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Hydrogen-bonding directed cocrystallization of flexible piperazine with hydroxybenzoic acid derivatives: Structural diversity and synthon prediction

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Four hydroxybenzoic acid building blocks, m-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic acid, and 5-hydroxyisophthalic acid, have been synthesized as robust cocrystallizing agents and employed in reactions with piperazine, including $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_3^-)_2]$ (**1**), $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_4^-)_2]$ (**2**), $[(C_4H_{12}N_2^{2+})\cdot(C_8H_5O_6^{2-})]$ (**3**), and $[(C_4H_{12}N_2^{2+})_{1/2}\cdot(C_8H_5O_5^-)]\cdot 2H_2O$ (**4**). Hydrogen-bonded directed assemblies of four salts were validated by single-crystal X-ray diffraction analysis. In compounds **1–4**, hydroxybenzoic acids are all deprotonated and piperazine molecules are all protonated to form piperazine dications and keep the chair conformation. Thermal stability of these compounds has been investigated.

crystal engineering, supramolecular synthons, piperazine, hydroxybenzoic acid

1 Introduction

The term "crystal engineering" was introduced as a new concept in crystallography by Pepinsky in 1955 [1], but it was first employed much later in the context of synthetic and mechanistic photochemistry by Schmidt in 1971 [2]. Two decades later, in the early 1990s, many achievements have been accomplished in crystal engineering field, where an important aspect was focused on the design of organic compounds with desired structures and properties engineered at the molecular level and derived from molecular building blocks associated by intermolecular interactions (e.g., supramolecular synthons) [3–5]. Hydrogen bonding plays an important role in constructing sophisticated assemblies owing to its strength and directionality [6–8].

Crystal engineering is predicted on the link between crystal structure and molecular structure owing to its rapidly growing discipline. It seeks to understand the role of solid-state materials with wanted physical and chemical properties. Many efforts toward this goal have focused on organic molecular solids [9]. In order to simplify the complexity of the link, the concept of the "supramolecular synthon" as a structural link has been used and defined as a "specific pattern of intermolecular interactions associated with a specific type of molecular array in the solid state" [10]. The reliable supramolecular synthons, such as the patterns formed by carboxylic acids-cyclic dimers and open catemer- or by azole derivatives-cyclic dimmers, trimers, tetramers, and open catemers-, have been widely investigated [11, 12]. Another supramolecular synthon that has been commonly employed in the formation of extended architectures in the solid state is the carboxylic acid…pyridine heterosynthon (COOH⋯pyridine) that consists of the primary O–H⋯N hydrogen bond and the auxiliary C–H⋯O weak interaction [13]. In the design and synthesis of crystalline solids in crystal en-

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gineering, supramolecular synthons are employed as robust structural units to control the structures of single- and multi-component solids [14–18].

Piperazine (Scheme 1) is often used in crystal engineering due to its robust geometry and relatively high solubility in different solvents. The two nitrogen atoms in the piperazine molecular are always protonated in the crystalline solids and piperazine molecule often keeps the chair conformation [19]. The N–H bonds can act as hydrogen bond donors to construct the strong N–H···O hydrogen bond interaction, and N atoms can act as hydrogen bond acceptors to form the strong O–H···N hydrogen bond interaction. Organic carboxylic acids are used as good hydrogen bond acceptors and donors in crystalline solids. The substitution pattern of the carboxyl groups introduces structural diversity into the networks. The hydroxyl group is also a good hydrogen bond donor and acceptor but is less deprotonated than the carboxylic acid. Components that contain both the carboxylic acid group and the hydroxyl group are thus of interest and deserve investigation.

In this contribution, we focus on the syntheses and structural characterization of cocrystallizing piperazine and four hydroxybenzoic acids: m-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic acid, and 5-hydroxyisophthalic acid (Scheme 1). Co-crystals of piperazine and various carboxylic acids have emerged as materials for studying their physical properties, as well as model components for studying preparation methods and structural effects associated with pharmaceutical co-crystals [16]. In this study, we used four kinds of hydroxybenzoic acids cocrystallizing with piperazine, resulting in four salts, namely, $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_3^-)_2]$ (**1**), $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_4^-)_2]$ (**2**), $[(C_4H_{12}N_2^{2+})\cdot(C_8H_5O_6^{2-})]$ (**3**), $[(C_4H_{12}N_2^{2+})_{1/2}\cdot(C_8H_5O_5^-)]\cdot 2H_2O$ (**4**).

2 Experimental

2.1 General experimental section

All materials were commercially available and used as received. The IR spectra were measured using a Nicolet Impact 410 FTIR spectrometer in the range of 400–4000 cm^{-1}. The melting points of all new compounds were recorded on a WRS-1B digital thermal apparatus without correction. C, H, and N microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer. Thermogravimetric analysis (TGA) experiments were carried out on a Perkin-Elmer TGA 7 thermogravimetric analyzer under N_2 atmosphere at a heating rate of 10 °C/min. The co-crystals were prepared as follows.

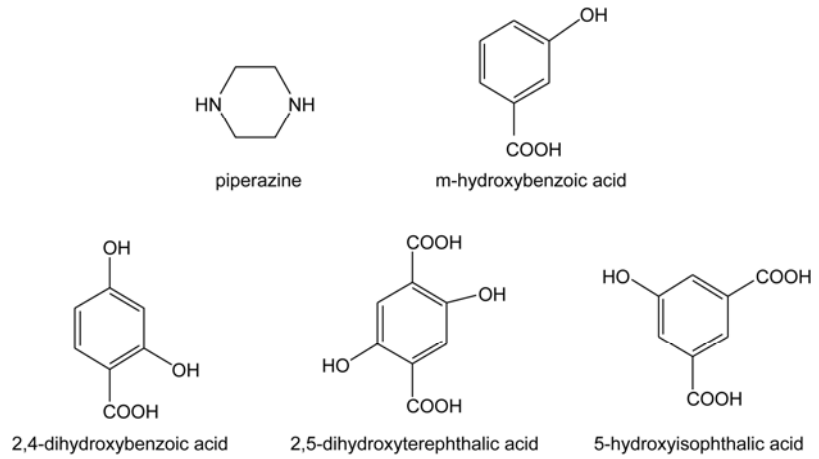
2.2 Synthesis and characterization

Synthesis of $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_3^-)_2]$ (***1***)

m-Hydroxybenzoic acid (0.138 g, 1.0 mmol) and piperazine hexahydrate (0.097 g, 0.5 mmol) were dissolved in MeOH/H_2O (5:1, 12 mL). The solution was allowed to evaporate at ambient conditions, resulting in clear, colorless block crystals after 5 days in 80% yield. Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.61; H, 6.07; N, 7.73. Found: C, 59.68; H, 6.15; N, 7.63%. IR (KBr, cm^{-1}): 3427m, 3320m, 3249m, 3026m, 2925m, 2853m, 2754m, 2663m, 2605m, 2460m, 2235w, 1647m, 1557s, 1482m, 1447m, 1396m, 1346m, 1309m, 1285m, 1263m, 1237m, 1115w, 1093w, 999w, 939w, 892w, 830w, 816w, 795m, 779m, 743w, 692w, 673w, 606m, 498m, 418m.

Synthesis of $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_4^-)_2]$ (***2***)

To a solution of 2,4-dihydroxybenzoic acid (0.154 g, 1.0 mmol) in ethanol (7 mL), a solution of piperazine hexahy-



Scheme 1

drate (0.049 g, 0.25 mmol) in methanol (3 mL) was added. The clear solution was allowed to stand in air for 7 days to give colorless crystals of **4**. Yield 80%. Anal. Calcd for $C_{18}H_{22}N_2O_8$: C, 54.77; H, 5.58; N, 7.10. Found: C, 54.65; H, 5.47; N, 7.15%. IR (KBr, cm^{-1}): 3424m, 3116m, 3031m, 2594m, 2349w, 2290w, 1913w, 1640s, 1607s, 1521m, 1481m, 1451m, 1409m, 1363m, 1338m, 1317s, 1217m, 1221m, 1171m, 1156m, 1100m, 1087m, 1073m, 1018w, 976m, 958m, 868w, 839m, 833m, 795m, 756w, 735w, 699m, 628m, 606w, 578m, 532w, 457w.

Synthesis of $[(C_4H_{12}N_2^{2+})\cdot(C_8H_5O_6^{2-})]$ (**3**)

2,5-Dihydroxyterephthalic acid (0.039 g, 0.25 mmol) was dissolved in 5 mL DMF, to which a mixture solution (3 mL ethanol and 2 mL H_2O) of piperazine hexahydrate (0.049 g, 0.25 mmol) was added with stirring for 30 min. The resultant light yellow solution was filtered and allowed to evaporate in air for 7 days, resulting in brown crystals after a period of time. Yield, 75%. Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.66; H, 5.63; N, 9.85. Found: C, 50.65; H, 5.45; N, 7.75%. IR (KBr, cm^{-1}): 3440m, 3123m, 2881m, 2713m, 2575m, 2317m, 1827w, 1604m, 1564s, 1529m, 1487m, 1445m, 1373m, 1340s, 1314m, 1295m, 1246s, 1111m, 1091m, 1062m, 1020w, 939m, 925m, 876m, 860m, 817m, 784s, 615w, 583m, 541m, 492m, 455w.

Synthesis of $[(C_4H_{12}N_2^{2+})_{1/2}\cdot(C_8H_5O_5^{-})]\cdot 2H_2O$ (**4**)

A solution of 5-hydroxyisophthalic acid (0.091 g, 0.5 mmol) in ethanol was added to a solution of piperazine (0.049 g, 0.25 mmol) in water. The clear solution was allowed to evaporate in air for 5 days. Colorless crystals of **6** were obtained in 70% yield. Anal. Calcd for $C_{10}H_{14}NO_7$: C, 46.11; H, 5.38; N, 5.38. Found: C, 46.15; H, 5.47; N, 5.35%. IR (KBr, cm^{-1}): 3570m, 3427s, 3247s, 2852m, 2586m, 2026w, 1709m, 1619m, 1552m, 1440m, 1387s, 1289m, 1218s, 1126w, 1087w, 1002w, 978m, 952w, 887w, 866w, 766m, 685m, 599m, 582m, 556m, 462m.

2.3 X-Ray structure determination

Single-crystal X-ray diffraction data for co-crystals **1–4** were collected on a Siemens Smart CCD diffractometer at 293(2) K with MoKα radiation (λ = 0.71073 Å) by ω scan mode. There was no evidence of crystal decay during data collection for all compounds. All the measured independent reflections were used in the structural analysis, and semiempirical absorption corrections were applied using the SADABS program. The program SAINT was used for integration of the diffraction profiles [20]. All structures were solved by direct methods using the SHELXS program of the SHELXTL package and refined with SHELXL [21]. The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for all the non-hydrogen atoms on F^2. Most of the hydrogen atoms were first observed in difference electron density maps and then placed in the calculated sites and included in the final refinement in the riding model approximation with fixed thermal factors. Further details for crystallographic data and structural analysis are listed in Table 1. CCDC No. 831525, 831528, 831529, and 831530 contains the supplementary crystallographic data for the structures in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; or E-Mail: deposit@ccdc.cam.ac.uk, www.ccdc.cam.ac.uk/data_request/cif).

3 Results and discussion

3.1 Preparation of compounds 1–4

m-Hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic acid, and 5-hydroxyisophthalic acid have slight solubility in water and good solubility in some common organic solvents, such as methanol, ethanol, and ether. All reactions between piperazine and the four different hydroxybenzoic acids were carried out in a 1:1, 1:2, or 1:4 molar ratio. For the preparation of **1**, hydroxybenzoic acids and piperazine were mixed directly in methanol and water solution, which were allowed to evaporate in air to give the final crystalline products. For compounds **2**, **3**, and **4**, the acid and base were dissolved in different solutions respectively and then mixed together to form clear solution for evaporation at ambient conditions. Then the final products

Table 1 Crystallographic data and structural refinement summary for compounds **1–4**

	1	**2**	**3**	**4**
Empirical formula	$C_{18}H_{22}N_2O_6$	$C_{18}H_{22}N_2O_8$	$C_{12}H_{16}N_2O_6$	$C_{10}H_{14}NO_7$
M	362.38	394.38	284.27	260.22
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$ (14)	$P2_1/n$ (14)	$P2_1/c$ (14)	$P2_1/c$ (14)
a (Å)	10.323(3)	8.480(1)	8.239(2)	8.842(1)
b (Å)	8.240(3)	9.757(1)	10.172(2)	16.878(2)
c (Å)	10.708(3)	11.337(2)	7.502(1)	8.058(1)
α (°)	90	90	90	90
β (°)	104.348(4)	111.96(5)	94.20(3)	100.107(2)
γ (°)	90	90	90	90
V (Å^3)	882.5(5)	869.9(2)	627.1 (2)	1183.9(3)
Z	2	2	2	4
ρ_{calcd} (g cm^{-3})	1.364	1.506	1.481	1.460
μ (mm^{-1})	0.131	0.126	0.133	0.130
F (000)	396	374	286	528
Parameters	118	127	91	179
R_{int}	0.0234	0.0190	0.0257	0.0196
R_1[a], wR_2[b]	0.0489, 0.1242	0.0439, 0.1203	0.0475, 0.1313	0.0469, 0.1261
GOF	1.087	1.049	1.086	1.078

R_1[a] = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$; w$R_2$[b] = $\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)]^2\}^{1/2}$.

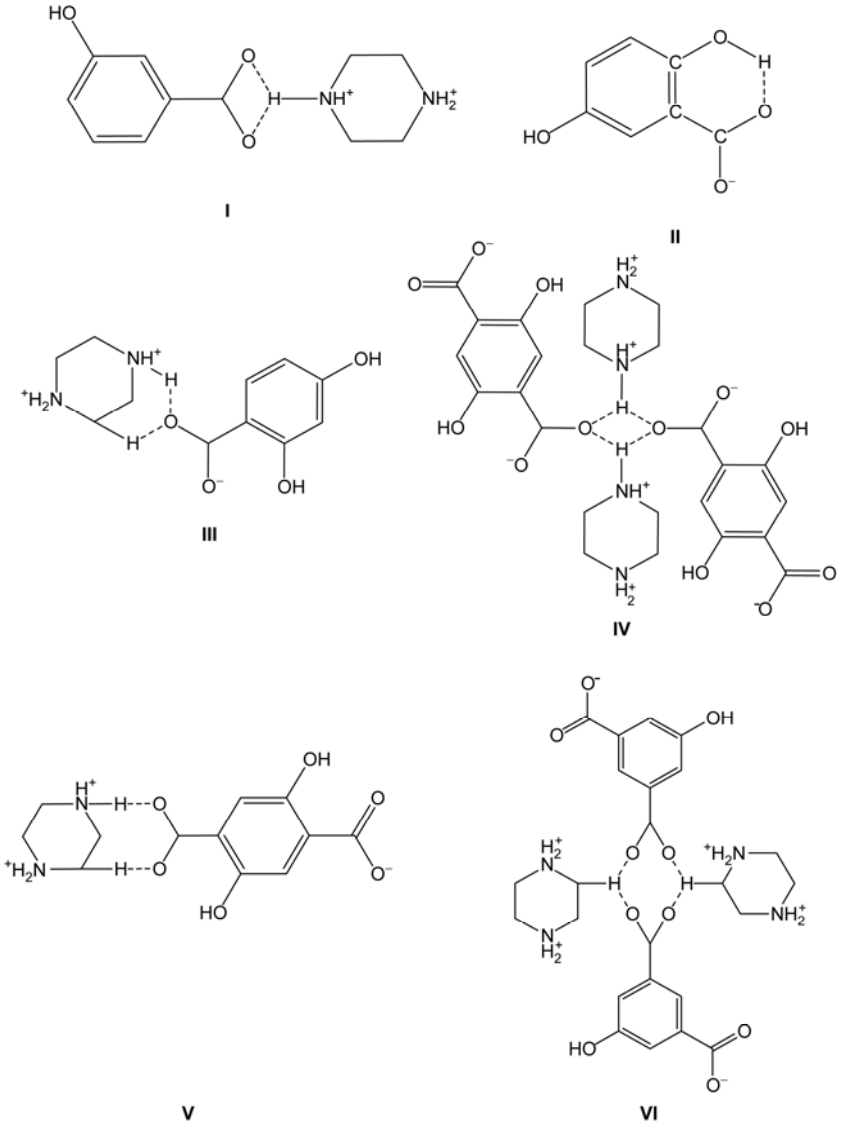
were obtained. It should be noted that the assembled reactions were firstly performed under the same C_2H_5OH/H_2O condition, but the work of obtaining good crystals for suitable single-crystal X-ray diffraction failed. The growth rate of crystals in different solvents may be a factor that influences the final crystal structures.

3.2 Molecular and supramolecular structural descriptions

The schematic representations of related hydrogen-bonding synthons are summarized in Scheme 2. Hydrogen-bond parameters of **1–4** are listed in Table 2.

*3.2.1 $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_3^-)_2]$ (**1**)*

Compound **1** crystallizes in the monoclinic $P2_1/c$ space group. In **1**, the m-hydroxybenzoic acid molecules are deprotonated and piperazine molecules are protonated. In the local structure of cocrystal **1** as shown in Figure 1(a), the asymmetric unit of **1** contains a m-hydroxybenzoic acid monoanion and an half piperazine dication (centrosym metry). The piperazine dications assume the chair conformation. The m-hydroxybenzoic acid monoanions are connected together by strong O3(–OH)–H3···O1(–COO^-) hydrogen bonds to form an zigzag chain along the crystallographic (010) direction (Figure 1(b)). As shown in Figure 1(c), each –COOH group of a m-hydroxybenzoic acid monoanion connects the adjacent piperazine dications via synthon I $R_1^2(4)$ [N1–H1B···O1(–COO^-) and N1–H1B···O2(–COO^-)] and N1–H1A···O2(–COO^-) to form a 2D layer network along the *b* axis. Then through strong O–H···O and N–H···O hydrogen bonds, 1D chain and 2D layer are joined together to result in a 3D network (Figure 1(d)). Similar to **1**, the reported co-crystal of p-hydroxybenzoic acid and piperazine also crystallizes in the monoclinic $P2_1/c$



Scheme 2

Table 2 Hydrogen-bond geometries in the crystal structures of **1–4**

Compound	D–H···A (Å)	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
1	O3–H3···O1[a)]	0.82	2.00	2.688	141
	N1–H1A···O2[b)]	0.90	1.86	2.736	165
	N1–H1B···O1	0.90	1.85	2.730	165
	N1–H1B···O2	0.90	2.52	3.238	137
2	O3–H3···O2	0.82	1.83	2.556	147
	O4–H4···O1[m)]	0.82	1.94	2.670	147
	N1–H1A···O1[n)]	0.90	2.16	2.847	133
	N1–H1A···O3	0.90	2.35	2.976	127
	N1–H1B···O2[o)]	0.90	1.89	2.743	157
	C8–H8B···O2	0.97	2.57	3.393	143
3	O3–H3···O2	0.82	1.83	2.554	146
	N1–H1A···O2	0.90	1.78	2.672	170
	N1–H1B···O1[p)]	0.90	2.20	2.811	133
	N2–H1B···O1[q)]	0.90	2.27	2.975	135
	C5–H5B···O3	0.97	2.51	3.089	118
	C6–H6B···O1	0.97	2.58	3.377	139
4	O5–H5···O1W	0.82	1.89	2.690	166
	O4–H4···O1[b)]	0.82	1.88	2.592	145
	O1W–H1WA···O2[r)]	0.97	1.86	2.801	164
	O1W–H1WB···O2[s)]	0.97	1.82	2.737	156
	O2W–H2WA···N1	0.99	1.54	2.393	141
	O2W–H2WB···O2[t)]	0.91	2.36	3.048	133
	C10–H10B···O3	0.97	2.60	3.424	14
	C10–H10B···O4	0.97	2.59	3.263	126

a) $-x$, 1/2+y, $-z$+1/2; b) $-x$+1, $-$1/2+y, $-z$+1/2; m) $-x$+1/2, y+1/2, 3/2$-z$; n) 1$-x$, 1$-y$, 1$-z$; o) 1$-x$, $-y$, $-z$; p) 1$-x$, y+1/2, $-z$+1/2; q) x, 3/2$-y$, 1/2+z; r) x+1, $-y$+3/2, $-$1/2+z; s) x+1, y, z; t) $-x$+1,$-y$+2, $-z$.

space group [22], and analysis of the intermolecular interactions in it reveals that this kind of the co-crystal contains the similar 1D chains but different 2D layers which are joined together to result in a 3D supramolecular array. In addition, the p-hydroxybenzoic acid monoanion and piperazine dication are held together by two strong N–H···O3(–COO^-) molecular interactions [synthon $R_4^4(12)$] which are not found in **1**.

3.2.2 $[(C_4H_{12}N_2^{2+})\cdot(C_7H_5O_4^-)_2]$ (**2**)

The centrosymmetric unit of **2** consists of one 2,4-dihydroxybenzoic acid monoanion and a half centrosymmetric piperazine dication in the asymmetric unit (Figure 2(a)). As shown in Figure 2(b) (top), 2,4-dihydroxybenzoic acid monoanions are connected together via strong O4–H4···O1 hydrogen-bonding to form a 1D waving chain along the (010) direction. Furthermore, different from compound **1**, the hydroxyl group of co-crystal **2** is involved in an intermolecular O(–OH)–H···O(–COO^-) hydrogen-bonded with the carboxylic group to form an $S(6)$ ring [synthon II]. Similar to the reported co-crystal of 3,5-dihydroxybenzoic acid and piperazine [23], 2,4-dihydroxybenzoic acid monoanions and piperazine dications are interlinked by strong N1–H1A···O1(–COO^-) and N1–H1A···O3(–OH) hydrogen bonds to form a double chain along the *ac* plane (Figure 2(b), bottom). The double chains are further linked together via N1–H1B···O2(–COO^-) hydrogen bonds into a 2D layer parallel to the *bc* plane, as shown in Figure 2(c). The 1D chain and 2D layer are interconnected to form a 3D supramolecular network. It is also notable that the weaker noncovalent interactions C–H···O exist in **2** and further stabilize the 3D network via weak C8–H8···O2(–COO^-) hydrogen-bonding and strong N1–H1B ··· O2(–COO^-) hydrogen-bonding [synthon III, $R_2^1(6)$] (Figure 2(d)).

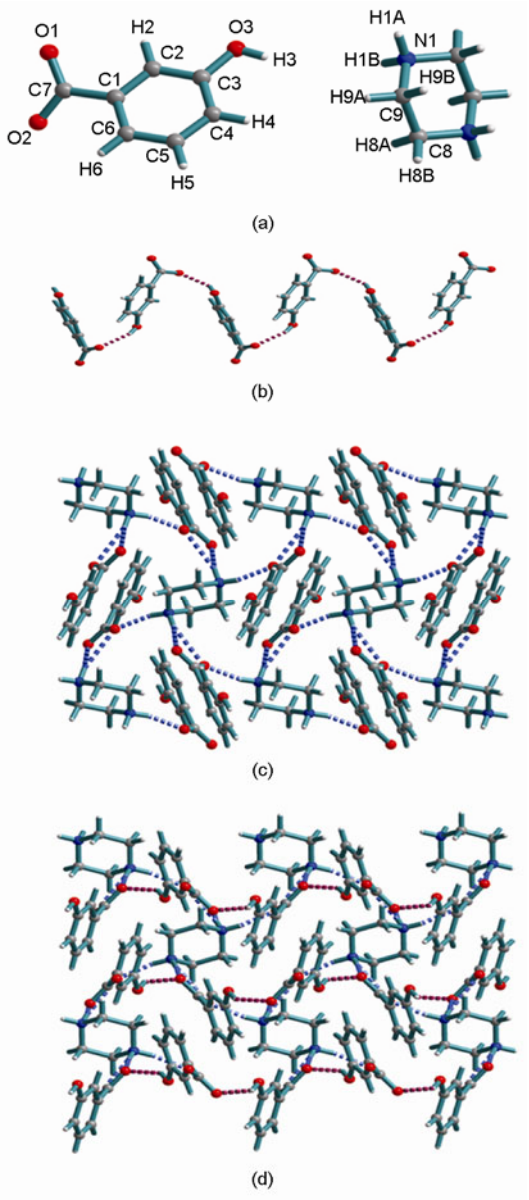


Figure 1 (a) Molecular structure of **1** with atom labeling of the asymmetric unit; (b) 1D zigzag hydrogen-bonding array in **1** along the (010) direction; (c) 2D layer network along the *b* axis; (d) 3D hydrogen-bonding architecture along the crystallographic *bc* plane. O, red; N, blue; C, gray; H, light gray in this and the subsequent figures.

3.2.3 $[(C_4H_{12}N_2^{2+})\cdot(C_8H_5O_6^{2-})]$ (**3**)

The molecular structure of **3** is depicted in Figure 3(a). The

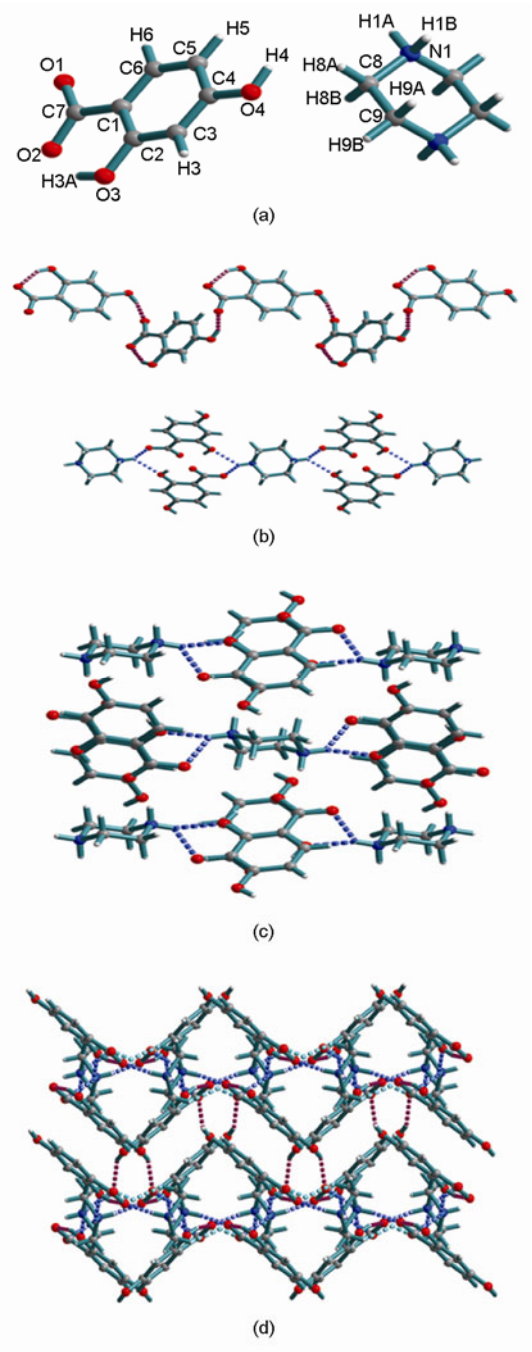


Figure 2 (a) Molecular structure of **2** with atom labeling of the asymmetric unit; (b) (top) an infinite chain formed by O–H···O hydrogen-bonding running along the (010) direction; (b) (bottom) a double chain along the *ac* plane; (c) 2D layer network joined by N–H···O hydrogen-bonding along *bc* plane; (d) 3D supramolecular network of **2**.

asymmetric unit of it contains a half 2,5-dihydroxyterephthalic acid dianion and a half piperazine dication and crystallizes in the space group $P2_1/c$. 2,5-Dihydroxyterephthalic acid dianions and piperazine dications are all centrosymmetric in this case. Analysis of the structure of **3** suggests that the hydroxyl group of compound **3**, the same as salt **2** and other salicylic acid co-crystals [24], is involved in an

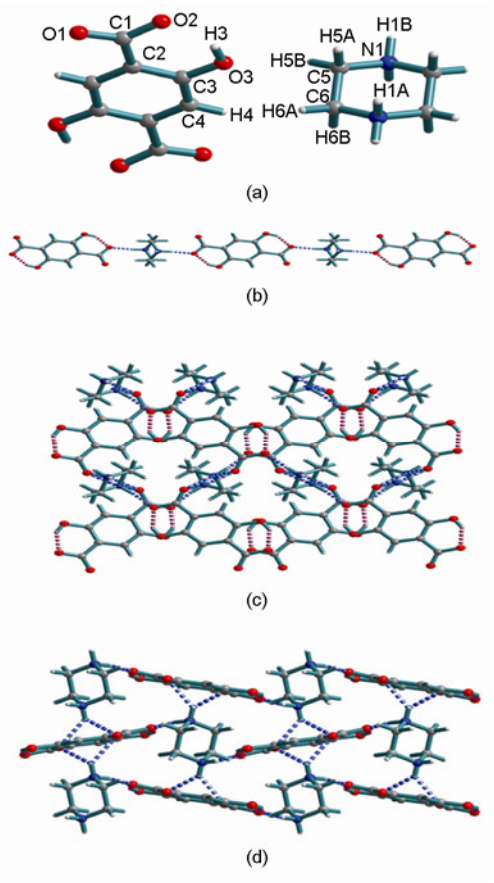


Figure 3 (a) Molecular structure of **3** with atom labeling of the asymmetric unit; (b) an infinite chain along the (010) direction; (b) (bottom) a double chain along the crystallographic *ac* plane; (c) 3D network joined by N–H···O hydrogen-bonding along *ab* plane; (d) 3D supramolecular network of **3**.

intermolecular O(–OH)–H···O(–COO^-) hydrogen-bonded with the carboxylic group to form an $S(6)$ ring [synthon II]. A 1D chain with 2,5-dihydroxyterephthalic acid dianions and piperazine dications is formed via strong N1–H1A···O2 (–COO^-) hydrogen-bonding along the *ab* plane (Figure 3b). These 1D motifs are further extended to a 3D supramolecular network via strong acid-base interactions N1–H1B···O1 (–COO^-) [H1B···O1(–COO^-) = 2.195 Å] and N1–H1B···O1 (–COO^-) [H1B···O1(–COO^-) = 2.273 Å] hydrogen bonds [synthon IV, $R^2_2(4)$], as depicted in Figure 3(c). In addition, multiple weak C–H···O forces coexist within such 3D noncovalent networks and consolidate the 3D network via C6–H6B···O1(–COO^-) and N1–H1A···O2(–COO^-) hydrogen bonds [synthon V, $R^2_2(8)$] (Figure 3(d)).

3.2.4 $[(C_4H_{12}N_2^{2+})_{1/2}\cdot(C_8H_5O_5^-)]\cdot 2H_2O$ (**4**)

The asymmetric unit contains a 5-hydroxyisophthalic acid monoanion, a half piperazine protonated cation and two solvent water molecules. The piperazine unit is centrosymmetric and assumes the chair conformation (Figure 4(a)). One of the two carboxyls of 5-hydroxyisophthalic acid is

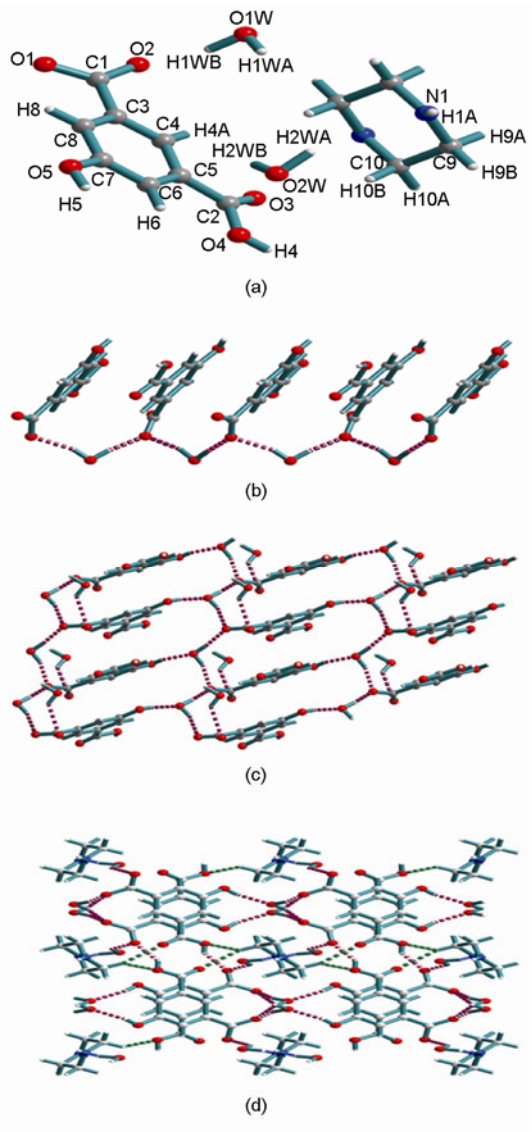


Figure 4 (a) Molecular structure of **4** with atom labeling of the asymmetric unit; (b) 1D infinite chain in **4** along the (001) direction; (c) 2D layer network along the crystallographic *ac* plane; (d) 3D hydrogen-bonding architecture of **4**.

deprotonated. These acid moieties and water solvents are linked via strong O1W–H1WB···O2(–COO^-) and O1W–H1WA···O2 (–COO^-) hydrogen bonds to form a 1D chain along the (001) direction (Figure 4(b)). Such adjacent 1D chains further join together by O5(–OH)–H5···O1W interactions to form a 2D layer network along the (100) direction (Figure 4(c)). Within the 2D array, one solvent water molecule that acts as the 3-connector, O1W joins three 5-hydroxyisophthalic acid monoanions via O5(–OH)–H5···O1W, O1W–H1WA···O2(–COO^-) and O1W–H1WB···O2 (–COO^-) interactions. Furthermore, the adjacent 2D layer networks are connected together by N1–H1A···O1 and O4(–COOH)–H4···O1(–COO^-) bonds to result in a 3D network. In the 3D structure of **4**, another solvent water molecule acts as 2-connector; O2W connects a piperazine dications and a 5-hydroxyisophthalic acid monoanion through O2W–H2WB···O1(–COO^-) and O2W–H2WA···N1 hydrogen bonds. Weak C10–H10B···O3(–COOH) and C10–H10B ··· O4(–COOH) forces [synthon **VI**, $R_2^4(8)$] within 3D network connect piperazine dication in the structure and consolidate the whole supramolecular system (Figure 4(d)).

3.3 Thermogravimetric analysis

All compounds **1**–**4** are air stable and can retain their structural integrity at ambient conditions for a considerable length of time. To study the stability of compounds **1**–**4**, thermogravimetric analyses (TGA) were conducted to determine the thermal stability of these compounds. For compound **1**, the first weight loss of 75.1% from 180 to 310 °C, peaking at 262 °C, corresponds to the loss of acid component (calculated: 75.7%). The residual base section loses weight of 23.8% (calcd: 24.3%), subsequently from 310 to 440 °C (peak: 405 °C). The TGA curve of **2** shows two consecutive weight losses of all samples from 140 to 210 °C (peaking at 182 and 209 °C, respectively). The network of **3** remains intact until three consecutive mass losses occur in the region of 240–350 °C with the peaking position of 278, 301 and 333 °C, corresponding to the stepwise removal of the acid and base subunits continuously. For compound **4**, the TGA curve is more complicated. Four consecutive weight losses of **4** occur in the 70–900 °C range (peak position: 87, 120, 297 and 467 °C).

4 Conclusions

Developing reliable synthetic strategies of predictable and periodic superstructures is one of the ultimate aims of supramolecular chemistry. In this study, four new aromatic building blocks: m-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic acid, and 5-hydroxyisophthalic acid with robust hydrogen-bonded sites have been successfully employed to result in four salts. They exhibit that the polycarboxylic acids have robust hydrogen-bonded acceptors and piperazine is considered as an excellent supramolecular reagent to fulfill the multiform supramolecular network structure. It is proved that layers based on piperazine carboxylic co-crystals are useful for the structures of organic crystal engineering, because they are good supramolecular building modules which can produce supramolecular crystals.

It should be indicated that piperazine plays an important role in constructing the supramolecular structures of these organic solids, and its special nature is generally used to fulfill the diverse and abundant hydrogen-bonded patterns. As expected, the N atoms of piperazine cations act as significant hydrogen-bonded donors that crosslink the supra-

molecular structures. Similar 1D chain supramolecular structures of co-crystal **1**–**4** are N–H···O or O–H···O. However, further lattice packing managed by strong or weak interactions leads to the formation of distinct 3D or 2D networks. Cocrystallization of 5-hydroxyisophthalic acid with piperazine presents **4**, which has O–H···N hydrogen-bonding instead of N–H···O hydrogen-bonding. Further studies on such flexible building blocks are desirable to deepen understanding of the crystal engineering of hydrogen-bonded solids, and the related exploration on this perspective is underway.

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