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# Unzipping the Dimer in Primary Amides by Cocrystallization with Sulfoxides.

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**ABSTRACT:** A systematic crystal engineering study was undertaken to investigate how different electronic substituents on the aromatic ring of primary aromatic amides impact on the ability of the amide to cocrystallize with dibenzyl sulfoxide. Amides which cocrystallize with dibenzyl sulfoxide form 1:1 cocrystals containing a discrete N-H•••O=S supramolecular synthon as well as the well-known C(4) amide chain. The combination of these two synthons give rise to linear chains of amide molecules, with each amide molecule capped by one sulfoxide molecule. Thus, the  $R_2^2(8)$  dimer typically seen for primary amides is no longer present in these cocrystals. The influence of the amide due to electronic effects is similar to that observed for acids in cocrystals.

## Introduction

Hydrogen bonding is one of the most important fundamental interactions involved in the association of organic molecules,<sup>1</sup> giving rise to a variety of different supramolecular synthons.<sup>2</sup> One of the most dominant supramolecular motifs in organic and organometallic chemistry is the  $R_2^2(8)$  dimer seen particularly in carboxylic acid and amides, Figure 1.<sup>3,4</sup> This motif is very commonly seen in the solid state structures of such systems.

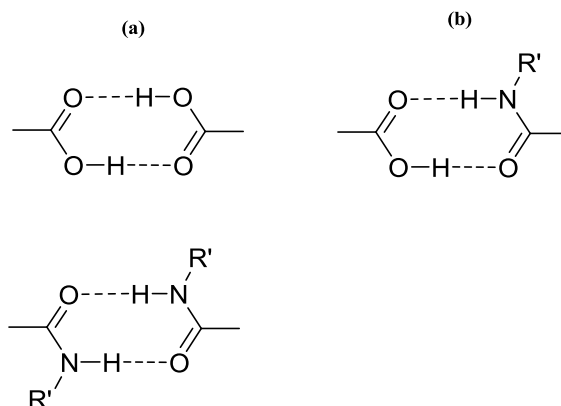


Figure 1. Schematic representation of supramolecular synthons between carboxylic acids and amides: (a) supramolecular homosynthons as exhibited by acid–acid and amide–amide dimers; (b) supramolecular heterosynthons as exhibited by acid–amide dimers.

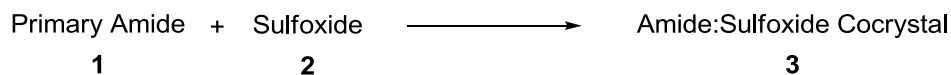
This amide dimer is a robust supramolecular synthon and is widely used in cocrystal design.<sup>5</sup> Polymorphs of primary amides generally exhibit different stacking of the dimer pairs.<sup>4,6-7</sup> It is also significant that for primary amides this motif persists even in the presence of other hydrogen-bonding features, often leading to the formation of complex 3-dimensional hydrogen-bonded arrays.<sup>8</sup>

The sulfoxide functional group is a potent hydrogen-bond acceptor, as detailed by Hunter,<sup>9</sup> and the simplest sulfoxide, dimethyl sulfoxide (DMSO), is commonly encountered as a solvate in the solid state.<sup>10</sup> We recently reported that the  $N-H\cdots O=S$  heterosynthon can be used to form cocrystals involving nitrogen bases and sulfoxides.<sup>11</sup> A search of the Cambridge Structural Database<sup>12</sup> reveals a significant number of structures which contain both the sulfoxide functionality and primary amides. This can occur with both functional groups present in the same molecule or in different molecules. Analysis of their

solid state structures reveals a number of interesting features. The  $R_2^2(8)$  dimer of the primary amide persists for many of these structures, for example carbamazepine with DMSO.<sup>13</sup> Mash and co-workers have incorporated dipropylsulfoxide with secondary amides in piperazine-2,5-diones,<sup>14</sup> and Kagan has crystallized (R)-methyl *p*-tolyl sulfoxide with a secondary amide during his studies on asymmetric sulfur oxidation.<sup>15</sup> In studies on hexakis(4-carbamoylphenyl)benzene Kobayashi has highlighted that the  $R_2^2(8)$  dimers present in this primary amide persist in DMSO.<sup>16</sup>

In view of this analysis and building on our previous report of the sulfoxide as a potent hydrogen bond acceptor,<sup>11</sup> a thorough investigation into the formation of the amide-sulfoxide heterosynthon for cocrystal formation was undertaken. Herein, we describe the results of the cocrystallisation experiments which were carried out with a range of functionalized aromatic amides, Scheme 1, and the possible design criteria for the formation of this motif.

Scheme 1. Cocrystal formers used.



## Experimental Section

**Materials and Physical Measurements.** The aromatic amides and dibenzyl sulfoxide were obtained from Sigma Aldrich and used as received. Solvents were obtained from commercial sources and distilled before use.

IR was recorded as KBr discs on a Perkin Elmer FT-IR spectrophotometer. Powder X-ray diffraction (PXRD) data were collected using a STÖE STADI MP diffractometer with Cu-K $\alpha_1$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ), 40 kV, 40 mA using a linear PSD over the  $2\theta$  range ( $3.5 - 60^\circ$ ) with a step size equal to 0.5 and step time of 90 seconds. Single-crystal X-ray diffraction data were collected on a Bruker APEX II DUO, with monochromated Mo K $\alpha$  radiation ( $\lambda = 0.7107 \text{ \AA}$ ) fitted with an Oxford Cryosystems Cobra

low temperature device. All calculations were performed using the *APEX2* software suite,<sup>17,18</sup> and the diagrams prepared using Mercury.<sup>19</sup> Melting Points were measured on an Electrothermal 9100 – Melting Point Apparatus. <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75 MHz) spectra were obtained for solutions in CDCl<sub>3</sub> using a Bruker 300 spectrometer. Chemical shifts were related to tetramethylsilane as the internal standard. DSC was performed on a TA instruments Q1000 incorporating a refrigerated cooling system. Microanalysis was performed by the microanalysis laboratory, University College Cork, on a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analyzers.

### **Cocrystallization Experiments.**

Initial screening was undertaken using both melt crystallization and grinding, with crystals suitable for single-crystal analysis grown from solution.

**Melt crystallization.** The amide:sulfoxide ratio was varied (1:1, 2:1 and 1:2 stoichiometries) with typically 0.5 or 1.0 mmol amounts of the cocrystal formers melted together at a temperature which was 10 °C higher than the temperature of the higher melting cocrystal former. This temperature was maintained for 10 - 20 min and then the mixture was cooled to ambient temperature.

**Grinding experiments.** Mechanical grinding experiments were conducted in a Retsch MM400 Mixer mill, equipped with 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. The amide:sulfoxide ratio was 1:1, with 0.4 mmol of each reagent used.

**Solution cocrystallization.** A 1:1 ratio of amide:sulfoxide (1 mmol) were mixed together in the solid state and then dissolved in solvent and allowed to stand at room temperature for 3-5 days. Crystals were harvested before all the solvent had evaporated and analysis was undertaken on the same batch of material.

**Benzamide:dibenzyl sulfoxide cocrystal (3a).**<sup>11</sup> Solid **1a** (0.132 g, 1.009 mmol) and solid **2** (0.231 g, 1.005 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), layered with *n*-hexane (1 mL), covered and left to stand. After 5 day colorless needle crystals of **3a** were obtained, mp 113 – 116 °C. Found C, 71.82; H, 6.18; N, 4.09; S, 8.95, C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>S requires C, 71.76; H, 6.02; N, 3.99; S, 9.12%.

***o*-Toluamide:dibenzyl sulfoxide cocrystal (3b).** Solid **1b** (0.135 g, 1.001 mmol) and solid **2** (0.230 g, 1.001 mmol) were dissolved in acetone (4 mL), covered and left to stand. After 3 days colorless needle crystals of **3b** were obtained, mp 108 – 110 °C. Found C, 72.49; H, 6.34; N, 3.73, S, 8.67, C<sub>22</sub>H<sub>23</sub>NO<sub>2</sub>S requires C, 72.30; H, 6.34; N, 3.83; S, 8.77%.

***m*-Toluamide:dibenzyl sulfoxide cocrystal (3c).** Solid **1c** (0.135 g, 1.001 mmol) and solid **2** (0.230 g, 1.001 mmol) were dissolved in acetonitrile (5 mL), covered and left to stand. After 5 days colorless needle crystals of **3c** were obtained, mp 104 – 108 °C. Found C, 72.11; H, 6.25; N, 3.61, S, 8.88, C<sub>22</sub>H<sub>23</sub>NO<sub>2</sub>S requires C, 72.30; H, 6.34; N, 3.83; S, 8.77%.

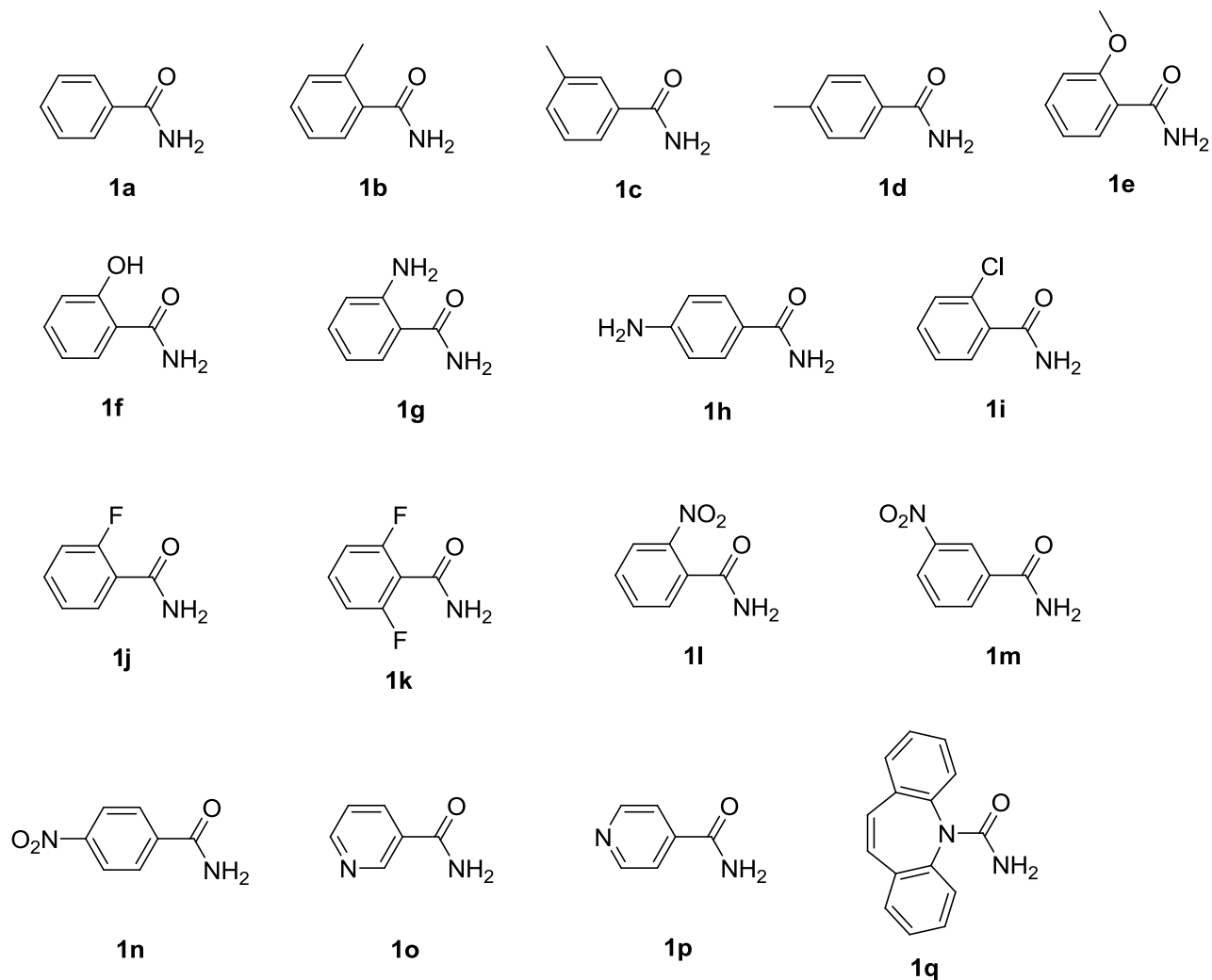
**2-Chlorobenzamide:dibenzyl sulfoxide cocrystal (3i).** Solid **1i** (0.156 g, 1.001 mmol) and solid **2** (0.231 g, 1.002 mmol) were dissolved in acetonitrile (5 mL), covered and left to stand. After 5 days colorless needle crystals of **3i** were obtained, mp 103 – 106 °C. Found C, 65.27; H, 5.36; N, 3.82; S, 8.25, C<sub>21</sub>H<sub>20</sub>ClNO<sub>2</sub>S requires C, 65.36; H, 5.22; N, 3.63; S, 8.31%.

<sup>1</sup>H NMR titration experiments were performed by adding varying concentrations of dibenzyl sulfoxide to pure samples of benzamide. The samples were carefully weighed out and a micropipette was used to accurately deliver equal volumes of deuterated chloroform to each NMR sample.

## Results and Discussion

The list of functionalized aromatic primary amides, **1**, which were screened for possible cocrystal formation with dibenzyl sulfoxide, **2**, is given in Scheme 2.

Scheme 2. The amides, **1**, investigated as possible cofomers with dibenzyl sulfoxide in this study.



Initial cocrystallization screening was carried out utilizing three different methods: melt crystallization, solvent-less grinding and crystallization from solution, for each primary amide with dibenzyl sulfoxide. The results are summarized in Table 1. Cocrystal formation was examined using a PXRD, IR and DSC. Chemical purity was confirmed by microanalysis and, in some cases,  $^1\text{H}$  NMR. Interestingly, despite the apparent simplicity of the two cofomers, and the presence of a good hydrogen bond acceptor in the form of the sulfoxide group, only four amides were found to form cocrystals. Solution crystallization and grinding led to successful formation of cocrystals in all four cases, while melt crystallization worked for three of them. The cocrystal **3a** has been communicated previously.<sup>11</sup>

Table 1. Screening results for the potential of cocrystallization between the primary aromatic amide, **1**, and dibenzyl sulfoxide, **2**.

	Melt	Grind	Solution		Melt	Grind	Solution
<b>1a</b>	√	√	√	<b>1j</b>	X	X	X
<b>1b</b>	X	√	√	<b>1k</b>	X	X	X
<b>1c</b>	√	√	√	<b>1l</b>	A	X	X
<b>1d</b>	X	X	X	<b>1m</b>	A	X	X
<b>1e</b>	X	X	X	<b>1n</b>	A	X	X
<b>1f</b>	X	X	X	<b>1o</b>	X	X	X
<b>1g</b>	X	X	X	<b>1p</b>	X	X	X
<b>1h</b>	X	X	X	<b>1q</b>	X	X	X
<b>1i</b>	√	√	√				

√ – Forms a cocrystal, X – starting materials, A – Amorphous material obtained.

The use of infra-red spectroscopy has been particularly useful as a fast method for screening and identifying cocrystal formation in this study. This is because a decrease in the  $\nu(\text{SO})$  symmetric stretching frequency of  $\sim 20 \text{ cm}^{-1}$  is observed in all four cases in which cocrystallization was successful, see Table 2. However, there was no change seen in the  $\nu(\text{SO})$  symmetric stretching frequency for any of the cocrystallization experiments which did not form cocrystals. This shift can be explained by the hydrogen-bonded interaction between the donor hydrogen and the sulfoxide oxygen leading to a decrease in the SO bond order, and hence, a corresponding decrease in the  $\nu(\text{SO})$  frequency. Similar effects have been seen for dilute solutions of DMSO in a variety of solvents.<sup>20</sup>

Table 2. IR stretching frequency for the S=O bond in the cocrystals and sulfoxide coformer.

	<b>2</b>	<b>3a</b>	<b>3b</b>	<b>3c</b>	<b>3i</b>
$\nu(\text{S=O}) / \text{cm}^{-1}$	1032	1013	1014	1012	1012

The DSC results for each co-crystal consist of a single endothermic peak as summarized in Table 3, which is lower than that of both starting materials for all cocrystals except **3c**, which has a melting point



higher than the amide but lower than the sulfoxide. The melting points of all cocrystals are similar, consistent with their structural features, as detailed later. Thus, although the amide **1c** has a significantly lower melting point than the other amides, this is not reflected in the cocrystals. A representative DSC of **3i** is shown in Figure 2.

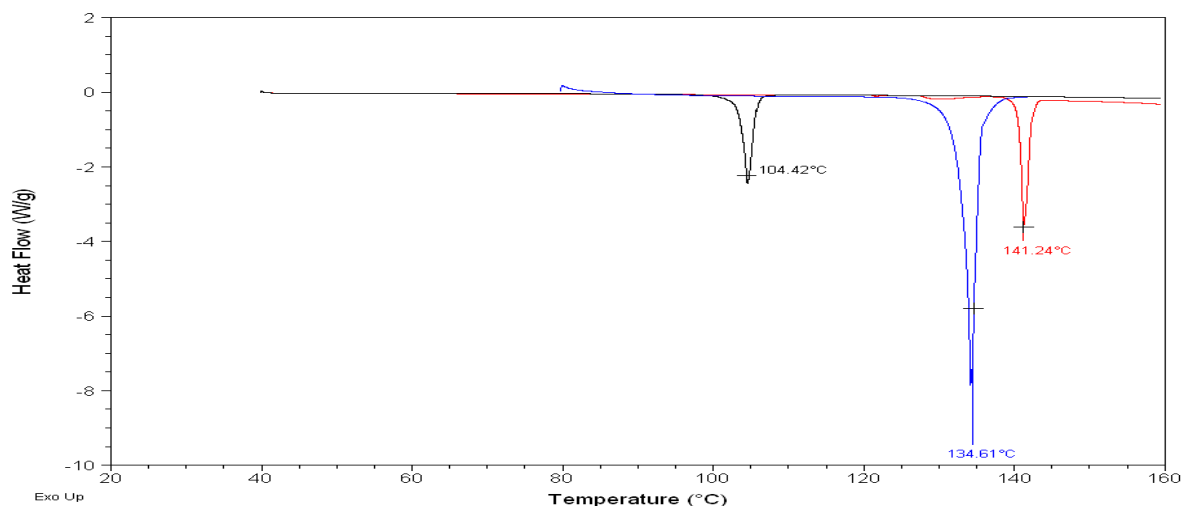


Figure 2. The DSC of amide **1i** (red), sulfoxide **2** (blue) and cocrystal **3i** (black).

Table 3. Melting points of the cocrystals and the corresponding sulfoxide and amide cofomers.

	Mp of cocrystal, °C	Mp of sulfoxide, °C	Mp of amide, °C
<b>3a</b>	115	135	127
<b>3b</b>	110	135	141
<b>3c</b>	106	135	93
<b>3i</b>	105	135	141

The use of solution phase  $^1\text{H}$  NMR spectroscopy has been employed as both a measure of purity and as a screening method for cocrystals in this research. Cocrystallization between the amide and the sulfoxide results in a splitting of the amido protons, from a broad singlet to two separate singlets, which

is useful in distinguishing between a mixture of starting material and the cocrystals. To show this trend, a  $^1\text{H}$  NMR titration experiment was conducted involving benzamide, **1a**, and the sulfoxide, **2** (Figure 3). Increasing the concentration of sulfoxide (top to bottom in Figure) leads to splitting of the amido protons from a broad singlet into two separate singlets.

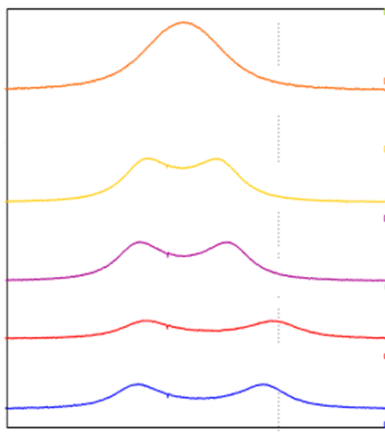


Figure 3.  $^1\text{H}$  NMR spectra of the amide hydrogen atoms for differing ratios of benzamide, **1a**, and dibenzyl sulfoxide, **2**. The ratios of **1a**:**2** are 100:0 (top), 83:17, 70:30, 54:46, and 51:49 (bottom).

The effect of changing the stoichiometry of the two coformers was also investigated using all three experimental methods, for all four systems which gave rise to cocrystals. The additional stoichiometries examined were a 1:2 ratio and a 2:1 ratio of amide : sulfoxide, respectively. For the experiment involving **1b**, no cocrystal formation was observed from the melt, consistent with the results discussed earlier in this paper. Significantly, in all the other experiments the 1:1 cocrystal was formed, as well as the starting reagent which was in excess, with no evidence of cocrystal formation with different stoichiometry or polymorphism.

The crystallographic data for the cocrystals is detailed in Table 4 and the hydrogen bonding present is detailed in Table 5. They each crystallize in the orthorhombic  $Pna2_1$  space group and have very similar hydrogen bonding patterns. However, they do not meet the criteria of isostructurality, using the method of Fábíán and Kálmán.<sup>21</sup> The sulfoxide does adopt the same conformation in all structures, with the only

significant difference between the cocrystals being the twist angle between the amide and phenyl ring on the primary aromatic amides, Figure 4.

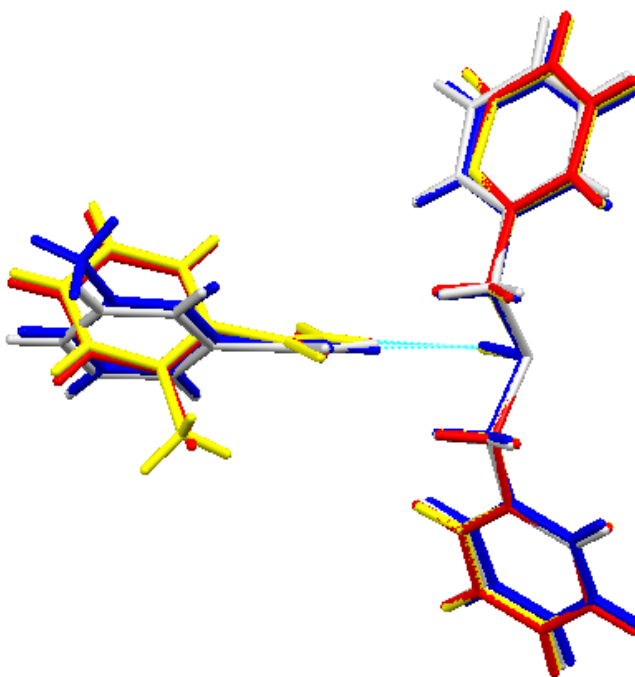


Figure 4. Overlay of the cocrystals **3a** (red), **3b** (yellow), **3c** (blue) and **3i** (grey).

The 1:1 cocrystal is sustained by the classical  $C=O \cdots H-N$  amide hydrogen bond between neighboring amides molecules, which facilitates an infinite C(4) chain (Figure 5). The amide hydrogen atom not involved in this C(4) chain is involved in a discrete 1:1 interaction with the sulfoxide group, meaning that the sulfoxide molecules are effectively capping the single strand hydrogen bonded amide chain. The nature of the hydrogen bonding in this single strand amide chain is similar to that in the double stranded chains in benzamide.

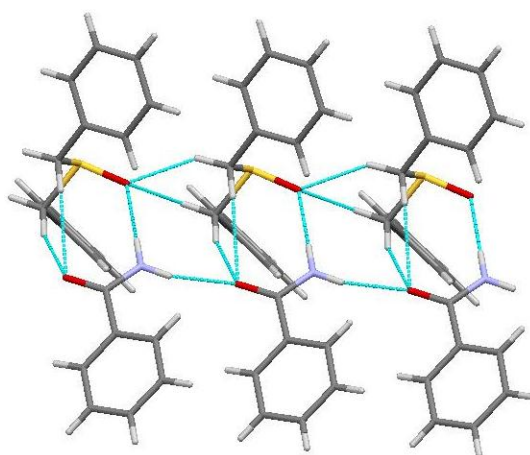


Figure 5. The 1:1 cocrystal of **3a** showing (i) the C(4) amide chains capped by dibenzyl sulfoxide and (ii) the weak hydrogen bonding involving all four of the hydrogen atoms  $\alpha$  to the sulfur atom.

In the cocrystal two of the four protons  $\alpha$  to the sulfoxide are involved in weak C-H $\cdots$ O=S hydrogen bonding between neighboring sulfoxide molecules (Table 5). This weak hydrogen bonding between the neighboring sulfoxides is similar to that seen in the crystal structure of dibenzyl sulfoxide itself.<sup>11,22</sup> The other two  $\alpha$  hydrogens are involved in weak C-H $\cdots$ O=C hydrogen bonding between the sulfoxide and amide molecules.

To test the importance of these benzylic protons in the cocrystals, cocrystallization involving benzamide with diphenyl sulfoxide or benzyl phenyl sulfoxide was undertaken. In all cases starting materials were obtained, highlighting the requirement for the two CH<sub>2</sub> groups  $\alpha$  to the sulfoxide functional group for these systems.

Table 4. Crystallographic Data for the Cocrystals.

	<b>3a</b> <sup>11</sup>	<b>3b</b>	<b>3c</b>	<b>3i</b>
Formula	C <sub>21</sub> H <sub>21</sub> NO <sub>2</sub> S	C <sub>22</sub> H <sub>23</sub> NO <sub>2</sub> S	C <sub>22</sub> H <sub>23</sub> NO <sub>2</sub> S	C <sub>21</sub> H <sub>20</sub> ClNO <sub>2</sub> S
<i>MW</i>	351.45	365.49	365.49	385.91
Crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic
Space group, <i>Z</i>	<i>Pna</i> 2 <sub>1</sub> , 4	<i>Pna</i> 2 <sub>1</sub> , 4	<i>Pna</i> 2 <sub>1</sub> , 4	<i>Pna</i> 2 <sub>1</sub> , 4
<i>a</i> , Å	18.2025(19)	19.136(11)	18.71(11)	18.822(3)
<i>b</i> , Å	19.566(2)	19.813(12)	20.13(5)	19.735(3)
<i>c</i> , Å	5.1336(5)	5.177(3)	5.197(16)	5.1366(5)
<i>V</i> , Å <sup>3</sup>	1828.3(3)	1963(2)	1957(14)	1908.0(4)
<i>D<sub>c</sub></i> gcm <sup>-3</sup>	1.277	1.237	1.240	1.343
$\mu$ , mm <sup>-1</sup>	0.191	0.180	0.181	0.325
$2\theta$ range, °	1.53–26.49	2.06–27.20	1.49–25.06	1.50–27.12
# unique reflns	3095	4361	3279	3397

# parameters	2731	245	244	243
$T$ /K	100	296	296	135
$R_1$ [ $I > 2\sigma(I)$ ]	0.0336	0.0431	0.0466	0.0466
$wR_2$	0.0716	0.0942	0.0991	0.0961
$S$	1.040	0.999	0.985	1.019
Flack	0.01(7)	0.14(8)	-0.02(11)	-0.01(9)

Table 5. Geometric Parameters of Hydrogen Bonding in the Cocrystals.

Cocrystal	Interaction	$d$ (H...A), Å	$D$ (D...A), Å	$\theta$ , °
<b>3a</b>	N-H...O=S	2.03	2.909(2)	176.7
	N-H...O=C	2.16	2.952(2)	149.8
	C-H...O=S	2.36	3.181(3)	142
	C-H...O=S	2.41	3.173(3)	135
	C-H...O=C	2.41	3.326(2)	158
	C-H...O=C	2.62	3.484(3)	148
	<b>3b</b>	N-H...O=S	2.187(17)	3.005(3)
N-H...O=C		2.19(2)	2.984(4)	159(2)
C-H...O=S		2.33	3.204(3)	149
C-H...O=S		2.44	3.238(3)	139
C-H...O=C		2.48	3.387(3)	155
C-H...O=C		2.63	3.515(3)	152
<b>3c</b>		N-H...O=S	2.05(4)	2.953(14)
	N-H...O=C	2.24(4)	3.010(10)	150(3)
	C-H...O=S	2.34	3.204(9)	148
	C-H...O=S	2.50	3.267(9)	136
	C-H...O=C	2.38	3.298(19)	157
	C-H...O=C	2.61	3.465(10)	147
<b>3i</b>	N-H...O=S	2.05(4)	2.978(4)	171(3)

N-H...O=C	2.24(5)	2.956(4)	154(4)
C-H...O=S	2.31	3.180(4)	149
C-H...O=S	2.43	3.223(4)	138
C-H...O=C	2.44	3.352(4)	156
C-H...O=C	2.68	3.546(4)	149

To investigate potential cocrystal polymorphism, the cocrystals were also crystallized from a variety of different solvents, namely acetonitrile, ethyl acetate, toluene and a mixture of CH<sub>2</sub>Cl<sub>2</sub> layered with hexane. In all cases only the 1:1 cocrystal described herein was obtained, indicating robust cocrystal formation.

As discussed, analysis of the crystal packing of the dibenzyl sulfoxide benzamide cocrystal shows the retention of the C(4) hydrogen bonded chain between neighboring amide molecules, which is a component of the packing of benzamide. Cocrystallisation with dibenzyl sulfoxide breaks the R<sub>2</sub><sup>2</sup>(8) dimer and instead capping of the spare hydrogen by the sulfoxide functional group is observed. A systematic study of the crystal packing of the free amide was undertaken in order to try and identify any possible design criteria for cocrystallisation. Thus, the hydrogen bond motifs seen in the amide cofomers are shown in Table 7.

Table 6. Hydrogen Bonding Motifs Observed in the Amide Cofomers.

Amide	R <sub>2</sub> <sup>2</sup> (8)	C(4)	mp, °C	Amide	R <sub>2</sub> <sup>2</sup> (8)	C(4)	mp, °C
<b>1a</b> <sup>7</sup>	√ <sup>1</sup>	√	125–128 <sup>23</sup>	<b>1j</b> <sup>32a</sup>	√	√	114 <sup>32b</sup>
<b>1b</b> <sup>24a</sup>	√	√	141–142 <sup>24b</sup>	<b>1k</b>	structure	unknown	145–148 <sup>33</sup>
<b>1c</b> <sup>25a</sup>	√	√	96 <sup>25b</sup>	<b>1l</b> <sup>34a</sup>	√	√	174–175 <sup>34b</sup>
<b>1d</b> <sup>26</sup>	√	√	160 <sup>25b</sup>	<b>1m</b> <sup>35</sup>	√	X	140–143 <sup>25b</sup>
<b>1e</b> <sup>27a</sup>	√	X	127–128 <sup>27b</sup>	<b>1n</b> <sup>36a</sup>	√	√	197–199 <sup>36c</sup>
<b>1f</b> <sup>28</sup>	√	X	139 <sup>28</sup>	<b>1n</b> <sup>36b</sup>	√	X	
<b>1g</b> <sup>29a</sup>	X	X	111–113 <sup>29b</sup>	<b>1o</b> <sup>37</sup>	√ <sup>i,ii</sup>	√	128–131 <sup>37c</sup>

<b>1h</b> <sup>30a</sup>	X	X	181–183 <sup>30b</sup>	<b>1p</b> <sup>37c,38</sup>	√ <sup>i,iii</sup>	√	155–157 <sup>6a</sup>
<b>1i</b> <sup>31a</sup>	√	√	142–144 <sup>31b</sup>	<b>1q</b> <sup>6a,6d,39a-c</sup>	√ <sup>iv</sup>	√	189–193 <sup>6d</sup>
<b>1i</b> <sup>31a</sup>	X	√		<b>1q</b> <sup>39d</sup>	X	√	

<sup>i</sup> Polymorphs exist, which all display both motifs. <sup>ii</sup> The beginning of melting of form II is 106 °C when heated at 70 Kmin<sup>-1</sup>. <sup>iii</sup> Form I is the stable polymorph. Forms II and III have transitions which begin at 130.5 and 131.7 °C, respectively, when heated at 70 Kmin<sup>-1</sup>. <sup>iv</sup> Four forms display both motifs, a fifth form with only the C(4) present is recently reported (with no mp data).<sup>39d</sup> Form I is the most stable polymorph, form II has a transition at 135–170 °C, form III has a transition at 162–175 °C and form IV has a transition at 178–187 °C.

Based on this data, there does not seem to be any single structural feature in the crystal structures of the amide cofomers which can be used to indicate whether cocrystallization will be successful. The difference in melting points of the cofomers is also not indicative of ease of cocrystal formation. Compounds **1b–h** have substituents which are electron donating into the aromatic ring, relative to benzamide, whereas those in compounds **1i–p** are electron withdrawing. Interestingly, of those cofomers which are electron donating, it is the *ortho*- and *meta*-substituted methyl derivatives, which do not possess alternative hydrogen bond donors and acceptors, which form cocrystals. For the cofomers which bear electron withdrawing substituents, it is the one with the weakest electron withdrawing ability (Cl) which forms a cocrystal. It seems likely, therefore, that the electron withdrawing substituents are deactivating the amide towards cocrystallisation by weakening the N–H•••O=S interaction. Similar observations have been seen for cocrystals involving acids, as discussed by Aakeröy.<sup>40</sup>

## Conclusion

A series of cocrystals involving dibenzyl sulfoxide with primary aromatic amides has been described. Cocrystals were formed in a 1:1 ratio between the sulfoxide and amide by neat grinding, crystallization from solution and, in three of the four cases, melt crystallization. Formation of the cocrystal causes a shift in the S=O stretching band region around 1032 cm<sup>-1</sup> to 1012 cm<sup>-1</sup> that is diagnostic for the existence of the cocrystals. Cocrystal formation appears to be influenced by the structure of the

sulfoxide, with two CH<sub>2</sub> groups  $\alpha$  to the sulfoxide required for the systems studied in this work. Interestingly, the structurally persistent R<sub>2</sub><sup>2</sup>(8) dimer typically seen for primary amides is no longer present in these cocrystals.

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**Supporting Information Available:** X-ray crystallographic information in CIF format, DSC and PXRD data, and additional figures. The crystallographic data for **3b**, **3c** and **3i** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 824879 – 824881. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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