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Mimics of a $R_2^2(8)$ Hydrogen-Bond Dimer Motif: Synthesis and Influence on the Crystallisation of Sulfathiazole and Sulfapyridine

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The bis[4-(hydroxyamino)phenylsulfonyl]piperazine **5**, diketopiperazine **10** and benzene **14** were synthesised as mimics of an $R_2^2(8)$ motif, which occurs in one crystal polymorph of sulfathiazole and in several polymorphs of sulfapyridine. When present in crystallisations of sulfathiazole and sulfapyridine, these mimics were found to have little or no effect under crystallisation conditions that favour the formation of polymorphs not containing $R_2^2(8)$ motifs. However, the mimics were found to completely or partially inhibit the formation of form I sulfathiazole, which contains the $R_2^2(8)$ dimer, in crystallisations of sulfathiazole from 1-propanol. In crystallisations of sulfapyridine, the mimics were found to promote the formation of form III, which does not contain the $R_2^2(8)$ motif. These compounds therefore appear to act as "tailor-made" additives, displaying polymorph-selective crystal nucleation inhibition based on interaction with hydrogen-bond network motifs.

Introduction

Crystal polymorphism[1] is an area of much current interest, largely because of the impact of polymorphism on the manufacture of pharmaceuticals,[2] and fine chemicals.[3] The antimicrobial compound sulfathiazole is one of the best studied examples of a polymorphic pharmaceutical.[4] Five crystal polymorphs, known as forms I to V,[5] and very many solvates[6] of this compound have been reported. The variation in hydrogen-bonding networks[7] in the polymorphs of sulfathiazole **1** [Figure 1, (a)] has also been rigorously analysed.[5] Four of the five crystal polymorphs of sulfathiazole have been shown to be based on hydrogen-bonded dimeric motifs. The crystal structure of form I sulfathiazole has been shown to contain dimers containing the $R_2^2(8)$ motif shown in Figure 1, (b), whereas forms II, III and IV have been shown to contain the $\mathbf{R_2^2}(18)$ motif shown in Figure 1, (c). These hydrogen-bonded dimer motifs also occur in the crystal structures of other sulfanilamide antimicrobials, for example, $R_2^2(8)$ motifs analogous to the dimer shown in Figure 1, (b) occur in four of the crystal polymorphs of sulfapyridine[8] **2** (Figure 2). Note that Figure 2 shows sulfapyridine in the sulfonimide tautomer for ease of comparison with sulfathiazole (which appears to exist exclusively in the sulfonimide tautomer in the solid state), but that both the sulfonimide and sulfonamide tautomers of sulfapyridine are found in the solid state.

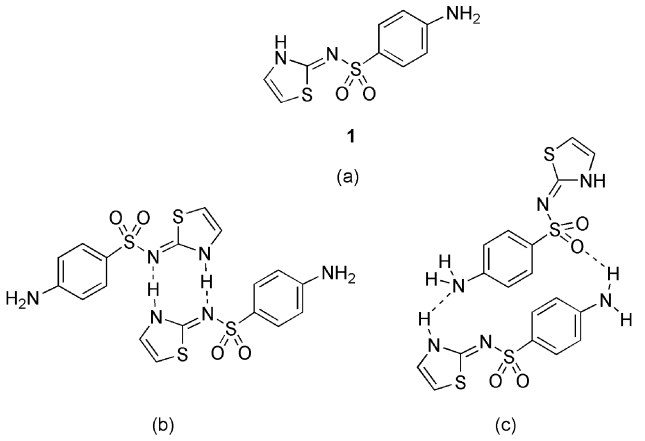

Figure 1. (a) Sulfathiazole, molecular structure. (b) $R_2^2(8)$ hydrogen-bonded dimer present in form I sulfathiazole. (c) $R_2^2(18)$ hydrogen-bonded dimer present in forms II, III and IV sulfathiazole.

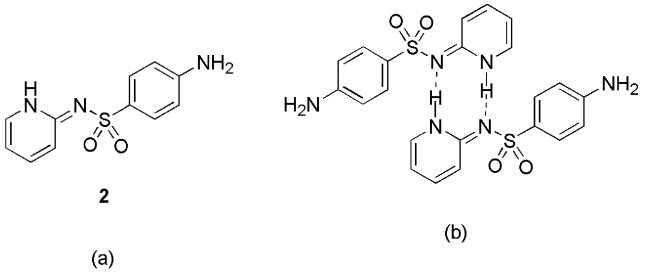

Figure 2. (a) Sulfapyridine, molecular structure. (b) $R_2^2(8)$ dimer present in four crystal polymorphs of sulfapyridine.

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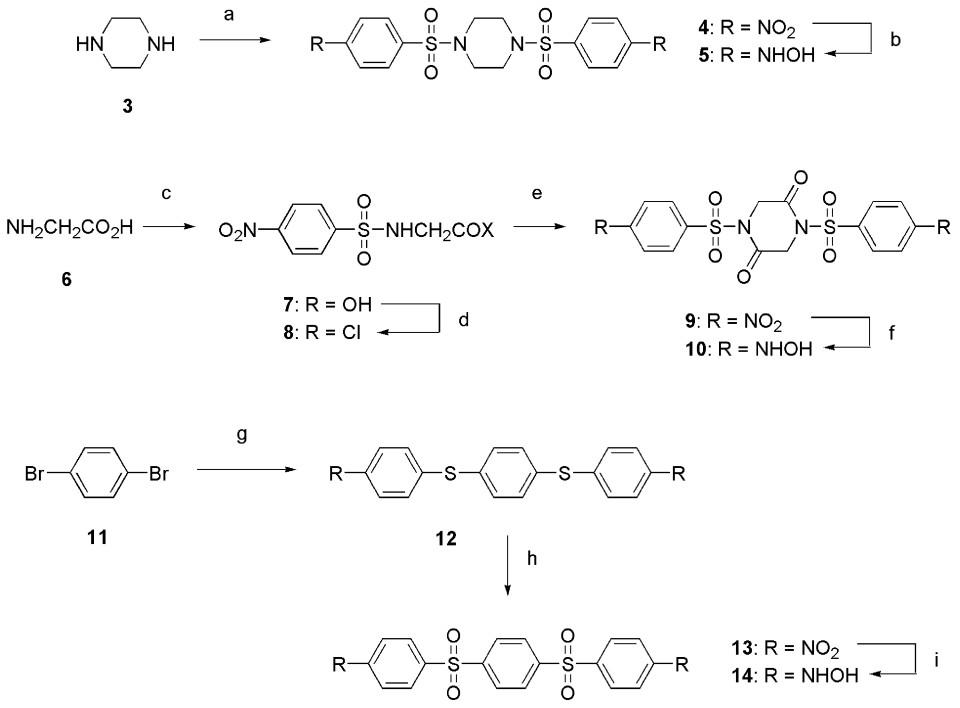
It has been shown that crystal nucleation and growth can be influenced at the molecular level by the use of additives. For example, rationally-designed tailor-made additives have been used to selectively inhibit the nucleation of specific crystal polymorphs.[9] Polymers have been used as crystal heteronuclei[10] and crystals of compounds related to the crystallising material have been used as pseudo-seeds.[11] During some recent research on the preparation of co-crystals, novel or unexpected crystal forms may have been obtained as a consequence of putative co-crystallising compounds acting as crystallisation additives.[12]

Rationally designed crystallisation additives are often based on features of the crystallising material. For example, additives may mimic the molecular conformation present in a particular crystal form,[13] or may exploit the symmetries of different forms.[14] One possibility for crystallisation additive design is mimicry of hydrogen-bond motifs. In the case of sulfathiazole, a single molecule which mimics the supramolecular binding features for the $R_2^2(8)$ dimer would be likely to affect the processes of sulfathiazole crystal nucleation and growth. For instance, such additives might direct the nucleation of form I by acting as templates for the nucleation and growth of the form I structure. Alternatively, such additives might selectively add to pre-critical nuclei of form I and inhibit their growth into mature crystals. Other additive effects might also be possible. In this paper, we report the preparation of three compounds, **5**, **10** and **14** (Scheme 1),which meet the above requirement for acting as single-molecule mimics of the sulfathiazole $R_2^2(8)$ dimer. All three possess the hydrogen-bond donating and accepting capabilities of the $R_2^2(8)$ dimer. We also report on the influences of these compounds as additives in crystallisations of sulfathiazole and sulfapyridine.

Results and Discussion

The three compounds, **5**, **10** and **14**, which mimic the R $_2^2(8)$ hydrogen-bond dimer were prepared by the routes shown in Scheme 1. In the case of each, the final step was reduction of a bis(4-nitrophenylsulfonyl) precursor, that is, compounds **4**, **9** and **13**. Precursor **4** was obtained by reaction of piperazine, **3**, with 4-nitrobenzenesulfonyl chloride. Precursor **9** was obtained by cyclodimerisation of the acid chloride **8** derived from *N*-(4-nitrophenylsulfonyl)glycine (**7**). Precursor **13** was obtained by reaction of 1,4-dibromobenzene, **11**, with copper 4-nitrothiophenylate, followed by oxidation of the resulting bis(sulfide), **12**, to the bis(sulfone) **13**.

Our original intention was to reduce the bis(4-nitrophenylsulfonyl) compounds **4**, **9** and **13** to the corresponding bis(4-aminophenylsulfonyl) derivatives. We therefore subjected compounds **4**, **9** and **13** to the following standard conditions for aromatic nitro to amine reduction: Sn, HCl, reflux; Fe, HCl, reflux; Fe, NH_4Cl, reflux; Na_2S, NH_4Cl, NH_4OH, reflux. No identifiable product was obtained from any of these reactions. Hydrogenation at 40 psi in ethanol solvent over palladium on carbon gave no reaction (compounds **4**, **9** and **13** were effectively insoluble in ethanol). Transfer hydrogenation using palladium on carbon in re-



Scheme 1. Preparation of $R_2^2(8)$ dimer mimics **5**, **10** and **14**. a) 4-$NO_2C_6H_4SO_2Cl$ (2.0 equiv.), NaOH (2.2 equiv.), H_2O, acetone, reflux (87%). b) H_2, 10% Pd/C, DMF, 50 psi (55%). c) 4-$NO_2C_6H_4SO_2Cl$, 1 M aq. NaOH (93%). d) PCl_5, EtOAc (79%). e) Et_3N, toluene (60%). f) H_2, 10% Pd/C, DMF, 50 psi (66%). g) 4-$NO_2C_6H_4SCu$ (2 equiv.) [from 4-$NO_2C_6H_4SH$, Cu_2O, EtOH, reflux (96%)], quinoline, pyridine, 200 °C (68%). h) 30% aq. H_2O_2, AcOH, reflux (86%). i) H_2, 10% Pd/C, DMF, 50 psi (64%).

fluxing ethanol – formic acid solvent also gave no reaction. To address the issue of the poor solubility of compounds **4**, **9** and **13** in ethanol, a 1 M aqueous sodium hydroxide/methanol mixture was instead used as solvent in attempted hydrogenations over palladium on carbon at 40 psi; however, no identifiable product was obtained. However, use of DMF as hydrogenation solvent did, in each case, give clean conversion to isolable products. These were found to be not the expected bis(4-aminophenylsulfonyl) compounds, but rather the bis(hydroxylamines) **5**, **10** and **14**. Compounds **5**, **10** and **14** contain all the required features to mimic the supramolecular interactions of the $R_2^2(8)$ dimers, namely cyclic core units replacing the $R_2^2(8)$ hydrogen-bond motif, and all the necessary hydrogen-bond donor and acceptor groups. Figure 3 gives a comparison of the $R_2^2(8)$ dimer motif from form I sulfathiazole with the diketopiperazine mimic **10**.

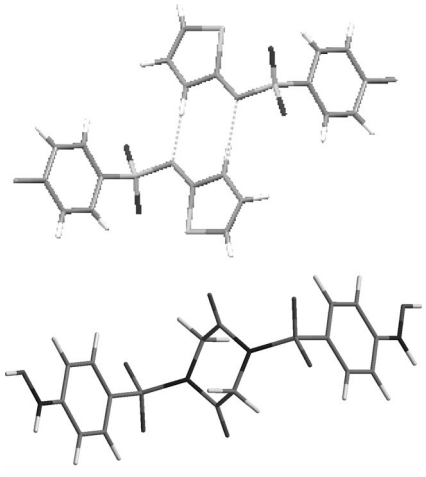


Figure 3. Top: crystallographic view of the $R_2^2(8)$ dimer motif of form I sulfathiazole. Bottom: model image of the $R_2^2(8)$ dimer mimic **10**.

Methods for the isolation of the five known polymorphs of sulfathizole as described in the literature[4,5] involve crystallisation from the following solvents: form I from 1-propanol, form II from nitromethane or from ethanol, form III from 20% aqueous ammonia solution and form IV from water. Isolation of form V by the evaporation to dryness of a boiling aqueous solution of sulfathiazole **9** has been described.[6] We thus undertook to isolate the five polymorphs of sulfathiazole **9** as reported. The materials obtained were analysed by powder X-ray diffraction (PXRD). Patterns were compared with the theoretical patterns generated from crystal structural data for each form obtained from the Cambridge Structural Database (CSD). The CSD reference codes for the structures of form I, II, III, IV and V used are, respectively, SUTHAZ01,[15] SUTHAZ,[16] SUTHAZ02,[15] SUTHAZ04,[17] SUTHAZ06.[5] As unit-cell dimensions (and consequently the positions of diffraction peaks) are temperature dependent, room-temperature unit-cell dimensions were used in generating theoretical patterns, so as to provide the best comparison with the room temperature PXRD data we obtained.

In our hands, crystallisation from 1-propanol gave needle-shaped crystals, the PXRD pattern of which correlated well with the theoretically simulated pattern for form I (ESI Figure 1, a). Recrystallisation from ethanol or from nitromethane gave crystals, which were identified as form II by the overlay of the experimentally isolated diffraction with the theoretically simulated pattern for form II (ESI Figure 1, b).

Recrystallisation from 20% aqueous ammonia yielded truncated hexagonal crystals which were consistent in morphology with the literature[5] description of the habit displayed by form III. However, subsequent PXRD analysis identified these as a mixture of forms III and IV (ESI Figure 1, c). From water, plate-like hexagonal crystals consistent with the reported morphology for form IV[5] were isolated. PXRD analysis yielded a diffraction pattern similar to that described above for the crystals isolated from 20% aqueous ammonia, showing the isolated crystals to be a mixture of forms III and IV. Finally, attempted isolation by us of form V by the evaporation of boiling water yielded cuboid-shaped crystals, which PXRD analysis identified as form II.

The effects of the three dimer mimics, **5**, **10** and **14**, on the recrystallisation of sulfathiazole **9** were subsequently evaluated. Water and 1-propanol were selected as solvents for these recrystallisations. Water was selected as forms III and IV are known to crystallise successfully from it, and so we wished to examine the possibility that the $R_2^2(8)$ dimer mimics **5**, **10** and **14**, might act as crystal nucleation-directing templates, inducing formation of form I from water. 1-Propanol was selected as the form I polymorph featuring the $R_2^2(8)$ dimer motif reliably crystallises from this solvent, and hence compounds, **5**, **10** and **14**, designed to be $R_2^2(8)$ dimer mimics, may have the potential to add to crystal nuclei of form I and so act as form I inhibitors. Examination of the solubilities of the additives indicated that the maximum amount of each which would dissolve in water was the equivalent of approximately 1.2 wt.-% of additive compared to sulfathiazole. As the use of a saturated solution of the additive could result in the precipitation of the additive before the formation of crystals of sulfathiazole **9**, it was decided to use a maximum concentration of 1 wt.-% additive in each case.

In the case of all three additives, it was found that recrystallisation of sulfathiazole from water with 1 wt.-% of additive present gave crystals which were observed to be a mixture of needle, plate-like hexagons and truncated hexagon morphologies, suggesting that a mixture of forms had been isolated. The PXRD pattern isolated (ESI Figure 1, d) from all three experiments was found to overlay exactly with the theoretically simulated pattern of form IV with only one unassigned peak. Thus, it was concluded that while the additives did appear to have an impact on the crystal habit, pure form IV was isolated.

The recrystallisation of sulfathiazole **1** from 1-propanol in the presence of 1,4-bis[4-(hydroxyamino)phenylsulfonyl]-piperazine **5** was subsequently investigated. Upon recrystallisation from a solution containing 1 wt.-% addi-

tive **5**, it was found that brittle needle-shaped crystals were isolated. PXRD analysis showed that crystals of pure form IV were isolated. Hence, at this concentration of compound **5** as additive, complete inhibition of crystallisation of form I sulfathiazole from 1-propanol was achieved. The additive concentration was subsequently reduced to 0.5 wt.-% and again resulted in the isolation of needle-shaped crystals. PXRD analysis of the isolated material suggested that the product consisted of a mixture of forms I and IV therefore suggesting that partial inhibition of form I was achieved at this concentration. When the additive concentration was further reduced to 0.1 wt.-%, the crystals isolated were again determined to consist of a mixture of forms I and IV by PXRD.

In the presence of 1 wt.-% of the diketopiperazine derivative **10**, needle-shaped crystals (morphology consistent with form I) were obtained in recrystallisations from 1-propanol. However, PXRD analysis showed a mixture of forms I and II to be present. This result suggested that a partial inhibitory effect had been observed. When this procedure was repeated with 0.5 wt.-% of additive **10**, PXRD analysis again showed a mixture of forms I and II to be present. This mixture was again observed when 0.1 wt.-% and 0.05 wt.-% of additive **10** was used. Hence it can be concluded that the diketopiperazine **10** is capable of partially inhibiting the crystallisation of form I sulfathiazole down to 0.05 wt.-%.

We subsequently repeated the crystallisations of sulfathiazole **1** from 1-propanol in the presence of 1,4-bis[4-(hydroxyamino)phenylsulfonyl]benzene **14**. In the presence of 1 wt.-% of additive **14**, the isolated crystals were observed to be opaque brittle needles which by PXRD analysis were found to consist of a mixture of forms II and IV. Thus at 1 wt.-% of additive **14**, complete inhibition of form I was achieved. Reduction of the additive concentration to 0.5 wt.-% caused no decrease in the inhibitory effects and a mixture of forms II and IV was again observed. Upon decreasing the additive concentration further to 0.1 wt.-% the additive effects were seen to lessen somewhat with a mixture of forms I, II and IV being isolated. This suggested that at this concentration of compound **14**, only partial control was exerted over the recrystallisation from 1-propanol. At 0.05 wt.-% of additive the effects of compound **14** was found to have completely diminished and PXRD analysis indicated the isolation of pure form I. Hence it can be concluded that 1,4-bis[4-(hydroxyamino)phenylsulfonyl]-benzene (**14**) is capable of completely inhibiting the crystallisation of form I of sulfathiazole down to 0.5 wt.-% with partial inhibition possible at 0.1 wt.-%.

While there have been reports of up to seven polymorphic forms of sulfapyridine **2**,[18] the crystal structures of only five forms have been solved to date. The numbering system used here is based on numbering used for the solved structures as follows: form II (BEWKUJ11[19]), form III (BEWKUJ12[19]), form IV (BEWKUJ05[20]), form V (BEWKUJ13[19]) and form VI (BEWKUJ14[21]). The hydrogen-bonding patterns of the five forms are all composed of hydrogen-bonded dimers. Forms II, IV, V and VI all display the $R_2^2(8)$ motif, but differ considerably in the arrangement of these within the structures. Form III, however, is composed of $R_2^2(12)$ hydrogen-bonded dimers, shown in Figure 4.[19] It is noteworthy that the dimeric motif shown in Figure 4 relies on sulfapyridine molecules existing in the sulfonimino ($RSO_2N{=}CR\text{-}NHR$) tautomer (as shown in Figure 2) and could not be constructed from the "classical" sulfonamido ($RSO_2NH{-}C{=}NR$) tautomer.

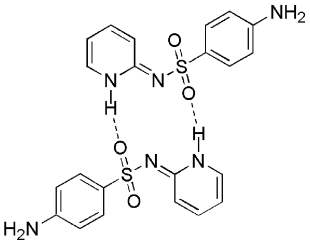


Figure 4. $R_2^2(12)$ hydrogen-bonded dimers occurring in form III sulfapyridine.

Literature methods for the crystallisation of the polymorphs of sulfapyridine can be summarised as follows:[22,19] form I from hot methanol or water; form II from 1-propanol cooled from 80 °C to 40 °C; form III from 1-butanol, 2-butanol or *n*-amyl alcohol cooled to 35 °C; form IV from rapidly cooled 1-propanol or by the evaporation of 1-butanol;[20] form V by allowing solutions in 1- and 2-propanol to cool to room temperature for a few hours; form VI by the careful addition of molten sulfapyridine **23** to boiling toluene.[21]

In our experiments, pure form III, identified by PXRD (ESI Figure 2, a) was isolated from water, ethanol, 1-propanol cooled from 80 °C to 40 °C and held at this temperature for twenty four hours, from 1-butanol at room temperature over twenty four hours, from methanol, and by the evaporation of 1-butanol. Pure form IV was isolated by us from solutions of sulfapyridine in 1-butanol held at 35 °C over twenty four hours (ESI Figure 2, b). We obtained form VI by addition of the molten sulfapyridine to the toluene, as described by Gelbrich et al.[21] The crystallographic data used to simulate the theoretical pattern for form VI was collected at 120 K. As the PXRD pattern isolated by us was isolated at room temperature it is likely that there are discrepancies between the unit cell dimensions of the crystals used by us and those used by Gelbrich et al.[21] Thus, a number of the diffraction peaks in the experimental pattern are shifted from the corresponding peaks on the theoretical pattern (ESI Figure 2, c). We were unable to isolate pure crystals of any of the other reported forms. Mixtures of forms II and V were isolated from 1-butanol at room temperature for three hours and also from a saturated solution of 1-propanol, which was rapidly cooled, on ice and the crystals isolated within one hour. A mixture of forms II, III and IV crystallised from a saturated solution of sulfapyridine in 1-propanol at room temperature over twenty four hours.

The effects of the three additives **5**, **10** and **14** on the recrystallisation of sulfapyridine were investigated. As with sulfathiazole, it was decided to carry out the recrystallisations both under conditions which favoured the formation of the $R_2^2(8)$ dimers, and under conditions which favoured the formation of the $R_2^2(12)$ dimers. As the $R_2^2(12)$ dimers occur exclusively in form III, conditions for the reliable crystallisation of form III (cooling a solution of sulfapyridine in 1-propanol to 80 °C and then further cooling to 40 °C for twenty four hours once the first crystals were seen to form) were selected. As recrystallisation from 1-butanol at room temperature for 3 h was found, in our hands, to give reliably forms II and V, both of which contain the $R_2^2(8)$ dimers, this method was selected to assess the impact of the additives on the formation of the $R_2^2(8)$ dimers.

In the case of all three additives, it was found that the recrystallisation of sulfapyridine from a solution of 1 wt.-% of additive in 1-propanol which was cooled from 80 °C to 40 °C and allowed to sit undisturbed for twenty four hours yielded cuboid-shaped crystals which were found to correlate with the theoretically simulated PXRD pattern of form III. These findings suggested that the additives had no influence on the recrystallisation from 1-propanol and hence had no effect on the formation of the $R_2^2(12)$ dimer.

The effects of additives **5**, **10** and **14** on the recrystallisation of sulfapyridine from 1-butanol at room temperature for three hours was subsequently examined. Upon recrystallisation of sulfapyridine from 1-butanol at room temperature for three hours in the presence of 1 wt.-% of the piperazine derivative **5** the product isolated was found (by PXRD) to consist of a mixture of forms II and III. In the presence of 0.5 wt.-% of additive **5**, the material isolated was observed to be a mixture of forms II, III, IV and V. When this was repeated in the presence of 0.1 wt.-% of additive, a mixture of forms II and V were obtained. These results would suggest that the piperazine derivative **5** had a partial inhibitory effect on the formation of the $R_2^2(8)$ dimer at 1 wt.-% and 0.5 wt.-% as mixtures containing form III was observed in both cases. The additive effect was seen to have completely subsided at 0.1 wt.-% additive as a mixture of forms II and V was isolated.

In the presence of 1 wt.-% of the diketopiperazine derivative **10**, it was found that it was not possible to obtain a consistent result. This experiment was carried out on ten occasions. On three occasions, a mixture of forms II and V was obtained. On two occasions, pure form IV was obtained. Pure form III was obtained on one occasion. On the remaining four occasions, differing mixtures of at least two of forms II, III, IV, V or VI were obtained. In our experiments, crystallisation of sulfapyridine (in the absence of additives) normally gives a mixture of forms II and V, or form III over longer cooling times. Clearly, the crystallisation of sulfapyridine from 1-butanol is finely balanced in terms of polymorphic outcome. In the presence of additive **10**, forms less easily obtained from 1-butanol, that is, IV and VI as well as a more frequent occurrence of form III, is observed, suggesting that this additive is affecting the nucleation and growth of forms II and V to some extent. We subsequently attempted recrystallisation in the presence of 0.1 wt.-% of the diketopiperazine derivative **10**. The crystals isolated were identified as a mixture of forms II, IV and V. While form IV was not found to be present in the mixture isolated from 1-butanol in the absence of an additive, this result indicates that the additive had little or no impact on the formation of the $R_2^2(8)$ dimer at this concentration.

In the presence of 1 wt.-% of additive **14** in 1-butanol the crystals isolated were identified by PXRD as a mixture of forms II and III. This suggested that the additive **14** had a partial $R_2^2(8)$ inhibitory effect and consequently some form III crystals were permitted to grow. When the additive concentration was reduced to 0.5 wt.-% a mixture of forms II, III and V was isolated. This mixture was found to persist down to 0.05 wt.-% of additive **14** suggesting that partial control over the polymorphism of sulfapyridine **23** was still present.

Conclusions

Compounds **5**, **10** and **14** were designed to mimic the $R_2^2(8)$ dimers found in form I sulfathiazole and forms II, IV, V and VI sulfapyridine. When present in crystallisations of sulfathiazole or sulfapyridine, these compounds might be expected to act as crystal nucleation directors, promoting the formation of $R_2^2(8)$-containing forms, or as selective nucleation inhibitors, impeding the nucleation of $R_2^2(8)$-containing forms, or to have other effects. The above findings show that the additives have little or no effect under conditions under which $R_2^2(8)$ dimers do not normally form, that is, they do not display a nucleation-directing effect. However, under conditions favouring the formation of $R_2^2(8)$ dimers, the compounds were found to have an inhibitory effect. For example, compounds **5** and **14** were found to completely inhibit the formation of form I sulfathiazole when present at 1% (wt./wt.) quantities in crystallisations of sulfathiazole from 1-propanol, while compound **10** was found to be partially inhibitory of form I under these conditions. This mode of activity is markedly different from that observed for "monomer-like" additives and impurities in these systems. For example, simple *N*-acylsulfathiazole derivatives have been found to promote the formation of form I sulfathiazole from water.[4] They therefore display a very different effect on crystallisation outcome than that observed for the $R_2^2(8)$ dimer mimics described in this paper.

The sulfapyridine system is more complex in terms of outcomes, different crystal forms being obtainable from the same solvent with small changes in conditions. However, even in the sulfapyridine system, compounds **5**, **10** and **14** were found to affect the outcome under conditions that normally favour the formation of $R_2^2(8)$ dimers. In particular, form III sulfapyridine, which does not contain $R_2^2(8)$ dimers, was found to be more likely to form in the presence of the additives, usually as part of a mixture containing other forms. The additives appear to have no impact under conditions that normally give sulfapyridine form III.

Compounds **5**, **10** and **14** have therefore been found to act as selective inhibitors of sulfathiazole and sulfapyridine

forms that contain the $R_2^2(8)$ dimer motif and to have little or no effect on forms that do not possess this motif. During crystallisation, dimerisation of the sulfa molecules may well be a process closely linked to that of nucleation and growth. It is possible that dimers present in solution may add directly to crystal nuclei, as well as or instead of single molecules. This concept is supported by NMR spectroscopic studies on a closely related compound, sulfamerazine.[23] An element of molecular recognition may be present, by which compounds **5**, **10** and **14**, as $R_2^2(8)$ dimer-mimics, are acceptable for binding to crystal nuclei possessing the $R_2^2(8)$ motif, but are rejected by nuclei not possessing that motif. Once bound to crystal nuclei, the additive inhibits further growth of the nucleus and so inhibits formation of $R_2^2(8)$-containing crystal forms. The presence of hydroxyamino rather than amino groups in compounds **5**, **10** and **14** may contribute to the inhibitory effect. The compounds would then be acting in a manner similar to that of tailor-made additives.[9]

It is also noteworthy that the compounds display inhibitory effects when present in quantities of 1% (wt./wt.) or less. Compounds **10** and **14**, for example, were found to exert observable effects in quantities of 0.05% (wt./wt.) Monomer-like tailor-made additives are often effective only when present in quite large quantities, for example, ca. 10% (wt./wt.). Additives effective in a quantity of 1% (wt./wt.) or less are more often polymeric in nature. The observation that compounds not considerably larger than the crystallising molecule can affect the crystallisation outcome, even when present in low quantities, is significant for "real life" industrial crystallisation processes in which structurally similar process impurities are often present in quantities less than 1%.

We would also like to note the benefits of using theoretical powder diffraction data to assign polymorphic form by matching to the whole experimental pattern. This allows very reliable assignment of experimental patterns to crystal structures held in the Cambridge Structural Database, rather than to nominal forms distinguished on the basis of properties such as melting point or morphology. This approach is even more effective when powder diffraction patterns are obtainable in the transmission mode, which avoids the need for grinding of the sample and the accompanying risk of solid-state transformation.

Experimental Section

General: All materials were purchased from Sigma–Aldrich. Infrared spectra were recorded with a Perkin–Elmer 1000 spectrometer in the range 4000–500 cm^{-1}. Melting points were determined with a Reichert hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded at 300 MHz wih a Bruker AVANCE 300 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz with a Bruker AVANCE 300 spectrometer. Splitting patterns in ^1H spectra are designated as s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) and m (multiplet). High-resolution mass spectra (HRMS) were recorded with a Waters LCT Premier LC-MS instrument in electrospray ionisation (ESI) positive mode using 50% acetonitrile/water containing 0.1% formic acid as eluant; samples were made up in acetonitrile. Elemental analysis was performed by the Microanalytical Laboratory UCC, using a Perkin–Elmer 240 or an Exeter Analytical CE440 elemental analyser. Powder X-ray diffraction was performed at ambient temperature using a Stoe Stadi MP PXRD operating in transmission mode with a linear PSD detector with an anode current of 40 mA, an accelerating voltage of 40 kV and Cu-$K_{\alpha1}$ radiation (λ = 1.5406 Å) over a scan range of 3.5–60° 2θ, scanning in steps of 2° for 90 s per step. Samples were held between acetate foils and were not ground. Calculated patterns were generated from crystallographic information files downloaded from the Cambridge Structural Database, using the THEO function on the Stoe $WinX^{POW}$ software with a pseudo-Voigt profile-shape function and a Gauss component of 0.8.

***N,N′*-Bis(4-nitrophenylsulfonyl)piperazine (4):** To piperazine (0.5 g, 5.8 mmol) in acetone (5 mL) was slowly added with cooling 4-nitrobenzenesulfonyl chloride (2.84 g, 12.8 mmol). Halfway through the addition of the 4-nitrobenzenesulfonyl chloride, a solution of sodium hydroxide (0.51 g, 12.8 mmol) in water (5 mL) was added. An exothermic reaction resulted and a precipitate was seen to immediately form. Once the exothermic reaction had ceased, the reaction mixture was heated at reflux for 1.5 h. The precipitate which formed was collected by filtration and washed with warm ethanol (2 × 10 mL) and water (2 × 10 mL). A yellow solid was isolated (2.3 g, 87%); m.p. 300 °C (dec.; ref.[24] m.p. 350 °C). IR (KBr): $\tilde{\nu}_{max}$ = 1609 (aromatic C–C), 1543 and 1310 (NO_2), 1351 and 1171 (SO_2). $C_{16}H_{16}N_4O_8S_2$ (456.42): calcd. C 42.10, H 3.53, N 12.27, S 14.05; found C 41.99, H 3.28, N 11.97, S 13.82.

***N,N′*-Bis(4-hydroxyaminophenylsulfonyl)piperazine (5):** *N,N′*-Bis(4-nitrophenylsulfonyl)piperazine (**4**, 0.5 g, 1.1 mmol) was dissolved in DMF (50 mL) and 0.05 g 10% Pd/C was added. The reaction mixture was shaken under hydrogen gas at 50 psi for 4 h. The reaction mixture was then filtered through Celite and most of the solvent was removed in vacuo. Water (100 mL) was added and the precipitate which formed was isolated by filtration to yield a yellow solid (0.24 g, 51%); m.p. 310 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 3420 (OH), 3303 (NH), 1596 (aromatic C–C), 1334 and 1155 (SO_2). ^1H NMR (300 MHz; [D$_6$]DMSO, 25 °C): δ = 2.88 (s, 8 H, CH_2 × 4), 6.91 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H, ArH × 4), 7.47 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H, ArH × 4), 8.79 (s, 2 H, OH × 2), 9.12 (s, 2 H, NH × 2) ppm. ^{13}C NMR (75 MHz; [D$_6$]DMSO, 25 °C): δ = 45.18 [CH_2], 111.30 [ArylCH], 122.55 [–C–SO_2], 128.95 [ArylCH], 155.74 [–C–NHOH] ppm. HRMS (ESI): Exact mass calculated for $C_{16}H_{19}N_4O_6S_2$ [(M – H)$^-$] 427.0746; found 427.0728.

***N*-(4-Nitrophenylsulfonyl)glycine (7):** Glycine (1.5 g, 39.96 mmol) was suspended in 5 mL water and completely dissolved by the addition of 1 M aqueous sodium hydroxide solution (10 mL). 4-Nitrobenzenesulfonyl chloride (6.2 g, 27.97 mmol) was added followed by the addition of further 1 M aqueous sodium hydroxide solution (20 mL) in small portions so as to keep the pH of the reaction mixture above 9. Once all the sodium hydroxide had been added, stirring was maintained for a further 30 min. The reaction mixture was then filtered so as to remove any undissolved 4-nitrobenzenesulfonyl chloride. The mother liquor was acidified with 5 M hydrochloric acid solution, until a precipitate was seen to form, and was then allowed to sit overnight. The precipitate which formed was collected by filtration to yield a yellow solid (4.68 g, 90%); m.p. 167–173 °C (ref.[25] m.p. 172 °C). IR (KBr): $\tilde{\nu}_{max}$ = 3296 (NH), 1732 (C=O), 1332 and 1165 (SO_2), 1529 and 1354 (NO_2). ^1H NMR (300 MHz; [D$_6$]DMSO, 25 °C): δ = 3.64 (s, 2 H, CH_2), 8.05 (dd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 1.9 Hz, 2 H, ArH × 2), 8.39 (dd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 1.9 Hz, 2 H, ArH × 2) ppm.

***N*-(4-Nitrophenylsulfonyl)glycinoyl Chloride (8):** *N*-(4-Nitrophenylsulfonyl)glycine (**7**, 4.68 g, 17.99 mmol) and phosphorus pentachloride (5.62 g, 26.99 mmol) were suspended in ethyl acetate (50 mL) and stirred at room temperature until all the acid had dissolved. Stirring was continued for a further 30 min following which the excess phosphorus pentachloride was removed by filtration. Hexane (80 mL) was then added to the mother liquor and the mixture was set aside at 0 °C for several hours. The precipitate which formed was isolated by filtration to yield a yellow solid (3.52 g, 70%); m.p. 133–138 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3256 (NH), 1802 (C=O), 1312 and 1162 (SO_2), 1551 and 1350 (NO_2). ^{1}H NMR (300 MHz. $CDCl_3$, 25 °C): δ = 4.37 (d, $^3J_{H,H}$ = 6.2 Hz, 2 H, CH_2), 5.41 (br. t, $^3J_{H,H}$ = 5.3 Hz, 1 H, NH), 8.06 (dd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 2.1 Hz, 2 H, ArH × 2), 8.40 (dd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 2.1 Hz, 2 H, ArH × 2) ppm. ^{13}C NMR (75 MHz; [D$_6$]DMSO, 25 °C): δ = 43.68 (CH_2), 124.35 (ArylCH), 128.08 (ArylCH), 146.43 (–C–SO_2), 149.43 (–C–NO_2), 170.09 (–COCl) ppm. $C_8H_7ClN_2O_5S$ (278.65): calcd. C 34.48, H 2.52, N 10.05, S 11.51, Cl 12.72; found C 34.55, H 2.55, N 9.78, S 11.20, Cl 13.00.

1,4-Bis(4-nitrophenylsulfonyl)piperazine-2,4-dione (9): *N*-(4-Nitrophenylsulfonyl)glycine acid chloride (**8**, 3.52 g, 12.64 mmol) was suspended in dichloromethane (50 mL). To this triethylamine (1.8 mL, 12.64 mmol) was added. The reaction mixture immediately turned yellow with the evolution of gas. The reaction mixture was stirred at room temperature for 5 h following which the solvent was removed in vacuo. The solid product which resulted was stirred for 1 h in 2-propanol (50 mL). The product was isolated by filtration to yield a yellow solid (2.58 g, 84%); m.p. 248 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 1710 (C=O), 1532 and 1350 (NO_2), 1389 and 1187 (SO_2). ^{1}H NMR (300 MHz; [D$_6$]DMSO, 25 °C): δ = 4.60 (s, 4 H, CH_2), 8.31 (dd, $^3J_{H,H}$ = 6.9, $^4J_{H,H}$ = 2.1 Hz, 4 H, ArH × 4), 8.44 (dd, $^3J_{H,H}$ = 6.9, $^4J_{H,H}$ = 2.1 Hz, 4 H, ArH × 4) ppm. ^{13}C NMR (75 MHz; [D$_6$]DMSO, 25 °C): δ = 48.95 (CH_2), 124.29 (ArylCH), 130.43 (ArylCHr), 142.21 (–C–SO_2), 150.83 (–C–NO_2), 162.95 (–C=O) ppm. $C_{16}H_{12}N_4O_{10}S_2$ (484.43): calcd. C 39.69, H 2.50, N 11.57, S 13.24; found C 40.06, H 2.40, N 11.23, S 13.48.

1,4-Bis[4-(hydroxyamino)phenylsulfonyl]piperazine-2,5-dione (10): 1,4-Bis(4-nitrophenylsulfonyl)piperazine-2,4-dione (**9**, 1.5 g, 3.09 mmol) was dissolved in DMF (50 mL) and 10% Pd/C (0.015 g) was added. The reaction mixture was shaken under hydrogen gas at 50 psi for 4 h. The reaction mixture was then filtered through Celite and most of the DMF was removed in vacuo. Water (50 mL) was then added and the precipitate which resulted was isolated by filtration to yield a beige solid (0.87 g, 62%); m.p. 280–283 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3396 (OH), 3314 (NH), 1694 (C=O), 1359 and 1165 (SO_2). ^{1}H NMR (300 MHz; [D$_6$]DMSO, 25 °C): δ = 4.42 (s, 4 H, CH_2), 6.78 (d, $^3J_{H,H}$ = 8.9 Hz, 4 H, ArH × 4), 7.66 (d, $^3J_{H,H}$ = 8.9 Hz, 4 H, ArH × 4), 8.82 (s, 2 H, OH), 9.27 (s, 2 H, NH) ppm. ^{13}C NMR (75 MHz; [D$_6$]DMSO, 25 °C): δ = 48.79 (CH_2), 110.40 (ArylCH), 123.98 (–C–SO_2), 130.22 (ArylCH), 156.57 (–C–NHOH), 163.37 (–C=O) ppm. HRMS (ESI): Exact mass calculated for $C_{16}H_{15}N_4O_8S_2$ [(M–H)$^-$] 455.0331; found 455.0328.

1,4-Bis(4-nitrophenylsulfenyl)benzene (12): A mixture of 4-nitrothiophenol (1 g, 6.44 mmol) and copper(I) oxide (0.46 g, 3.22 mmol) in 95% ethanol (50 mL) was heated at reflux for 48 h. The reaction mixture was cooled to room temperature and copper(I) 4-nitrothiophenylate was isolated by filtration to yield a brown solid (1.35 g, 96%); m.p. 282 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 3093 (Ar C-H), 1594 (aromatic C=C), 1512 and 1340 (NO_2). $C_6H_4CuNO_2S$ (217.71): calcd. C 33.10, H 1.85, N 6.43, S 14.73, Cu 29.19; found C 33.17, H 1.76, N 6.06, S 14.27, Cu 29.11. A mixture of copper(I) 4-nitrothiophenylate (1.00 g, 4.59 mmol) and 1,4-dibromobenzene (0.49 g, 2.09 mmol) in quinoline (15 mL) and pyridine (1.5 mL) was heated to 200 °C for 2 h. The reaction mixture was then allowed to cool to approximately 100 °C and was poured onto a mixture of ice (60 mL) and hydrochloric acid (16 mL) and stirred for 2 h. The mixture was filtered and the solid residue was dissolved in ethyl acetate (50 mL). The aqueous filtrate was extracted with ethyl acetate (2 × 20 mL). The combined organic washings were washed with 10% hydrochloric acid solution (2 × 20 mL) followed by water (1 × 20 mL). The organic phase was dried with magnesium sulfate, filtered and concentrated to yield a dark brown oil (1.95 g). The product was then dissolved in ethyl acetate and passed through a short silica plug yielding a sticky orange solid (1.15 g). This was then triturated in 2-propanol to yield a brown solid (0.55 g, 68%); m.p. 210–219 °C (ref.[26] m.p. 215–218 °C). IR (KBr): $\tilde{\nu}_{max}$ = 1594 (aromatic C=C), 1578 and 1334 (NO_2). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, $^3J_{H,H}$ = 8.95 Hz, 4 H, ArH × 4), 7.52 (s, 4 H, ArH × 4), 8.14 (d, $^3J_{H,H}$ = 8.95 Hz, 4 H, ArH × 4) ppm.

1,4-Bis(4-nitrophenylsulfonyl)benzene (13): A mixture of 1,4-bis(4-nitrophenylsulfenyl)benzene (**12**, 0.4 g, 1.04 mmol), 30% aqueous hydrogen peroxide (0.09 mL, 8.32 mmol) and acetic acid (15 mL) was slowly heated to reflux and maintained at this temperature for 2 h. The reaction mixture was then allowed to cool to room temperature and the solid which precipitated was isolated by filtration to a yellow solid (0.4 g, 86%); m.p. 316–319 °C (ref.[27] m.p. 325 °C). IR (KBr): $\tilde{\nu}_{max}$ = 1610 (aromatic C=C), 1546 and 1333 (NO_2), 1350 and 1161 (SO_2). ^{1}H NMR (300 MHz. $CDCl_3$, 25 °C): δ = 8.20 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, ArH × 4), 8.22 (s, 4 H, ArH × 4), 8.33 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, ArH × 4) ppm. $C_{18}H_{16}N_2O_8S_2$ (448.42): calcd. C 48.21, H 2.70, N 6.25, S 14.30; found C 48.70, H 2.59, N 6.01, S 14.10.

1,4-Bis[4-(hydroxyamino)phenylsulfonyl]benzene (14): 1,4-Bis(4-nitrophenylsulfenyl)benzene **13** (0.2 g, 0.446 mmol) was dissolved in DMF (30 mL) and to this 10%Pd/C (0.02 g) was added. The reaction mixture was then shaken under an atmosphere of hydrogen gas at 50 psi for 4 h. The reaction mixture was then filtered through Celite and most of the DMF was removed in vacuo, after which water (50 mL) was added until a precipitate was seen to form. The product was isolated by filtration to yield a yellow solid (0.11 g, 64%); m.p. 240 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 3427 (OH), 3298 (NH), 1592 (aromatic C=C), 1305 and 1151 (SO_2). ^{1}H NMR (300 MHz. $CDCl_3$, 25 °C): δ = 6.77 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, ArH × 4), 7.61 (d, $^3J_{H,H}$ = 8.8 Hz, 4 H, 4 × ArH), 7.95 (s, 4 H, ArH × 4), 8.74 (s, 2 H, OH × 2), 9.17 (s, 2 H, NH × 2) ppm. ^{13}C NMR (75 MHz; [D$_6$]DMSO, 25 °C): δ = 111.33 (ArylCH), 127.06 (–*C*–SO_2), 127.88 (ArylCH), 129.28 (ArylCH), 146.38 (SO_2–*C*–), 156.16 (–C–NHOH) ppm. HRMS (ESI): Exact mass calculated for $C_{18}H_{15}N_2O_6S_2$ [(M – H)$^-$] 419.0372; found 419.0358.

Crystallisations: All recrystallisations were carried out in 250 mL conical flasks for experiments at room temperature and in 100 mL round-bottomed flasks where a higher temperature was required. All solutions were prepared by dissolving 0.5 g of sulfathiazole or sulfapyridine followed by filtration to remove any undissolved material. Form I sulfathiazole was obtained from a 13 g L^{-1} solution of 1-propanol, form II from a 26 g L^{-1} solution of nitromethane and a 10 g L^{-1} solution in ethanol, form III from an 83 g L^{-1} solution of 20% aqueous ammonia and form IV from a 22 g L^{-1} solution in water. With the exception of the recrystallisation from 20% aqueous ammonia which required three days for the crystals to form, all these experiments were carried out over a twenty four hour period. In all cases the recrystallisation solutions were unstirred. The effects of the three $R_2^2(8)$ dimer mimics, **5**, **10** and **14**,

on the recrystallisation of sulfathiazole were evaluated by dissolving 1 g of sulfathiazole in a pre-prepared solution of the additive under investigation in the appropriate solvent.

For sulfapyridine, all recrystallisation experiments were carried out by dissolving 1 g of sulfapyridine in a minimum amount of the relevant solvent in a 250 mL conical flask and allowing to sit at room temperature. Pure sulfapyridine form VI was isolated by the addition of 1 g of molten sulfapyridine to 30 mL of boiling toluene. The addition was carried out with great care as rapid addition can result in bumping of the toluene. Upon addition of the molten sulfapyridine to the toluene a certain amount of the material was seen to solidify immediately resulting in the formation of a solid globule. When allowed to stand for a few minutes, crystals were seen to form. The crystals were collected by filtration however the solid globule was discarded. For assessment of the effects of the additives **5**, **10** and **14** on the crystallisation of sulfapyridine, recrystallisations were carried out by dissolving 1 g of sulfapyridine in a solution of the additive in the appropriate solvent.

Supporting Information (see also the footnote on the first page of this article): Examples of PXRD patterns of sulfathiazole forms I, II, III and IV, and sulfapyridine forms III, IV and VI, including experimentally recorded and overlaid theoretical patterns.

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