I <sub>p</sub>	<i>P</i> 2 <sub>1</sub> (2)	13.842	8.381	9.812	99.67
ANINAM	Ib <sub>m</sub>	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> (4)	13.192	8.064	20.898	
ANINAP	– <sup>b</sup>	<i>P</i> 2 <sub>1</sub> (2)	12.196	7.689	12.414	96.68

<sup>a</sup> Types I<sub>m</sub> and I<sub>p</sub> refer to the same kind of crystal packing, but for M-salts and P-salts, respectively. <sup>b</sup> The crystal packing of ANINAP is similar to that of the other structures, but cannot be classified in one of the three categories. Both H-bond ribbons and crystal arrangement are slightly different from those encountered in the other crystal packings.

basis of the characteristics of these ribbons and the packing mode, the structures (except ANINAP) can be classified into three categories (classes I, II, and III).<sup>11</sup> Two compounds belonging to the same class exhibit similar crystallographic parameters. Although ANINAM crystallizes in a different space group, its crystal packing is closely similar to that of class I. This structural analogy can be highlighted by the derived crystal packings (DCP) model.<sup>12,13</sup> Indeed, the extraction of the slice (002) from the structure of ANINAM and the addition of a translation normal to it generates a new crystal packing in space group *P*2<sub>1</sub>, which belongs to class I.<sup>14</sup>

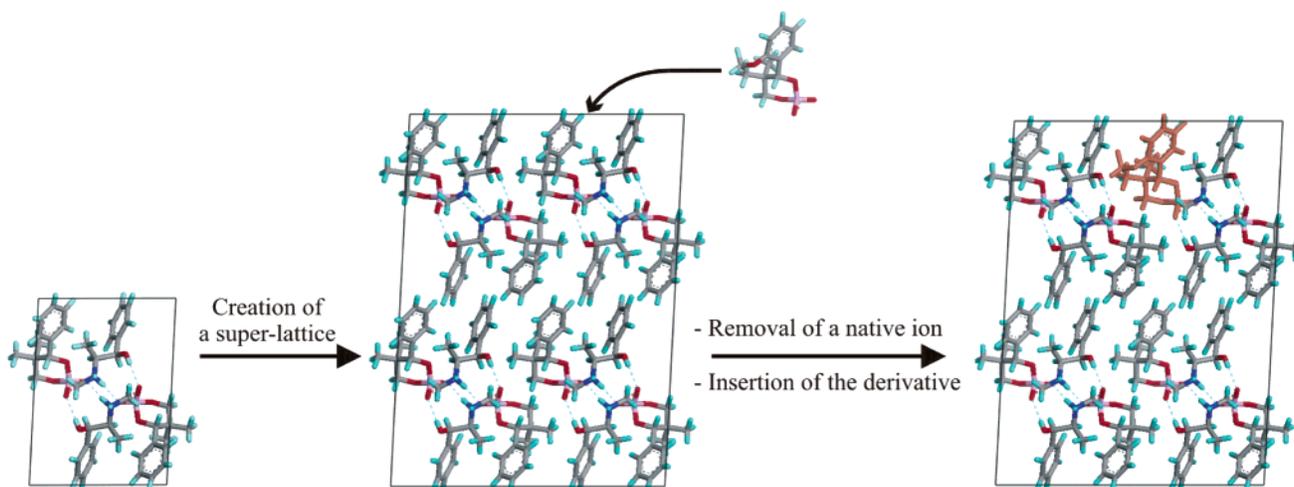
### Molecular Modeling Procedure

**Simulation of the Solid Solutions.** The construction as well as the optimization of the crystal structures has been performed with the aid of Cerius2 software.<sup>15</sup> The virtual solid solutions are obtained as follows (Figure 2). A super-lattice is constructed by extending the unit-cell to the size of several cells and by defining the space group as *P*1. One or several cyphos anions (called “native”) are then removed and replaced by derivatives (in Figure 2, one phencyphos anion of the super-lattice is replaced by an anicyphos anion).

Several ratios of native and derivative ions have been investigated (Table 2). For ratios 1:1 and 3:1, a preliminary study has shown that it is preferable to choose a super-lattice possessing “mixed H-bonded ribbons”, that is, composed of both native and derivative ions, instead of “separated H-bonded ribbons”.<sup>16</sup> To obtain these mixed ribbons, the super-lattice is built by extending the direction of the H-bonded ribbons (i.e., along the *b* axis).

- (8) Nieuwenhuijzen, J. W.; Grimbergen, R. F. P.; Koopman, C.; Kellogg, R. M.; Vries, T. R.; Pouwer, K.; van Echten, E.; Kaptein, B.; Hulshof, L. A.; Broxterman, Q. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4281.
- (9) (a) ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508. Wynberg, H.; ten Hoeve, W. Eur. Pat. Appl. EP 180276. (b) Haest, A. D. v. d.; Wynberg, H.; Leusen, F. J. J.; Bruggink, A. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 523. (c) Leusen, F. J. J.; Bruins-Slot, H. J.; Noordik, J. H.; Haest, A. D. v. d.; Wynberg, H.; Bruggink, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 13. (d) Leusen, F. J. J.; Bruins-Slot, H. J.; Noordik, J. H.; Haest, A. D. v. d.; Wynberg, H.; Bruggink, A. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 111. (e) Haest, A. D. v. d.; Wynberg, H.; Leusen, F. J. J.; Bruggink, A. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 230. (f) Leusen, F. J. J.; Noordik, J. H.; Karfunkel, W. R. *Tetrahedron* **1993**, *49*, 5377.
- (10) Moers, F. G.; Smits, J. M. M.; Beurskens, P. T.; Ariaans, G. J. A.; Zwanenburg, B.; Leusen, F. J. J.; Bruggink, A. *J. Chem. Crystallogr.* **1994**, *24*, 179.

- (11) Leusen, F. J. J. Rationalization of racemate resolution. A molecular modeling study. Ph.D. Thesis, University of Nijmegen, 1993 (ISBN: 90-9005690-4).
- (12) Gervais, C.; Coquerel, G. *Acta Crystallogr.* **2002**, *B58*, 662–672.
- (13) Gervais, C. Elaboration of a model generating crystal structures derived from a given lattice. Ph.D. Thesis, University of Rouen, 2002.
- (14) Because of its structural relationships with class I, the class of the experimental structure of ANINAM is noted class Ib. It is noteworthy that this new type of crystal packing might be regarded as a possible metastable polymorph for all of the derivatives crystallizing in class I. Indeed, this *P*2<sub>1</sub>2<sub>1</sub> crystal packing is expected to have a relative low lattice energy, because a great part of its stability is supplied by the two-dimensional H-bonded periodic fragment (slice (002)), already existing experimentally in class I.
- (15) Cerius2, *Accelrys Inc.*, version 4.6, Cambridge, U.K. web site: www.accelrys.com.
- (16) This result is understandable. Indeed, the packing of mixed ribbons exhibiting an average periodicity is more efficient than the packing of two types of H-bond ribbons, with can exhibit a rather different periodicity (see, for example, INAP and ANINAP for which *b* = 8.095 Å and *b* = 7.689 Å, respectively).



**Figure 2.** Construction of a simulated solid solution.

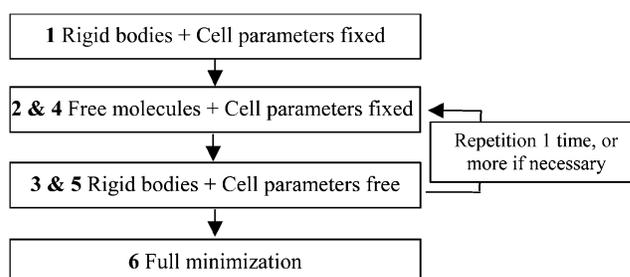
**Table 2.** Characteristics of the Simulated Solid Solutions

super-lattice ( $a \times b \times c$ )	$2 \times 2 \times 2$	$1 \times 2 \times 1$	$1 \times 1 \times 1$
ratio native:derivative	15:1	3:1	1:1
% mol derivative in the native structure	6.25	25	50

It is of note that the constructed mixed crystals do not reproduce exactly solid solutions, because the two different anions are not randomly distributed among the crystal. However, the construction of these simulated mixed crystals followed by the computation of their lattice energy is not time-consuming and should give a good estimation of the “affinity” between the two different salts and thus their ability to form solid solutions.

**Parameters Used To Minimize and Compute the Lattice Energies.** The constructed mixed crystals as well as the native structures have been optimized by use of a six-step procedure (Figure 3). This procedure allows a smooth relaxation of the crystal structures and reduces bias in the minimization that could arise from large steric bumps present in the simulated solid solutions.

The chosen force field is Dreiding 2.21.<sup>17</sup> Ewald summation is used for both Coulombic and van der Waals interactions. ESP charges are computed using Gaussian 98 (method B3LYP/6-31G(d,p)).<sup>18</sup> Charges are calculated on each ion separately, applying a total net charge of (+1) for ephedrine and (−1) for cyclophosphoric acid. Despite the fact that this distribution of charges is unrealistic because charge transfer and polarization are important in such structures,<sup>19</sup> this simplification was necessary to allow easy replacement of the anion by a derivative.



**Figure 3.** Minimization procedure employed in Cerius2 with the OFF module.<sup>15</sup>

Following the procedure adopted by Leusen who pointed out the significance of the dielectric constant value ( $\epsilon$ ) for the Cyphos system,<sup>9b,11</sup> the optimization of every crystal structure was performed with different  $\epsilon$  values, from 1 to 50.

**Validation of the Minimization Procedure.** Three criteria based on experimental data<sup>10,11</sup> have been chosen to validate the minimization procedure: (1) The polymorph CLINAM-1 is more stable than CLINAM-2,<sup>20</sup> so that it must have the lowest lattice energy. (2) CLINAM-1 and ANINAM are less soluble and therefore more stable than CLINAP and ANINAP, respectively. Consequently, their lattice energies have to be lower. (3) INAP is slightly less soluble than INAM so that its lattice energy should be slightly lower than that of INAM.

Results show that the latter criterion 3 is respected whatever the  $\epsilon$  value (see Supporting Information), which is not the case for criteria 1 and 2 (Figure 4). The  $\epsilon$  value has to be greater than 8 or 12 to obtain, respectively, the correct stability order between CLINAM-1 and CLINAM-2 (criterion 1) and between CLINAM-1 and CLINAP (criterion 2).

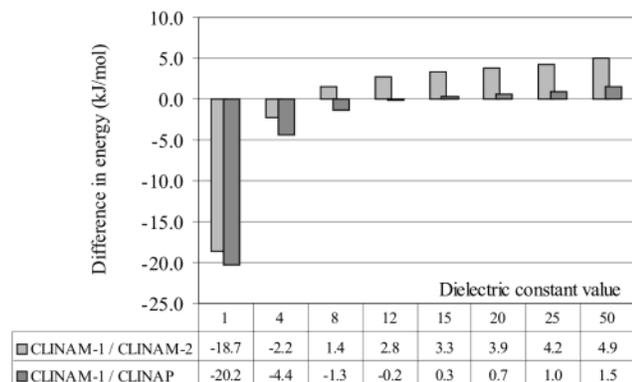
The dielectric constant is defined in Cerius2 as an empirical, dimensionless scaling factor between electrostatic and van der Waals interactions, the latter term being predominant for high  $\epsilon$  values. The fact that the minimization procedure is correct only for  $\epsilon > 12$  indicates that the problem of reverse stability order for low  $\epsilon$  values lies in the treatment of the electrostatic interactions, which are too complex or overestimated. Polarization effects, which play an important role in the ionic structures,

(17) Mayo, S. L.; Olafson, B. D.; Goddard, W. A. *J. Phys. Chem.* **1990**, *94*, 8897.

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

(19) For example, semiempirical and ab initio quantum mechanical calculations performed on small clusters of organic/HCl salts, in which ions are kept in their crystal orientation, result in partial charges of −0.8 and +0.8 (Leusen, F. J. J., manuscript in preparation).

(20) The relative stability of polymorph CLINAM-2 is unknown due to the lack of experimental data on this structure, but ref 10 indicates stability of CLINAM-1 at room temperature.



**Figure 4.** Influence of the dielectric constant value ( $\epsilon$ ) on the relative stability between the chloxyphos salts. The difference in energy is calculated with respect to the lattice energy of CLINAM-1, taken as reference.

are poorly reflected by a single  $\epsilon$  value. To reproduce the anisotropic polarization of the molecules, a direction-dependent dielectric function might be employed. Improvement could also be obtained by deriving the atomic Coulomb parameters via low X-ray diffraction studies<sup>21</sup> or performing atomic charges calculations on the ions surrounded by a set of point charges, to recreate the crystal environment. However, the crystal environment varies with the number of derivative molecules in the structure, so that atomic charge sets should be recalculated for every solid solution constructed. This prevents easy replacement of one ion by another and is time-consuming.

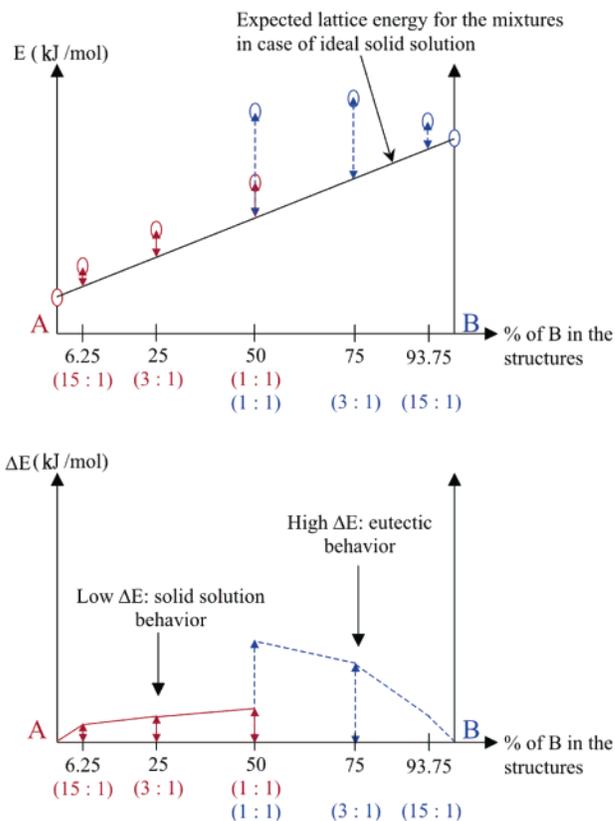
Therefore, as the aim of the study is to predict in a fast and simple way the possibility of solid solution formation, the optimization of the structures is performed using a constant dielectric constant.  $\epsilon$  values of 5, 10, and 15 are chosen to check for the sensitivity of our method with respect to the three criteria mentioned.

### Exploitation of the Molecular Modeling Results

To link the calculated lattice energies to the miscibility of the two salts, the following comments have to be pointed out.

The thermodynamics of the surfaces of the crystal is not considered here. The occlusion of guest molecules onto the growing crystal surfaces and its influence on the crystal growth, nucleation, and morphology have been extensively studied in the past two decades.<sup>22,23</sup> It has been shown that the adsorption of the guests, labeled tailor-made additives, can retard the growth of the considered faces leading to morphological changes and in extreme cases can inhibit the growth or even the nucleation. Moreover, such guests are usually not equally adsorbed on the different surface sites, so that identical equi-energetic sites of the host crystal are not equally populated by the guest molecules. Consequently, a reduction of the crystal symmetry of the solid solutions is usually observed.

In contrast to these surface studies, which deal with the mechanisms of formation of the solid solution, our thermodynamic approach of molecular modeling and phase diagrams deals with the thermodynamic end situation of mixed crystals. We follow the same assumption as Kitaigorodsky:<sup>4</sup> “*guest*



**Figure 5.** Top: The lattice energies computed for the mixed salts. Bottom: Difference  $\Delta E$  between the expected lattice energies of the virtual ideal solid solutions and those of the computed mixed crystals. The ratios shown in red (respectively, blue) represent the molar ratios A:B (respectively, B:A) for the mixed crystals generated from the structure of A (respectively, B).

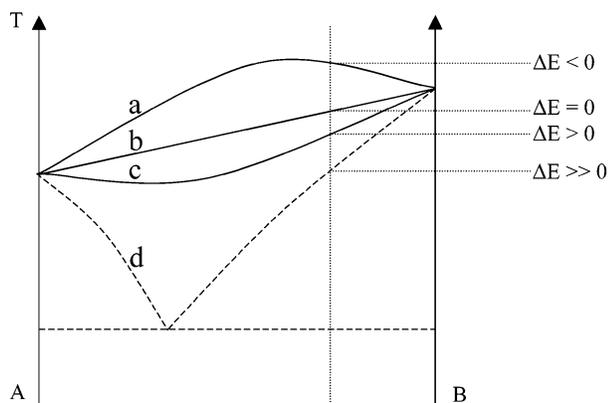
*molecules will occupy all symmetry-related sites in the crystal with equal probability*”, and we do not take into account the dissymmetry in the structure due to crystal growth.

This can lead to small deviations between modeling and experiments, and results could be more accurate if crystal growth studies are considered. In that sense, our approach and crystal growth studies can be seen as complementary: The first one answers the question “is it possible to find a stable structure with a given A:B ratio?”, and the second one deals more with the distribution of the two components in the crystal and the possible resulting morphological variations.

Therefore, if we consider here that a full ideal solid solution is described as a structure containing randomly distributed A and B molecules and that all of the symmetry-sites are energetically identical, virtual solid solutions are characterized by lattice energies varying linearly with the ratio A:B (Figure 5, top).

In that case, the energy difference  $\Delta E$  between the computed mixed crystals and these virtual ideal solid solutions taken as references should reflect the real “affinity” between the two compounds and thus provide information about the putative binary phase diagram (Figure 6). In case the computed lattice energy of the mixed crystal is much higher than the ideal value ( $\Delta E \gg 0$ ), it is likely that the two compounds will crystallize separately (eutectic behavior). On the other hand, if it is close to the ideal value ( $\Delta E \approx 0$ ), a solid solution might be expected. Finally, a negative value for  $\Delta E$  might indicate the formation of a solid solution with maximum melting temperature. The

(21) Jacquemain, D.; Grayer Wolf, S.; Leveiller, F.; Frolow, F.; Eisenstein, M.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1992**, *114*, 9983.  
 (22) Weissbuch, I.; Addadi, L.; Lahav, M.; Leiserowitz, L. *Science* **1991**, *253*, 637.  
 (23) Weissbuch, I.; Popovitz-Biro, R.; Lahav, M.; Leiserowitz, L. *Acta Crystallogr.* **1995**, *B51*, 115.



**Figure 6.** Simple binary phase diagrams between compounds A and B, and relationship with  $\Delta E$ . Full solid solution with (a) maximum, (b) ideal, (c) minimum melting temperature, or (d) eutectic behavior.

computational results are summarized in a graph representing the variation of  $\Delta E$  with respect to the molar ratio between the native and derivative ions (Figure 5, bottom).

As shown in Figure 5, 1:1 solid solutions can possess different lattice energies, whether the structure is produced starting from pure A or pure B. This distinction arises especially if the two native structures have different packings. In that case, one of the two constructed 1:1 solutions is less stable than the other.

## Results

The procedure has been applied to the six possible pairs of Cyphos diastereomeric salts, that is, INAM/CLINAM, INAP/CLINAP, CLINAM/ANINAM, CLINAP/ANINAP, INAM/ANINAM, and INAP/ANINAP. Only the polymorph CLINAM-1 is considered here. Molecular modeling results are compared to the experimental ternary (solubility) phase diagrams of these systems established at 25 °C in ethanol (Figure 7).

**Measurement and Interpretation of the Ternary Phase Diagrams.** The following procedure has been used to determine the six ternary phase diagrams. Quantities of the diastereomeric salts with the selected ratio were accurately weighed into a sample tube (100–200 mg scale). The mixture was suspended in absolute ethanol (0.2–1 mL, depending on the solubility of the sample; some undissolved material must remain), and the sample tube was tightly closed. The mixture was stirred for at least 24 h at 25 °C in a thermostated water bath. Part of the mother liquor was drawn from the sample using a syringe fitted with a Whatman 0.2  $\mu\text{m}$  filter. This saturated solution (approximately 50 mg) was accurately weighed into a 10 mL volumetric flask, diluted with ethanol, and analyzed by HPLC.<sup>24</sup> The composition of the solid salt was not experimentally determined, but was calculated according to the method of Hill and Ricci,<sup>25</sup> that is, based on the known quantities of salts and solvent, and the composition of the mother liquor. The software TriDraw 2.6 was used to plot the solubility triangle diagrams.<sup>26</sup> The six ternary phase diagrams are depicted in Figure 7, right.

All of the systems exhibit solid solution behavior for at least a small composition range, extreme cases being INAM/

CLINAM or INAP/CLINAP systems in which a full solid solution is observed (Figure 7a and b), and the INAM/ANINAM system (Figure 7e) in which only end solid solution occurs in the domain of composition close to 100% of ANINAM. In the CLINAP/ANINAP system (Figure 7d), a metastable phase could be possible for ratios around 50:50, according to the composition of the mother liquors obtained for these ratios.

**Molecular Modeling Results.** Computational results are summarized in Figure 7, left. Provided the threshold  $\Delta E$  value delimiting a solid solution from a eutectic behavior is fixed at 4 kJ per mol<sup>27</sup> of ionic pair (kJ/mol hereafter), it seems that the phase behavior is successfully predicted for all of the systems (except INAM/ANINAM). For more clarity, systems are classified in the following section according to the type of experimentally observed behavior, full solid solution, partial solid solution with a large composition range, and finally eutectic behavior with a small end solid solution.

**Full Solid Solution. INAM/CLINAM, INAP/CLINAP, and CLINAP/ANINAP Systems (Figure 7a,b,d).** For the first two systems, a good match between experimental ternary phase diagrams and computational results is found, because the  $\Delta E$  values do not exceed 4 kJ/mol whatever the ratio of native anion and derivative. Moreover, they seem to be related closely to the type of solid solution (i.e., with minimum, maximum, or ideal): The  $\Delta E$  values for the system INAP/CLINAP are close to zero and thus indicate an ideal solid solution, as found experimentally. For the system INAM/CLINAM, the slight increase of the  $\Delta E$  values indicates a solid solution with a minimum (i.e., increased solubility), as observed experimentally in ethanol.

In the third system (CLINAP/ANINAP), the insertion of a high amount of chlocyphos in the ANINAP structure leads to high  $\Delta E$  values, which should indicate eutectic behavior with partial solid solutions. Although a full solid solution is found experimentally, a deep minimum is observed. This is in accordance with the  $\Delta E$  values, which are close to those found for a eutectic.<sup>28</sup> Therefore, it seems that this system is at the limit between a full solid solution and a eutectic behavior, and external factors such as solvent or temperature are likely to influence it.

**Partial Solid Solution in a Large Range. CLINAM/ANINAM and INAP/ANINAP Systems (Figure 7c,f).** For these two systems, computational results are in good agreement with the phase diagram, because  $\Delta E$  values less than 4 kJ/mol are obtained in the composition range corresponding to a partial solid solution experimentally (i.e., for high ratios of ANINAM and INAP, respectively).

**Eutectic Behavior with End Solid Solution in a Small Range. INAM/ANINAM System (Figure 7e).** The insertion of phenicyphos into the ANINAM structure does not induce an excess of energy and should thus give experimentally a solid

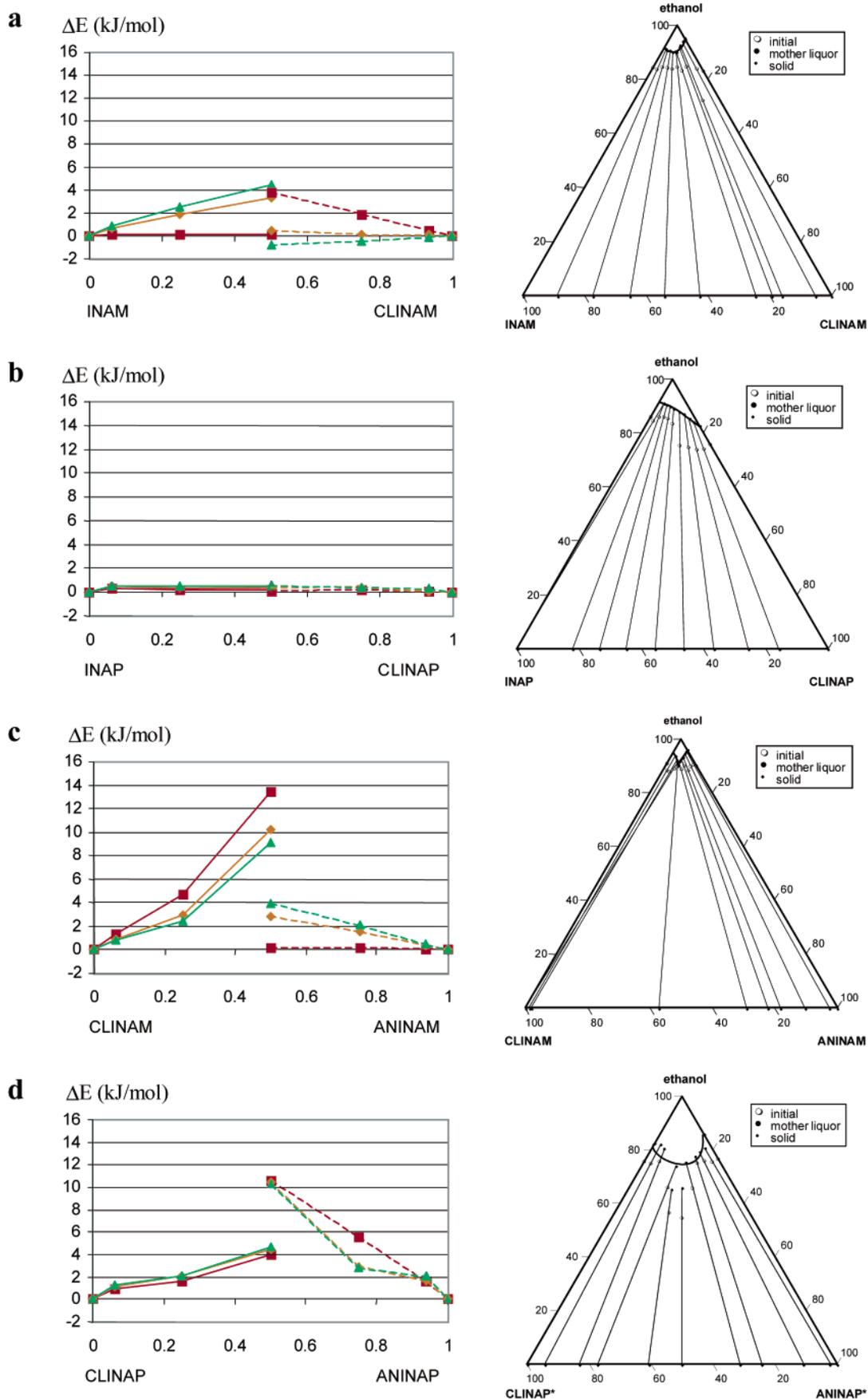
(24) A Shimadzu VP series HPLC system with CLASS VP software version 5.03 and an ECONOSPHERE C8 5 $\mu$  column by Alltech were used (Solvent: 20% acetonitrile/80% 20 mM  $\text{KH}_2\text{PO}_4$  in water. Flow rate: 1 mL/min. Detection: UV 210 and 220 nm).

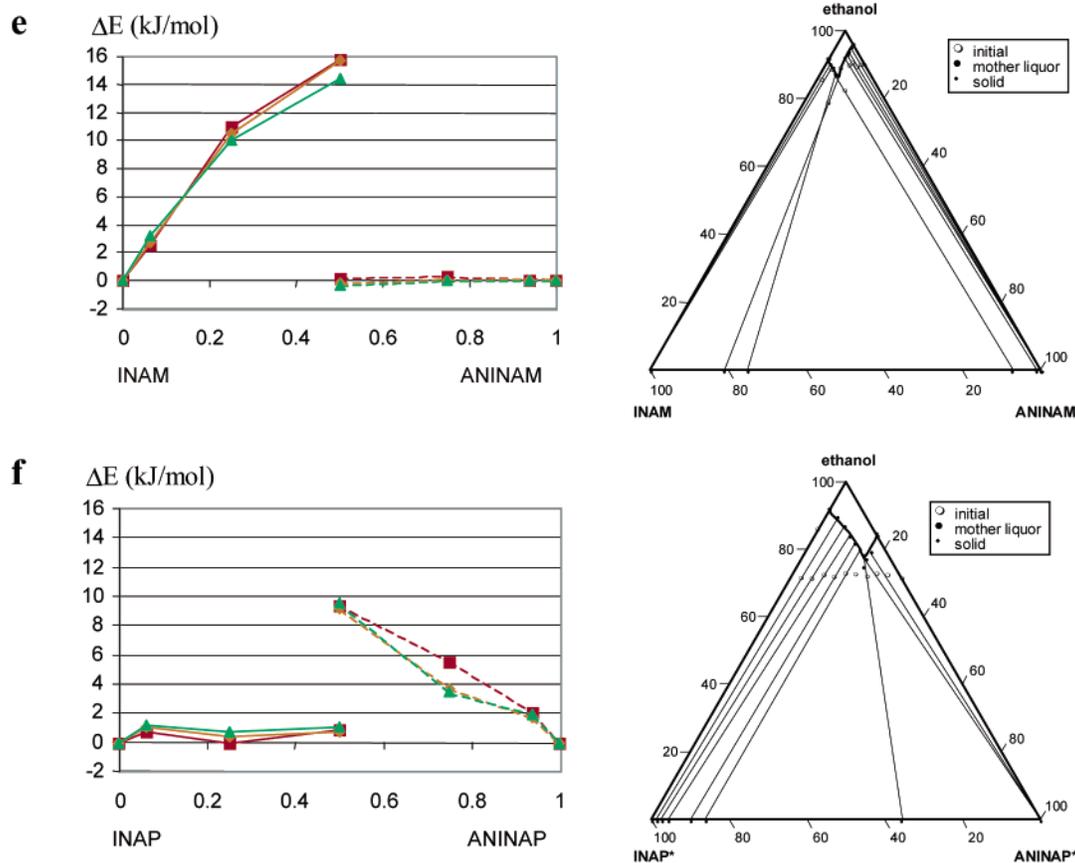
(25) Hill, A. E.; Ricci, J. E. *J. Am. Chem. Soc.* **1931**, *53*, 4305.

(26) Shareware available on the following web site: <http://secure.reg.net/product.asp?ID=5109>.

(27) From our calculations, it appears that the threshold  $\Delta E$  value delimiting a solid solution with a minimum and a eutectic behavior is of the order of 4 kJ/mol. Note that the calculated  $\Delta E$  value can be regarded as the  $\Delta H_{\text{mix}}$  in the equation of free energy of mixing:  $\Delta G_{\text{mix}} = \Delta H_{\text{mix}} - T\Delta S_{\text{mix}}$ , in which  $\Delta S_{\text{mix}}$  for an ideal solid solution with 50:50 composition is equal to  $\Delta S_{\text{mix}} = R \ln 2$ . Substituting  $T = 298$  K (experimental temperature), the calculated  $\Delta H_{\text{mix}} = 4$  kJ/mol, and  $\Delta S_{\text{mix}} = R \ln 2$  J/mol K, we found a value of  $\Delta G_{\text{mix}} = 2.3$  kJ/mol. This value is very close to the thermal energy at  $T = 298$  K (2.5 kJ/mol).

(28) It has to be noted that the melting point diagram of the CLINAP/ANINAP system shows eutectic behavior. For all other systems, the binary and ternary phase diagram are congruent.





**Figure 7.** Comparison between the computational results (left), based on the representation described in Figure 5, and the experimental ternary phase diagrams obtained in ethanol at 25 °C (right). Values of  $\Delta E$  obtained at  $\epsilon = 5, 10,$  and  $15$  are represented, respectively, with green, orange, and red colors. For convenience, the CLINAP/ANINAP and INAP/ANINAP ternary phase diagrams have been determined from the enantiomeric form of the salts (indicated with \*).

solution in a large composition range, whereas solid solution behavior is observed only for very small INAM ratios. Two main reasons may be given, the presence of a metastable polymorphic form for ANINAM and the fact that neither temperature nor solvent is taken into account in the predictions.

## Discussion

Among the six systems studied, at least four predictions are in complete agreement with the experimental solubility phase diagrams in ethanol. In some favorable cases, even the type of solid solution (with minimum, maximum, or ideal) might be predicted. It has to be noted that the  $\epsilon$  value does not have a great influence on the energy difference. This can be explained by the fact that the solid solutions have a crystal structure similar to the native structure; thus the electrostatic interactions are treated in the same manner in both types of structures. On the other hand, the  $\epsilon$  value plays a major role in the energy difference between two polymorphs, because the crystal packing can be drastically different. An example of this influence has been shown for CLINAM-1 and CLINAM-2.

To date, the only criteria to detect solid solutions are (i) compare the molecular shapes, and (ii) choose compounds that have similar crystal packings (this is one of the first conditions for a full solid solution, so that a continuous replacement of one compound by the other one is possible). As already noticed by Kitaigorodsky, criterion (i) is not sufficient to predict the

formation of a solid solution. An example in this paper is the insertion of anicyphos leading to a partial solid solution in INAP but not in INAM (see Figure 7f and 7e, respectively), whereas the molecular volumes are identical in the two systems. Besides, criterion (ii) has to be used with care because solid solution may occur in a large composition range even if the stable crystal structures of the two compounds are not similar. For instance, the INAM/CLINAM system (Figure 7a) seems to exhibit a full solid solution behavior, whereas the individual crystal packings are different (types  $I_m$  and III, respectively). This can be explained by two main hypotheses. Either there is a discontinuity in the system that has not been detected (e.g., the presence of a eutectic in a small range of ratios or the presence of two types of solid solution), or one of the two compounds crystallizes in another polymorphic form that has a crystal arrangement similar to that of the other.<sup>29</sup> This is the case for CLINAM, which crystallizes in a metastable phase with the type  $I_m$  packing, as INAM. Another example is the CLINAM/ANINAM system. CLINAM exhibits a metastable structure with type  $I_m$  packing, and ANINAM packing type  $Ib_m$  is closely related to it. It would be interesting to investigate the possible correlation between structural similarity and solid solution formation between two compounds by searching possible “common crystal packings”

(29) To conclude on these different hypotheses, it should be interesting to perform X-ray powder diffraction (XRPD) patterns of the crops obtained in ethanol. Their comparison with the calculated XRPD patterns of the pure compounds would give information about the crystal packings adopted by the solid solutions.

(for instance, by comparing all of the structures generated *ab initio* or by using the DCP model).

An alternative to these two qualitative criteria could be the method described in this paper. Even though it does not permit one to give precise answers in the case of a eutectic with partial solid solutions (i.e., the exact composition ranges cannot be predicted accurately) or for systems showing complex behavior<sup>30</sup> (such as CLINAP/ANINAP, Figure 7d, in which a metastable phase is probably present), this simple molecular modeling procedure gives a fast and simple overview of a two-component system. It has been shown to be particularly successful in predicting the occurrence of full solid solutions and gives an answer to the probability of formation of partial solid solutions with large compositions. This could be particularly interesting as a prescreening before any experimental work specifically to select or discard systems in which the probability to have solid solution behavior is high.

Concerning the relationship with Dutch Resolution, the analysis of the ternary phase diagrams does not indicate that the formation of solid solution could enhance the resolution between P and N salts. Even though the direct comparison between P and N mixed salts is not easy (e.g., it is not possible to compare the solubilities of CLINAP/INAP and CLINAM/INAM for a given ratio, because the initial compositions are not the same), one can observe that the solubility of the solid solution is not lower than that of the less-soluble pure salt. Therefore, the thermodynamic explanation for Dutch Resolution, which presupposes that solid solution behavior increases the solubility difference between P and N mixed salts, is not convincing. Dutch Resolution seems to be mainly driven by a kinetic effect, the nucleation inhibition of one of the diastereomeric salt by the added derivative.<sup>8</sup>

(30) Coquerel, G. *Enantiomer* **2000**, *5*, 481.

## Conclusion

The possibility of solid solution formation in diastereomeric salt systems ephedrine/cyclophosphoric acids has been investigated by using a simple and relatively fast molecular modeling procedure, which consists of (i) insertion of a given ratio of B molecules into the A structure, and vice versa, (ii) computation of the lattice energies and comparison with the energy of virtual ideal solid solutions (calculated by a linear combination of pure A and pure B lattice energies), and (iii) deduction of the behavior of the two-component system according to this energy difference.

A good prediction of the different experimental phase behaviors observed for these systems has been achieved, with at least four out of the six predictions being successful. In the computational procedure, the role of the dielectric constant was shown to be of importance to obtain the good order of stability between two polymorphs, but it was also shown to play a negligible role in determining the energy difference between a native structure and a simulated solid solution.

The described molecular modeling method represents a good alternative to the two known empirical rules utilized to predict solid solution behavior (i.e., similarity in molecular shape and crystal packing), which are shown to be of little support in the case of the Cyphos system. Although the presence of solid solution seems to not be the core of Dutch Resolution efficiency, the described procedure could be of help when the co-resolution of two racemates (and resolving agent) is preferred.

**Supporting Information Available:** Variations of the relative energy between INAM and INAP with respect to the dielectric constant (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0366437