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Variable Temperature Neutron Diffraction Analysis of a Very Short O−H···O Hydrogen Bond in 2,3,5,6-Pyrazinetetracarboxylic Acid Dihydrate: Synthon-Assisted Short O_{acid}−H···O_{water} Hydrogen Bonds in a Multicenter Array

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Very short O−H···O hydrogen bonds (O···O = 2.2−2.5 Å) usually occur when the H-bond is stabilized by a negative or positive charge (O−H···O^-, O^+−H···O) or by resonance assistance (···O=C−C=C−O−H···). We have characterized a very short *inter*molecular O_{acid}−H···O_{water} hydrogen bond in the title crystal structure, **1**, by variable temperature neutron diffraction (O···O = 2.4751(11), 2.4765(10), 2.4807(12), and 2.4906(16) Å at 20, 100, 200, and 293 K). The COOH donor is activated by π-cooperative hydrogen bonding (O_{acid}−H···O=C_{acid}), and the water-acceptor ability is enhanced by polarization assistance (σ-cooperative, O_w−H···O_{acid}, O_w−H···$N_{pyrazine}$). The absence of proton migration in the temperature range 20−293 K to give ionic or tautomer forms rules out contribution from the charge- or resonance-assisted H-bonds in **1**. The shortening of the O_{acid}−H···O_w hydrogen bond through synergistic π- and σ-cooperativity in the finite, neutral array **I**, named as a synthon-assisted hydrogen bond (SAHB), adds a new category to the current classification of very short hydrogen bonds in three main types: negative charge-assisted H-bonds ((−)CAHBs), positive charge-assisted H-bonds ((+)CAHBs), and resonance-assisted H-bonds (RAHBs). The very short hydrogen bond in the X-ray crystal structure of 2,3,5-pyrazinetricarboxylic acid dihydrate, **5** (O···O = 2.4726(12) Å at 120 K), and the short hydrogen bonds in pyrazine dicarboxylic acids **2**−**4** (2.5513(11), 2.5269(12), and 2.5148(13) Å) validate the novel SAHB model. A comparison of the short O_{acid}−H···O_w hydrogen bond with short O_w−H···O_{acid} distances in carboxylic acids with similar motifs, for example, **1** and **5** and **2** and **4**, shows that the activation of water oxygen by polarization assistance makes a significant contribution to the SAHB. The behavior of the short O_{acid}−H···O_w bond in **1** is similar to short-strong CAHB/RAHB systems: (1) quasi-covalent character of 0.27−0.30 valence units, (2) red shift in the O−H stretching frequency to 1200−1400 cm^{-1}, and (3) hydrogen-bond energy of ~16 kcal mol^{-1}. Some examples retrieved from the Cambridge Structural Database together with crystal structures from this study provide 21 cases of short O_{acid}−H···O_w hydrogen bonds in multicenter synthons.

Introduction

A hydrogen bond, X−H···A, arises from the attractive force that exists between the donor covalent pair, X−H, in which a hydrogen atom, H, is bound to the more electronegative atom, X, and the other noncovalently bound nearest neighbor electronegative acceptor atom, A.[1] Properties of hydrogen bonds, methods of studying them, and their structural and functional roles in proteins and other macromolecules, supramolecular chemistry, and crystal engineering have been discussed in books by Jeffrey and Saenger,[1] Jeffrey,[2] Scheiner,[3] and Desiraju and Steiner.[4] Detailed studies by Emsley, Gilli, Huggins, Jeffrey, Olovsson, Speakman, Steiner, Wilson, and others on the nature and properties of very short hydrogen bonds (VSHBs,[5a] also referred to as short-strong or low-barrier hydrogen bonds (SSHBs or LBHBs)) have contributed to a better understanding of this important phenomenon.[5,6] These studies show that strong O−H···O hydrogen bonds (O···O = 2.5−3.0 Å) have a significant electrostatic character in the interaction and an unsymmetrical potential such that the proton is confined to being near the covalent atom. As the bond shortens (VSHB, O···O = 2.2−2.5 Å), the interaction becomes stronger with increasing covalent character. The decrease in the O···O distance is accompanied by a lengthening of the O−H bond and a shortening of the H···O bond until a symmetrical hydrogen bond is reached at O···O ≈ 2.40 Å. Very strong hydrogen bonds are essentially three-center-four-electron covalent bonds. They have been studied by infrared spectroscopy,[7] valence bond analysis,[8] bond order parameter analysis,[9] NMR spectroscopy,[10] and X−N electron density measurements.[11] There is great current interest in the strongest types of hydrogen bonds because of their significance in enzyme catalysis,[12] chelating surfactants,[13] proton transfer,[14] drug-receptor recognition/binding,[15] and supramolecular chemistry.[16] They have been shown to exist in a high-pressure phase of ice.[17]

O−H···O hydrogen bonds (H-bonds) have been categorized by Gilli and co-workers[18] on the basis of extensive neutron and

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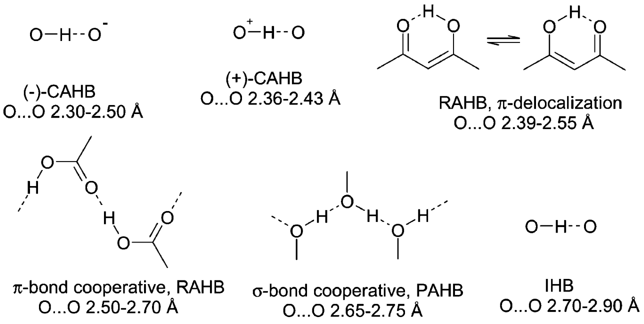
CHART 1: Different Categories of Hydrogen Bonds Discussed in This Paper



X-ray crystallographic data (Chart 1). (1) Very strong H-bonds are of three main types: (i) negative charge-assisted H-bonds ((−)CAHBs), $O-H\cdots O^-$; (ii) positive charge-assisted H-bonds ((+)CAHBs), $O^+-H\cdots O$; and (iii) resonance-assisted H-bonds (RAHBs), or π-cooperative H-bonds, $\cdots O{=}C-C{=}C-O-H\cdots$. (2) Moderate H-bonds consist of chains of polarization-assisted, or σ-cooperative, H-bonds (PAHBs). (3) Weak, isolated H-bonds (IHBs) are neither charge nor σ- or π-cooperative. Typical examples of (−)CAHBs ($O\cdots O = 2.30-2.50$ Å) are the well-known Speakman salts[5a] with $RCOOH\cdots RCOO^-$ hydrogen bonding, H-bonds between inorganic oxoacids and their conjugate bases (e.g., hydrogen phosphates and sulfates), and short, intramolecular $O-H\cdots O^-$ H-bonds in dicarboxylic acids (e.g., hydrogen maleate and hydrogen phthalate). (+)CAHBs ($O\cdots O = 2.36-2.43$ Å) are present in pseudo-hydrates, hydroxonium ions, and protons donated to oxygen by strong acids. The β-diketone enol fragment, formed by the conjugated $\cdots O{=}C-C{=}C-O-H\cdots$ group, is the most common example of a strong RAHB ($O\cdots O = 2.39-2.55$ Å).[19] Thus, H-bond shortening in (+)CAHBs is due to the electropositive donor hydrogen, that in (−)CAHBs is due to the electronegative acceptor oxygen, and that in RAHBs is due to π-delocalization in the heterodiene fragment of the β-diketone enol group.[5d] Common examples of PAHBs are σ-cooperative chain and ring motifs in crystals of ice, alcohols, and phenols (2.65−2.75 Å). Isolated H-bonds occur in the range 2.70−2.90 Å. In summary, very short (strong) H-bonds are observed when either the donor or the acceptor is charged or the H-bond is strengthened by synergism due to increased π-delocalization, often in intramolecular situations.[20]

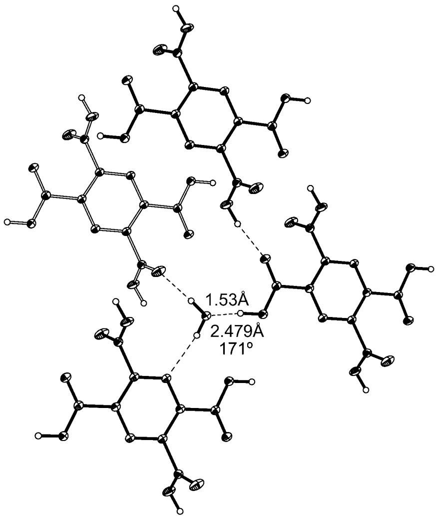
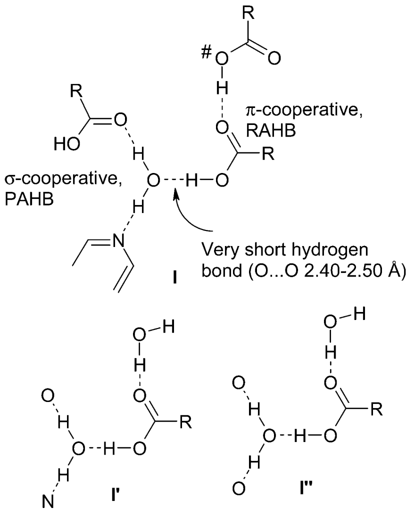


Figure 1. Finite π-cooperative and σ-cooperative hydrogen-bond array **I** in the X-ray crystal structure of pyrazine tetraacid **1** at 123 K. The water molecule forms $O-H\cdots O$ and $O-H\cdots N$ hydrogen bonds with the carboxylic acid and pyrazine groups. Molecules of the next layer are shaded differently. Displacement ellipsoids are drawn at a 50% probability level for non-hydrogen atoms. Metrics of the very short $O_{acid}-H\cdots O_w$ bond are shown.

CHART 2: *π*-Cooperative and *σ*-cooperative Hydrogen-Bond Array I and the Related Motifs I′ and I″ [a]



[a] Such motifs are categorized as a synthon-assisted hydrogen bond in this paper. Synthons **I** or **I′** are observed in the crystal structures of **1**, **3**, and **5**.

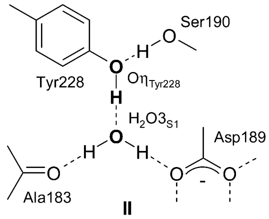
Vishweshwar et al.[21] recently reported the low-temperature (123 K) X-ray crystal structure of the title molecule (Figure 1) with a very short intermolecular $O_{acid}-H\cdots O_w$ hydrogen bond ($O\cdots O = 2.4791(13)$ Å, $H\cdots O = 1.53$ Å, $\angle O-H\cdots O = 171(2)°$). Hydrogen-bond shortening in 2,3,5,6-pyrazinetetracarboxylic acid dihydrate, **1**, was ascribed to the finite array of π-cooperative H-bonds and the polarization of water oxygen in motif **I**. As shown in Chart 2, the COOH donor is activated because it accepts a hydrogen bond from another COOH group (labeled #, π-cooperative assistance) and the acceptor ability of oxygen is enhanced because the water donates H-bonds to COOH and pyrazine N groups (polarization assistance, σ-cooperative). The short $O_{acid}-H\cdots O_w$ hydrogen bond in multicenter motif **I** is in the CAHB/RAHB distance range of strong H-bonds ($O\cdots O = 2.30-2.50$ Å), but the shortening resembles PAHBs of moderate strength ($O\cdots O = 2.65-2.75$ Å). The short $O_{acid}-H\cdots O_w$ hydrogen bond in **1** does not appear to be of the (−)CAHB, (+)CAHB, or RAHB type because there is no evidence of ionic donor/acceptor groups and/or delocalization.[21] Its shortness cannot be due to geometric compression because the H-bond is intermolecular. We have now carried out variable temperature neutron diffraction (VT-ND) on a single crystal of **1** at 20, 100, 200, and 293 K to examine the properties and structural behavior of the very short $O_{acid}-H\cdots O_w$ H-bond in the neutral motif **I**. Hydrogen atom positions are determined with limited accuracy by X-ray diffraction. The precise location of hydrogen atoms in the crystal structure is of paramount importance in hydrogen-bond studies.[22] We sought to answer some of the following questions with the neutron diffraction crystal structure of **1**: (1) Does the O−H bond lengthen with decreasing $H\cdots O$ distance? (2) Is there proton transfer in the short $O-H\cdots O$ H-bond to give ionic or resonant species? (3) Does the very short $O-H\cdots O$ bond have quasi-covalent character, or is it largely electrostatic? The presence of a short $O-H\cdots O$ H-bond in a *neutral* array justifies detailed analysis of this system. Although several very short and ionic $O_{acid}-H\cdots O^-$ H-bonds have been characterized by neutron diffraction,[6c,f,23] there is only one neutron study of a very short and

TABLE 1: Neutron Diffraction Crystallographic Data of Pyrazine Tetracarboxylic Acid 1 ($\lambda = 0.83970$ Å) at Different Temperatures[a]

	123 K[b]	293 K	200 K	100 K	20 K
empirical formula	$C_8H_4N_2O_8{\cdot}(H_2O)_2$	$C_8H_4N_2O_8{\cdot}(H_2O)_2$	$C_8H_4N_2O_8{\cdot}(H_2O)_2$	$C_8H_4N_2O_8{\cdot}(H_2O)_2$	$C_8H_4N_2O_8{\cdot}(H_2O)_2$
fw	292.16	292.16	292.16	292.16	292.16
cryst syst	triclinic	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	5.4409(3)	5.4950(10)	5.4606(10)	5.4385(10)	5.4361(10)
b (Å)	6.4041(3)	6.4410(10)	6.4133(10)	6.3885(10)	6.3699(10)
c (Å)	8.6995(3)	8.7670(10)	8.7164(10)	8.6809(10)	8.6672(10)
α (deg)	98.572(3)	99.393(6)	98.962(5)	98.381(5)	97.911(5)
β (deg)	107.374(3)	107.565(7)	107.408(5)	107.406(5)	107.546(5)
γ (deg)	105.519(3)	105.174(7)	105.348(5)	105.573(5)	105.718(5)
Z	1	1	1	1	1
volume (Å^3)	269.97(2)	275.44(8)	271.57(7)	268.72(7)	267.48(7)
D_{calc} (g/cm^3)	1.797	1.761	1.785	1.804	1.813
T (K)	123(2)	293(1)	200(1)	100(1)	20(1)

[a] Full crystallographic data and structure refinement parameters are given in the Supporting Information. [b] X-ray data[21] are given for comparison.

CHART 3: Short Hydrogen Bond in a Multicenter Array in the Crystal Structure of the Trypsin-CRA-10991 Complex[a]

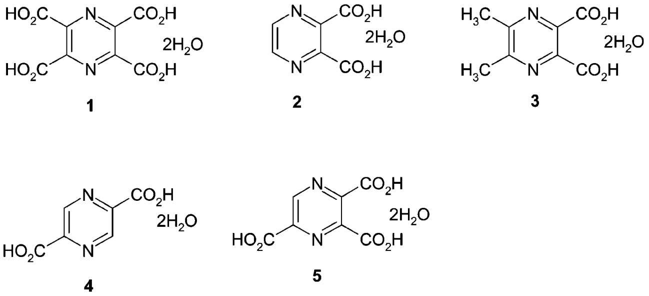


II

Oη$_{Tyr228}$–H...O(H$_2$O3$_{S1}$)
2.50(04) Å, 153(4)°

[a] See ref 15 for details.

CHART 4: Crystal Structures of Pyrazinecarboxylic Acids 1−5 Discussed in This Paper



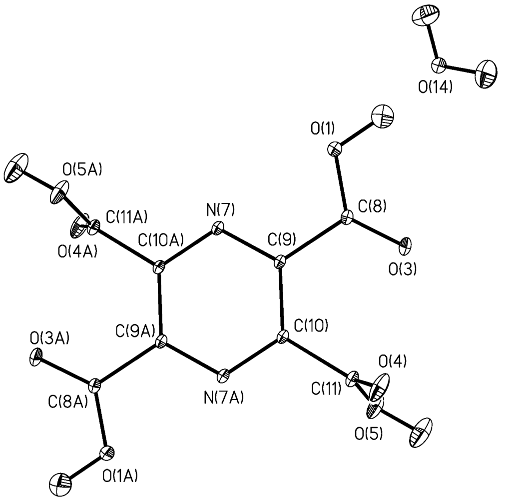


Figure 2. Oak Ridge thermal ellipsoid plot (ORTEP) of 2,3,5,6-pyrazinetetracarboxylic acid dihydrate, **1**, at 100 K by neutron diffraction. Atom numbering and displacement ellipsoids at a 50% probability for all atoms are shown. The C8 carboxylic acid is coplanar with the pyrazine ring (N7−C9−C8−O1 = 9.31(7)°), and C11A is out of the plane (N7−C10A−C11A−O5A = 80.25(6)°).

neutral O_{acid}−H···O bond.[24] Recent reports[15,25] of multicentered short hydrogen-bond arrays (e.g., motif **II**, O···O = 2.50(04) Å, Chart 3)[15] in serine protease crystal structures imply that the results of this study are relevant in drug design research on enzyme catalysis and inhibitor potency.

We discuss in this paper variable temperature neutron diffraction of the very short O−H···O hydrogen bond in tetraacid **1**. Similar neutral O−H···O motifs (**I** and **I′**) with short and very short H-bonds are identified in the X-ray crystal structures of pyrazine di- and tricarboxylic acids **2**−**5** (Chart 4). The short hydrogen bonds in oxalic acid dihydrate crystal structures (motif **I″**) are compared with our results to highlight their similarities. These crystallographic results provide evidence of short O−H···O hydrogen bonds in synergistic π- and σ-cooperative neutral, finite arrays. We name this new hydrogen-bond shortening model the synthon-assisted hydrogen bond (SAHB, Chart 2) model and justify our terminology at the end of this paper.[26] The nature of the very short H-bond (VSHB) in tetraacid **1** is compared with short-strong CAHB/RAHB bonds in terms of the O−H versus H···O distance function, the valence bond order parameter, s, covalent versus electrostatic character, and ν_s(O−H) in the IR spectrum.

Results and Discussion

Crystallization of **1** from 20% aqueous HCl gave diffraction-quality millimeter-size crystals at room temperature after a few weeks. A single crystal of 0.6 mm × 1.6 mm × 2.8 mm (calculated volume, 3.65 mm^3), obtained after multiple recrystallizations, was selected from the mother liquor for neutron diffraction. The D9 instrument at the Institut Laue-Langevin is equipped with an 8° × 8° multiwire (32 × 32) position-sensitive detector and is optimized for accurate neutron intensity measurements at short wavelengths. At the chosen wavelength $\lambda = 0.8397(1)$ Å from a Cu(220) monochromator in transmission, the crystal was cooled slowly at 2° per minute to 20 K, while monitoring a strong low-angle reflection. Data were collected at 20 K, and the crystal was then warmed slowly to 100 K, to 200 K, and finally to 293 K, and the structure, redetermined at each temperature (precision better than ±1 K).[27] Gratifyingly, the dihydrate crystal did not become opaque, crack, or undergo a phase transition during the week-long variable temperature experiment. The neutron diffraction crystal structure of **1** is in

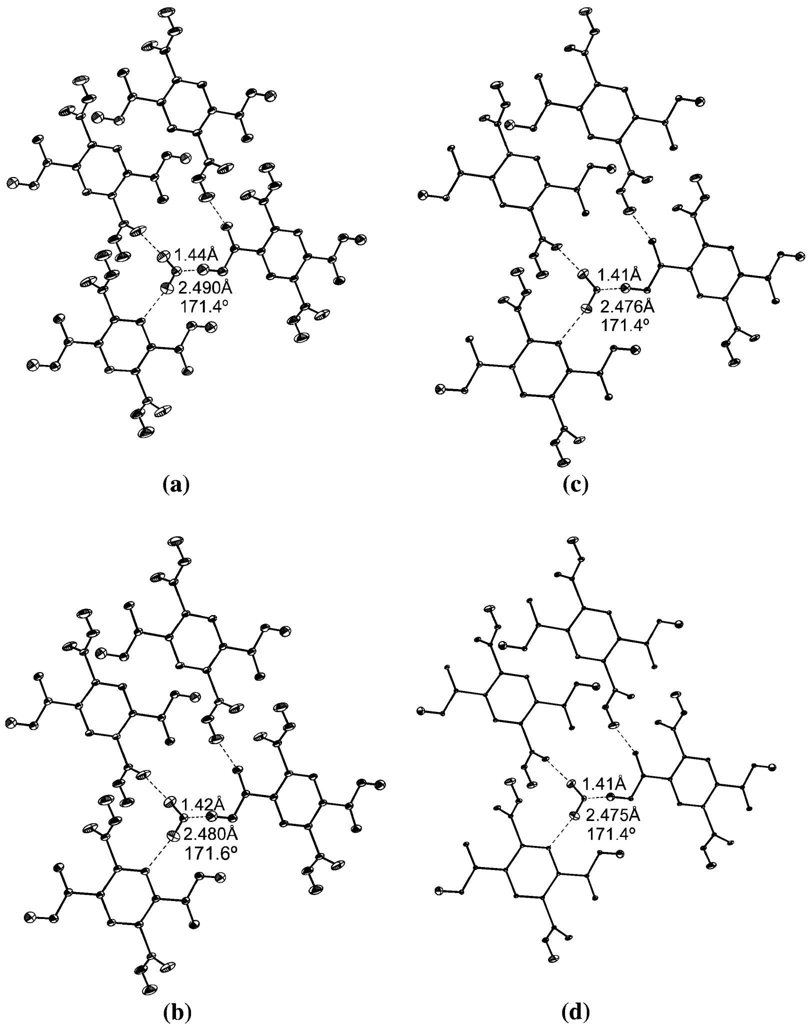


Figure 3. π-Cooperative and σ-cooperative hydrogen-bond motif **I** in the crystal structure of pyrazine tetraacid **1** from variable temperature neutron diffraction. Displacement ellipsoids are drawn at a 50% probability level for all atoms. (a) 293 K; (b) 200 K; (c) 100 K; (d) 20 K. Metrics of the very short $O_{acid}-H\cdots O_w$ hydrogen bond are indicated. Note the reduced thermal vibration of atoms at low temperature. All protons are fully ordered (also see Figure 4). The synergy of π- and σ-cooperative H-bonds in motif **I** results in a synthon-assisted hydrogen bond (SAHB), discussed in the text.

agreement with its X-ray structure[21] (cell parameters, space group, Table 1), so only the neutron structures are analyzed.

Crystal Structure of 1 from Neutron Diffraction Data. The crystal structure of **1** was solved (X-ray data) and refined (neutron data) in the $P\bar{1}$ space group. The molecule lies across the inversion center ($Z' = 0.5$) with one carboxylic acid in the plane of the pyrazine ring (torsion angle N7−C9−C8−O1 = 9.31(7)°) and the other one out of the plane (N7−C10A−C11A−O5A = 80.25(6)°), as shown in Figure 2. The coplanar COOH group forms a very short $O-H\cdots O$ hydrogen bond with water (Figure 3). The $O_{acid}-H\cdots O_w$ bond is within the VSHB range ($H\cdots O < 1.5$ Å, $O\cdots O < 2.5$ Å)[2,4,20] with $H\cdots O$ distances of 1.4430(20) and 1.4098(17) Å at 293 and 20 K, respectively. There are no significant changes in the unit cell parameters (∼1% compression in each dimension, ∼3% decrease in volume), hydrogen-bond distances, and angles upon cooling the crystal, except the usual shortening at low temperature (Tables 1 and 2). This means that there is no phase transition in the temperature range 293−20 K. An important issue with very short hydrogen bonds is how precisely the hydrogen atom is located in the structure. Examination of Table 3 (and Figure 3) shows that the mean square displacement of the proton in the very short hydrogen bond is small. The average displacement of the proton that is involved in the very short H-bond (U_{eq} = 0.0167(5) Å^2) is smaller than those of the other protons that are engaged in short and moderate H-bonds at a given temperature (0.0205(6), 0.0239(6), and 0.0236(6) Å^2 at 20 K). This confirms that the proton in the short-strong hydrogen bond is sharply located and the quality of the neutron diffraction data is satisfactory for a detailed analysis of hydrogen bonding. Dihydrate **1** has three categories of H-bonds: very short $O_{acid}-H\cdots O_w$, short $O_{acid}-H\cdots O_{acid}$, and moderate $O_w-H\cdots O_{acid}$ and $O_w-H\cdots N$. This trend of increasing hydrogen-bond distance depending on the strength of donor/acceptor groups is typical of carboxylic acid hydrates.[28] Water is a good hydrogen-bond acceptor but has moderate donor groups.

The polarization of a water molecule as an enhanced acceptor group has been illustrated[29] in an exceptionally short $C-H\cdots O_w$ H-bond (1.96 Å, 169.3°) in the complex (1,4-diethynylbenzene)·(water)$_2$·(triphenylphosphine oxide)$_4$. The donation of water hydrogens to P=O groups (1.85 Å, 161°; 1.77 Å, 168°) creates a more negative electrostatic potential around the oxygen atom which results in a very short $C-H\cdots O$ H-bond. In tetraacid **1**, the donor COOH group of the very short H-bond is activated because it accepts an $O-H\cdots O=C$ hydrogen bond from another COOH group (π-bond cooperativity). The basicity of the water molecule is enhanced because the oxygen atom is polarized by H-bond donation to the COOH and pyrazine groups. We have

TABLE 2: Geometrical Parameters of Hydrogen Bonds in Pyrazine Tetraacid 1 (Neutron Diffraction)

H-bond	T (K)	r (Å)	d (Å)	D (Å)	θ (deg)
$O_{acid}-H\cdots O_w$	20	1.0721(15)	1.4098(17)	2.4751(11)	171.45(15)
	100	1.0720(13)	1.4113(14)	2.4765(10)	171.46(11)
	200	1.0640(16)	1.4233(18)	2.4807(12)	171.60(16)
	293	1.0550(20)	1.4430(20)	2.4906(16)	171.35(17)
	123 (XRD)[a]	0.96	1.53	2.4791(13)	171.0
$O_{acid}-H\cdots O_{acid}$	20	0.9861(17)	1.7393(18)	2.6919(12)	161.28(18)
	100	0.9871(14)	1.7365(14)	2.6931(9)	162.14(13)
	200	0.9895(19)	1.7370(19)	2.6996(14)	163.28(19)
	293	0.9839(19)	1.7490(20)	2.7080(15)	163.70(20)
	123 (XRD)[a]	0.91	1.81	2.7010(12)	163.3
$O_w-H\cdots O_{acid}$	20	0.9670(18)	1.8174(19)	2.7794(12)	172.80(20)
	100	0.9670(14)	1.8151(14)	2.7781(10)	173.51(17)
	200	0.9652(20)	1.8231(20)	2.7836(14)	173.03(21)
	293	0.9607(19)	1.8450(20)	2.8001(15)	172.70(30)
	123 (XRD)[a]	0.89	1.90	2.7811(12)	172.0
$O_w-H\cdots N$	20	0.9690(20)	1.9982(19)	2.9256(12)	159.56(17)
	100	0.9699(18)	2.0050(17)	2.9340(9)	159.70(12)
	200	0.9630(20)	2.0300(20)	2.9534(13)	159.90(17)
	293	0.9560(20)	2.0600(20)	2.9777(14)	160.28(18)
	123 (XRD)[a]	0.85	2.14	2.9393(16)	157.6

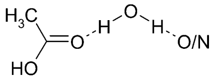
[a] X-ray data[21] are given for comparison.

TABLE 3: Mean Square Displacement (U_{eq}, Å^2) of Protons in Pyrazine Tetraacid 1 (ND Data)

proton	20 K	100 K	200 K	293 K
$O_{acid}-\mathbf{H}\cdots O_w$	0.0167(5)	0.0218(3)	0.0291(6)	0.0379(6)
$O_{acid}-\mathbf{H}\cdots O_{acid}$	0.0205(6)	0.0265(4)	0.0404(7)	0.0515(8)
$O_w-\mathbf{H}\cdots O_{acid}$	0.0239(6)	0.0306(4)	0.0415(7)	0.0554(9)
$O_w-\mathbf{H}\cdots N$	0.0236(6)	0.0256(4)	0.0348(7)	0.0434(7)
$O_{acid}-\mathbf{H}\cdots O_w$[a]	0.0166(5)	0.0236(3)	0.0326(6)	0.0427(6)

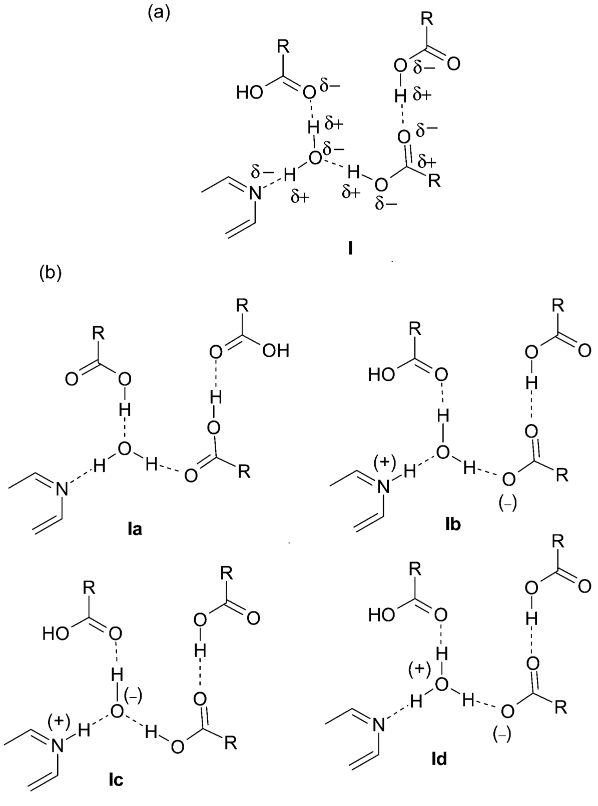
[a] Displacement of the hydrogen atom along the $O-H\cdots O$ H-bond.

CHART 5: Hydrogen-Bonded Complexes $AcOH{\cdot}H_2O{\cdot}$pyrazine IIIa and $AcOH{\cdot}H_2O{\cdot}AcOH$ IIIb Showing the Polarization of Water Oxygen through Spartan Calculations



IIIa: pyrazine N
IIIb:acetic acid O=C

CHART 6: (a) The Continuous Array of Partial Positive and Negative Charges on the Donor and Acceptor Groups in the Cooperative, Neutral Motif I; (b) Proton Transfer Can Result in Resonance (Ia) and/or Ionic (Ib−d) Tautomers[a]



[a] The absence of motifs **Ia**−**d** in the crystal structure rules out contributions from charge and resonance assistance to the neutral synthon **I**.

confirmed this computationally in model hydrogen-bonded complexes, that is, acetic acid•water•pyrazine and acetic acid•water•acetic acid (Chart 5), that resemble the polarization of water in hydrogen-bond array **I**. The negative electrostatic potential (ESP) at the water oxygen (Spartan,[30] RHF 6-31G*) increases from −46.2 kcal mol^{-1} in free water to −64.4 and −65.2 kcal mol^{-1} in complexes **IIIa** and **IIIb**, respectively (see the Supporting Information for ESP plots). The negative ESP of the hydrogen-bonded water oxygen is comparable to that for $P{=}O$ oxygen, a very strong H-bond-acceptor group. In effect, synergy of a finite π-bond cooperative array and polarization-assisted H-bonds is able to shorten the $O-H\cdots O$ bond into the very short distance range ($O\cdots O = 2.30-2.50$ Å).

Proton migration in phenol•pyridine and carboxylic acid•pyridine cocrystals ($O-H\cdots N \rightleftharpoons O\cdots H\cdots N \rightleftharpoons O\cdots H-N$) has been studied by variable temperature neutron diffraction.[31] The absence of proton transfer in pyrazine tetraacid **1** is crucial to the proposed π- and σ-cooperative hydrogen-bond shortening. If there is proton transfer in **I** to one or more of the motifs **Ia**, **Ib**, **Ic**, and **Id** (Chart 6),[32] or a delocalized hybrid structure, then H-bond shortening could well be a result of ionic donor/acceptor groups and/or resonance assistance, that is, CAHB/RAHB. $O-H$ and $H\cdots O$ distances in the neutron diffraction crystal structure of **1** at different temperatures (Table 2) indicate the absence of ionic and resonance forms **Ia**−**d**. Furthermore, the $C{=}O$ and $C-O$ bond distances in the COOH group and the $C-N{=}C$ angle in the pyrazine ring (Table 4) are in agreement with these hydrogen-bonding groups being present in a neutral form rather than as ionic/resonant species.[33] The unambiguous location of the hydrogen atom in the $O_{acid}-H\cdots O_w$ bond and the absence of disorder/delocalization/proton transfer

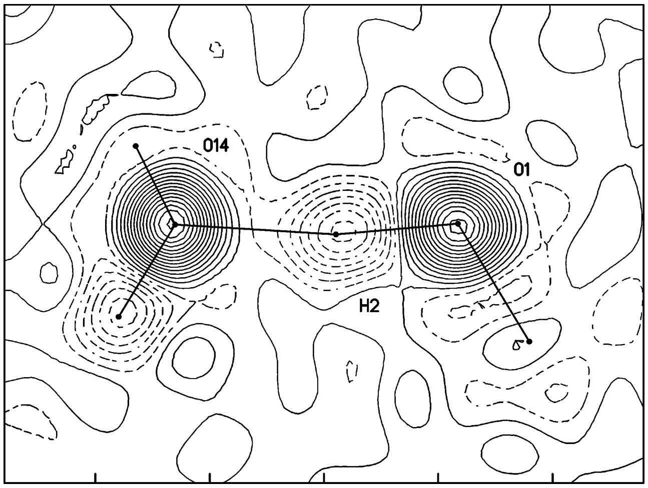


Figure 4. Fourier map (F_{obs}) calculated from the 20 K neutron diffraction crystal structure of **1**. The projection is perpendicular to the plane of O1, O14, and H2. The contours are at a nuclear scattering density of 1 fm Å^{-3}, and dashed lines indicate negative contours. Contours are shown at intervals of 3 units from −21 (minimum, −21.71) to +42 (maximum, +42.70). The nuclear density is localized on the hydrogen atom, and there is no evidence of disorder.

TABLE 4: C—O and C═O Bond Lengths in the COOH Group and C—N═C Bond Angles in the Pyrazine Ring of Acids 1−5 (Taken from X-ray Experiments)

acid	C—O (Å)	C═O (Å)	C—N═C (deg)
1	1.3113(17)	1.2022(15)	117.63(11)
	1.2957(16)	1.2174(14)	
2	1.3115(13)	1.2119(13)	117.85(9)
3	1.3143(13)	1.2122(13)	118.53(9)
4	1.3067(16)	1.2140(15)	116.86(11)
5	1.3078(14)	1.2009(14)	117.51(10)
	1.3064(14)	1.2124(14)	116.86(9)
	1.2997(14)	1.2149(14)	

in the multicenter H-bond array are confirmed by the Fourier map of **1** from neutron diffraction data (Figure 4).

Very Short and Short Hydrogen Bonds in Pyrazine Di- and Triacids 2−5. The X-ray crystal structures of 2,3-pyrazinedicarboxylic acid dihydrate, **2** (123 K),[34] 5,6-dimethyl-2,3-pyrazinedicarboxylic acid dihydrate, **3** (123 K),[21] and 2,5-pyrazinedicarboxylic acid dihydrate, **4** (153 K),[35] were analyzed (Table 5).[36] These three diacids crystallize as dihydrates, akin to tetraacid **1**, and contain similar hydrogen-bond motifs except that a water molecule replaces the COOH donor that initiates the H-bond array (#COOH in **I**, motif **I′**). The water oxygen is polarized through H-bonds with the COOH and pyrazine groups as before. The O_{acid}—H···O_w H-bond shortens progressively from **2** to **3** to **4** (O···O = 2.5513(11), 2.5269(12), and 2.5148(13) Å, Table 6), but these distances are longer than the short H-bond in **1**. Diacids **2** and **4** aggregate through the cooperative, cyclic H-bond motif **IV** (Chart 7), whereas molecules of **3** are connected in a catemer arrangement via motif **I′** (Figure 5).

2,3,5-Pyrazinetricarboxylic acid dihydrate, **5**,[36] was crystallized from 20% aqueous HCl. The asymmetric unit has one acid molecule and two water molecules because the triacid molecule is devoid of an inversion center. In contrast, diacids **1−4** with a C_2 axis or inversion symmetry reside on the special position. Two COOH groups of **5** are roughly coplanar with the pyrazine ring, and the third COOH group is out of the plane (N1—C3—C6—O5 = 10.45(14)°, N2—C2—C5—O4 = 4.29(14)°, and N1—C1—C4—O1 = 81.02(14)°). The in-plane COOH group (C5) participates in the VSHB through the H-bond array **I**, similar to the crystal structure of tetraacid **1**. The O_{acid}—H···O_w bond in **5** (O4···O8 = 2.4726(12) Å) is stabilized by the synergy from π-cooperative and polarization assisted H-bonds (Figure 6). The other H-bonds in synthon **I** have short to moderate distances, similar to tetraacid **1**. The third carboxylic acid (C6) forms the centrosymmetric hydrate motif **IV** with the second water molecule (O5···O7 = 2.5137(13) Å). The O_{acid}—H···O_w H-bond of motif **IV** is short, akin to diacid **4**, while the other O—H···O/N H-bonds are of moderate length (Table 6). The crystal structure of triacid **5**, analyzed as a combination of H-bond motifs in tetraacid **1** and diacid **4**, contains H-bonds of increasing distance from very short and short O_{acid}—H···O_w bonds to short and moderate O_{acid}—H···O_{acid}, O_w—H···O_{acid}, and O_w—H···N interactions. Before closing the X-ray crystal structure discussion, we emphasize that all the protons in **2−5** are located in difference electron density maps and the neutral form of the COOH group is concluded from C═O and C—O bond distances and N—C═N angles[33] (Table 4).

Hydrogen-bonding trends in acids **1−5** are now discussed. The short O_{acid}—H···O_w H-bond is longer in **2**, **3**, and **4** compared to **1** for two reasons. The carboxylic acid group is a stronger H-bond donor than water, so the role of finite π-bond cooperativity is enhanced in **1** compared to **2−4** (motif **I** vs motif **I′**). The carboxylic acid donor in tetraacid **1** is stronger than diacids **2−4** because more electron-withdrawing groups are loaded on the pyrazine ring. In addition to these factors, the more important reason for H-bond shortening in array **I** is the polarization of the water molecule. We say this because the VSHB is shorter in triacid **5** (O···O = 2.4726(12) Å at 120 K) compared to tetraacid **1** (2.4791(13) Å at 123 K, XRD data from Tables 2 and 6), even though the COOH donor is marginally stronger in **1** because of an extra electron-withdrawing group. Incidentally, the short O···O distance in **5** at 120 K is comparable to the distance in **1** at 20 K. That this shortening of O_{acid}—H···O_w is due to an increase in the acceptor strength of water oxygen by polarization-assisted hydrogen bonding is evident from the comparison of O_w—H···O_{acid} and O_w—H···N distances. These σ-cooperative H-bonds, which polarize the water oxygen, are shorter in **5** compared to **1** (O···O = 2.7461(12) Å (**5**), 2.7811(12) Å (**1**); O···N = 2.8947(13) Å (**5**), 2.9393(16) Å (**1**); XRD data from Tables 2 and 6). A similar correlation between the shortness of the O_{acid}—H···O_w bond and the stronger polarization of water oxygen through O_w—H···O_{acid} in the cooperative synthon **IV** is observed for diacids **2** and **4** too (Figure 5, Table 6). All this shows that *the polarization of the water oxygen acceptor through σ-cooperative hydrogen bonding makes a significant contribution to H-bond shortening in neutral array **I***, with auxiliary support coming from π-cooperative H-bonding. These results illustrate that stronger donor and acceptor groups in motif **I** shorten (strengthen) the O_{acid}—H···O_w bond, similar to the behavior of very short and short (very strong and strong) hydrogen bonds in well-studied CAHB/RAHB categories.[2,5,18] Such graded effects show that H-bond shortening in motif **I** is due to chemical (electrostatic) reasons, that is, the strengthening of donor and acceptor groups, and not a chance consequence of geometric compression, steric congestion, or crystal packing effects. This synergistic π- and σ-cooperative H-bond shortening in a neutral multicenter array contributes to the growing number of studies toward understanding these interactions in terms of a unified electrostatic−covalent hydrogen-bond model,[5d,18e] which represents a continuum in energy from weak interactions to strong H-bonds and from very strong H-bonds to covalent bonds.[37]

TABLE 5: X-ray Crystallographic Data of Pyrazine Di- and Triacids 2−5 ($\lambda = 0.71073$ Å)[a]

	2[b]	**3**[c]	**4**[d]	**5**[b]
empirical formula	$C_6H_4N_2O_4{\cdot}(H_2O)_2$	$C_8H_8N_2O_4{\cdot}(H_2O)_2$	$C_6H_4N_2O_4{\cdot}(H_2O)_2$	$C_7H_4N_2O_6{\cdot}(H_2O)_2$
fw	204.14	232.19	204.14	248.15
cryst syst	monoclinic	orthorhombic	triclinic	triclinic
space group	*C*2/*c*	*Pbcn*	$P\bar{1}$	$P\bar{1}$
a (Å)	5.3470(2)	12.6454(3)	5.2101(2)	5.2830(3)
b (Å)	13.0286(4)	9.0812(3)	6.8261(2)	6.6497(3)
c (Å)	11.7443(4)	8.8800(3)	6.8713(2)	13.8423(7)
α (deg)	90	90	119.144(2)	93.064(2)
β (deg)	99.036(1)	90	99.808(2)	90.513(2)
γ (deg)	90	90	99.927(2)	103.009(2)
Z	4	4	1	2
volume (Å^3)	808.00(5)	1019.74(5)	200.85(1)	473.02(4)
D_{calc} (g/cm^3)	1.678	1.512	1.688	1.742
T (*K*)	123(2)	123(2)	153(2)	120(2)

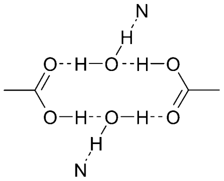
[a] Full crystallographic data and structure refinement parameters are given in the Supporting Information. [b] This paper. [c] Reference 21. [d] Reference 35.

TABLE 6: Geometrical Parameters of the Hydrogen Bonds in Pyrazine Acids 2−5

acid	H-bond	*d* (Å)	*D* (Å)	θ (deg)
2	$O_{acid}-H\cdots O_w$	1.61	2.5513(11)	168.0
	$O_w-H\cdots O_{acid}$	2.10	2.8993(11)	156.9
	$O_w-H\cdots N$	1.95	2.8143(12)	166.4
	$C-H\cdots O$	2.44	3.3121(13)	150.5
3	$O_{acid}-H\cdots O_w$	1.57	2.5269(12)	167.4
	$O_w-H\cdots O_{acid}$	2.03	2.8747(12)	163.4
	$O_w-H\cdots N$	2.08	2.8963(13)	156.5
	$C-H\cdots O$	2.62	3.4980(14)	147.5
	$C-H\cdots O$	2.72	3.6459(14)	159.1
4	$O_{acid}-H\cdots O_w$	1.57	2.5148(13)	171.0
	$O_w-H\cdots O_{acid}$	2.03	2.8024(12)	155.0
	$O_w-H\cdots N$	1.99	2.8492(16)	166.6
	$C-H\cdots O$	2.60	3.4524(16)	147.9
5	$O_{acid}-H\cdots O_w$ [a]	1.50	2.4726(12)	170.0
	$O_{acid}-H\cdots O_w$ [b]	1.64	2.5137(13)	168.0
	$O_{acid}-H\cdots O_{acid}$ [a]	1.83	2.7193(12)	163.9
	$O_w-H\cdots O_{acid}$ [a]	1.92	2.7461(12)	172.0
	$O_w-H\cdots O_{acid}$ [b]	1.99	2.7802(13)	156.5
	$O_w-H\cdots N$ [b]	2.06	2.8810(14)	162.8
	$O_w-H\cdots N$[a]	2.06	2.8947(13)	160.6
	$C-H\cdots O$	2.60	3.4238(14)	142.3

[a] Motif **I**. [b] Motif **IV**.

CHART 7: Cyclic Hydrogen-Bond Motif IV in the Crystal Structures of 2, 4, and 5



IV

There is a pronounced preference in pyrazine di- and higher acids for crystallization with the inclusion of water, whereas pyrazine monocarboxylic acids aggregate via the robust acid···pyridine heterosynthon.[35] Pyrazine acids with two or more COOH groups are rich in H-bond acceptors, and the water molecule, with two donors and one acceptor, compensates for this difference to give a saturated hydrogen-bond adduct.[38] The number of hydrogen-bond synthons in crystal structures **1**−**5** with varying numbers of COOH groups is essentially two: H-bond synthons **I** and **IV**. The analysis of crystal structures in terms of a limited number of supramolecular synthons[39] (recurring motifs) is the first step toward crystal engineering,[40] the rational design of solid-state architectures from functionalized molecules.

Synthon-Assisted Hydrogen Bonds. A survey of the Cambridge Structural Database[41] for $COOH\cdots OH_2$ hydrogen bonds in the distance range $O\cdots O = 2.30-2.50$ Å and $\angle O-H\cdots O = 160-180°$ provided two examples[42] of neutral carboxylic acids (Chart 8), other than the title tetraacid and oxalic acid. The COOH group in CACTUW is activated as an alkyne carboxylic acid, and the pyrone ring in ZZZSSY02 is sufficiently electron withdrawing to shorten the $O-H\cdots O$ bond (motif **I″**). The $O_{acid}-H\cdots O_w$ bond in ZZZSSY02 is the shortest hydrogen bond in a neutral array (Figure 7), possibly because the COOH donor group is attached to a doubly activated electron-withdrawing position (α to O and β to enone) on the pyrone ring. The reason for H-bond shortening in a neutral array may therefore be generalized as follows. *If an activated carboxylic acid donor* (pK_a 1−3) *hydrogen bonds to a water molecule that is in turn H-bonded to O/N acceptors, then the $O_{acid}-H\cdots O_w$ H-bond can be very short because the H-bond donor is strengthened by π-cooperativity, or resonance assistance, and the water oxygen acceptor strength is enhanced by σ-cooperativity, or polarization assistance.* We name this novel hydrogen-bond shortening phenomenon, a result of synergy from finite RAHB and PAHB (π- and σ-bond cooperative motifs in Chart 1), *synthon-assisted hydrogen bonding*. All the hydrogen bonds of the multicenter SAHB motif **I**, $O_{acid}-H\cdots O_{acid}$, $O_w-H\cdots O_{acid}$, and $O_w-H\cdots N_{pyr}/O_{acid}$, contribute to the shortening of the $O_{acid}-H\cdots O_w$ bond. Moreover, while the RAHB and PAHB hydrogen bonds in carboxylic acids and alcohols/phenols have typical $O\cdots O$ distances of 2.50−2.70 Å, the combination of these motifs in a cooperative array can lead to further shortening of the hydrogen bond ($O\cdots O < 2.50$ Å). Thus, hydrogen-bond shortening results from the extended synthon and not from a single interaction. In this respect, SAHBs are different from the two-center CAHBs in which shortening is ascribed either to the electropositive donor hydrogen or to the electronegative acceptor atom. Three variants of SAHBs are illustrated in synthons **I**, **I′**, and **I″** (Chart 2).

The low-temperature X-ray crystal structures of oxalic acid dihydrate **6** have a very short $O_{acid}-H\cdots O_w$ H-bond in motif **I″**. A plot of $O\cdots O$ distance versus $O-H(D)\cdots O$ angle in oxalic acid **6** (and its perdeuterated dihydrate),[43] tetraacid **1**, triacid **5**, CACTUW, and ZZZSSY02 is shown in Figure 7. This distance−angle scatter plot of 21 neutron and/or X-ray crystal structures shows that we have characterized a very short $O_{acid}-H\cdots O_w$ hydrogen bond by variable temperature neutron diffraction. Even though the oxalic acid dihydrate crystal structures have been investigated extensively,[43] the shortening of the hydrogen bond through a synthon-assisted hydrogen bond, or synergy from π- and σ-cooperative H-bonds, is not mentioned

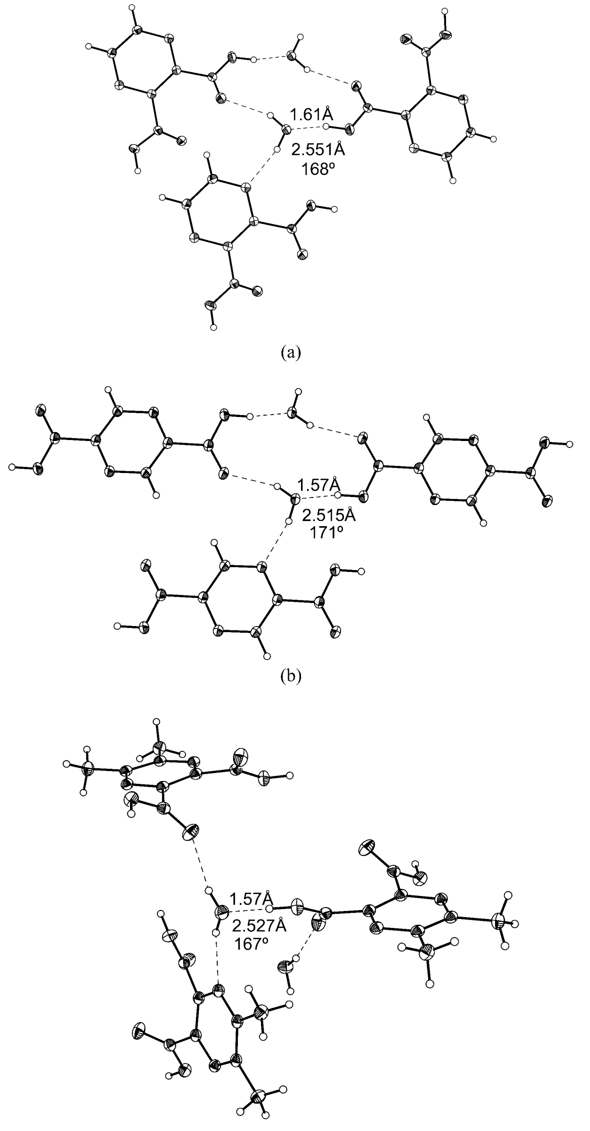


Figure 5. Short $O_{acid}-H\cdots O_{w}$ hydrogen bond in the X-ray crystal structures of (a) 2,3-pyrazinedicarboxylic acid dihydrate, **2**, (b) 2,5-pyrazinedicarboxylic acid dihydrate, **4**, and (c) 5,6-dimethyl-2,3-pyrazinedicarboxylic acid dihydrate, **3**. Diacids **2** and **4** have the dimer motif **IV**, and diacid **3** has the catemer arrangement via motif **I′**. The shorter $O_{acid}-H\cdots O_{w}$ hydrogen bond in **4** compared to **2** correlates with a shorter $O_{w}-H\cdots O_{acid}$ hydrogen bond in the former structure, highlighting the importance of polarization assistance toward hydrogen-bond shortening. See the text and Table 6 for details. Displacement ellipsoids are drawn at a 50% probability for non-hydrogen atoms.

in the earlier publications.[42−44] The occurrence of short synthon-assisted hydrogen bonds with similar extended motifs in diverse crystal structures justifies the proposal for adding the new SAHB category to the existing classification of CAHBs and RAHBs.

Other Characteristics of Synthon-Assisted Short H-Bonds in 1. The nature of the very short O−H···O hydrogen bond in **1** was examined by a few other parameters to compare its behavior with conventional CAHB/RAHB very short or short-strong hydrogen bonds.

Empirical Bond Order of a Hydrogen Bond. A quantitative measure of the covalent character in a hydrogen bond is the valence or bond order, *s*, which measures the sharing of electron density between the X−H and H···A bonds.[9] The bond orders, *s* values, for the very short and short O−H···O bonds in **1** were calculated from the empirically derived equations listed in the

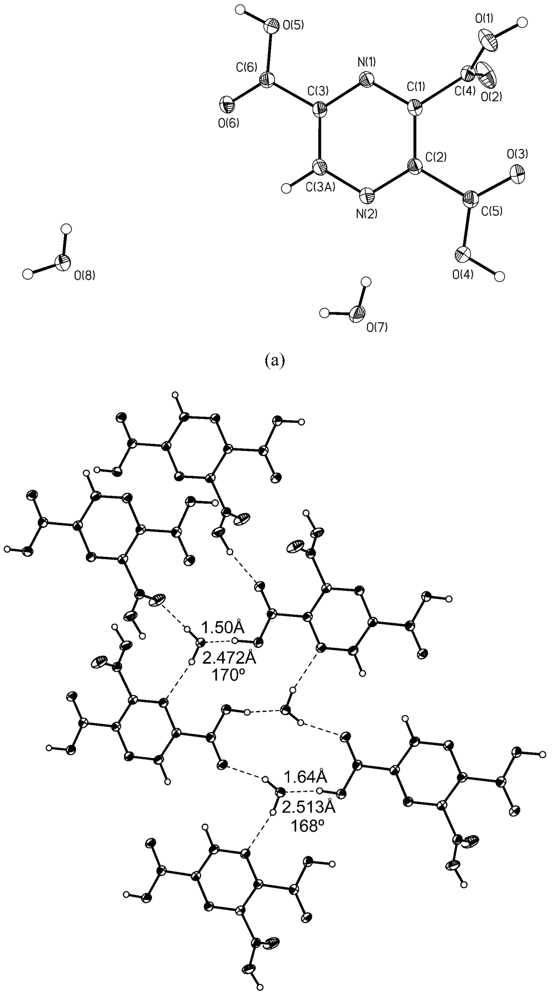
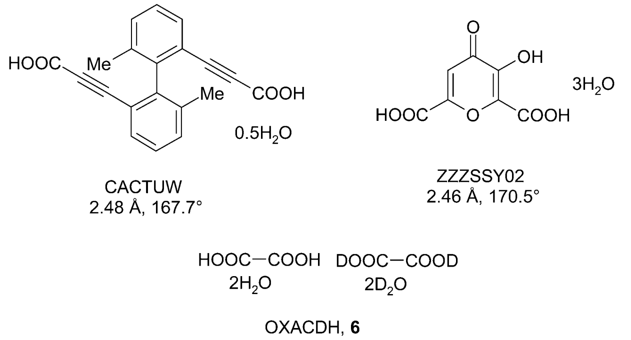


Figure 6. X-ray crystal structure of 2,3,5-pyrazinetricarboxylic acid, **5**. (a) ORTEP with displacement ellipsoids drawn at a 50% probability for non-hydrogen atoms. The dihedral angles of the carboxylic acid groups with the pyrazine ring are N1−C3−C6−O5 = 10.45(14)°, N2−C2−C5−O4 = 4.29(14)°, and N1−C1−C4−O1 = 81.02(14)°. (b) Metrics of the $O_{acid}-H\cdots O_{w}$ hydrogen bond in motifs **I** and **IV** are indicated. Tricarboxylic acid **5** has the shortest $O_{acid}-H\cdots O_{w}$ hydrogen bond (O···O = 2.4726(12) Å) in this family of structures. The crystal structure of triacid **5** is analyzed as a combination of H-bonds in tetraacid **1** and diacids **2** and **4**.

CHART 8: CSD Refcodes of Crystal Structures with a Synthon-Assisted Short $O_{Acid}-H\cdots O_{w}$ Hydrogen Bond



footnotes of Table 7. Values of $s_{O-H} = 0.691$ and $s_{H\cdots O} = 0.295$ for the $O_{acid}-H\cdots O_{w}$ H-bond (r = 1.0721(15) Å and d = 1.4098(17) Å at 20 K) mean that the hydrogen atom has bonded ~70% of the valence unit to the covalent bond and ~30% to the hydrogen bond. The O−H···O interaction in **1** therefore is well within the quasi-covalent regime defined for interanion

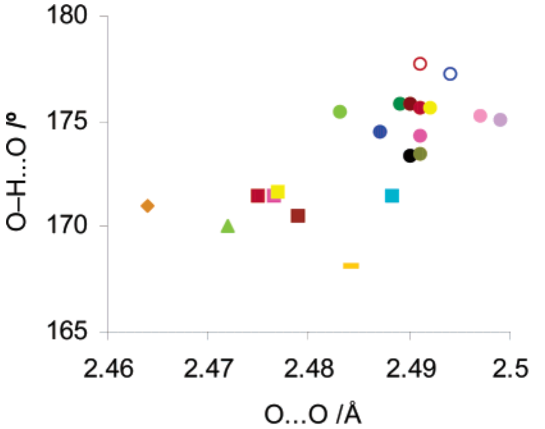


Figure 7. Distance−angle scatter plot of the very short $O_{acid}-H\cdots O_w$ hydrogen bond in 21 crystal structures with synthon-assisted hydrogen bonds (SAHBs). Pyrazine tetraacid **1** is represented by filled squares (■), oxalic acid **6** is represented by filled circles (●), the deuterated oxalic acid structures are represented by open circles (○), triacid **5** is represented by a filled triangle (▲), ZZZSSY02 is represented by a filled diamond (◆), and CACTUW is represented by a bold dash (−). Tetraacid **1**: ND (red filled square) 20 K, (magenta filled square) 100 K, (yellow filled square) 200 K, (light blue filled square) 293 K; XRD (maroon filled square) 123 K. Triacid **5**: (light green filled triangle) 120 K. Oxalic acid: XRD (light green filled circle) 15 K, (dark blue, dark green, and maroon filled circles) 100 K, (black and olive green filled circles) 130 K, (red, magenta, and yellow filled circles) 170 K, (pink and purple filled circles) 225 K. Deuterated oxalic acid: (red open circle) 15 K, (dark blue open circle) 100 K. ZZZSSY02: (orange filled diamond) 161 K. CACTUW: (orange bold dash) 150 K.

TABLE 7: Bond Order,[a,b] *s*, of Hydrogen Bonds in Pyrazine Tetraacid 1 (from ND Data)

H-bond	*T* (K)	r_{O-H} (Å)	s_{O-H}	$d_{H\cdots O}$ (Å)	$s_{H\cdots O}$
$O_{acid}-H\cdots O_w$	20	1.0721(15)	0.691	1.4098(17)	0.295
	100	1.0720(13)	0.691	1.4113(14)	0.293
	200	1.0640(16)	0.704	1.4233(18)	0.285
	293	1.0550(20)	0.721	1.4430(20)	0.271
$O_{acid}-H\cdots O_{acid}$	20	0.9861(17)	0.857	1.7393(18)	0.128
	100	0.9871(14)	0.855	1.7365(14)	0.129
	200	0.9895(19)	0.850	1.7370(19)	0.129
	293	0.9839(19)	0.862	1.7490(20)	0.125

[a] Calculated using the equations $s = \exp[(r_0 - r)/b]$ and $r_{X-H} = r_0 - b\ \ln\{1 - \exp[(r_0 - r_{H\cdots X})/b]\}$, with $r_{0,OH} = 0.925$ and $b_{OH} = 0.397$. [b] $\Sigma s = s_{X-H} + s_{H\cdots A} = 1$ according to hydrogen-bond order conservation. See ref 9 for details.

short O−H···O bonds; for example, the $O-H\cdots O^-$ H-bond in potassium hydrogen oxalate has values of $s_{O-H} = 0.73$ and $s_{H\cdots O} = 0.26$.[6c] In comparison, the strong hydrogen bonds in **1** have a less covalent and more electrostatic character (for $O_{acid}-H\cdots O_{acid}$, $s_{O-H} = 0.857$, $s_{H\cdots O} = 0.128$, $r = 0.9861(17)$ Å, and $d = 1.7393(18)$ Å at 20 K). Bond order, *s*, is meaningful only when calculated from accurate neutron diffraction crystal structures and at short H···O distances ($d < 1.8$ Å).[5e]

A plot of $d_{H\cdots O}$ versus r_{O-H} displays the expected inverse relation for the very short and short O−H···O hydrogen bonds in **1** (Figure 8). Experimental values of *r* and *d* in **1** fit perfectly the continuous solid curve derived from neutron diffraction crystal structures when due allowance is made for the usual dispersion of H-bond data. The three clusters of the four VT measurements at $d = 1.41-1.44$, $1.74-1.75$, and $1.81-1.84$ Å (Table 2) lie on the solid curve with about the same scatter as the points from the CAHB and RAHB crystal structures reported by Gilli et al.[18c,45] Thus, the synthon-assisted short H-bond in **1** exhibits characteristics similar to conventional short H-bonds in terms of an inverse O−H distance relation and a hydrogen-bond order of ∼0.3 valence units. The quantum chemical approach to the calculation of covalent bond orders and atomic valence indices[46] is not used in this paper.

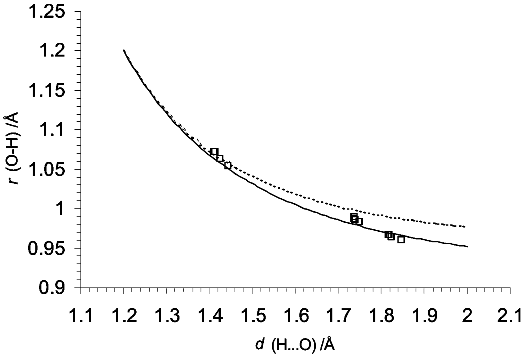


Figure 8. Plot of $d(H\cdots O)$ vs $r(O-H)$ (Å) in pyrazine tetraacid **1** from neutron diffraction data (Table 2). The points for the $O_{acid}-H\cdots O_w$, $O_{acid}-H\cdots O_{acid}$, and $O_w-H\cdots O_{acid}$ bonds overlay nicely on the solid curve for the equation, $r_{X-H} = r_0 - b\ \ln\{1 - \exp[(r_0 - r_{H\cdots X})/b]\}$. The solid line is the curve from experimentally derived parameters from neutron diffraction data, $r_{0,OH} = 0.925$, $b_{OH} = 0.397$. The dashed line is interpolated from gas-phase electron diffraction values, $r_{0,OH} = 0.96$, $b_{OH} = 0.346$. The dispersion of points in **1** along the solid curve is comparable to the conventional CAHB/RAHB short O−H···O bonds, shown in Figure 5 of ref 18c.

Hydrogen-Bond Potential Energy Well. The hydrogen-bond potential energy function can have one of these three forms: (i) an unsymmetrical double-well potential such that the proton lies in a sufficiently deep minimum and is covalently bonded, O−H···O; (ii) a shallow, symmetrical double-well potential such that the proton has sufficient vibrational energy to tunnel through the small activation barrier, $O-H\cdots O \rightleftharpoons O\cdots H-O$; or (iii) a single well minimum with the proton centered between the two oxygen atoms, O···H···O. Usually, short-strong hydrogen bonds lie in a potential well that resembles function ii or iii. The electrostatic−covalent character increases toward a quasi-covalent nature as the H-bond shortens and the potential function changes from i to ii to iii. The potential energy well in tetraacid **1** is unsymmetrical (like case i) because the hydrogen atom is covalently bonded to the COOH group and there is no proton migration to H_2O at all the temperatures studied. Proton transfer is a characteristic of short-strong hydrogen bonds with potential function ii. SSHBs are present when $\Delta pK_a \approx 0$ (e.g., COOH, COO−) because the covalent bond and hydrogen bond can lengthen and shorten, respectively, thereby increasing the strength of the hydrogen bond.[6f,12h,31a] Proton transfer is not observed in **1** because the donor and acceptor groups do not have an acid−conjugate base relationship. The migration of a proton from COOH to H_2O is unlikely even in the strongest H-bonds because of the large difference in their pK_a values (COOH, ∼2; H_2O, ∼15). There are examples in biochemistry wherein pK_a matching is not really necessary, for example, short hydrogen bonds in enzyme−inhibitor crystal structures of serine proteases.[12g,15,25] We demonstrate from this study that short hydrogen bonds are possible in multicenter, neutral arrays even if the pK_a values are far apart because the network of hydrogen bonds activates both the donor group and the acceptor group, thereby stabilizing the short H-bond. Interestingly, the donor and acceptor functional groups involved in the short hydrogen bonds discussed in this paper (synthon **I** and related motifs) and those in protease−inhibitor complexes (synthon **II** and other motifs in ref 15) have similar pK_a values. A systematic survey of the protein crystal structure database will possibly reveal more examples of short-strong, neutral hydrogen bonds akin to the SAHB array.

Red Shift in the O—H Infrared Stretching Vibration. In accordance with the covalent O—H bond lengthening in short-strong H-bonds, the stretching frequency ,ν_s, of the COOH group in **1** shows a red shift in the IR spectrum (KBr). The O—H stretching vibrations of O_{acid}—H···O_w in solid **1** appear at 1454, 1386, 1338, 1277, 1213, 1174, and 1134 cm^{-1}. The broad peaks at 3462 and 3219 cm^{-1} arise from the O—H stretching vibrations of the COOH and water groups (see the Supporting Information). These IR frequencies match the empirical ν_s(O—H) versus O···O distance relation.[7b,47] The hydrogen-bond energy of O_{acid}—H···O_w (O···O = 2.49 Å, ν_s(O—H) = 1350 cm^{-1}) is estimated as $E_{HB} \approx 16$ kcal mol^{-1} through comparison with a closely related crystal structure.[48] Differential scanning calorimetry and thermal gravimetric analysis confirm the phase purity and stoichiometry of tetraacid dihydrate **1** (T_{onset} H_2O release at 144 °C; T_{onset} melting at 207 °C, decomposes).

Conclusions

We report the occurrence of short hydrogen bonds in pyrazine di-, tri-, and tetracarboxylic acid dihydrates **1**—**5**. A very short O—H···O hydrogen bond is characterized in tetraacid **1** and triacid **5**, and short O—H···O hydrogen bonds are analyzed in diacids **2**, **3**, and **4**. The variable temperature neutron diffraction analysis of dihydrate **1** and low-temperature X-ray diffraction of dihydrates **2**—**5** provide an in-depth understanding of the short hydrogen bond in multicenter synthons **I** and **I′**. The synergy from resonance and polarization assistance in the finite, neutral array is sufficient to result in short (strong) O—H···O hydrogen bonds when the carboxylic acid donor is activated. This novel synthon-assisted hydrogen-bond shortening phenomenon is postulated from the neutron diffraction crystal structure of **1**, verified through the X-ray structures of **2**—**5**, and examples retrieved from the Cambridge Structural Database (CSD) that obey SAHB. The present study shows that not only charge and resonance assistance but also polarization assistance can lead to very short intermolecular O—H···O hydrogen bonds (O···O = 2.4—2.5 Å). This is the first study of a very short O_{acid}—H···O_w hydrogen bond by variable temperature neutron diffraction and, in general, a systematic analysis of short O—H···O hydrogen bonds in neutral arrays. The similarity of hydrogen-bonded synthons discussed in this paper to multicenter short H-bonds in enzyme—inhibitor crystal structures extends these results to structure-based drug design. Tetraacid **1** and its amide have potential in the crystal engineering of square network architectures.

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Supporting Information Available: Synthesis of pyrazine acids **1**, **3**, and **5**, neutron diffraction and X-ray diffraction experimental details, tables of crystal data, crystallographic files of neutron and X-ray structures (cif format), electrostatic surface potential maps of water, difference Fourier maps of **1**, and IR spectra of **1** (KBr and Nujol). This material is available free of charge via the Internet at http://pubs.acs.org.

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(48) See ref 18d. The Cambridge Structural Database (CSD) Refcode DETSBR01 with $\mathrm{O\cdots O}$ = 2.465 Å and ν_s $\sim$1200 cm^{-1} has an E_{HB} value of 15.5 kcal mol^{-1}. The empirical correlation of $\mathrm{O\cdots O}$ with ν_s and E_{HB} is approximate. We mention these values to show that the numbers for tetraacid **1** are similar to strong RAHB systems.