CRYSTAL GROWTH & DESIGN

Article

pubs.acs.org/crystal

Utilizing Sulfoxide···Iodine Halogen Bonding for Cocrystallization

Kevin S. Eccles,[†] Robin E. Morrison,[†] Stephen P. Stokes,[†] Graham E. O'Mahony,[†] John A. Hayes,[†] Dawn M. Kelly,[†] Noel M. O'Boyle,[†] László Fábián,[‡] Humphrey A. Moynihan,[†] Anita R. Maguire,[§] and Simon E. Lawrence*,[†]

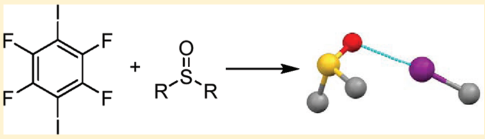
[†]Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

[‡]School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, U.K.

[§]Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

Supporting Information

ABSTRACT: The propensity of a range of different sulfoxides and sulfones to cocrystallize with either 1,2- or 1,4-diiodotetrafluorobenzene, via I···O=S halogen bonding, was investigated. Cocrystallization occurred exclusively with 1,4-diiodotetrafluorobenzene in either a 1:1 or 1:2 stoichiometry of the organohalide and the sulfoxide, respectively, depending on the sulfoxide used. It was found that the stoichiometry observed was not necessarily related to whether the oxygen acts as a single halogen bond acceptor or if it is bifurcated; with I···π interactions observed in two of the cocrystals synthesized. Only those cocrystals with a 1:2 stoichiometry exhibit C−H···O hydrogen bonding in addition to I···O=S halogen bonding. Examination of the Cambridge Structural Database shows that (i) the I···O=S interaction is similar to other I···O interactions, and (ii) the I···π interaction is significant, with the distances in the two cocrystals among the shortest known.



INTRODUCTION

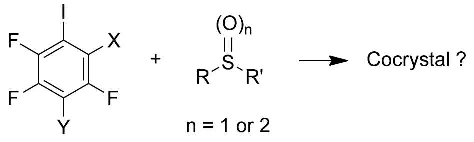
Cocrystals have attracted significant interest as novel crystalline materials, particularly within the pharmaceutical industry[1] due to their potential to alter and optimize the physical properties of an active pharmaceutical ingredient. The use of strong hydrogen bonding involving reliable supramolecular synthons has recently attracted attention,[2] and the utilization of weaker, noncovalent, interactions is also a developing area.[3] In addition, screening methodologies have been developed to accommodate this demand, with neat grinding,[4] liquid assisted grinding,[5] and sonication[6] commonly used.

Halogen atoms are known to form strong, specific, and directional interactions, termed halogen bonds, which have been exploited in the development of new solid materials.[7] The strength of a halogen bond is dependent on the halogen atom involved, although there is some debate about the extent to which fluorocarbons can participate in halogen bonding.[8] The nature of halogen bonding is greatly influenced by the electronic features of the functional group with which the halogen atom is associated.[9] For example, the halogen bond interaction is strengthened upon fluorination of the aryl ring, which is reflected in a shortening of the halogen bond distance.[10]

The use of sulfur functional groups as coformers in cocrystallization is relatively understudied, although recent work has shown that the potent hydrogen bond acceptor ability of the sulfoxide group can be used to form cocrystals with a range of nitrogen functional groups via N−H···O=S hydrogen bonds.[11] However, there are few reports of cocrystallization involving organoiodine interactions with sulfur functional groups specifically as a cocrystal former,[12,13] and a search of the Cambridge Structural Database (CSD)[14] for halogen bonding between iodine atoms and the sulfinyl or sulfonyl functional groups, within organic molecules, yielded 142 hits. Multicomponent systems account for 58 of these: 47 are salts and 11 are DMSO solvates, including a disordered 1:1 DMSO solvate with 1,4-diiodotetrafluorobenzene.[15]

We were interested in whether the I···O=S synthon could be utilized for cocrystallization, as outlined in Scheme 1, and if so, what stoichiometry of the coformers would be most frequently observed? How many iodine atoms, or lone pairs on the oxygen atom, would be utilized in cocrystal formation, and would these influence the stoichiometry observed?

Scheme 1. Hypothesis under Investigation



1 X=F, Y=I
2 X=I, Y=F

EXPERIMENTAL SECTION

Chemicals. The sulfide precursors for compounds (±)-**d**, (±)-**e**, and **h** (Figure 1) were synthesized according to the literature.[16,17] Compounds (±)-**d**, (±)-**e**, and **l** were synthesized using oxone

Received: February 8, 2012
Revised: May 8, 2012
Published: May 17, 2012

oxidation.[18] The literature procedure for the synthesis of (R)-**d**[19] was used. Compounds **f** and **h** were synthesized as described below. All other compounds were purchased from Sigma-Aldrich and used without further purification, including *m*-CPBA, which was >77% purity grade.

Thianthrene 5-Oxide (f). A solution of *m*-CPBA (2.72 g, 12.60 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 1 h to a stirred solution of thianthrene (2.16 g, 12.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for an additional 2 h at 0 °C, washed with saturated NaOH solution (1.0 M, 3 × 20 mL) and brine (3 × 20 mL), dried with $MgSO_4$, and concentrated under reduced pressure to yield the crude product as a white solid. Purification by column chromatography with hexane/ethyl acetate (80:20) gave **f** as a white solid (2.40 g, 86%), mp 142–143 °C, lit. 143 °C.[20] Anal. Calcd for $C_{12}H_8OS$: C, 62.04; H, 3.47. Found: C, 62.39; H, 3.47. IR (KBr) ν_{max}/cm^{-1}: 1033 (S=O). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.43 (2H, ddd, $J = 7.6$, $J = 7.6$, $J = 1.4$ Hz, 2 × ArH), 7.55 (2H, ddd; $J = 7.6$, $J = 7.6$, $J = 1.1$ Hz, 2 × ArH), 7.63 (2H, dd, $J = 7.6$, $J = 1.1$ Hz, 2 × ArH), 7.87 (2H, dd, $J = 7.6$, $J = 1.4$ Hz, 2 × ArH).

Di(2-phenyl)ethyl Sulfoxide (h). A solution of *m*-CPBA (2.17 g, 15.75 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 1 h to a stirred solution of di(2-phenyl)ethyl sulfide (3.63 g, 15.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for an additional 2 h at 0 °C, washed with saturated NaOH solution (1.0 M, 3 × 20 mL) and brine (3 × 20 mL), dried with $MgSO_4$, and concentrated under reduced pressure to yield the crude product as a white solid. Purification by column chromatography with hexane/ethyl acetate (80:20) gave **h** as a white solid (3.34 g, 83%), mp 54–58 °C. Anal. Calcd for $C_{14}H_{14}OS$: C, 74.38; H, 7.02. Found: C, 74.51; H, 6.98. IR (KBr) ν_{max}/cm^{-1}: 1028 (S=O). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.82–3.17 (8H, m, 4 × CH_2), 7.20–7.35 (10H, m, 10 × ArH).

Neat Grinding. Screening involving mechanical grinding was employed with subsequent crystallization by slow evaporation from solution in all cases—even where grinding and IR indicated cocrystallization had not occurred. Screening was performed initially with a 1:1 ratio (0.2 mmol) of the coformers. For those experiments involving the sulfoxides, a 1:2 ratio (organohalide/sulfoxide) was also investigated. Mechanical grinding experiments were conducted in a Retsch MM400 Mixer mill, equipped with two stainless steel 5 mL grinding jars and one 2.5 mm stainless steel grinding ball per jar. The mill was operated at a rate of 30 Hz for 30 min.

Solution Cocrystallization. For cocrystallization from solution, either a 1:1 or 1:2 ratio of the organohalide/sulfoxide, respectively (0.3 mmol), was mixed together in the solid state, dissolved in acetonitrile, and allowed to stand at ambient temperature until the solvent had completely evaporated, between 3–9 days. The resulting crystalline material was analyzed by PXRD, IR, DSC, and, where appropriate, single crystal X-ray diffraction. For the cocrystals, **1c**, (±)-**1d**, (±)-**1e**, **1f**, and **1h**, the possibility of polymorphism was investigated by varying the solvent system used.

1,4-Diiodotetrafluorobenzene/Diphenyl Sulfoxide 1:1 Cocrystal (1c). Solid **1** (0.120 g, 0.30 mmol) and solid **c** (0.060 g, 0.30 mmol) were used. In all cases, needle crystals were obtained in quantitative yield, mp 102–106 °C. Anal. Calcd for $C_{18}H_{10}F_4I_2OS$: C, 35.79; H, 1.67. Found: C, 36.22; H, 1.76. IR (KBr) ν_{max}/cm^{-1}: 1026 (S=O).

1,4-Diiodotetrafluorobenzene/(±)-Phenyl 4-Tolyl Sulfoxide 1:1 Cocrystal, *α* Form (*α*-(±)-1d). Solid **1** (0.120 g, 0.30 mmol) and solid (±)-**d** (0.064 g, 0.30 mmol) were used. Crystalline needles were obtained from ethanol in quantitative yield, mp 80–82 °C. Anal. Calcd for $C_{19}H_{12}F_4I_2OS$: C, 36.92; H, 1.96. Found: C, 36.96; H, 2.27. IR (KBr) ν_{max}/cm^{-1}: 1046 (S=O).

1,4-Diiodotetrafluorobenzene/(±)-Phenyl 4-Tolyl Sulfoxide 1:1 Cocrystal, *β* Form (*β*-(±)-1d). Solid **1** (0.120 g, 0.30 mmol) and solid (±)-**d** (0.064 g, 0.30 mmol) were used. In all cases prismatic crystalline blocks were obtained from solutions of acetone, toluene, acetonitrile, or ethyl acetate, in quantitative yield, mp 60–62 °C. Anal. Calcd for $C_{19}H_{12}F_4I_2OS$: C, 36.92; H, 1.96. Found: C, 36.85; H, 1.81. IR (KBr) ν_{max}/cm^{-1} 1027 (S=O).

1,4-Diiodotetrafluorobenzene/(±)-Phenyl 2-Methoxyphenyl Sulfoxide 1:1 Cocrystal ((±)-1e). Solid **1** (0.120 g, 0.30 mmol) and solid (±)-**e** (0.070 g, 0.30 mmol) were used. Needle crystals were obtained in quantitative yield, mp 81–84 °C. IR (KBr) ν_{max}/cm^{-1}: 1017 (S=O).

1,4-Diiodotetrafluorobenzene/Thianthrene 5-Oxide 1:2 Cocrystal (1f). Solid **1** (0.120 g, 0.30 mmol) and solid **f** (0.139 g, 0.600 mmol) were used. Crystalline rods were obtained in quantitative yield, mp 122–124 °C. Anal. Calcd for $C_{30}H_{16}F_4I_2O_2S_4$: C, 41.58; H, 1.86. Found: C, 42.00; H, 1.92. IR (KBr) ν_{max}/cm^{-1}: 1031 (S=O).

1,4-Diiodotetrafluorobenzene/Di(2-phenyl)ethyl Sulfoxide 1:2 Cocrystal (1h). Solid **1** (0.120 g, 0.30 mmol) and solid **h** (0.154 g, 0.600 mmol) were used. Using ethyl acetate as solvent led to a mixture of **1h** with a slight contamination of both starting reagents **1** and **h** impurities. For all other solvents investigated, block crystals were obtained in quantitative yield, mp 72–74 °C. Anal. Calcd for $C_{38}H_{36}F_4I_2O_2S_2$: C, 49.68; H, 3.95. Found: C, 49.95; H, 3.92. IR (KBr) ν_{max}/cm^{-1}: 1015 (S=O).

Infrared Spectroscopy. Infrared spectra were recorded on a Perkin-Elmer 1000 spectrometer in the range of 4000–500 cm^{-1}.

Differential Scanning Calorimetry. Thermal analysis was recorded on a DSC Q1000 instrument. Samples (2–6 mg) were crimped in nonhermetic aluminum pans and scanned from 30 to 180 °C at a heating rate of 4 °C min^{-1} under a continuously purged dry nitrogen atmosphere.

Elemental Analysis. Elemental analysis was performed by the Microanalysis Laboratory, University College Cork, on a Perkin-Elmer 240 or an Exeter Analytical CE440 elemental analyzer.

Powder Diffraction. PXRD data were collected using a Stoe Stadi MP diffractometer with Cu Kα_1 radiation (λ = 1.5406 Å) at 40 kV and 40 mA using a linear PSD over the 2θ range of 3.5–45° with a step size equal to 0.5° and step time of 60 s.

Single Crystal Diffraction. Single crystal data for **f**, **h**, **1c**, *α*-(±)-**1d**, *β*-(±)-**1d**, (±)-**1e**, and **1f** were collected on a Bruker APEX II DUO diffractometer, as previously described.[11b] A Bruker SMART X2S diffractometer[21] was used for (R)-**d** and **1h**. All calculations and refinements were made using the APEX2 software,[22,23] and all diagrams were prepared using Mercury.[24]

The detailed crystallographic data and structure refinement parameters for these compounds are summarized in Tables 1 and 2.

Table 1. Crystallographic Data for the Coformers

	(*R*)-**d**	**f**	**h**
formula	$C_{13}H_{12}OS$	$C_{12}H_8OS_2$	$C_{16}H_{18}OS$
MW	216.29	232.32	258.38
crystal system	orthorhombic	orthorhombic	triclinic
space group, *Z*	$P2_12_12_1$, 4	*Fdd*2, 8	$P\bar{1}$, 2
a, Å	5.6947(10)	16.011(3)	5.5050(5)
b, Å	8.1334(13)	32.093(6)	9.1593(9)
c, Å	25.063(5)	4.0823(8)	13.5985(13)
α, deg	90	90	83.769(2)
β, deg	90	90	86.622(2)
γ, deg	90	90	84.422(2)
V, Å^3	1160.8(3)	2097.7(7)	677.57(11)
D_c, g·cm^{-3}	1.238	1.471	1.266
μ, mm^{-1}	0.249	0.473	0.224
2θ range, deg	2.63–25.46	2.54–25.88	1.51–28.41
T, K	300(2)	293(2)	100(2)
total ref	9085	2741	16152
unique ref	2101	907	3351
obs ref, $I > 2\sigma(I)$	1688	826	3161
no. parameters	137	73	163
R_1 [$I > 2\sigma(I)$]	0.0386	0.0296	0.0297
wR_2	0.1029	0.0685	0.0816
S	1.064	1.1125	1.063
Flack	0.00(11)	0.25(11)	

Table 2. Crystallographic Data for the Cocrystals

	1c (1:1)	α-(±)-**1d** (1:1)	β-(±)-**1d** (1:1)	(±)-**1e** (1:1)	**1f** (1:2)	**1h** (1:2)
formula	$C_{18}H_{10}F_4I_2OS$	$C_{19}H_{12}F_4\ I_2OS$	$C_{19}H_{12}F_4\ I_2OS$	$C_{19}H_{12}F_4I_2O_2\ S$	$C_{15}H_8F_2IOS$	$C_{19}H_{18}F_2IOS$
MW	603.85	618.15	618.15	634.15	433.23	459.29
crystal system	triclinic	monoclinic	monoclinic	triclinic	monoclinic	triclinic
space group, *Z*	$P\bar{1}$, 2	$P2_1/c$, 4	$P2_1/c$, 4	$P\bar{1}$, 2	$P2_1/c$, 4	$P\bar{1}$, 2
a, Å	10.2726(19)	9.5808(6)	14.198(4)	8.1472(17)	4.1227(7)	5.5989(10)
b, Å	10.3038(19)	22.0739(15)	5.8227(17)	8.474(2)	27.533(4)	12.993(3)
c, Å	11.177(2)	9.5433(6)	24.354(5)	15.551(4)	13.440(2)	13.328(3)
α, deg	113.093(4)	90	90	99.470(4)	90	100.050(7)
β, deg	108.007(5)	91.1500(10)	90.205(5)	98.137(8)	97.344(3)	95.129(7)
γ, deg	100.815(5)	90	90	94.507(4)	90	95.360 (7)
V, Å^3	968.3(3)	2017.9(2)	2013.3(9)	1042.6(4)	1513.1(4)	945.0(3)
D_c, g·cm^{-3}	2.072	2.035	2.039	2.020	1.902	1.614
μ, mm^{-1}	3.396	3.262	3.270	3.163	2.407	1.826
2θ range, deg	2.19−25.79	1.85−27.12	1.67−27.20	1.34−26.49	1.70−26.50	1.56−24.99
T, K	296(2)	296(2)	296(2)	296(2)	296(2)	300(2)
total ref	21496	24478	24206	47697	18003	9328
unique ref	3704	4440	4452	4275	3101	3311
obs ref, $I > 2\sigma(I)$	2985	3213	3057	3514	2666	2639
no. parameters	235	245	245	254	190	217
R_1 $[I > 2\sigma(I)]$	0.0265	0.0388	0.0330	0.0365	0.0572	0.0415
wR_2	0.0590	0.1025	0.0731	0.0942	0.1492	0.1312
S	1.066	1.025	1.028	1.032	1.198	1.142

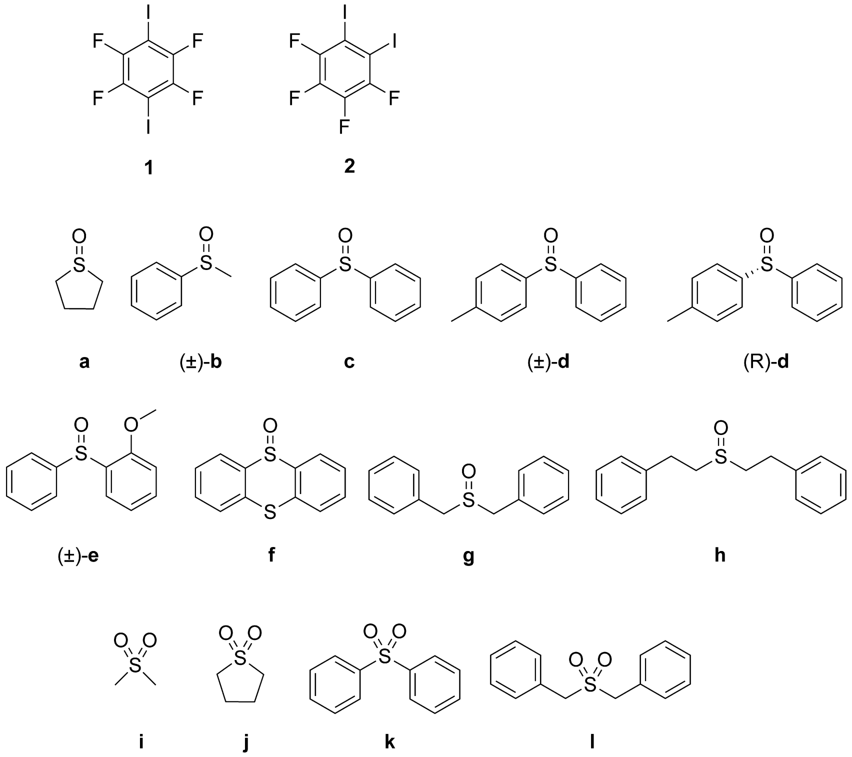


Figure 1. The organohalides, **1**−**2**, investigated as coformers with the sulfoxides and sulfones, **a**−**l**.

Database Analysis of Iodine···π-ring Interactions. The radial distribution plot (Figure 3) was created from a search of the CSD, version 5.32 (November 2010), with the ConQuest 1.13 program.[25] The following general search flags were set: *R* factor of ≤0.10, "3D coordinates determined", not disordered, no ions, no errors, not polymeric, and only organic. This search yielded all 1-coordinate iodine atoms interacting with an aromatic ring, which were within 7.0 Å to the centroid of the ring, and it reported the distance to the centroid *r* as well as the orthogonal distance between the iodine atom and the plane of the aromatic ring *h*. From *h* and *r*, the value of the centroid shift, *s* (the in-plane distance between the centroid of the aromatic ring and the iodine atom) was calculated using Pythagoras' theorem ($r^2 = h^2 + s^2$). The radial distribution plot was created by counting hits in bins of size 0.1 Å × 0.1 Å (*h* versus *s*) and scaling the results by $1/4\pi r^2$, where *r* was the distance between the centroid and an atom at the center of the bin.

Density Functional Theory Calculations. Density functional theory (DFT) calculations were carried out using Gaussian09[26] and the M062X hybrid meta functional.[27] The 6-31G(d,p) basis set was used for all atoms apart from iodine, for which the LANL2DZdp

Table 3. Screening Results for Successful Cocrystal Formation, Based on PXRD Data

coformer	grinding	CH_2Cl_2	acetone	ethyl acetate	ethanol	acetonitrile	toluene
c	**1c**	**1c**^{a}	**1c**^{a}	**1c**^{b}	**1c**^{c}	**1c**^{b}	**1c**^{d}
(±)-**d**	(±)-**1d**^{e}	(±)-**1d**^{a,e}	(±)-**1d**^{a,f}	(±)-**1d**^{b,e}	(±)-**1d**^{c,f}	(±)-**1d**^{b,f}	(±)-**1d**^{d,e}
(±)-**e**	(±)-**1e**	not attempted	(±)-**1e**^{a}	not attempted	(±)-**1e**^{c}	(±)-**1e**^{c}	(±)-**1e**^{d}
f	**1f**^{g}	**1f**^{a}	**1f**^{a}	**1f**^{c,h}	**1f**^{c}	**1f**^{c}	**1f**^{i}
h	**1h**^{j}	**1h**^{a}	**1h**^{a}	**1h**^{c,k}	**1h**^{c}	**1h**^{c}	**1h**^{l}

[a] Left to stand for 2 days. [b] Left to stand for 5 days. [c] Left to stand for 4 days. [d] Left to stand for 9 days. [e] Exclusively the α-(±)-**1d** polymorph. [f] Mixture of α-(±)-**1d** and β-(±)-**1d** polymorphs. [g] Mixture of **1** and **f** using 1:1 stoichiometry; 1:2 stoichiometry gave exclusively **1f**. [h] Mixture of **1f** and small amount of coformers. [i] Left to stand for 8 days. [j] Mixture of **1** and **h** using 1:1 stoichiometry; 1:2 stoichiometry gave exclusively **1h**. [k] Mixture of **1h** and small amount of coformers. [l] Left to stand for 7 days.

pseudopotential and basis set was used[28] (taken from the EMSL basis set exchange[29]). After geometry optimization, structures were verified to be at a minimum by the absence of an imaginary frequency, and all energies were corrected for zero-point error. The systems containing both coformers were optimized using the counterpoise correction to account for basis set superposition error. Wiberg bond orders were calculated using the NBO program (as part of Gaussian09).[30]

■ RESULTS AND DISCUSSION

Cocrystallization screening investigated 1,4-diiodotetrafluorobenzene, **1**, with a range of sulfoxides and sulfones, **a**–**l** as shown in Figure 1. The 1,2- analogue, **2**, was investigated with the sulfoxides **a**, **c**, **g**, and **h**. The sulfoxides and sulfones were specifically chosen to minimize competing intermolecular interactions and, thereby, maximize the likelihood of the desired I···O=S synthon prevailing. At the outset, it was anticipated that cocrystals with either a 1:1 or 1:2 stoichiometry could be possible because (i) either one or both iodine atoms are available for halogen bonding and (ii) the lone pairs on each oxygen atom allow the oxygen atoms to potentially participate in either a discrete (capping) arrangement with the iodine atoms, or a bifurcated arrangement.[31]

Table 4. Melting Point, °C, and ν(S=O), cm^{-1}, for Cocrystals Formed in This Work

sulfoxide coformers[a]			cocrystals		
	mp, °C	ν(S=O), cm^{-1}		mp, °C	ν(S=O), cm^{-1}
c	70–71[34]	1037[34]	**1c**	102–106	1026
(±)-**d**	64–65[35]	1015	α-(±)-**1d**	80–84	1013
			β-(±)-**1d**	60–62	1028
(±)-**e**	98–99[36]	1032[36]	(±)-**1e**	81–84	1017
f	142–143[20]	1033	**1f**	122–124	1031
h	54–58	1028	**1h**	72–74	1015

[a] mp of **1** is 108–110 °C.[33]

Table 5. Calculated and Experimental Parameters for Two Cocrystals, 1c and 1e, and the Corresponding Sulfoxide Coformers

	c		**e**	
	calcd	exptl	calcd	exptl
O···I distance, Å	2.835	2.851(2)	2.820	2.815(4)
S=O···I angle, deg	119	122.75(14)	124	124.1(2)
interaction energy, kJ/mol	4.9		30.1	
S=O in sulfoxide	1.506	1.4953(12)[38]	1.507	unknown
S=O in cocrystal	1.517	1.491(3)	1.518	1.483(4)
S=O bond order in sulfoxide	1.22		1.21	
S=O bond order in cocrystal	1.17		1.17	

The initial screening was performed via neat grinding of an equimolar mixture of the two coformers in the mill for 30 min at 30 Hz, and the material generated was analyzed using PXRD. In addition, the individual components were dissolved in a range of solvents, and solution crystallization, via slow evaporation, was undertaken. The reasons for this were twofold: (i) for comparison with the grinding experiments and (ii) to obtain crystals suitable for single crystal X-ray diffraction analysis. The results of the successful grinding experiments and the solution crystallization experiments, based on PXRD data, are presented in Table 3. In all cases the results from the grinding experiments were consistent with those obtained from solution crystallization, with cocrystallization observed in five combinations of **1** and the sulfoxide, namely the cocrystals **1c**, (±)-**1d**, (±)-**1e**, **1f**, and **1h**. There was no evidence for cocrystallization involving **2** or any of the sulfones (**i**–**l**) in this study.

In combination with PXRD, IR and DSC were used to confirm cocrystal formation, as well as to aid in the determination of stoichiometric composition. DSC analysis was undertaken on the material obtained from the grinding experiments. In addition to the presence of new crystalline material, melting events due to **1** were observed in the samples involving **f** and **h** that were obtained by grinding, indicating the formation of cocrystals containing an excess of the sulfoxide coformer. Table 4 lists the melting points and the changes in the ν(S=O) stretching frequency for those combinations of coformers that gave rise to successful cocrystallization. A decrease in the melting point was observed for all complexes relative to that of the highest coformer. This is consistent with the major trend found in the melting point of cocrystals, whereby the melting point of the cocrystal is between the melting points of the two coformers.[32]

In all cocrystals a bathochromic shift in the S=O stretching frequency relative to that of the sulfoxide starting material was observed. There is a red shift seen for **1c**, α-(±)-**1d**, (±)-**1e**, **1f**, and **1g** relative to that of the starting material, which is due to halogen bonding interactions between the halogen atom and the sulfoxide oxygen, leading to a decrease in the sulfoxide bond order and, hence, a decrease in the sulfoxide stretching frequency upon complexation. Similar effects have been seen involving hydrogen bonding to sulfoxides and sulfonamides.[11,37]

To investigate the S=O···I interaction further, gas-phase DFT calculations were carried out on two coformer pairs, **1** with **c**, and **1** with **e**, using the M062X hybrid functional, as well as on the individual sulfoxides (Table 5). The calculations indicate a slight increase in the S=O bond length and a corresponding

Table 6. Details of the Intermolecular Interactions Observed in the Cocrystals

cocrystal	stoichiometry	nature of interaction	distance,[a] Å	angle at I, °	angle at O, °	no. of interactions with O
1c	1:1	I···O	2.851(2)	172.46(7)	122.75(14)	1
		I···π	3.38[b]	76.00[c]		
α-(±)-**1d**	1:1	I···O	3.096(4)	160.99(16)	139.17(19)	2
		I···O	2.912(4)	178.10(14)	103.03(17)	
β-(±)-**1d**	1:1	I···O	2.850(3)	172.05(12)	159.79(18)	1
		I···π	3.46[b]	75.48[c]		
(±)-**1e**	1:1	I···O	2.815(4)	178.50(15)	124.1(2)	1
		I···I	3.8577(9)	170.27(16)	105.80(12)[d]	
1f	1:2	I···O	2.857(6)	175.5(3)	123.3(4)	2
		C−H···O	2.51[e]	168[f]		
1h	1:2	I···O	2.985(3)	173.71(11)	119.75(13)	2
		C−H···O	2.47[g]	154[f]		

[a] Note that the sum of the van der Waals radii is 3.50 Å.[31] [b] The distance from the I to the plane of the benzene ring. [c] The angle between the C−I bond and the plane of the benzene ring. [d] The angle at the 2nd I. [e] This is the H···O distance; the C···O distance is 3.421(10) Å. [f] The angle subtended at the H. [g] This is the H···O distance; the C···O distance is 3.372(4) Å.

Figure 2. 2:2 arrangement of coformers found in **1c**.

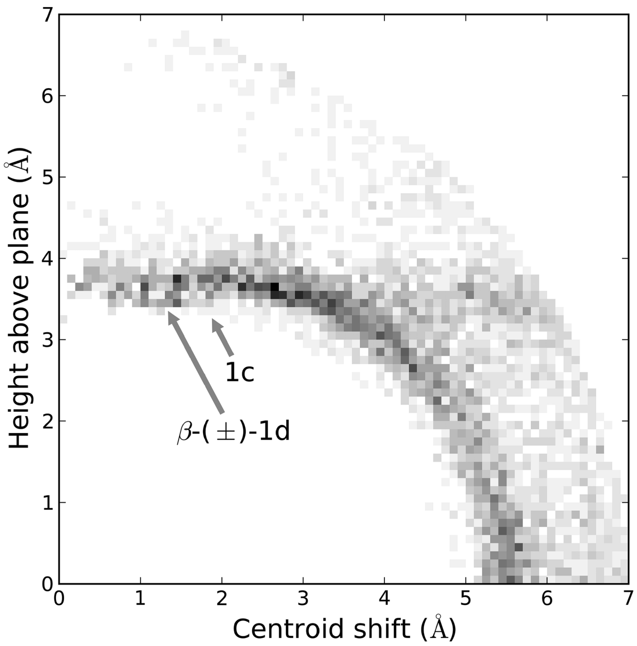


Figure 3. Radial distribution plot of I···π interactions in the CSD. The *y* axis shows the height of the iodine atom above the plane of the phenyl ring, while the *x* axis indicates the distance between the iodine atom and the centroid of the phenyl ring, measured in the plane of the ring. The interactions observed in the structures of **1c** and β-(±)-**1d** are also included and are indicated by the arrows. The total number of interactions depicted is 6,645, which were obtained from a total of 839 crystal structures.

small decrease in the S=O bond order, upon cocrystallization, which is consistent with the IR data. The overall interaction energy is quite low for **1** with **c** but appreciable for **1** with **e**.

All cocrystals were grown from multiple solvents to investigate the potential for stoichiometric or polymorphic cocrystals. In all cases the neat grinding and solution crystallization matched the theoretical pattern obtained from single crystal analysis, as detailed in the Supporting Information. All cocrystals grown from the solution crystallization experiments exhibited a single endotherm in the DSC, consistent with the data presented in Table 4.

The crystal structures of three coformers, (R)-**d**, **f**, and **h**, were unknown at the start of this work, and so these were determined to help with PXRD identification of any possible cocrystals (see the Supporting Information). There is significant similarity between the structure of the monosulfoxide **f** and the α form of the related bissulfoxide, *cis*-thianthrene-5,10-dioxide, which is in the CSD with no 3D coordinates (refcode: TANTOX).[39] Consideration of the reduced cell, the microanalysis data, and the melting points[20,40] (see the Supporting Information) strongly suggests that the unit cell of *cis*-thianthrene 5,10-dioxide in the CSD is actually that of the monosulfoxide, **f**, although the possibility that they are (almost) isostructural cannot be ruled out.

The crystal structure of the cocrystal **1c** shows a 1:1 stoichiometry of the two coformers. As anticipated, halogen bonding is observed between the iodine and the oxygen of the sulfoxide group (Table 6). The oxygen atom does not interact in a bifurcated manner, as may be expected from the 1:1 stoichiometry. Instead, the second iodine atom is involved in I···π bonding with the phenyl ring of the sulfoxide. Together, these two halogen interactions combine to form discrete 2:2 molecular complexes (Figure 2).

The I···π interactions observed in the structure of **1c** are also observed in that of β-(±)-**1d**, as detailed in Table 6. Therefore, a search of the CSD was undertaken and the results analyzed

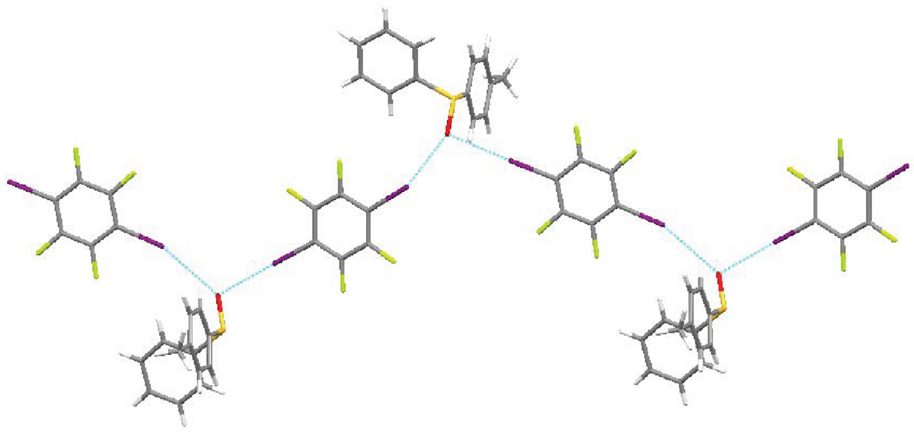


Figure 4. I···O=S interactions present in *α*-(±)-**1d**.

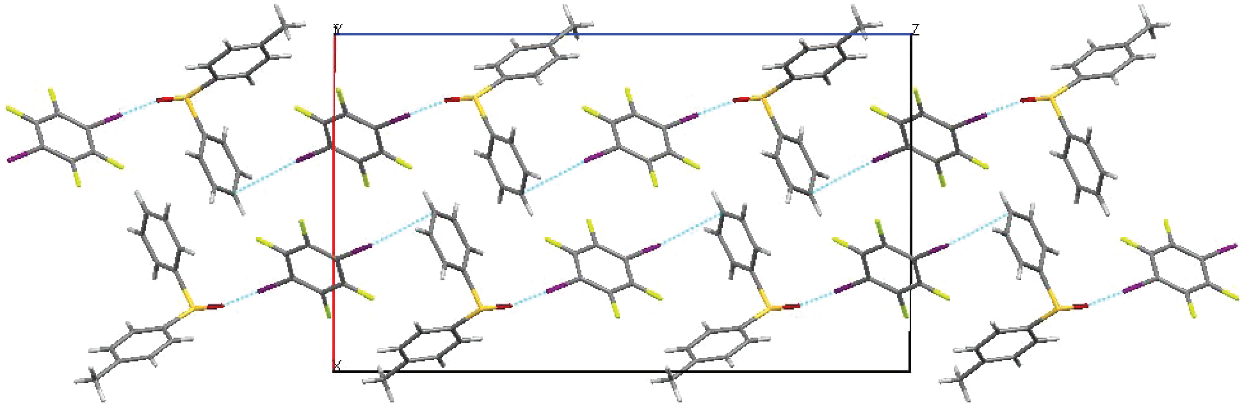


Figure 5. I···O=S and I···*π* interactions present in *β*-(±)-**1d**.

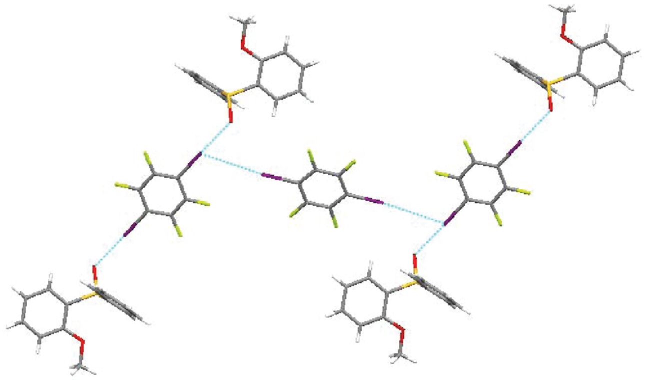


Figure 6. I···O=S and I···I interactions present in (±)-**1e**.

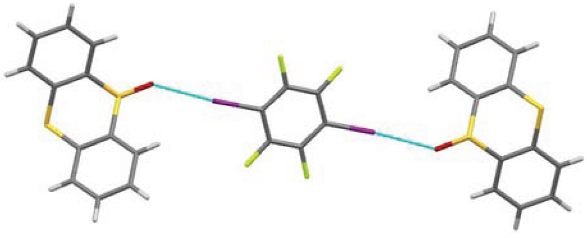


Figure 7. Halogen interactions in cocrystal **1f**.

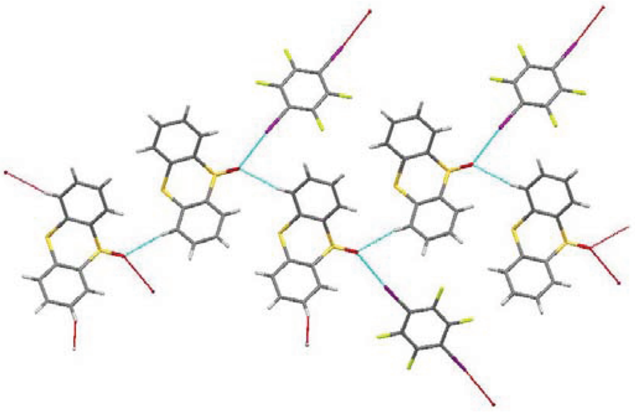


Figure 8. Zigzag C(6) hydrogen-bonded chain present in cocrystal **1f**.

using the method described by Bissantz,[41] who had examined F···*π* and Cl···*π* interactions. The results observed for the I···*π* interactions are shown as a radial distribution plot (Figure 3) with the location of the I···*π* interactions from structures **1c** and *β*-(±)-**1d** highlighted in relation to those found in the CSD. Both interactions have among the shortest centroid to iodine distances found for a particular angular location from the ring centroid.

The cocrystal (±)-**1d** forms two polymorphs of 1:1 stoichiometry. Crystals grown from ethanol gave rise to the *α* form, *α*-(±)-**1d**, in which the iodine forms the intended I···O=S interaction, although in this case the oxygen is bifurcated between neighboring molecules of **1**, resulting in an infinite zigzag chain (Figure 4). The packing in this crystal structure is

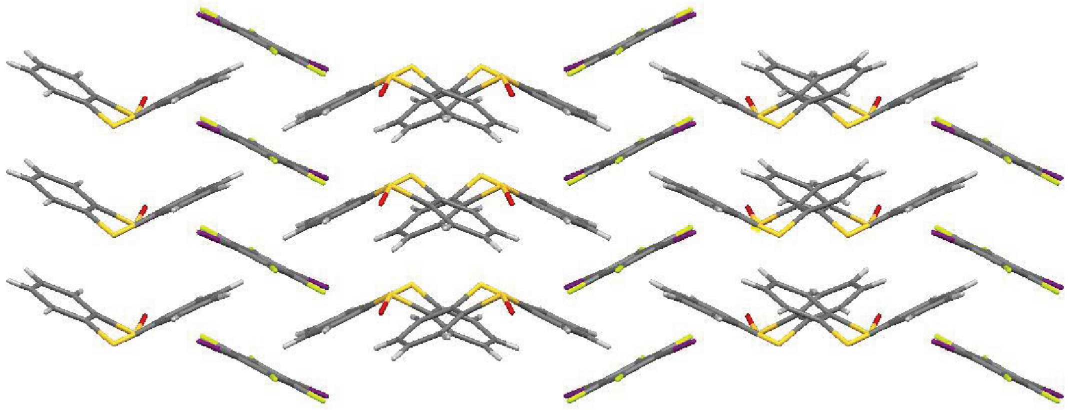


Figure 9. Packing in **1f**, viewed along the *c*-axis.

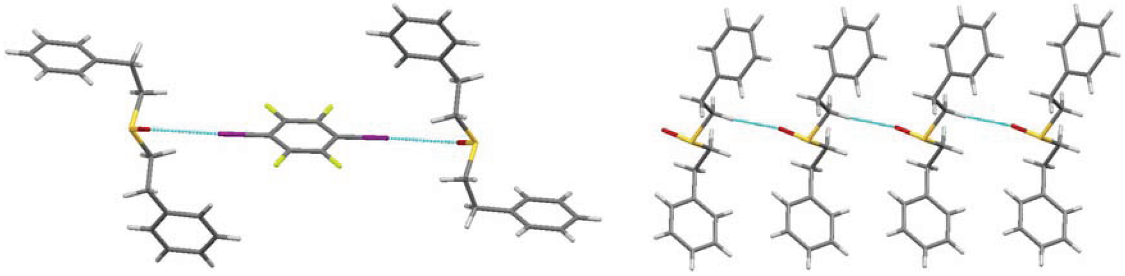


Figure 10. Halogen bonds bridging the sulfoxides in **1h**, left, and the C(4) chain between sulfoxides, right.

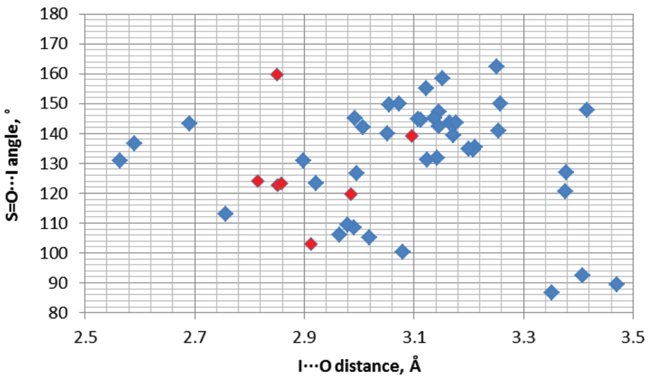


Figure 11. Plot of S=O···I angle versus I···O distance for S=O···I halogen bonding found in these cocrystals (red) and the crystal structures deposited in the CSD (blue).

similar to that seen in the cocrystal between **1** and triphenyl phosphine oxide, of which one form is known.[31]

Crystals grown from acetonitrile gave rise to the *β* form, *β*-(±)-**1d**, which displays the anticipated I···O=S halogen bonding (Table 6). Similar to the crystal structure of **1c**, it consists of the oxygen interacting with one iodine atom, as well as I···*π* bonding involving the phenyl ring of the sulfoxide (Figure 5). However, there is a difference in the overall packing, with the formation of infinite linear chains rather than the discrete 2:2 complex seen in **1c**. The *α* polymorph is obtained from solutions of CH_2Cl_2, ethyl acetate, or toluene. A mixture of both polymorphs is initially obtained from acetone, acetonitrile, or ethanol solutions, as evidenced by DSC and PXRD. The harvested crystals converted to the *α* polymorph after standing at room temperature over a period of two months. It was concluded that the *β* polymorph is metastable with respect to the *α* polymorph.

The crystal structure of (±)-**1e** shows a 1:1 stoichiometry of the two coformer components. The asymmetric unit consists of one molecule of (±)-**e** and two crystallographically unique half molecules of **1**, both located over an inversion center.

The iodine of one molecule of **1** forms a halogen bonding interaction to the oxygen of the sulfoxide, so that the molecule of **1** is capped by two sulfoxide molecules, forming a linear three-molecule motif. The other molecule of **1** bridges neighboring motifs via I···I halogen bonding (Figure 6). Notably, there is no significant interaction with the oxygen of the methoxy group.

The 1:2 cocrystal **1f** crystallizes with **1** located over the inversion center. The anticipated halogen bonding between the iodine and the oxygen of the sulfoxide group is observed (Table 6 and Figure 7). The oxygen acts in a bifurcated fashion, with additional weak hydrogen bonding to one of the aryl protons, forming a zigzag C(6) chain along the *c*-axis (Figure 8). Thus, the structure consists of chains of sulfoxide molecules linked together by the halogen-substituted aromatic molecules (Figure 9). The crystal structure of **1f** provides further evidence that the crystal structure of **f** is correct, as it is highly unlikely that grinding of the bissulfoxide with **1** would result in a loss of oxygen in forming **1f**. This was investigated by grinding a sample of **f** in the absence of **1**, which showed no change to the material, as evident from DSC, microanalysis, and PXRD. Of all the cocrystals formed in this work, **1f** is the only one that exhibits some instability; in the solid state it decomposes into the two coformers in approximately 2 weeks in ambient conditions.

The crystal structure of **1h** is similar to that of **1f**, as it too has a 1:2 stoichiometry. The molecule of **1** lies over the inversion center, and the sulfoxide acts in a bifurcated manner, exhibiting both halogen bonding and weak hydrogen bonding (Figure 10). In **1h** the protons *α* to the sulfoxide are involved in weak hydrogen bonding, forming C(4) chains in a similar manner to that seen in the structure of the parent sulfoxide, **h** (see the Supporting Information). Such interactions have been shown to be structure-directing in sulfoxides.[42] The combination of halogen interactions and weak hydrogen bonds results in infinite 1D ladders in which the C(4) chains are bridged by the iodine species.

Examination of the CSD showed that the S=O····I halogen bonding in these cocrystals is similar to those found in other crystal structures present in the CSD (Figure 11).

CONCLUDING REMARKS

Cocrystallization involving I···O=S halogen bonding was successful for five of the nine sulfoxides studied, in all cases with the *para*-substituted organohalide, **1**. This may not be surprising; there are more reports of **1** being used in halogen bonding studies than **2**. For all cocrystals, the I···O intermolecular interaction was the dominant interaction in all cases, with a distance range of 2.82−3.09 Å, indicating strong halogen bonding. The length and directionality of the halogen bonds is consistent with the literature.[7a] In all cases the organohalide molecule bridges the sulfoxide molecules.

Both 1:1 and 1:2 stoichiometries, of **1** and sulfoxide respectively, are observed; for the latter case, this was always seen with a combination of both halogen bonding and weak hydrogen bonding. Despite the presence of the robust I···O=S synthon, it was found that it is the weak hydrogen bonding that is significant in determining the 3D architectures observed in the solid state. The stoichiometry observed is not necessarily related to whether the oxygen acts in a discrete fashion or if it is bifurcated, with I···π interactions observed in two of the cocrystals examined.

Two of the sulfoxides that did not cocrystallize with **1**, **a** and **b**, have melting points just above ambient temperature. A third, **g**, is more interesting for two reasons: first, it crystallizes with Z' = 2,[11,43] and compounds with high Z' have been shown to be good coformers,[44] although this is best used to indicate likely candidates for cocrystallization, as it is an empirical observation. Second, the chemical structure of **g** is closely related to that of **c** and **h**, both of which did form cocrystals. The enantiopure sulfoxide (*R*)-**d** did not form a cocrystal with **1**.

Cocrystallization was not observed with any of the sulfones studied, which, similar to the results of other studies,[11] suggests that the increased polarity of the sulfoxide functional group, in comparison with the sulfone functional group, is a significant contributor to the strength of the intermolecular interactions that promote cocrystal formation.

In conclusion, cocrystals between 1,4-diiodotetrafluorobenzene and sulfoxides show that I···O=S halogen bonding is a robust supramolecular synthon and merits further attention. For each of the cocrystals formed in this work, there were two significant noncovalent interactions present, regardless of the stoichiometry found in the cocrystals. For the 1:1 cocrystals, there were three sets of significant intermolecular interactions observed: (i) two I···O=S halogen bonds, or (ii) one I···O=S halogen bond, and one I···π interaction, or (iii) one I···O=S halogen bond and one I···I interaction. For the 1:2 cocrystals, one I···O=S halogen bond is seen in conjunction with one weak C−H···O hydrogen bond.

ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic information in CIF format, DSC and PXRD data, optimized coordinates from DFT calculations, and additional figures. This material is available free of charge via the Internet at http://pubs.acs.org. The crystallographic data for (R)-**d**, **f**, **h**, **1c**, *α*-(±)-**1d**, *β*-(±)-**1d**, (±)-**1e**, **1f**, and **1h** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 863887−863895. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.lawrence@ucc.ie. Tel.: +353 21 490 3143. Fax: +353 21 427 4097.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This publication has emanated from research conducted with the financial support of Science Foundation Ireland, under Grant Nos. 07/SRC/B1158 (K.E., S.S., J.H., D.K.), 05/PICA/B802 TIDA 09 (L.F.), and 05/PICA/B802/EC07; the Irish Research Council for Science, Engineering and Technology (G.O'M.), and a Health Research Board Career Development Fellowship PD/2009/13 (N.O'B.). We thank the SFI/HEA Irish Centre for High-End Computing (ICHEC) for the provision of computational facilities.

REFERENCES

(1) (a) Trask, A. V. *Mol. Pharmaceutics* **2007**, *4*, 301−309. (b) Shan, N.; Zaworotko, M. J. *Drug Discovery Today* **2008**, *13*, 440−446.

(2) (a) Aakeröy, C. B.; Salmon, D. J. *CrystEngComm* **2005**, *7*, 439−448. (b) Stahly, G. P. *Cryst. Growth Des.* **2009**, *9*, 4212−4229.

(3) Fábián, L. *Cryst. Growth Des.* **2009**, *9*, 1436−1443.

(4) Trask, A. V.; Jones, W. *Top. Curr. Chem.* **2005**, *254*, 41−70.

(5) (a) Weyna, D. R.; Shattock, T.; Vishweshwar, P.; Zaworotko, M. J. *Cryst. Growth Des.* **2009**, *9*, 1106−1123. (b) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Chem. Commun.* **2004**, 890−891.

(6) McCausland, L. PCT Int. Appl. WO2007075793, 2007.

(7) (a) Rissanen, K. *CrystEngComm* **2008**, *10*, 1107−1113. (b) Metrangolo, P.; Neukirch, H.; Pilati, T.; Resnati, G. *Acc. Chem. Res.* **2005**, *38*, 386−395. (c) Sarma, J. A. R. P.; Allen, F. H.; Hoy, V. J.; Howard, J. A. K.; Thaimattam, R.; Biradha, K.; Desiraju, G. R. *Chem. Commun.* **1997**, 101−102. (d) Thallapally, P. K.; Desiraju, G. R.; Bagieu-Beucher, M.; Masse, R.; Bourgogne, C.; Nicoud, J.-F. *Chem. Commun.* **2002**, 1052−1053.

(8) (a) Chopra, D. *Cryst. Growth Des.* **2012**, *12*, 541−546. (b) Chopra, D.; Nagarajan, K.; Guru Row, T. N. *J. Mol. Struct.* **2008**, *888*, 70−83. (c) Thakur, T. S.; Kirchner, M. T.; Bläser, D.; Boese, R.; Desiraju, G. R. *CrystEngComm* **2010**, 2079−2085. (d) Dikundwar, A. G.; Guru Row, T. N. *Cryst. Growth Des.* **2012**, *12*, 1713−1716.

(9) Weiss, R.; Schwab, O.; Hampel, F. *Chem.—Eur. J.* **1999**, *5*, 968−974.

(10) Aakeröy, C. B.; Schultheiss, N. C.; Rajbanshi, A.; Desper, J.; Moore, C. *Cryst. Growth Des.* **2009**, *9*, 432−441.

(11) (a) Eccles, K. S.; Elcoate, C. J.; Stokes, S. P.; Maguire, A. R.; Lawrence, S. E. *Cryst. Growth Des.* **2010**, *10*, 4243−4245. (b) Eccles, K. S.; Elcoate, C. J.; Maguire, A. R.; Lawrence, S. E. *Cryst. Growth Des.* **2011**, *11*, 4433−4439.

(12) Arman, H. D.; Gieseking, R. L.; Hanks, T. W.; Pennington, W. T. *Chem. Commun.* **2010**, *46*, 1854−1856.

(13) Cinčić, D.; Friščić, T.; Jones, W. *Chem.—Eur. J.* **2008**, *14*, 747−753.
(14) Allen, F. H. *Acta Crystallogr.* **2002**, *B58*, 380−388.
(15) Britton, D. *Acta Crystallogr.* **2003**, *E59*, o1332−1333.
(16) Xu, H. J.; Zhao, X. Y.; Fu, Y.; Feng, Y. S. *Synlett* **2008**, *19*, 3063−3067.
(17) Eccles, K. S.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *ARKIVOC* **2010**, *ix*, 216−228.
(18) Hirano, M.; Tomaru, J.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3752−3754.
(19) Drabowicz, J.; Bujnicki, B.; Mikołajczyk, M. *J. Org. Chem.* **1982**, *47*, 3325−3327.
(20) Gilman, H.; Swayampati, D. R. *J. Am. Chem. Soc.* **1955**, *77*, 3387−3389.
(21) Eccles, K. S.; Stokes, S. P.; Daly, C. A.; Barry, N. M.; McSweeney, S. P.; O'Neill, D. J.; Kelly, D. M.; Jennings, W. J.; Ní Dhubhghaill, O. M.; Moynihan, H. A.; Maguire, A. R.; Lawrence, S. E. *J. Appl. Crystallogr.* **2011**, *44*, 213−215.
(22) *APEX2 v2009.3-0*; Bruker AXS: 2009.
(23) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122.
(24) Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. *J. Appl. Crystallogr.* **2008**, *41*, 466−470.
(25) Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. *Acta Crystallogr.* **2002**, *B58*, 389−397.
(26) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision B.1; Gaussian, Inc.: Wallingford, CT, 2009.
(27) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(28) Check, C. E.; Faust, T. O.; Bailey, J. M.; Wright, B. J.; Gilbert, T. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2001**, *105*, 8111−8116.
(29) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model.* **2007**, *47*, 1045−1052.
(30) NBO Version 3.1. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F.
(31) Cinčić, D.; Friščić, T.; Jones, W. *CrystEngComm* **2011**, *13*, 3224−3231.
(32) Schultheiss, N.; Newman, A. *Cryst. Growth Des.* **2009**, *9*, 2950−2967.
(33) Syssa-Magalé, J. L.; Boubekeur, K.; Palvadeau, P.; Meerschaut, A.; Schöllhorn, B *CrystEngComm* **2005**, *7*, 302−308.
(34) Oae, S.; Zalut, C. *J. Am. Chem. Soc.* **1960**, *82*, 5359−5363.
(35) Noguchi, Y.; Kurogi, K.; Sekioka, M.; Furukawa, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 349−350.
(36) Meyers, C. Y. *Gazz. Chim. Ital.* **1963**, *93*, 1206−1221.
(37) Goud, N. R.; Babu, N. J.; Nangia, A. *Cryst. Growth Des.* **2011**, *11*, 1930−1939.
(38) Casarini, D.; Lunazzi, L.; Mazzanti, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2536−2540.
(39) Hosoya, S.; Wood, R. G. *Chem. Ind. (London)* **1957**, 1042.
(40) Bonchio, M.; Conte, V.; De Conciliis, M. A.; Di Furia, F.; Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M. *J. Org. Chem.* **1995**, *60*, 4475−4480.
(41) Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061−5084.
(42) Brondel, N.; Moynihan, E. J. A.; Lehane, K. N.; Eccles, K. S.; Elcoate, C. J.; Coles, S. J.; Lawrence, S. E.; Maguire, A. R. *CrystEngComm* **2010**, *12*, 2910−2927.
(43) (a) Fuller, A. L.; Aitken, R. A.; Ryan, B. M.; Slawin, A. M. Z.; Woollins, J. D. *J. Chem. Crystallogr.* **2009**, *39*, 407−415. (b) Zeng, Y. X.; Xu, Z. G.; Zhan, Q. G.; Liu, H. Y. *Acta Crystallogr.* **2011**, *E67*, o177.
(44) Anderson, K. M.; Goeta, A. E.; Steed, J. W. *Cryst. Growth Des.* **2008**, *8*, 2517−2524.