Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state

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Co-grinding sulfadimidine [4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide] with several aromatic carboxylic acids in the solid state produces 1 : 1 hydrogen bonded cocrystals which are identical to those obtained from reaction between the components in solution. The kinetics of solid state formation of selected cocrystals have been measured using X-ray powder diffraction. Sulfadimidine selectively cocrystallizes with 2-aminobenzoic acid when the latter is present in binary mixtures of acids. Solid state reaction of the cocrystal sulfadimidine•2-hydroxybenzoic acid with 2-aminobenzoic acid results in elimination of 2-hydroxybenzoic acid and formation of the cocrystal sulfadimidine•2-aminobenzoic acid.

Introduction

There is growing interest in the hydrogen bond directed molecular recognition properties of organic molecules. Many systems of this type have been studied by X-ray analysis to determine the structures of molecular assemblies after association has occurred while cocrystallization studies have been useful in monitoring competitive interactions that determine the selectivity of recognition processes.[1-7]

The terms 'cocrystal' and 'molecular complex' are used widely and interchangeably to describe hydrogen bonded structures of the type discussed in this paper.

The carboxylic acids referred to in this study, together with their abbreviated designations, are: benzoic acid (BA), 2-aminobenzoic acid (anthranilic acid, AA), 2-hydroxybenzoic acid (salicylic acid, SA), 2-acetoxybenzoic acid (acetylsalicylic acid, AC), benzene-1,2-dicarboxylic acid (*o*-phthalic acid, PHA), 4-chlorobenzoic acid (*p*-chlorobenzoic acid, PCL), 4-aminobenzoic acid (*p*-aminobenzoic acid, PAB) and 4-amino-2-hydroxybenzoic acid (*p*-aminosalicylic acid, PAS).

The first X-ray crystal structure of a 1 : 1 molecular complex between the sulfa drug sulfadimidine, {[4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide], hereinafter SD} and an aromatic carboxylic acid, namely 2-hydroxybenzoic acid, was reported by Patel *et al.*[8] We subsequently extended the study of compounds of this type and reported the preparation and X-ray crystal structures of the 1 : 1 cocrystals SD•2-aminobenzoic acid[9] (SD•AA), SD•4-aminobenzoic acid[9] (SD•PAB), SD•*p*-aminosalicylic acid[10] (SD•PAS) and SD•acetylsalicylic acid[10] (SD•AC). We have also prepared and elucidated the crystal structures of SD•*p*-chlorobenzoic acid (SD•PCL) and SD•*o*-phthalic acid[11] (SD•PHA). Fig. 1 shows the structure of a representative example, the 1 : 1 sulfadimidine•benzoic acid (SD•BA) complex unit in its cocrystal,[11] the most recent addition to the series. Molecular association between SD and BA is effected by two intermolecular hydrogen bonds, namely N–H ··· O=C and N ··· H–O, involving the N atom of the sulfonamide group, one pyrimidine N atom and the carboxylic group of the acid. The same hydrogen bonding pattern occurs in all of the cocrystals listed above. The complex motif has a graph set $R_2^2(8)$ in the notation of Etter,[12] indicating that the hydrogen bonds result in the formation of an eight-membered ring and that two donors and two acceptors are used in assembling the motif.

Hitherto, each of the cocrystals in this series was obtained by crystallization from a solution containing the two components in equimolar ratio using solvents such as EtOH, Me_2CO and MeCN. We now report the facile formation of the cocrystals SD•BA, SD•AA, SD•SA, SD•AC, SD•PHA and SD•PCL, by co-grinding SD with the respective acid in the solid state and we demonstrate their structural identity with the cocrystals obtained by crystallization from solution. The results of a study of the kinetics of formation of two selected cocrystals (SD•SA and SD•AA) by X-ray powder diffraction (XRD) are also described. Finally, we present novel results from competition experiments involving, on the one hand, co-grinding SD with an equimolar mixture of carboxylic acids to investigate the possibility of selective cocrystallization, and on the other, co-grinding a 1 : 1 SD–aromatic carboxylic acid cocrystal with a different acid from that contained in the cocrystal, to ascertain whether an exchange of the complexing partners is possible.

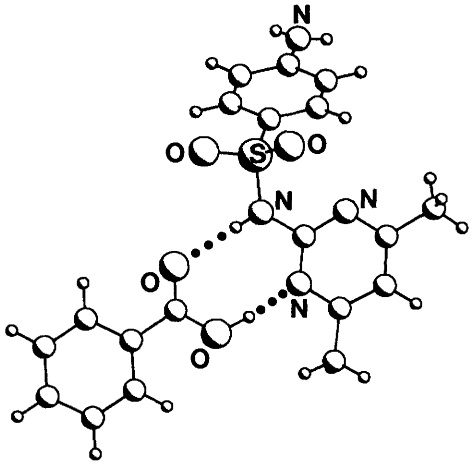

Fig. 1 Hydrogen bonded motif in the complex SD•BA

The products of co-grinding were analysed by IR spectroscopy, differential scanning calorimetry and X-ray powder diffraction. Unambiguous identification of the solid phases produced by co-grinding experiments relied on the availability of the single crystal X-ray data for the cocrystals. The latter were used to compute XRD patterns for comparison with the experimental patterns of co-ground materials. The single crystal X-ray analyses[8-11] have revealed different unit cell dimensions and space groups for the co-crystals described here, so that each has a unique XRD pattern.

Experimental

SD was co-ground with an equimolar amount of each of the acids BA, AA, SA, AC, PHA and PCL. In a typical experiment, 140 mg SD (0.5 mmol) and 61 mg BA (0.5 mmol) were mixed and ground manually in a mortar and pestle for 4 min. The mixture was then ground for 3 min in a Grindex ball grinder using a 12 mm iron ball (8.34 g) in a stainless steel cylinder of internal diameter 14 mm and length 35 mm. The products of co-grinding were analysed by differential scanning calorimetry (DSC) using a Perkin-Elmer PC7 Series thermal analysis system, by IR spectroscopy (hexachlorobutadiene mulls, CsI plates) on a Perkin Elmer model 983 IR spectrophotometer and by X-ray powder diffraction (XRD) on a Philips PW1050/80 goniometer using Ni-filtered Cu-Kα radiation (λ = 1.5418 Å).

The program Lazy Pulverix[13] was used to generate XRD patterns for cocrystals whose single crystal X-ray structures have been determined.[8–11] Input data comprised space group information, unit cell parameters, atomic coordinates and thermal parameters.

The kinetics of cocrystallization formation were followed by measuring the intensities of non-overlapping reflections of SD and the product cocrystal (SD•SA or SD•AA) as a function of grinding time. Manual grinding in a mortar and pestle at a constant rate was used since the reactions proceeded too rapidly in the ball grinder. Grinding for up to 60 min was required for complete reaction.

Competition experiments involved co-grinding SD and two acids in a 1:1:1 molar ratio using the apparatus described above and analysing the product phases by XRD.

Prior to the co-grinding experiments, the XRD patterns of the individual components were recorded before and after 10 min grinding to ascertain whether polymorphic changes occurred. No changes were observed.

Results and discussion

Cocrystal formation

Representative results are given for the pair SD and BA. The DSC trace of the co-ground material yielded a melting endotherm at 215 °C which differs from the melting point of either SD (197 °C) or BA (122 °C). This was the first indication of the formation of a new phase. The N–H stretching frequencies in SD occurring at 3436, 3337 and 3236 cm^{-1} appeared in the product at 3464, 3375 and 3259 cm^{-1}. Finally, as shown in Fig. 2, for the product of co-grinding, XRD yielded a pattern which was identical to that calculated using the single crystal X-ray data for the 1:1 SD–benzoic acid cocrystal, SD•BA.[11]

Analogous and equally convincing results were obtained with the acids AA, SA, AC, PHA and PCL. Table 1 lists the measured melting points and N–H stretching frequencies in the cocrystals. In all cases, the products were obtained in under 5 min grinding time at room temperature and in a pure state as gauged from the absence of DSC fusion endotherms or XRD peaks corresponding to the reactants. Control of the temperature during mechanical grinding was not feasible and temperatures as high as 40 °C were registered in the stainless steel vial.

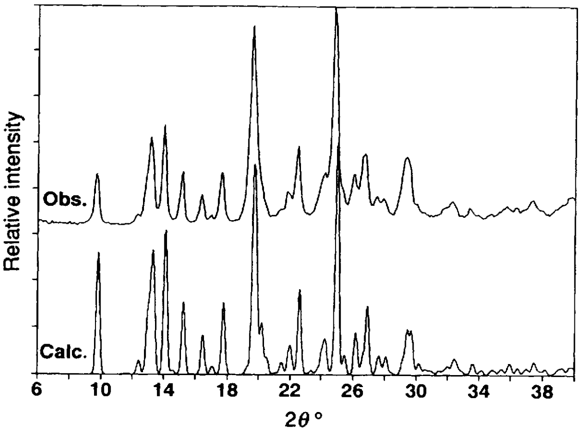

Fig. 2 Comparison between the experimental XRD pattern of the product of co-grinding SD and BA (obs.) with the XRD pattern of the cocrystal SD•BA calculated from its crystal structure (calc.)

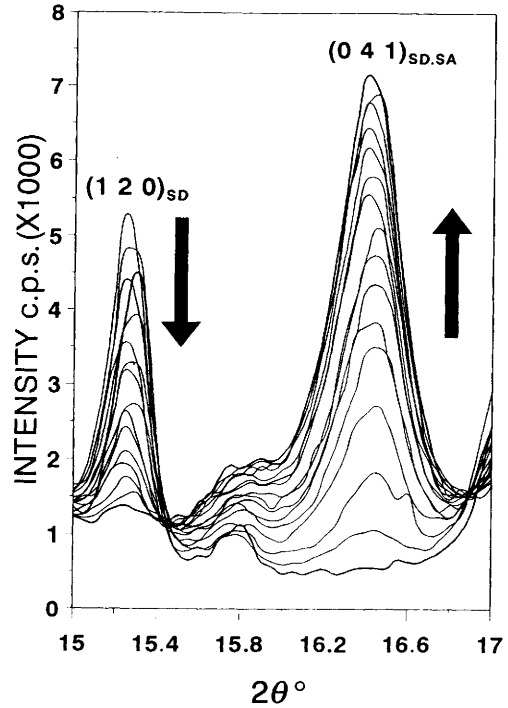

Fig. 3 Variation in peak intensities for reflections (1 2 0) of SD and (0 4 1) of the cocrystal SD•SA as co-grinding of SD and SA proceeded

Table 1 Melting points and N–H stretching frequencies for cocrystals SD·A (A = aromatic carboxylic acid)

A	Mp (°C)	N–H stretch/cm^{-1}
—	197	3436, 3337, 3236
BA	215	3464, 3375, 3259
AA	206	3490, 3463, 3371
SA	196	3475, 3381, 3256
AC	138	3487, 3398
PHA	180	3493, 3379
PCL	207	3469, 3376, 3256

Kinetics of cocrystallization

To obtain meaningful kinetic results, manual grinding at room temperature (25 °C) was employed to minimize localized heating effects. Fig. 3 shows successive traces of the (1 2 0) reflection of SD and the (0 4 1) reflection of SD•SA as co-grinding of SD and SA proceeded. The integrated intensities (areas under the curves) decreased and increased respectively for these reflections. That representing the formation of SD•SA was used to plot the extent of reaction (α) *versus* time curves shown in Fig. 4(*a*). Analysis of the latter curve yielded a fit of the data to the equation $-\ln(1 - \alpha) = kt$ with $k = 0.11$ min^{-1}. The plot of $-\ln(1 - \alpha)$ *versus* t is shown in Fig. 4(*b*). This first-order behaviour indicates that cocrystallization involves a

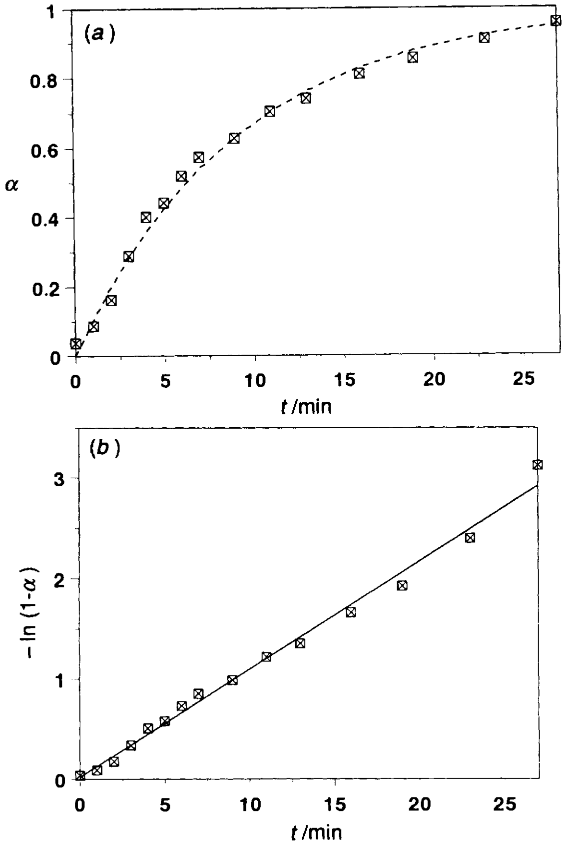

Fig. 4 (*a*) Extent of reaction (α) *versus* time for the cocrystallization of SD and SA in the solid state, experimental points are indicated by squares while dashed curve represents theoretical first-order behaviour; (*b*) plot of $-\ln(1-\alpha)$ *versus* time for the formation of cocrystal SD•SA

random nucleation mechanism.[14] Analogous results were obtained for the formation of the cocrystal SD•AA, with a rate constant $k = 0.08\ \mathrm{min}^{-1}$.

Competition experiments

Competition experiments involved co-grinding equimolar ternary mixtures of SD and selected pairs of acids. The results of a typical experiment, in which SD was co-ground with SA and AA, are shown in Fig. 5. The XRD pattern of the product of co-grinding is dominated by peaks for the cocrystal SD•AA. It also contains peaks of low intensity representing the unreacted SA and traces of the phase SA•AA. (The existence of the latter cocrystal was proven by a separate experiment in which the acids SA and AA were co-ground. The XRD pattern of the product contained peaks not present in the patterns of either of the pure components.) The reaction occurring in the competition experiment can thus be represented by eqn. (1) with the product SD•AA predominating.

$$\mathrm{SD + AA + SA \longrightarrow SD{\bullet}AA + SA + SA{\bullet}AA} \qquad (1)$$

Analogous experiments using SD and the pairs AC and AA, BA and AA, were carried out and the major products of cocrystallization were similarly identified by XRD. The reactions occurring were confirmed as (2) and (3). In (2),

$$\mathrm{SD + AC + AA \longrightarrow SD{\bullet}AA + AC} \qquad (2)$$

$$\mathrm{SD + BA + AA \longrightarrow SD{\bullet}AA} \qquad (3)$$

exclusive formation of the cocrystal SD•AA was indicated. In (3), SD•AA was the dominant product but the expected XRD peaks for unreacted BA were not observed. The presence of only one extraneous peak among those for SD•AA suggested that BA was converted into an essentially amorphous phase (possibly BA•AA).

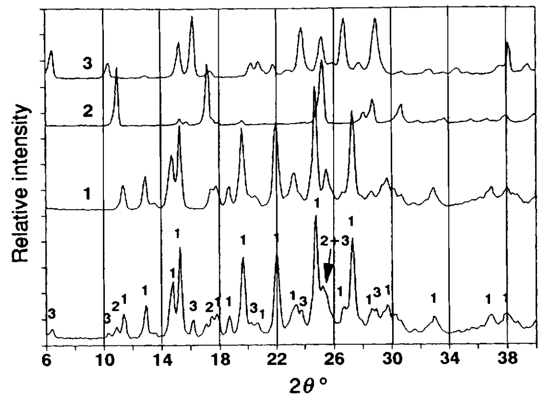

Fig. 5 XRD traces for interpretation of the competition reaction (1): (**1**) calculated from the crystal structure of SD•AA; (**2**) the acid SA; (**3**) the cocrystal SA•AA; (**4**) product of co-grinding SD, SA, and AA [reaction (1)]

A solid state substitution reaction

Noting the tendency for preferential formation of SD•AA in competition experiments, we carried out an experiment to test whether reaction of AA with a complex SD•A′ (A′ = an acid other than AA) might lead to formation of SD•AA, as this would represent an unusual instance of substitution in the solid state.

The cocrystal SD•SA and the pure acid AA in 1 : 1 molar ratio were co-ground for 3 min. The XRD pattern of the resulting material is shown in Fig. 6 where it is compared with the XRD pattern for the product obtained from the competition reaction (1). The identical nature of these patterns proves that the major product of co-grinding SD•SA and AA is SD•AA and that pure SA and the cocrystal SA•AA are also present in the final mixture. The substitution reaction we observed may therefore be represented by eqn. (4).

$$\mathrm{SD{\bullet}SA + AA \longrightarrow SD{\bullet}AA + SA + SA{\bullet}AA} \qquad (4)$$

The displacement of SA from the cocrystal SD•SA and its replacement by AA in the solid state is remarkable and we are not aware of a previous account of such a process.

Similar co-grinding experiments with a mixture of SD•SA and BA did not, however, result in substitution of SA by BA and the success of reaction (4) appears to depend on the unusual stability of the cocrystal SD•AA.

Our experiments have demonstrated the ready formation of 1 : 1 cocrystals between SD and aromatic carboxylic acids in the solid state, as well as proving that the cocrystals thus formed have identical structures to their counterparts crystallizing from solutions containing the two components. The kinetic study shows that XRD is a useful method for following the course of solid state cocrystallization and that further experiments may give us more insight into the mechanism of solid state reactions of this type.

In attempting to explain the outcome of the competition reactions (1)–(3), we have considered the relative strengths of binding between the components of the cocrystals as reflected in their N••• O intermolecular hydrogen bonded distances. In the case of reaction (2), where the cocrystals SD•SA and SD•AA are potential products, the relevant N•••O distances for the hydrogen bonds N–H•••O, O–H···N are respectively 2.784(4), 2.639(3) Å in SD•SA[8] and 2.838(2), 2.663(2) Å in SD•AA.[9] If stronger hydrogen bonds in the product were the only factor favouring cocrystallization, the significantly shorter

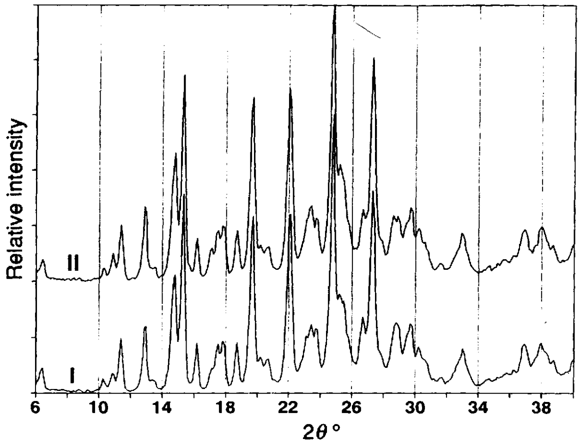

Fig. 6 XRD traces obtained by co-grinding (I) SD·SA and AA [reaction (4)], (II) SD, AA and SA [reaction (1)]

and stronger hydrogen bonds in SD·SA should favour its formation over SD·AA, whereas the reverse was observed. We have in fact indicated previously[10] that the intermolecular N · · · O hydrogen bond distances in this series of cocrystals vary significantly and, in the case of SD·PCL which crystallizes with two complex units in the asymmetric unit,[11] we have found significantly different N · · · O distances for chemically identical bonds in the two complex units. These observations clearly indicate that considerations of additional factors, *e.g.*, crystal packing and lattice energies, are also important in explaining the results of competition experiments. With regard to the preferred formation of SD·AA, the following qualitative explanation is offered. Cocrystal formation between SD and an acid A involves competition between homomeric aggregation (SD · · · SD, A · · · A) and heteromeric aggregation (SD · · · A). When two acids A and A′ are present, as in the competition reactions (1)–(3) above, weaker intermolecular attractive forces in crystals of, *e.g.*, A, compared with those in A′, should favour the formation of the cocrystal SD·A over SD·A′. In crystals of SA, AC and BA, the molecules aggregate in a manner typical of carboxylic acids, namely by formation of stable hydrogen bonded dimers with a graph set $R_2{}^2(8)$.[12] However, in crystals of AA, the situation differs.[15] The crystallographic asymmetric unit comprises two molecules, one neutral and the other a zwitterion. Consequently, stable hydrogen bonded dimers do not occur in the crystal and instead, the hydrogen bonding arrangement propagates unidirectionally in a helical pattern parallel to the polar axis of the crystal. We have confirmed that the sample of AA used in our experiments is the same polymorph as that described above and we conclude that the tendency for the cocrystal SD·AA to form preferentially in competition experiments (1)–(3) is probably due to the relative ease of de-aggregation of AA, owing to the absence of stable dimers, as compared with the other acids.

Further studies, including the calculation of lattice energies, competition reactions in solution and computer modelling of the cocrystallization process, are needed for a deeper insight into the mechanisms involved.

We have found a plausible explanation for some of the results obtained here, but several questions require further investigation, *e.g.* the mechanism of the substitution reaction, which involves subtle processes between homomeric and heteromeric hydrogen bonded aggregates, quite distinct from those occurring between dissolved molecules. This complexity was underscored in a recent account of self-organization of nucleotide bases in the solid state by Etter *et al.*,[4] where the failure to explain certain observations relating to selectivity was attributed to our current lack of understanding of the intricate processes involved in cooperative hydrogen bonding arrangements and solid state phase transformations.

Acknowledgements

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