Electronic Supplementary Material for CrystEngComm

The crystal structures of chloro and methyl ortho-benzoic acids and their co-crystal: rationalizing similarities and differences

Supporting Information

1. Experimental

A range of solvents were used in an attempt to crystallise both *o*-toluic and *o*-chlorobenzoic acid both by room temperature solvent evaporation, and by cooling a heated supersaturated solution.

Crystallizations by room temperature solvent evaporation

In a typical experiment 100 mg of *o*-chlorobenzoic acid or *o*-toluic acid have been dissolved in 5 mL of the following solvents: toluene, dichloromethane, acetonitrile, ethanol, nitromethane, acetone, ethyl acetate.

Crystallizations by cooling a heated supersaturated solution

In a typical experiment 1000 mg of *o*-chlorobenzoic acid or *o*-toluic acid have been dissolved in 10 mL of the following boiling solvents: water, dichloromethane, acetonitrile, ethanol, nitromethane, acetone, ethyl acetate. The solutions have been left cooling slowly in the oil bath and then filtered.

A range of experiments seeding of *o*-toluic acid with 1-50% *o*-chlorobenzoic acid both at room temperature and during cooling from high temperature were also attempted.

Room temperature seeding procedure

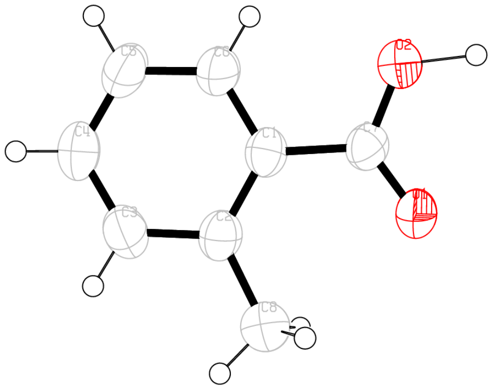
A set of four saturated solutions have been prepared dissolving *o*-chlorobenzoic acid or *o*-toluic acid in 5 mL of each of the following solvents: toluene, dichloromethane, acetonitrile, ethanol, nitromethane, acetone, ethyl acetate. The four saturated solutions of *o*-toluic acid in each solvent have been seeded with 5 mg, 10 mg, 25 mg and 50 mg of *o*-chlorobenzoic acid. *Vice versa*, the four saturated solutions of *o*-chlorobenzoic acid in each solvent have been seeded with 5 mg, 10 mg, 25 mg and 50 mg of *o*-toluic acid. The solutions have been left in the air until complete solvent evaporation.

Supersaturated solution seeding procedure

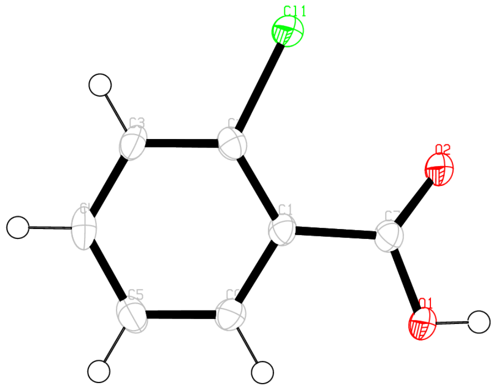
A set of four solutions have been prepared of 1000 mg of *o*-chlorobenzoic acid or *o*-toluic acid in 10 mL of each of the following boiling solvents: water, dichloromethane, acetonitrile, ethanol, nitromethane, acetone, ethyl acetate. The four supersaturated solutions have been left cooling slowly in the oil bath and have been seeded with 5 mg, 10 mg, 25 mg and 50 mg of *o*-chlorobenzoic acid before the beginning of the crystallization process. *Vice versa*, the four solutions of *o*-chlorobenzoic acid in each solvent have been seeded with 5 mg, 10 mg, 25 mg and 50 mg of *o*-toluic acid. The solutions have been left cooling slowly in the oil bath and then filtered.

2. ORTEP Plots (50% probability thermal ellipsoids)

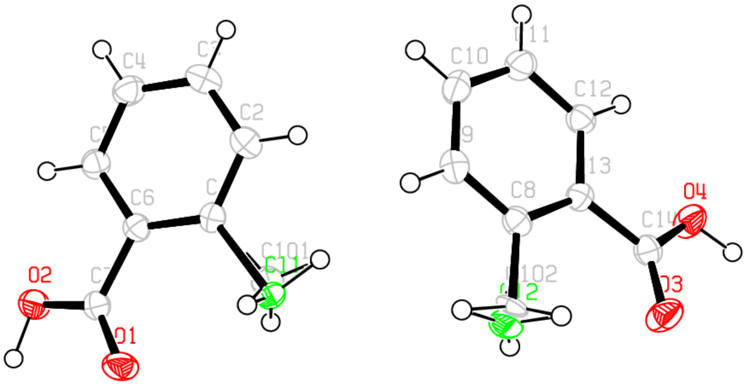
o-toluic acid



o-chlorobenzoic acid



Co-crystal



3. Cells dimensions determined at 293 K.

	o-toluic acid form I (293 K)	*o*-toluic acid form III[a] (293 K)	*o*-chlorobenzoic acid (293 K)	co-crystal **(1)** (293 K)
space group	$P2_1/n$	-	C2/c	$P2_1$
a /Å	4.831(3)	7.746(4)	14.699(2)	3.892(3)
b /Å	19.420(6)	10.764(3)	3.8857(8)	23.376(6)
c /Å	7.761(2)	12.974(2)	23.960(4)	7.6723(18)
α /°	-	100.28(2)	-	-
β /°	106.87(3)	96.09(2)	101.364(18)	104.12(4)
γ /°	-	102.68(3)	-	-
V /Å^3	696.7(5)	1026.4(7)	1341.7(4)	676.9(5)

4. Ordered models of the cocrystal

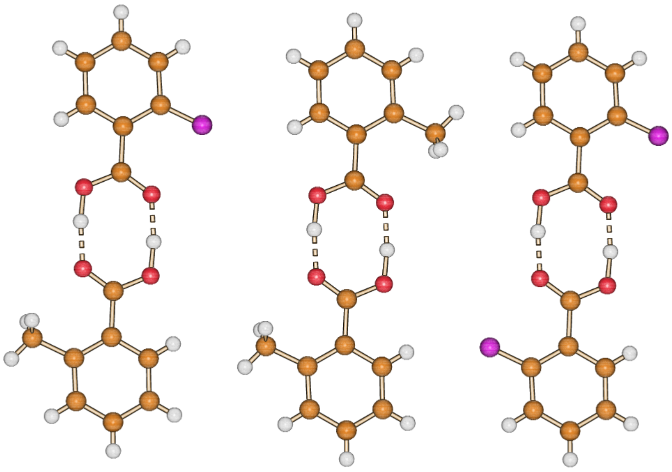


Figure 1. The hydrogen bonded dimers in the ordered models of the cocrystal (and the pure forms). From the left: the hetero-dimer in two ordered models and the homo-dimers in the other ordered cocrystal.

The ordered heterodimer 1 (Table 4) has the ortho substituent of molecule 1 (as defined by the experimental .cif file) as methyl, and molecule 2 as chloro. These are reversed in the second heterodimer, with both structures being $P2_1$. The homodimer was created by having the ortho subsitutent of molecule 1 methyl and having a chloro substituent on the molecule generated by the two-fold axis in the experimental structure, giving a P1- cell.

5. Crystal Predictor search: computational details

Conformational analysis suggests that ortho substituted benzoic acids can exist in two conformations differing in the orientation of the carboxylic group with respect to the ortho group. Conformation A with the carbonyl group adjacent to the methyl group is approximately 4.8 kJ/mol more stable than B, with the hydroxyl group adjacent to the methyl at the HF/6-31G(d,p) level of theory for *o*-toulic acid. Although all our experimental structures had the molecule in conformation A, and a survey of the

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Cambridge Structural database showed that this was the preferred orientation, the energy difference for *o*-toulic acid is sufficiently small that this conformational region was also explored in the search for the *o*-toluic acid crystal structures and confirmed that no stable crystal structures were produce for region B. Thus, we have not explored the conformation B for *o*-chlorobenzoic acid.

The torsion angles denoted in Scheme 1 of the paper, φ_1=O2-C7-C1-C2, φ_2=H-O2-C7-O1, and for *o*-toluic acid φ_3=H-C8-C2-C1 were allowed to vary in response to the packing forces in both the generation of putative structure and crystal energy minimisation. To do so we constructed intramolecular energy penalty tables around the two conformational minima for *o*-toulic acid and conformation A for *o*-chlorobenzoic acid at the HF/6-31G(d,p) level of theory. We also constructed tables for the conformational variation of the MP2/6-31G(d,p) atomic charges fitted to the molecular electrostatic potential arising from the MP2/6-31G(d,p) charge density on a dense geodesic mesh around the molecule.

The 50000 minimisations per conformational region were sufficient for all low energy minima to be located multiple times for *o*-toluic acid. All CrystalPredictor minimisations were performed with the Williams repulsion-dispersion intermolecular potential and with conformational-dependent atomic charges.

The CrystalPredictor results were clustered on the basis of interatomic distances and the most stable, unique structures were re-minimised using a distributed multipole electrostatic model with DMAflex-Quick. We have re-minimized 500 such structures for both conformations of *o*-toluic acid and 400 for conformation A of *o*-chlorobenzoic acid. DMAflex-Quick utilises the same intramolecular energy penalty table as CrystalPredictor but improves the relative accuracy of the lattice energies by using a distributed multipole description for the intermolecular electrostatic interactions. However, the conformational dependence of the multipoles is approximated by analytically rotation with their local environment as the molecule changed its conformation during the crystal energy minimisation. The multipoles are computed by GDMA analysis of the MP2 6-31G(d,p) wavefunction, and the DMAflex-Quick procedure avoids the need to recalculate this wavefunction for every change in conformation, in contrast to DMAflex. For *o*-toluic acid, we used the MP2/631G(d,p) multipoles computed for the corresponding gas phase minimum for all DMAflex-Quick optimisations. However, it was found that for *o*-chlorobenzoic acid, it was necessary to use the multipoles calculated for each starting conformation. Figure 2 shows this dependence of the minimised lattice energy on the conformation used for the initial multipoles. The outliers correspond to conformations of *o*-chlorobenzoic acid which are very different from the gas phase minimum. Since a similar range of conformations were found in the o-toluic acid search, it appears that the changes in the multipoles with conformation were significantly larger for the chloro than methyl substituent. This is reasonable, given the more diffuse charge density associated with the chlorine atom, as the overlap with the carboxyl oxygen atoms will change significantly with conformation.

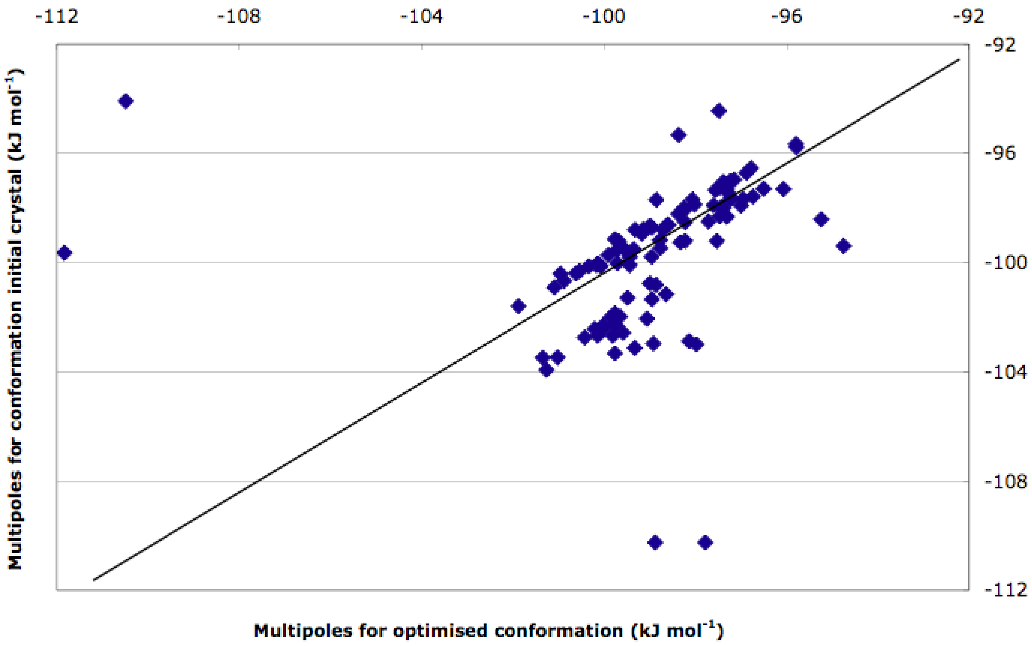

Figure2: DMAflex-Quick minimized lattice energies, for *o*-chlorobenzoic acid, showing the dependence on whether the analytically rotated multipoles were calculated for the ab initio optimized conformation or the initial conformation in the crystal structure produced by Crystal Predictor.

The lowest energy structures were then refined by DMAflex, involving a constrained optimisation of the molecule at each value of the three (two for *o*-chlorobenzoic acid) torsion angles and calculation of the corresponding distributed multipoles for every change in conformation. The resulting lattice energy minima therefore have all conformational degrees of freedom, except the explicitly varied torsions, corresponding to the HF 6-31G(d,p) gas phase values for those torsion angles, and allows for effects of redistribution of charge density with the conformational changes. The pre-optimisation by DMAflex-Quick ensures that these relative energy changes are sufficiently small to reduce the number of computationally demanding DMAflex optimisations to a reasonably small number. For *o*-toluic acid, only the 10 lowest energy structures generated by DMAflex-Quick were re- optimised by DMAflex. For *o*-chlorobenzoic acid the DMAflex calculation was performed for the 8 lowest energy stable structures and for 5 structures with greater conformational changes because of uncertainty in the accuracy of the DMAflex-Quick. Then, the structures were again clustered, resulting in structures reported in the paper, and given in the following tables.

The unique minima after DMAflex refinement of the 10 hypothetical structures of *o*-toluic acid that were lowest in energy after DMAflex-Quick

Structure	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Crystal lattice energy /kJ mol^{-1}
2	7.90	7.90	6.73	98.16	124.35	80.15	-93.13
19	11.39	7.92	8.13	90.00	109.94	90.00	-92.32
11	4.81	7.69	10.10	76.56	94.21	74.65	-91.45
6	7.66	7.33	12.41	90.00	100.78	90.00	-91.35
35	15.21	4.76	28.56	90.00	137.20	90.00	-91.03
48	11.01	7.91	15.91	90.00	86.75	90.00	-90.87
21	7.54	6.70	7.92	104.30	67.08	83.32	-90.81
1	**4.67**	**19.80**	**7.85**	**90.00**	**106.38**	**90.00**	**-90.32**

Minimum corresponding to form I is in bold.

The unique minima after DMAflex refinement of 15 hypothetical structures of *o*-chlorobenzoic acid.

Structure	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Crystal lattice energy /kJ mol^{-1}
212	13.78	13.78	14.03	90.00	90.00	90.00	-101.70
12	7.46	3.71	12.26	92.79	100.94	80.24	-101.25
26	**14.81**	**3.69**	**24.65**	**90.00**	**101.51**	**90.00**	**-100.55**
31	3.66	24.33	7.74	90.00	106.64	90.00	-100.31
37	3.66	7.26	24.92	90.00	96.33	90.00	-100.14
96	20.68	5.78	15.63	90.00	159.06	90.00	-98.95
334	9.20	14.53	5.12	90.00	90.00	90.00	-97.53
224	5.27	15.21	17.38	90.00	90.00	90.00	-96.24
388	12.21	14.51	3.69	90.00	90.00	90.00	-95.50
36	12.21	5.31	14.62	90.00	46.56	90.00	-93.73

Minimum corresponding to experimental structure is in bold.

The initial Crystal Predictor search for the co-crystal generated 42000 structures. However, the search for co-crystal polymorphs is beyond the scope of this work, so we restricted our consideration to those more similar to the known structure, in order to confirm the experimental structure. The last 17 analysed structures are those whose 15 molecule coordination cluster could be overlaid, with wide tolerances by Compack. We have compared the hetero and homodimer ordered structures with the first 1000 most stable structures. The resulted structures were calculated using the DMAflex; the results are collected in the following tables together with the crystal lattice energy value. No minimum structure has been found corresponded to the experimental ordered homodimer structure because it is Z′=2 and the search is concerning only the structures with Z′=1.

DMAflex refined structures of 18 hypothetical structures of co-crystal for hetero (above blank line) and homo (below) dimers.

Structure	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Crystal lattice energy /kJ mol^{-1}
339	3.81	15.17	28.06	90.00	56.00	90.00	-189.51
378	7.69	23.61	3.80	90.00	78.34	90.00	-188.76
518	**3.80**	**23.59**	**9.25**	**90.00**	**54.52**	**90.00**	**-188.76**
473	3.83	15.13	28.01	90.00	56.64	90.00	-187.40
305	**7.85**	**23.63**	**3.82**	**90.00**	**107.11**	**90.00**	**-187.18**
513	3.82	23.63	7.66	90.00	78.60	90.00	-187.18
48	3.83	22.97	7.81	90.00	78.68	90.00	-186.75
134	7.81	22.97	3.83	90.00	78.69	90.00	-186.74
623	14.76	3.74	24.53	90.00	90.00	90.00	-186.72
936	14.88	3.70	24.64	90.00	90.00	90.00	-185.63
847	15.04	3.70	24.39	90.00	90.00	90.00	-180.79
136	3.75	23.59	8.55	90.00	63.81	90.00	-180.49
262	3.75	23.57	7.68	90.00	90.09	90.00	-180.49
908.00	3.81	48.38	7.81	107.77	75.37	150.29	-185.19
615.00	3.86	46.36	7.93	130.51	73.34	136.84	-184.63
443.00	7.46	3.77	48.12	90.00	90.68	90.00	-183.70
910.00	30.47	3.75	15.04	90.00	126.76	90.00	-179.45
884.00	7.79	3.71	24.64	90.00	106.55	90.00	-177.82

Minima corresponding to the ordered heterodimer cocrystal are in bold.