Crystal Design

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Designing a Cocrystal of γ-Amino Butyric Acid**

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Organic salts are generally the preferred crystal form of active pharmaceutical ingredients because of their higher solubilities and/or increased degree of crystallinity. The potential number of suitable organic salts is limited to the counterions specified by the food and drug association (FDA) as GRAS (generally regarded as safe). A recently suggested alternative to the common inorganic salts is the preparation of cocrystals[1] or organic salts, some of which have been shown to improve therapeutic utility while reducing side effects.[2–4]

Candidates for cocrystal formation with a particular structural motif for achieving desired physical properties[5,6] are chosen on the basis of their ability to utilize known intermolecular interactions in forming those crystals. Because hydrogen bonds are among the strongest and most preferentially directional intermolecular interactions, they have been the leading candidates for the interactions to be utilized in forming cocrystals,[7–10] although other interactions have also been suggested.[11a,b]

Particular preference in the development of the strategy for cocrystal formation utilizing hydrogen bonds has traditionally been based on the tendency of carboxylic acids and amides[12,13] to form the homo- or heterointermolecular synthons[14–16] described in Etter's graph-set notation[17,18] as

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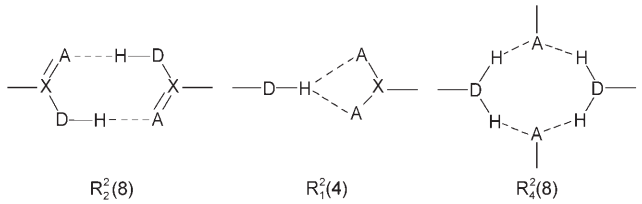
an $R_2^2(8)$ ring (which interprets as a ring (R) motif containing eight atoms with two hydrogen-bond donors (subscript) and two hydrogen-bond acceptors (superscript); Scheme 1). However, other hydrogen-bonding motifs such as $R_1^2(4)$ (Scheme 1), have also been investigated.[19,20] Herein we demonstrate the potential for utilizing another, as yet little recognized and not yet utilized, hydrogen-bonded synthon $R_4^2(8)$ (Scheme 1).



Scheme 1. The $R_2^2(8)$, $R_1^2(4)$, and $R_4^2(8)$ synthons. Some possible acceptors (A) and donors (D) for the $R_4^2(8)$ synthon: A: =O, =S, −F, −Cl, −Br, −I, F^-, Cl^-, Br^-, I^-, C≡N, C=O; D: $=CH_2$, $-NH_2$, $-OH_2$, $-CRH_2$, $-N^+RH_2$, $^+OH_3$.

A survey of the Cambridge Structural Database (CSD version 1.8, 2006) has identified over 12000 instances of this synthon, virtually all of which involve four individual and nonconnected (but not necessarily chemically different) moieties in the solid state. Many of these cases involve two chemically different moieties, often resulting in a pattern that is crystallographically centrosymmetric or pseudocentrosymmetric. Perhaps the most remarkable feature about this synthon in terms of cocrystal formation is that it potentially involves the intermolecular recognition and supramolecular synthesis of four different molecules.

In the CSD, there are 918 hits for structures utilizing the $R_4^2(8)$ synthon (Scheme 1) in which the donor is the amino group (NH_2) and the acceptor is the carbonyl group (C=O). These are broken down into specific functional groups like (C=O)O^-, N(C=O), N(C=O)N, (C=O)OH, C(C=O)C, C(C=O)H, -NH_3^+, C−NH_2, NH_4^+, and N−NH_2. This survey clearly indicates that the highest incidence of participation in the $R_4^2(8)$ synthon is for carboxylate acceptors and ammonium cation donors.

In our cocrystallization attempts to achieve this synthon, we chose to use amino acids, starting with γ-amino butyric acid (GABA). As the CSD search indicated a preference for the ionized species -NH_3^+ and COO^- in the formation of the desired $R_4^2(8)$, we attempted crystallization in the pH range for which the amino group of GABA will be in the form of -NH_3^+ and the carboxylic group of the oxalic acid and benzoic acid will be in the form of -CO_2^-. The molar fractions[21] for the ionized species in different pH ranges can be calculated from the pK_a values of the acid and base. Figure 1 represents the calculated molar fraction for GABA and oxalic acid. For GABA, pK_a = 10.43, pK_b = 9.77, and the isoelectric point is pI = 7.33. For oxalic acid, pK_{a1} = 1.23 and pK_{a2} = 4.19. It is clear from Figure 1 that the crystallization for a 1:1 GABA/oxalic acid cocrystal should be carried out in the pH range 0–4.19 and crystallization for 2:1 cocrystal ratio should be carried out in the pH range 4.19–10.43. Our initial experiments were carried out at pH 5.

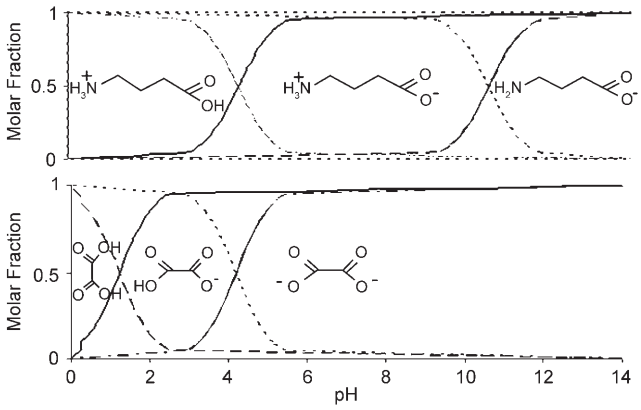


Figure 1. Solution speciation of GABA (top) and oxalic acid (bottom) showing the relative amounts of protonated and unprotonated species at each pH value.

The same calculations and molar fraction diagrams were prepared for the crystallization of GABA and benzoic acid. The pK_a value for benzoic acid is 4.19, which is the same as GABA. The crystallization attempts were carried out at three different pH values: 4, 6, and 12. At pH 4, the two species of benzoic acid and the two species of first dissociation of GABA are in equilibrium (see the Supporting Information). Experiments on oxalic acid and GABA yielded a 1:2 cocrystal of GABA/oxalic acid. As expected from Figure 1, GABA is protonated and the oxalic acid is a dianion. Charge neutrality therefore requires a 1:2 ratio of GABA and oxalic acid.

The crystal structure shown in Figure 2 clearly reveals three of the four hydrogen bonds required to complete the

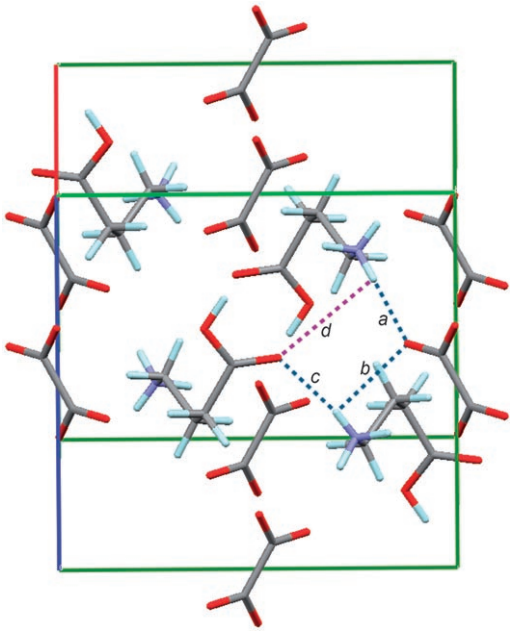


Figure 2. Unit cell of the 2:1 cocrystal of GABA/oxalic acid with hydrogen bonds (in blue) indicating the incipient formation of the $R_4^2(8)$ synthon. The pink line indicates the questionable hydrogen bond. The D···A distances are a = 1.913, b = 2.517, c = 2.063, and d = 3.242 Å. Other hydrogen bonds have been omitted for clarity. C gray, H light blue, N violet, O red.

$R_4^2(8)$ synthon. The donor–acceptor (D···A) distances, a = 1.913 Å, b = 2.517 Å, and c = 2.063 Å, are in the range of normal hydrogen bonds. The distance d (3.242 Å) is considerably long for an N–H···O hydrogen bond, but the incipient pattern of the synthon $R_4^2(8)$ still appears to be utilized in this structure.

Additional crystallizations were carried out at pH 0, 3, and 12. The results of X-ray powder diffraction (XRPD) studies, when compared with those of the starting materials (Figure 3 A), indicate the presence of new crystalline phases

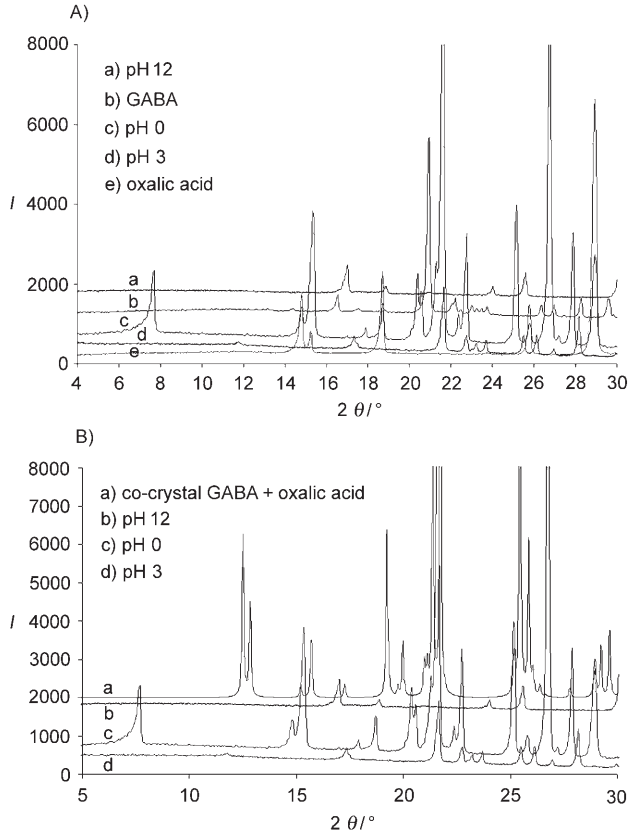


Figure 3. A) Comparison of the XRPD analyses from products of cocrystallization experiments at pH 0, 3, and 12 with the starting materials GABA and oxalic acid. B) Comparison of the XRPD analyses from products of cocrystallizations experiments at pH 0, 3, and 12 with the calculated XRPD from the single-crystal structure of the cocrystals of GABA and oxalic acid cocrystallized at pH 5.

(polymorph, hydrate, or differing stoichiometry) of the resulting powders. However, crystals suitable for structure analysis have not yet been obtained. These new phases can result from the different species coexisting at each pH value. From the crystal structure obtained at pH 5 (Figure 2), the acceptor that participates in the hydrogen bonds that are labeled *a*–*d* is the carboxylate group of GABA. This species can exist only above pH 4 (Figure 1). This fact can account for the different phases at the pH values of 0 and 3. One possibility for the appearance of a different phase obtained at pH 12 is that the donor for all the hydrogen bonds that participates in the hydrogen bonding is the amino group of GABA, which is protonated below pH 10 (see Figure 1); above this pH value (e.g. pH 12), the amino group will not be protonated and will likely participate in different hydrogen-bonding patterns.

A cocrystal of 1:1 benzoic acid/GABA was obtained from aqueous solution at pH 4. The small colorless crystals appeared a few minutes after adding water to a mixture of the solids. In the structure, the GABA is protonated and the benzoic acid is in the anionic form. Charge neutrality therefore requires a 1:1 ratio of GABA and benzoic acid. Figure 4 clearly reveals that the crystal structure utilizes two instances of the $R_4^2(8)$ synthon with hydrogen bonds *a* and *b* common to the two synthons.

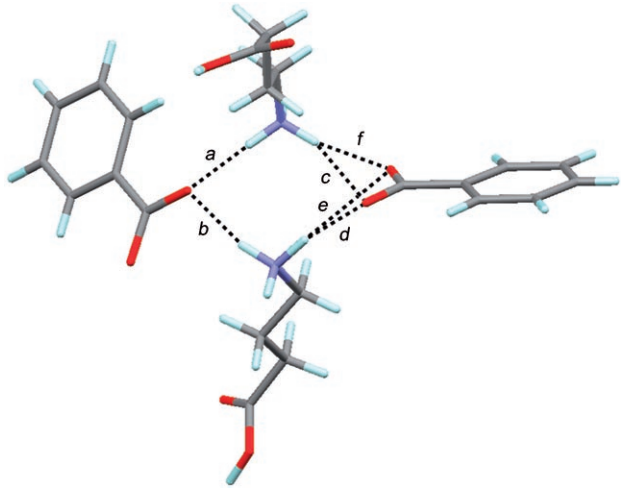


Figure 4. $R_4^2(8)$ synthons utilized in the structure of the cocrystal of 1:1 benzoic acid/GABA. The D···A distances in the first $R_4^2(8)$ synthon are a = 1.892, b = 1.909, c = 2.866, d = 1.799, e = 2.982, and f = 1.909 Å. Other hydrogen bonds have been omitted for clarity.

We have described a strategy to design cocrystals based on the $R_4^2(8)$ synthon by using pH as a controlling tool. Two cocrystals were obtained with the active pharmaceutical ingredient GABA, namely $(GABA)_2$ oxalate and GABA benzoate. The identification of other robust and versatile synthons can be utilized as an aid in the selection of potential cocrystal formers. Note that in the course of this work, we have also isolated and obtained the crystal structure of two previously unreported hydrates of oxalic acid, a dimorphic sesquihydrate. These will be reported in due course.

Experimental Section

Oxalic acid and GABA were weighed into a vial in a 1:1 stoichiometric ratio (likewise benzoic acid and GABA), water was added to dissolve the mixture, and then the pH was adjusted to pH 0, 3, 5, or 12 with NaOH or HCl solutions as needed.

X-ray crystal structural analysis for the cocrystal of oxalic acid/GABA: Data were collected at 297 K by using a Bruker SMART 6000 CCD diffractometer with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) M_r = 98.76, monoclinic space group $R2_1/c$, a = 7.4566(9), b = 10.2685(13), c = 9.7924(12) Å, β = 108.478(3)°, V = 711.13(15) Å^3, Z = 4, ρ_{calcd} = 1.384 g cm^{-3}, $\mu(Mo_{K\alpha})$ = 0.120 mm^{-1}, $F(000)$ = 316, θ_{min} = 2.9°, θ_{max} = 28.3°, R = 0.056, wR = 0.1374 observed data (with $I > 2\sigma I$) = 1646,

total = 7832, unique = 1762, R(int) = 0.0293, Goof = 1.117 for 131 parameters.

X-ray crystal structural analysis for the cocrystal of benzoic acid/GABA: Data were collected at 297 K by using a Bruker SMART 6000 CCD diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) M_r = 225.4, monoclinic space group $P2_1/n$, $a = 13.424(3)$ Å, $b = 6.212(1)$ Å, $c = 13.999(3)$ Å, $\beta = 101.748(4)°$, $V = 1142.8(4)$ Å^3, $Z = 4$, ρ_{calcd} = 1.309 gcm^{-3}, $\mu(Mo_{K\alpha}) = 0.100$ mm^{-1}, $F(000) = 480$, $\theta_{min} = 1.9°$, θ_{max} = 28.3°, $R = 0.046$, $wR = 0.1128$ observed data (with $I > 2\sigma I$) = 1663, total = 7108, unique = 2710 R(int) = 0.034, Goof = 1.011 for 205 parameters.

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