Sulfoxides: Potent Co-Crystal Formers

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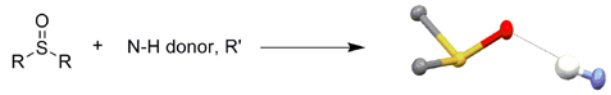
ABSTRACT

The design of co-crystals requires the knowledge of robust supramolecular synthons. The sulfoxide is a potent hydrogen bond acceptor and has been used as a co-crystal former with a range of NH functional groups, via N-H…O=S hydrogen bonds. The NH functional group retains favorable hydrogen bond motifs from its own structure in all cases where this is possible, with the sulfoxide interacting in a discrete, capping, fashion in four cases and in a bifurcated, bridging, fashion in the three other cases presented here.

There is great interest in co-crystals in recent years, especially within the pharmaceutical arena.[1] This is primarily because co-crystals have the potential to alter and optimize physical properties such as crystalline form, solubility, and stability of an active pharmaceutical ingredient (API) without detrimentally affecting its activity.[2] To date, most work has involved hydrogen bonds as the structure determining feature,[1] although recent work has shown that weaker non-covalent interactions can also be used.[3]

The design of co-crystals requires the knowledge of robust supramolecular synthons. The highly polar sulfoxide moiety, a potent hydrogen bond acceptor,[4] attracted our attention as a powerful co-crystal former (co-former) with hydrogen bond donors. There are few reports of the sulfoxide functional group specifically as a co-crystal former: Nangia investigated co-crystallization of trans-1,4-dithiane-1,4-dioxide,[1i] and Bernstein noted that diphenyl sulfoxide, **1a**, does not tend to form co-crystals.[1e] Indeed, a co-crystal with benzidine was only achieved when water was present in the lattice, which acted as a bridge between the N-H donor and the sulfoxide group, with N-H...O-H...O=S hydrogen bonding.[1e] Related to these reports, research in the area of chiral resolution has also shown that hydrogen bonding involving the sulfoxide moiety as acceptor is possible, although the majority of the examples to date involve alcohols and carboxylic acids.[1h,5] There have been reports of dipeptides interacting with the sulfoxide group via hydrogen bonding; interestingly, this has involved positively charged ammonium groups.[6] In addition, Kagan showed that *p*-tolylmethyl-sulfoxide crystallizes with a chiral secondary amide, although the focus of this work is in asymmetric synthesis rather than in crystal engineering.[7]

Herein we describe co-crystal formation of sulfoxides **1a** and **1b** with a range of N-H containing compounds, Figure 1, and extension to a broader series is underway, including O-H donors.[8] In addition, the sulfoxide group is very poorly basic, and thus complications due to salt formation, via complete proton transfer from donor to an acceptor, are avoided.



R = Ph, **1a**	R' = cyclohexanecarbothioamide, **2a**	**3a**
R = Ph, **1a**	R' = 4-aminobenzoic acid, **2b**	**3b**
R = Bn, **1b**	R' = thiourea, **2c**	**3c**
R = Bn, **1b**	R' = 2-aminobenzothiazole, **2d**	**3d**
R = Bn, **1b**	R' = benzamide, **2e**	**3e**
R = Bn, **1b**	R' = saccharin, **2f**	**3f**
R = Bn, **1b**	R' = benzensulfonamide, **2g**	**3g**

Figure 1. The co-formers investigated in this work.

In this study co-crystals were prepared by two techniques: (i) solid-state grinding and (ii) slow growth from the solution phase. In all cases a 1:1 stoichiometry of **1** and **2** respectively was observed, except **3d**, which has a 1:2 stoichiometry.[9]

In all cases there is a decrease in the ν(SO) symmetric stretching frequency, from 1031 cm^{-1} and 1037 cm^{-1} for **1a** and **1b** respectively.[9] Thus, in these cases IR is a viable screening tool for monitoring co-crystal formation. The largest shift, 33 cm^{-1}, is seen for **3f** and the smallest shift, 4 cm^{-1}, for **3a**. 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 a corresponding decrease in the ν(SO) frequency. Similar effects have been seen for dilute solutions of DMSO in a variety of solvents.[10] There is also an increase of 20cm^{-1} in the ν(CO) frequency in **3f**, indicative of an increase in the CO bond order.

DSC experiments confirm co-crystal formation with one sharp endotherm evident in all cases.[9] The mp for **3b**, **3d**-**3g** is lower than either co-crystal former. For **3a** it is only 3 ºC above that of **1b**, whereas for **3c** it is effectively the average of the two co-formers. In a study of APIs Newman showed that 51% of co-crystals have a mp between the two co-formers, whilst for 39% the mp was below that of either co-former, 6% were higher than either co-former and 4% the same as one co-former.[11]

In the solid state **2a**,[9] **2b**,[12] **2c**,[13] **2d**,[14] **2e**[15] and **2f**[16] form the hydrogen-bonded $R_2^2(8)$ dimers commonly observed in the solid state for carboxylic acids, primary amides and thioamides. The crystalline form of **2g** exhibits C(4) chains and $R_4^4(14)$ tetramers giving rise to elegant layers parallel to the *bc* plane.[17]

Polymorphism is known for **2b**, **2c** and **2e**, with the $R_2^2(8)$ dimer motif present in all cases except the β form of **2b**.[12b]

Interestingly, the structures of the co-crystals **3a**-**3f** reveal different motifs, despite the similar $R_2^2(8)$ dimers observed in the co-formers mentioned above. The co-crystals can be grouped into two categories: (i) the $R_2^2(8)$ dimers of the co-former are retained, with the sulfoxide capping the dimers and (ii) chains or discrete entities, with the sulfoxide capping the N-H donor, and the $R_2^2(8)$ dimer is lost. Specifically, **3a**-**3d** all retain the $R_2^2(8)$ dimer. In **3a** this results in a discrete 2 + 2 complex with the sulfoxide capping the free amide hydrogen, Figure 2.

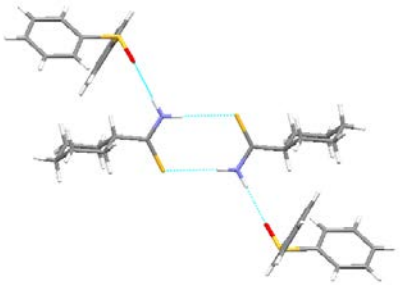


Figure 2. The $R_2^2(8)$ dimer in **3a**, capped by the sulfoxide.

The oxygen-based $R_2^2(8)$ dimer of the carboxylic acid in **3b** is retained, and, in combination with $R_4^2(8)$ rings involving the aniline hydrogens and the sulfoxide oxygens, link the molecules into one-dimensional chains.[9]

Thiourea, **2c**, is well known to form channel clathrates,[18] and the structure of **3c** is fairly typical of such materials. Thus, the sulfoxide oxygen forms a bifurcated hydrogen-bond with the two hydrogens, *anti* to the sulfur atom, within the same molecule, effectively capping the side of the thiourea molecule opposite the sulfur atom, and allowing the remaining amide hydrogens to form a zig-zag linear motif of $R_2^2(8)$ rings in one-dimension.[9]

The cocrystal **3d** is the only one in this work which showed a different stoichiometry (1:2) of sulfoxide to base: the reasons for this are unclear. The structure shows the sulfoxide is utilizing the amide hydrogens which are not part of the dimer motif and acting as a bridge between crystallographically distinct dimer pairs.[9]

The second category, **3e**-**3g**, involves disruption of the $R_2^2(8)$ dimer. Thus, for **3e** the only hydrogen-bonded feature that is retained from the co-former, **2e**, is the well known amide N-H...O=C C(4) chain,[19] see Figure 3. The amide hydrogen which is not involved in this chain is capped by the sulfoxide. Notably, the weak hydrogen bonds between the benzylic protons and the oxygen of dibenzyl sulfoxide, which are present in **1b**,[9,20] are also retained in this co-crystal. Such interactions have been shown to be structure directing in organosulfur compounds.[20,21]

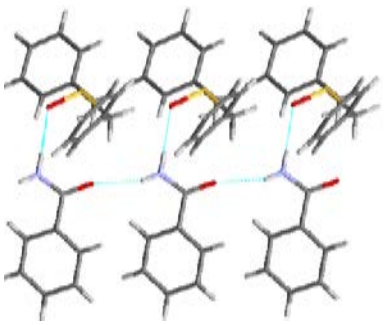


Figure 3. The N-H...C=O hydrogen bond leading to the C(4) chains in **3e**, with the individual units of the chain capped by the sulfoxide.

As expected, the $R_2^2(8)$ dimer in **2f** is not retained in **3f** as hydrogen bonding between the single N-H and the strong sulfoxide acceptor overcomes the N-H...O=C seen in **2f**, and the sulfoxide caps the N-H in a discrete fashion.[9] As the C=O bond is no longer involved in hydrogen bonding, an increase in the C=O bond order and ν(CO) frequency is seen as mentioned above.

While co-former **2g** is the only compound studied which does not exhibit a dimer motif, interestingly the structure of **3g** is similar to the other co-crystals. There is a N-H...O=S C(4) chain linking the sulfonamide molecules, which is retained from the structure of **2e**, with the sulfoxide capping the remaining hydrogen, in a similar fashion to **3e**.[9]

For all structures there are no significant differences in the S=O bond distance between the sulfoxide co-former[9,20,22] and the sulfoxide in the co-crystals, despite the observed changes in the ν(SO) frequencies.

As mentioned in the introduction, the sulfoxide group has been shown to interact via hydrogen bonding with alcohols and carboxylic acids,[1h,1i,5] as well as with the positively charged ammonium group.[6] In view of the report by Bernstein that **1a** does not tend to form co-crystals,[1e] it is particularly significant that we have shown sulfoxides acting as a general co-former with a series of NH compounds ranging from amines, (thio)amides, sulfonamides, thiourea *etc.* Critically, N-H...O=S hydrogen bonding is a key component of these structures, in direct contrast with Bernstein's observation that water was required to bridge the two components.

Interestingly, for six of the seven co-crystals key structure determining hydrogen bond motifs are retained from the co-former, whilst this is not possible for the seventh, **3f**. The $R_2^2(8)$ dimer is retained in four cases, and C(4) chains retained in a further two. The sulfoxide is bifurcated in three cases when the dimer is retained, and acts in a discrete fashion in all other cases. Further work is underway to gain a fuller understanding of the influence of the sulfoxide on the final hydrogen bonded motifs found in the co-crystals.

In conclusion, the potent hydrogen bonding acceptor ability of sulfoxides render them excellent co-formers with a wide variety of N-H donors. Notably, co-crystallization with sulfoxides is not complicated by proton transfer and salt formation since they are poorly basic, as exemplified by formation of cocrystal **3f** containing the relatively acidic saccharin, which displays a high propensity for salt formation in the solid state. Preliminary results have been obtained using sulfoxides as co-formers with phenols and sulfonic acids, among other groups, which will be published in due course.

As the sulfoxide functionality is common in a significant number of APIs, this fundamental exploration into its ability as a co-former may well lead to improvements in drug development.

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Supporting Information Available. Crystallographic data of **1b**, **2a**, **3a**-**3f**, Figures showing the hydrogen-bonding in **3b**-**3d**, **3f**, and **3g**, and experimental details for **3a**-**3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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