CHAPTER TWO
CARBOXYLIC ACID–PYRIDINE SUPRAMOLECULAR SYNTON

2.1 Introduction

Crystal engineering is the design and construction of target crystal structures from molecular components. It is a type of non-covalent synthesis of target crystal structures with hydrogen bonding as the key recognition element between molecules. A crystal structure may be analyzed in terms of supramolecular synthons and crystal engineering carried out by the identification of a molecular skeleton with specific functional groups that will predictably and persistently lead to robust synthons and therefore to the desired crystal structure. The repeating array in a crystal structure may be a single interaction, a small pattern, or a larger pattern. The subjective distinction between a pattern and a supramolecular synthon is based on its frequency of occurrence and is thus related to its reliability as an indicator of crystal packing. If a pattern appears repeatedly enough, then it may more confidently be termed as a synthon. The more often a synthon occurs within a family or across families of compounds, the more robust and useful it is in crystal design.

Carboxylic acids are among the most common hydrogen bond functionalities in crystal engineering. The crystal packing patterns of various carboxylic acids have been examined in depth and thus they are considered as the most important building blocks in deliberate crystal design. Since they possess a hydrogen bond donor as well as an acceptor site, carboxylic acids are well-known to form centrosymmetric dimer I as the dominant recognition motif; however, hydrogen bond catemer II, and singly/doubly bridged aggregation motifs III and IV incorporating one or two alcohol (or water) molecules are also known (scheme 1).

Formation of motif I is not very reliable and in competitive situations, it is often displaced by other hydrogen bond configurations. In a recent database analysis,
Scheme 1. Hydrogen bond synthons of carboxylic acid discussed in this chapter.

Allen et al. determined the global probabilities of formations of 75 bimolecular hydrogen bonded ring synthons in organic crystal structures. Carboxylic acids are the second most common category of molecules archived in the Cambridge Crystallographic Database (CSD). For the carboxylic acid dimer motif I, the probability of formation is found to be only 33% averaged over all competitive situations and this relatively low probability is explained by competition with other hydrogen bonded acceptors (e.g. COO\textsuperscript{-}, pyridine N, S=O, P=O). However, the
probability increases to 96% in mono-carboxylic acids when competing donor and acceptor groups are absent, making synthon I a robust and reliable crystal design element.

2.2 Complementarity of Carboxylic Acid with Pyridine Functional Group

Many of the best-known supramolecular synthons rely on the complementarity of two hydrogen-bonding groups. Such complementarity of two motifs has been utilized to synthesize many supramolecular architectures. A perusal of supramolecular synthon schemes\textsuperscript{3,5,6} 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 new hydrogen bond patterns are discovered. A recent database study by Steiner\textsuperscript{7} on carboxyl donors shows that recognition of CO\textsubscript{2}H with pyridine is 9 times favoured through O–H⋯N hydrogen bond compared to dimer I and catemer II motifs with itself. The participation of weak C–H⋯O hydrogen bond between pyridine and acid results in heterodimer ring motif V. The study indicates that the acid-acid dimer motif I does not generally form when a better acceptor is present in the system. Thus crystal design may be implemented by exploiting robust recognition in a heterosynthon. The carboxylic acid-pyridine synthon is the most reliable supramolecular motif and exploited in crystal engineering to obtain desirable architectures.\textsuperscript{8} Synthon V has been used to design liquid-crystalline materials, two-dimensional β-networks and to expand the trimesic acid (TMA) honeycomb network. Furthermore, depending on the pK\textsubscript{a} of carboxylic acid and pyridine, O–H⋯N hydrogen bonding will result when ΔpK\textsubscript{a} < 3.75 and proton transfer when ΔpK\textsubscript{a} > 3.75.\textsuperscript{8c,9} The pK\textsubscript{a} of pyrazinic acid is 2.92\textsuperscript{10} and pyridine 5.23 giving ΔpK\textsubscript{a} of 2.31, a value that is in agreement with O–H⋯N hydrogen bonding observed in these crystal structures. For example, adducts of formic acid with pyridine crystallize as 1:1
molecular complex and also as a 4:1 ionic salt.\textsuperscript{11} Cyclohexane-1, 3\textit{cis}, 5\textit{cis}-
tricarboxylic acid (CTA) forms O–H⋯N hydrogen bond with 4,4′-bipyridine and 12-
\textit{bis}(4-pyridyl)ethane whereas proton transfer occurs with 1,2-\textit{bis}(4-pyridyl)ethylene and 
\textit{trans}-1,4-\textit{bis}(2-(4-pyridyl)ethenyl)benzene.\textsuperscript{12} In a variation to synthon V, and 
containing one strong (O–H⋯N) and one weak (C–H⋯O) hydrogen bond, 
supramolecular assemblies of predictable one- and two-dimensional arrays were 
constructed using co-crystals of carboxylic acids with phenazine (synthon VI).\textsuperscript{13}

23 Advantages of Single Component Over Binary System

While binary crystals are excellent systems to study new synthons and their 
robustness, difficulties in obtaining a particular co-crystal because of mismatched 
solubility between the two components is a vexing problem. For example, Jones and 
co-workers\textsuperscript{13b} were interested in mixed crystals of terephthalic acid with phenazine to 
synthesise molecular tapes but instead had to use malonic acid because solubility 
considerations favoured complexation with the latter acid. Recently our research 
group have identified, \textit{trans}-1,4-dithiane-1,4-dioxide as a new spacer ligand for 
carboxylic acids.\textsuperscript{14} The molecule is highly soluble in water but almost insoluble in 
organic solvents. Only four co-crystals were isolated among a large number of acids 
used in crystallization experiments even though the acid–sulfoxide synthon is 
calculated to be more stable than acid-acid and sulfoxide-sulfoxide recognition. This 
could be because the sulfoxide is strongly hydrogen bonded to water molecules and 
so it does not form complexes readily. Generally, the more soluble component 
dictates the choice of complementary molecules in co-crystallization 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\textsubscript{2}H, CONH\textsubscript{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. By modifying the nature of donor and acceptor groups in a graded manner through chemical synthesis, it is possible to probe the supramolecular behaviour 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 yet obtain the same or similar crystal packing, and also the limit at which a different hydrogen bond pattern is adopted.

2.4 Objective of the Study

Pyrazine carboxylic acids are exemplified by pyrazinic acid, 1 (scheme 2) a rare category of molecules in the CSD. The crystal 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 heterosynthon V in the family of substituted pyrazinic acids. (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) 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 **mono-carboxylic** acids. (4) The crystal structure of pyrazine-2,5-dicarboxylic acid 11 contains synthon **VII**, a new motif common to pyrazine di- and tetracarboxylic acids.

2.5 5-Methylpyrazine-2-Carboxylic Acid, 2

5-Methylpyrazine-2-carboxylic acid, 2 crystallizes in the monoclinic crystal system (space group **P2_1/n**, Z = 4). Screw axis related molecules form a zigzag, hydrogen bonded tape along [0 1 0] with synthon V. The metrics of O-H⋯N and C-
Hydrogen bonds are 1.70 Å, 174.3° and 2.49 Å, 129.9°. The hydrogen bonded tapes of synthon V are connected through C–H⋯N dimer VIII (2.43 Å, 122.7°) and C–H⋯O bonds to produce a lamellar structure in the (102) plane (Figure 1). It is likely that the layered structure of 2 is stabilised 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. Six molecules of 2 assemble in a brick-shaped array, with the hydrophobic core occupied by methyl groups of inversion related molecules. The metrics of intermolecular distances are shown in Table 1.

Scheme 2. Pyridine and pyrazine carboxylic acids analyzed in this chapter.
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) Space-filling representation of six molecules of 2 to show the rectangular array of 12.8 x 7.4 Å. Methyl groups fill the internal hydrophobic core.
Table 1. Geometrical parameters of selected intermolecular interactions.

<table>
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<tr>
<th>Acid</th>
<th>Interaction</th>
<th>$d$ (Å)</th>
<th>$D$ (Å)</th>
<th>$\theta$ (°)</th>
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<td>1</td>
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</table>

$^a$O–H and C–H distances are neutron-normalized to 0.983 and 1.083 Å. $^b$Ref. 18. $^c$Hydrogen bonds in synthon V. $^d$Hydrogen bonds in synthon VII. $^e$Ref. 19.
2.6 3-Methylpyrazine-2-Carboxylic Acid, 3

3-Methylpyrazine-2-carboxylic acid, 3 crystallizes in the monoclinic system with one molecule in the asymmetric unit (space group $P2_1/c$, $Z = 4$). Screw related molecules are assembled with linear tapes of acid–pyridine synthon $V$ (1.67 Å, $176.4^\circ$; 2.42 Å, $130.1^\circ$) along [1 0 –1] direction which are in turn connected by weak centrosymmetric C–H···N dimer motif $\mathrm{VHII}$ and C–H···O hydrogen bonds (Figure 2). Compared to the brick pattern of 2, hydrogen bonded molecules of 3 produce a pseudo-hexagonal core that is occupied by methyl groups.

2.7 6-Methylpyrazine-2-Carboxylic Acid, 4

6-Methylpyrazine-2-carboxylic acid, 4 crystallizes in the polar space group $Pca2_1$ with one molecule in the asymmetric unit ($Z = 4$). Zigzag tapes of 2$_1$-related molecules connected by synthon $V$ (1.69 Å, $177.5^\circ$; 2.39 Å, $132.3^\circ$) along [0 0 1] extend into a pleated sheet through (pyrazine)C–H···N and (methyl)C–H···O hydrogen bonds (Figure 3). Cyclic C–H···N synthon $\mathrm{VIII}$ 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 non-centrosymmetric, polar crystal structure. In centrosymmetric structures 2 and 3, the layers stack with the more common anti-parallel alignment. The arrangement of molecules and hydrogen bonding motifs in 4 are similar to the crystal structure of pyrazinic acid 1 ($Pna2_1,Z = 4$).$^{18}$

In the structure 1, C5-H is involved in a bifurcated C–H···O/N motif while C6–H makes a long contact (Table 1, Figure 4). In methyl-substituted acid 4, C5-H is engaged in a C–H···N interaction and C6 position is occupied by methyl group. Thus, replacement of H with Me at the position on the pyrazine ring that is only weakly C-H···O bonded 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 H atom. The above analysis also explains why crystal structures of isomeric acids 2 and 3 are very different and adopt centrosymmetric packing in $P2\tilde{n}1$ and $P2\tilde{n}c$ space groups. Replacement of H with Me at C3 or C5 position of 1 results in global structural changes because these H atoms are intimately involved in hydrogen bonding.

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) Pseudo-hexagonal network of 3.
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. Notice that synthon VIII is not possible here. (b) Stacking of pleated sheets with (Me)C–H···O interactions between the layers.
2.8 Pyrazine-2,5-Dicarboxylic Acid, 11

Pyrazine-2,5-dicarboxylic acid, 11 crystal structure is analysed in order to compare this structure with the 2,3-diacid. Pyrazine-2,5-diacid crystallizes as a dihydrate, 11•2(H$_2$O) (space group $P\bar{1}$). The structure contains a short (carboxyl)O–H···O(water) hydrogen bond (1.54 Å, 170.3°) that is part of motif VII. The carbonyl oxygen accepts hydrogen bond from a water molecule (O–H···O=C: 1.88 Å, 153.5°) and the water molecule is polarised because it donates to the pyrazine N-atom (1.88 Å, 165.8°), resulting in a cyclic cooperative array (Figure 5).
Figure 5. Lamellar structure parallel to (1 2 1) mediated by synthon VII in pyrazine-2,5-dicarboxylic acid 11. The extended hydrogen bond array $\text{O-H}\cdots\text{O}=\text{C}=\text{O}-\text{H}\cdots\text{O}^2\cdots\text{O}/\text{N}$ is stabilized through cooperativity and polarisation resulting in the strong (carboxyl)$\text{O-H}\cdots\text{O}(\text{water})$ hydrogen bond.

2.9 Hierarchy in Acid-Pyridine Recognition

The recurrence of synthon V in 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 are scrutinized. It is known that hydrogen bond strength increases with acidity of the donor atom and basicity of the acceptor group. Predictable target architectures result from hydrogen bond hierarchy rules formulated by Etter: the best donor hydrogen bonds to the best acceptor and the second best donor and acceptor groups hydrogen bond next. In acids, 1-4 the carboxyl O-H bonds to the more basic pyridine moiety, namely the N-atom adjacent to the H/Me group, and not the N-atom ortho- to the electron-withdrawing CO$_2$H group. Furthermore, this preference is observed even for the weak C-H···O hydrogen bond in pyrazinic acids 1 and 4. C3-H donor, activated by the ortho- CO$_2$H group, forms the C-H···O bond that is part of synthon V, and not C5-H. Thus, both the CO$_2$H 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 3). 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 VII later in this chapter.

![Observed hydrogen bonding](image1)

![Not observed](image2)

Scheme 3. Selectivity in hydrogen bonding between CO₂H group and chemically different H-C=N moiety.

2.10 Supramolecular Synthons in Pyridine and Pyrazine mono and dicarboxylic Acids: Synthon V vs VII

A comparison of hydrogen bonding in closely related crystal structures gives an idea of the molecular features that favour the recurrence of a particular synthon and also of the factors that result in different crystal packing motifs. Crystal structures of pyrazinic acids 1–4 were compared with pyridine and pyrazine mono and dicarboxylic acids. Crystal packing in some simple pyridine and pyrazine mono- and dicarboxylic acids may be summarised as follows: pyrazine mono carboxylic acids 1-4, nicotinic acid 5, isonicotinic acid 6, and dinicotinic acid 8 contain synthon V; dipicolinic acid 9, pyrazine-2,3-dicarboxylic acid 10, pyrazine-2,5-dicarboxylic
acid 11, 5,6-dimethylpyrazine-2,3-dicarboxylic acid 12 and pyrazine-2,3,5,6-tetracarboxylic acid 13 crystallize as dihydrates via motif VII. Picolinic acid 7 has a complex hydrogen-bonding network between neutral and zwitterionic molecules. Crystals of 10 and 11, as well as related compounds diacid 12 and tetraacid 13, are hydrated because these molecules are rich in hydrogen bond acceptor groups (CO2H, N-atom). The inclusion of water, a donor rich molecule, compensates this imbalance and completes the hydrogen bond network in these crystal structures. The (carboxyl)O–H···O(water) hydrogen bond is short and linear compared to isolated hydrogen bonds of synthon VII (Table 1). A reason for the absence of synthon V in 10-13 could be either the inclusion of water molecule that opens the possibility for strong (carboxyl)O–H···O(water) motif, and/or because the ortho- CO2H group deactivates the pyrazine N-atom as the O–H···N acceptor. A very short (carboxyl)O–H···O(water) hydrogen bond in the crystal structure of 13 is attributed to the cumulative stabilization from σ- and n- bond cooperativity, a phenomenon that will be discussed in Chapter 4. In any case, acid-acid homodimer I is not formed either in pyrazine mono- or di-carboxylic acids. Acid-pyridine synthon V is a recurring (robust) structural pattern in pyridine and pyrazine mono-carboxylic acids while di- and tetra-acids adopt motif VII in hydrate crystal structures (Table 2). Such a molecule → synthon correlation is an essential exercise for the rational supramolecular synthesis of target crystal structures from functionalised molecules. 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, activated C–H donor, and heterocyclic ring. Therefore, reliable correlation is possible only within families of homogeneous crystal structures. As the structural diversity is expanded to cover the entire database, the probability of occurrence of the synthon is reduced.
2.11 Restricted Hartree Fock Computation of Charge and Energy

The synthon energy\(^{30}\) of acid-acid I, acid-pyridine V and pyridine dimer VHI were calculated in Restricted Hartree Fock (RHF) with 6-31G* basis set using Spartan program.\(^{31}\) The molecules selected for energy calculation are the 1:1 \(\text{CH}_3\text{CO}_2\text{H}\text{-pyridine}\) adduct and isonicotinic acid 6 so that energies of these synthons may be compared in two types of chemical systems, molecular complex and single molecule. Energy of the synthon was computed by calculating the difference between the minimised energy of the hydrogen bonded complex and that of the isolated molecules. For example, energy of synthon V was calculated by minimizing the energy of \(\text{CH}_3\text{CO}_2\text{H}\text{-pyridine}\) complex and subtracting from this value the energy of \(\text{CH}_3\text{CO}_2\text{H}\) and pyridine. The computed energy of synthons I, V and VIII is listed in Table 3. The hydrogen bond geometry in the minimized configuration is in the

\[
\begin{array}{cccc}
\text{Molecule} & \text{Synthon} & \text{Molecule} & \text{Synthon} \\
1 & V & 8 & V \\
2 & V & 9 & VII \\
3 & V & 10 & VII \\
4 & V & 11 & VII \\
5 & V & 12 & VII \\
6 & V & 13 & VII \\
\end{array}
\]

**Table 2.** Dominant synthon in some pyridine and pyrazine carboxylic acids

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\(^{30}\) Synthon energy

\(^{31}\) Spartan program
normal distance-angle range for these interactions. From these data it is clear that crystallization through heterodimer V (2 x -9.97 = -19.94 kcal/mol) is energetically favoured compared to a combination of O–H···O and C–H···N homosynthons I and VIII [–(15.62 + 2.67) = -18.29 kcal/mol] by -1.65 kcal/mol in isonicotinic acid 6. Similarly acid-pyridine molecular complex formation is favoured 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 on energy considerations. Recently our research group have shown that the acid–sulfoxide recognition is favoured over acid-acid and sulfoxide-sulfoxide dimer synthon by -4.7 kcal/mol. A possible reason why crystal structures with combination of strong and weak hydrogen bond synthons are formed is that propagation in crystal nuclei into larger aggregates and then to stable crystal is more likely in the former case. Crystal structures with isoenergetic combination of strong-strong and weak-weak hydrogen bonding motifs presumably dissociate at the weak-weak interface prior to reaching the final stages of crystallization. The calculated Mulliken charge (RHF/6-31G*) on donor/acceptor atoms in pyrazinic acid 1 is displayed in Scheme 4. 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 synthon formation summarised in Scheme 3.

<table>
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<th>Synthon</th>
<th>Isonicotinic acid</th>
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<tr>
<td>V</td>
<td>-9.97</td>
<td>-9.95</td>
</tr>
<tr>
<td>VHI</td>
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Aaker6y has suggested in a recent paper6 that formation of acid-pyridine synthon V may be rationalised by the formation of O–H⋯N hydrogen bond between the best donor (CO2H) and best acceptor (pyridine N atom) in the crystal, based on the hydrogen bond rules formulated by Etter. The electronegativity of the C=O oxygen is moderately better than the pyridine nitrogen in 1 based on Mulliken charge (−0.528 e, −0.469 e). 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 favoured via heterosynthon V compared to homosynthon I because of energetic factors. Since different atoms in different chemical environments are the potential acceptors, namely C=O and pyridine-N, the final outcome in terms of 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-centre four-electron multi-component interaction and a dissection of the various contributions to the total energy is non-trivial. The issue of hydrogen bonding in competitive situations is discussed in more detail in chapter 5.
2.12 Networks

The description of crystal structures as networks may be carried out by representing the molecules as points or nodes and the intermolecular interactions connecting the molecules as node connectors. The network representation facilitates in the understanding of 3D architectures and in the comparison of structures assembled with the same or different molecular constituents. The network topology in coordination polymers can be usually designed by selecting the coordination geometry of metal and the chemical structure of organic ligand. A metal geometry of particular interest because of its potential range of network structures is simple and prototypal "T-shaped" module. The T-shape node has thus far produced examples of 1D, 2D and 3D networks. Self-assembly of T-node molecules with three recognition sites can produce ladder, brick wall, herringbone or bilayer networks in crystal structures as shown in Scheme 5. 2D brick wall and herringbone networks are topologically identical to the honeycomb grid because these are (6,3) nets. Ladder, brick wall, herringbone, and bilayer networks are relatively common in coordination polymers, i.e., crystal structures assembled with metal-ligand and hydrogen bonds. However, examples of organic structures in these network categories are rare.

2.12.1 Coordination Polymer and Organic T-Modules: Recent Literature

The T-node coordination polymers that produce network structures with (6,3) topology may be obtained with a 1:1.5 ratio of metal ions to a linear spacer ligands (such as 4,4'-bipyridine, 4,4'-azopyridine, 1,2-dipyridyl ethane etc.). For example, the metal complex \([\text{Cd}_2(\text{azpy})_3(\text{NO}_3)_4]\) was obtained by reaction of cadmium(II)nitrate and 4,4'-azopyridine (azpy) in ethanol/acetone (2:3 ratio). The cadmium has distorted pentagonal bipyramidal geometry with three pyridyl nitrogen atoms and four oxygen atoms of two bidentate nitrate anions. A T-shaped module is recognized from the geometry. The two pyridine rings of the azpy B are nearly
coplanar, while the two pyridine rings of the azpy A is not coplanar with dihedral angle of $65^\circ$. 14 exhibits a herringbone type 2D network, (Figure 6) which is comprised of rectangular cavities with dimensions of 23 x 11 Å. Such networks are triply interpenetrated. Despite the interpenetration, there are channels (about 5 x 5) in the sheets, which include acetone molecules.

Scheme 5. Self-assembly of a T-module into (a) Brick Wall, (b) Herringbone, (c) Ladder, (d) Bilayer, (e) Long and short brick, (f) Basket Weave. Motifs (e) and (f) are yet to be realized.
Figure 6. (a) ORTEP plot of T-shaped molecule 14 to show the A, A and B sites. (b) Herringbone 2D network formed by one A-A and two A-B type Cd···N interactions.

The factors that should be considered for the crystal engineering of organic networks with T-modules are: (i) a T-geometry at the metal centre is easily achieved in square planar, octahedral and trigonal bipyramidal coordination with appropriate ligands, but it is difficult to design a T-shaped organic molecule given that the
standard angles at carbon are 109°, 120° or 180°; (ii) in coordination polymer networks, the metal atom acts as the node and the ligands serve as the node connectors, whereas in organic networks the molecule is the node and hydrogen bonds are the node connectors; (iii) metal-ligand coordination bonds are strong and directional (40-80 kcal/mol), whereas hydrogen bonds (2-15 kcal/mol) exhibit moderate directionality in crystals. Very recently, 5-nitrosalicylic acid was identified as an organic T-node molecule in our research group, with three hydrogen bonding recognition sites on its molecular periphery (Figure 7).\textsuperscript{35a} If the T-module is viewed as having two A and one B type hydrogen bond sites, then recognition via two A\textendash A and one B\textendash B interactions results in the brick wall architecture as shown in Figure 8.

2.12.2 Herringbone Network in 5-Methylpyrazine-2-Carboxylic Acid, 2

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 through hydrogen bonding in the case of an organic molecule. In the nomenclature of Scheme 5, acid 2 may be viewed as a T-shaped molecule (Figure 9a) with pyridyl groups making A type hydrogen bonding and carboxylic acid representing B type recognition site. In the crystal structure of 2, two acid-pyridine synthons V and one pyridine dimer VHI at each molecule (node) produce the herringbone network in the (102)-plane (Figure 9b). It may be noted that Cd\textendash N bonding with A and B type azpy ligands in 14\textbullet 2Me\textsubscript{2}CO is replaced by synthons V and VIII in 2. In effect, the 2D network formed by an organic molecule and a metal-organic clathrate is identical. Such topological comparison of crystal structures and their connectivity is possible only through the network representation. Acid 2 is the first example of an organic crystal structure with a herringbone network.
Figure 7. T-shaped 5-nitrosalicylic acid with O→H⋯O, C→H⋯O and C→H⋯O hydrogen bond donors that furnish T-shape to the molecule.

Figure 8. Crystal structure of 5-nitrosalicylic acid to show the brick wall network. Note the self-assembly of T-module via like recognition, A→A and B⋯B produces the brick wall architecture.
Figure 9. (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 2D herringbone network via two A-B (synthon V) and one A-A (synthon VHI) type interactions.

2.13 Database Analysis

The significance of C–H⋯O hydrogen bonds in supramolecular synthon V has been analyzed using the Cambridge Crystallographic Database (CSD, Version 5.24, 272066 entries). A sub-data base (110 hits) of organic structures that contain CO$_2$H and pyridine moiety with at least one ortho-H atom (no disorder, 3D coordinates present, no errors, no ions, not polymorphic, and with R factor <0.1 constraints were applied) was created in the O–H⋯N distance and angle range: 1.5-2.4 A, 130–180°. Of these, 64 compounds were found to exhibit C–H⋯O hydrogen bonds (C–H⋯O: 2.0–3.0 A, 110–180°) with mean CO distance and angle of 3.36 A and 125° respectively. The 46 compounds that do not exhibit these interactions are
engaged in other strong/weak hydrogen bonds (4 O–H⋯O, 31 N–H⋯O and 11 C–H⋯O) which compete with the weak C–H⋯O hydrogen bond formation or motif V. This observation suggests that C–H⋯O interactions afford additional stability and rigidity to synthon V and the generality of this interaction is further supported by the existence of this interaction in crystal structures 1–4.

2.14 Conclusions

Hydrogen bonding supramolecular synthons in a family of crystalline pyrazine carboxylic acids have been studied with X-ray diffraction. The present study reveals that heterosynthon V, assembled by (carboxyl)O–H⋯N(pyridine) and (pyridine)C–H⋯O(carbonyl) hydrogen bonds, is a robust recognition motif that is largely insensitive to the substitution and placement of functional groups in pyridine and pyrazine mono-carboxylic acids. However, a pyridyl N with an ortho-CO₂H group is sufficiently deactivated that it does not form synthon V. Both the O–H⋯N and C–H⋯O hydrogen bonds in synthon V result from activated acidic donor and basic acceptor atoms in 1–4. Pyridine and pyrazine dicarboxylic acids crystallize as dihydrates with (carboxyl)O–H⋯O(water) hydrogen bond as the strong and dominant interaction in synthon VII. The structural analysis shows that pyrazine mono- and dicarboxylic acids exhibit distinct hydrogen bonding patterns. The recurrence of acid-pyridine heterodimer V compared to the more common acid-acid homodimer I in these crystal structures of pyridine and pyrazine monocarboxylic acids is supported by ab initio computations. The lamellar and pleated architectures of pyrazinic acids discussed in this chapter provide a novel system for the design of nanostructures from tailored molecules. The 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.
2.15 Experimental Section

Synthesis

The pyrazinecarboxylic acids were synthesized and characterized by IR and \textsuperscript{1}H-NMR spectroscopy. IR spectra were recorded on a Jasco 5300 spectrophotometer and \textsuperscript{1}H-NMR was recorded at 200 MHz on a Brucker ACF instrument.

1. Synthesis of 5-methylpyrazine-2-carboxylic acid, 2

This compound was synthesized in three steps. First step involves the preparation of methyl quinoxaline and oxidation to pyrazine dicarboxylic acid followed by decarboxylation to mono acid.

(a) 2-Methyl Quinoxaline:\textsuperscript{36} 5.5 g (51 mmol) of o-phenylene diamine was dissolved in 90 ml of water, and the solution was heated to 70 °C. With stirring, a solution of 8.6 ml of 40 % methyl glyoxal (50 mmol) in 65 ml of hot water was added to the o-phenylene diamine solution. The mixture was allowed to stand for 15 minutes and then was cooled to room temperature. 21 g of sodium carbonate monohydrate was added to the mixture. Methyl quinoxaline was extracted with three 15 ml portions of diethyl ether solvent. The combined extracts were dried over anhydrous MgSO\textsubscript{4}, filtered, and concentrated. The residual liquid, consisting of almost pure methyl quinoxaline was collected. Yield: 5.4 g (74 %). \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): \delta 8.7 (s, 1H), 8.04-7.99 (m, 2H), 7.74-7.69 (m, 2H), 2.77 (s, 3H). IR (neat): 3435, 3063, 3016, 1637, 1560, 1493, 1437, 1410, 1369 cm\textsuperscript{-1}.

(b) 5-Methylpyrazine-2,3-dicarboxylic acid:\textsuperscript{37} To 2 g (14 mmol) of methyl quinoxaline, 50 ml of water was added and heated to 80 °C. With rapid stirring a saturated aqueous solution of 12.8 g (81 mmol) of KMnO\textsubscript{4} was added, stirred for 30 minutes and filtered the reaction mixture to remove MnO\textsubscript{2}. The filtrate (about 150 ml) was evaporated under reduced pressure to about 50 ml. The solution was stirred gently while 7 ml of conc. HCl was cautiously added. Evaporation under reduced
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Pressure was then continued until a moist cake of solid KCl and the product remained in the flask. Some water and 25 ml of acetone was added to the solid material and the mixture was boiled under reflux for 15 minutes, then cooled to room temperature and filtered. The acetone filtrate was distilled to obtain the product 5-methylpyrazine-2,3-dicarboxylic acid. Yield: 1.5 g (60%). M.p.: 171-176 °C. \(^1\)H-NMR (DMSO-d\(_6\)): 8 8.72 (s, 1H), 2.59 (s, 3H). IR (KBr): 2847, 1712, 1577, 1421, 1234, 1194, 1097, 794, 760 cm\(^{-1}\).

(c) 5-Methylpyrazine-2-carboxylic acid: \(^{37}\) 250 mg (1.4 mmol) of 5-methylpyrazine-2,3-dicarboxylic acid was placed in a vacuum sublimation apparatus and was decarboxylated by heating to 175-185 °C at 2 mm of Hg, resulted in the formation of 5-methylpyrazine-2-carboxylic acid. Yield: 134 mg (71%). M.p.: 134–137 °C. \(^1\)H-NMR (DMSO-d\(_6\)): 8 9.06 (s, 1H), 8.69 (s, 1H), 2.60 (s, 3H). IR (KBr): 1894, 1728, 1379, 1336, 1307, 1275, 1184, 1045 cm\(^{-1}\).

2. 3-Methylpyrazine-2-carboxylic acid, \(^3\)\(^{38}\)

To 1 ml (9.3 mmol) of 2,3-dimethylpyrazine in 10 ml water at 70–75 °C, 3.3 g (21 mmol) of KMnO\(_4\) was added in 50 ml of water. After decolourisation of purple colour, the MnO\(_2\) cake was filtered and washed with water several times. The filtrate was acidified to pH 1.5 with HNO\(_3\), the solution heated to 50 °C, cooled to room temperature and extracted with EtOAc. Work up afforded 350 mg (28 %) of acid 3. M.p.: 170–171 °C. \(^1\)H-NMR (DMSO-d\(_6\)): 8 2.65 (s, 3H), 2.66 (s, 1H), 2.75 (s, 1H). IR (KBr): 3749, 1684, 1508, 1413, 1288, 1018 cm\(^{-1}\).

3. 6-Methylpyrazine-2-carboxylic acid, \(^4\)

Prepared in 21 % yield using the above procedure starting from 2,6-dimethylpyrazine. M.p.: 200–201 °C. \(^1\)H-NMR (DMSO-d\(_6\)): 8 2.59 (s, 3H), 8.85 (s, 1H), 9.05 (s, 1H). IR (KBr): 3435, 1732, 1383, 1296, 1257, 1018 cm\(^{-1}\).
Pyrazine-2,5-dicarboxylic acid, 11 (dihydrate) was purchased from Acros Chemicals and used as such for crystallization without further purification.

Crystallization

Diffraction quality single crystals were obtained by recrystallizing compound 2 from 4:1 EtOH/H$_2$O, 3 and 4 from $n$-hexane/EtOAc and 11 from 20% aqueous HCl.

X-ray Data Collection and Crystal Structure Determinations

X-ray data for acid 2 was collected at H.C.U. on Enraf-Nonius CAD-4 diffractometer. Data for acids 3, 4 and 11 were collected by Dr. Vincent M. Lynch (University of Texas, Austin, U.S.A.) by Nonius Kappa CCD diffractometer. The incident radiation is Mo-Kα X-ray ($\lambda = 0.71073\text{Å}$) on both instruments. Data on crystal of 2 was collected at 293 K whereas crystals of 3, 4 and 11 were cooled with Oxford Cryostream device attached to the CCD machine. Data reduction was performed using Xtal 3.5 (CAD-4) and DENZO-SMN (CCD). Structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on $F^2$ with anisotropic displacement parameters for the non-H atoms using SHELXL-97. Geometrical analysis was carried out in PLATON on Silicon Graphics Octane2 workstation.
2.16 References and Notes


16. The CSD (November 2002, 272066 entries) was searched for synthon V from good quality (R < 0.10, 3D coordinates present) 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°), O–H and C–H distance was neutron-normalized. Out of the 82 hits...
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retrieved, 17 structures are single component crystals and 65 are molecular complexes. The only example of a pyrazine carboxylic acid with synthon V in the database is 1.


31. Spartan Pro 1.0. Wave function Inc., 18401 von Karman Avenue, Suite 370, Irvine CA 92612, USA.

