Recurrence of Carboxylic Acid−Pyridine Supramolecular Synthon in the Crystal Structures of Some Pyrazinecarboxylic Acids

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X-ray crystal structures of pyrazinic acid **1** and isomeric methylpyrazine carboxylic acids **2**−**4** are analyzed to examine the occurrence of carboxylic acid−pyridine supramolecular synthon **V** in these heterocyclic acids. Synthon **V**, assembled by (carboxyl)O−H···N(pyridine) and (pyridine)-C−H···O(carbonyl) hydrogen bonds, controls self-assembly in the crystal structures of pyridine and pyrazine monocarboxylic acids. The recurrence of acid−pyridine heterodimer **V** compared to the more common acid−acid homodimer **I** in the crystal structures of pyridine and pyrazine monocarboxylic acids is explained by energy computations in the RHF 6-31G* basis set. Both the O−H···N and the C−H···O hydrogen bonds in synthon **V** result from activated acidic donor and basic acceptor atoms in **1**−**4**. Pyrazine 2,3- and 2,5-dicarboxylic acids **10** and **11** crystallize as dihydrates with a (carboxyl)O−H···O(water) hydrogen bond in synthon **VII**, a recurring pattern in the diacid structures. In summary, the carboxylic acid group forms an O−H···N hydrogen bond in pyrazine monocarboxylic acids and an O−H···O hydrogen bond in pyrazine dicarboxylic acids. This structural analysis correlates molecular features with supramolecular synthons in pyridine and pyrazine carboxylic acids for future crystal engineering strategies.

Introduction

The retrosynthesis of crystal structures from multifunctional molecules may be carried out with supramolecular synthons,[1] defined as structural units within supermolecules that can be assembled by hydrogen bonds and/or intermolecular interactions. Thus, crystal engineering[2] is a kind of supramolecular (noncovalent) synthesis of target crystal structures with hydrogen bonding as the key recognition element between molecules.[1,3] O−H···O, O−H···N, and N−H···O hydrogen bonds[4] are frequently used to construct crystalline architectures[5] because of their strength and directionality. Supramolecular synthons assembled with weak hydrogen bonds (C−H···O, C−H···N)[6] and heteroatom interactions (Br···Br, I···O, I···N)[7] have emerged in complementary strategies.[8] These studies have advanced our understanding of hydrogen bonding and heteroatom interactions for the construction of target nanostructures with desired architectures and functions. Some applications of supramolecular chemistry in organic synthesis include enantioselective reactions in a chiral host lattice,[9] catalysis in the constrained microenvironment,[10] and stereospecific topochemical reactions[11] between molecules aligned in the crystal.

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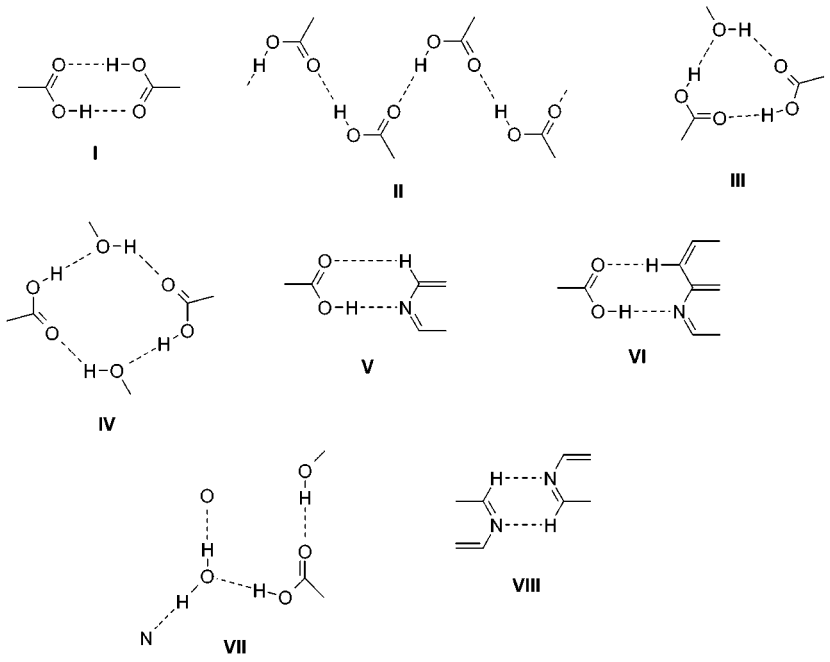
Scheme 1. Hydrogen Bond Synthons of Carboxylic Acid Discussed in This Paper



Hydrogen bond patterns of carboxylic acids in the solid state[12] are summarized in Scheme 1. Carboxylic acids are well known to form centrosymmetric dimer **I** as the dominant recognition motif; however, hydrogen bond catemer (or chain) **II** and single- and double-bridged aggregation motifs **III** and **IV** incorporating one and two alcohol (or water) molecules, respectively, are also known.[12d] There is a one-to-many relationship between the functional group present in the molecule and supramolecular synthons observed in the crystal structure, even for a strong O−H···O hydrogen bonding group like CO_2H. From a supramolecular retrosynthesis perspective, only those synthons that occur repeatedly in crystal structures, namely, robust synthons,[13] are useful in crystal design. In this context, the occurrence frequencies of 75 common ring motifs assembled with O/N−H···O/N hydrogen bonds in the Cambridge Structural Database (CSD, October 1996, ca. 160 000 entries) were classified recently.[14] Carboxylic acids are the second most common category of molecules archived in the CSD, with an occurrence frequency of 33% for dimer **I** formation. Furthermore, the probability increases to 96% in monocarboxylic acids when competing donor and acceptor groups are absent, making synthon **I** a robust and reliable crystal design element.

A perusal of supramolecular synthon schemes[1,13,14] shows that there are examples of bimolecular motifs with two strong hydrogen bonds or with two weak hydrogen bonds, but motifs with one strong and one weak bond are rare. However, as more crystal structures are deposited in the CSD (April 2001, 233 218 entries), new hydrogen bond patterns are discovered. A very recent database study[15] on carboxyl donors shows that recognition of CO_2H with pyridine is favored 10 times more through an O−H···N hydrogen bond compared to dimer **I** and catemer **II** motifs with itself. The participation of a weak C−H···O hydrogen bond between the pyridine and the acid results in heterodimer ring motif **V**. To our knowledge, synthon **V** is the only example of a mixed strong−weak hydrogen bonded motif, O−H···N and C−H···O, that has been systematically exploited in the crystal engineering of molecular complexes by a number of research groups.[16] These studies indicate that an acid−acid dimer (O−H···O) does not generally form when the pyridine functional group is present. However, both O−H···N and N^+−H···O^- hydrogen bondings are possible depending on the acidity of the CO_2H group and the basicity of the pyridyl moiety. For example, adducts of formic acid with pyridine crystallize as a 1:1 molecular complex and a 4:1 ionic salt.[17] In a variation to synthon **V**, and yet containing one strong and one weak hydrogen bond, supramolecular assemblies of predictable one- and two-dimensional arrays were constructed using cocrystals of carboxylic acids with phenazine (synthon **VI**).[18] Car-

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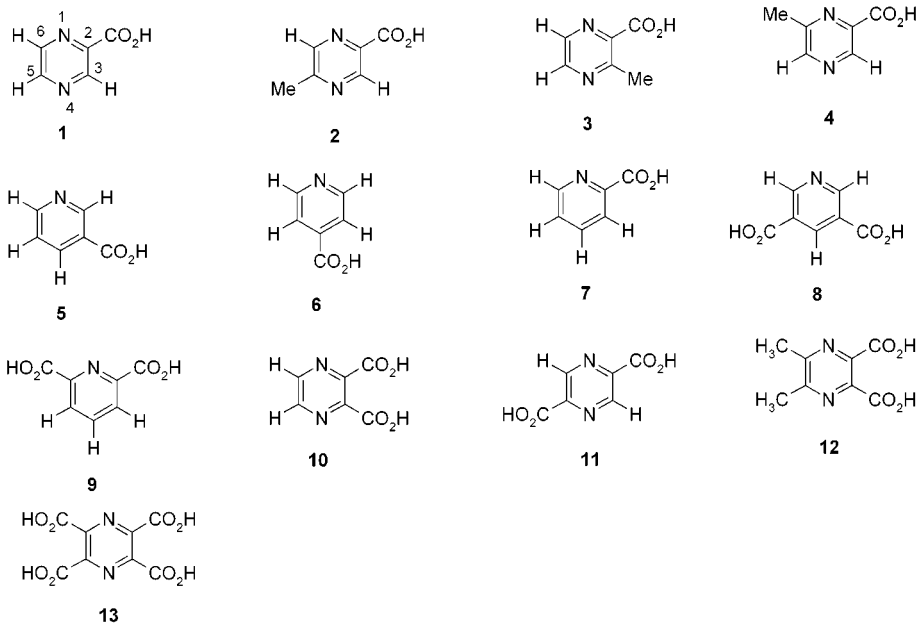
Scheme 2. Pyridine and Pyrazine Carboxylic Acids Analyzed in This Paper. Pyrazine Ring Atoms Are Numbered as Shown in 1, and the CH_3 Group is C7



boxylic acids that are insoluble in conventional solvents can be crystallized from pyridine as solvates[19] on the basis of the enthalpic advantage of multipoint recognition during crystallization.[20]

The examples cited above relate to molecular complexes. While binary crystals are excellent systems to study new synthons and their robustness, difficulties in obtaining a particular cocrystal because of mismatched solubility between the two components is a vexing problem. For example, Jones and co-workers[18] were interested in mixed crystals of terephthalic acid with phenazine to synthesize molecular tapes but instead had to use malonic acid because solubility considerations favored complexation with the latter acid. Generally, the more soluble component dictates the choice of complementary molecules in cocrystallization experiments. On the other hand, single-component crystals can be recrystallized from a wide variety of solvents depending on the solubility profile of that particular molecule. Therefore, one can systematically study crystal packing characteristics in a family of structures with the same functional group (e.g., CO_2H, $CONH_2$, OH) and different substituents (e.g., alkyl, phenyl, halogen), or with the same substituent in isomeric positions. Crystal engineering studies that deal with functional group ⇔ supramolecular synthon correlation in closely related structures continue to elicit interest from organic and supramolecular chemists.[5,8,21] By modifying the nature of donor and acceptor groups in a graded manner through chemical synthesis, it is possible to probe the supramolecular behavior of a particular synthon in the crystal. The idea in these studies is to find out the extent to which one can perturb the molecule and still obtain the same or similar crystal packing and also the limit at which a different hydrogen bond pattern is adopted.

Pyrazine carboxylic acids (Scheme 2), exemplified by pyrazinic acid **1**, are a rare category of molecules in the CSD.[22] In methylpyrazine carboxylic acids **2**−**4**, the CO_2H group and the pyridine moiety are covalently linked, thus overcoming the necessity of preparing molecular complexes as a route to studying synthon **V**. Crystal packing in some simple pyridine and pyrazine mono- and dicarboxylic acids may be summarized in the following manner:[23] acids **1**,[23d] **5**,[23f] **6**,[23e] and **8**[23b] contain synthon **V**; **9**[23a] and **10**[23c] crystallize as dihydrates via motif **VII**. In view of the structural diversity observed in the published crystal structures,[23] further studies on hydrogen bond patterns in pyrazine mono- and dicarboxylic acids will be useful in crystal engineering. The structures of acids **2**−**4** and diacid **11** were determined by single-crystal X-ray diffraction with the following objectives: (1) To find out the occurrence of synthon **V** in the family of substituted pyrazinic acids. This crystallographic study will complement earlier reports on molecular complexes. (2) To examine the formation of O−H···N and C−H···O hydrogen bonds in competing situations of donor acidity and acceptor basicity in the same crystal structure. (3)

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(22) Allen, F. H.; Kennard, O. *Chem. Des. Automat. News* **1993**, *8*, 31. The Cambridge Structural Database (April 2001, 233 218 entries) was searched for synthon **V** from good quality ($R < 0.10$) organic crystal structures in the normal distance−angle range: O−H···N (1.4−2.3 Å, 130−180°), C−H···O (2.0−3.0 Å, 110−180°), and the O−H and C−H distance was neutron normalized. Out of the 45 hits retrieved, 10 structures are single-component crystals and 35 are molecular complexes. The only example of a pyrazine carboxylic acid with synthon **V** in the database is **1**.

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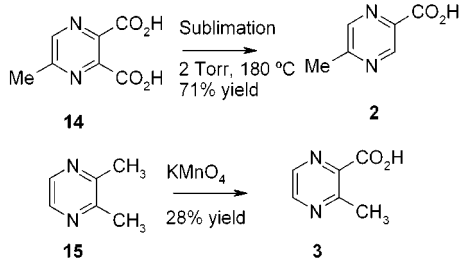
Table 1. Crystallographic Data and Structure Refinement Parameters

	2	**3**	**4**	**11**
empirical formula	$C_6H_6N_2O_2$	$C_6H_6N_2O_2$	$C_6H_6N_2O_2$	$C_6H_4N_2O_4{\cdot}2H_2O$
fw	138.13	138.13	138.13	204.14
crystal system	monoclinic	monoclinic	orthorhombic	triclinic
crystallization solvent	ethanol/water	hexane/EtOAc	hexane/EtOAc	20% aqueous HCl
space group	$P2_1/n$	$P2_1/c$	$Pca2_1$	$P\bar{1}$
a [Å]	4.1037(8)	5.0546(2)	14.494(3)	5.2101(2)
b [Å]	11.597(2)	13.2795(6)	3.8090(8)	6.8261(2)
c [Å]	13.556(3)	9.1067(4)	11.269(2)	6.8713(2)
α [deg]	90	90	90	119.144(2)
β [deg]	93.34(3)	95.315(3)	90	99.808(2)
γ [deg]	90	90	90	99.927(2)
Z	4	4	4	1
volume [Å^3]	644.0(2)	608.64(5)	622.1(2)	200.85(1)
λ [Å]	0.71073	0.71073	0.71073	0.71073
D_{calc} [g/cm^3]	1.425	1.507	1.475	1.688
μ [mm^{-1}]	0.110	0.116	0.114	0.153
2θ [°]	4.62−59.92	7.60−54.98	7.24−55.06	6.9−54.86
range h	0 to 5	−6 to 6	−18 to 18	−6 to 5
range k	0 to 16	−17 to 16	−4 to 4	−8 to 7
range l	−18 to 18	−11 to 11	−14 to 14	−8 to 8
reflections collected	1870	8509	3793	1268
unique reflections	1870	1392	1399	875
observed reflections	1265	1174	1346	781
R_1 [$I > 2\sigma(I)$][a]	0.063	0.040	0.027	0.032
wR_2 [all]	0.176	0.114	0.070	0.091
T [K]	293(2)	123(2)	173(2)	153(2)
Diffractometer	Nonius CAD4	Nonius CCD	Nonius CCD	Nonius CCD
C_k* [%][b]	69.5	74.3	72.7	77.1

[a] R_1, crystallographic reliability index. [b] C_k*, packing fraction calculated with PLATON.[46]

Scheme 3. Synthesis of Methylpyrazine Carboxylic Acids



To calculate the energy of heterodimer **V** and homodimer **I** in order to explain the preference for synthon **V** in the crystal structures of pyridine and pyrazine monocarboxylic acids. (4) The crystal structure of pyrazine-2,5-dicarboxylic acid **11** contains synthon **VII**, a new motif common to pyrazine diacids.

Results and Discussion

Acid **2** was obtained by vacuum sublimation of diacid **14** with concomitant decarboxylation.[24a] Acids **3** and **4** were synthesized by mono-oxidation of the corresponding dimethyl pyrazine with $KMnO_4$ (Scheme 3).[24b] Recrystallization of **2** from 4:1 EtOH/H_2O and of **3** and **4** from *n*-hexane/EtOAc afforded diffraction quality single crystals. Diacid **11** was recrystallized from 20% aqueous HCl. Details of X-ray data collection on crystals of **2**−**4** and **11** are listed in Table 1. The arrangement of molecules and hydrogen bonding interactions (Table 2) in these structures are analyzed and compared, specifically with reference to synthons **V** and **VII**.

Table 2. Geometrical Parameters of Hydrogen Bonds

acid	H-bond	d (Å)[a]	D (Å)	θ (deg)
1[b]	O−H···N[c]	1.68	2.66	173.4
	C3−H···O[c]	2.32	3.10	127.2
	C5−H···O	2.33	3.16	132.7
	C6−H···O	2.76	3.68	143.2
	C5−H···N	2.51	3.53	157.2
2	O−H···N[c]	1.70	2.683(1)	174.3
	C3−H···O[c]	2.49	3.294(2)	129.9
	C6−H···O	2.72	3.805(2)	172.1
	C6−H···N	2.43	3.158(2)	122.7
3	O−H···N[c]	1.67	2.655(1)	176.4
	C5−H···O[c]	2.42	3.227(1)	130.1
	C6−H···O	2.37	3.458(1)	175.5
	(Me)C7−H···O	2.76	3.633(1)	137.5
	C6−H···N	2.53	3.224(1)	120.6
4	O−H···N[c]	1.69	2.680(2)	177.5
	C3−H···O[c]	2.39	3.225(2)	132.3
	(Me)C7−H···O	2.54	3.540(2)	152.9
	(Me)C7−H···O	2.49	3.536(2)	160.1
	C5−H···N	2.62	3.658(2)	158.4
11	O−H···O(H_2O)[d]	1.54	2.514(1)	170.3
	(H_2O)O−H···O[d]	1.88	2.802(1)	153.5
	(H_2O)O−H···N[d]	1.88	2.849(2)	165.8
	C3−H···O	2.49	3.452(2)	146.3
12[e]	O−H···O(H_2O)[d]	1.55	2.527(1)	167.2
	(H_2O)O−H···O[d]	1.92	2.874(1)	162.4
	(H_2O)O−H···N[d]	1.97	2.896(1)	155.1
13[e]	O−H···O(H_2O)[d]	1.50	2.479(1)	170.3
	(H_2O)O−H···O[d]	1.74	2.701(1)	162.6
	(H_2O)O−H···N[d]	2.01	2.939(2)	156.1

[a] O−H and C−H distances are neutron-normalized to 0.983 and 1.083 Å. [b] Ref 23d. [c] Hydrogen bonds in synthon **V**. [d] Hydrogen bonds in synthon **VII**. [e] Ref 29.

The ORTEP plots of acids **2**−**4** (see Supporting Information for figures) show that the assignment of isomers in the literature is incorrect. Decarboxylation of diacid **14** afforded the 5-methyl isomer **2** and not the 6-methyl isomer **4**, as described in the preparation.[24a] The melting point of **2** is in agreement with the value reported in a later report.[24b] 6-Methyl isomer **4** was prepared in the

(24) (a) Leonard, F.; Spoerri, P. E. *J. Am. Chem. Soc.* **1946**, *68*, 526. (b) Pitre, D.; Boveri, S.; Grabitz, E. B. *Chem. Ber.* **1966**, *99*, 364. (c) For preparation of pyrazine dicarboxylic and related acids, see: Jones, R. G.; McLaughlin, K. C. *Organic Syntheses, Coll. Vol. 4*, 1963, 824.

same way as **3** by $CH_3 \rightarrow CO_2H$ oxidation (see Experimental Section for details).

Crystal Packing in Acids 1−4. 5-Methylpyrazine-2-carboxylic acid **2** crystallizes in the space group $P2_1/n$ ($Z = 4$). Screw axis related molecules form a zigzag, hydrogen bonded tape along [010] with synthon **V**. The metrics of O−H···N and C−H···O hydrogen bonds are 1.70 Å, 174.3° and 2.49 Å, 129.9°, respectively. O−H and C−H distances are normalized to the neutron diffraction value of 0.983 and 1.083 Å, respectively.[25] The hydrogen bonded tapes of synthon **V** are connected through C−H···N dimer **VIII** (2.43 Å, 122.7°) and C−H···O bond (2.72 Å, 172.1°) to produce a lamellar structure in the $(10\bar{2})$ plane (Figure 1a). It is difficult to assess whether the C−H···N or the C−H···O interaction is more significant in the bifurcated motif[26] of C6−H (atom numbering as in acid **1**, Scheme 2), because the former has a short-bent geometry while the latter is long-linear. It is likely that the layered structure of **2** is stabilized by a combination of synthon **V** and C−H···O/N hydrogen bonds; the sheets are in turn stacked with slight offset through van der Waals interactions (Figure 1b). Six molecules of **2** assemble in a brick-shaped array, with the hydrophobic core occupied by methyl groups of inversion-related molecules (Figure 1c). In 3-methylpyrazine-2-carboxylic acid **3** (space group $P2_1/c$, $Z = 4$), the layers are assembled with linear tapes of acid−pyridine synthon **V** and C−H···N dimer **VIII** (Figure 2, see Table 2 for hydrogen bond metrics). Compared to the brick pattern of **2**, hydrogen bonded molecules of **3** produce a hexagonal core that is occupied by methyl groups. The occurrence of C−H···N synthon **VIII** in these crystal structures is not surprising because this recognition motif was identified in a recent analysis of some pyrazine crystal structures.[27]

6-Methylpyrazine-2-carboxylic acid **4** crystallizes in the polar space group $Pca2_1$ ($Z = 4$). Zigzag tapes of 2_1-related molecules connected by synthon **V** (1.69 Å, 177.5°; 2.39 Å, 132.3°) along [001] extend into a pleated sheet through (pyrazine)C−H···N and (methyl)C−H···O (2.62 Å, 158.4°; 2.54 Å, 152.9°) hydrogen bonds (Figure 3). Cyclic C−H···N synthon **VIII** is not possible in **4** because ortho substituents flank the second N-atom. (Me)C−H···O and (pyrazine)C−H···N hydrogen bond chains run in opposite directions within a pleated layer. Significantly, adjacent layers stack in a parallel fashion resulting in the noncentrosymmetric, polar crystal structure. In centrosymmetric structures **2** and **3**, the layers stack with the more common antiparallel alignment. The arrangement of molecules and hydrogen bonding motifs in **4** are similar to the crystal structure of pyrazinic acid **1** ($Pna2_1$, $Z = 4$, $a = 11.35$ Å, $b = 7.36$ Å, $c = 6.45$ Å).[23d] In **1**, C5−H is involved in a bifurcated C−H···O/N motif while C6−H makes a long contact (Table 2, Figure 4). In methyl-substituted acid **4**, C5−H is engaged in a C−H···N interaction and the C6 position is occupied by a methyl group. Thus, replacement of H with Me at the position on the pyrazine ring that is only weakly C−H···O bonded

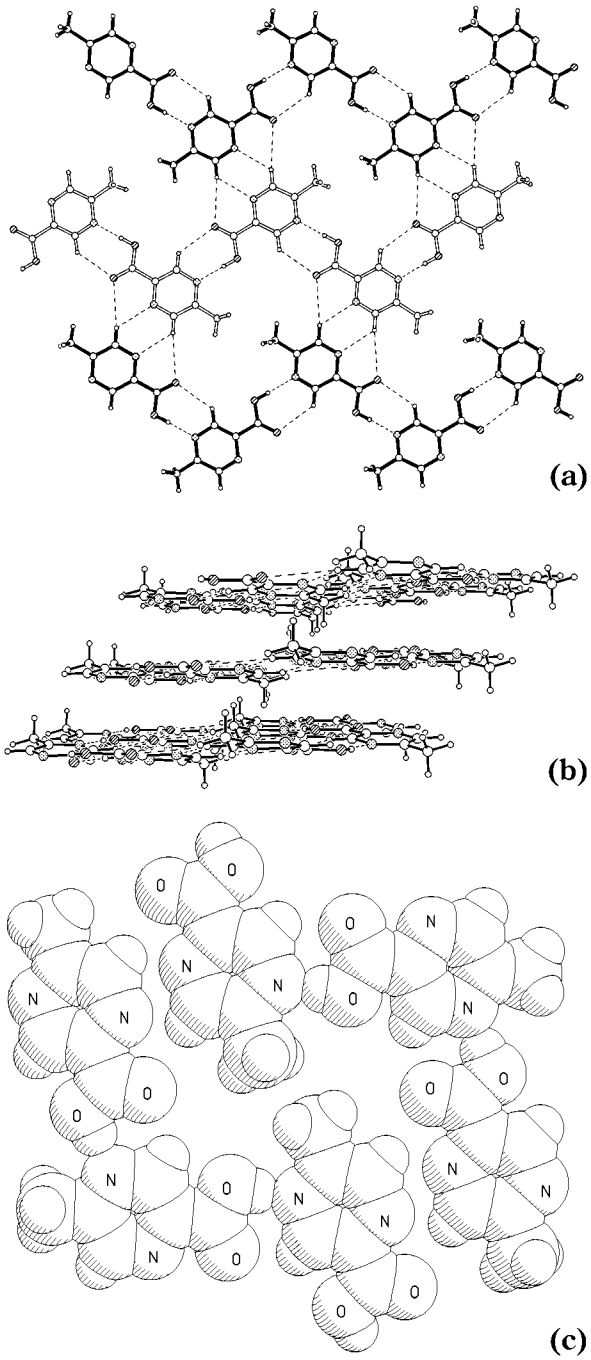


Figure 1. (a) Zigzag hydrogen bonded tapes mediated by synthon **V** along [010] in 5-methylpyrazine-2-carboxylic acid **2**. Inversion-related tapes (shaded differently) are connected by C−H···O/N hydrogen bonds (synthon **VIII**). (b) Interlayer region with a slight offset is stabilized by van der Waals interactions. (c) Space-filling representation of six molecules of **2** to show the rectangular array of 7.4 × 12.8 Å. Methyl groups fill the internal hydrophobic core.

results in minimal structural perturbation. A minor difference between these structures is that the layer is flat in **1** but pleated in **4**, a structural adjustment that accommodates the bulkier Me group in place of the H atom. The above analysis also explains why crystal structures of isomeric acids **2** and **3** are very different and adopt centrosymmetric packing in $P2_1/n$ and $P2_1/c$ space groups. Replacement of H with Me at the C3 or C5 position of **1** results in global structural changes

(25) Since H-atom positions are systematically underestimated and cannot be determined accurately by X-ray diffraction, D−H bonds are uniformly normalized to the neutron distance so that comparison of hydrogen bond geometry in different crystal structures is more reliable.

(26) If there are two acceptors bonded to the same H-atom, the motif is a bifurcated hydrogen bond. For a recent paper on bifurcated hydrogen bonds, see: Parra, R. D.; Zeng, H.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Eur. J.* **2001**, *7*, 4352.

(27) Thalladi, V. R.; Gehrke, A.; Boese, R. *New J. Chem.* **2000**, *24*, 463.

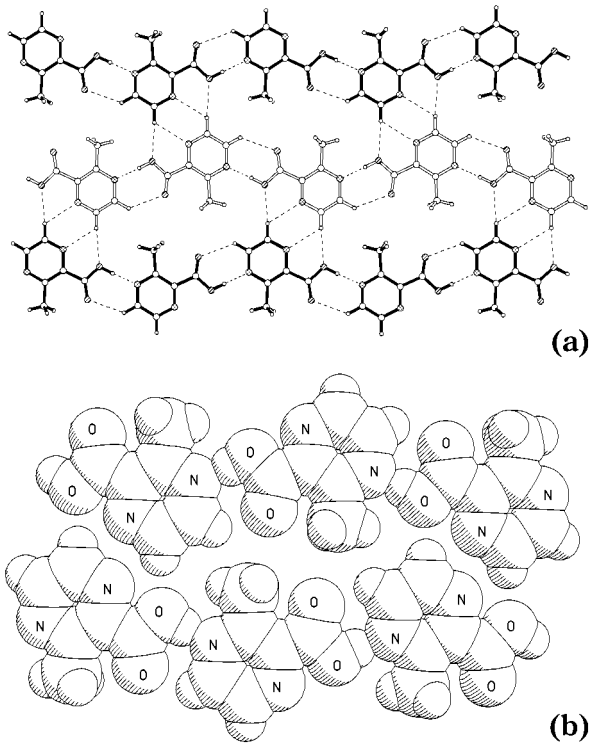


Figure 2. (a) Linear tapes of synthon **V** in 3-methylpyrazine-2-carboxylic acid **3**. Inversion-related tapes produce the layer structure in (101). (b) Space-filling view of the hexagonal array formed by six molecules of **3**.

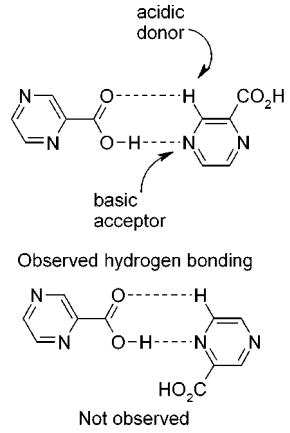
because these H atoms are intimately involved in hydrogen bonding.

Analysis of Synthon V in Acids 1−4. The recurrence of synthon **V** in the crystal structure of pyrazinic acids **1**−**4** confirms the robustness of this recognition motif. Since synthon **V** can result from more than one O−H···N hydrogen bond orientation in pyrazinic acids, the nature of acceptor group in these crystal structures was scrutinized. It is known that hydrogen bond strength increases with the acidity of the donor atom and the basicity of the acceptor group.[28] In acids **1**−**4**, the carboxyl O−H bonds to the more basic (electronegative) pyridine moiety, namely, the N-atom adjacent to the H/Me group, and not the N-atom ortho to the electron-withdrawing CO_2H group. Furthermore, this preference is observed even for the weak C−H···O hydrogen bond in pyrazinic acids **1** and **4**. The C3−H donor, activated by the ortho CO_2H group, forms the C−H···O bond that is part of synthon **V**, and not C5−H. Thus, both the CO_2H group and the H−C=N moiety form the best combination of O−H···N and C−H···O hydrogen bonds (synthon **V**) in pyrazinic acids **1**−**4** (Scheme 4). These results imply that not only the strong O−H···N (7−8 kcal/mol) but also the weak C−H···O (1−2 kcal/mol) hydrogen bond contribute to the stability of synthon **V**. This issue is substantiated by computation of charges on donor/acceptor atoms in pyrazinic acid **1** and energies of synthons **I**, **V**, and **VIII** later in this paper.

Hydrogen Bonding in Pyrazinic and Related Acids. We now compare crystal structures of pyrazinic acids **1**−**4** with pyridine carboxylic acids and pyrazine dicarboxylic acids, molecules that are less and more densely functionalized, respectively, than the title acids.

(28) (a) Ref 4b, pp 11−16. (b) Ref 6, pp 50−56.

Scheme 4. Selectivity in Hydrogen Bonding between the CO_2H Group and the Chemically Activated H−C=N Moiety



Acid−pyridine synthon **V** is present in nicotinic acid **5**,[23f] isonicotinic acid **6**,[23e] and dinicotinic acid **8**;[23b] picolinic acid **7**[23g] has a complex hydrogen bonding network between neutral and zwitterionic molecules. Pyrazine-2,3-dicarboxylic acid **10**[23c] crystallizes as a dihydrate with motif **VII**. A reason for the absence of synthon **V** in **10** could be either the inclusion of a water molecule that opens the possibility for a strong (carboxyl)-O−H···O(water) motif or because the *ortho* CO_2H group deactivates the pyrazine N-atom as the O−H···N acceptor. In any case, acid−acid homodimer **I** is not formed in pyrazine mono- and dicarboxylic acids. Since **10** is the only pyrazine diacid in the CSD, we determined the X-ray crystal structure of pyrazine-2,5-dicarboxylic acid **11**.

Pyrazine-2,5-diacid crystallizes as a dihydrate, **11**·2(H_2O) (space group $P\bar{1}$). The structure contains a (carboxyl)O−H···O(water) hydrogen bond (1.54 Å, 170.3°) that is part of motif **VII**. The carbonyl oxygen accepts a hydrogen bond from a water molecule (O−H···O=C: 1.88 Å, 153.5°), and the water molecule is polarized because it donates to the pyrazine N-atom (1.88 Å, 165.8°), resulting in a cyclic cooperative array (Figure 5). Crystals of **10**[23c] and **11**, as well as related compounds diacid **12**[29] and tetraacid **13**,[29] are hydrated because these molecules are rich in hydrogen bond acceptor groups (CO_2H, N-atom). The inclusion of water, a donor-rich molecule, compensates for this imbalance and completes the hydrogen bond network in these crystal structures.[30] The (carboxyl)O−H···O(water) hydrogen bond is short and linear compared to isolated hydrogen bonds of synthon **VII** in diacids **11**−**13** (Table 2). We have recently ascribed the unusual shortening of (carboxyl)O−H···O(water) (1.50 Å, O···O 2.479(1) Å, 170.3°) in pyrazine tetraacid **13** into the short hydrogen bond regime (O···O < 2.5 Å) to the cumulative stabilization from σ- and π-bond cooperativity in the extended array **VII**.[29]

A comparison of hydrogen bonding in closely related crystal structures gives an idea of the molecular features that favor the recurrence of a particular synthon and also of the factors that result in different crystal packing motifs. In the present case, acid−pyridine synthon **V** is

(29) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *Chem. Commun.* **2001**, 179.

(30) (a) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1991**, 426. (b) Krygowski, T. M.; Grabowski, S. J.; Konarski, J. *Tetrahedron* **1998**, *54*, 11311. (c) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *Acta Crystallogr.* **2000**, *C56*, 1512.

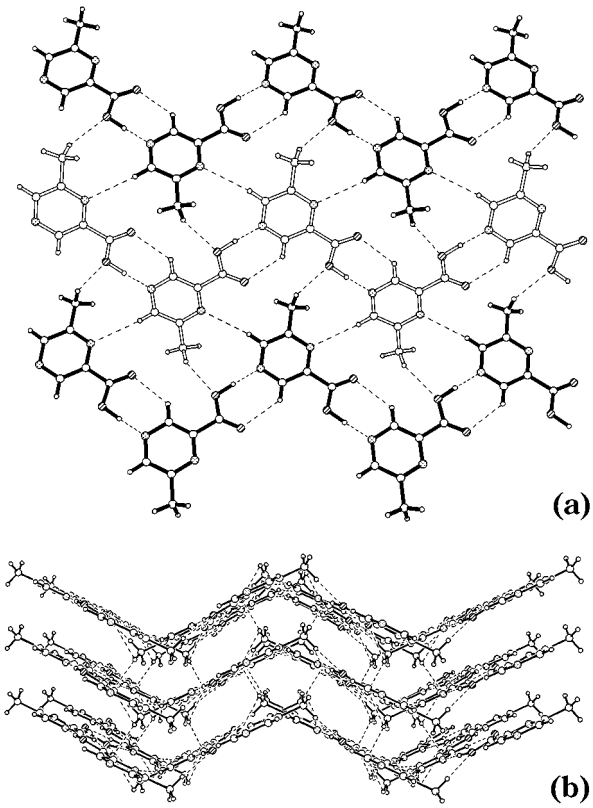


Figure 3. (a) Zigzag tapes of 6-methylpyrazine-2-carboxylic acid **4** assembled with synthon **V** along [001]. Translation-related tapes are connected by C−H···O/N hydrogen bonds into a pleated sheet structure. Note that synthon **VIII** is not possible here. (b) Stacking of pleated sheets with (Me)-C−H···O interactions between the layers.

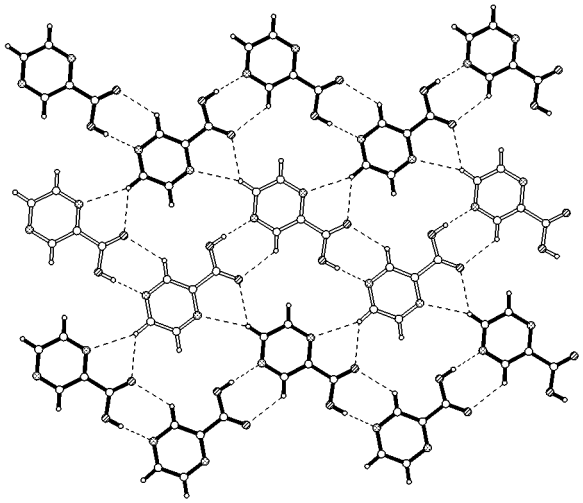


Figure 4. Laminated sheet parallel to (001) in pyrazinecarboxylic acid **1**. Note the similarity with Figure 3a. The layer in **1** is flat, while it is pleated in **4**.

a recurring (robust) structural pattern in pyridine and pyrazine monocarboxylic acids, while di- and tetraacids adopt motif **VII** in hydrate crystal structures (Table 3).[31] Such a molecule → synthon correlation is an essential exercise for the rational supramolecular synthesis of

(31) However, if a CO_2H group is present ortho to the pyridine/pyrazine N-atom (e.g., **7**, **10**, and **11**), then the likelihood of O−H···N hydrogen bonding is diminished because the adjacent electron-withdrawing group weakens the basicity of the N-acceptor.

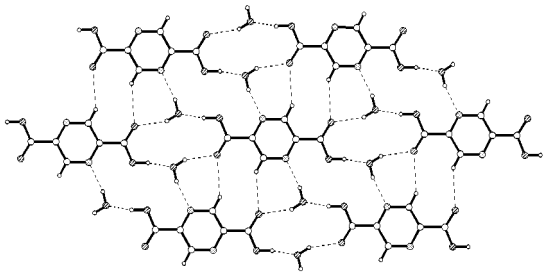


Figure 5. Lamellar structure parallel to $(1\bar{2}1)$ mediated by synthon **VII** in pyrazine-2,5-dicarboxylic acid **11**. Note that the extended hydrogen bond array O−H···O=C−O−H···OH_2···O/N is stabilized through cooperativity and polarization resulting in the short (strong) (carboxyl)O−H···O(water) hydrogen bond.

Table 3. Dominant Synthon in Some Pyridine and Pyrazine Carboxylic Acids

molecule	synthon	molecule	synthon
1	**V**	**8**	**V**
2	**V**	**9**	**VII**
3	**V**	**10**	**VII**
4	**V**	**11**	**VII**
5	**V**	**12**	**VII**
6	**V**	**13**	**VII**

target crystal structures from functionalized molecules.[13] While establishing such relationships, it may be noted that carboxylic acids participate in a variety of hydrogen bond motifs depending on the presence of other functional groups,[12d] activated C−H donors,[21c] and heterocyclic rings.[32] Therefore, reliable correlation is possible only within families of homogeneous crystal structures. As the structural diversity is expanded to cover the entire database,[14] the probability of the occurrence of the synthon is reduced.

RHF Computation of Charge and Energy. The next step in our study was to compute the energy of acid−pyridine synthon **V**, acid−acid synthon **I**, and pyridine dimer **VIII**.[33] Energies of these synthons were calculated in the Restricted Hartree−Fock (RHF) 6-31G* basis set using Spartan Pro 1.0.[34] The molecules selected for energy calculation are the 1:1 CH_3CO_2H−pyridine adduct and isonicotinic acid **6**, so that energies of these synthons may be compared in two types of chemical systems, molecular complexes, and in single-component crystals. The energy of the synthon was computed by calculating the difference between the minimized energy of the hydrogen bonded complex and that of the isolated molecules. For example, the energy of synthon **V** was calculated by optimizing the energy of CH_3CO_2H−pyridine complex and subtracting from this value the energy of CH_3CO_2H and pyridine molecules. The computed energy of synthons **I**, **V**, and **VIII** is listed in Table 4. The hydrogen bond geometry in the computed configuration was found to be in the normal distance−angle

(32) Pyrazole-4-carboxylic acid forms ribbons of O−H···N and N−H···O hydrogen bonds in the solid state: Foces-Foces, C.; Echevarría, A.; Jagerovic, N.; Alkorta, I.; Elguero, J.; Langer, U.; Klein, O.; Minguet-Bonvenhí, M.; Limbach, H.-H. *J. Am. Chem. Soc.* **2001**, *123*, 7898.

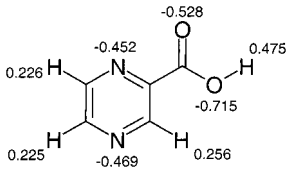
(33) For recent papers on hydrogen bond energy computations, see: (a) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750. (b) Kobko, N.; Paraskevas, L.; del Rio, E.; Dannenberg, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 4348. (c) Raymo, F. M.; Bartberger, M. D.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 9264.

(34) *Spartan Pro 1.0.*; Wave Function, Inc.: 18401 von Karman Avenue, Suite 370, Irvine, CA 92612.

Table 4. Energy of Synthons Calculated in RHF 6-31G* (in kcal/mol)

	CH_3CO_2H−pyridine	isonicotinic acid
synthon **V**	−9.95	−9.97
synthon **I**	−15.54	−15.62
synthon **VIII**	−2.50	−2.67

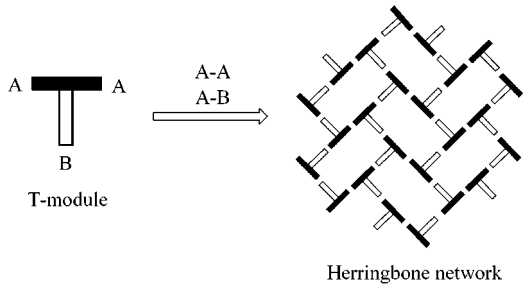
Scheme 5. Mulliken Charges on Donor and Acceptor Atoms in Pyrazinecarboxylic Acid 1



range for these interactions. From these data, it is clear that crystallization through heterodimer **V** ($2 \times -9.97 = -19.94$ kcal/mol) is energetically favored compared to a combination of O−H···O and C−H···N homodimers **I** and **VIII** [$-(15.62 + 2.67) = -18.29$ kcal/mol] by −1.65 kcal/mol in isonicotinic acid **6**. Similarly, the CH_3CO_2H−pyridine molecular complex formation is favored over acid−acid and pyridine−pyridine hydrogen bonded aggregates by −1.86 kcal/mol. Thus, the recurrence of mixed strong−weak hydrogen bonded synthon **V** in crystal structures is explained by energy considerations. The calculated Mulliken charge (RHF 6-31G*) on donor/acceptor atoms in pyrazinic acid **1** is displayed in Scheme 5. It is clear that the more basic N-acceptor (electronegative) and the more acidic C−H donor (electropositive) participate in the hydrogen bonds of synthon **V**. These charges are in agreement with the selectivity for the synthon formation summarized in Scheme 4.

It has been suggested in a recent paper[35] that formation of acid−pyridine synthon **V** may be rationalized by the formation of an O−H···N hydrogen bond between the best donor (CO_2H) and the best acceptor (pyridine N-atom) in the crystal. The electronegativity of the C=O oxygen is moderately better than the pyridine nitrogen in **1** on the basis of Mulliken charge (−0.528, −0.469 e). Our computations suggest that hydrogen bonding of carboxylic acid O−H group is equally likely with both C=O oxygen and pyridine N for electrostatic and basicity reasons. However, self-assembly of molecules in the crystal is favored via synthon **V** compared to synthon **I** because of energetic factors. Furthermore, depending on the pK_a of the carboxylic acid and pyridine, O−H···N hydrogen bonding will result when $\Delta pK_a < 3.75$ and proton transfer (hence salt formation) when $\Delta pK_a > 3.75$.[16g,36] The pK_a of pyrazinic acid **1** is 2.92[37] and that of pyridine is 5.23,[36,38] giving ΔpK_a of 2.31, a value that is in agreement with the O−H···N hydrogen bonding observed in these crystal structures. Since different atoms in different chemical environments are the potential acceptors, namely, C=O and pyridine−N, the final outcome in terms of the O−H···O vs O−H···N hydrogen bonding is determined by a combination of electronegativity and basicity factors. A hydrogen bond is a three-center, four-electron multicomponent interaction, and a dissection of the various contributions to the total energy is not trivial. Tables of hydrogen bond acidity and basicity constants for aliphatic, aromatic, and heterocyclic compounds published recently[39] should aid in our further understanding of hydrogen bonding in multifunctional molecules.

Scheme 6. Self-Assembly of a T-Module into a Herringbone Network



Herringbone Network in 5-Methylpyrazine-2-carboxylic Acid. The description of crystal structures as networks may be carried out by representing the molecules as nodes and the intermolecular interactions between them as node connectors.[40] The network representation facilitates the understanding of three-dimensional architectures and the comparison of structures assembled with the same or different molecular constituents. The topology of metal−organic crystal structures, or coordination polymers, is frequently described in terms of chain, ladder, brick wall, square grid, rhombus grid, and hexagonal networks.[41] Self-assembly of a T-module with recognition sites A, A, and B produces a herringbone network through one A−A and two A−B type metal−ligand or metal−metal bonding, or through hydrogen bonding in the case of an organic molecule (Scheme 6). For example, $[Cd_2(azpy)_3(NO_3)_4]$ (azpy = 4,4′-azopyridine) **16** is a T-shaped molecule in which pyridine rings of azpy B are nearly coplanar, while pyridine rings in azpy A have a dihedral angle of 65°. Recrystallization from ethanol/acetone afforded **16**·2Me_2CO, which exhibits a herringbone-type two-dimensional network[41,42] (Figure 6) with rectangular cavities of 23 × 11 Å. Acetone molecules are included in the voids of the triple-interpenetrated three-dimensional structure.

In the nomenclature of Scheme 6, acid **2** may be viewed as a T-shaped molecule (Figure 7a) with pyridyl groups making A-type hydrogen bonding and a carboxylic acid representing B-type recognition site. In the crystal structure of **2**, two acid−pyridine synthons **V** and one pyridine dimer **VIII** at each molecule (node) produce the herringbone network in the $(10\bar{2})$ plane (Figure 7b). Similarly, acid **3** exhibits a hexagonal network (Figure 7c). It may be noted that Cd···N bonding with A- and B-type azpy ligands in **16**·2Me_2CO is replaced by synthons **V** and **VIII** in **2**. In effect, the two-dimensional network formed by an organic molecule and a metal−

(35) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3240.
(36) Johnson, S. L.; Rumon, K. A. *J. Phys. Chem.* **1965**, *69*, 74.
(37) The Merck Index, 11th ed.; Merck & Co.: Rahway, 1989; p 1266.
(38) The pK_a of pyridinium ion is 5.23 (ref 36). This is taken as the approximate pK_a for the protonated form of pyrazine N4 in **1**.
(39) Abraham, M. H.; Platts, J. A. *J. Org. Chem.* **2001**, *66*, 3484.
(40) (a) Desiraju, G. R. *Chem. Commun.* **1997**, 1475. (b) Zaworotko, M. J. *Chem. Commun.* **2001**, 1.
(41) Kondo, M.; Shimamura, M.; Noro, S.; Minakoshi, S.; Asami, A.; Seki, K.; Kitagawa, S. *Chem. Mater.* **2000**, *12*, 1288.
(42) For other examples of two-dimensional herringbone networks, see: (a) Ref 40b. (b) Dong, Y.-B.; Layland, R. C.; Pschirer, N. G.; Smith, M. D.; Bunz, U. H. F.; Loye, H.-C. *Chem. Mater.* **1999**, *11*, 1413. (c) Carlucci, L.; Ciani, G.; Proserpio, D. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1799. (d) Masse, R.; Nicoud, J.-F.; Bagieu-Beucher, M.; Bourgogne, C. *Chem. Phys.* **1999**, *245*, 365. (e) Withersby, M. A.; Blake, A. J.; Champness, N. R.; Coole, P. A.; Hubberstey, P.; Schröder, M. *New. J. Chem.* **1999**, *23*, 573.

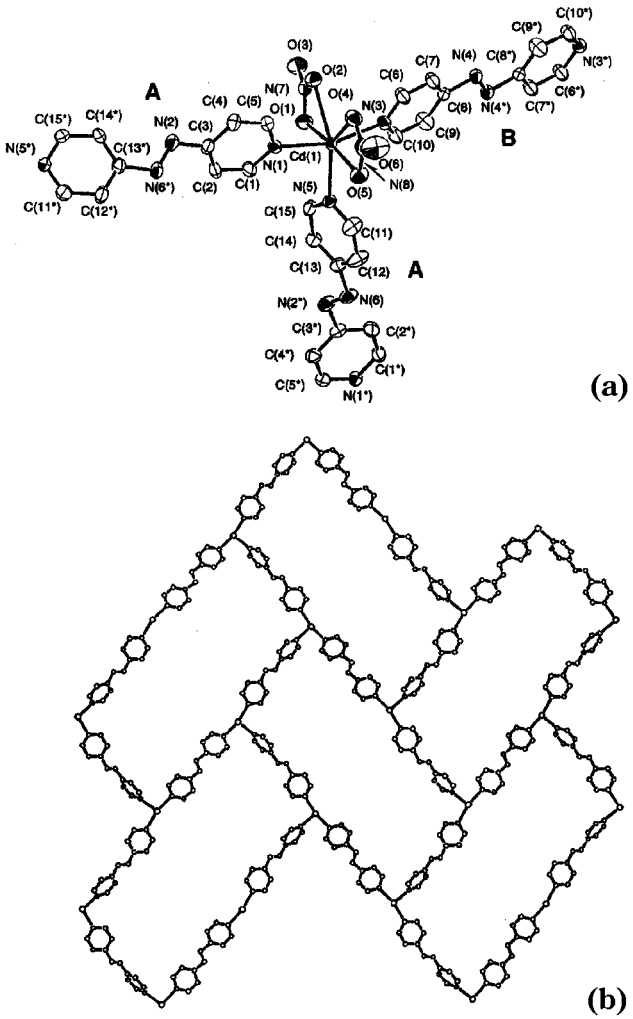


Figure 6. (a) ORTEP plot of T-shaped molecule **16** to show the A, A, and B sites. (b) Herringbone two-dimensional network formed by one A−A and two A−B type Cd···N interactions. (Adapted from ref 41.)

organic clathrate is identical. Such a topological comparison of crystal structures and their connectivity is possible only through the network representation. To our knowledge, acid **2** is the first example of an organic crystal structure with a herringbone network. Staircase-type networks have been recently identified in some organic structures.[11f,16e,30c]

Conclusions

We have studied hydrogen bonding supramolecular synthons in a family of crystalline pyrazine carboxylic acids by X-ray diffraction. Strong−weak O−H···N and C−H···O hydrogen bonded synthon **V** is a robust recognition motif that is largely insensitive to the substitution and placement of functional groups in pyridine and pyrazine monocarboxylic acids. However, a pyridyl N with an ortho CO_2H group is sufficiently deactivated that it does not form synthon **V**. Pyrazine dicarboxylic acids crystallize as dihydrates with a (carboxyl)O−H···O(water) hydrogen bond as the strong and dominant interaction in synthon **VII**. Our structural analysis shows that pyrazine mono- and dicarboxylic acids exhibit distinct hydrogen bonding patterns. The recurrence of acid−pyridine synthon **V** compared to the more common acid−

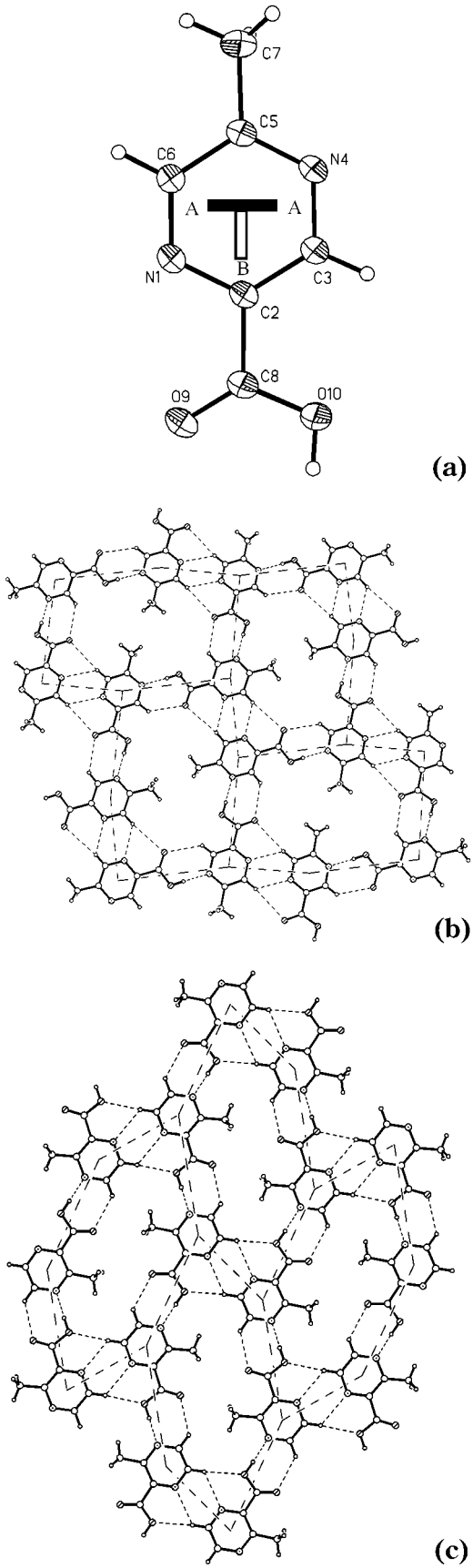


Figure 7. (a) ORTEP plot of 5-methylpyrazine-2-carboxylic acid **2** to show the A, A, and B hydrogen bonding sites. (b) Self-assembly of the T-shaped molecule **2** into a two-dimensional herringbone network via two A−B (synthon **V**) and one A−A (synthon **VIII**) type interactions. (c) Hexagonal network in 3-methylpyrazine-2-carboxylic acid **3**.

acid dimer **I** in these crystal structures is supported by ab initio computations. Synthon **V** results from hydrogen bonding between activated acidic donor and basic acceptor atoms.

Previous studies on molecular complexes of acid and pyridine derivatives have focused on the construction of one-dimensional tape and two-dimensional layer architectures from simple molecular building blocks. The lamellar and pleated architectures of pyrazinic acids discussed in this paper provide a novel system for the design of nanostructures from tailored molecules. The present study on pyrazine mono- and dicarboxylic acids examines crystal packing in complex and competing chemical environments and hence provides a better understanding of a useful supramolecular synthon in crystal engineering.

Experimental Section

Synthesis: 5-Methylpyrazine-2-carboxylic Acid 2.[24a] 5-Methylpyrazine-2,3-dicarboxylic acid **14** (250 mg, 1.4 mmol) was placed in a vacuum sublimation apparatus and decarboxylated by heating to 175−185 °C at 2 Torr. Yield: 130 mg (71%) of acid **2**. Mp: 167−8 °C (166−167 °C).[24b] ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H), 8.68 (s, 1H), 9.06 (s, 1H). IR (cm^{-1}): 3450, 2507, 1892, 1734, 1273, 1184.

3-Methylpyrazine-2-carboxylic Acid 3.[24b] To 1 mL (9.3 mmol) of 2,3-dimethylpyrazine **15** in 10 mL of water at 70−75 °C was added 3.3 g (20.9 mmol) of $KMnO_4$ in 50 mL of water. After decolorization of a purple color, the MnO_2 cake was filtered and washed with water several times. The filtrate was acidified to pH 1.5 with HNO_3 and the solution heated to 50 °C briefly, cooled to room temperature, and extracted with EtOAc. Workup afforded 350 mg (28%) of acid **3**. Mp: 170−1 °C. ^{1}H NMR (DMSO-d_6): δ 2.65 (s, 3H), 2.66 (s, 1H), 2.75 (s, 1H). IR (cm^{-1}): 3749, 1684, 1508, 1413, 1288, 1103.

6-Methylpyrazine-2-carboxylic Acid 4.[24b] Compound **4** was prepared in 21% yield using the above procedure starting from 2,6-dimethylpyrazine. Mp: 200−1 °C (201−202 °C). ^{1}H NMR (DMSO-d_6): δ 2.59 (s, 3H), 8.85 (s, 1H), 9.05 (s, 1H). IR (cm^{-1}): 3435, 1732, 1383, 1296, 1257, 1018.

Pyrazine-2,5-dicarboxylic Acid 11. Pyrazine-2,5-dicarboxylic acid 11 (dihydrate) was purchased from Acros Chemicals and used as received for crystallization.

Single crystals of acid **2** were obtained from 4:1 EtOH/H_2O; **3** and **4** from *n*-hexane/EtOAc; and **11** from 20% aqueous HCl.

X-ray Diffraction. Reflections were collected on an Enraf-Nonius CAD-4 diffractometer (for acid **2**) and on a Nonius Kappa CCD diffractometer (for acids **3**, **4**, and **11**). The incident radiation is Mo Kα X-ray (λ = 0.71073 Å) on both instruments. Data on the crystal of **2** was collected at 293 K, and crystals of **3**, **4**, and **11** were cooled with an Oxford Cryostream device attached to the CCD machine. Data reductions were performed using Xtal 3.5 (CAD-4) and DENZO−SMN (CCD).[43] Structures were solved by direct methods using the SHELXS-97 program and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for the non-H atoms using the SHELXL-97 program.[44] The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0415*P)^2 + (0.9360*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. Equations for calculating $R(F)$, $R_w(F^2)$, and the goodness of fit, S, are given below. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are taken from the International Tables for X-ray Crystallography.[45] Geometrical analysis was carried out in PLATON[46] on a Silicon Graphics Octane2 workstation. Details of cell parameters, data collection, and structure refinement are summarized in Table 1. Hydrogen bond metrics are listed in Table 2. $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$, where w is the weight given to each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\Sigma(F_o))$. $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

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Supporting Information Available: X-ray data with details of refinement procedures (cif files) and ORTEP plots of acids **2**−**4** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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