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Polymorphism in 4′-Hydroxyacetophenone: A Molecular Dynamics Simulation Study

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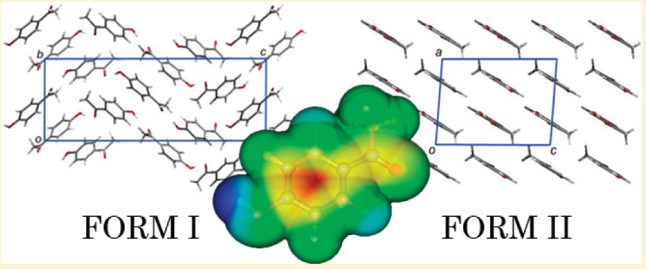
ABSTRACT: A molecular dynamics simulation study of the two known polymorphs of 4′-hydroxyacetophenone (HAP; form I, monoclinic; form II, orthorhombic) is described. The modeling of the lattice energetics was found to be particularly sensitive to the atomic point charge (APC) selection method, to the number of molecules in the asymmetric unit (Z'), and to the flexibility allowed for the molecules. In order to improve the quality of the APCs, a new strategy that attempts to simulate the polarizability effects of the molecules in the crystal lattice was developed. This method relies in the application of the CHelpG methodology to a molecular aggregate with the same spatial arrangement present in the crystal lattice of the compound. This approach led to $\Delta_{trs}H^{o}_{m}(II \rightarrow I) = +2.4 \pm 0.3$ kJ·mol^{-1} and $\Delta_{trs}H^{o}_{m}(II \rightarrow I) = +2.0 \pm 0.9$ kJ·mol^{-1} when rigid and flexible models were used, respectively, in good agreement with the corresponding experimental value $\Delta_{trs}H^{o}_{m}(II \rightarrow I) = +0.49 \pm 0.13$ kJ·mol^{-1}. Concerning the volumetric properties (density and unit cell parameters), it was concluded that the use of a flexible molecular model was largely insensitive to the chosen methodology for the selection of the APC. Overall, it was concluded that the best performance in the prediction of the energetic and volumetric properties of the two HAP polymorphs was achieved by combining a flexible molecular framework with atomic charges obtained for a molecular aggregate mimicking the crystal packing.



INTRODUCTION

Many organic molecular solids exhibit polymorphism, i.e., the ability to exist in more than one crystalline phase.[1−3] The various polymorphs differ by their packing arrangements and, sometimes, by the conformations of the molecules in the lattice. These structural dissimilarities normally impart significant changes to physical properties so that different polymorphs behave, in fact, as different materials. Moreover, distinct polymorphic forms can frequently coexist under the same pressure and temperature conditions, but they may convert over time to the most thermodynamically stable one. The control of polymorphism has therefore become an issue of considerable interest, particularly in view of its strong impact in the production, shelf life, and patenting of pharmaceuticals.[1−3] This has also fostered fundamental studies aiming to rationalize and predict the occurrence of polymorphic forms of a given compound and define their stability hierarchy.[1,4,5]

During the past decades, several strategies, based on molecular dynamics (MD) and Monte Carlo (MC) simulations, have been proposed to address these two problems.[1,6,7] The accuracy of the crystal structures and lattice energies predicted by those methods bears a direct relationship with the force-field selected for the computations. A common problem in the development of force-field models is the availability of reliable experimental data that can be used for the validation of the simulation results, both in terms of structural and energetic properties.[8,9] While the crystal structures of many polymorphs can be found in the Cambridge Structural Database,[10] accurate thermodynamic data that can be related to the corresponding absolute (e.g., enthalpies of sublimation) or relative (e.g., enthalpies of phase transition) lattice energies are rather scarce.

We have recently reported that two different polymorphs of 4′-hydroxyacetophenone (HAP) can be selectively obtained and stored at ambient temperature and pressure for long periods of time without any apparent interconversion.[11] Single crystal X-ray diffraction showed that, at 298.15 K, form I is monoclinic, space group $P2_1/c$, and has $Z' = 1$, and the previously known form II,[12−14] is orthorhombic, space group $P2_12_12_1$, with $Z' = 2$. At the molecular level, they differ by the relative conformations of the OH and C═O groups (Figure 1, *anti* in form I and *syn* in form II). The two polymorphs have also been thermodynamically characterized by a variety of methods (combustion and solution calorimetry, differential scanning calorimetry, drop-sublimation Calvet microcalorimetry, and Knudsen effusion technique). It was concluded that they are enantiotropically related, with form II first transforming into form I at 351.2 ± 2.7 K, followed by fusion of form I at 381.9 ± 0.1 K, and that, on enthalpic grounds, form II

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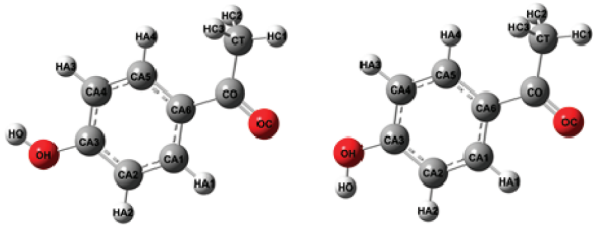

(a) (b)

Figure 1. Molecular conformations of two polymorphic structures of (a) form I and (b) form II of HAP, according to the single-crystal X-ray diffraction structures in ref 11.

is more stable than form I at 298.15 K by ~0.5 kJ mol^{-1}. This last conclusion was essentially supported by two consistent results:[11] (i) solution calorimetry experiments indicated that at 298.15 K the enthalpy of the II → I phase transition is $\Delta_{trs}H^{o}_{m}$(II → I) = 0.49 ± 0.13 kJ mol^{-1}; (ii) the standard molar enthalpies of sublimation derived at that same temperature from drop-sublimation Calvet microcalorimetry results were $\Delta_{sub}H^{o}_{m}$(HAP, crI) = 103.2 ± 0.8 kJ.mol^{-1} and $\Delta_{sub}H^{o}_{m}$(HAP, crII) = 104.3 ± 0.4 kJ.mol^{-1}, thus leading to $\Delta_{trs}H^{o}_{m}$(II → I) = 0.9 ± 0.9 kJ mol^{-1}. The enthalpic difference between the two forms is therefore known with sufficient accuracy to provide a reliable and demanding benchmark value for testing force fields widely used in the computational study of the organic solid state.

In this work, the combination of the OPLS-AA force-field[15,16] with a CHelpG methodology[17] for atomic point charge (APC) calculations, was tested as an inexpensive computational method to investigate polymorphism in HAP. The choice of this model was based on the following criteria: (i) in a recent communication Cheong and Boon[18] found that, from a set of four force fields, OPLS-AA was the one that better reproduced the experimental lattice energy and structure of glycine; (ii) OPLS-AA allows the use of flexible molecules in the simulation, and since many organic molecules can show significant flexibility, it was interesting to test whether the use of a flexible parametrization leads to an improvement of the reliability of the predicted structural and energetic data; (iii) in recent reports,[8,9,19] we have successfully used the OPLS-AA/CHelpG methodology to develop a comprehensive force field for organometallic compounds, and therefore it seemed a natural extension of this work to explore the same strategy in the study of organic polymorphs.

METHODS

MD Simulations. The MD runs were performed with the DL_POLY 2.20 package.[20] The two polymorphic phases were modeled in simulation boxes containing 480 and 560 molecules for form I and form II, respectively (8640 and 10080 atoms). A cutoff distance of 1.8 nm was used in all simulations, with the Ewald summation technique (k-values set to 5 and α = 0.185 Å) applied to account for interactions beyond that distance. The simulation boxes and initial configurations were prepared taking into account the dimensions and occupancy of the unit cells of the published experimental crystalline structures at 298 K.[11] Since the unit cell dimensions of the crystals were too small to accommodate a sufficiently large cutoff distance, well-proportioned simulation boxes consisting of several stacked cells were used. The simulations were performed at 298 K and 0.1 MPa, under the anisotropic isothermal−isobaric ensemble (N-σ-T). Typical runs consisted of an equilibration period of ca. 160 ps followed by a production stage of 200 ps each. These simulation times were found to be appropriate, since the initial configurations are close to the equilibrium structure, and it was observed that the relaxation was complete before the end of the equilibration period. The parametrization used in the simulation runs combined the 12−6 Lennard-Jones potential function present in the OPLS-AA force-field[15,16] to describe the van der Waals interactions, with the atomic charges calculated according with the procedures described below. Two simulations scenarios were considered: in the first case, molecules were assumed to be rigid, while in the second case, flexibility of the bonds, angles, and dihedrals was allowed by the use of corresponding OPLS-AA force-field parameters.[15,16]

APCs. All density functional theory (DFT) calculations were carried out by using Becke's three-parameter hybrid method[21] with the Perdew and Wang PW91[22] correlation functional (B3PW91) and the 6-311+G(d,p) basis set.[23] The APC evaluation was based on the CHelpG methodology.[17] This methodology was selected according to the following criteria: (i) in recent works, it was found that the use of the CHelpG procedure allowed the accurate computation of APCs in organometallic compounds,[8,9,19] and (ii) since the B3PW91/6-311+G(d,p) level of theory requires a small computational effort, it is ideal to determine the APC in molecular aggregates (see below). The calculations were performed with the Gaussian-03 package.[24]

As mentioned in the Introduction (see also Figure 1), at the molecular level, the two polymorphs of HAP differ by the orientation of the hydroxyl group relative to the acetate group and also by the fact that form I has just one molecule in the asymmetric unit while form II has two. To assess the effect of these structural features in the definition of the APCs, three different types of charges were considered:

OPLS-AA Charges (q_{OPLS}). These corresponded to the "default" point charges for different types of atoms given in the parameter list of the OPLS-AA force-field.[15,16]

Gas Phase Charges (q_{ISOL}). In this case, the CHelpG methodology was used to evaluate the APCs for the two conformations of HAP shown in Figure 1. The calculations were based on molecular geometries optimized at the B3PW91/6-311+G(d,p) level of theory. Due to the possibility of fast and easy rotation of the methyl group of HAP (rotation barrier ~5 kJ·mol^{-1}, see Supporting Information of ref 11), the APC values of its hydrogen atoms have been averaged for each conformation.

Lattice Charges (q_{CLST}). As mentioned above, the two HAP polymorphs exhibit distinct numbers of molecules in the asymmetric unit, namely, Z' = 1 for form I and Z' = 2 for form II. In the latter case, the two molecules are exposed to slightly different environments and polarizability effects, and this may be expected to impart to them different APCs. Conversely, in the case of form I, all molecules in the crystal lattice must have identical APCs. Furthermore, the HAP molecules present in any of the two crystalline structures must exhibit APCs different from those obtained for an isolated molecule in the gas phase. On the basis of this line of thought, the APCs for the HAP molecules contained in the two polymorphs, q_{CLST}, were evaluated as follows: (i) The molecules in both crystal lattices are connected by O−H···O hydrogen bonds, forming infinite adjacent chains (Figure 2).[11] Assuming that most of the polarizability/induction effects present in HAP(cr) are due to the existence of these bonds, small clusters of four molecules

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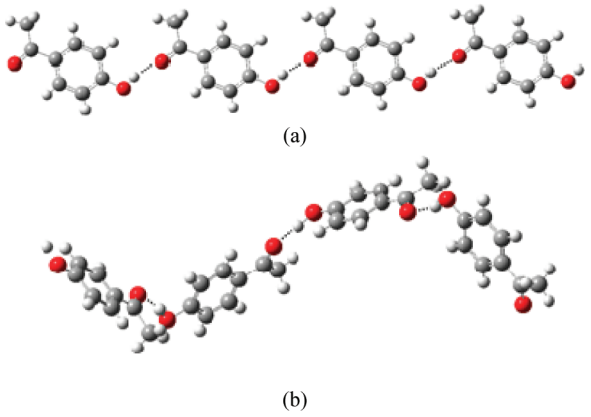

Figure 2. Molecular aggregate used in the APC calculation of the molecules in crystal structures of (a) form I and (b) form II polymorphs of HAP.

with the same structural arrangement as the chains present in each crystalline lattice were selected to obtain the corresponding APCs. In fact, the molecules of both HAP polymorphs mainly interact via dispersive forces and hydrogen bonds, and we assumed that only the later ones have the ability to induce charge modifications. This approximation is supported by previous evidence related to the development of a force field for organometallic compounds, where only dispersive forces are present and where the use of APCs calculated for a single molecule in the gas phase is sufficient for an accurate determination of the lattice energies.[8,9,19] (ii) The APCs were determined at the B3PW91/6-311+G(d,p) level of theory, through a fit to the molecular electrostatic potential, using the CHelpG procedure. (iii) The APCs on the two central molecules of each aggregate were retrieved and analyzed. It was found that the total charge on each central molecule was slightly different from zero [$(0 < q \leq 0.032)$ a.c.u] due to small charge-transfer effects. In order to preserve the electric neutrality of the molecules in the simulation boxes, this small excess charge was equally proportionally redistributed among all their atoms. As in the q_{ISOL} APC calculations, the charges of hydrogen atoms of the methyl group of HAP were also averaged. In the case of form II, distinct APCs were attributed to the two asymmetrical molecules contained in the unit cell. The APCs of the single molecule present in the unit cell of form I were obtained by averaging the APCs of the two central molecules of the cluster used in the calculations. This approximation seemed appropriate because, in the case of form I, the maximum and average differences between the charges of the two central molecules in the aggregate were 0.03 and 0.01 a.c.u., respectively, while for form II, the corresponding differences were 0.1 and 0.03 acu. These results, therefore, support the assumption that in crystalline structures with $Z' = 1$, all molecules have the same APCs, while in those with $Z' = 2$, two sets of molecules with different point charges are found in the crystal network.

Enthalpy of Sublimation Calculations. The standard molar enthalpy of sublimation ($\Delta_{sub}H^{o}_{m}$) of each polymorph, at 298.15 K, was estimated from the difference between the total molar configurational energy of the simulation boxes modeling the crystalline phases, $U^{o}_{conf,\,m}(cr)$, and that of the simulation boxes modeling isolated molecules in the gas phase:

$$\Delta_{sub}H^{o}_{m} = U^{o}_{conf,m}(g) - U^{o}_{conf,m}(cr) + RT \quad (1)$$

In eq 1, $R = 8.314472\ J{\cdot}K^{-1}{\cdot}mol^{-1}$ is the gas constant, and $T = 298.15$ K. The term $RT = 2.48\ kJ{\cdot}mol^{-1}$ refers to the internal energy-to-enthalpy correction considering the gas phase as ideal. For simulations using rigid molecules (with no intramolecular contributions to the configurational energy), $U^{o}_{conf,\,m}(g)$ can be neglected. In the case of the flexible model, it was estimated via single-molecule simulations under canonical (N-V-T) ensemble conditions at 298.15 K and 0.1 MPa. Due to the poor statistics associated with the very small size of the system (one molecule per simulation box), each production run had the duration of 20 ns, and 20 such runs were used to calculate average $U^{o}_{conf,\,m}(g)$ values.

The enthalpies of sublimation were estimated using three different models defined by the distinct sets of APCs considered in this work, namely, q_{OPLS}, q_{ISOL}, and q_{CLST}: (i) Model A uses the q_{OPLS} set exclusively, and, in this case, an OPLS charge was assigned to each interaction center in all HAP molecules, regardless of their conformation and presence in the gaseous or crystalline phases. (ii) Model B uses APCs obtained from DFT/CHelpG calculations on isolated molecules, i.e., the q_{ISOL} set. The gas phase molecules were given the charges of an isolated molecule in its most stable conformation. This corresponds to that depicted in Figure 1b, which, according to previous quantum chemistry calculations,[11] is 0.7 $kJ{\cdot}mol^{-1}$ more stable than the one shown in Figure 1a. The APCs of the molecules in forms I and II of HAP were taken from the corresponding isolated molecules with the appropriate conformation (Figure 1a for form I HAP and Figure 1b for form II). (iii) Model C uses APCs obtained from DFT calculations on isolated molecules and small molecular clusters, i.e., the q_{ISOL} and q_{CLST} sets. In this case, the gas phase molecules were given the same q_{ISOL} charges used in model B. The molecules present in the crystalline polymorphs were given the APCs corresponding to the q_{CLST} set.

Finally, the lattice enthalpy difference at 298.15 K, $\Delta_{trs}H^{o}_{m}(II \rightarrow I)$, between the two polymorphs of HAP was calculated as

$$\begin{aligned}\Delta_{trs}H^{o}_{m}(II \rightarrow I) &= \Delta_{sub}H^{o}_{m}(HAP,\ cr\ II) - \Delta_{sub}H^{o}_{m}(HAP,\ cr\ I)\\ &= U^{o}_{conf,m}(cr\ I) - U^{o}_{conf,m}(cr\ II)\end{aligned} \quad (2)$$

where $\Delta_{sub}H^{o}_{m}(HAP, crI)$ and $\Delta_{sub}H^{o}_{m}(HAP, crII)$ represent the enthalpies of sublimation of HAP forms I and II, respectively, and $U^{o}_{conf,m}(cr\ I)$ and $U^{o}_{conf,m}(cr\ II)$ are the corresponding configurational energies. Again, these enthalpy differences were calculated using the three alternative A, B, or C models.

RESULTS AND DISCUSSION

The APCs calculated for the different conformations of HAP in the two polymorphs and in the gas phase are given in Table 1.

As anticipated, the rotation of the hydrogen atom of the hydroxyl group toward the oxygen atom of the carbonyl group, from the conformation shown in Figure 1a to that of Figure 1b, drastically changed the APCs of all HAP atoms (cf. q_{ISOL}(1a) and q_{ISOL}(1b) values in Table 1: the changes are greater (more than 0.1 a.c.u.) on atoms CA1, CA2 and CA4). These results suggest that the simulation of each polymorph must be performed using atomic charges specifically determined for each molecular conformation present in the simulation box modeling each type of crystal.

The experimental energetic and structural data for the two HAP polymorphs[11] are compared in Table 2 with the

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Table 1. APCs: q_{OPLS}, Default OPLS-AA Force-Field APCs; q_{ISOL}(1a) and q_{ISOL}(1b), APCs Calculated for Isolated HAP Molecules in the Conformations of Figure 1a,b, Respectively; q_{CLST}(2a), APC Calculated for the HAP Molecule in the Crystal Lattice of Form I; q_{CLST}(2b) and q_{CLST}(2b′), APCs Calculated for the Two HAP Molecules in the Asymmetric Unit of the Crystal Structure of Form II[a]

label	q_{OPLS}	q_{ISOL}(1a)	q_{ISOL}(1b)	q_{CLST}(2a)	q_{CLST}(2b)	q_{CLST}(2b′)
HA1	0.115	0.100	0.092	0.113	0.060	0.087
CA1	−0.115	−0.021	0.056	−0.026	0.120	0.027
CA2	−0.115	−0.250	−0.345	−0.251	−0.380	−0.332
HA2	0.115	0.158	0.133	0.157	0.160	0.144
CA3	0.150	0.440	0.451	0.430	0.515	0.463
CA4	−0.115	−0.320	−0.233	−0.270	−0.240	−0.237
HA3	0.115	0.131	0.153	0.122	0.135	0.150
CA5	−0.115	−0.053	−0.092	−0.084	−0.085	−0.113
HA4	0.115	0.110	0.106	0.122	0.110	0.112
CA6	−0.115	−0.100	−0.135	−0.119	−0.200	−0.105
CO	0.585	0.469	0.487	0.458	0.520	0.437
OC	−0.470	−0.486	−0.499	−0.483	−0.535	−0.514
CT	−0.180	−0.149	−0.146	−0.168	−0.055	−0.039
HC1	0.060	0.045	0.047	0.058	0.025	0.025
HC2	0.060	0.045	0.047	0.058	0.025	0.025
HC3	0.060	0.045	0.047	0.058	0.025	0.025
OH	−0.585	−0.578	−0.587	−0.552	−0.650	−0.595
HO	0.435	0.414	0.418	0.377	0.450	0.440

[a]The labels used in the table are according to Figure 1. APCs are in a.c.u.

simulation results for both rigid and flexible A, B, and C models. The errors assigned to the MD results in Table 2 correspond to standard deviations of the mean of the $U^{o}_{conf,m}$ values computed throughout the simulation runs.

Table 2 shows that the rigid model A, based on OPLS-AA SCPs, yields the worse results from both the structural and energetic points of view: the unit cell dimensions are not well reproduced (the *b* and *c* parameters show deviations from the experimental values greater than 1.1 Å), and, in the case of form I, the monoclinic unit cell is distorted ($\Delta\beta$ = 10.05°). Furthermore, the enthalpies of sublimation are more than 6 kJ·mol^{-1} apart from the measured values and, if the lattice enthalpy difference between the two polymorphs is calculated, an inverse order of stability is obtained (−12.7 ± 0.3 kJ.mol^{-1}) when compared with the most precise experimental value (0.49 ± 0.13 kJ.mol^{-1}).[11] These results are not unexpected since the OPLS-AA force-field was developed for the simulation of liquids, where the neighborhood of each molecule is constantly changing in time, and, thus, the selection of the APCs (which represent averaged values) is not as important as in solid state simulations.[15]

The results obtained using the rigid B and C models, which were based on CHelpG APCs (q_{ISOL} and q_{CLST}) are, in all cases, in better agreement with the experimental data than those found with the rigid model A. This suggests that once a better (and more specific) approximation for the calculation of APCs is used, the accuracy of the structural and energetic parameters is improved. It was, however, observed that both rigid B and C models yielded non-negligible deviations in terms of unit cell dimensions. In the case of polymorph II, model C gave larger deviations in the *b* and *c* parameters (∼0.85 Å) than model B (∼0.34 Å), but, in the case of polymorph I, the opposite was observed: on average, $|\Delta c| \sim 0.44$ Å for model B and $|\Delta c| \sim 0.16$ Å for model C. Furthermore, in the case of polymorph I, the β parameter obtained with the rigid model B led to a considerable

Table 2. Experimental Enthalpies of Sublimation and Unit Cell Parameters of the Two Polymorphs of HAP at 298.15 K (Second Column, in Italics) and Deviations of the MD Simulation Data from the Experimental Results (All Other Columns)[a]

			rigid			flexible		
	experimental[11]		model A	model B	model C	model A	model B	model C
Polymorph I								
$\Delta_{sub}H^{o}_{m}$/kJ·mol^{-1}	*103.2 ± 0.8*	$\Delta\Delta_{sub}H^{o}_{m}$/kJ·mol^{-1}	6.3 ± 0.2	4.7 ± 0.2	0.9 ± 0.2	5.6 ± 1.3	2.3 ± 1.3	2.1 ± 1.3
a /Å	*7.720(2)*	Δa /Å	−0.440	−0.280	−0.040	−0.202	0.171	0.219
b/Å	*8.360(2)*	Δb/Å	−0.122	−0.127	−0.107	−0.169	−0.135	−0.126
c/Å	*11.280(2)*	Δc/Å	1.119	0.761	0.213	1.529	0.087	0.010
α/°	*90.00*	$\Delta\alpha$/°	0.00	0.00	0.00	0.00	0.00	0.01
β/°	*95.02(3)*	$\Delta\beta$/°	10.05	7.03	2.20	18.26	1.28	0.59
γ/°	*90.00*	$\Delta\gamma$/°	0.00	−0.01	−0.01	0.00	0.01	−0.02
ρ/g·cm^{-3}	*1.247*	$\Delta\rho$/g·cm^{-3}	0.012	0.007	0.004	0.002	−0.014	−0.016
Polymorph II								
$\Delta_{sub}H^{o}_{m}$/kJ·mol^{-1}	*104.3 ± 0.4*	$\Delta\Delta_{sub}H^{o}_{m}$/kJ·mol^{-1}	−7.5 ± 0.2	−6.6 ± 0.2	2.2 ± 0.2	−5.1 ± 1.3	0.1 ± 1.3	3.0 ± 1.3
a /Å	*6.110(1)*	Δa /Å	−0.058	0.170	0.007	0.057	0.146	0.087
b/Å	*9.529(1)*	Δb/Å	1.085	0.329	0.846	0.421	0.062	0.148
c/Å	*24.313(4)*	Δc/Å	−1.157	−0.350	−0.867	−0.102	0.160	0.092
α/°	*90.00*	$\Delta\alpha$/°	−0.01	0.00	0.00	−0.01	0.00	0.00
β/°	*90.00*	$\Delta\beta$/°	0.00	0.00	0.00	−0.01	−0.01	−0.01
γ/°	*90.00*	$\Delta\gamma$/°	0.00	0.00	0.00	0.00	0.00	−0.01
ρ/g·cm^{-3}	*1.278*	$\Delta\rho$/g·cm^{-3}	−0.062	−0.059	−0.062	−0.061	−0.046	−0.042
Δ Polymorphs								
$\Delta_{trs}H^{o}_{m}$(II → I)/kJ·mol^{-1}	*+0.49 ± 0.13*		−12.7 ± 0.3	−10.1 ± 0.3	+2.4 ± 0.3	−9.7 ± 0.8	−1.1 ± 0.8	+2.0 ± 0.9

[a]The last row lists the experimental and simulated enthalpy differences between the two polymorphs of HAP.

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deviation from the experimental value ($|\Delta\beta| = 7.03°$), when compared with that given by the rigid model C ($|\Delta\beta| = 2.20°$).

The simulated enthalpies of sublimation exhibited larger deviations from the experimental results in the case of the rigid model B ($|\Delta\Delta_{sub}H^o_m| = 5.7$ kJ·mol^{-1}) than the corresponding values for the rigid model C ($|\Delta\Delta_{sub}H^o_m| = 1.6$ kJ·mol^{-1}). Finally, the rigid model B predicted the enthalpic difference between the two polymorphs with a deviation of more than 10 kJ·mol^{-1} to the most precise experimental result, $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = +0.49 \pm 0.13$ kJ·mol^{-1}[111] and with the wrong order of stability (Table 2). In contrast, rigid model C predicted a value of $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = +2.4 \pm 0.3$ kJ·mol^{-1}, with the correct stability order and with a much smaller deviation from the recommended experimental value.

From the above results, it can be concluded that the use of the rigid model C led to a marked improvement in the accuracy of the calculated data, especially if the energetic results are considered.

The use of flexible molecules with model A (based on OPLS-AA SPCs) instead of its rigid counterpart also yielded large differences from the experimental values. The transition enthalpy between the two polymorphs using flexible model A was $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = -9.7 \pm 0.8$ kJ·mol^{-1}, closer to the experimental value of $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = +0.49 \pm 0.13$ kJ·mol^{-1} than the value obtained with the rigid model A, namely, $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = -12.7 \pm 0.3$ kJ·mol^{-1}, but still with a deviation of more than 10 kJ·mol^{-1}. The simulated structure of form I using the flexible model A was even more distorted than that obtained using the rigid model A (cf. the corresponding Δc and $\Delta\beta$ values in Table 2).

By contrast, all simulations performed using flexible models B and C show significant improvements in the prediction of structural and energetic data of the two HAP polymorphs. In fact, the difference between the predicted enthalpies of sublimation and the experimental results is in all cases lower than 3 kJ·mol^{-1}, and the deviations in the unit cell parameters are smaller than 0.22 Å. Only in the case of polymorph I does the flexible model B yield a slightly more distorted unit cell ($\Delta\beta = 1.28°$) than the one obtained using the flexible model C ($\Delta\beta = 0.59°$). Nevertheless, despite the significant improvement of the simulation results by the introduction of flexible molecules, the predicted transition enthalpy between the two polymorphs using flexible model B, $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = -1.1 \pm 0.8$ kJ.mol^{-1}, still reveals an inverse order of stability when compared with the experimental value ($\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = +0.49 \pm 0.13$ kJ.mol^{-1}). This result contrasts (again) with that obtained with flexible model C that predicts not only the correct stability order ($\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I}) = +2.0 \pm 0.9$ kJ.mol^{-1}) but also the enthalpic difference between the two polymorphs almost within the corresponding uncertainty bars.

The inspection of Table 2 also reveals a slight decrease in both the accuracy and precision of the enthalpies of sublimation calculated in the simulations with model C, when the rigid approach was replaced by the flexible one ($\Delta\Delta_{sub}H^o_m$ varies from 0.9 ± 0.2 kJ·mol^{-1} to 2.1 ± 1.3 kJ·mol^{-1} for phase I and from 2.2 ± 0.2 kJ·mol^{-1} to 3.0 ± 1.3 kJ·mol^{-1} for phase II, when the model was changed from rigid to flexible, respectively). This observation probably has a 2-fold origin: (i) the main one is, most likely, the large intrinsic inaccuracy associated with the calculation of $U^o_{conf,m}(g)$ from runs where only one molecule per simulation box is used. Indeed, in this case, the uncertainty in $U^o_{conf,m}(g)$ (typically of ~1.3 kJ·mol^{-1}) is essentially the same as the total error of $\Delta\Delta_{sub}H^o_m$ (1.3 kJ·mol^{-1}, see Table 2). This problem only arises when a flexible model is used because, for a rigid model, $U^o_{conf,m}(g) = 0$. (ii) Another, albeit related, source may be the fact that the bond, angle, and dihedral functions used in this work to describe molecular flexibility were taken from the OPLS-AA force field,[14,15] which was developed for a specific set of APCs. Thus when the OPLS-AA charges are replaced by q_{ISOL} and q_{CLST}, a small change in the potential functions (particularly in the case of dihedrals) occurs, which may ultimately lead to a decrease in the accuracy of the enthalpies of sublimation estimated with model C charges. Note, however, that the changes introduced in the OPLS-AA force field parametrization do not seem to have a strong impact on the results. In fact, as can be seen in Table 2, the differences between the $\Delta\Delta_{sub}H^o_m$ values corresponding to the rigid and flexible model C are within the uncertainty of the results. These uncertainties are, in turn, almost fully explained by the error assigned to $U^o_{conf,m}(g)$.

Finally, a better accuracy is achieved if $\Delta_{trs}H^o_m(\text{II} \rightarrow \text{I})$ instead of $\Delta_{sub}H^o_m$ is considered, because, in this case, the contribution from $U^o_{conf,m}(g)$ is not present and, in addition, errors arising from changes in the force field parametrization are likely to be attenuated when the difference $U^o_{conf,m}(\text{cr I}) - U^o_{conf,m}(\text{cr II})$ is computed (eq 2).

The above results, therefore, suggest that the use of flexible models in the simulation of crystalline structures allows a better adjustment of the molecules within the lattice and, as a result, more accurate predictions of the unit cell parameters and the lattice energetics.

CONCLUSION

MD simulations were performed for the two known polymorphs of HAP, using several methodologies for APC assignment—generic (OPLS-AA), CHelpG charges on isolated molecules (ISOL), or CHelpG charges on small molecular clusters (CLST)—and assuming different models: rigid versus flexible molecules with different SPCs schemes.

The models based on the calculation of molecule-specific CHelpG charges (models B and C) proved superior relative to the model based on generic OPLS-AA charges (model A). Moreover, when the evaluated APCs reflected the charge distribution of small clusters representative of the crystal lattice of a specific polymorph (model C), better predictions of the energetics of the systems relative to the results obtained using isolated-molecule SPCs (model B) were obtained.

This novel methodology for the calculation and assignment of APCs also suggests that the number of molecules in the asymmetric unit (Z') has to be accounted for in the evaluation of the APCs for use in MD simulations of crystalline structures with $Z' > 1$. In fact, the refinement of the OPLS-AA parametrization using the evaluation of individual charges for each type of atom present in the asymmetric unit (model C APCs) allows for the implicit incorporation of polarizability effects that are present in the crystalline structure of each polymorph.

This approach has the potential to become a simple and inexpensive computational method to investigate molecular organic crystals. However, due to the limited number of structures evaluated in this work, this method must still be used with caution until more extensive tests (currently being performed) are available.

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Notes
The authors declare no competing financial interest.

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