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Sulfoxides: Potent Co-Crystal Formers

Kevin S. Eccles, Curtis J. Elcoate, Stephen P. Stokes, Anita R. Maguire and Simon E. Lawrence

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. 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. To date, most work has involved hydrogen bonds as the structure determining feature, although recent work has shown that weaker non-covalent interactions can also be used.

The design of co-crystals requires the knowledge of robust supramolecular synthons. The highly polar sulfoxide moiety, a potent hydrogen bond acceptor, attracted our attention as a co-crystal former: Nangia investigated co-crystal formation of trans-1,4-dithiane-1,4-dioxide, and Bernstein noted that diphenyl sulfoxide, does not tend to form co-crystals. 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. 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. There have been reports of dipeptides interacting with the sulfoxide group via hydrogen bonding; interestingly, this has involved positively charged ammonium groups. 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.

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. 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.

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.

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. 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. 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. The mp for 3b, 3d-3g is lower than either co-crystal former. For 3a it is only 3 °C above that of 1b, whereas for 3e 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.

In the solid state 2a, 2b, 2c, 2d, 2e and 2f 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.
Polymorphism is known for 2b, 2c and 2e, with the R \( \frac{2}{2} \) (8) dimer motif present in all cases except the \( \beta \) form of 2b.12b

Interestingly, the structures of the co-crystals 3a-3f reveal different motifs, despite the similar R \( \frac{2}{2} \) (8) dimers observed in the co-formers mentioned above. The co-crystals can be grouped into two categories: (i) the R \( \frac{2}{2} \) (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 \( \frac{2}{2} \) (8) dimer is lost. Specifically, 3a-3d all retain the R \( \frac{2}{2} \) (8) dimer. In 3a this results in a discrete \( 2 + 2 \) complex with the sulfoxide capping the free amide hydrogen, Figure 2.

The oxygen-based R \( \frac{2}{2} \) (8) dimer of the carboxylic acid in 3b is retained, and, in combination with R \( \frac{2}{2} \) (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 3e 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 \( \frac{2}{2} \) (8) rings in one-dimension.9

The co-crystal 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 \( \frac{2}{2} \) (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

As expected, the R \( \frac{2}{2} \) (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 \( \nu(CO) \) 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-former9,20,22 and the sulfoxide in the co-crystals, despite the observed changes in the \( \nu(SO) \) frequencies.

Polymorphism is known for 2b, 2c and 2e, with the R \( \frac{2}{2} \) (8) dimer motif present in all cases except the \( \beta \) form of 2b.12b

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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.


(8) While DMSO solvates are technically co-crystals, the common usage has been applied in this study and the term 'sulfoxide' here refers to sulfoxides other than DMSO.

(9) This work, see Supplementary Information.


