JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 8
1990

The Use of Cocrystallization as a Method of studying Hydrogen Bond Preferences of 2-Aminopyrimidine

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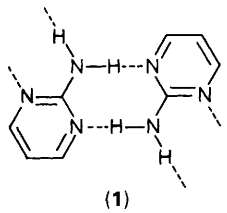
Rules describing hydrogen bond preferences of 2-aminopyrimidine were derived from the crystal structure of 2-aminopyrimidine, stoicheiometries of cocrystals of 2-aminopyrimidine with mono- or di-carboxylic acids, and the crystal structure of the 1 : 1 2-aminopyrimidine/succinic acid cocrystal.

Hydrogen bond interactions between organic molecules occur selectively in patterns that reflect hydrogen bond affinities of the competing functional groups. It has been shown recently that empirical hydrogen bond rules, useful for designing new materials and for deconvoluting complex hydrogen bond patterns, can be derived from crystal structures of organic molecules.[1] In this paper we show that a similar procedure can be used for deriving hydrogen bond rules from cocrystal structures of molecules that selectively self-assemble by hydrogen bonding into heteromeric rather than homomeric assemblies. Hydrogen bond preferences of 2-aminopyrimidines and of carboxylic acids are evaluated from a series of cocrystals made by both solution and solid-state methods. In these systems steric constraints are kept to a minimum so the independent contribution of hydrogen bonding to the molecular recognition properties of aminopyrimidines and carboxylic acids can be evaluated.

A single molecule of 2-aminopyrimidine (2AP) has two equivalent proton donors and two equivalent proton acceptors available for hydrogen bonding to neighbouring molecules. All proton donors and acceptors are used in the hydrogen bond pattern of 2AP found in its crystal structure[2] [shown as 2AP dimer (**1**)]. Such a hydrogen bond pattern could be perturbed by addition of a guest that preferentially forms hydrogen bonds to 2AP rather than to itself. Carboxylic acids were chosen as possible guest molecules for cocrystallization with 2AP since they are better acids than 2AP and, like 2AP, they form cyclic hydrogen bonded dimers (**2**).[3,4]

The cocrystallization experiments test whether 2AP-acid heterodimers (**3**) form and whether predictable ratios of mono- and di-acids can be incorporated into cocrystals with 2AP. Cocrystals that were prepared are listed in Table 1. Solution cocrystallizations were carried out by slow evaporation of solutions containing 2AP and a carboxylic acid.



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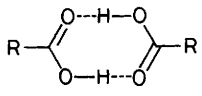

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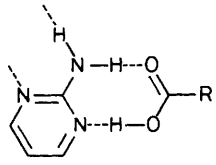

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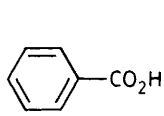

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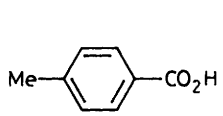

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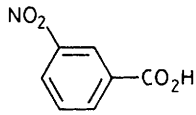

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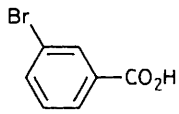

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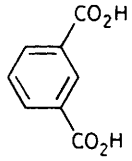

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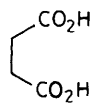

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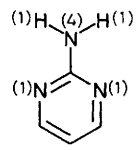

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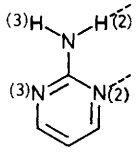

(12)

Solid-state cocrystallizations were carried out by grinding the two reagents together.[5] Cocrystallization was verified by a combination of techniques, in particular solid-state IR analysis, solution NMR, *X*-ray powder diffraction, and single crystal structure analysis.

Cocrystal stoicheiometry is controlled in part by starting material ratios. For compounds (**4**—**6**) either 1:1 or 1:2 2AP/acid stoicheiometries were obtained corresponding to the ratios of starting materials in solution or to the ratio of starting materials ground together in the solid state. Compounds (**7**—**9**), however, had a single preferred stoicheiometry of 1:1 regardless of the starting material ratio (up to 100% excess) or of method of preparation. Succinic acid (**10**) was unusual in that two different pyrimidine : acid ratios were obtained in the solid state, but only the 1:1 product could be obtained from solution.

X-ray powder pattern analyses showed clearly that cocrystals formed from solution are structurally identical to the cocrystal powders prepared in the solid state, and are not isomorphous with either starting material.† Strong OH···N hydrogen bonds form in all the 2AP-acid cocrystals reported in Table 1, as shown by solid-state IR studies. The attenuated-OH stretching bands found at very low frequencies (2500 and 1900 cm^{-1}) are characteristic of a carboxylic acid hydrogen bonded to an aromatic ring nitrogen.[6] The IR spectra also indicated that proton transfer had not occurred, although this analysis would not be reliable if a diacid cocrystal had one neutral and one ionic carboxyl group.‡

The crystal structure of (**10a**)§ shows a neutral alternating acid/2AP hydrogen bond pattern corresponding to a chain of heterodimers in pattern (**C**), Figure 2.¶ The secondary structure of the chain is helical, Figure 1. Other possible primary structures of heterodimers of 2AP with monoacids and diacids are shown in Figure 2. Experimentally determined cocrystal stoicheiometries show that monoacids can form 1:1 and 1:2 cocrystals with 2AP [their most likely patterns are (**A**) and (**B**)] while diacids can form 1:1 and 2:1 cocrystals [(**C**) and (**D**)].

The following specific hydrogen bond preferences for 2-aminopyrimidine can be derived from the crystal structure of 2AP, the crystal structure of (**10a**), and the patterns shown

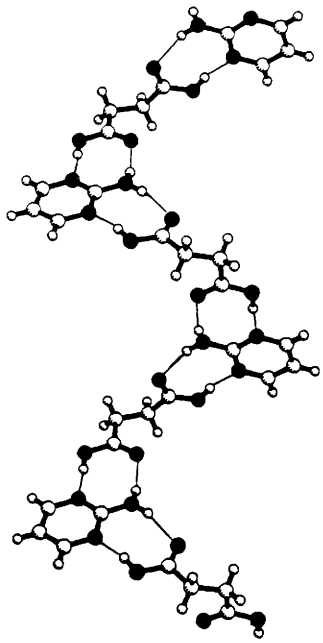

Figure 1. Hydrogen bond pattern seen in 1:1 2-aminopyrimidine/succinic acid cocrystal.

Table 1. Observed stoicheiometries (2AP : acid) of solution and solid state cocrystals.

Acids that form 1:2 and 1:1 cocrystals	(**4**)	(**5**)	(**6**)
Acids that form only 1:1 cocrystals	(**7**)	(**8**)	(**9**)[a]
Acids that form 1:1 and 2:1 cocrystals		(**10**)[b]	

[a] One of two polymorphs was obtained only from solution. [b] The 2:1 cocrystal was obtained only by solid state grinding.

† Major peaks from *X*-ray powder patterns of starting materials and products: [compound name: $d(I/I_0\%)$] 2AP: 3.82(100), 3.06(71), 3.61(66), 5.55(55); (**4**): 5.17(100), 3.22(99); (**5**): 3.35(100), 5.14(67); (**6**): 3.88(100), 6.60(42); (**7**): 3.39(100); (**8**): 3.18(100); (**9**): 3.75(100), 2.71(44); (**10**): 4.44(100); (**4a**): 3.25(100), 3.57(34); (**4b**): 3.27(100); (**5a**): 3.39(100); (**5b**): 5.57(100), 3.52(57); (**6a**): 3.26(100); (**6b**): 3.45(100); (**7a**): 3.28(100); (**8a**): 3.42(100); (**9a**) (polymorph A): 3.13(100); (**9a**) (polymorph B): 3.20(100); (**10**): 3.35(100); (**10b**): 3.26(100).

‡ A value of about 3 for the ΔpK_a between an acid and a protonated pyridine has been used to estimate when an ionic complex will form in preference to a neutral hydrogen bonded complex[6] (a comparable value for pyrimidines was not available). The pK_1 values of the acids in Table 1 range from 2.8 (for malonic acid) to 4.4 (for *p*-toluic acid), and the calculated value for pK_a of a 2-aminopyrimidinium ion is 2.8.[7] Based on ΔpK_a criteria used for pyridines, the cocrystals reported here should be neutral.

§ *Crystal data* for (**10a**): $C_4H_5N_3{\cdot}C_4H_6O_4$, M = 213.19, $P2_1/n$, a = 5.045(4), b = 13.426(5), c = 15.148(5) Å, β = 95.45(5)°, Z = 4, D_c = 1.39 g cm^{-3}. Structure solution: Enraf-Nonius CAD-4, Mo-K_α radiation, direct methods, R = 0.054, R_w = 0.068; $I > 3\sigma(I)$, 1567 observed reflections.[8] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

¶ There are two acid–pyrimidine hydrogen bond dimers per asymmetric unit with N(H)···O 2.981(2) and 2.955(3) Å, N–H···O angle 165(2) and 166(2)°, and N···(H)O 2.665(2) and 2.690)2 Å, N···H–O angle 169(2) and 176(3)°. The hydrogen atoms were found in difference maps with the following distances (Å) confirming that proton transfer had not occurred: acid hydrogens O–H 0.90(3) and 0.99(3), and H···N 1.77(3) and 1.70(3), amino hydrogens N–H 0.88(3) and 0.91(2) and H···O 2.09(2) and 2.09(2).

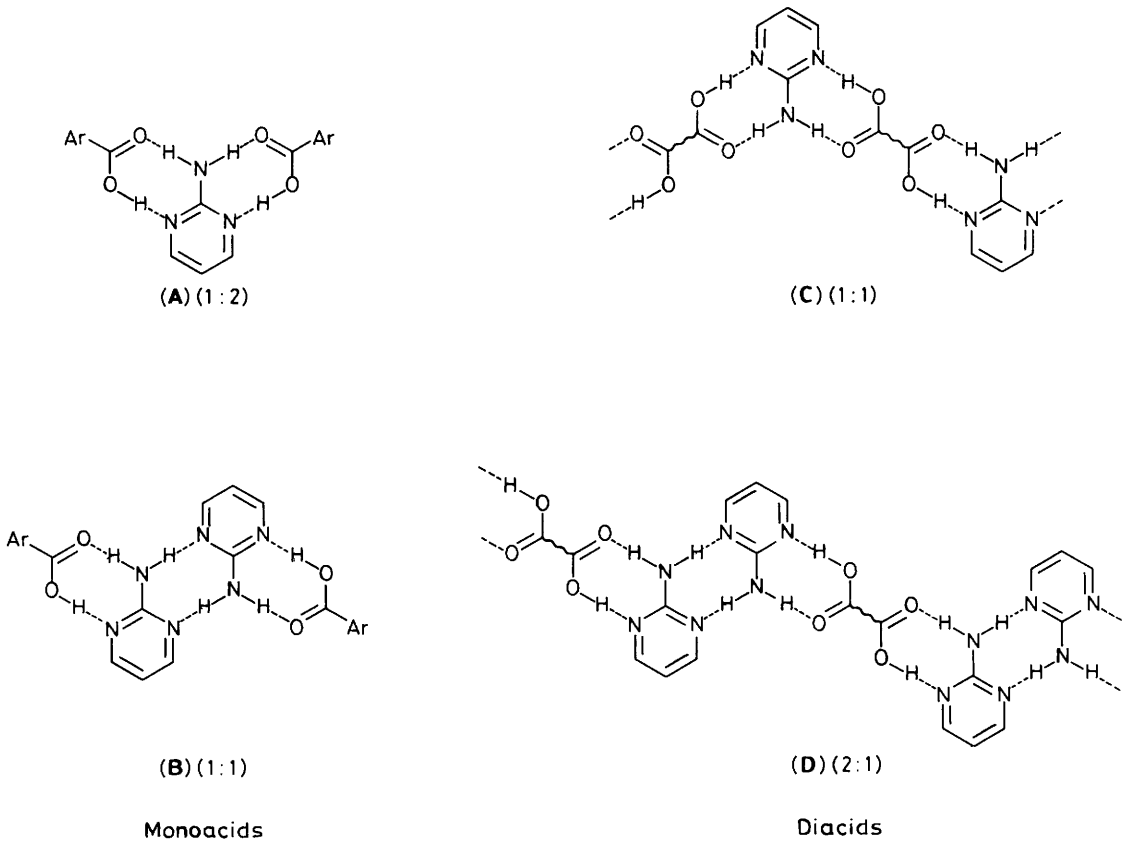

Figure 2. Possible hydrogen bond patterns for 2AP/acid cocrystals consistent with their experimentally determined stoicheiometries and the presence of heterodimers.

in Figure 2. (i) Both –NH protons and both ring nitrogens are used in hydrogen bonds; (ii) hydrogen bonds to acids are preferred over hydrogen bonds to other 2AP molecules; (iii) 2AP prefers cyclic eight-membered ring hydrogen bond patterns; (iv) the two amino protons need not form hydrogen bonds to identical groups, and likewise for the ring nitrogens; (v) a ranking of proton-accepting ability consistent with these structures is: N(1) > N(3) > acid carbonyl > N(2), or N(4), where the numbered pyrimidine atoms are those indicated in the monomeric and hydrogen bonded structures (**11**) and (**12**); (vi) a ranking of proton donors consistent with these structures is: acid –OH > –NH(1) > –NH(3) > NH(2).

The cocrystallization process in solution can be pictured as initial formation of the strongest hydrogen bond which is the OH···N bond. This interaction leads to a cyclic heterodimer of 2AP and an acid. Thereafter other interactions occur such that the next best proton donors and acceptors associate, *etc.* until all the proton donors and acceptors are used, consistent with the hydrogen bond preferences listed above. That the hydrogen bond patterns of crystals grown from solution and grown in the solid state are the same despite significant differences in cocrystallization mechanism attests to the exceptional directing abilities of hydrogen bonding groups. Further work is in progress to test whether the hydrogen bond preferences derived here for 2AP will apply for substituted aminopyrimidines and for other host–guest complexes of 2AP.

We gratefully acknowledge crystallographic assistance from Prof. Doyle Britton, University of Minnesota, and financial support from the Office of Naval Research (N00014-89-J-1301).

Received, 21st August 1989;|| Com. 9/03573G

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|| Received in revised form, 24th January 1990.