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A Molecular Dynamics Test of the Different Stability of Crystal Polymorphs under Thermal Strain

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Methods for the computer generation of crystal structures from molecular structure for organic compounds have not yet reached a stage of maturity such as to evolve into real crystal structure predictors. Systematic tests are arduous, and even the best organized effort so far in this direction[1] gave results which can at best be defined as sporadic. Various reasons for this state of affairs have been discussed previously:[2−4] first of all, energy and density differences among different crystal phases (polymorphs) are said to be very small. These computational polymorphs are mostly obtained in what could be called the "static approximation", that is, by lattice energy calculations[5,6] which neglect molecular vibrations. Some of these prediction methods have then reached some success under the assumption that entropy differences are zero and that lattice energy differences are independent of temperature, in oblivion of both principles of thermodynamics.

Molecular dynamics offers a unique opportunity to simulate the structural and energetic evolution of organic crystal structures at a molecular level. Although the calculation of entropies is not straightforward, at least density and energy differences among phases become temperature-dependent, and simulations may even offer a glimpse on the kinetics of crystal dissociation.[7] A comparison of dynamic simulations of different crystal polymorphs under a constant heating protocol is described here, with preliminary evidence that temperature-dependent calculations may help in the prediction of crystal structures which are likely to appear at room conditions.

The crystal structure of coumarin[8] was chosen as a test system, because the molecule is small and rigid, and the UNI force field[9] was adopted because of its simplicity. The particular molecule and polymorphs used are not critical; we are not attempting a quantitative estimate of the properties of the coumarin crystal itself, nor a crystal structure prediction, and we hope that the main features of the general phenomenon studied here, the different response to thermal stress, be independent of any (reasonable) choice of parameters. Only one crystal form of coumarin is known experimentally; therefore, a number of computational polymorphs were generated in the static approximation using Zip-Promet[10] (see Table 1). This required a few minutes human and a few hours CPU time on a personal computer. For example, structure I was sorted and optimized out of 10254 raw structures generated overnight, structure II by stopping the search after just 200 hits, or about 1 h of CPU time. The GROMOS package was then used for the dynamic simulations.[11]

Table 1. The Experimental (X-ray diffraction) and Four Computer-Generated Crystal Structures of Coumarin (cell parameters from the Zip-Promet static simulation)

structure	*a* (Å)	*b* (Å)	*c* (Å)	V_{cell} per molecule (Å^3)	E(MD)[a] (kJ/mol)	E(static)[b] (kJ/mol)
X-ray,[c] $Pca2_1$	15.466	5.676	7.917	173.8		
X-ray, opt[d]	14.87	5.44	8.01	162	93.4	91.5
I, $P2_12_12_1$	7.85	5.80	14.35	164	92.1	90.5
II, $P2_12_12_1$	7.91	6.95	12.13	167	92.2	89.5
III, $P2_12_12_1$	8.67	3.68	21.02	168	90.0	86.7
IV, *Pbca*	18.06	11.06	6.82	170	90.1	87.7

[a] Lattice energy from MD run at 10 K. [b] Lattice energy from Zip-Promet. [c] From ref 8. [d] X-ray structure after lattice energy minimization.

The five crystal structures were first cooled in a 1 ps simulation at 10 K: while the X-ray crystal structure showed a 7% decrease in cell volume, computational polymorphs showed no unit cell shrinkage, confirming that computer-generated structures, having gone through a potential energy minimization, are in fact 0 K structures. Density and energy differences among trial structures are indeed small, hence the difficulties in prediction. The dynamic calculation reshuffles the energy ordering and further lowers energy differences, but as seen in Table 1, density increases with lattice energy.

After several test runs, a heating protocol sweeping across the real melting temperature of the crystal (343 K) was fixed as follows: 10 ps each at 100 and 200 K, then 4 ps at 290 K, followed by 6 and 8 ps at 310 and 330 K; and finally, two 30 ps runs at 350 and 370 K. This procedure combines a somewhat smooth heating rate with a reasonable computing time. Figure 1 shows the evolution of crystal densities with temperature. All simulations duly end at the liquid state with density of about 1.12 g/cm^3 at 370 K, but the melting profiles are quite different. The experimental structure shows signs of melting at, and definitely melts slightly above, the observed melting temperature, while density traces for structures II−IV clearly show incipient melting just above room temperature (for structure IV, a separate 300 ps simulation shows complete melting at 312 K). We are a long way from claiming prediction of melting temperatures, but as far as the relative chances of appearance of possible polymorphs at room conditions are concerned, our calculations show that 0 K energy differences are amplified by the introduction of thermal motion, and that a small difference in 0 K density can have catastrophic consequences on crystal stability when a realistic thermal regime is considered. A "static" 1 kJ/mol lattice energy difference or a "0 K" 4% density difference between polymorphs are indeed small with respect to our ability to reproduce them by simulations, but can be quite significant in their physical consequences.[12] The analysis of heating profiles is thus of potential help in selecting plausible crystal structures and in crystal structure prediction. Although time-consuming, the procedure is practical if only a few top-ranking candidate structures are considered.

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(10) Gavezzotti, A. *Zip-Promet, a Computer Program Package for the Generation of Crystal Structures from Molecular Structure*; University of Milano, 1999 (available from the author upon request). See also: Gavezzotti, A. *J. Am. Chem. Soc.* **1991**, *113*, 4622.

(11) van Gunsteren, W. F.; Billeter, S. R.; Eising, A. A.; Hunenberger, P.-H.; Kruger, P.; Mark, A. E.; Scott, W. R. P.; Tironi, I. G. *Biomolecular Simulation: The GROMOS96 Manual and User Guide*; BIOMOS b.v.: Zürich-Groningen, 1996. As in previous work:[7] intramolecular bond lengths and angles constrained to crystal values, an improper torsion at each trigonal center, no intramolecular nonbonded energy, intermolecular summations truncated at 10 Å; periodic boundary conditions, 96 molecules in the computational box, edges 25−30 Å long (unfortunately, in GROMOS96 pressure coupling works only on orthorhombic boxes, so all polymorphs had to be orthorhombic). Internal and center-of-mass degrees of freedom separately coupled to a thermal bath, pressure (isotropic) at 1 atm (weak-coupling constants 0.1 and 0.5 ps, respectively); integration steps of 2 fs. Low-temperature simulations started by assigning Boltzmann velocities, runs at higher temperatures from the final frame of the simulation at the nearest lower temperature.

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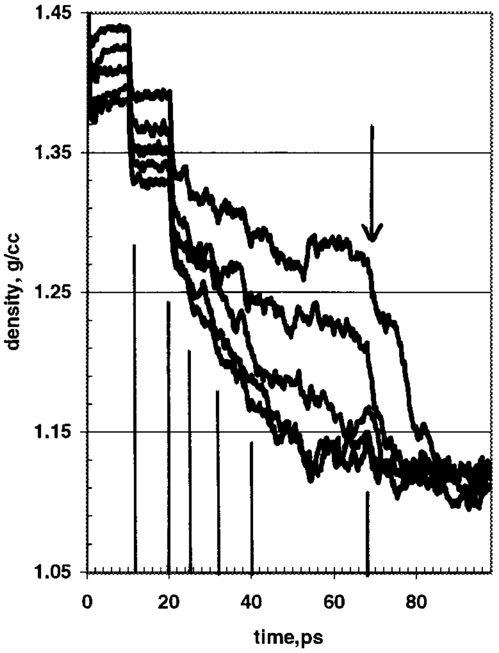

Figure 1. Density as a function of simulation time for structures (top to bottom): experimental, I, II, III, and IV as in Table 1. Vertical bars mark temperature changes (100, 200, 290, 310, 330, 350, 370 K, left to right). The arrow denotes the possible divide between crystalline and liquid structure (see text and Figure 2).

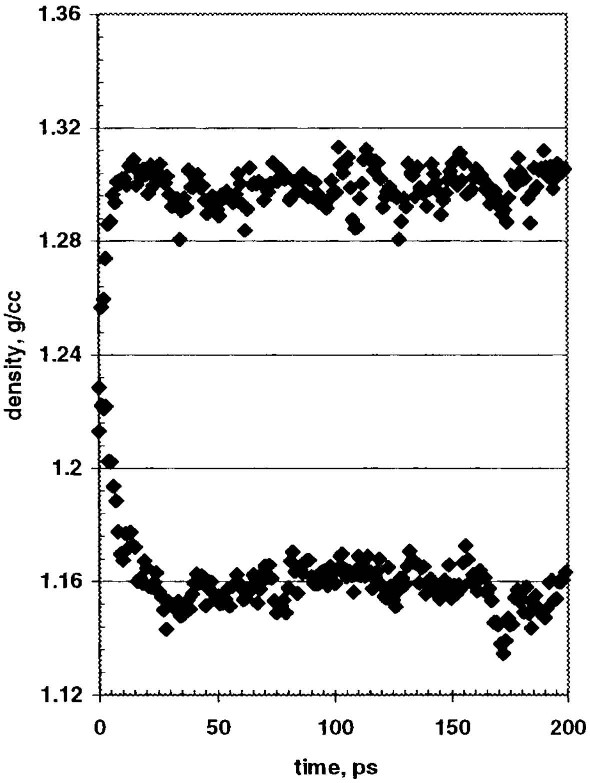

Figure 2. Density evolution during a cool-back simulation at 330 K of frames from the $T = 370$ K simulation of the experimental structure. Top profile: the frame just left of the arrow in Figure 1 evolves back to crystal. Bottom profile: the frame just right of the arrow in Figure 1 evolves to the melt.

The analysis of melting profiles rises a corollary question: is there a clear-cut structural separation between the solid and the liquid state? Frames along the melting step at 370 K for the experimental structure were extracted from the trajectory and cooled back at 330 K for 200 ps. The divide seems to be at a density of 1.22 g/cm^3, with an abrupt change in slope of the density profile, 7 ps after the start of the 370 K simulation (see arrow in Figure 1), because the frame at $t = 6$ ps reverts back to a crystalline structure, while the frame at $t = 8$ ps evolves into the melt (Figure 2). A preliminary visual inspection and search over the distribution of intermolecular distances revealed no major structural differences. A more detailed investigation of the MD picture of the melting catastrophe could reveal some of its thermodynamic and kinetic components, providing further information on crystal stability.

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(12) Melting entropies of organic compounds span the 30−100 J/(K mol) range (Chickos, J. S.; Braton, C. M.; Hesse, D. G.; Liebman, J. F. *J. Org. Chem.* **1991**, *56*, 927), or a ΔT_{melt} of 30−10 K for a 1000 J/mol variation in ΔH_{melt} at constant ΔS_{melt}. We believe that our conclusions are independent of force field and heating protocol, while, admittedly, the argument loses some of its force for high-melting compounds or for highly disordered phases with anomalous ΔS_{melt}.