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Cocrystal Design Gone Awry? A New Dimorphic Hydrate of Oxalic Acid

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Abstract: The crystal chemistry of oxalic acid has been studied since 1880, including 37 published structure determinations of the two anhydrous forms (α, β) and the dihydrate, the latest in 2000. In attempts to cocrystallize asparagine or glutamine with oxalic acid, utilizing the particular hydrogen bond synthon $R_4^2(8)$, we unexpectedly obtained two previously unreported sesquihydrates of oxalic acid. Form 1 is orthorhombic, *Pnma*, and the unit cell is $a = 11.231(2)$ Å, $b = 12.330(2)$ Å, $c = 6.908(1)$ Å. Form 2 crystallizes in the triclinic crystal system in space group $P\bar{1}$, and the unit cell is $a = 6.337(2)$ Å; $b = 7.247(3)$ Å, $c = 10.571(4)$Å, $\alpha = 94.34(1)°$, $\beta = 100.244(9)°$, $\gamma = 97.67(1)°$. Both of the new hydrate forms of oxalic acid utilized the $R_4^2(8)$ hydrogen bonded synthon.

Keywords: Cocrystals; polymorphs; hydrates

Introduction

Due to their high energy and directionality hydrogen bonds are among the most important intermolecular interactions, which are responsible for different crystal packing.[1] It has been observed that the strength of these directional forces and, consequently, their ability to control the formation of intermolecular synthons depend on the nature and polarity of the donor and acceptor groups and are significantly increased when the hydrogen bond is assisted by resonance[2] or by charge.[3,4] The recognition and utilization of a particular hydrogen bond motif can serve as a basis for cocrystal engineering. Candidates for cocrystal formation of a particular component may be chosen on the basis of their ability to utilize specific hydrogen bond synthons. Our present strategy consists of investigating the potential for utilizing the hydrogen bond synthon $R_4^2(8)$[5] (Chart 1).

The most remarkable feature about this synthon is that it potentially involves the intermolecular recognition and supramolecular synthesis of four individual molecules. A survey of the Cambridge Structural Database (CSD) version 1.8 (2006) has identified over 12,000 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

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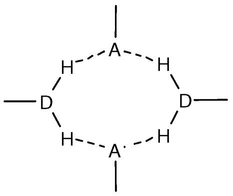
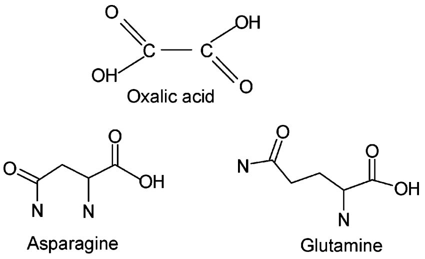
Chart 1. Synthon $R_4^2(8)$



$\mathbf{R_4^2(8)}$

Chart 2. Compounds Cited in Text



chemically different moieties, often resulting in a pattern that is crystallographically centrosymmetric or pseudocentrosymmetric. In the work presented here we attempted to cocrystallize molecules with amino group ($-NH_2$) that will participate as donors (D) and molecules with carbonyl group ($C{=}O$) that will participate as an acceptor (A). A CSD survey revealed 918 hits for structures with these particular donors and acceptors that utilize the $R_4^2(8)$ synthon. The CSD search also indicated a statistical preference for the ionized species NH_3^+ and COO^- in the formation of the desired $R_4^2(8)$ synthon. The combined species increase the stabilization energy of the synthon by approximately an order of magnitude over that of the neutral species.[6] Candidates for cocrystal formation are chosen on the basis of their ability to utilize known hydrogen bond synthons.

One potential hydrogen bond acceptor molecular building block that was used in this program is oxalic acid OA. A CSD survey revealed that OA tends to utilize the $R_4^2(8)$ synthon; in some cases this synthon appears up to 6 times in the same structure (58 hits of OA with this synthon).

Attempts were made to cocrystallize OA with the amino acids gluthamine (Gln) and aspargine (Asn) (Chart 2) as donors. In our cocrystallization attempts to achieve this synthon we chose to use amino acids as building blocks for the following reasons: (1) The amino and carboxylic groups are donor and acceptor groups that exhibit a high tendency, according to the CSD, to crystallize utilizing $R_4^2(8)$ synthon. A CSD search on structures of cocrystals of amino acids exhibiting this synthon yielded 93 cases. (2) By varying the pH it is possible to control the degree of ionization of the species potentially participating in the desired synthon.[7] (3) Amino acids have important established and potential pharmaceutical applications. Hence, developing new crystal forms for amino acids can also have practical applications, in formulation, delivery, and performance as well as potential intellectual property implications.

Although the cocrystallization design strategy went awry, the experiments yielded a pair of dimorphic hydrates, stoichiometrically defined as sesquihydrates of OA, whose formulas, based on the molecular moieties found in the two crystal structures, are given as $HC_2O_4^{-}2[{}^1/_2(H_3O^+)]{}^1/_2(H_2O)$ in form 1 and $2[{}^1/_2(C_2O_4H_2)]HC_2O_4^{-}(H_3O^+)2(H_2O)$ in form 2.

A routine check of the CSD version 1.8 (2006) for the structure of OA, a relatively common, perhaps even "classic" molecule, revealed that the crystal structure of OA has been studied intensively at various temperatures since 1935; 37 structure determinations have been published, the latest in 2000. All those studies described either one or both of the structures of two anhydrous forms (α,β) of OA or the structure of the dihydrate of OA. Briefly, the crystal chemistry of OA is as follows. A drawing of an orthorhombic crystal with axial ratios (based on the interfacial angles) is included in Groth's compendium,[8] citing an 1880 paper by Villiers[9] and a 1909 paper by Wagner.[10] The axial ratios match those of the α anhydrate form. At that time there apparently was no awareness of the polymorphic character of the anhydrate. Groth's compendium also included a drawing of a monoclinic crystal with axial ratios that match the structure of the published dihydrate in the CSD citing an 1823 paper by Brooke.[11] There are also theoretical calculations of the hydrated oxalate dianion in the gas-phase $C_2O_4^{2-}{\cdot}n(H_2O)$ ($n = 3-40$).[12] There is apparently no precedent for the sesquihydrate. Several papers have been published lately describing the serendipitous crystallization of a new crystal form of one of the components in the attempted preparation of cocrystals.[13]

Experimental Section

Materials. Oxalic acid 99+% , L-glutamine 98%, and L-asparagine monohydrate 99% (Sigma-Aldrich) were used

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Table 1. Crystallographic Data for Sesquihydrate Forms 1 and 2

	form 1	form 2
temp (°C)	22	23
color, shape	colorless, prism	colorless, prism
crystal system	orthorhombic	triclinic
space group	*Pnma*	$P\bar{1}$
a (Å)	11.231(2)	6.337(2)
b (Å)	12.330(2)	7.247(3)
c (Å)	6.908 (1)	10.571(4)
α (deg)		94.34 (1)
β (deg)		100.244(9)
γ (deg)		97.67 (1)
V (Å)^3	956.6(3)	471
z	8	2
d_{calcd} (Mg/m^3)	1.626	1.651
F(000)	488	244
reflections used	1248	2343
R; R_w	0.0571, 01775	0.0518, 0.1514

as received for the attempted preparation of the cocrystals in aqueous solution of triply distilled water. Oxalic acid sesquihydrate polymorph 1: Oxalic acid and glutamine were weighed into a vial in a 1:1 stoichiometric ratio; water was added to dissolve the mixture. Oxalic acid sesquihydrate polymorph 2: Oxalic acid and asparagines were weighed into a vial in a 1:1 stoichiometric ratio; water was added to dissolve the mixture.

Powder X-ray Diffraction (XRPD). X-ray powder data were collected on a Huber Guinier Camera 670 which was installed on an Ultrax 18-Rigaku X-ray rotating Cu anode source, with a monochromator (focal length $B = 360$ mm) providing pure Kα radiation. A position sensitive image plate camera was used for powder diffraction in transmission geometry. This configuration enabled fast scanning with high resolution.

Single-Crystal X-ray Diffraction. Single-crystal crystallographic data of the two forms (Table 1) were collected on a Bruker SMART 1000K diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) with a graphite monochromator. The data were reduced by SAINT,[14] solved with SHELEX,[15] and then refined with SHELXL.[16]

Hot Stage Microscopy (HSM). HSM examinations were performed on a Wagner and Munz Kofler Hot Stage equipped with digital video recorder facilities.

Results and Discussion

The two forms of OA were obtained by slow evaporation at room temperature from aqueous solutions containing a 1:1 molar ratio of OA with Gln (form 1) and with Asn (form 2). Both of the crystals are colorless prisms.

XRPD of the products indicated that they differed from all the structures of the starting materials.

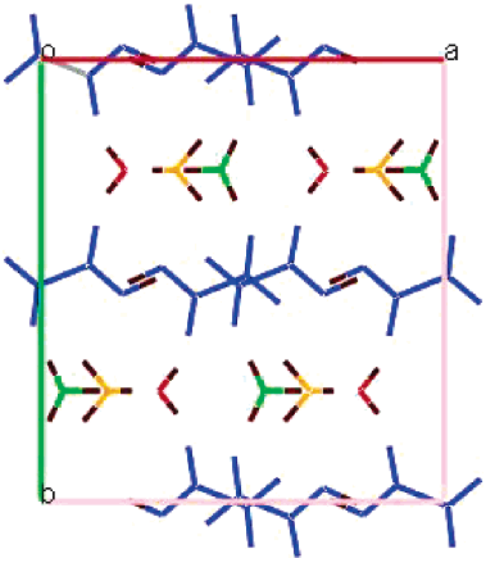

Figure 1. Unit cell of OA sesquihydrate form 1. The oxygens of the three water molecules lying on the mirror plane perpendicular to the *b*-axis are plotted in red, orange, and green; the latter two are hydronium ions.

Single-Crystal X-ray Data. Crystallographic data of sesquihydrate forms 1 and 2 are summarized in Table 1.

Form 1 of sesquihydrate OA crystallizes in the orthorhombic crystal system in space group *Pnma*. The unit cell is shown in Figure 1. The asymmetric unit includes one OA monoanion lying on a general crystallographic position, two hydronium ions (H_3O^+), and one neutral water molecule. All three water molecules lie on a crystallographic mirror plane, with site occupancy factor 0.5. The stoichiometry is thus [1 OA]:[3 ($^1/_2H_2O$)], compatible with a sesquihydrate.

Form 2 of sesquihydrate OA crystallizes in the triclinic crystal system in space group $P\bar{1}$. The unit cell is shown in Figure 2. There are one complete monoanion of OA on a general crystallographic position and two neutral molecules each lying on an inversion center; the asymmetric unit thus contains two full OA molecules. There are two neutral water molecules and one hydronium providing electrical neutrality and the sesquihydrate stoichiometry. The hydronium ion is disordered, and the three hydrogens occupy four positions which refined to site occupancy factors 0.75, 0.80, 0.65, 0.80.

The calculated densities are as follows: 1.626 Mg/m^3 for form 1 and 1.651 Mg/m^3 for form 2. Comparison with the known forms indicates that the density of the anhydrate α form is 1.90 Mg/m^3, of the anhydrate form β is 1.86 Mg/m^3, and of the dihydrate is 1.65 Mg/m^3, which is very similar to both of the forms of sesquihydrate.

The structure solution of the two new sesquihydrate forms of OA revealed that both of them utilize the $R_4^2(8)$ synthon twice (Figure 3). Table 2 summarizes the hydrogen bond lengths for the hydrogen bond participating in the synthon.

By varying the pH it is possible to alter the relative ratio of O, O$^-$, and O^{2-} in solution which could also result in cocrystals or hydrates of different stoichiometric ratio. The pH of the cocrystallization solutions of OA with Gln and

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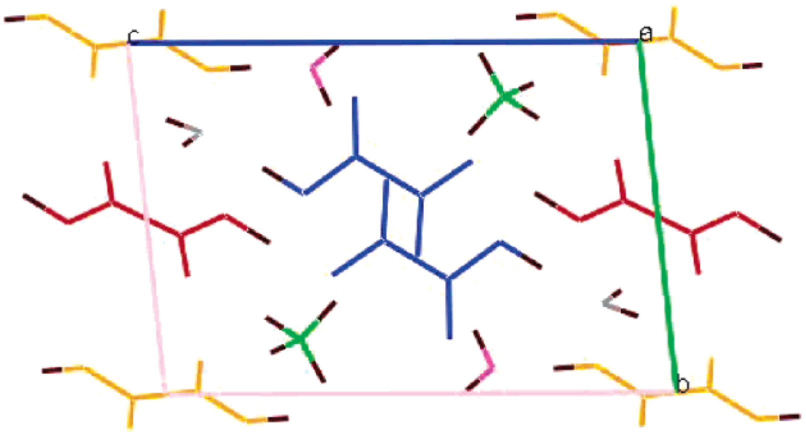

Figure 2. Unit cell of OA sesquihydrate form 2. Water molecules are plotted in gray, purple, and green; the latter one is a hydronium ion, disordered as shown.

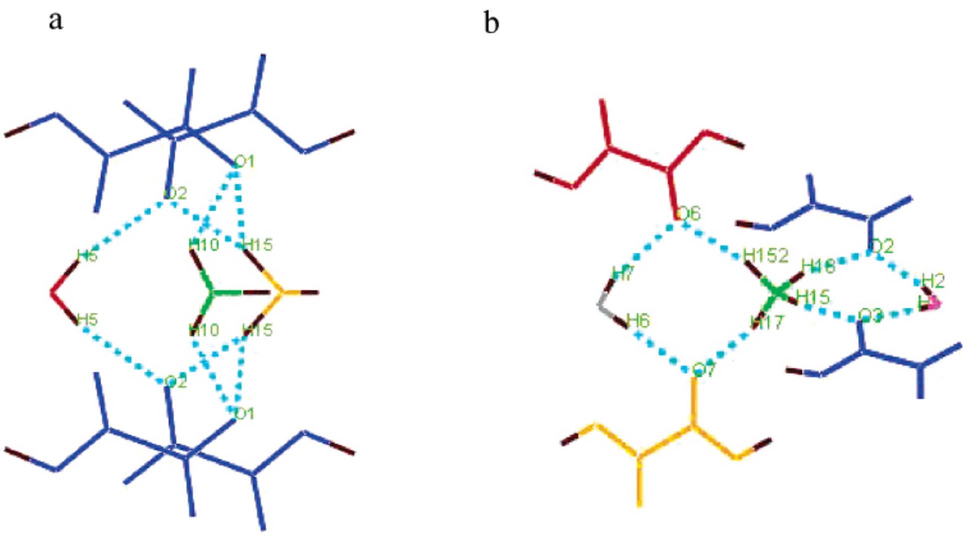

Figure 3. The $R_4^2(8)$ synthons in each of the sesquihydrate forms of OA: (a) form 1 and (b) form 2. Other hydrogen bonds have been deleted for clarity.

Table 2. Hydrogen Bond Distances for the Synthons in Forms 1 and 2[a]

form 1		form 2			
hydrogen bond	bond distance (Å)	hydrogen bond	bond distance (Å)	hydrogen bond	bond distance (Å)
$O-H_5 \cdots O_2$	2.003	$O-H_7 \cdots O_6$	2.164	$O-H_{18} \cdots O_2$	1.910
$O-H_{15} \cdots O_2$	2.020	$O-H_6 \cdots O_7$	1.949	$O-H_{15} \cdots O_3$	1.959
$O-H_{10} \cdots O_1$	2.050	$O-H_{17} \cdots O_7$	1.891	$O-H_1 \cdots O_3$	2.004
$O-H_{15} \cdots O_1$	2.050	$O-H_{152} \cdots O_6$	1.929	$O-H_2 \cdots O_2$	1.895

[a] In form 1 the hydrogen bonds are symmetric; therefore only four of them are included.

Asn was found to be pH = 1 in both cases. Subsequently, crystallization of OA was carried out at pH's 0, 1, 2, 3, 4, 5, 10, 12, and 14. XRPD was used to monitor the results. The diffractogram of the product obtained at each pH was compared with the calculated diffractograms of the known crystal forms of OA from the CSD as well as the newly obtained sesquihydrate forms.

At pH's 0 and 1 we obtained the dihydrate form-[OXADH11]. At pH's 10, 12, and 14 we obtained anhydrous sodium oxalate [NAOXAL].

The XRPD's indicate that cocrystallization at pH's 2, 3, 4, and 5 yielded new crystal forms (Figure 4). Those for pH's 2 and 3 are identical. The diffractogram corresponding to pH's 4 and 5 appears to be a mixture containing the material from pH = 2, 3 and perhaps another solid.

None of the crystallizations at various pH's resulted in the crystal form corresponding to OA sesquihydrate form 1 or 2.

Summary

The increasing interest in cocrystals in recent years is due to the recognition of the important potential commercial value of generating new crystal forms, with improved properties and intellectual property value.[17] New polymorphic and hydrate forms obtained serendipitously from attempts at cocrystallization have been reported previously by others.[13] For instance, we obtained four polymorphic forms of

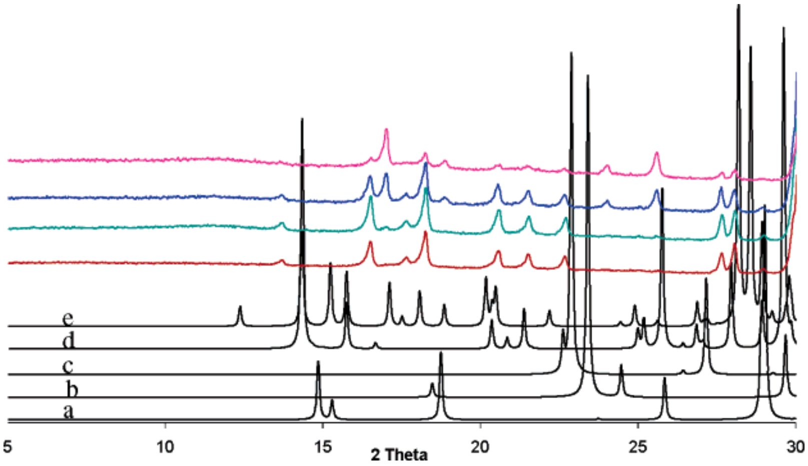

Figure 4. Overlay of calculated XRPD data for known forms of OA dihydrate [OXADH11] (a), anhydrate α [OXALAC04] (b), anhydrate *β* [OXALAC06] (c), and the two new sesquihydrate forms 1 (d) and 2 (e), together with the measured XRPD's of OA in pH's 2 (red), 3 (green), 4 (blue), and 5 (pink).

benzidine in the attempts to cocrystallize it with a number of hydrogen bond acceptors.[18] In the present case attempts to cocrystallize OA with Asn or with Gln yielded previously unreported dimorphic sesquihydrates of OA, presumably due to the creation of a new crystallization medium for OA. Understanding such processes can lead to strategies for growing new crystal forms. In the present case the influence of pH was investigated, and it was found that at low pH 0−1 the dihydrate form was obtained while at high pH 10−14 sodium oxalate is obtained. At intermediate pH's there is crystallographic evidence that two new forms may have been obtained, which are currently under investigation.

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Supporting Information Available: X-ray crystallographic information files (CIF) for forms 1 and 2. Refcode list for structures of oxalic acid utilizing the $R_4^2(8)$ synthon. This material is available free of charge via the Internet at http://pubs.acs.org.

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