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Sulfa Drugs as Model Cocrystal Formers

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Abstract: A review of several aspects of cocrystallization involving sulfonamide drugs is presented, with a focus on other drug molecules as cocrystallization partners. Some earlier exploratory studies outlined here led to more recent systematic investigation of processes such as cocrystal preparation by solid-state cogrinding of individual components, selective cocrystal formation in competition experiments, and exchange reactions. These are discussed with reference to the drug sulfadimidine, which featured prominently as a model cocrystal former. Apart from their potential as medicinal agents, cocrystals and salts of sulfa drugs frequently display multiple related physicochemical phenomena including polymorphism, crystal isostructurality, and solvate formation, justifying past and current interest in their solid-state chemistry.

Keywords: Sulfonamides; cocrystallization; solid-state reactions; X-ray diffraction

Introduction

From the early 1970s, sulfa drugs were shown to have a strong tendency toward crystal polymorphism.[1,2] Molecules in this drug class typically contain multiple hydrogen bond donor and acceptor functions (Figure 1), allowing for the formation of a diverse range of stable supramolecular motifs in solution and hence the possible crystallization of a given sulfa drug in multiple forms. Though newer antibacterial and antimicrobial drugs have supplanted many sulfonamides, the latter still enjoy widespread use because of their low cost and relatively efficient action against common bacterial diseases. Studies probing the mechanism of sulfa drug resistance by the target dihydropteroate synthase continue,[3] indicating that certain questions regarding the action of these drugs still remain unanswered.

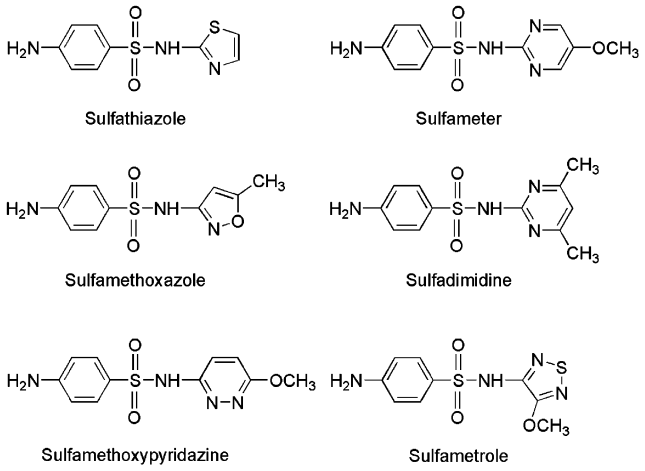

Figure 1. Chemical structures of common sulfonamide drugs.

The focus of this brief review is the interaction of sulfa drugs with drug molecules in other classes to form cocrystals, a natural extension of the solid-state chemistry of the sulfonamides. While a compound between sulfathiazole and proflavin containing equimolar proportions of the two had been employed to treat bacterial infections as early as the 1940s,[4] more systematic investigation of cocrystallization phenomena involving sulfonamides was resumed somewhat later, numerous studies in this area having been reported during the last three decades, some of them serving as models for more recent work in pharmaceutical cocrystallization in

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(2) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid-State Chemistry of Drugs*; SSCI, Inc.: West Lafayette, IN, 1999; pp 160−180.
(3) Giordanetto, F.; Fowler, P. W.; Saqi, M.; Coveney, P. V. Large Scale Molecular Dynamics Simulation of Native and Mutant Dihydropteroate Synthase-Sulphanilamide Complexes Suggests the Molecular Basis for Dihydropteroate Synthase Drug Resistance. *Philos. Trans. R. Soc. London, Seri. A: Math., Phys. Eng. Sci.* **2005**, *363*, 2055−2073.

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general. Factors contributing to the ongoing interest in the investigation of interactions between sulfonamides and drugs in other classes included commercial interest in exploiting synergistic antibacterial effects (e.g., co-trimoxazole, containing sulfamethoxazole and trimethoprim in a 1:5 molar ratio),[5] continued use of sulfonamides in third-world countries, and the ready availability and relatively low cost of these drugs.

Several relevant studies are described here to highlight insights into cocrystallization afforded by sulfonamides as model partners. Specific phenomena and processes exemplified by these studies include cocrystal formation in solution, the kinetics of solid-state cocrystallization, and "exchange" reactions that take place in the solid state (e.g., cocrystal A·B(s) + C(s) → cocrystal A·C(s) + B(s)) or, in the case of solvated cocrystals, their conversion to other solvates by exposure to different solvent vapors.

Single-crystal X-ray diffraction and powder X-ray diffraction (PXRD) were the major techniques employed in the investigation of these phenomena because of their respective abilities to establish the molecular structures of cocrystals unequivocally and quantify them in mixtures. While the current definition of a cocrystal excludes salts,[6] some of the compounds described in this review contain identical hydrogen-bonded motifs to those found in "genuine" cocrystals, their formation, however, being mediated by proton transfer from one partner molecule to the other. These compounds nevertheless merit inclusion in the discussion, as this subtle structural feature should not preclude their exploitation as potential medicinal agents. Furthermore, the possibility of such a salt transforming into a cocrystal cannot be ruled out and an example of such behavior is cited below.

Representative Structures of Molecular Associates Containing Sulfa Drugs. As a class, cocrystals between sulfa drugs and antibacterials such as trimethoprim [2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, TMP] embody a well-established synergy between the component drugs (a desirable property of pharmaceutical cocrystals) that results, in this case, from sequential blocking of bacterial dihydropteroate synthetase and dihydrofolate reductase.[5] This feature favors their use in genuine pharmaceutical applications. An early physicochemical study of the 1:1 molecular compound between sulfamethoxazole (SMX) and TMP (Figure 2) was carried out by Giordano et al.[7] who used DSC, PXRD, and FTIR to characterize this material. The precise

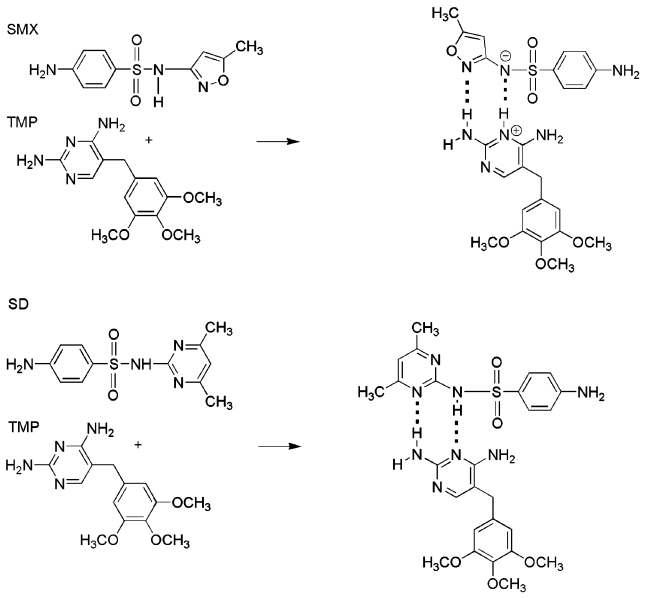

Figure 2. Salt formation between sulfamethoxazole (SMX) and trimethoprim (TMP) (top) and cocrystal formation between sulfadimidine (SD) and trimethoprim (bottom).

nature of the molecular association, namely, hydrogen bonding between the partners, was established in later studies.[8,9] In this case, owing to the relatively strong acidic character of SMX ($pK_a = 5.7$), proton transfer from the sulfonamide to a pyrimidine nitrogen atom of TMP accompanies their reaction, leading to formation of an eight-membered hydrogen-bonded ring with graph set $R_2^2(8)$ (Figure 2). This compound, $TMP^+ \cdot SMX^-$, is technically a salt and therefore does not satisfy the current definition of a cocrystal.[6] On the other hand, reaction between TMP and the less acidic sulfa drug sulfadimidine ($pK_a = 7.4$) in methanolic solution does not involve proton transfer and a cocrystal TMP·SD results instead (Figure 2), also characterized by a hydrogen-bonding motif $R_2^2(8)$, which in this case is "symmetrical", each component acting as both H-bond donor and H-bond acceptor.[10] Sardone at al. had earlier noted that acid strength is a key parameter in determining the outcome of such interactions.[11]

Other earlier examples of 1:1 salts containing sulfonamides include complexes between the antiseptic 9-aminoacridine and sulfamethoxypyridazine,[12] 9-aminoacridine and sulfadi-

(4) McIntosh, J. M.; Robinson, R. H. M.; Selbie, F. R.; Reidy, J. P.; Elliott Blake, H.; Guttmann, L. Acridine-Sulphonamide Compounds as Wound Antiseptics. Clinical Trials of Flavazole. *Lancet* **1945**, *246*, 97−99.

(5) Jawetz, E. Sulfonamides and Trimethoprim. In *Basic & Clinical Pharmacology*, 2nd ed.; Katzung, B. G. Ed.; Lange Medical Publications: Los Altos, CA, 1984; pp 554−558.

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(8) Giuseppetti, G.; Tadini, C. The Crystal Structure of a Sulfamethoxazole-Trimethoprim 1:1 Molecular Compound. *Farmaco, Ed. Sci.* **1980**, *35*, 138−151.

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(10) Bettinetti, G.; Sardone, N. Methanol Solvate of the 1:1 Molecular Complex of Trimethoprim and Sulfadimidine. *Acta Crystallogr.* **1997**, *C53*, 594−597.

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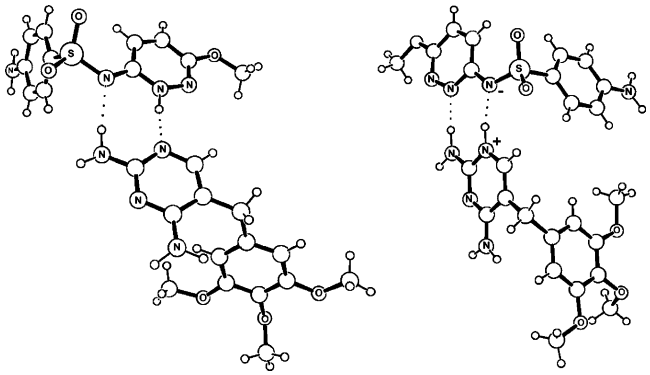

Figure 3. X-ray structures of the TMP·SMPD cocrystal (left) and the salt TMP^{+}·$SMPD^{-}$ (right).

midine,[13] (both associates containing an acridinium−sulfanilamidate ion pair), and the complex between trimethoprim and sulfametrole,[14] discussed in detail in a later section.

As emphasized recently,[6] unequivocal distinction between such salts and "genuine" cocrystals depends crucially on accurate H atom location. This is usually achieved by single-crystal X-ray analysis, although complementary techniques such as solid-state NMR (SSNMR) may be employed. A recent example of the latter is the unequivocal location of H atoms by ^{15}N SSNMR in a compound described as a cocrystal of a monophosphate salt of an active pharmaceutical ingredient (API) and phosphoric acid.[15]

The assumption that the molecular association between a given pair of drug molecules invariably belongs to one or the other of these types (salt/cocrystal) must be treated with circumspection, especially in view of the possibility of tautomerism in the component molecules. This is exemplified by the interaction between trimethoprim (TMP) and sulfamethoxypyridazine (SMPD), which was shown to result in a cocrystal when the crystallization medium was methanol but as a hydrated salt when crystallization was from water (Figure 3).[16]

In the cocrystal TMP·SMPD (no proton transfer involved), the SMPD molecule occurs in the imido-tautomeric form, and the hydrogen bond acceptor and donor pairs are shared between the aminopyrimidine moiety of TMP and the imidopyridazine unit of SMPD. However, in the salt TMP^{+}·$SMPD^{-}$, the SMPD molecule is in the amide tautomeric form, with the sulfonamide N atom deprotonated while a pyrimidine N atom of TMP is protonated; both hydrogen bonds are thus donated by the TMP cation. It will also be noted that in proceeding from the cocrystal to the salt, there is an exchange of hydrogen-bonded partners (the TMP units are drawn in a roughly parallel orientation while the SMPD units in Figure 3 are in antiparallel orientation). The physical conditions for interconversion of these species have been described,[16] and the forward and reverse processes clearly involve profound changes in the hydrogen-bonding arrangements. This system has pharmaceutical significance as SMPD and TMP are used in combination (as a physical mixture) in a commercial product (Velaten, Hoechst Pharma, Milan, Italy).

The few examples cited above serve to illustrate some of the variety of molecular associations possible between sulfonamides and other drugs, highlighting also subtle molecular changes that may accompany the formation of specific cocrystals or salts.

A systematic study of the interaction between sulfadimidine (Figure 1) and small, pharmacologically relevant molecules commenced in the early 1990s with a report on the X-ray structures of the cocrystals SD·2-aminobenzoic acid **1** and SD·4-aminobenzoic acid **2** (Figure 4).[17] The partner molecule 2-aminobenzoic acid is active as vitamin L_1, a factor necessary for lactation, while 4-aminobenzoic acid (widely known as PABA, for *p*-aminobenzoic acid) is of academic interest here given its role as an essential metabolite in dihydrofolic acid synthesis, the process which is competitively inhibited by sulfonamide drugs. In both cocrystals, molecular association was confirmed to be the same as that found in the cocrystal SD·2-hydroxybenzoic acid,[18] namely, complementary hydrogen bonding between the carboxyl group of the acid molecule and the imino N atom and a pyrimidinyl N atom of SD, giving rise to the $R_2^2(8)$ motif. Owing to the possibilities of tautomerism for the sulfonamide component and internal charge transfer for the partner molecules (e.g., 2-aminobenzoic acid contains zwitterions in one of its polymorphs),[19] care was exercised in the location of all hydrogen atoms in the crystallographic studies.

The report describing cocrystals **1** and **2** was soon followed by a second one featuring the X-ray structures of the

(12) Ghose, S.; Chakrabarti, C.; Dattagupta, J. K. Structural Studies on Molecular Complexes, I: Crystal and Molecular Structure of 9-aminoacridine-sulfamethoxypyridazine (1:1), $C_{13}H_{10}N_2$·$C_{11}H_{12}N_4O_3S$. *J. Crystallogr. Spectrosc. Res.* **1987**, *171*, 197−206.

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(16) Bettinetti, G.; Caira, M. R.; Callegari, A.; Merli, M.; Sorrenti, M.; Tadini, C. Structure and Solid-State Chemistry of Anhydrous and Hydrated Forms of the Trimethoprim-Sulfamethoxypyridazine 1:1 Molecular Complex. *J. Pharm. Sci.* **2000**, *89*, 478−489.

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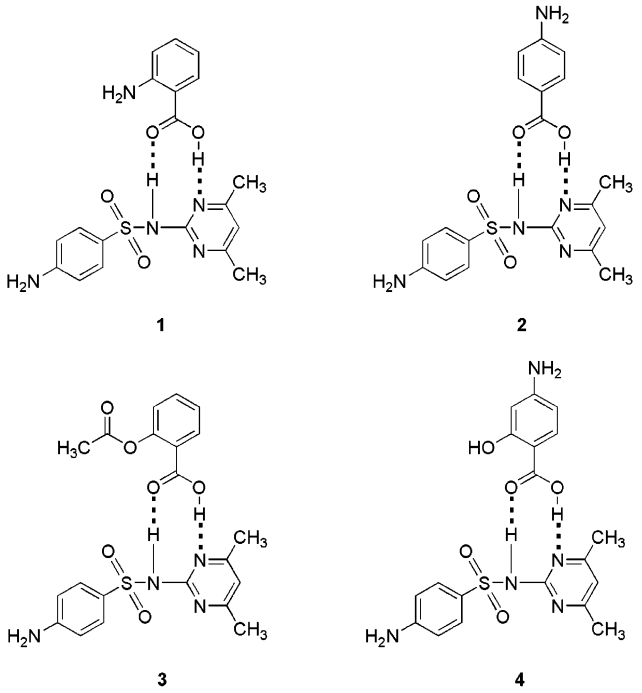

Figure 4. Structures of cocrystals formed between sulfadimidine and the pharmacologically active molecules 2-aminobenzoic acid (**1**), 4-aminobenzoic acid (**2**), aspirin (**3**), and 4-aminosalicylic acid (**4**).

analogous sulfadimidine cocrystals **3** and **4** (Figure 4), containing acetylsalicylic acid (aspirin) and 4-aminosalicylic acid (PAS, for *p*-aminosalicylic acid) as the respective partner molecules.[20] The latter were chosen for their important pharmacological properties, namely, the analgesic, anti-inflammatory, and antipyretic effects of aspirin, and the tuberculostatic effect of PAS. In compound **3**, the first aspirin-containing cocrystal to be structurally characterized, the aspirin molecule was found to adopt a significantly different conformation from that observed in the crystal of pure aspirin. Compounds **1**−**4** have recently been cited as examples of binary supramolecular assemblies of pharmaceutical relevance.[21]

In a later study, the 1:1 cocrystal between 5-methoxysulfadiazine and aspirin (Figure 5, **5**) was isolated and structurally characterized.[22] The conformation of the aspirin molecule in **5** was found to match that found in its cocrystal with sulfadimidine (Figure 4, **3**). In this context, it is interesting to note that very recent pharmaceutical cocrystallization

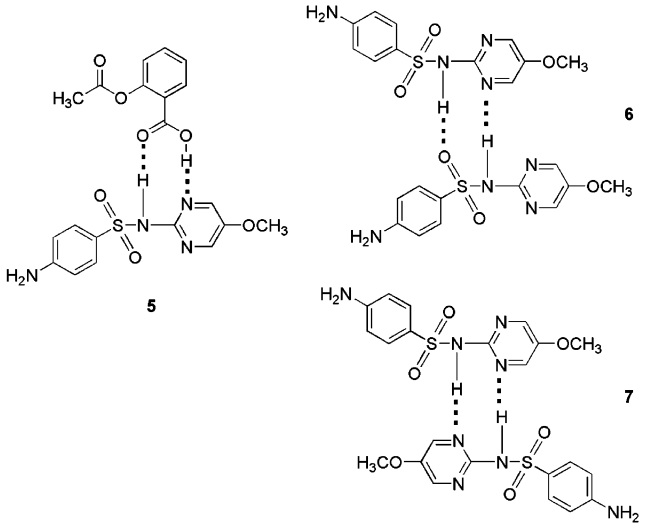

Figure 5. Structure of the cocrystal formed between 5-methoxysulfadiazine (SMD) and aspirin (**5**) and the hydrogen-bonded motifs occurring in polymorphic forms I and II of SMD (**6** and **7**, respectively).

strategies have focused on aspirin as a partner molecule. For example, a 1:1 carbamazepine−aspirin cocrystal, in which the partner molecules are associated by a carboxylic acid−amide supramolecular heterosynthon with graph set $R_2^2(8)$, has recently been described.[23]

In another important related development, attempted cocrystallization of aspirin with acetamide or levetiracetam failed to produce the expected products, resulting instead in the serendipitous appearance of the "elusive" second polymorphic form of aspirin, a most significant discovery nonetheless.[23] A similar occurrence of serendipitous crystallization of a different polymorph of one of the components was reported earlier in an attempt to grow a cocrystal between 5-methoxysulfadiazine (sulfameter, Figure 1; SMD) and 4-aminosalicylic acid (PAS) from acetonitrile solution.[22] In this case, the polymorph of SMD employed as starting material corresponded to form I, with the hydrogen-bonded motif shown as **6** in Figure 5. The attempted cocrystallization with PAS yielded relatively large monocrystals of polymorphic form II of SMD, containing the centrosymmetric motif **7** (Figure 5), as confirmed by subsequent X-ray analysis.

Interestingly, form II is the biologically most active polymorph of SMD, previously isolated in the form of very fine particles with little or no geometrical form by rapid quenching of an ethanolic solution of SMD to −12 °C.[24]

Returning to the cocrystals of sulfadimidine, all of those shown in Figure 4 were obtained as prismatic crystals of excellent quality by slow evaporation of acetonitrile or ethanol-

(20) Caira, M. R. Molecular Complexes of Sulfonamides. 2. 1:1 Complexes Between Drug Molecules: Sulfadimidine-acetylsalicylic acid and Sulfadimidine-4-aminosalicylic acid. *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 193−200.

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(23) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. J. The Predictably Elusive Form II of Aspirin. *J. Am. Chem. Soc.* **2005**, *125*, 16802−16803.

(24) Bettinetti, G. P.; Giordano, F.; La Manna, A.; Giuseppetti, G. Preparation and Characterization of 2-Sulfanilamido-5-methoxypyrimidine Crystal Forms. *Farmaco, Ed. Prat.* **1974**, *29*, 493−507.

ic solutions containing equimolar mixtures of the components, and they were found to be stable compounds. These initial findings prompted an extension of the series and further exploration of methods for their preparation, their properties, and their solid-state reactions, as described in the next section.

Sulfadimidine as a Model Cocrystal Former. Earlier isolation from solution of cocrystals between sulfadimidine (SD) and aromatic carboxylic acids such as 2-hydroxybenzoic acid (salicylic acid, SA),[18] 2-aminobenzoic acid (anthranilic acid AA),[17] 4-aminobenzoic acid (*p*-aminobenzoic acid, PABA),[17] 4-amino-2-hydroxybenzoic acid (*p*-aminosalicylic acid, PAS),[20] and 2-acetoxybenzoic acid (aspirin, or acetylsalicylic acid, AC),[20] and their structural characterization, indicated the versatility of sulfadimidine as a cocrystal former, prompting further investigation. Thus, the above series of acids was extended to include benzoic acid (BA), benzene-1,2-dicarboxylic acid (*o*-phthalic acid, PHA), and 4-chlorobenzoic acid (*p*-chlorobenzoic acid, PCL). The corresponding cocrystals with SD, subsequently grown from solution, were likewise shown by X-ray diffraction to be based on complementary hydrogen bonding with the graph set $R_2^2(8)$. The entire series of cocrystals was used as a model system in a comprehensive study[25] aimed at exploring a number of fundamental processes associated with cocrystallization, as summarized below.

Cogrinding, in the absence of solvent, of equimolar amounts of SD and each of the acids BA, AA, SA, AC, PHA, and PCL in a mechanical ball-grinder was pursued in order to establish the tendency for cocrystal formation in the solid state.[25] In each case, the PXRD pattern of the coground material (recorded with Cu Kα radiation) was found to be identical to that computed from the known single-crystal X-ray structure of the corresponding cocrystal. A representative example is shown in Figure 6. Remarkably, pure cocrystals could typically be obtained by cogrinding in under 5 min, whereas growth of different cocrystals from solution required anything from a few days to several weeks by spontaneous evaporation from identical vials. The relatively slow rates of cocrystallization from solution, partly due to undersaturation and the possibly low driving force of 1:1 component stoichiometric ratios,[21] favored formation of high quality crystals for X-ray structure determination.

The purity of the cocrystals obtained by cogrinding was also evident from their DSC traces, which generally displayed single endotherms corresponding to cocrystal fusion at temperatures that differed from the melting points of the individual components. Of a sample of eight cocrystals of SD with aromatic carboxylic acids, four displayed melting points greater than those of the individual components and four had melting points between those of the components. Preparation of cocrystals by ball-milling for periods of a few minutes only did not result in any significant differences in the appearance of the melting endotherms relative to those of cocrystals grown from solution. Additional characterization data for this series included FTIR spectral confirmation of significant shifts in the N−H stretching frequencies of SD upon cocrystallization.[25]

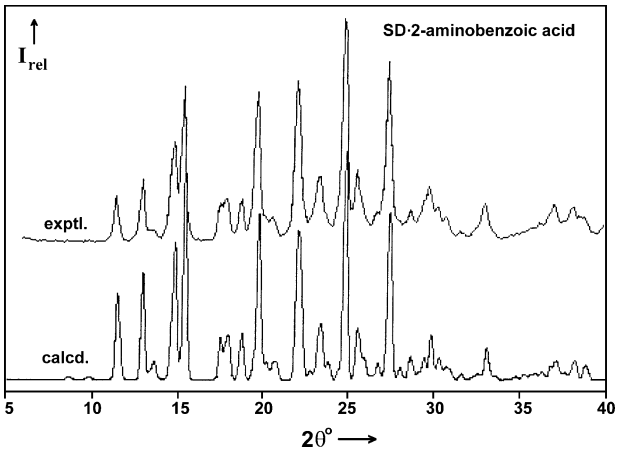

Figure 6. Experimental PXRD pattern (top) for the product obtained from cogrinding SD and 2-aminobenzoic acid and the computed PXRD pattern (bottom) based on the refined single-crystal X-ray structure of the cocrystal SD·2-aminobenzoic acid.

Kinetic aspects of the solid-state cocrystallization reaction SD + SA → SD·SA were investigated by manual cogrinding of an equimolar mixture of the components at 25 °C and following the course of reaction using PXRD, monitoring either the decrease in the integrated intensity of the (120) reflection of SD or the increase in intensity of the (041) reflection of the product cocrystal SD·SA, to extract the extent of reaction (α) as a function of time. A convincing fit of the data to the rate law $-\ln(1 - \alpha) = kt$ indicated adherence to a random nucleation mechanism, with a rate constant $k = 0.11$ min^{-1}. Analogous results were obtained for the kinetics of the solid-state reaction SD + AA → SD·AA, with $k = 0.08$ min^{-1} at 25 °C. In this case, the increase in the intensity of the (122) reflection due to the cocrystal was monitored for the kinetic study.

Competition experiments involving manual and mechanically aided solid-state grinding of 1:1:1 mixtures of SD and selected pairs of aromatic carboxylic acids followed, the products being identified by PXRD. These experiments were modeled on the work of Etter et al.[26] who demonstrated selective, complementary base-pairing in the solid state for nucleotide bases. Thus, for example, when an equimolar mixture of SD, SA, and AA was ground for several minutes, the outcome could be represented by

$$\text{SD} + \text{SA} + \text{AA} \rightarrow \text{SD·AA} + \text{SA} + \text{SA·AA} \qquad (1)$$

with the cocrystal SD·AA present as the major product in the final mixture. PXRD peak intensities due to the unreacted

(25) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, A. F. Selective Formation of Hydrogen Bonded Co-crystals Between a Sulfonamide and Aromatic Carboxylic Acids in the Solid State. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2213−2216.

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SA and the cocrystal SA·AA (whose existence was proven in a separate cogrinding experiment using only SA and AA) were very low, indicating an overwhelming preference for cocrystal formation between SD and AA under these competitive conditions. In an analogous experiment to establish which of AA and AC in an equimolar mixture is the preferred SD partner, the outcome was found to be

$$\mathrm{SD} + \mathrm{AA} + \mathrm{AC} \rightarrow \mathrm{SD{\cdot}AA} + \mathrm{AC} \qquad (2)$$

in this case, indicating exclusive formation of the cocrystal SD·AA under competitive conditions. Additional competition experiments in which one of the partner acids was AA revealed that the cocrystal SD·AA was generally the preferred product and it was necessary to rationalize its stability. Hydrogen bond strengths inferred from accurately measured N···O distances for the N−H···O and O−H···N bonds binding the partner molecules were found to be unreliable indicators of complex stability in these cocrystals. The stability of the cocrystal SD·AA in particular was instead attributed to the ease of deaggregation of the specific polymorph of AA employed in the competition experiments,[19] relative to those of the competing partners.

The tendency for preferred formation of SD·AA in the competition experiments described above suggested an unusual experiment, namely, that of cogrinding the acid AA with a cocrystal SD·A′ (A′ = an aromatic carboxylic acid other than AA). Thus, the well-characterized cocrystal SD·SA was chosen for cogrinding with an equimolar amount of AA. The outcome, based on quantitative PXRD analysis, can be represented by

$$\mathrm{SD{\cdot}SA} + \mathrm{AA} \rightarrow \mathrm{SD{\cdot}AA} + \mathrm{SA} + \mathrm{SA{\cdot}AA} \qquad (3)$$

with the cocrystal SD·AA as the major product. This remarkable result not only reaffirmed the unusual stability of the cocrystal SD·AA but also proved to be a unique instance of the substitution of one partner molecule by another in solid-state cocrystallization.[25]

In concluding this summary of observations, we note that the cocrystals of sulfadimidine described here served as a useful model system, readily lending themselves to an exploration of a number of intriguing facets of solid-state cocrystallization. Continued interest in the sulfa drug SD as a cocrystal former is evidenced by the appearance of more recent reports on its reaction with other molecules. For example, cocrystallization of SD with indole-2-carboxylic acid and 2,4-dinitrobenzoic acid was reported recently.[27]

As mentioned earlier, Bettinetti et al. isolated the methanol solvate of a 1:1 cocrystal between SD and the antibacterial trimethoprim (TMP)[10] (Figure 2). Using different preparative conditions, the monohydrate of a 2:1 cocrystal between SD and TMP was obtained.[11] Here, one SD molecule and a TMP molecule share the same $R_2^2(8)$ hydrogen-bonded motif as in the 1:1 cocrystal, while association with the second SD molecule (SD′) occurs through a hydrogen bond N−H···N, involving the common pyrimidine N atom of TMP (acting as a double acceptor) and the imino NH function of SD′. Thus, SD lends itself to stoichiometry variation, an important parameter for expanding cocrystallization opportunities.[28]

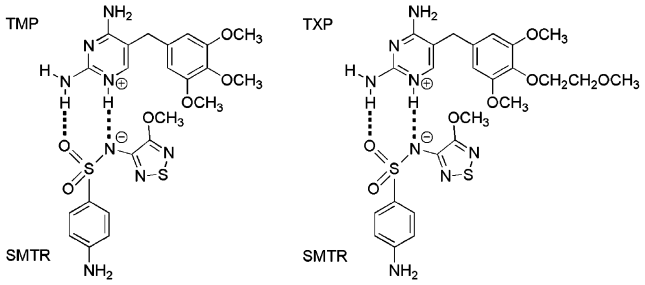

Figure 7. Common hydrogen bond motifs observed in the 1:1 salts $TMP^+{\cdot}SMTR^-$ and $TXP^+{\cdot}SMTR^-$.

Structures and Physicochemical Properties of TMP−Sulfametrole and TXP−Sulfametrole Complexes. The pharmaceutical significance of cocrystals and salts formed between sulfa drugs and antibacterials such as trimethoprim (TMP) was highlighted earlier, and a common form of association was found to be based on combinations of N−H···N and $NH^+{\cdots}N^-$ hydrogen bonds (Figures 2 and 3). Giuseppetti et al. found that a different mode of association between TMP and the drug sulfametrole (SMTR) occurs in the solid-state.[14] As shown in Figure 7, proton transfer from SMTR to TMP occurs, leading to the formation of one hydrogen bond of type $NH^+{\cdots}N^-$, the $R_2^2(8)$ hydrogen-bonded motif being completed by a hydrogen bond (N−H···O) involving the 2-aminopyrimidine group of TMP and an O atom of the sulfonamido group of SMTR. The same hydrogen-bonding arrangement occurs in the compound formed between SMTR and the antibacterial tetroxoprim (TXP), a potent analogue of TMP.[29]

The compound $TXP^+{\cdot}SMTR^-$ and crystalline species derived from it proved to have a rich solid-state chemistry, manifesting a variety of structural and thermodynamic relationships. Very briefly, these included (a) a monotropic relationship between two unsolvated polymorphs $TXP^+{\cdot}SMTR^-$, (b) isostructurality of the solvated crystals $TXP^+{\cdot}SMTR^-{\cdot}H_2O$, $TXP^+{\cdot}SMTR^-{\cdot}$MeOH, and $TXP^+{\cdot}SMTR^-{\cdot}$EtOH, and (c) enantiotropic dimorphism of the hydrated form $TXP^+{\cdot}SMTR^-{\cdot}H_2O$.

In their isostructurality, the solvated forms of $TXP^+{\cdot}SMTR^-$ mimic those of macrolide antibiotics such as dirythromycin, being virtually indistinguishable from their PXRD patterns. Furthermore, Bettinetti et al. showed that the solvates readily

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display solvent exchange.[30] This was effected by separate exposure of powdered samples of each solvate of $TXP^+ \cdot SMTR^-$ to a saturated atmosphere of each solvent of the complementary solvate pair. The ensuing exchange processes, of the type

$$TXP^+ \cdot SMTR^- \cdot X(s) + Y(g) \rightarrow TXP^+ \cdot SMTR^- \cdot Y(s) + X(g) \quad (4)$$

where X and Y are any two of the solvents water, methanol, and ethanol, were monitored quantitatively by TG and DSC techniques and found to be reversible in all cases. A possible mechanism for solvent migration and exchange was proposed, based on the single-crystal X-ray structures of the solvates.[30] These observations are of some interest given the current technological and pharmaceutical significance of drug solvates, and of hydrates in particular.

Conclusion

The systems of cocrystals and salts cited in this review were chosen to support the author's view that "old" drugs such as sulfonamides, in the form of novel molecular associates, not only have potential as candidates for pharmaceutical development but, when probed by a variety of experiments and measuring techniques, continue to yield new insights into the relationship between solid-state structure and physicochemical behavior. Though solubilities of the cocrystals between sulfadimidine and carboxylic acids described above were not measured, any differences relative to pure sulfadimidine might have practical advantage. If, for example, a suitable carboxylic acid partner were to yield a cocrystal with sulfadimidine with significantly higher solubility than that of an amorphous form of the drug, the longer-term chemical and physical stability of the cocrystal could be advantageous. This has been suggested for cocrystals of *cis*-itraconazole with 1,4-dicarboxylic acid partners.[31]

Limitations of space necessitated selection of a series of representative sulfonamide−drug cocrystals and salts, and the reader is referred to further examples discussed by Adsmond and Grant.[32] Cocrystallization of sulfonamides with entities other than drugs is also of current pharmaceutical interest, as indicated for example by recent registration of a patent describing novel and unexpected cocrystals between 5-phenylpyrazolyl-1-benzenesulfonamides and polyethylene glycols.[33]

Finally, we note renewed interest in the solid-state chemistry of sulfa drugs as a class for their ability to aid crystal structure prediction of pharmaceutical solids through systematic exploration of their hydrogen-bonding patterns,[32] and for gaining an understanding of the kinetics of solvent-mediated transformations[34] as well as the role of additives in stabilizing metastable polymorphs.[35] Careful study of these works would benefit future research on the cocrystallization of sulfonamides.

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