

of composite silica films was carried out by initially heating for 12 h at 100 °C, followed by heating for 3 h at 450 °C in a Yamato F0810 muffle furnace.

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Characterization of a Planar Cyclic Form of Water Hexamer in an Organic Supramolecular Complex: An Unusual Self-Assembly of Bimesityl-3,3'-Dicarboxylic Acid**

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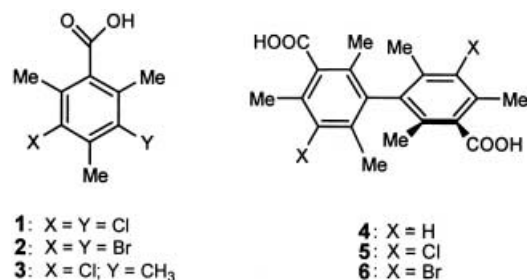
Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday

There is an upsurge of interest in contemporary theoretical and experimental research to unravel the structural details of water clusters.^[1–8] The clusters are believed to be the perfect means for characterizing the structural changes and bonding mechanisms in passing from isolated molecules to a macroscopic collection, namely, bulk water, whose anomalous properties still remain mysteries.^[1,2,9] A variety of modern theoretical and experimental methods have been employed to characterize the clusters. Both experiment and theory strongly suggest that the water trimer, tetramer, and pentamer have cyclic and quasiplanar minimum-energy structures. The larger clusters are expected to have 3D geometries, with the hexamer behaving as the transition from 2D to 3D structures.^[1,2] The X-ray structural characterization of a decamer^[10] and an octamer water cluster (cubic^[11] and cyclic^[12] forms) have been reported recently. Theoretical calculations for the hexamer have revealed the existence of several energy minima corresponding to “ring”, “book”, “bag”, “cage”, and “prism” topologies within 0.7 kcal mol^{−1}.^[13–15] The lowest energy conformer is the “cage” followed by the “book” and “prism” structures, which are less than 0.1 and 0.2 kcal mol^{−1} higher in energy, respectively.^[13–15] The “ring” and “bag” structures have been shown to be 0.5 and 0.7 kcal mol^{−1} higher in energy than the “cage”. To date, “chair”^[16,17] and “boat”^[18] cyclic hexamers included in host lattices have been characterized by X-ray crystallographic analysis. While Saykally and co-workers characterized the cage form of the hexamer,^[15] Nauta and Miller reported the detection of a “quasiplanar” hexamer in a helium droplet.^[19] Herein, we report the first X-ray structural characterization of the high-energy cyclic form of the water hexamer trapped in an organic supramolecular complex with the bimesityl dicarboxylic acid **4**. The planar ring constitutes the basic structural motif of the high-pressure Ice II modification,^[20] and is also one of the prominent morphologies found in the computer simulation of liquid water.^[21]

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Our recent study has shown that sterically encumbered mesitoic acids (**1–3**) adopt neither a centrosymmetric dimer motif nor a catemer motif in their crystal structures, but self-assemble into helical organizations when substituted in *meta*-



positions with chloro or bromo substituents.^[22] The helical self-assembly was found to be mediated by a composite of the X...X and C–H...X interactions. This discovery prompted us to explore the possibility of propagation of helical assemblies in two dimensions with halogen-substituted dicarboxylic acids such as **5** and **6**. Thus, we synthesized bimesityl dicarboxylic acids **4–6** to examine the molecular packing in **5** and **6**, and to establish the influence of halogen atoms by a comparison with the crystal packing of the acid **4**. Our numerous attempts at crystallizing the acids **5** and **6** were unsuccessful, which suggests that these acids do not exploit the stronger (O–H...O) and weaker (X...X and C–H...X) interactions jointly to stabilize the crystal lattice. Remarkably, the dicarboxylic acid **4** crystallized readily in MeOH–CH₂Cl₂ mixture by incorporating water (1 equiv) in its crystal lattice (trigonal, *R* $\bar{3}$; Figure 1).^[23] As expected, the two aromatic rings of the

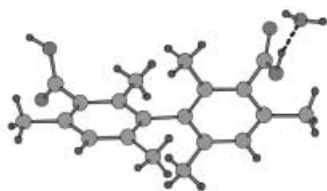


Figure 1. The molecular structure of acid **4** with one of its carboxy groups linked to the water molecule through an O–H...O hydrogen bond.

bimesityl moiety are almost orthogonal, with an angle of 82.4° between the two planes. The symmetry operation about the *c* axis generates a hexameric cluster of water (Figure 2). Figure 3 shows the overall association of water molecules with themselves and with the carboxy groups of the diacid molecules **4**. The space-group symmetry imposes a perfect planarity on the oxygen atoms of the water cluster. One of the two hydrogen atoms of each water molecule is involved in hydrogen bonding with an oxygen atom of the symmetry-related molecule, while its own oxygen atom is simultaneously hydrogen-bonded to another molecule of water, to complete the ring (see the hydrogen bond HB1 in Figure 3). The second hydrogen atom of the water molecule forms a hydrogen bond to the carboxy oxygen atom of the host diacid **4** (HB2). Furthermore, each of the cluster water molecules participates in hydrogen bonding with the carboxylic proton of the diacid **4** by engaging one of its lone pair of electrons (HB3). Overall,

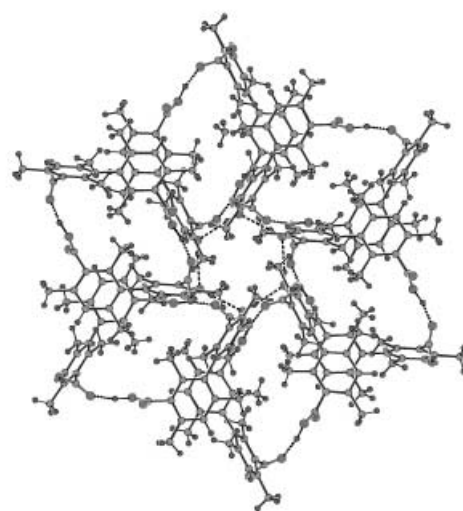
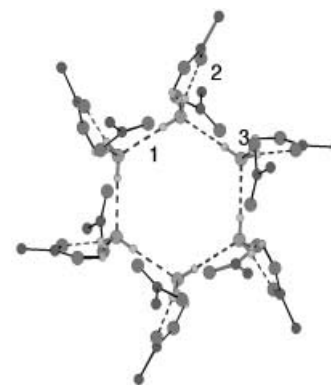


Figure 2. The crystal packing (projection down *c* axis) of **4**·H₂O complex. The hydrogen bonds (O–H...O) between the host and water molecules and between the two host molecules themselves are shown with broken lines.



Parameter	HB1	HB2	HB3
$d_{\text{O–H}}/\text{\AA}$	0.92	0.92	0.95
$d_{\text{O–H}}/\text{\AA}$	2.167	1.905	1.664
$\theta_{\text{O–H–O}}/^\circ$	136.59	169.55	168.73
$d_{\text{(O–O)}}/\text{\AA}$	2.905	2.816	2.606

Figure 3. The water hexamer together with the acid molecules (only –COOH are shown for clarity) linked through O–H...O hydrogen bonds (projection down *c* axis). The bonding parameters for the hydrogen bonds are given.

the six water molecules are bound to the host lattice through 12 O–H...O hydrogen bonds and the water molecules of the cluster typically assume a tetrahedral geometry. The hydrogen bonding parameters for all of the O–H...O bonds suggest that the interaction in all the cases is moderate^[7] and that the hydrogen bond between the water oxygen atom and the carboxylic hydrogen atom (HB3, Figure 3) is stronger than the other two, that is, HB1 and HB2. Regarding the interactions between the host acids, the second carboxylic hydrogen atom of the acid **4** forms a hydrogen bond with the carboxy oxygen atom of the symmetry-related molecule, which in turn forms another hydrogen bond (with its second carboxylic hydrogen atom) with the carboxy oxygen atom of the original acid (Figure 4). The protons of the carboxy group form hydrogen bonds with water molecules, while their carbonyl oxygen atoms accept hydrogen bonds from the water hydrogen atoms, to complete the crystal packing

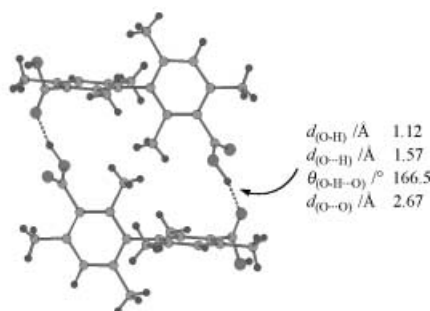


Figure 4. The unusual dimeric association of the acids through O–H...O hydrogen bonds.

(Figure 2). Thus, it appears that the water cluster acts as a template around which the acid molecules pack and vice versa.

To characterize the vibrational stretching frequency associated with the O–H bond of the water cluster, the FTIR spectrum of the complex was recorded (Figure 5). The broad band centered about 3400 cm^{-1} in Figure 5 is readily attributed to the O–H stretching frequency of the water cluster. It should

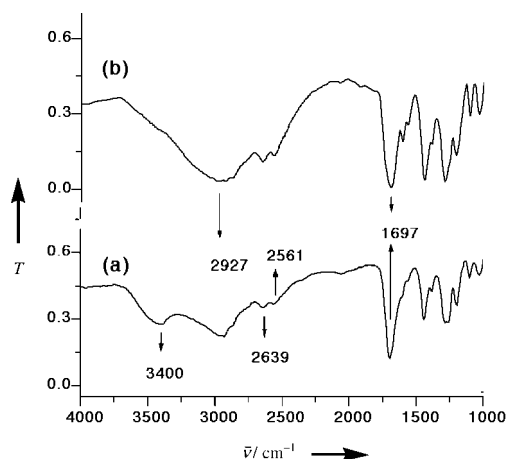


Figure 5. The FTIR spectra of acid **4**·H₂O complex before (a) and after (b) heating under vacuum at 100°C .

be noted that the carboxylic OH group gives rise to a broad band with some structure in the region around about $2600\text{--}3200\text{ cm}^{-1}$, which slightly obscures the C–H stretching vibrations. The IR spectrum of the same crystals when heated at about 100°C under vacuum (0.1 mm) for 2 h is also shown in Figure 5. The broad band corresponding to the water hexamer disappears, which suggests that the associated water molecules escape from the crystal lattice. Deliberate re-exposure of these crystals to water vapor for 2 days, monitored by FT-IR spectroscopy, did not lead to reversible absorption into the lattice. Powder X-ray diffractograms of the crystals before and after expulsion of water at about 100°C under vacuum (Figure 6) reveal only marginal differences in the diffraction patterns and intensities, which suggests that the integrity of the host lattice is robust to the exclusion of water. The crystal packing is reminiscent of polymer imprinting in that it is generated utilizing the water cluster as a template and it carries the imprint of the water hexamer after exclusion of the template (water cluster) on heating under vacuum.

As mentioned at the outset, tremendous effort has gone into establishing the structural details of water clusters. For a

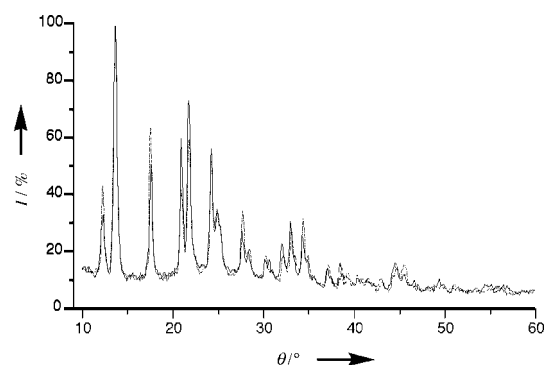


Figure 6. The X-ray diffraction patterns of **4**·H₂O complex before (solid line) and after heating under vacuum at 100°C for 2 h (broken line).

hexamer, the highest level ab initio calculations have revealed the cage structure as the minimum energy form.^[15] Indeed, this structure has been confirmed by Saykally and co-workers from their pioneering work utilizing Far-Infrared (FIR) Vibration–Rotation Tunneling (VRT) spectroscopy.^[15] From a comparison of the experimentally observed infrared O–H stretches of water clusters formed in a helium droplet with those of the clusters formed in free jet expansion, and extensive theoretical calculations, Nauta and Miller have characterized the high-energy ring form of the water hexamer in a helium droplet.^[19] Accordingly, the absorption caused by the O–H stretch occurs at about 3325 cm^{-1} . Similarly, the O–H stretches of the hexamers in the Ice I and II phases were reported to occur at about 3220 cm^{-1} .^[24] In comparison, the same absorption for the hexamer in the present supramolecular complex occurs at about 3400 cm^{-1} (Figure 5). Thus, the observed differences in the absorptions arising from the O–H stretch should be explained by the differences in the matrices in which the clusters are formed. In a similar vein, a comparison of the structural parameters of the planar hexamer with those found in the Ice I and II forms is quite instructive; the average O...O distances reported for the Ice I and II phases are 2.75 and 2.77–2.84 Å, respectively.^[9] This distance for the water cluster reported herein is 2.905 Å, which is remarkable given that the planar hexamer is implicated in bulk water. Notably, the bulk water has a short-range order in the O...O X-ray diffraction radial-distribution curve at 2.85 Å (for the gas phase it is 0.1 Å longer).^[9]

The packing of the acid molecules **4** does not conform to any of the known association patterns of carboxylic acids. A recent Cambridge Structural Database analysis has shown that the dimer motif is found in 90% of the crystal structures reported for the acids, while the catemer motif is found in 4%; the dimer motif expanded by one or two solvent water molecules is found in the remaining 6%.^[25] Given the importance of the centrosymmetric dimer motif of the carboxylic group in supramolecular network design and synthesis,^[26,27] the observed departure of the packing of **4** from any of the known motifs emphasizes the need to understand the factors that enforce a paradigm shift in the association. Obviously, the observed packing must be a result of compact packing that maximizes the crystal lattice stabilization, which appears to be best achieved in the present instance by incorporation of the water as a guest molecule in the crystal lattice. In the absence of any readily perceivable

influences, we believe that the crystal packing, contrary to that expected based on centrosymmetric dimer motifs, is most likely manifest in compounds, whose structures are 1) characterized by steric hindrance about the carboxy group and 2) endowed with certain interacting groups that are non-linearly built into the molecules (at the *meta* position). We are continuing to investigate the self-assembly of aromatic carboxylic acids of varying structures and a variety of interactions.

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- [23] Crystal data for 4·H₂O: Slow evaporation of **4** in methanol–dichloromethane (2:1) mixture yielded suitable crystals for diffraction studies. The intensity data were collected on a Siemens P4 single-crystal diffractometer equipped with a molybdenum sealed tube ($\lambda = 0.71073 \text{ \AA}$) and highly oriented graphite monochromator. The lattice parameters and standard deviations were obtained by a least-squares fit to 40 reflections ($9.58^\circ < 2\theta < 25.55^\circ$). The data were collected in 2θ scan mode with a variable scan speed ranging from 2.0° to a maximum of $60.0^\circ \text{ min}^{-1}$. The structure was solved by direct methods using SHELX-97 (G. M. Sheldrick, Program for the solution and refinement of crystal structures, University of Göttingen, Göttingen (Germany), **1997**) package and also refined using the same program. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms, except those of the water molecule, were stereochemically fixed on their ideal positions with fixed isotropic U values and their C–H distances were refined freely. The hydrogen atoms of the water molecule were identified from the difference Fourier transform and the O–H distances were varied freely during the refinement. A weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ was used. The difference Fourier map, after the refinement, was featureless. Crystal dimensions: $0.21 \times 0.18 \times 0.14 \text{ mm}$; $T = 293(2) \text{ K}$; trigonal, $R\bar{3}$ (hexagonal axes); $a = b = 25.543(2) \text{ \AA}$, $c = 15.384(2) \text{ \AA}$; $V = 8692.5(2) \text{ \AA}^3$; $Z = 18$; $\rho_{\text{calc}} = 1.184 \text{ g cm}^{-3}$; $2\theta_{\text{max}} = 47^\circ$; 2952 reflections collected of which 2713 were unique; 239 parameters; GOOF = 1.012; $R_1 = 0.0599$, $wR_2 = 0.1103$ for $I > 2\sigma(I)$; residual electron density: 0.215 and $-0.161 \text{ e \AA}^{-3}$. CCDC-186118 (**4**) contains the supplementary

crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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NMR Reporter Screening for the Detection of High-Affinity Ligands

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The ability to detect protein–ligand interactions in a robust and sensitive manner (“NMR screening”) is one of the prime assets of biomolecular NMR spectroscopy in drug discovery.^[1–6] It is being used for validation of hits identified in other biological assays, or for the discovery of high-affinity ligands for a given target. NMR screening can be performed by observation of either target resonance signals or ligand resonance signals. Observation of target resonance signals requires large amounts of isotopically labeled protein, very-soluble protein, and has an upper limit for protein size. Since many therapeutically interesting targets do not fall into this class, observation of ligand resonances is the more generally applicable method. A variety of NMR techniques are available to perform these studies. None of them requires isotopically labeled protein, and some of them require only very small amounts of protein.^[7–9] A general drawback of all ligand-observation methods, however, is their inability to detect high-affinity ligands—these are false negative and appear to be non-binding. The cause of this significant drawback lies in that for ligand-observation methods, only unbound ligand is observed because of the high excess of ligand over protein. In the case of weak or medium binding affinity (K_D typically less than $1 \mu\text{M}$), the dissociation rate is generally so large that a significant exchange between bound and free ligand occurs during the time scale of the experiment, typically a few hundred milliseconds. This exchange process transfers ligand properties from the bound state (e.g. fast relaxation, large negative NOEs) to the free ligand, so that information about binding has been conveyed to the unbound ligand. In strongly bound ligands (sub-micromolar K_D), the

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