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Encapsulation of Conventional and Unconventional Water Dimers by Water-Binding Foldamers

Wei Qiang Ong,[†] Huaiqing Zhao,[†] Xiao Fang,[†] Susanto Woen,[†] Feng Zhou,[‡] Weiliang Yap,[†] Haibin Su,[‡] Sam F. Y. Li,[†] and Huaqiang Zeng*,[†]

Department of Chemistry and NUS MedChem Program of the Office of Life Sciences,
3 Science Drive 3, National University of Singapore, Singapore 117543, and Division of
Materials Science, 50 Nanyang Avenue, Nanyang Technological University,
Singapore 639798

chmzh@nus.edu.sg

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ABSTRACT

Water-binding foldamers have been rarely studied. By orienting both H-bond donors and acceptors toward their interior, two pyridine-derived crescent-shaped folding oligoamides were found to be capable of trapping both conventional and unconventional water dimer clusters in their cavity (~2.5 Å radius). In the unconventional water dimer cluster, the two water molecules stay in contact via an unusual H−H interaction (2.25 Å) rather than the typical H-bond.

Supramolecules have been known to be able to host water molecules in their cavities, channels, or layers in the solid state. Depending on the sizes of the cavity and the functionalities present in the host molecules, water molecules can interact through H-bonding to form various kinds of water clusters containing 2−45 water molecules.[1] Stabilizing the water clusters in the crystal lattice offers an attractive avenue whereby various topographies or architectures of the water clusters and the system's H-bonding networks can be more easily studied, allowing us to better understand the unusual physical and chemical properties of bulk water and its interactions with surfaces. In particular, numerous theoretical and experimental investigations of smaller water clusters, ranging from a dimer to hexamer cluster,[1m−t] had provided good insights into the structure, cooperativity, and rearrangement dynamics of the H-bonding network in bulk water, which still remains quite poorly understood at the present time. As the simplest form of water clusters, a water dimer, $(H_2O)_2$, is of paramount importance and had been extensively studied[1s,t,2] due to its significant roles in several existing

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[†] National University of Singapore.

[‡] Nanyang Technological University.

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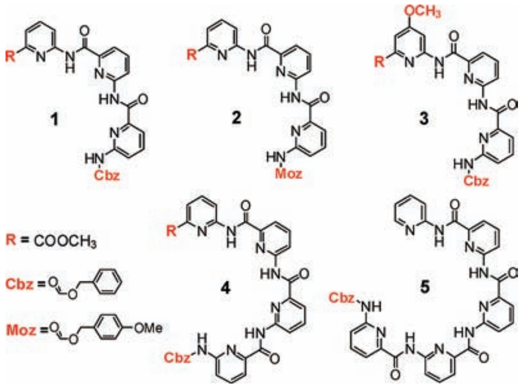
environmental issues, including the formation of acid rain,[3] vapor−liquid nucleation,[4] absorption of solar radiation in the atmosphere,[5] and greenhouse effect.[6]

On the other hand, the hitherto reported supramolecular water hosts have largely relied on conformationally more flexible organic or organometallic molecules with respect to foldamers[7] whose well-defined backbones are primarily stabilized by noncovalent forces such as solvophobic forces, $\pi-\pi$ stacking interactions, and H-bonds. Despite their great diversities,[7] only a few foldamer molecules of similar type have been reported recently by Lehn and Huc, accommodating up to three water molecules in their cavities.[8] This communication presents a foldamer approach toward encapsulating both conventional and unconventional water dimers and discusses their topologies and energetic profiles constrained within the cavities of two water-binding pyridine-based foldamers, i.e., trimer **3** and pentamer **5**.



Pyridine-based H-bond enforced folding backbones of oligoamides **1**, **2**, **4**, and **5** have been recently confirmed to have a crescent structure in both solution and solid states.[9] Longer oligomers such as tetramer **4** and pentamer **5** take up a helical conformation that requires ~4.3 repeating units per helical turn. The inward-pointing amide protons (H-bond donors) and pyridine nitrogens (H-bond acceptors) in **1**−**5** enclose a cavity of ~2.5 and 3.1 Å in radius, respectively, and seem to be large enough to accommodate water molecules. *Ab initio* calculations performed on trimer **1**, tetramer **4**, and pentamer **5** at the B3LYP/6-311G* level show that the water complexes of $\boldsymbol{n{\bullet}H_2O}$ (n = **1**, **4**, and **5**) have a respective stability of 9.11, 11.39, and 7.80 kcal/mol more than its individual components with $\mathbf{4{\bullet}H_2O}$ being energetically most favored (see the Supporting Information). Undoubtedly, the crystal packing effect may override this energetic favorability order.

Experimentally, obtaining water complexes was not that straightforward. After screening numerous conditions involving various combinations of all the common organic solvents by methods of either slow evaporation or diffusion, **1** cannot be crystallized out under all the conditions tested, crystals of **2** and **3** can only be obtained respectively from acetone and dichloromethane by slow evaporation, and slow diffusion of cyclohexane into dichloromethane over a few weeks led to X-ray quality crystals for **4** and **5**.

Examination of these crystal structures reveals the absence of water molecules in both **2** and **4**. Since **2** was crystallized from water-sequestering acetone molecules, seclusion of trace amounts of acetone-solvated water may occur that prevents **2** from binding to water molecules. In **4**, rather than water molecules, dichloromethane molecules were either trapped in the crystal lattice or bound by **4** in its cavity.

Nevertheless, the water-binding abilities of this series of pyridine-derived cavity-enclosing oligoamides can be proven by the water-containing crystal structures of **3** and **5**. Of further note is that both were crystallized from water-immiscible solvents such as dichloromethane and cyclohexane, and only trace amounts of water molecules can be found under these crystallization conditions.

The crystal structure[9a] of **3** expectedly shows a crescent-shaped structure as those found in **1**, **2**, **4**, and **5** recently reported by us,[9b] a result of an efficient backbone rigidification by the stabilizing forces from the continuous intramolecular H-bonding network made up of five H-bonds (Figure 1). Molecules of **3** stack in a linear,

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(9) (a) The crystal structure of **3** was refined at atomic resolution by a full-matrix least-squares method with anisotropic temperature factors. H-atoms at water molecules and from amide bonds were located from difference Fourier maps and refined independently; all others were placed on calculated positions and refined as riding atoms. The refinement converged at an R-value of 0.0687. (b) Ong, W. Q.; Zhao, H. Q.; Du, Z. Y.; Yeh, J. Z. Y.; Ren, C. L.; Tan, L. Z. W.; Zhang, K.; Zeng, H. Q. *Chem. Commun.* **2011**, DOI:10.1039/C1CC11532D.

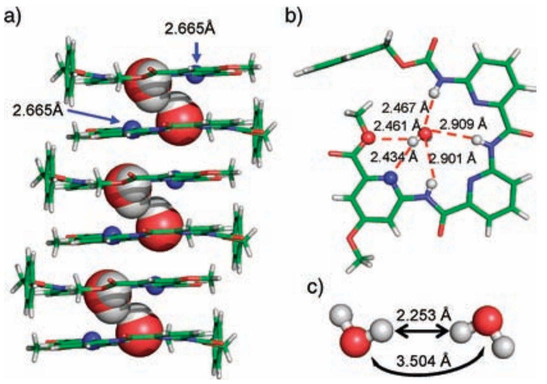

Figure 1. (a) Cylindrical packing by **3**; blue solid arrows indicate the weak H-bond formed between the pyridine N and the respective closer proton from the water dimer. (b) Intermolecular H-bonds of varying lengths found among the trapped water molecule, amide protons, pyridine N-atoms, and ester O-atoms in **3**; atoms participating in H-bonds are represented by small balls of varying colors. (c) Unconventional water dimer cluster from (a) that is mediated by the van der Walls interaction involving two H-atoms (d_{H-H} = 2.253 Å). H-bonds in (b) are shown as dotted red lines.

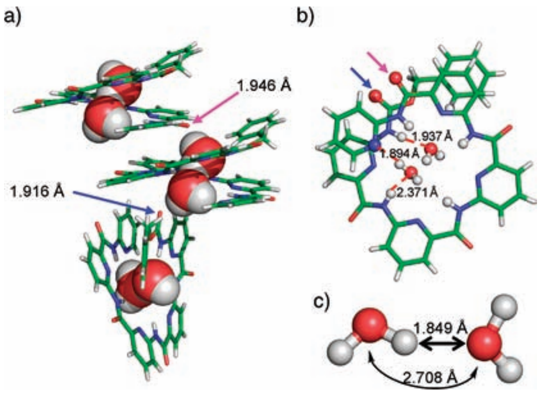

Figure 2. (a) Intermolecular zigzag packing by **5**. (b) Intermolecular H-bonds of varying lengths found among a trapped water molecule, amide protons, pyridine N-atoms, and ester O-atoms in **3**; atoms participating in H-bonds of within 3.0 Å are represented by small balls of vaying colors, and strong H-bonds are labeled with the H-bond lengths. (c) Conventional water dimer cluster from (a) or (b) that is mediated by one strong H-bond of 1.849 Å with a very short interatomic distance of 2.71 Å between the two water oxygens. In both (a) and (b), carbonyl O-atoms from the two ends form two strong intermolecular H-bonds with the water dimer cluster and are indicated by single-headed solid lines. H-bonds in (b) are shown as dotted red lines.

cylindrical fashion with an ~180° offset from each other, due to the benzene ring of the carboxybenzyl (Cbz) protecting group lying in a perpendicular position to the plane of the aromatic backbone (Figure 1a). The five intramolecular H-bonds formed between amide protons and neighboring pyridine nitrogens have H-bonding distances 2.144– 2.347 Å in length. The resultant H-bond enforced small cavity in **3** has a radius of ~2.51 Å, measured from the center of the cavity to the amide proton, and is found to enclose a water molecule in each asymmetric unit despite using a nonpolar solvent, dichloromethane, with low water content as the crystallizing medium. The water molecule sits almost in the center of the cavity (Figure 1b) with its O-atom forming a medium strength H-bond (d_{O-H} = 2.467 Å) with the amide proton of the Cbz group and two weak H-bonds with the other two amide protons (d_{O-H} = 2.909 and 2.901 Å). One of the waters additionally forms two medium strength H-bonds with the pyridine N (d_{H-O} = 2.434 Å) and the ester O (d_{H-O} = 2.462 Å). The other water proton forms a medium strength H-bond with the pyridine N (d_{H-O} = 2.665 Å, Figure 1a) that stays below or above the proton.

Interestingly, the arrangement of the two water molecules in the cluster observed in **3** is quite unusual: there is no intermolecular H-bond found in the water dimer (Figure 1c), making it not belong to any of the 16 unique water dimer clusters suggested by Dyke with invariably each containing one intermolecular H-bond.[1s,t] Instead, the water molecules in the cluster are in close contact with each other through H–H interaction with a H···H distance of 2.253 Å that is ~0.15 Å less than twice the van der Waals radius of the H-atom (VdW = 1.20 Å). The distance between the two water oxygens is 3.504 Å. As the water dimer clusters elongate, a zigzag-like discrete infinite water chain is observed, with a distance of 6.92 Å between the two adjacent water dimers, which is approximately twice that of the typical intermolecular $\pi-\pi$ stacking distance (Figure 1a). This unconventional water dimer cluster is formed possibly as a result of strong intermolecular H-bonds between the water molecule and the protons and nitrogens of **3** (Figure 3b) that "freeze" the water molecule in the cavity of **3**, followed by the aromatic $\pi-\pi$ stacking forces that pack the water-containing **3** in a way that brings pairs of water molecules in close proximity, yet without allowing them to reorient as they would since their rotations are greatly restricted by intermolecular H-bonds.

Similar to **3**, water molecules are also found in the cavity of **5**. But differing from **3** that encloses one water molecule per molecule of **3**, every molecule of **5** is able to accommodate two waters in its cavity. Apparently, this difference can be attributed to the differential structures between them: while **3** adopts a planar structure and so contains a roughly 2D planar cavity, **5** being helically folded encloses a cavity that is 3D-shaped.

In **5**, there are nine intramolecular H-bonds (2.133–2.394 Å) that lead to a helical conformation to enclose a small cavity with a radius of ~2.57 Å, measured from the center of the cavity to the amide proton. Its 3D packing is stabilized by two strong H-bonds among the water dimer and the carbonyl oxygens from the end amide and Cbz groups (d_{H-O} = 1.946 and 1.916 Å, respectively, Figure 2a and 2b). In this case, the water dimer cluster also serves as an *exo*-bidentate ligand, bridging molecules of **5** and forming a zigzag-like chain with an intermolecular distance

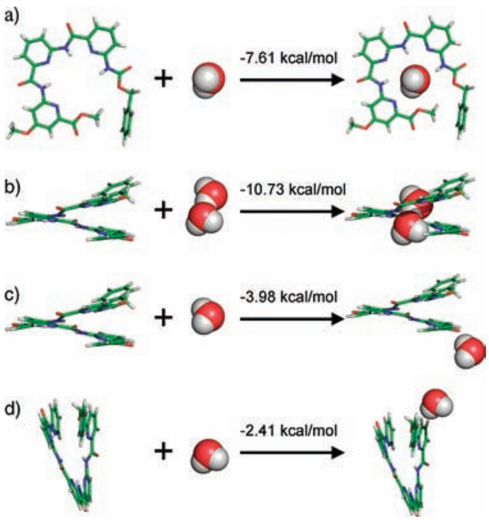

Figure 3. Binding energies derived by comparing the calcluated single-point energies of structural motifs directly taken out from the H-bonding networks found in **3** and **5** at the B3LYP/6-311G+(2d,p) level. (a) H-bonds formed between a water molecule and **3** are worth ~7.61 kcal/mol. (b) H-bonds formed between the water dimer cluster and **5** are worth ~10.73 kcal/mol. (c) An axial H-bond of 1.946 Å formed between a water molecule and neighboring **5** from Figure 2a is worth ~3.98 kcal/mol. (d) An axial H-bond of 1.916 Å formed between a water molecule and neighboring **5** from Figure 2a is worth ~2.41 kcal/mol.

of 6.821 Å between two crystallographically equivalent water oxygens (Figure 2a).

The water dimer cluster in **5** is stabilized by forming two strong H-bonds with the pyridine N (d_{H-N} = 1.894 Å) and Cbz amide proton (d_{O-H} = 1.937 Å), one medium strength of H-bond (d_{O-H} = 2.371 Å) with amide proton, and other weak H-bonds of less than 3.0 Å with other amide protons (Figure 2b). Out of five pyridine N-atoms, only the one from the first pyridine ring at one end participates in forming a strong H-bond with the water dimer (d_{H-N} = 1.894 Å, Figure 2b). As illustrated in Figure 2c, seemingly like a conventional water dimer containing a strong H-bond (d_{H-O} = 1.849 Å), the O–O distance was however found to be very short at 2.708 Å for the water dimer cluster found in **5**. This distance is even shorter than that observed in regular ice (d_{H-O} = 2.74 Å), an indication of the strong and positive cooperativity in the H-bonding network shown in Figure 2b.

The binding energies dictating the formation of unconventional and conventional water dimer clusters in **3** and **5** were computed to be 2.22 and 3.88 kcal/mol, respectively, at the level of M06-2X/aug-cc-pvtz.[10] Compared to the binding energy (BE) of 5.21 kcal/mol for the most stable H-bonded water dimer (Figure S2c), the water dimers found in **3** and **5** are destabilized by 2.99 and 1.33 kcal/mol, respectively, due to the structural restrictions imposed by the surrounding molecular scaffolds.

The energetic profiles of the H-bonding networks in **3** and **5** were provided by carrying out single point-energy calculations at the B3LYP/6-311G+(2d,p) level on the corresponding structural motifs taken from their crystal structures. As shown in Figure 3a and 3b, monomeric **3** (Figure 1b) and **5** (Figure 2b) contribute a respective total stabilizing energy of 7.61 and 10.73 kcal/mol to the water molecule and water dimer in their cavities by forming H-bonds of varying strengths. For the two axially orienting H-bonds of 1.946 and 1.916 Å in length found in **5** (Figure 2a), their H-bond strengths were computed to be 3.98 kcal/mol (Figures 3c and S2b) and 2.41 kcal/mol (Figures 3d and S2a), respectively. Although we are not certain why the shorter H-bond (1.916 Å) is weaker than the longer H-bond (1.946 Å) by 1.57 kcal/mol, this discrepancy may be due to the nonlinear relationship among atoms O_1, H, and O_2 and a shorter distance of 2.757 Å between the two repulsive O_1 and O_2 atoms for the former H-bond (Figure S2a) with respect to those found in the latter (Figure S2b). Apparently, the formation of these stabilizing H-bonding networks can more than compensate for the energetic penalties of 2.99 and 1.33 kcal/mol experienced by the water dimer clusters constrained in **3** and **5**, respectively, adopting stable yet less favored conformations with regard to the most stable water dimer conformation.

In summary, we report here for the first time a crystallographic observation of an unconventional water dimer mediated by a rather unusual H···H interaction. Compared to the computationally derived BE of 5.21 kcal/mol for the most stable water dimer cluster, those water dimer clusters in **3** and **5** are destabilized by 2.99 and 1.33 kcal/mol, respectively. The ability to trap both conventional and unconventional water dimer clusters of varying stabilities and topographies by **3** and **5** highlights the potential use of other analogous pyridine-derived foldamers as the water-binding molecules, allowing for the creation of enlarged 3D-shaped cavities for encapsulating larger water clusters of diverse topographies in their interiors.

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Supporting Information Available. Synthetic procedures and a full set of characterization data including ^{1}H NMR, ^{13}C NMR, MS, crystal data, and molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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