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Cocrystals of U-shaped ureadicarboxylic acid with 2-aminopyrimidine and melamine: rhombus-shaped cyclic heterotetramer motifs

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ABSTRACT

Single crystal X-ray structures of cocrystals, **1**·**2** and **1**·**3**, derived from U-shaped ureadicarboxylic acid (**1**) with 2-aminopyrimidine (**2**) and melamine (**3**), respectively, were examined. Cocrystals were obtained as a 1:1 mixture of **1** and the corresponding base. Two molecules of **1** and two molecules of the base were combined together via intermolecular H-bonding creating a supramolecularly assembled cyclic heterotetramer motif of rhombus shape. In the case of cocrystal **1**·**3**, the cyclic heterotetramers were connected via H-bonding by utilizing a remaining amino group of melamine resulting in the formation of a tape of cyclic heterotetramer.

Numerous efforts have been devoted over the last two decades on cocrystals by developing their design strategies and growing techniques.[1] Their importance is greatly emphasized in the last decade as pharmaceutical cocrystals,[2] because of their ability to alter physicochemical properties without impairing the pharmaceutical activities of ingredients. We are interested in new types of cocrystals with cyclic self-assembly motifs utilizing aromatic carboxylic acids as building blocks for hydrogen bonding (H-bonding) heterosynthons. Carboxylic acids are well-studied building blocks for supramolecular design of organic crystals.[3] Even for H-bonding homosynthons, examples of cyclic self-assembly in organic crystals are limited. Well-known examples are cyclic self-assemblies of trimesic and its derivatives creating cyclic hexamer motifs.[4] Owing to the direction of H-bonding in aromatic carboxylic acids it requires some design strategies to furnish cyclic self-assembly other than hexagon. For heterosynthons, an example of super hexagon was reported in cocrystals of 1,3,5-cyclohexanetricarboxylic acid with 4,4′-bipyridine homologues.[5]

Recently, we demonstrated the versatility of our U-shaped building block, aromatic ureadicarboxylic acids, for the construction of a variety of crystal structures, zigzag, triple helix, ladder, and channel in a supramolecular way.[6] In the creation of helical chain, spacer molecules possessing two pyridyl moieties as H-bonding sites at their termini were sandwiched by two urea building blocks affording a helical strand (Scheme 1a). Rigid and linear shaped spacer molecules in which the direction of H-bonding is straight have been utilized. We now examine the cyclic self-assembly of aromatic ureadicarboxylic acid (**1**) and organic bases possessing two H-bonding sites located 120° with respect to each other. Because of the bending positions of two H-bonding sites for both the acid and the base, it can be possible to generate a cyclic structure. The 2:2 supramolecular assembly of **1** with the organic bases can result in the formation of rhombus-shaped cyclic heterotetramers (Scheme 1b). As such organic bases are capable to form bent-type hydrogen bonding, we have chosen 2-aminopyrimidine (**2**) and melamine (**3**). These hetero aromatics are known as good hydrogen-bonding partners for carboxylic acids to form cocrystals.

In the case of carboxylic acid with 2-aminopyrimidine, two types of H-bonding patterns are possible by creating hydrogen-bonded eight membered rings, $R^2_2(8)$ heteroassembly. H-bonding heterosynthons I[7] and II[8] (Scheme 2) are responsible for 2:1 and 1:1 cocrystal formations, respectively. Dicarboxylic acids are capable to create one-dimensionally arrayed H-bonding networks. By applying synthon I, terephthalic acid and **2** afford a 1D zigzag tape which creates sheet structure.[7b,f] An interesting molecular capsule was reported by the self-assembly of cavitand tetracarboxylic acid with **2** by multiple hydrogen bonding utilizing synthon I.[7h] Cocrystal of **2** was also known with phenol derivatives.[7f] Similarly, supramolecular heterosynthons of **3** involving ionic H-bonding together with carboxylic acids,[9] imides,[9d,10] phenols,[11] and disulfonic acids[12] are known. Four types of synthons, III–VI, have been reported for **3** with carboxylic acids (Scheme 2). The stoichiometry

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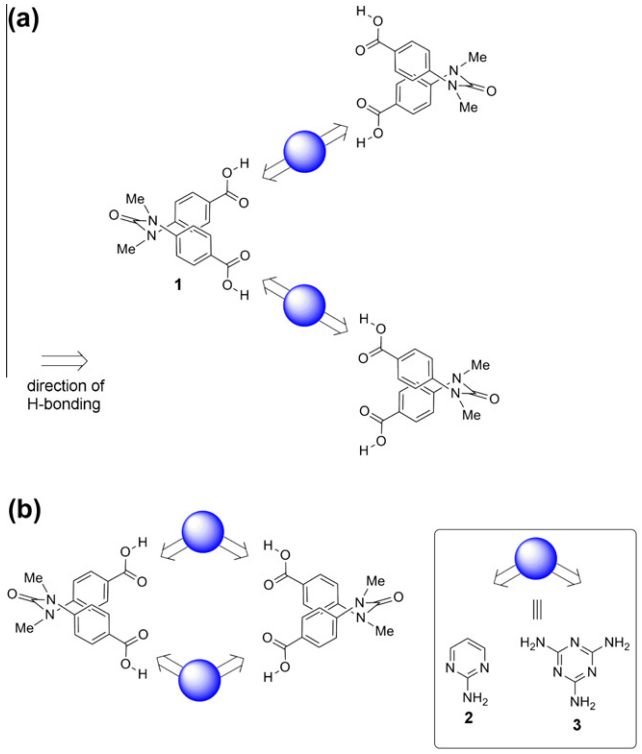


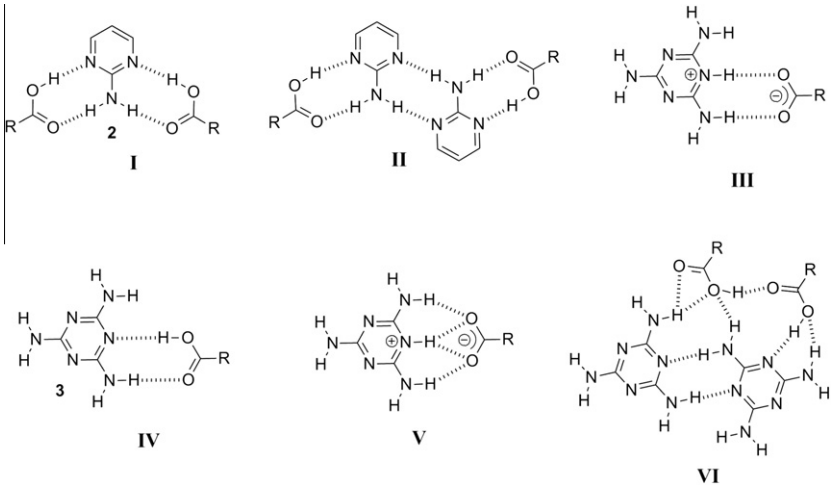
Scheme 1. Two types of supramolecular assembly of **1** with H-bonding building blocks possessing two H-bonding sites. (a) Helical and (b) cyclic assembling.

of melamine–imide complexes was controlled by tuning the steric hindrance of imide carbonyl groups.[10c] The H-bonded cyclic hexamer of melamine was known with aliphatic carboxylic acids with long alkyl chains by applying synthon VI.[9d]

Cocrystallization of **1** and **2** were carried out in methanol with diffusion of water vapor. The ^{1}H NMR analysis of the obtained cocrystal **1**·**2**[13] in $CDCl_3$ showed that it consisted of **1** and **2** in an equimolar amount. Single crystal X-ray diffraction analysis revealed that it was a 2:2 complex. Figure 1 shows its X-ray structure. Ureadicarboxylic acid **1** possesses a twisted U-shaped conformation. The angle θ and torsion angle φ between the two phenyl rings of **1** (Fig. 1e) are 27° and 43°, respectively. It means that **1** can direct two H-bonds with this angle. Two molecules of **1** sandwich two molecules of **2** via H-bonding to create a rhombus-shaped cyclic heterotetramer. The way of sandwiching of **2** by carboxy groups is as follows. The upper and bottom carboxy groups participate in H-bonding cooperatively with the upper and bottom carboxy groups, respectively. Consequently, the formation of zigzag-type H-bonding network is avoided.

The H-bonding distances between the oxygen atoms of hydroxyl groups and the ring nitrogen atoms and between the oxygen atoms of carbonyls and the nitrogen atoms of amino groups are ranged from 2.64–2.69 Å to 2.90–2.97 Å, respectively (Fig. 1a). The cyclic heterotetramer is not planar due to the U-shaped structure of **1**. The distance between the centroid of one of the pyrimidine ring and the plane where the other pyrimidine ring is placed in the cyclic heterotetramer is 5.4 Å (Fig. 1a). Therefore, the cyclic heterotetramer has a narrow slit of ca. 2 Å (Fig. 1b). Among cyclic heterotetramers, C–H···O= C interactions take place to create an array of cyclic heterotetramers (Fig. 1c). Figure 1d shows space-filling presentation of an array of cyclic heterotetramers and their packing diagram viewed along the direction of the *b*-axis.

In a similar manner as for the cocrystallization of **1**·**2**, the cocrystal of **1** and **3** was prepared. Single crystal X-ray diffraction analysis of the cocrystal **1**·**3**[13] showed that it was the cyclic heterotetramer analogous to that of **1**·**2**. The crystals include some water molecules. The distances between the oxygen atoms of hydroxyl groups and the ring nitrogen atoms and the distances between the oxygen atoms of carbonyls and the nitrogen atoms of amino groups are presented in Figure 2a. In the cocrystal **1**·**2**, all the hydroxy groups are placed outside in the cyclic heterotetramer. In contrast, both outside and inside positions of hydroxy groups were involved in one of the acids of the cyclic heterotetramer in the cocrystal **1**·**3**. Figure 2b shows the superimposed drawing of the X-ray structures of two acids observed in the cocrystal **1**·**3**. Both have nearly the same angle θ and the torsion angle φ except the geometry of carboxy groups. Using this geometrical adjustment of carboxy groups, **1** can assemble with **3** to afford the corresponding cyclic heterotetramer. The distance between the centroid of one of the melamine ring and the plane where the other melamine ring is placed in the cyclic heterotetramer is 4.0 Å. The results indicate that almost no slit (less than 1 Å) exists in the cyclic heterotetramer (Fig. 2c). A slightly narrow angle θ (25°) of **1**·**3** resulted in the narrower slit size than that of **1**·**2**. It has a relatively planar structure. Unlike the cocrystal **1**·**2**, its shape is not symmetrical. One of the melamine molecules has a similar way of H-bonding as observed in **1**·**2**. One of its amino groups is H-bonded with two carboxy groups. In the other melamine molecule, two amino groups are utilized for H-bonding with carboxy groups. Each of



Scheme 2. Supramolecular synthons of **2** and **3** with carboxylic acids.

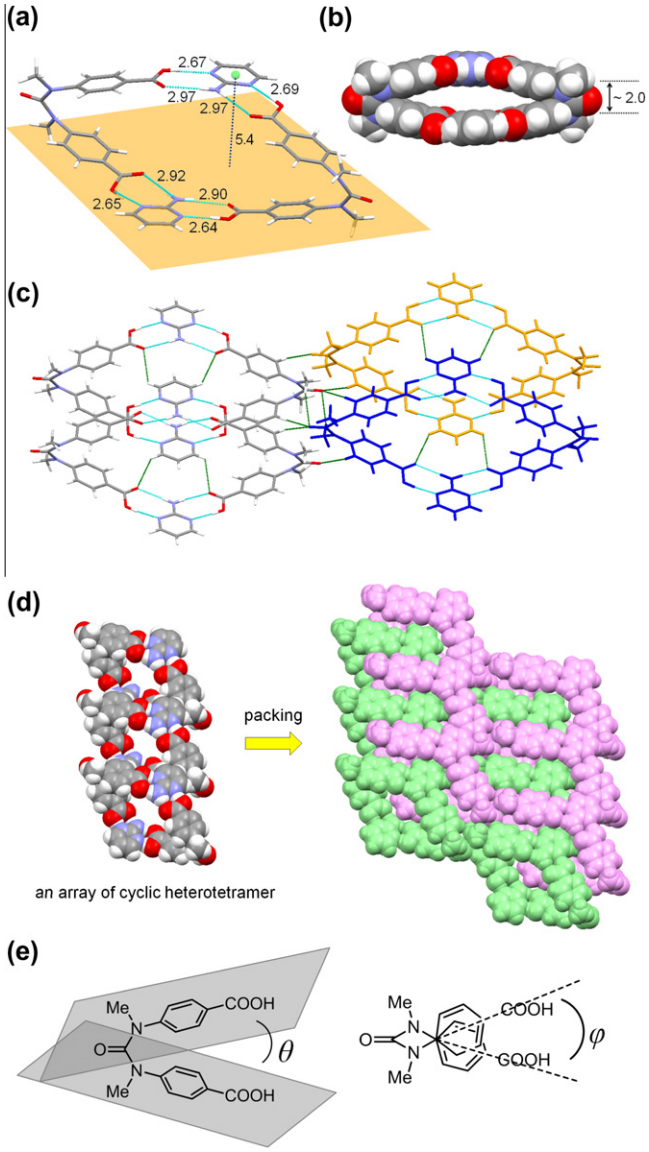


Figure 1. Crystal structure of **1**·**2** in which H-bonding and C–H···O=C interaction are indicated with blue and green lines, respectively. (a) A front-view of rhombus-shaped cyclic heterotetramer. Numbers in the figure correspond to the atomic distances (Å) between the oxygen atoms of hydroxyl groups and the ring nitrogen atoms or the oxygen atoms of carbonyls and the nitrogen atoms of amino groups. (b) A side-view of the cyclic heterotetramer to show its slit. Distance in an Å unit. (c) C–H···O=C interactions among cyclic heterotetramers. (d) Space-filling presentation of an array of cyclic heterotetramers and their packing diagram viewed along the direction of the *b*-axis. (e) Angle θ and torsion angle φ between two phenyl rings.

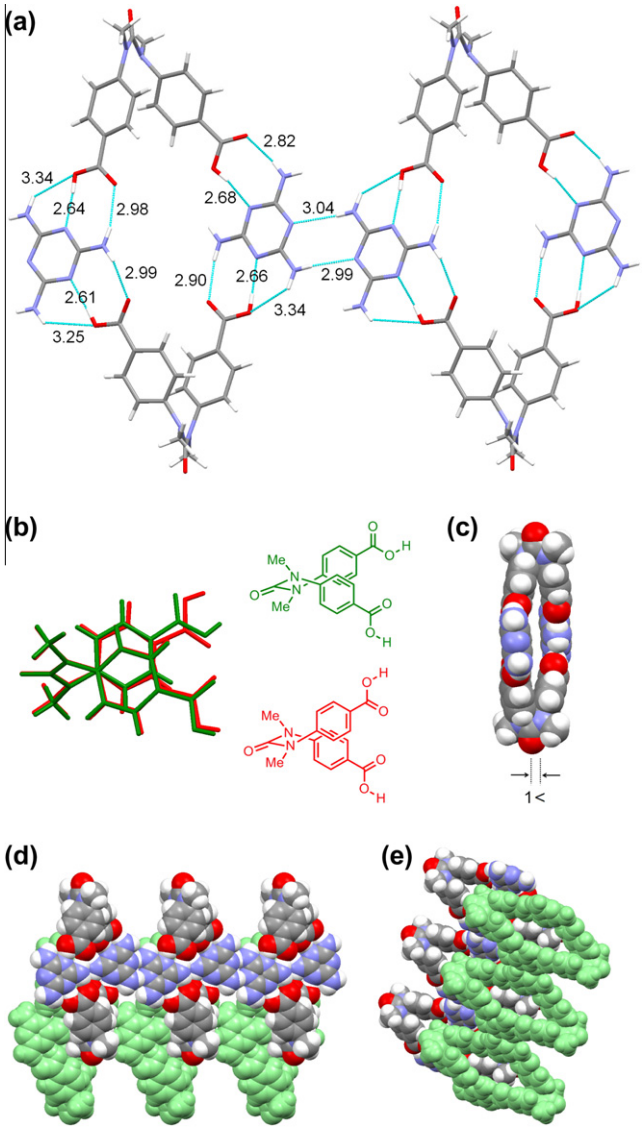


Figure 2. Crystal structure of **1**·**3**. (a) H-bonded cyclic heterotetramers in which H-bonds are indicated with blue lines. Numbers in the figure correspond to the atomic distances (Å) between the oxygen atoms of hydroxyl groups and the ring nitrogen atoms or the oxygen atoms of carbonyls and the nitrogen atoms of amino groups. (b) Superimposed drawings of the two conformations of **1** observed in the crystal. (c) A side-view of the cyclic heterotetramer. Space-filling presentation of H-bonded 1D tapes of cyclic heterotetramers viewed along the direction of the *a*-axis (d) and the *b*-axis (e), respectively. Included water molecules are omitted for clarity.

them is H-bonded with one carboxy group. The cyclic heterotetramer units created in this way are H-bonded linearly between the remaining amino group and the nitrogen atom of melamine forming a 1D tape of cyclic heterotetramers in the direction of the *b*-axis (Fig. 2d and e).

We demonstrated the versatility of aromatic ureadicarboxylic acid **1** as a U-shaped building block. Assembling of **1** with bent-type H-bonding spacers, **2** and **3**, afforded cyclic heterotetramer motifs. One-dimensional tapes of cyclic heterotetramer were created in cocrystals **1**·**2** and **1**·**3**.

Crystallographic data of the structural analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC 872806 for cocrystal **1**·**2**, and CCDC 872807 for **1**·**3**. Copies of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uko or web: http://www.ccdc.cam.ac.jk).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.065. These data include MOL files and InChiKeys of the most important compounds described in this article.

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13. X-ray diffraction data for the crystals were measured on CCD diffractometers with graphite monochromated Mo Kα (λ = 0.71073 Å). Data collections were carried out at 173 K for both **1**·**2** and **1**·**3**·1/2H_2O by using liquid nitrogen. All structures were solved by direct methods SHELXS-97 (A short history of SHELX, Sheldrick, G.M. *Acta Cryst.* **2008**, *A64*, 1) and the non-hydrogen atoms were refined anisotropically against F^2, with full-matrix least square methods SHELXL-97. Hydrogen atoms were included at their calculated positions, except for that of water molecules. About a water molecule in the cocrystals of **1**·**3**, the position of hydrogen atoms was not calculated. Solvent water molecules show disorder around the inversion center. *Crystal data for* **1**·**2**: triclinic, *P*-1, a = 10.677(3) Å, b = 11.126(3) Å, c = 19.175(5) Å, α = 73.158°(3), β = 82.120°(3), γ = 68.241°(3), V = 2023.8(9) Å^3, Z = 4, D_c = 1.390 Mg m^{-3}, T = 173 K, μ = 0.102 mm^{-1}, GOF on F^2 = 0.997, R_1 = 0.0557, wR_2 = 0.1307 ([I >2σ (I)]). *Crystal Data for* **1**·**3**: triclinic, *P*-1, a = 11.068(9) Å, b = 13.020(10) Å, c = 16.691(13) Å, α = 108.279°(9), β = 104.061°(10), γ = 99.274°(10), V = 2141(3) Å^3, Z = 4, D_c = 1.435 Mg m^{-3}, T = 173 K, μ = 0.108 mm^{-1}, GOF on F^2 = 0.980, R_1 = 0.0623, wR_2 = 0.1520 ([I >2σ (I)]).