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Organic Assemblies of 2-pyridones with Dicarboxylic Acids

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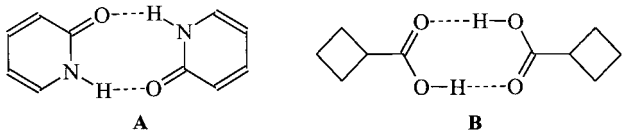
Abstract—The syntheses and crystal structures of four cocrystals; 2-pyridone fumaric acid (2/1), 2-pyridone *meso*-2,3-dibromosuccinic acid (2/1), 5-chloro-2-pyridone adipic acid (2/1) and 6-methyl-2-pyridone (*S*)-malic acid (2/1), are reported. The competition between two self- and mutually-complementary hydrogen-bond moieties (carboxylic acid and 2-pyridone) are examined and compared with results obtained from an earlier study of 2-pyridone and unsubstituted aliphatic dicarboxylic acids.

Introduction

Molecular assembly is a vital aspect of crystal engineering, an area of considerable and widespread attention.[1–4] The primary goal in this field is to control the way in which individual molecules are brought together into extended architectures in the solid state, allowing us to affect solid state reactivity, and to design new functional materials. The synthetic tools available for the construction of such assemblies are non-covalent forces, many of which are poorly understood and difficult to calculate and measure. Consequently, controlling the chemical reactivity and properties of a solid through precise control over its crystal structure is a formidable task. The good news is that many assemblies and structural patterns have been constructed through intermolecular interactions, and the use of molecules or ions (instead of atoms) as building blocks of ordered networks has become an important synthetic strategy in chemistry and materials science.[5] However, crystal engineering is still in its infancy and thus it is necessary to assemble structural information, to identify recurring packing motifs and to correlate these with intermolecular interactions.[6] Many intermolecular connectors rely on the complementarity of various hydrogen-bonding moieties. Examples of such connectors include carboxylic acid/2-aminopyridine,[7] carboxylic acid/urea,[8] amides/acids,[9] carboxylic acid/oxime, and hydroxyl/amino.[10] The robustness and reliability of the self-complementary 2-pyridone moiety, Scheme 1A, have also been utilized for crystal engineering: Wuest and co-workers have constructed both low-dimensional[11] and diamondoid[12] assemblies based upon intermolecular hydrogen bonds between neighboring 2-pyridone moieties.

Although 2-pyridone moieties are known to form rigid dimers in the solid-state, the crystal structure of 2-pyridone[13] actually displays a catemer motif (infinite chains), indicating that it is possible to obtain alternative intermolecular arrangements despite the prevalence of 2-pyridone head-to-head dimers. Historically, probably the most well-known hydrogen-bond motif is the carboxylic acid head-to-head dimer,[14] Scheme 1B, which has been utilized extensively in crystal engineering both in the organic and the inorganic/organic solid state. Recent database studies have revealed, however, that carboxylic acids do engage in a variety of intermolecular hydrogen bonds and the self-complementary $R_2^2(8)$[15] motif is not as reliable as initially thought.[16] An earlier study of five co-crystals of 2-pyridone and some aliphatic dicarboxylic acids showed that each crystal structure contained planar dimers of 2-pyridone bridged by a dicarboxylic acid via a combination of O–H···O and C–H···O hydrogen bonds, resulting in infinite 1-D ribbons.[17] In order to further examine competition between complementary intermolecular forces we have determined the crystal structures of four cocrystals; 2-pyridone fumaric acid (2/1) **1**, 2-pyridone *meso*-2,3-dibromosuccinic acid (2/1) **2**, 5-chloro-2-pyridone adipic acid (2/1) **3** and 6-methyl-2-pyridone (*S*)-malic acid (2/1) **4**. These structures allow an examination of possible changes in packing patterns that may appear due to substituents on the 2-pyridone and/or acid moieties (**2**–**4**), or due to increased rigidity of the acid backbone (**1**).



Scheme 1. (A) Hydrogen-bonded dimer formed by two 2-pyridone moieties; (B) head-to-head dimer of two carboxylic acid moieties.

Keywords: 2-pyridones; dicarboxylic acids; hydrogen bonded ribbon.
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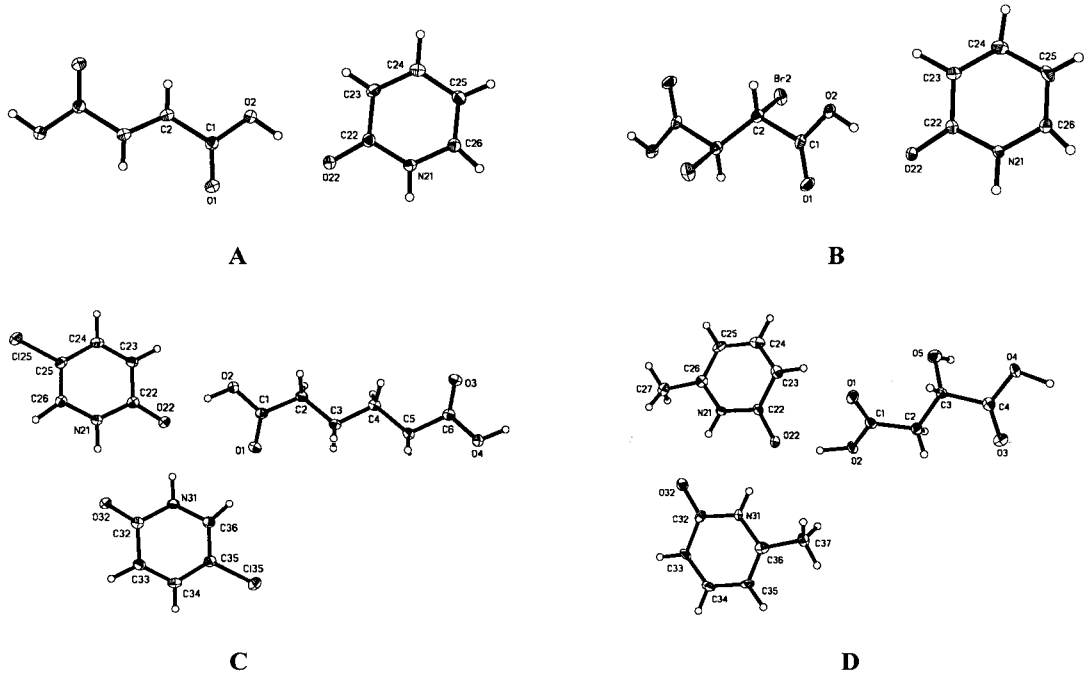


Figure 1. Molecular structure (30% ellipsoids) and labeling scheme (asymmetric unit only) for **1**–**4** (**A**–**D**, respectively).

Results

The reactions of 2-pyridone with fumaric acid and 2,3-dibromosuccinic acid, and the reaction of 5-chloro-2-pyridone with adipic acid and 6-methyl-2-pyridone with malic acid, result in co-crystals containing two pyridone molecules for each molecule of dicarboxylic acid. Structures **1** and **2** contain a dicarboxylic acid located on an inversion center, leading to an asymmetric unit consisting of one pyridone molecule and one half of a dicarboxylic acid. In **3** and **4** the asymmetric unit contains two pyridone molecules and one dicarboxylic acid. As expected, the pyridone (not the pyrid*ol*) tautomer is present in all structures, as evidenced by the exocyclic C–O bond distance (1.260–1.271 Å), which is considerably shorter than the C–O(H) bond distances noted in 6-chloro-2-hydroxypyridine (1.35 Å)[19] and 3-hydroxypyridine (1.32 Å).[20] Further support for the pyridone tautomer is provided by the location of the hydrogen atom on the pyridine nitrogen from a difference map in **1**–**3**.

In **1**, the two carboxylic acid moieties and the alkene unit of the acid backbone are coplanar, resulting in an overall planar conformation of fumaric acid. The 2-pyridone molecules form dimers via two symmetry-related N–H···O hydrogen bonds. Fumaric acid molecules link neighboring dimers through O–H···O and C–H···O hydrogen bonds, Fig. 2. These interactions lead to infinite dimer···acid···dimer···acid chains. Pyridone dimers and fumaric acid molecules within chains are co-planar, resulting in a flat one-dimensional ribbon. The ribbons are stacked parallel to each other in layers, and neighboring layers are related by ~80° rotation. There are no strong hydrogen bonds between neighboring chains in each layer or between adjacent layers.

In **2**, the molecular conformation of 2,3-dibromosuccinic acid is antiperiplanar with a 180° torsion angle of the carbon backbone. The near-planar carboxylic acid moieties are twisted slightly out of the plane of the carbon backbone, with torsion angle $\angle$[O(1)–C(1)–C(2)–C(2A)] = 25.7°. The 2-pyridone molecules assemble into dimers via symmetry-related N–H···O hydrogen bonds. As in **1**, the acid molecules link adjacent pyridone dimers together into infinite chains through two hydrogen bonds, O–H···O and C–H···O, Fig. 3. Pyridone dimers and the backbone of

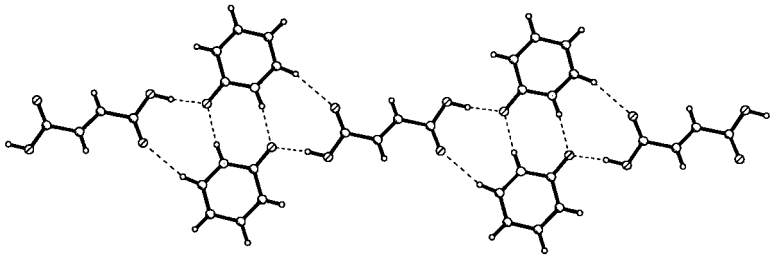


Figure 2. Hydrogen-bonded ribbon in **1**, with alternating fumaric acid molecules and 2-pyridone dimers.

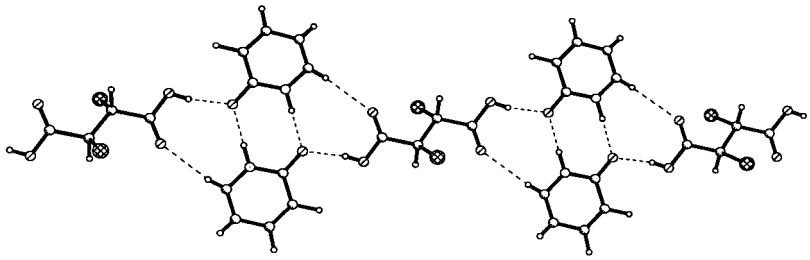


Figure 3. Hydrogen-bonded ribbon in **2**, where bromine atoms are above and below the plane of the ribbon.

2,3-dibromosuccinic acid molecules within chains are in the same plane resulting in a flat one-dimensional ribbon. Similar to **1**, these ribbons are stacked parallel in layers, and adjacent layers are nearly perpendicular, rotated by ~85°. As in **1**, there are no strong hydrogen bonds between neighboring ribbons.

The crystal structure of **3** is the only layered structure; the 5-chloro-2-pyridone dimers are formed via two equivalent N–H···O hydrogen bonds, and adipic acid molecules link these dimers (as in **1** and **2**) through two hydrogen bonds, O–H···O and C–H···O, into infinite ribbons, Fig. 4. However, these ribbons are further linked by C–H···O hydrogen bonds, Fig. 5, thereby generating an infinite layer. Adipic acid adopts an antiperiplanar conformation with a torsion angle of the carbon backbone close to 180°. The near-planar carboxylic moieties are slightly twisted out of the plane of the carbon backbone, with a torsion angle $\angle$[O(1)–C(1)–C(2)–C(3)] = 10.7°.

Compound **4** contains the expected 6-methyl-2-pyridone dimer formed via two complementary N–H···O hydrogen bonds, which are bridged by malic acid molecules to form ribbons similar to those in **1**–**3**. While the presence of the

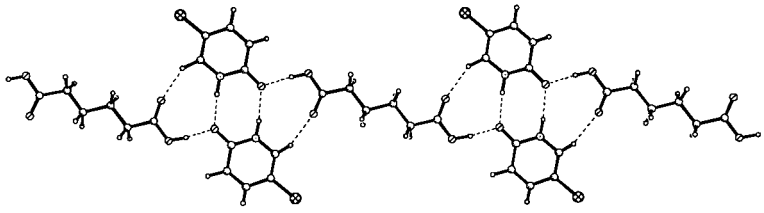


Figure 4. Hydrogen-bonded ribbon in **3**, exhibiting the same 1-D motif as in **1** and **2**.

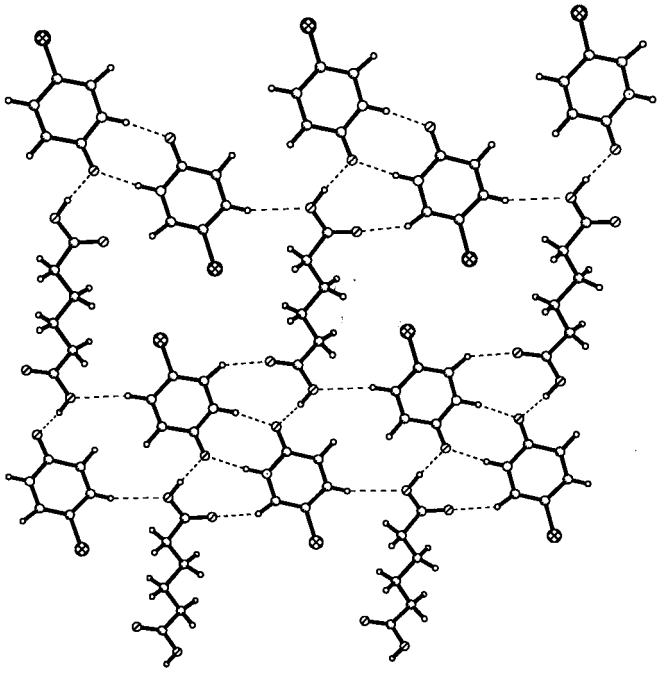


Figure 5. C–H···O hydrogen bonds link adjacent chains in **3**, forming a planar layer.

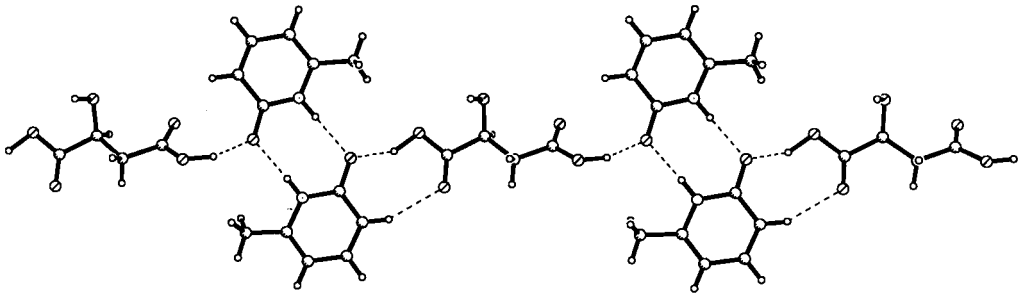


Figure 6. Hydrogen-bonded ribbon in **4**; the C–H···O hydrogen bonds no longer bridge the pyridone dimers.

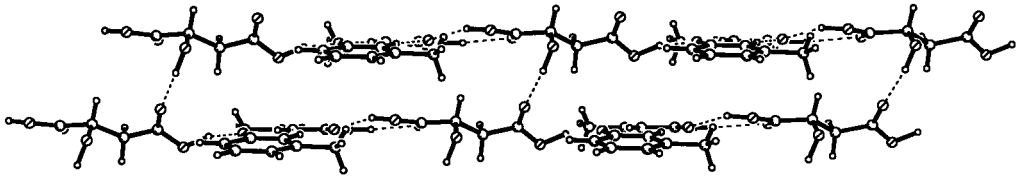


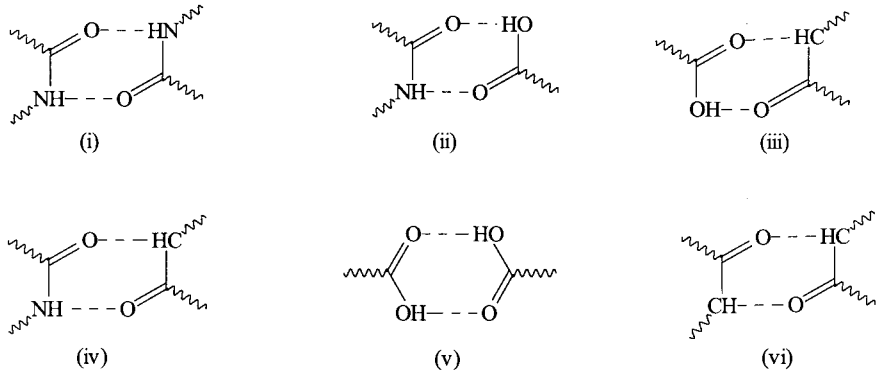
Figure 7. O–H···O hydrogen bonds link ribbons into infinite layers in **4**.

pyridyl methyl group does not allow the formation of the same C–H···O hydrogen bond seen previously in **1**–**3**, the carbonyl group does link via a C–H···O hydrogen bond to the *same* pyridyl moiety, rather than across the pyridone dimer, Fig. 6. The ribbons are stacked to form layers, and the adjacent layers are oriented nearly perpendicular to each other, as in **1** and **2**. An additional hydrogen bond is formed between parallel ribbons: one of the carbonyl oxygen atoms is rotated out of the acid-pyridone plane to accept a hydrogen bond from the malic acid's hydroxyl group, Fig. 7. Thus these O–H···O hydrogen bonds link the ribbons to form a 2-D hydrogen bonded layer of ribbons.

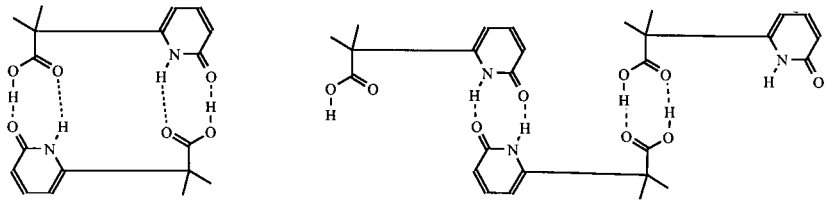
Discussion

An integral part of useful intermolecular design is the ability to predict the structural outcome of a competition between two self-complementary moieties that can also form heteromeric dimers. The carboxylic acid and 2-pyridone groups represent two such moieties: both are known to form homomeric dimers, but they also have the potential to interact with each other. Thus the functional groups present in these molecules have the potential to engage in a range of possible $R_2^2(8)$ motifs, Scheme 2.

In an earlier study, the crystal structures of five co-crystals between 2-pyridone (un-substituted) and some aliphatic dicarboxylic acids (also un-substituted) revealed that the 1-D ribbon motif (formed by 2-pyridone dimers bridged by dicarboxylic acids) occurred in all cases. Likewise, regardless of substituents present on the 2-pyridone ring and on the acids, the four crystal structures **1**–**4** in the present study exhibit the same basic 1-D ribbon—the same 'supermolecule'. The self-complementarity of the 2-pyridone motif is not disrupted by the presence of a carboxylic acid moiety. The ribbon is generated by two strong hydrogen-bond interactions, N–H···O and O–H···O, both of which lie in the plane containing the two lone pairs of the amide oxygen atom. Within this plane, the H···O=C angles are very close to 120° in all four cases which demonstrates the directional preference of X–H···O (X=N, O) (contacts are directed towards the location of oxygen's two lone pairs). This geometric preference is in accordance with an earlier study of X-H···O (X=N,O) interactions



Scheme 2. Possible $R_2^2(8)$ motifs within co-crystals **1**–**4**.



Scheme 3. (A) Schematic representation of the molecular dimers 2,2-dimethyl-4-(2-oxo-1*H*-6-pyridyl)-3-butynoic acid.[25]; (B) hypothetical alternative motif of 2,2-dimethyl-4-(2-oxo-1*H*-6-pyridyl)-3-butynoic acid.

involving carbonyl oxygen atoms.[21] The recurrence of the acid-carbonyl hydrogen bond, O–H···O=C, should not be surprising, as it has been shown that in co-crystals of carboxylic acids and amides (2-pyridone can be considered a cyclic amide) the acid O–H tends to hydrogen bond to the amide oxygen atom.[22]

A search of the CSD[23] uncovered 59 non-ionic organic molecules or co-crystals that contain the 2-pyridone moiety. Of these, 47 structures (80%) exhibit pyridone–pyridone interactions (5 structures, including 2-pyridone itself, form catameric motifs, and 42, contain pyridone dimers). Eight co-crystals contain both a carboxylic acid and a 2-pyridone moiety.[24] Four of the structures exhibit the pyridone dimer with acids hydrogen bonded to the pyridone carbonyl oxygen atom (as in **1**–**4**), two show pyridone–pyridone dimers without additional hydrogen bonding to the acid, and two of these, for example 2,2-dimethyl-4-(2-oxo-1*H*-6-pyridyl)-3-butynoic acid[25] (**I**, Scheme 3) give an acid-pyridone heteromeric dimer (ii, Scheme 2). The structure of **I** contains dimers held together by two pyridone-acid interactions, Scheme 3A. However, the formation of molecular dimers connected by two homomeric interactions is precluded due to the positioning of the pyridone moiety, so this option is not available (although it is possible to envisage chains of molecules, Scheme 3B).

The results of the CSD search indicate that the 2-pyridone self-complementary interaction is a particularly reliable motif, and often persists even in the presence of other good hydrogen bond donors and acceptors. In fact, the dominant feature of the materials in the present study is the reliability of the 2-pyridone dimer irrespective of the nature of the co-crystalizing acid; i.e. the presence of substituents on either the acid or the pyridone ring does not perturb the formation of this dimer. However the choice of acid can affect how these dimers are arranged in the lattice with respect to each other, either herringbone as in **1**,**2** and **4** or coplanar as in **3**. This observation is consistent with that of the previous study on the unsubstituted system.

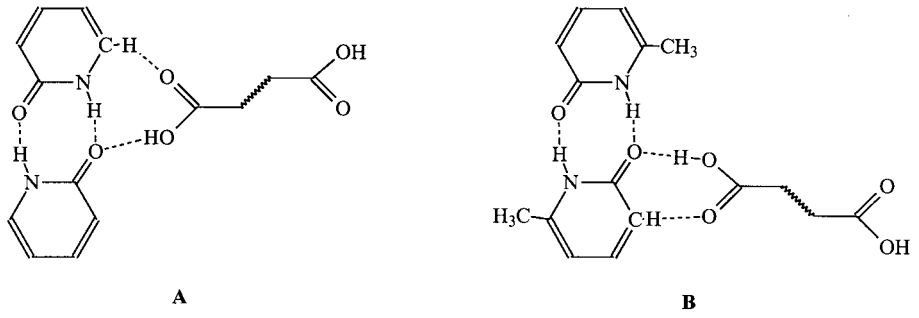
While the positioning of the substituents does not affect the formation of the dimer, it can be used to subtly modify the bridging motif of the acid group. In **4**, a methyl substituent in the six position precludes the formation of the usual hydrogen bonded chain, Scheme 4A. Instead the acid hydrogen bonds with the C–H moiety adjacent to the C=O moiety, Scheme 4B. Furthermore, substituents on the acid moiety do not affect the formation of the dimer···acid··· dimer···acid chains in **2** and **4**. Also in **4**, the chains are linked into layers via an O–H···O hydrogen bond from the hydroxyl group of the (*S*)-malic acid molecules to the carbonyl oxygen atoms of (*S*)-malic acid molecules in the chains below thereby stabilizing the layers.

Apparantly a combination of the size of the acid and substituents on the acid and/or the pyridone ring can be used to alternate between the layered structure observed in **3** (which is also observed with the 2-pyridone oxalic acid 2/1 co-crystal in the previous study[17]) and the dominant motif, the perpendicular layers observed in **1**, **2** and **4**.

Experimental

Preparation of 2-pyridone fumaric acid (2/1), 1

2-Pyridone (0.20 g, 2.22 mmol) and fumaric acid (0.26 g, 2.22 mmol) were dissolved together in a hot water–ethanol (1:1) mixture (50 ml). Colorless, rectangular prism-like crystals were formed after four weeks upon evaporation of the solvent (mp 217–219°C).



Scheme 4. Schematic of two possible hydrogen-bonding motifs for 2-pyridone dimers and dicarboxylic acids.

Table 1. Data collection and refinement for **1**–**4**

Crystal data	**1**	**2**	**3**	**4**
Empirical formula	$C_7H_7NO_3$	$C_7H_7NO_3Br$	$C_{16}H_{18}N_2O_6Cl_2$	$C_{16}H_{20}N_2O_7$
CCDC deposit no.				
MW	153.14	233.05	405.22	352.34
Crystal size (mm)	0.4×0.2× 0.2	0.58×0.46×0.45	0.46×0.44×0.28	0.44×0.16×0.14
Crystal system	Monoclinic	Monoclinic	Triclinic	Orthorhombic
Space group	P2(1)/n	P2(1)/c	P-1	P2(1)2(1)2(1)
a (Å)	8.636 (1)	12.220 (2)	8.031 (1)	5.187 (1)
b (Å)	5.0337 (5)	4.854 (2)	10.503 (2)	9.727 (1)
c (Å)	16.473 (1)	14.367 (3)	12.269 (1)	32.812 (5)
α (°)	90	90	65.64 (1)	90
β (°)	96.135 (6)	103.10 (1)	83.53 (1)	90
γ (°)	90	90	77.62 (1)	90
Volume (Å^3)	712.0 (1)	830.0 (4)	920.5 (2)	1655.5 (4)
Z	4	4	2	4
D_{calc} (g cm^{-3})	1.429	1.865	1.462	1.414
F(000)	320	460	420	744
μ, Mo-K$_\alpha$ (mm^{-1})	0.113	4.917	0.388	0.112
Temperature (K)	173 (2)	173 (2)	173 (2)	153 (2)
Goodness of fit	1.053	1.171	1.012	1.044
R/R$_w^2$ (obs. data)	0.0313/0.0813	0.0250/0.0635	0.0331/0.1136	0.0678/0.1348
R/R$_w^2$ (all data)	0.0395/0.0875	0.0275/0.0648	0.0420/0.1248	0.1501/0.1699

Preparation of 2-pyridone meso-2,3-dibromosuccinic acid (2/1), 2

2-Pyridone (0.10 g, 1.05 mmol) was dissolved in a hot water–ethanol (1:1) mixture (50 ml) together with *meso*-2,3-dibromosuccinic acid (0.29 g, 1.05 mmol). Rectangular prism-like, colorless crystals were formed after three weeks upon evaporation of the solvent (mp 163–165°C).

Preparation of 5-chloro-2-pyridone adipic acid (2/1), 3

5-Chloro-2-pyridone (0.20 g, 2.22 mmol) and adipic acid (0.23 g, 2.22 mmol) were dissolved together in a hot water–ethanol (1:1) mixture (50 cm^3). Rectangular prism-like crystals were obtained after four weeks upon evaporation of the solvent (mp 125–127°C).

Preparation of 6-methyl-2-pyridone (*S*)-malic acid (2/1), 4

Malic acid (0.355 g: 2.65 mM) and 6-methyl-2-pyridone (0.294 g; 2.69 mM) were dissolved in hot ethanol (30 cm^3). The solution was allowed to cool, whereupon a white solid was formed. The solid was collected and recrystallised from ethanol (40 cm^3). Colorless needle-like crystals appeared upon slow evaporation of the solvent.

X-Ray crystallography

Crystal data were collected using a Siemens P4 four-circle diffractometer with graphite monochromated Mo-Kα radiation. Hydrogen-atom positions were located from difference Fourier maps, except for **4**, in which non-acid or -hydroxy hydrogen atoms were placed at calculated positions, and a riding model with fixed thermal parameters [u_{ij}=1.2U_{ij}(eq) for the atom to which they are bonded] was used for subsequent refinements. The SHELXTL PC and SHELXL-93 packages were used for data reduction and structure solution and refinement.[18] Table 1 contains crystallographic details and Fig. 1 displays labeling schemes and thermal ellipsoids for **1**–**4**.

Acknowledgements

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