

Supplementary Information for “Solution and selection: how a solvent interacts with structures from the crystal energy landscape of tetrolic acid”

S1 Parameters for exp-6 potential

The exp-6 potential is used to absorb all intermolecular interactions apart from the electrostatic (see section 2.1). It is an atom-atom potential of the form

$$U_{SR} = \sum_{i \in 1, k \in 2} (A_{ii} A_{\kappa\kappa})^{1/2} \exp(-(B_{ii} + B_{\kappa\kappa})R_{ik} / 2) - \frac{(C_{ii} C_{\kappa\kappa})^{1/2}}{R_{ik}^6}$$

where atom i in molecule 1 is of the type i and atom k in molecule 2 is of the type κ . The parameters A , B and C were chosen to reproduce available structural and thermodynamic data, as confirmed with molecular dynamics runs.

In the case of chloroform, all chlorine atoms were assigned as the same atom type. Potentials were tested using a simulation cell of 500 molecules. The van der Waals interaction parameters of the AMBER forcefield^{1,2} (C and H classified as AMBER types CT and H3) were found to reproduce the density and enthalpy change of vaporization well when converted from Lennard-Jones 12-6 format to exp-6 format using the formula³ of Filippini and Gavezzotti and a ‘steepness parameter’ of $\lambda = 13.5$. The values given by a 1 ns simulation following a 0.2 ns equilibration period yielded $\Delta H_{vap} = 32.2 \pm 0.45 \text{ kJ mol}^{-1}$ (calculated as $-U + RT$ for potential energy U) and $\rho = 1.44 \pm 0.001 \text{ g cm}^{-3}$ as compared to experimental values⁴ of 31.4 kJ mol^{-1} and 1.483 g cm^{-3} .

In the case of ethanol, atom types were assigned to the group of all carbon atoms, the oxygen atom, the group of all the alkyl hydrogen atoms, and the alcoholic hydrogen atom. Potentials were tested using a simulation cell of 500 molecules run for a 1 ns simulation plus an equilibration period of 0.2 ns. It was found that a modified version of the FIT potential, widely used in crystal structure prediction and fitted to organic crystal structures,⁵⁻⁷ gave good reproduction of the density and enthalpy change of vaporization. The FIT potential was modified by multiplying all C values by 1.15. The physical values were hence calculated as $\Delta H_{vap} = 41.5 \pm 0.55 \text{ kJ mol}^{-1}$ and $\rho = 0.77 \pm 0.001 \text{ g cm}^{-3}$ as compared to experimental values⁴ of 42 kJ mol^{-1} and 0.79 g cm^{-3} .

In the case of tetrolic acid, atom types were assigned to the group of all carbon atoms, the group of all oxygen atoms, the group of all the methyl hydrogen atoms, and the carboxyl hydrogen atom. Simulation cells were generated by pasting the relaxed molecular structure into each of the experimental crystal structures and then generating a supercell of that structure. There were 420 molecules in the α – polymorph cell and 450 molecules in the β polymorph cell. Test simulations were carried out for a run length of 1 ns plus 0.2 ns equilibration. Again, a modified version of the FIT potential gave good reproduction of structural parameters (see Table S1.1). In this case, the FIT potential was modified by multiplying all A values by 1.1 and all C values by 1.25.

	a (Å)	b (Å)	c (Å)	α (°)	β (°)	γ (°)	ρ (g cm ⁻³)	ΔH_{sub} (kJ mol ⁻¹)
α (exp)	7.32	5.10	7.23	83.9	117.5	112.0	1.262	Unknown
α (sim)	7.13 ± 0.03	5.18 ± 0.03	7.22 ± 0.03	84.0 ± 0.01	114.9 ± 0.01	114.7 ± 0.01	1.272 ± 0.001	82.9 \pm 0.60
β (exp)	7.89	7.12	3.94	90.0	100.18	90.0	1.283	Unknown
β (sim)	7.82 ± 0.02	7.13 ± 0.02	3.97 ± 0.02	90.0 ± 0.00	102.0 ± 0.00	90.0 ± 0.00	1.288 ± 0.001	84.5 \pm 0.55

Table S1.1. Comparison of simulated MD and experimental cell parameters for the α and β polymorphs of tetrolic acid. Experimental parameters are taken from the CSD.⁸

From Table S1.1 it can be seen that the potential used is slightly overbinding, particularly with respect to the α polymorph. Overall, the α polymorph is less well reproduced, most notably with respect to the a cell parameter, which is 2.5 % too short. This is to be expected, since the α polymorph is in fact disordered, so the crystal structure simulated here is really only an ordered analogue of the polymorph. Although methods for simulating disordered organic crystal structures exist,⁹ they either deal with static disorder in static simulations of crystals, or dynamic disorder, and are therefore not suitable for this study, which would require simulation of static disorder in a molecular dynamics simulation of a crystal. Nevertheless, crystal structure reproduction was judged to be sufficiently good with this potential.

The sublimation enthalpies match the experimentally established stability order, i.e. $\beta > \alpha$. Unfortunately experimental sublimation enthalpies are not available for tetrolic acid. An analogous compound is butanoic acid with¹⁰ $\Delta H_{sub} = 76$ kJ mol⁻¹, which appears to be consistent with the magnitude of the calculated enthalpies, especially given the findings of Ouvrard et al that molecules with the same chemical compositions will have similar sublimation enthalpies.¹¹

The final values are shown in Table S1.2. Cross terms were calculated using the usual geometric and arithmetic averages.

Atom type	A (eV)	1/B (Å)	C (eV Å ⁶)
Chloroform types			
Cl	6452.7	0.296296	81.528
C (CHF)	2768.3	0.282667	26.368
H (CHF)	397.3	0.175852	0.219
Ethanol types			
C (ETH)	3832.1	0.277778	29.08
O (ETH)	2384.5	0.252525	13.392
H (ETH, polar)	52.1	0.214592	0.256
H (ETH, alkyl)	124.1	0.267380	1.626
Tetrolic acid types			
C (TTA)	4215.3	0.277778	31.521
O (TTA)	2622.9	0.252525	14.557
H (TTA, polar)	57.3	0.214592	0.278
H (TTA, methyl)	136.5	0.267380	1.766

Table S1.2. Parameters for the exp-6 potential used in this study.

S3 Cluster stabilities in 298K solvent

These stabilities were calculated for each of the clusters cut from each of the test set crystal structures in contact with chloroform and ethanol in molecular dynamics simulations. A modified version of DL_MULTI allowed two different thermostats to be applied to the system; one thermostat held the cluster at 0K while the other solvent at 298K. Simulations were carried out for 1ns plus 200ps of equilibration.

Structure	Potential energy [kJ mol ⁻¹]	
	in chloroform	in ethanol
Spherical clusters		
cat1	-65.7	-65.4
cat2 (β)	-69.1	-62.7
dim1	-58.5	-61.7
dim2 (α)	-62.9	-63.6
BFDH clusters		
cat1	-61.2	-66.0
cat2 (β)	-68.1	-60.0
dim1	-56.9	-60.3
dim2 (α)	-61.5	-59.2

Table S3.1. Potential energies for clusters cut from the four predicted crystal structures, held at 0K, in contact with solvent at 298K.

Reference List

1. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179-5197.
2. Fox, T.; Kollman, P. A. *J. Phys. Chem. B* **1998**, *102*, 8070-8079.
3. Filippini, G.; Gavezzotti, A. *Acta Crystallogr. , Sect. B* **1993**, *49*, 868-880.
4. Lide, D. R. *CRC Handbook of Chemistry and Physics*; 83rd ed.; 2003.
5. Coombes, D. S.; Price, S. L.; Willock, D. J.; Leslie, M. *J. Phys. Chem.* **1996**, *100*, 7352-7360.
6. Williams, D. E.; Cox, S. R. *Acta Crystallogr. , Sect. B* **1984**, *40*, 404-417.
7. Cox, S. R.; Hsu, L. Y.; Williams, D. E. *Acta Crystallogr. , Sect. A* **1981**, *37*, 293-301.
8. Allen, F. H. *Acta Crystallogr. , Sect. B* **2002**, *58*, 380-388.

9. Habgood, M.; Grau-Crespo, R.; Price, S. L. *Phys. Chem. Chem. Phys.* **2011**, *13*, 9590-9600.
10. NIST Chemistry Webbook. <http://webbook.nist.gov> **2011**.
11. Ouvrard, C.; Mitchell, J. B. O. *Acta Crystallogr. , Sect. B* **2003**, *59*, 676-685.
12. Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. *J. Appl. Crystallogr.* **2008**, *41*, 466-470.