Polymorphic Forms of Organic Crystals at Room Conditions: Thermodynamic and Structural Implications

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Abstract: A total of 204 pairs of different crystal structures for the same organic molecule (polymorphs), determined at room conditions, were retrieved from the Cambridge Structural Database. Crystallographic, chemical, and pharmaceutical aspects of the phenomenon were considered. Correlations between differences in density, calculated packing energy, and lattice-vibrational entropy, and other crystal properties, are presented. Indices to quantify conformational polymorphism and differences in coordination sphere in the crystal are proposed. Differences in lattice-vibrational entropy between polymorphs are seldom, if ever, large enough to equal or to exceed differences in packing energy (enthalpy) at room temperature. Although few experimental estimates of energy differences between polymorphs are available, the overall results and some detailed comparisons with calculated lattice energies confirm the good performance of the parameters of the crystal potential. A tentative polymorph for aspirin is proposed by a structure generation procedure. The occurrence of polymorphism in organic crystals is very frequent, if the proper temperature range is explored, but at room conditions, the appearance of several polymorphic forms is not as pervasive as it is sometimes said to be.

Introduction and Perspective

Organic molecules are recognizable in condensed phases as being held together by forces which are orders of magnitude stronger than those acting outside them. By allowing for conformational variance, usually torsional, and for minor valence tautomerism, we define polymorphism in this paper as the appearance of different crystal structures for the same molecule.

This phenomenon, sometimes elusive,[1] has been of considerable interest to crystal chemists for a long time; there is still dispute on whether it is pervasive,[2] or restricted to a few cases, under unusual temperature or pressure conditions. The focus of this paper is on the possible coexistence of polymorphs at room temperature and pressure conditions, rather than on the solid-state phase diagrams of the materials.

Conformational polymorphism has been studied over the years by Bernstein and co-workers,[3] in connection with the effect of crystal environment on molecular structure. On the computational side, calculations on energy differences betwween polymorphs[4] and attempts at crystal structure prediction for polymorphs[5] have appeared.

The phenomenon is actively studied in pharmaceutical sciences[6,7] because of the relevance of crystal form to bioavailability and to the mechanical and rheological properties of formulations; a very large experimental effort has been devoted to the characterization of drug polymoprhs.[8−10] Powder X-ray analysis is routinely performed, but only in very few instances could single-crystal X-ray determinations be carried out, since it is usually difficult to grow suitable crystals for all polymorphs.[9b] In fact, work without the support of such determinations may be contaminated by undetected solvation, amorphous materials, and even mistaking different crystal habits for different polymorphs. Inconsistent nomenclature of the polymorphs by different authors is common, due to inconsistent characterization.[11]

Dissolution studies are also routinely conducted.[12] The thermodynamic part of such work carries in principle information on relative stabilities of polymorphs, but kinetic results are sensitive to experimental conditions (solvent, pH, sample

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(1) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193.

(2) Haleblian, J.; McCrone, W. *J. Pharm. Sci.* **1969**, *58*, 911.

(3) See: Bernstein, J.; Bar, I. *J. Phys. Chem.* **1984**, *88*, 243 and references therein. Bernstein, J. In *Organic Crystal Chemistry*; Garbarczyk, J. B., Jones, D. W., Eds.; International Union of Crystallography Book Series, Oxford University Press: Oxford, U.K., 1991; Chapter 2, pp 6−26. Bernstein, J. *J. Phys. D Appl. Phys.* **1993**, *26*, B66.

(4) (a) Berkovitch-Yellin, Z.; Leiserowitz, L. *J. Am. Chem. Soc.* **1982**, *104*, 4052. (b) Ellern, A.; Bernstein, J.; Becker, J. Y.; Zamir, S.; Shahal, L. *Chem. Mater.* **1994**, *6*, 1378 and references therein. (c) Royer, J.; Decoret, C.; Tinland, B.; Perrin, M.; Perrin, R.; *J. Phys. Chem.* **1989**, *93*, 3393.

(5) (a) Bernstein, J.; Sarma, J. A. R. P.; Gavezzotti, A. *Chem. Phys. Lett.* **1990**, *174*, 361. (b) Gavezzotti, A.; Filippini, G. Synth. Metals **1991**, *40*, 257. (c) Braga, D.; Grepioni, F.; Orpen, A. G. *Organometallics* **1994**, *13*, 3544. (d) Gavezzotti, A. *Acc. Chem. Res.* **1994**, *27*, 309 and references therein. (e) Gavezzotti, A. *J. Am. Chem. Soc.* **1991**, *113*, 4622. (f) Filippini, G.; Gavezzotti, A. *Chem. Phys. Lett.* **1994**, *231*, 86. (g) Gavezzotti, A. *Acta Crystallogr.* **1995**, in press. (h) Karfunkel, H. R.; Gdanitz, R. J. *J. Comput. Chem.* **1992**, *13*, 1171. (i) Perlstein, J. *J. Am. Chem. Soc.* **1994**, *116*, 11420. (l) Van Eijck, B. P.; Moij, W. T. M.; Kroon, J. *Acta Crystallogr.* **1995**, *B51*, 99.

(6) For general reviews, see ref 2 and also: (a) Haleblian, J. K. *J. Pharm. Sci.* **1975**, *64*, 1269. (b) Sato, K. *J. Phys. D. Appl. Phys.* **1993**, *26*, B77. (c) Borka, L.; Haleblian, J. K. *Acta Pharm. Jugosl.* **1990**, *40*, 71 with a list of hundreds of pharmaceuticals exhibiting polymorphism and 529 refs. (d) Borka, L. *Pharm. Acta Helvetiae* **1991**, *1*, on crystal polymorphism of substances in the European Pharmacopeia. (d) Byrn, S. R. *Solid State Chemistry of Drugs*; Academic Press: New York, 1982.

(7) For the thermodynamic aspects, see: (a) Burger, A. In *Topics in Pharmaceutical Sciences*; Breimed, D. D., Speiser, P., Eds.; Elsevier: 1983. (b) Burger, A. *Pharm. Int.* **1982**, *3*, 158.

(8) For thermoanalytical and infrared work, see the extensive work by Kuhnert-Brandstaetter and co-workers: Kuhnert-Brandstaetter, M.; Sollinger, H. W. *Mikrochim. Acta (Wien)* **1990**, *3*, 247 and previous papers.

(9) For multitechnique studies (microcalorimetry, IR, powder X-ray, solubility), see for example: (a) Burger, A.; Griesser, U. *Eur. J. Pharm. Biopharm.* **1991**, *37*, 118. (b) Burger, A.; Lettenbichler, A. *Pharmazie* **1993**, *48*, 262.

(10) (a) For sulfathiazole, one of the best studied cases, see: Anwar, J.; Tarling, S. E.; Barnes, P. *J. Pharm. Sci.* **1989**, *78*, 337. (b) For sulfonamides: Yang, S. S.; Guillory, J. K. *J. Pharm. Sci.* **1972**, *61*, 26.

(11) For cimetidine, for example: (a) Shibata, M.; Kokubo, H.; Morimoto, K.; Morisaka, K.; Ishida, T.; Inoue, M. *J. Pharm. Sci.* **1983**, *72*, 1436. (b) The structure of a "novel" phase was studied by X-rays: Parkanyi, L.; Kalman, A.; Hegedus, B.; Harsanyi, K.; Kreidl, J. *Acta Crystallogr.* **1984**, *C40*, 676, while the same phase had been reported earlier, see ref 11a. For sulfathiazole, see ref 10a.

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preparation, grinding, and stirring speed), as well as to crystal morphologies. Complex equilibria between polymorphic forms are often established in solution, and interconversions are frequent.[13] Free energy differences calculated from ratios of equilibrium solubilities may be smaller than those obtained from packing energy calculations or from differences in melting enthalpies, as the equilibria may be in fact between solute and an unknown admixture of solid phases.

Tailor-made stereospecific additives have been used to induce crystallization of unstable polymorphs;[14] the optical properties of polymorphs have been studied,[15] although the specific relationship between the solid-state property (for example, crystal color[15a]) and the solid-state structure is not always clear. Connections betwen polymorphism and morphology have been investigated.[16]

Polymorphism has been mainly studied in its phenomenological aspects, while its structural and energetic aspects have been alluded to in diverse fields of research, but, in spite of a large body of data, have never been considered in a systematic way. The reasons for undertaking a systematic study of crystal polymorphism are of both theoretical and practical nature; being the outcome of different applications of the same cohesive forces, it should provide better information on these forces than the study of single forms; the prediction of crystal structures is, in fact, an extended study in polymorphism, supplemented by methods for deciding which of the many likely structures a crystal will adopt.[5d] The control of crystal polymorphism has practical advantages in many branches of the chemical industry, in fact, all those which deal with the organic solid state.[5d]

We tackle the problem in our usual manner,[17,18] that is, by retrieving information from already described structures through use of the Cambridge Structural Database[19] (CSD). Such an approach has many limitations and biases but is the only one that allows a statistical treatment of hundreds of compounds.

Sample Selection and Adaptation

The CSD has been searched for complete X-ray crystallographic structural determinations of more than one polymorphic form, at room temperature and with comparable refinement accuracy. Atomic species considered were C, H, N, O, F, Cl, and S in any combination, admitting almost any connectivity and any type of intermolecular interaction (see the discussion of the intermolecular force field). Hydrogen atoms were, as usual, positioned using geometrical criteria.[18] $-NH_2$ groups often show substantial pyramidalization, especially in sulfonamides; we have chosen to standardize their location in a planar conformation, with 120° angles, having checked that this procedure does not alter the relative energies of polymorphs and does not produce significant repulsive intermolecular interactions. The only exception is sulfathiazole, for which crystallographic coordinates had to be used to avoid significant repulsions.

A group of two or more polymorphs will be called a cluster. A total of 163 clusters were eventually accepted, 147 of them with two, 13 with three, and three with four partners, for a total of 345 crystal structures. Assuming that the number of crystal polymorphs fully characterized by X-ray diffraction is but a small percent of the total occurrences of the phenomenon, this is a first evidence of the high frequency of polymorphism in organic crystals. Besides, a large number of single structures carry the "form" or "polymorph" qualifier in the CSD and, thus, have polymorphic partners whose crystal structures were not determined (in some instances, polymorphs do not carry the proper tag in the database, since polymorphism was not explicitly mentioned in the original paper). Table S1 (deposited as supporting information) contains the CSD refcodes or literature citations for the crystal structures here considered.

Since one of the most important quantities which determine crystal structures is the calculated lattice energy, we discuss briefly the force field (FF) used. Its backbone was described in previous papers,[18,20] with empirical parameters for a "6-exp" atom−atom potential optimized for crystals containing C, H, N, O, S, and Cl atoms including hydrogen bonds in monofunctional alcohols, carboxylic acids, and amides, as well as the N−H···N hydrogen bond. Parameters for the N−H···O hydrogen bond in nitro−amino derivatives[5f] and for F···F interactions[21] have been also recently obtained. Since the molecules to be considered here are polyfunctional, with a wide variety of chemical functions, several adaptations and averages were devised to upgrade the FF. A few zwitterions were considered, while the FF parameters were not calibrated for charged species. The complete FF is collected in Table S2 (deposited).

The lattice-vibrational entropy was calculated by standard lattice-dynamical procedures;[22] here, FF parameters are more critical, and for some structures, imaginary roots of the dynamical matrix were found, so that the vibrational entropy could not be calculated. Minor structure optimization shifts might have removed many of these singularities,[17,18] but an exhaustive treatment was not attempted.

Polymorphic structures in each cluster were arranged in order of decreasing density (as calculated from the X-ray cell volume). Differences in molecular and crystal properties between cluster members i and j were then calculated as

$$\Delta P = P_j - P_i \quad \text{or} \quad \Delta P = 100(P_j - P_i)/P_j \quad (j < i)$$

Each n-membered cluster supplies $n(n-1)/2$ Δ's, so that the total number of Δ data points is 204. Density differences are positive by definition. Other differences may be negative or positive; a list follows:

- ΔD density (molecular mass/cell volume, %)
- ΔV molecular volume (%)
- ΔK Kitaigorodski packing coefficient (molecular volume[23]/cell volume, %)
- ΔE packing energy (%)

(12) A few examples: (a) Amobarbital: Kato, Y.; Kohketsu, M. *Chem. Pharm. Bull.* **1981**, *29*, 268. (b) Cimetidine: ref 11a. (c) Furosemide: Matsuda, Y.; Tatsumi, E. *Int. J. Pharm.* **1990**, *60*, 11. (d) Tegafur: Uchida, T.; Yonemochi, E.; Oguchi, T.; Terada, K.; Yamamoto, K.; Nakai, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1632. (e) Sulfamethoxypyridazine: Rambaud, J.; Maury, L.; Pauvert, B.; Lasserre, Y.; Berge, G.; Audran, M.; Declercq, J. P. *Il Farmaco* **1985**, *40*, 152.

(13) (a) Phenylbutazone: Kaneniwa, N.; Ichikawa, J.; Matsumoto, T. *Chem. Pharm. Bull.* **1988**, *36*, 1063. (b) Indomethacin: Kaneniwa, N.; Otsuka, M.; Hayashi, T. *Chem. Pharm. Bull.* **1985**, *33*, 3447.

(14) Staab, E.; Addadi, L.; Leiserowitz, L.; Lahav, M. *Adv. Mater.* **1990**, *2*, 40.

(15) (a) Toma, P. H.; Kelley, M. P.; Borchardt, T. B.; Byrn, S. R.; Kahr, B. *Chem. Mater.* **1994**, *6*, 1317. (b) Serbutoviez, C.; Nicoud, J.-F.; Fischer, J.; Ledoux, I.; Zyss, J. *Chem. Mater.* **1994**, *6*, 1358.

(16) Davey, R. J.; Maginn, S. J.; Andrews, S. J.; Black, S. N.; Buckley, A. M.; Cottler, D.; Dempsey, P.; Plowman, R.; Rout, J. E.; Stanley, D. R.; Taylor, A. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1003.

(17) Filippini, G.; Gavezzotti, A. *Acta Crystallogr.* **1992**, *B48*, 230.

(18) Gavezzotti, A.; Filippini, G. *J. Phys. Chem.* **1994**, *98*, 4831.

(19) Data for the present work are from the 1993 release. See: Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, C. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. J.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331. See also: Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 1631.

(20) Filippini, G.; Gavezzotti, A. *Acta Crystallogr.* **1993**, *B49*, 868.

(21) Filippini, G.; Gavezzotti, A. Unpublished work.

(22) Filippini, G.; Gramaccioli, C. M. *Acta Crystallogr.* **1986**, *B42*, 605.

(23) Kitaigorodski, A. I. *Organic Chemical Crystallography*; Consultants Bureau: New York, 1961.

ΔH packing energy (enthalpy and energy are assumed to coincide, as a result of the force field optimization procedure), kJ/mol

ΔS lattice-vibrational entropy, J/(K·mol)

ΔG free energy, $= \Delta H - 300\Delta S$, kJ/mol

$\Delta Z'$ number of molecules in the asymmetric unit (Z' was reduced to an integer number, when the asymmetric unit consisted of fractions of a molecule, by using the appropriate crystallographic subgroup)

$\Delta I = (\Delta I_x^2 + \Delta I_y^2 + \Delta I_z^2)^{1/2}$, the ΔI_i's being percent differences between the moments of inertia of the molecule (calculated with reference to the principal axes in each conformation) in the two crystal forms.

ΔH refers to intermolecular energies only. ΔG was estimated as the balance between ΔH and ΔS at 300 K. While the theoretical basis for such an assumption is very shaky, we justify it at least partially by remembering that the FF parameters were explicitly calibrated to reproduce room temperature thermodynamic and structural properties of organic crystals.

Results and Discussion

ΔD and $\Delta Z'$ are parameter-free quantities and depend only on the accuracy of the X-ray work. For ΔH and ΔS, comparison with experiment is possible when fusion or sublimation enthalpies are available for all polymorphs—a very unlikely occurrence for sublimation, less so for fusion. A problem arises when the molecule has largely different conformations in the two polymorphs because the conformational energy difference comes into play; the temperature dependence of these ΔH's is also problematic (again, less so for fusion). Heats of polymorphic phase transition determined from areas of DSC peaks may be unreliable due to sample history and to the detailed mechanism of the transition, which may not be a quantitative, crystal-to-crystal one. Another source of enthalpy differences between polymorphs (at least in principle) is van't Hoff treatment of solubility data, giving access to dissolution enthalpies.

(a) Monovariate Statistics. Figure 1 shows histograms of ΔD, $|\Delta E|$, $|\Delta S|$, and $|\Delta Z'|$. The difference in crystal density between polymorphs seldom exceeds a few percent (93% of the ΔD's are $< 5\%$). All structures are close-packed, since molecules arrange themselves in different ways, but never at the expense of a substantial decrease in compactness. Cases with $\Delta D > 7\%$ may in part be due to undetected inaccuracy in crystal structure determinations or to special reasons: for one outlier with $\Delta D = 12\%$ (CSD refcode TORSEM), a proton transfer tautomery and a large conformational change appear between the two forms. A density difference of 8.8% has been quoted[9a] as a clear exception.

Similar conclusions are drawn by inspection of the ΔE histogram. A few outliers may depend on undetected disorder or slightly inaccurate positioning of some key atoms in the X-ray experiments. Eighty five percent of the ΔE's are within 10%, in agreement with previous experience.[5] Typical values of lattice energies being 100−200 kJ/mol, 25 kJ/mol is the upper limit for the difference. If conformational energy differences compensate for less favorable packing energies, true enthalpy differences between polymorphs may be even smaller.

Lattice-vibrational entropy differences are also very small. To some extent, this is because lattice vibration frequencies invariably fall within a rather narrow range (10−150 cm^{-1}) for the substances considered here and, indeed, for most if not all organic crystals. We assume differences in internal vibrational entropy to be negligible, which is certainly true for rigid molecules, less so for conformationally flexible molecules. Also neglected is the possible coupling of intra- and intermolecular modes. The typical value for the vibrational entropy of an organic crystal is between 85 and 130 J/(K·mol), and differences never exceed 15 J/(K·mol).

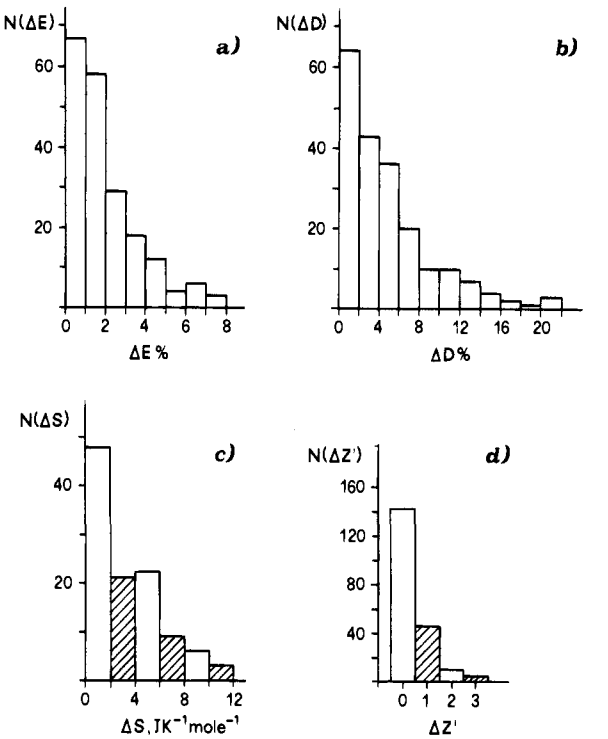

Figure 1. Histograms of differences in properties between polymorph pairs: (a) ΔE (packing energy, %), (b) ΔD (density, %), (c) ΔS (lattice-vibrational entropy, J K^{-1} mol^{-1}), (d) $\Delta Z'$ (number of molecules in the asymmetric unit).

More intriguing are the results on the number of molecules in the asymmetric unit, Z'. Sixty two structures (18%) have $Z' > 1$, and 46 clusters (28%) have one partner with $Z' = 1$ and at least one partner with $Z' > 1$. These values are certainly higher than the overall percentage in the CSD, which is 8.3;[24] thus, the occurrence of $Z' > 1$ in at least one member of polymorph clusters is rather common. In the search for different molecular arrangements in the solid, crystal compactness is preserved at the expenses of crystal symmetry, and not vice-versa.

(b) Bivariate Statistics. There is a very strict, and expected, linear correlation between ΔD and ΔK, with unit slope. This implies that differences in molecular volume are very small; the very few outliers have been traced back to slight valence tautomerism or to extensive conformational rearrangement between molecules in the two phases.

The ΔD vs ΔE scatter plot (Figure 2) shows that in most cases a higher packing energy goes with a higher density, although one can hardly speak of a true correlation. This result confirms the general rule that the more dense the polymorph, the lower its internal energy (here assumed to be represented by the packing energy). Outliers with higher energy and lower density could not be traced to have unusually strong and directional intermolecular hydrogen bonds; most of them belong to classes of compounds for which some crucial H-atom positions (alcohols, NH_2) were inaccurately located in the X-ray work. Some large ΔE's correspond to couples in which one partner had a large crystallographic R factor. In a few cases, ΔE is off balance because one polymorph has an intramolecular hydrogen bond not included in the calculated intermolecular energy. To summarize, apparent deviations from the general rule are affected by a large experimental or computational noise.

(24) Padmaja, N.; Ramakumar, S.; Viswamitra, M. A. *Acta Crystallogr.* **1990**, *A46*, 725.

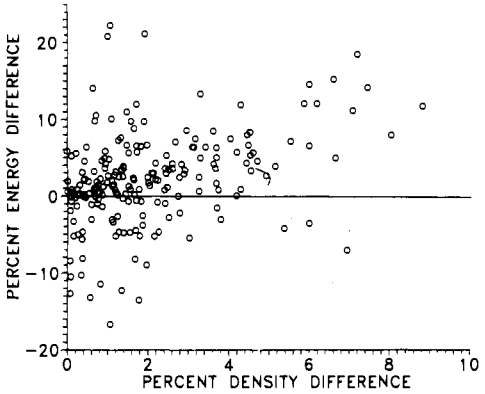

Figure 2. Scatter plot of differences in density (ΔD, %) and in packing energy (ΔE, %) between polymorph pairs. One outlier with ΔD = 12% not shown (see text).

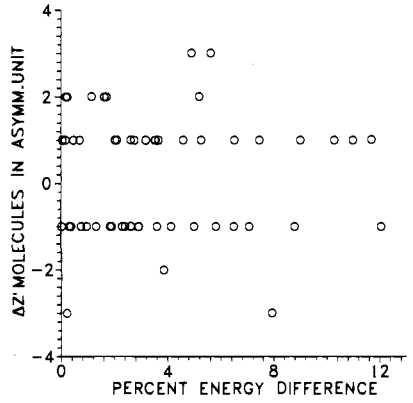

Figure 3. Scatter plot of differences in packing energy (ΔE, %, absolute value) and in number of molecules in the asymmetric unit ($\Delta Z'$) between polymorph pairs (only for $\Delta Z' \neq 0$).

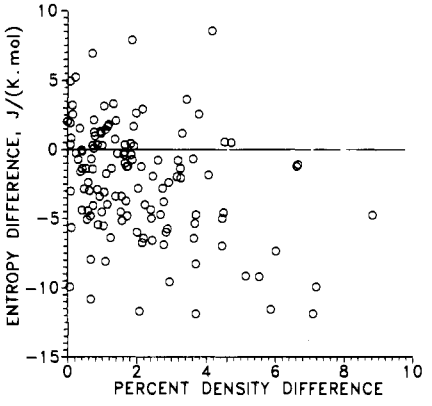

Figure 4. Scatter plot of differences in density (ΔD, %) and in lattice-vibrational entropy (ΔS) between polymorph pairs.

The $\Delta Z'$ vs ΔE plot is shown in Figure 3. The structure with $Z' > 1$ is more stable in about 50% of the occurrences. Therefore, having more than one molecule in the asymmetric unit is not detrimental to crystal stability. No clear trends in $\Delta Z'$ vs ΔS could be detected.

Figure 4 shows that higher density is mostly associated with lower entropy, as expected. Although no information on transition temperatures is normally available in our collection, according to a general rule, the form with lower density, smaller packing energy, and higher entropy should be stable at higher temperatures. As already suggested in the discussion of monovariate statistics, entropy differences are never large enough to have $300\Delta S$ exceed ΔH (Figure 5). Within our approximations, we conclude that the relative stability among polymorphs at room temperature can be judged on the basis of packing energy (enthalpy) alone.

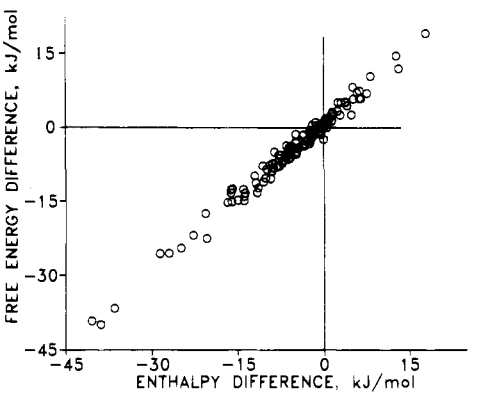

Figure 5. Free energy (ΔG) versus enthalpy (lattice energy) differences between polymorph pairs.

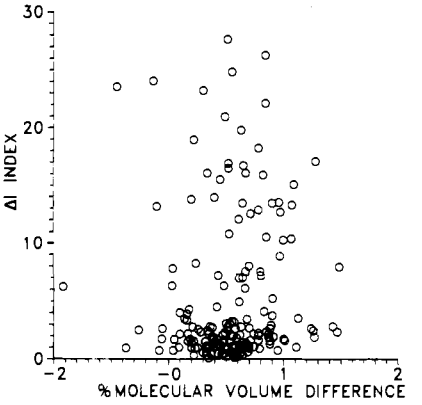

Figure 6. Scatterplot of the ΔI index (see text for definition) versus differences in molecular volume (ΔV, %) between polymorph pairs. A few points with very large ΔI not shown.

Figure 6 shows the ΔI vs ΔV plot. Molecular volume is only scarcely sensitive to conformational differences. Inspection of the molecular structures confirms that a large ΔI is an indicator of conformational polymorphism—although a small ΔI may not rule it out. We propose a threshold of ΔI = 10 for the occurrence of conformational polymorphism.

(c) Coordination Sphere in the Crystal. Polymorphs may be considered as different conformers of the supramolecule which is the crystal structure itself; as such, they should be identified by a few overall structural or energetic parameters. Geometrical data can sometimes help, like when different hydrogen bonding schemes are detected.

For obvious reasons of nonuniqueness, cell dimensions are not appropriate parameters for quantitative comparisons. The space group is the same for 28% of the polymorphic pairs (7% with a different Z'). Eighty two percent of these space group retentions were in $P2_1/c$, the rest being divided between $P\bar{1}$, *Pbca*, $C2/c$, and $P2_12_12_1$. $P2_1/c$ confirms here its role of favorite for organics and appears also as the one space group which most easily allows for different choices of spatial arrangement for the same molecule. Quite often, one of the polymorphs has $Z' > 1$ in a subgroup of the space group of the partner with $Z' = 1$; although a detailed analysis of such cases cannot be presented here for conciseness, a preliminary consideration of the data reveals some instances in which the partners in the asymmetric unit are correlated by pseudosymmetry.

Twenty four percent of the polymorphic couples comprise a centrosymmetric and a non-centrosymmetric partner; most frequent (10 cases) is the $P2_1/c$–$P2_12_12_1$ pair, followed by $P2_1/c$–$P2_1$ (six cases) and $P2_1/c$–$Pna2_1$ and $P2_1/c$–Pc (four cases each). Apparently, many molecules can freely choose between crystal centrosymmetry and non-centrosymmetry. There is no sign of trends in density with respect to the presence or absence

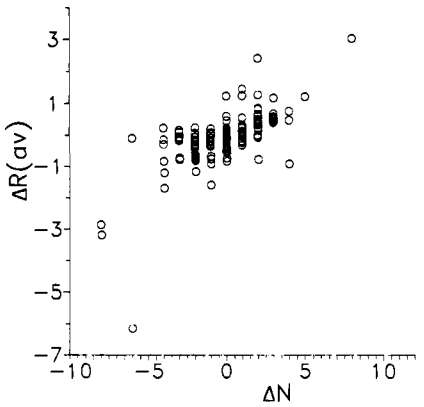

Figure 7. Scatter plot of differences in average coordination distance (ΔR_{av}, Å) and in number of molecules in the coordination sphere (ΔN) between polymorph pairs. Structures with $Z' = 1$ only.

of the inversion center in the crystal. Polymorphism is in many ways akin to the different crystallization of enantiomers and racemates:[25] there, too, no clear trends as regards crystal density were found.[25a]

Looking for broader structure determinants, we resort to the old definition of coordination sphere in the crystal.[26,27] The total lattice energy was partitioned into contributions (E_j) between a reference molecule and each of the surrounding ones. The coordination sphere is defined as the collection of N molecules for which $E_j > 5\%$ of the total lattice energy; each of these molecules is also identified by a symmetry operator, O_j, by which it is related to the reference one, and by the distance, R_j, between its center of mass and that of the reference one. A structure determinant can then be written as

$$N;\ (E_1, O_1, R_1);\ (E_2, O_2, R_2);\ \ldots\ (E_N, O_N, R_N)$$

When $Z' > 1$, there is no symmetry operator between partners in the asymmetric unit. The structure determinant can be written in the same way, however, designating the asymmetric relationship between the m molecules A, B, C ... in the asymmetric unit as AB, AC, BC ..., and so on. The number of molecules in the coordination sphere, N, loses some of its meaning, there being in fact m separate coordination spheres, and hence it is omitted; the percent contributions, E_j, sum up to $m \times 100$. Care must be exerted when the asymmetric unit is a fraction of a molecule, since the operator is not uniquely defined (in a typical example, for a molecule located on a crystallographic center of symmetry, inversion and translation, or screw and glide, operators are undistinguishable).

A large N value, along with small E_j's and large R_j's, is indicative of a scattered coordination sphere,[27] while the opposite is indicative of a compact coordination sphere. The average coordination distance, R_{av}, is defined as the average of the R_j's. ΔN and ΔR_{av} are the corresponding differences between polymorphic structures. Figure 7 shows the expected rough correlation between ΔN and ΔR, but the choice of packing pattern is wide: polymorphs exist with the same number of molecules in the coordination sphere ($\Delta N = 0$), but with a difference in average distance as large as 1 Å; or with large values of both ΔN and ΔR, implying that the molecule may take up both a scattered or a compact coordination sphere without significant variation in crystal stability, since no correlation was found between either ΔN or ΔR and the difference in packing energy.

(25) (a) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811. (b) Weissbuch, I.; Kuzmenko, I.; Vaida, M.; Zait, S.; Lieserowitz, L.; Lahav, M. *Chem. Mater.* **1994**, *6*, 1258.

(26) Kitaigorodski, A. I. *Molecular Crystals and Molecules*; Academic Press: New York, 1973.

(27) Gavezzotti, A. *Acta Crystallogr.* **1990**, *B46*, 275.

Table 1. Experimental Thermodynamic Parameters for Polymorphic Transformations (kJ/mol and J/(K·mol))

		ΔH		ΔS	
compd	forms	van't Hoff	calorim.	van't Hoff	calorim.
sulfamethoxypyridazine[a]	I/III	5.04	10.27[b]	11	
progesterone[c]	α/β	4.8		4.4	
chlorpropamide[d]	II/A	10.0		25	
(α-bromoisovaleryl)urea[e]	I/II	4.5		13	
	I/III	3.0		10	
acetazolamide[f]	A/B	2.6		7.2	
furosemide[g]	III/VI		1.2[h]		
	II/VI		2.0[h]		
	I/VI		2.6[h]		
cyclopenthiazide[i]	I/II	0.2			
	I/III	9.1			
phenylbutazone[j]	α/δ	0.7	7.9[b]	3	24
	α/β	3.9	9.5[b]	11	27
phenobarbital[k]	II/IIBa	1.0		3	
	II/IIICy	3.9		12	
sulphamethoxydiazine[l]	II/III	5.9		16	
glibenclamide[m]	I/II	10.2			
sulfamerazine[n]	I/II		1.4[h]		
piracetam[o]	II/III		0.6[b]		
thalidomide[p]	I/III		1.5[b]		
carbamazepine[q]	β/α		1.2[b]		
sulfanilamide[r]	II/I		1.8[h]		
	III/I		2.1[h]		
sulfapyridine[s]	I/III		2.3[h]		
	I/V		3.2[h]		
	I/IV		6.5[h]		

[a] Reference 12e. [b] From differences in ΔH_m. [c] Muramatsu, M.; Iwahashi, M.; Takeuchi, U. *J. Pharm. Sci.* **1979**, *68*, 175. [d] Ueda, H.; Nambu, N.; Nagai, T.; *Chem. Pharm. Bull.* **1984**, *32*, 244. [e] Kojima, H.; Kiwada, H.; Kato, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1824. [f] Umeda, T.; Ohnishi, N.; Yokoyama, T.; Kuroda, T.; Kita, Y.; Kuroda, K.; Tatsumi, E.; Matsuda, Y. *Chem. Pharm. Bull.* **1985**, *33*, 3422. [g] Reference 12c. [h] From area of DSC transition peak. [i] Gerber, J. J.; vanderWatt, J. G.; Lotter, A. P. *Int. J. Pharm.* **1991**, *73*, 137. [j] Reference 13a. [k] Kato, Y.; Okamoto, Y.; Nagasawa, S.; Ishihara, I. *Chem. Pharm. Bull.* **1984**, *32*, 4170. [l] Reference 28. [m] Suleiman, M. S.; Najib, N. M. *Int. J. Pharm.* **1989**, *50*, 103. [n] Caira, M. R.; Mohamed, R. *Acta Crystallogr.* **1992**, *B48*, 492. [o] Kuhnert-Brandstaetter, M.; Burger, A.; Voellenklee, R. *Sci. Pharm.* **1994**, *62*, 307. [p] Caira, M. R.; Botha, S. A.; Flanagan, D. R. *J. Chem. Crystallogr.* **1994**, *24*, 95. [q] Lowes, M. M. J.; Caira, M. R.; Loetter, A. P.; Van Der Watt, J. G. *J. Pharm. Sci.* **1987**, *76*, 744. [r] Burger, A. *Sci. Pharm.* **1973**, *41*, 290. [s] Burger, A.; Schulte, K.; Ramberger, R. *J. Therm. Anal.* **1980**, *19*, 475.

(d) Detailed Comparisons. Table 1 collects some experimental values of enthalpy and entropy differences, from several measurement techniques. All of these data fall within the range observed in the corresponding calculated quantities, a confirmation of the reasonable performance of the potential parameters in our crystal force field. Whenever relative stability is mentioned in the following discussion, reference is made to enthalpy (not to free energy).

For cimetidine, conformational polymorphism appears ($\Delta I = 16$). The melting enthalpy for the A phase (refcode CIMETD) is larger than that of other forms, as measured by DSC peak areas, but the A phase is the most soluble among the non-hydrated forms.[11a] The calculated intermolecular interaction energy for form D (refcode CIMETD01) is larger (by 10%, or 21 kJ/mol), but form A has an intramolecular hydrogen bond worth just about that energy difference. Form A is said to be the only one for which a reproducible preparation and unique precipitation is observed.[11b] For progesterone, qualitative and almost quantitative (ΔH(calcd) = 6.3 kJ/mol) agreement between calculation and experiment for the relative stability of forms is obtained. Both crystal structures are

$P2_12_12_1$, $Z = 4$, but their structure determinants are different (S = screw, T = translation):

PROGST01 (β) 8; 2(13, S, 8.6); 2(11, T, 6.3); 2(10, S, 6.6); 2(6, S, 12.4)

PROGST10 (α) 6; 2(16, S, 6.2); 2(12, S, 8.5); 2(6, S, 8.7)

The β-polymorph thus has a more open coordination sphere, with insertion of an extra couple of translation-related molecules, according to the presence of a short (6.3 Å) cell axis.

Tegafur[12d] (5-fluoro-1-(tetrahydro-2-furyl)uracil) is a typical borderline case. The α-polymorph (refcode (BIPDEJ; $P\bar{1}$, $Z = 4$) is calculated to be more stable by 2.9 kJ/mol, but the calculated entropy of the β-polymorph (refcode BIPDEJ02; $P2_1/c$, $Z = 4$) is lower by 5.0 J/(K·mol), in agreement with the higher (1.2%) density. These are all small numbers, and accordingly, the dissolution rate constants of the two forms in water at 37 °C are very similar (9.5×10^{-7} vs 11×10^{-7} mol/min).[12d] The structure determinants of the two forms are considerably different. Both forms apparently transform to a third one (γ-form, whose crystal structure is unknown) before melting.

Form II of amobarbital (refcode AMYTAL11; $P2_1/c$, $Z = 8$) is calculated to be more stable than form I (refcode AMYTAL10; $C2/c$, $Z = 8$) by 0.9 kJ/mol and to have a higher (by 3 J/(K·mol)) entropy, hardly significant numbers. The density is the same in both phases, and yet form II dissolves in water at 37 °C 1.6 times faster than form I,[12a] indeed a significant difference. In spite of the difference in space group, the structure determinants are strikingly similar (A = 2-fold axis, I = inversion center, G = glide):

AMYTAL11 (18, AB, 6.4); (15, AB, 7.7); (10, I, 7.3); (10, I, 7.4); (9, AB, 6.7); (8, AB, 7.2); (7, AB, 7.6); (7, AB, 7.5); (6, G, 8.0); (6, G, 8.5)

AMYTAL10 9; (18, A, 6.4); (16, A, 6.7); (11, I, 6.4); (10, I, 7.3); (8, I, 7.5); 2(6, G, 7.7); 2(6, G, 7.9)

Most likely, the closest AB interactions in AMYTAL11 conceive a 2-fold symmetry axis. In any case, there seems to be no connection between differences in structure determinant and differences in energy.

The interconversion of polymorphic forms of sulfamethoxydiazine has been investigated.[28,29] Heating to 150 °C transforms all polymorphs to form I, while form III is obtained in wet conditions. Commercial samples of the drug contain a mixture of forms I and III, but form I changes during storage to form III.[29a] We calculate form III (refcode SAMPYM01; $C2/c$, $Z = 8$) to be more stable than form I (refcode SAMPYM; $P2_1/c$, $Z = 8$) by 6.4 kJ/mol^{-1}, a result which is in general agreement with the stability of form III at room temperature. This form has also a 1% higher density.

Data for the polymorphism of sulfathiazole are collected in Table 2. Calculations agree with experiment[30] that form III is more stable than form I, and almost quantitative agreement is obtained for ΔH. Also the similarity in thermal behavior of forms III and IV[10a] is confirmed by the similar values of the packing energies. The crystal structure of form II is not available, while the CSD reveals a polymorph (called form XXX in Table 2) for which thermochemical data are not available, but is calculated to be the most stable of all (in agreement with its significantly higher density). A comparison of the structure determinants reveals the similarity of forms III, IV, and XXX and the uniqueness of form I. The AB interactions in form II most likely conceive a screw pseudosymmetry.

Table 2. Data for the Polymorphism of Sulfathiazole

refcode	SUTHAZ01	SUTHAZ02	SUTHAZ03	SUTHAZ04
form	I	III	IV	XXX
space group, Z	$P2_1/c$, 8	$P2_1/c$, 8	$P2_1/c$, 4	$P2_1/n$, 4
a, Å	10.554	17.570	8.239	10.867
b, Å	13.220	8.574	8.592	8.543
c, Å	17.050	15.583	15.556	11.456
β, deg	108.06	112.93	86.34	91.87
density, g/cm^3	1.499	1.568	1.543	1.595
PE, kJ/mol	−175	−183[a]	−182[a]	−187[a]
structure determinants				
	24, I, 6.7	19, AB, 6.5	20, S, 6.4	19, S, 6.4
	23, I, 7.0	18, AB, 6.3	20, S, 6.4	19, S, 6.4
	12, AB, 5.1	10, AB, 6.1	10, I, 6.1	9, I, 6.0
	8, AB, 6.8	8, I, 8.2	8, I, 8.2	
	8, AB, 7.4	7, AB, 8.2	7, T, 8.2	7, G, 8.0
	7, G, 8.8	7, AB, 8.0	7, T, 8.2	7, G, 8.0
	6, AB, 8.0	6, AB, 5.8	7, I, 5.8	6, I, 5.9
	6, S, 9.0			6, S, 7.9
				6, S, 7.9

	ΔH, kJ/mol		ΔS(obsd), J/(K·mol)
	obsd[10a]	calcd	
forms I/II	2.6,[b] 2.7[c]		6
forms I/III	6.9,[b] 1.7,[c] 6.9[d]	7.0	7

[a] Hydrogen atoms at NH_2 groups: crystallographic coordinates. These were not available for SUTHAZ01, where it was checked that a planar conformation at NH_2 is energetically favorable. [b] From Arrhenius plots on initial dissolution velocities. [c] From differences in melting enthalpy. [d] From the area of the DSC transition peak.

Table 3. Data on the Conformational Polymorphism of Probucol[a]

form	crystal density[b]	conformational energy[b]	ΔH_m[b]	packing energy
I	1.102	182.8	33.0	−171
II	1.049	209.2	35.1	−163

[a] Density in g/cm^3, energies in kJ/mol. [b] Gerber, J. J.; Caira, M. R.; Loetter, A. P. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 863.

The heats of transformation to form I of sulfanilamide from forms II and III have been accurately measured (Table 1); our calculated values of enthalpy differences are 16 and 15 kJ/mol, respectively. Thus, calculation agrees with experiment that form I is the less stable one and that forms II and III are of comparable stability, although absolute values are not reproduced. On the contrary, for sulfapyridine the calculated order of stability is IV > II > V > III, at complete variance with the order resulting from thermochemical measurements (see Table 1). In this case, however, large conformational differences between polymorphs appear; besides, form V is quoted as having a density of 1.458 g/cm^3 in the thermochemical work, while crystallographic work assigns this density to form IV (1.456), that of form V being 1.403, too large a deviation to be ascribed to experimental error. Suspiciously enough, the crystal structure of the most stable form (I) has apparently not been determined; some mismatch in the form identification cannot be excluded. Also for sulfamerazine we calculate form I to be more stable than form II by 5.4 kJ/mol, reversing the thermochemical order (see Table 1); here, forms are unequivocally identified since the thermochemical and crystallographic analyses were carried out on the same material in the same study.

For piracetam, form III is calculated to be more stable than form II by 2.5 kJ/mol, in close agreement with thermochemistry (Table 1). In this case thermochemical and crystallographic identification match on the basis of crystal density. Agreement was obtained also for thalidomide (calculated, form I more stable

(28) Moustafa, M.; Ebian, A. R.; Khalil, S. A.; Motawi, M. M. *J. Pharm. Pharmacol.* **1971**, *23*, 868.

(29) (a) Moustafa, M. A.; Khalil, S. A.; Ebian, A. R.; Motawi, M. M. *J. Pharm. Pharmacol.* **1972**, *24*, 921. (b) Bettinetti, G. P.; Giordano, F.; La Manna, A.; Giuseppetti, G. *Il Farmaco Ed. Pratica* **1974**, *29*, 493.

(30) Lagas, M.; Lerk, C. F. *Int. J. Pharm.* **1981**, *8*, 11.

Table 4. Calculated Structures for Aspirin[a]

space group	cell parameters						lattice energy	cell volume	density
	a	*b*	*c*	α	*β*	γ			
$P\bar{1}$	6.75	8.70	7.64	81.9	75.7	77.1	−113	421.9	1.417
	6.72	7.47	10.68	87.3	126.7	92.8	−113	428.7	1.394
	10.59	8.69	9.03	91.9	120.2	44.4	−113	422.5	1.415
$P2_1/c$	12.34	4.55	15.49		99.5		−107	858.9	1.392
	12.35	4.88	14.82		79.0		−108	876.0	1.364
	10.16	7.24	12.12		86.7		−106	890.2	1.342
	11.07	6.62	11.04		89.8		−123	809.9	1.475
X-ray[b] ($P2_1/c$)	11.05	6.61	10.98		90.3		−123	801.6	1.491

[a] Energies in kJ/mol, cell parameters in Å and degrees, densities in g/cm^3, cell volumes in Å^3. [b] Reference 33.

than form III by 5.0 kJ/mol) and for carbamazepine (calculated, *β* more stable than α by 10 kJ/mol; see Table 1 for experimental data). For probucol, conformational polymorphism appears (Table 3); form I has a larger packing energy, in keeping with its higher melting point and density, and is predicted to be more stable than form II by 33 kJ/mol (the sum of the differences in conformational and packing energy), consistent with the transformation of form II into form I both in solution and upon grinding. Somewhat unexpected is the higher melting enthalpy of form II; the composition of the conformational equilibrium in the melt is of course unknown.

(e) A Case Study: Aspirin. Polymorphism in aspirin has been announced and then discarded in favor of morphology differences between crystals of the same phase.[31] We have generated a number of theoretical polymorphs for aspirin, using a structure−construction procedure[5e] updated and modified.[32] Formation of a centrosymmetric dimer over the carboxylic function has been assumed,[18] and only the most frequent centrosymmetric space groups, $P2_1/c$, $Z = 4$ and $P\bar{1}$, $Z = 2$, have been considered.

The results appear in Table 4 (Table S3, deposited, collects the corresponding atomic coordinates). The X-ray structure[33] has by far the lowest energy and highest density. This structure was promptly generated during the search, testifying the effectiveness of the procedure. From the data in Table 4 and the results of the statistical work so far described, we conclude that only one $P2_1/c$ structure is possible for aspirin, since differences in energy and density with other structures (14 and 9%, respectively) exceed the range usually found in polymorphs. A $P\bar{1}$ structure cannot be ruled out, having $\Delta E = 8\%$ and $\Delta D = 4\%$.

Conclusions

(1) We doubt that quantitative agreement between calculation and experiment for the relative stability of crystal polymorphs could ever be demonstrated, since both calculated and experimental quantities are subject to large uncertainties. The qualitative or semiquantitative agreement presented here is reasonable, meaning that the order of stability of polymorphs (when no large differences in conformational energy are present) is reproduced by packing energy differences calculated with our potential energy parameters, whose possible inaccuracies seem to affect in the same manner all of the polymorphic forms.

(2) Instances where many polymorphic crystal forms can be prepared and handled at room temperature are numerous.[34] However, the thermochemical literature[8,9] shows that many forms appear only under nonstandard or even extreme temperature conditions. The pharmaceutical literature reveals that quite often one form comes out as the most stable and most regularly appearing at laboratory conditions, other forms being even morphologically less attractive (sometimes, amorphous materials and solvates are quoted among the "solid" forms). We confirm anyway that energy differences between forms are small, as clearly demonstrated also by computational work.[5]

(3) In many instances, as exemplified by sulfathiazole, the distinction between polymorphs seems to appear only in the very detailed picture afforded by single-crystal X-ray diffraction methods. Differences in crystallochemical properties between many such "X-ray polymorphs" may be negligible. On the other hand, there is no way of assessing how many of the polymorphs prepared and tentatively identified as such in the pharmaceutical literature may in fact be solvates, conglomerates, or different morphological forms of the same polymorph. The occurrence of polymorphism has been said to be "pervasive",[5d] but if room conditions only are considered, "X-ray" polymorphs are discarded, and even a cautionary percentage of described polymorphs are surmised to be false assignments, a more appropriate adjective would perhaps be "frequent".

(4) Densities, packing energies, and lattice-vibrational entropies are very similar for polymorphic crystal structures; in all cases, free energy differences had the same sign as enthalpy differences.

(5) Polymorphs with more than one molecule in the asymmetric unit ($Z' > 1$) are as stable, or even more stable, than those with one molecule in the asymmetric unit; the chances of having at least one structure with $Z' > 1$ in a polymorph cluster are higher than the occurrence of $Z' > 1$ in general organic crystals.

(6) Higher density goes with higher packing energy and lower lattice vibrational entropy, an expected[34a] result which confirms the good performance of the force-field parameters.

(7) A descriptor of the coordination sphere, the structure determinant, has been defined and can be used for quantitative comparisons between crystal structures. Polymorphs often have widely different coordination spheres, implying that molecules have in some cases a wide choice of spatial arrangements in the solid. Space group $P2_1/c$ is the one in which this choice is apparently wider.

(8) The link between molecular properties and crystal centrosymmetry is apparently weak, as the occurrence of polymorph pairs with one member centrosymmetric and the other non-centrosymmetric is relatively high (24%).

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Supporting Information Available: Table S1 (CSD refcodes and literature citations for crystal structures), Table S2 (parameters of the force field), and Table S3 (cell parameters and atomic coordinates for calculated structures of aspirin) (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(31) Kim, Y.; Matsumoto, M.; Machida, K. *Chem. Pharm. Bull* **1985**, *33*, 4125 and references therein.

(32) Gavezzotti, A. PROMET III, A Program for the Generation of Possible Crystal Structures from Molecular Structure for Organic Compounds. The program is described also in refs. 5d,e.

(33) Kim, Y.; Machida, K.; Taga, T.; Osaki, K. *Chem. Pharm. Bull.* **1985**, *33*, 2641.

(34) (a) One classical example has been given by Dunitz and coworkers: Richardson, M. F.; Yang, Q.-C.; Novotny-Bregger, E.; Dunitz, J. D. *Acta Crystallogr.* **1990**, *B46*, 653. This paper and its references also provide illuminating remarks on the thermodynamics of polymorphism. (b) Browsing through recent issues of *Acta Crystallographica* several instances are found, for example: Jasinski, J. P.; Woudenberg, R. C. *Acta Crystallogr.* **1995**, *C51*, 107. Jasinski, J. P.; Paight, E. S. *Acta Crystallogr.* **1994**, *C50*, 1928 (where "polymorphic" is misnamed as "polymeric").