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Over one hundred solvates of sulfathiazole†

Ann L. Bingham,[a] David S. Hughes,[a] Michael B. Hursthouse,*[a] Robert W. Lancaster,[b] Stewart Tavener[c] and Terence L. Threlfall*[c]

[a] *Chemistry Dept., University of Southampton, Southampton, UK SO17 1BJ. E-mail: mbh@soton.ac.uk*
[b] *Glaxo Wellcome R&D, Stevenage, Herts, UK SG2 9NY*
[c] *Chemistry Dept., University of York, York, UK YO10 5DD*

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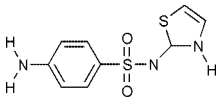
The sulfadrug sulfathiazole forms an extensive family of solvates and adducts, the crystal structures of which show a large variety of hydrogen-bonded frameworks.

In a recent communication, Nangia and Desiraju[1] analysed the relative solvate-forming propensities of fifty common solvates, and highlighted the need for systematic studies of the formation and structure of solvates. We have been engaged in such a study, largely based on one compound, the sulfadrug sulfathiazole, I,



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with remarkable solvate forming abilities, which developed out of a detailed reinvestigation of the polymorphism of this compound[2]. We present here a preliminary report of our findings.

The sulfadrugs show extensive polymorphism.[2,3] They also crystallise erratically from solution, despite the contrary impression that might be gained from the literature. In the search for reliable crystallisation procedures for sulfathiazole polymorphs, several less common solvents were tried and in quite a number of cases solvates were obtained. This was surprising, since the only well-defined solvate encountered in over 40 papers[4] during 60 years of investigation was that from dioxane.[5] Shirotani *et al.*[6] have described 3 further solvates of sulfathiazole, but their work seems to have been subsequently overlooked. In the belief that a detailed preparative and structural study of solvate formation may give an insight into the crystallisation behaviour of the parent materials, we have explored this topic further. The first solvate we produced was that from cyclohexanone. Reasoning from the analogy between the structures of dioxane and cyclohexanone, we tried numerous other 6- and 5-membered saturated heterocyclic and carbocyclic rings possessing at least one polar group, the function of the latter being presumed to involve hydrogen bonding with one of the 5 acceptors and 3 donors in the sulfathiazole molecule. Single crystal X-ray determinations however showed a remarkable variety of structures with varying propensity for hydrogen bonding between the sulfathiazole and the solvent guest. The study was extended to a wider range of solvents with different molecular shapes and sizes, different polarities and different functional groups, and also to the preparation of mixed crystals with partners that are solids at ambient temperature. The solvates are easily made by crystallisation from the appropriate solvent, sometimes with the help of chloroform as a crystallisation aid. Sulfathiazole has a solubility at elevated temperatures of around 10% in typical solvate-forming solvents. It is very soluble (30–60%) in more polar solvents such as dimethylformamide or tetramethylurea but generally fails to form solvents from such solutions. It has a limited solubility in solvents of low polarity and usually only sulfathiazole polymorphs crystallise from these solutions. Surprisingly, we found that molecules with long aliphatic hydrocarbon chains can form solvates provided a solvatophilic group such as lactone or lactam is present. The two-component solid–solid adduct crystals can be made by fusion or sometimes by crystallisation of the components using an inert solvent. The presence of a third component is detrimental on thermodynamic grounds,[7] but in practice, as noted above for chloroform, may be favourable for kinetic reasons.

More than 100 solvates plus many related 2-component systems containing sulfathiazole have now been made, including inter-sulfa-drug combinations such as sulfapyridine with sulfathiazole.‡ All have been characterised by near- and mid-infrared spectroscopy, powder XRD and hot-stage microscopy, and studied, in some cases also by DSC/TGA, solid state NMR, Raman spectroscopy and microscopy. The crystal structures of more than 60 solvates and adducts have so far been determined; others are in progress. The existence of such a large collection of data allows a unique opportunity for the comparative investigation of the structural and spectral characteristics and of the factors determining solvate formation. Detailed consideration of this is beyond the scope of a Communication, and is the central theme of a series of full papers, now in preparation. However, the results obtained can be usefully summarised as follows.

No solvent containing an aromatic carbocyclic group has given a solvate. Virtually every saturated carbocycle or heterocycle of appropriate polarity, and of ring size 3 to 8 produces a solvate. Only the behaviour of aliphatic solvates is difficult to predict, although polarity can be distinguished as a key factor. A wide range of groups including cyano, ester, ether. keto, sulfonyl, and amido groups are capable of providing the necessary polar characteristics. A hydroxy group generally seems to be detrimental to solvate formation, although a very unstable solvate has been made from *n*-propanol. The identification of the latter solvate together with that of acetonitrile raises the question as to whether many of the outcomes of sulfathiazole polymorph preparation procedures are mediated by the intervention of unstable solvates. Competitive experiments, in which sulfathiazole is crystallised from mixed solvates, have shown a stability sequence of lactams > lactones > cyclic carbonates > cyclic ketones, which parallels the order of solvent polarity. The relative stabilities of adducts with different sized rings have not been determinable so far because the crystalline product from these competition reactions has often not been one of the expected products. Some of these may be polymorphs of solvates, since DSC shows that some of the solvates are di- or tri-morphic. (Fig. 1.) The infrared spectra of the solvates are almost always close to that of the highest melting polymorph I (mp 203 °C), (the structure of which contains two crystallographically independent molecules, and which we regard as a sulfathiazole solvate of sulfathiazole), and unlike those of the three mutually similar low-melting polymorphs, even though the solvates always desolvate to the lower melting polymorphs, especially polymorph IV.§ This may be explained by the fact that in the structures so far determined the

† Electronic supplementary information (ESI) available: solvates and adducts of sulfathiazole. See http://www.rsc.org/suppdata/cc/b0/b009540k/

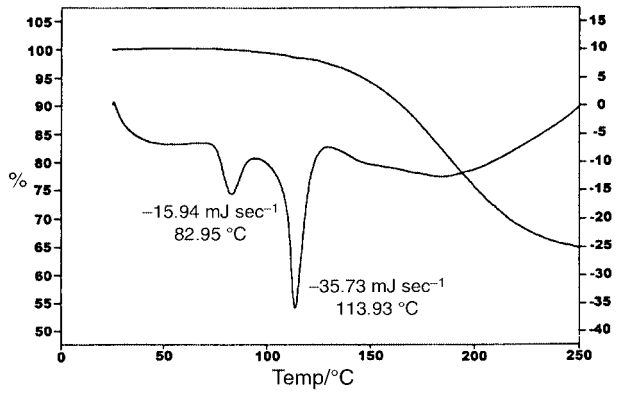

Fig. 1 DSC and TGA traces of the sulfathiazole-ε-caprolactone adduct. The endotherms without mass loss indicate phase transitions to new polymorphs, confirmed by hot-stage microscopy.

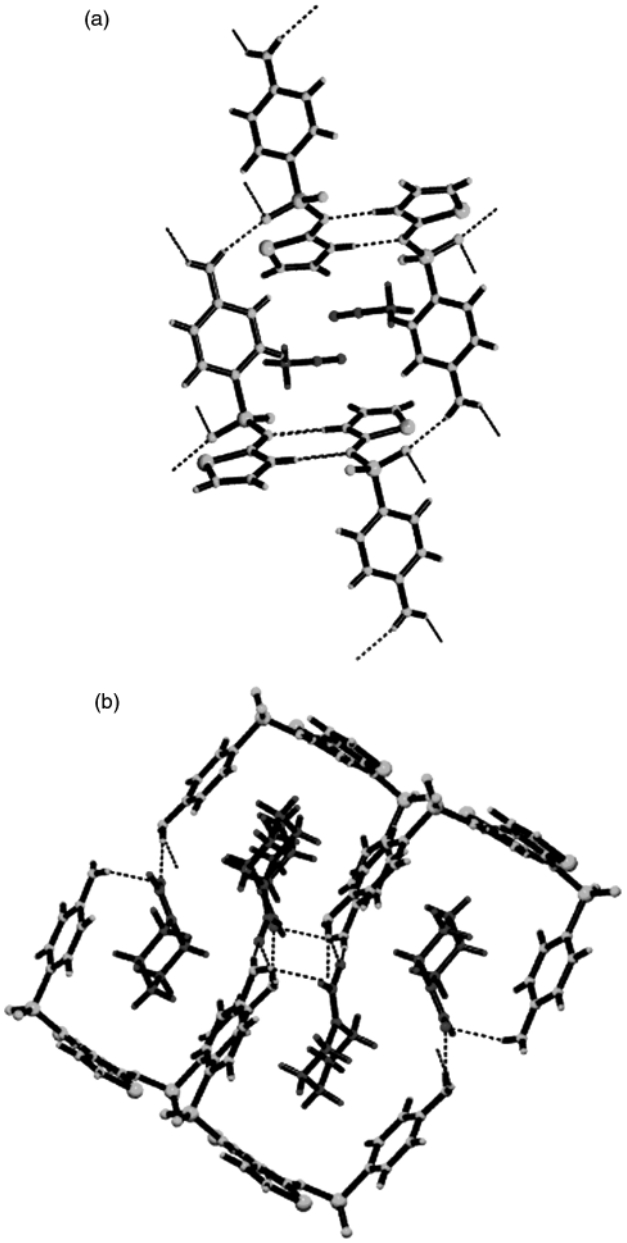

Fig. 2 (a) Detail from the crystal structure of the 1:1 adduct sulfathiazole–acetonitrile—a clathrate. (b) Detail from the crystal structure of the 1:1 adduct sulfathiazole–*N*-formylpiperidine—a co-crystal.

close amido–imido dimer present in sulfathiazole polymorph I but not in any of the others, features extensively in the solvate structures. The similarity of IR spectra for systems that are found to have quite different crystal structures is explained in terms of the presence of similar H-bonding associations but different supramolecular assemblies.

Terminology for the description of solid state molecular structures is unsatisfactory, even for single component systems.[8,9] Consideration of the multitude of structures displayed by the solvates listed in Nangia and Desiraju's paper raises the question as to whether nomenclature is even less adequate for the greater complexity resulting from two-component systems.

On the basis of the structure determinations so far completed in our study, we identify two types of structure which might provide a more generally useful classification—a) *clathrates*, or, more generally *inclusion phases*, in which the main function of the guest molecule is cavity filling, with or without additional weak H-bonding, in a host molecule assembly having a channel, layer or 3D framework structure, and b) *co-crystals* in which the partner molecule forms an essential part of the hydrogen bonded framework. In each class we have also found salts where proton transfer has occurred from the sulfathiazole molecule to a basic function on the guest. An example of each of the two main structure types is shown in Figs. 2a and 2b.¶

Multiple solvates have been reported for a variety of compounds, but these invariably show a large degree of isostructurality.[10] By contrast, our study has shown that sulfathiazole would appear to show more solid state structural versatility than any other organic molecule. We are investigating why this might be the case and whether other compounds form huge numbers of overlooked solvates or whether sulfathiazole is unique. To this end, the solvate forming propensities of other sulfadrugs are being examined. Preliminary experiments indicate that sulfapyridine forms many solvates, but not so extensively as sulfathiazole, and often with different solvates. The host–solvent relationship appears to be a very specific one even for such closely related hosts as the sulfadrugs, as might be expected from the huge variety of structures displayed by the sulfadrug polymorphs.

Notes and references

‡ A list of the solvates and adducts prepared so far, is given in the Supplementary Material.

§ The numbering scheme used here for the five fully characterised polymorphs is that described in D. C. Apperley, R. A. Fletton, R. K. Harris, R. W. Lancaster, S. Tavener and T. L. Threlfall, *J. Pharm. Sci.*, 1999, **88**, 1275.

¶ *Crystal data:* compound **1**, sulfathiazole–acetonitrile, $[C_9H_9N_3O_2S_2][C_2H_3N]$ M_r = 296.37, monoclinic, a = 10.741(2), b = 7.592(2), c = 16.748(3) Å, β = 103.99(3)°, U = 1325.2(5) Å^3, space group $P2_1/c$, Z = 4, T = 150 K. Reflections measured 5364 (θ_{max} = 25.35°, 82.6% complete), observed [$I > 2\sigma(I)$] 1997, R_{int} = 0.15. R = 0.059, ωR_2 = 0.111, 211 parameters. Compound **2**, sulfathiazole–*N*-formylpiperidine, $[C_9H_9N_3O_2S_2][C_6H_{11}NO]$ M_r = 368.47, triclinic, a = 10.539(2), b = 12.189(2), c = 13.981(3), α = 95.29(30), β = 107.38(3), γ = 90.63(3)°, U = 1705.3(6) Å^3, space group $P\bar{1}$, Z = 2, T = 150 K. Reflections measured 10626, θ_{max} 24.97°, 91.7% complete), observed 2877, Rint = 0.044. R = 0.0450, ωR_2 = 0.0955, 557 parameters. CCDC 154065 and 154066. See http://www.rsc.org/suppdata/cc/b0/b009540k/ for crystallographic data in .cif or other electronic format.

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