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Selective Recognition of Highly Hydrophilic Molecules in Water by Endo-Functionalized Molecular Tubes

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Supporting Information

ABSTRACT: Selective recognition of neutral hydrophilic molecules in water is a challenge for supramolecular chemistry but commonplace in nature. By mimicking the binding pocket of natural receptors, endo-functionalized molecular tubes are proposed to meet this challenge. We found that two molecular tubes with inwardly directed hydrogen-bond donors recognize highly hydrophilic solvent molecules in water with high selectivity. In the complexes, hydrogen bonding occurs in the deep and hydrophobic cavity. The cooperative action between hydrogen bonding and hydrophobic effects accounts for the high affinity and selectivity. The molecular receptor is fluorescent and can detect concentrations of 1,4-dioxane—a known carcinogen and persistent environmental contaminant—in water at a limit of 119 ppb. The method simplifies the analytic procedure for this highly hydrophilic molecule.

It is generally accepted that selective recognition of neutral hydrophilic molecules in water is challenging for synthetic molecular receptors,[1] and few systems are up to this task.[2] Effective solvation of hydrophilic molecules thwarts their interactions with receptor molecules,[1c,d] and it is also very difficult to exploit hydrogen bonding for synthetic molecular recognition in water.[1a] However, hydrophilic biomolecules, such as sugars, can be recognized by natural receptors even with high selectivity.[3]

Unlike ions, neutral hydrophilic molecules contain not only polar groups but also nonpolar (hydrophobic) groups (Figure 1a). Selective recognition of these molecules would require favorable interactions with both polar and nonpolar groups simultaneously. Natural receptors indeed work this way: the hydrophobic binding cavities of natural receptors are usually decorated with inwardly directed functional groups. Hydrophobic effects and non-covalent interactions, such as hydrogen bonds, work synergistically to achieve high binding affinity and selectivity; recognition of hydrophilic biomolecules in water requires shape, electrostatic, and hydrophobic complementarity.

Synthetic receptors with a hydrophobic cavity having polar groups can selectively recognize neutral hydrophilic molecules in water.[2] To be more effective, two more criteria should be met: (a) the binding cavity should be deep enough to be separated from the bulk water, allowing hydrophobic effects to operate in the recognition of the nonpolar groups, and (b) complementary functional groups, such as hydrogen-bonding sites, should be positioned in the deep cavity away from the portal, allowing non-covalent interactions to operate in a relatively nonpolar environment and avoiding competition with water.[4] The polar groups are then satisfied by their complements and the nonpolar

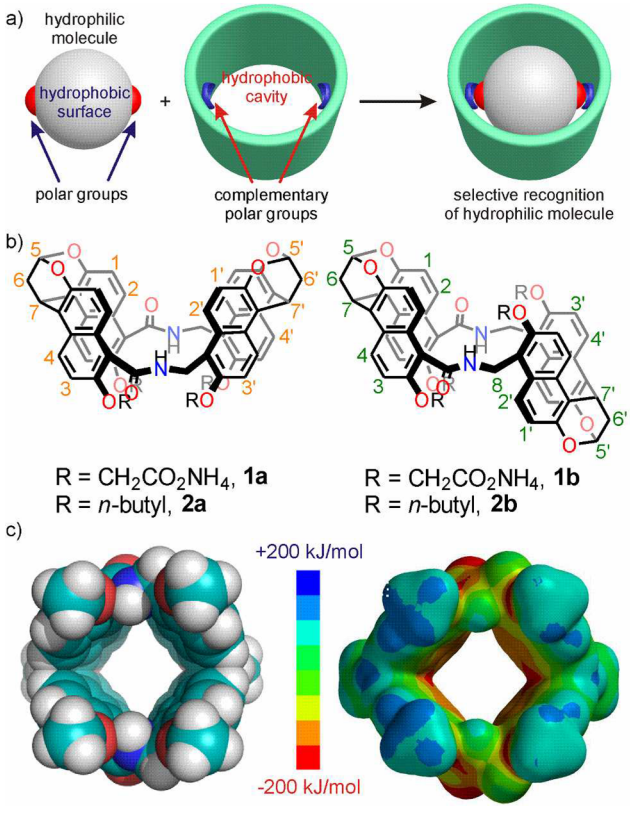

Figure 1. (a) Cartoon representation of selective recognition of neutral hydrophilic molecules in water by endo-functionalized molecular tubes. (b) Chemical structures of molecular tubes **1a**, **1b**, **2a**, and **2b**. Numbering in the structures is used for the assignments of NMR signals. (c) Energy-minimized structure and electrostatic potential surfaces of the syn isomer calculated at the PM06 level of theory. The peripheral feet were shortened to methyl groups for convenience.

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groups enjoy a hydrophobic environment in the cavity by releasing water molecules. Hydrophobic effects and non-covalent interactions can thus work cooperatively in this way.

A deep tubular structure offers a promising cavity shape (Figure 1a). However, it is difficult to find a structural element that can be used to construct a well-defined tubular cavity having inwardly directed functional groups. Glass and co-workers[5] earlier reported a pair of molecular tubes (the acid forms of molecular tubes **1a** and **1b**; Figure 1b) based on a bisnaphthalene cleft.[6] These molecular tubes were used to recognize lipid molecules in water through hydrophobic effects. We employed the same scaffold to construct organic-soluble endo-functionalized molecular receptors.[7] However, a close look at **1a** and **1b** (Figures 1c and S1) shows that the amide N−H groups are directed into the cavity; thus, they are endo-functionalized molecular tubes and meet the criteria mentioned above for recognizing hydrophilic molecules in water. We resynthesized and characterized Glass's water-soluble molecular tubes, their ammonium salts, and their organic-soluble versions (Experimental Section in the Supporting Information and Figures S2–S9). The binding pockets of **1a** and **1b** are neutral since the charged carboxylate groups only provide water solubility.

The cavities of molecular tubes **1a** and **1b** are electron-rich and hydrophobic in water since they are defined by four naphthalene units (Figure 1c). As amide N−H protons are directed into the cavity, hydrophilic molecules with one or two hydrogen-bond acceptors and hydrophobic surfaces should be accommodated very comfortably in these cavities, provided that they are the right size. An ideal guest was found in 1,4-dioxane: its two oxygen atoms are positioned in the right geometry as hydrogen-bond acceptors while the rest of the molecular surface is hydrophobic.

Large upfield shifts were observed in the NMR spectra of 1,4-dioxane when either **1a** or **1b** was present in water: −1.46 ppm for **1a** and −1.90 ppm for **1b** (Figure 2). This shielding effect is

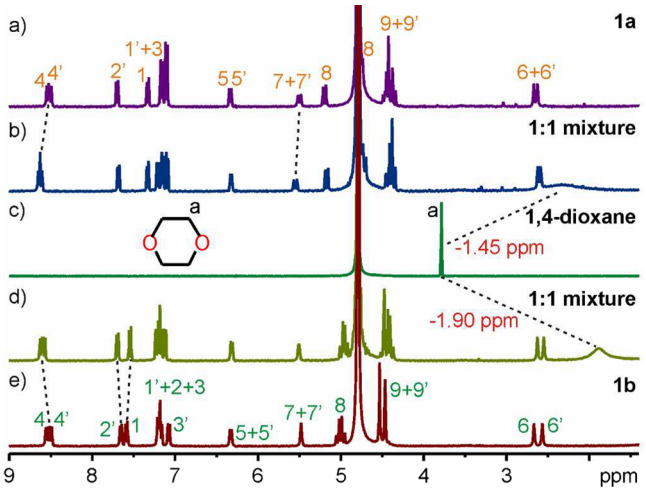

Figure 2. Partial ^{1}H NMR spectra (400 MHz, D_2O, 1.0 mM, 25 °C) of (a) **1a**, (b) a 1:1 mixture of **1a** and 1,4-dioxane, (c) 1,4-dioxane, (d) a 1:1 mixture of **1b** and 1,4-dioxane, and (e) **1b**.

expected as four naphthalene panels surround the 1,4-dioxane bound inside the cavity. NMR titrations and Job's plots (Figures S10–S15) provide association constants (K_a) for the complexes: 13 500 M^{-1} for **1a** and 3150 M^{-1} for **1b**.

In water, 1,4-dioxane is well solvated—it is even miscible—and should be difficult to extract into the binding cavity of any receptor. Water-soluble macrocycles, such as β-cyclodextrin and cucurbit[6]uril, cannot effectively bind this hydrophilic molecule.[8] Only recently, Diederich and co-workers[9] reported the first effective 1,4-dioxane receptor: a helicage that is able to recognize 1,4-dioxane (K_a = 8200 M^{-1}) in 19:1 H_2O/MeOH. The binding data in H_2O were not obtained because of the poor water solubility of the helicage. The binding cavity of the helicage is charged, and the recognition is probably through cation−dipole interactions and hydrophobic effects. In contrast, the binding cavities of **1a** and **1b** are essentially neutral but feature hydrogen-bond donors that recognize 1,4-dioxane. Such high binding affinity of a highly hydrophilic molecule in H_2O in a neutral cavity is unprecedented.

The affinity, however, is not limited to 1,4-dioxane: dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetone, and tetrahydrofuran (THF)—all of which are miscible with water—are also complexed by **1a** and **1b**. Molecules with structures similar to 1,4-dioxane, such as 1,3-dioxane, oxetane, tetrahydropyran (THP), and oxepane are also guests in **1a** and **1b** in water (Table 1 and Figures S16–S47). Generally speaking, these

Table 1. Association Constants K_a of Molecular Tubes 1a and 1b with Various Neutral Hydrophilic Molecules in Water at 25 °C As Determined by NMR Titration (D_2O) and Fluorescence Titration (H_2O)[a]

	NMR		fluorescence			
	1a	**1b**	**1a**		**1b**	
guest	K_a (M^{-1})	K_a (M^{-1})	K_a (M^{-1})	I_{sat}/I_0[b]	K_a (M^{-1})	I_{sat}/I_0[b]
1,4-dioxane	13500	3150	10500	3.9	3880	4.3
DMF	311	117	–[c]	–[c]	78	2.0
DMSO	31	130	–[c]	–[c]	76	1.7
acetone	100	109	–[c]	–[c]	73	0.68
1,3-dioxane	210	207	214	1.4	–[c]	–[c]
oxetane	308	232	304	1.7	244	2.0
THF	228	90	51	0.68	–[c]	–[c]
THP	68	60	77	1.8	–[c]	–[c]
oxepane	376	147	292	1.5	–[c]	–[c]

[a]Error = ±10%. [b]I_{sat} is the fluorescence intensity at 403 nm at saturation taken from the best fit of the titration data; I_0 is the initial fluorescence intensity at 403 nm. [c]The fluorescence response was too weak to obtain accurate binding data.

molecules contain at least one hydrogen-bond acceptor atom and hydrophobic surfaces. The results suggest that the cavities of **1a** and **1b** provide better solvation of these molecules than water does.

Even though all of these hydrophilic molecules can fit in the cavities of **1a** and **1b**, 1,4-dioxane is still the superior guest. The association constants with 1,4-dioxane (10^3–10^4 M^{-1}) are generally 1 or 2 orders of magnitude larger than those with other hydrophilic molecules (~10^2 M^{-1}). In particular, 1,3-dioxane, the structural isomer of 1,4-dioxane, can be clearly differentiated by **1a** and **1b**: 13500 versus 210 M^{-1} for **1a**; 3150 versus 207 M^{-1} for **1b**. This selectivity is higher than that of Diederich's helicage (8200 vs 860 M^{-1} in 19:1 H_2O/MeOH) under comparable conditions.[9]

Molecular tubes **1a** and **1b** are fluorescent in water and also show fluorescence response to most of these hydrophilic molecules. For those guests, whose binding induces changes in the hosts' fluorescence, fluorescence titrations (Figures 3 and S48–S57) were used to confirm the binding data from NMR titrations. Overall, the same picture arises (Table 1),[10] although no fluorescence changes were observed for DMF, DMSO, and

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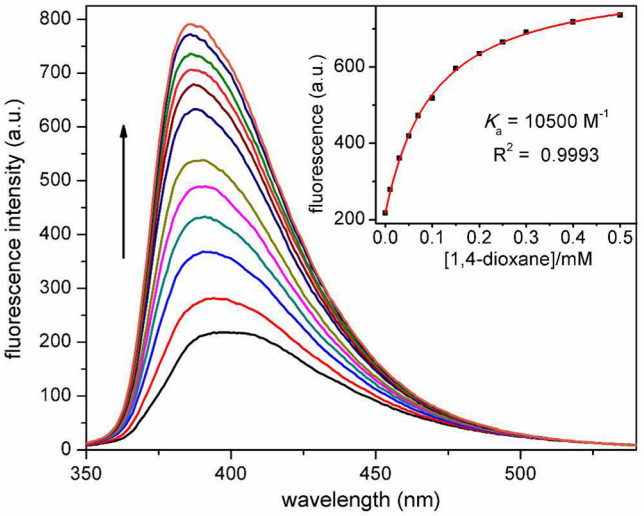

Figure 3. Fluorescence spectra of **1a** (1.0×10^{-5} M) when titrated with 1,4-dioxane in deionized H_2O at 25 °C. Inset: curve fit of the titration data according to a 1:1 binding stoichiometry.

acetone with **1a** or for 1,3-dioxane, THF, THP, and oxepane with **1b**. In most cases, the fluorescence of these molecular tubes is enhanced in the presence of guests, presumably as a result of conformational fixation upon guest binding. However, THF and acetone quench the fluorescence of **1a** and **1b**, respectively. The underlying causes are not clear.

How can **1a** and **1b** achieve such high binding affinity and selectivity to the highly hydrophilic molecule 1,4-dioxane? In order to answer this question, several control experiments were performed: (a) **1a** was titrated with 1,4-dioxane in 9:1 H_2O/D_2O, and the amide NH protons were visible and shifted downfield in the ^{1}H NMR spectra (Figure S58), indicating that hydrogen bonding is involved in the association. This is further supported by the fact that molecules with only one hydrogen-bond acceptor atom bind less strongly to **1a** or **1b** in water. (b) Isothermal titration calorimetry (ITC) experiments (Figures 4a and S59) were performed to dissect entropy and enthalpy contributions. In both **1a** and **1b**, the associations with 1,4-dioxane are largely driven by enthalpy (−17.3 kJ/mol for **1a**; −17.2 kJ/mol for **1b**) with minor contributions from entropy

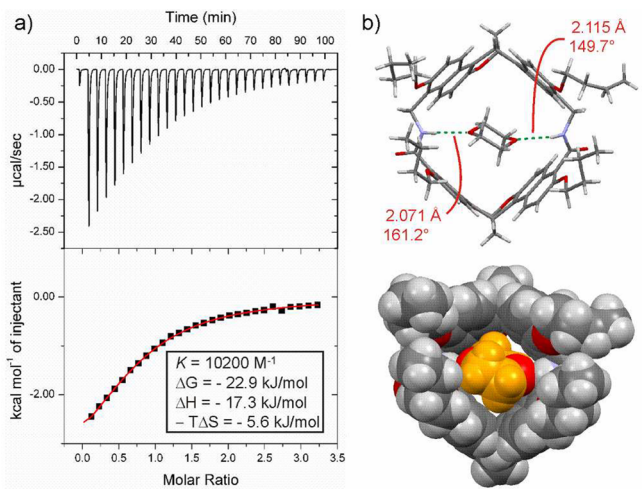

Figure 4. (a) ITC titration data for **1a** and 1,4-dioxane (H_2O, 25 °C). (b) Single-crystal structure of 1,4-dioxane@**2a**.

($-T\Delta S$ = −5.6 kJ/mol for **1a**; $-T\Delta S$ = −2.6 kJ/mol for **1b**; T = 298 K). The enthalpic contribution may come from both hydrogen bonding and the release of high-energy water in the host's cavity.[11] (c) Further experiments with the host analogues **2a** and **2b** (Figure 1b), which are soluble in organic solvents, provide additional support: in the single-crystal structures of 1,4-dioxane@**2a** (Figure 4b) and 1,4-dioxane@**2b** (Figure S66), rather short and thus presumably quite strong hydrogen bonds are involved, but no obvious C−H···π interactions are observed. This further endorses the important role of hydrogen bonding in the guest binding behavior of **1a** and **1b** in water; the association constants of 1,4-dioxane with **2a** and **2b** in $CDCl_3$ (61 and 101 M^{-1}, respectively; Figures S60−S65) are 2 orders of magnitude smaller than those of 1,4-dioxane with **1a** and **1b** in D_2O, supporting that water and thus hydrophobic effects play an important role in the association as well. In short, the hydrophobic cavity protects the hydrogen bonds between the host and the guest from competition with water, and hydrogen bonds and hydrophobic effects work synergistically to achieve high association. In addition, the high binding selectivity can be attributed to the perfect complementarity of the hydrogen-bonding sites in the hosts with those of 1,4-dioxane but not other guests. This is supported by the observation that no obvious association between **2a**/**2b** and other molecules, including 1,3-dioxane in $CDCl_3$, was detected.

1,4-Dioxane is widely used as a solvent stabilizer for chlorinated solvents and produced as a byproduct in cosmetics.[12] The International Agency for Research on Cancer (IARC) classified it as Group 2B (possibly carcinogenic to humans).[13] This molecule is highly hydrophilic and cannot be absorbed by soil. Once released into the environment, it accumulates in water. Therefore, 1,4-dioxane is recognized as a persistent environmental contaminant in groundwater.[14] Conventional laboratory analysis of 1,4-dioxane involves tedious and expensive sample preparation or separation steps, for example, solid-phase extraction coupled to GC−MS.[15] Quick and selective detection of this molecule would be advantageous for environmental control and remediation, and fluorescence is an inexpensive and accessible analytical method.

Molecular tube **1a** shows the highest association affinity to 1,4-dioxane, and the increase in the fluorescence intensity of **1a** at saturation (3.9-fold at 403 nm) is also the largest (Table 1). Accordingly, **1a** is an ideal fluorescent receptor to selectively detect 1,4-dioxane in water even in the presence of other interfering molecules (Figure 5). To inhibit the interference of the salt in water on the detection, a phosphate-buffered saline solution (pH 7.4) was used (Figures S67 and S68). According to the standard methods,[16] the limit of detection (3σ/slope) was estimated to be 119 ppb, and the detection range was up to 5.2 ppm with reasonably good linear performance (R^2 = 0.9835; Figure S69). Although the detection limit is higher than the WHO guideline value for 1,4-dioxane in drinking water (50 ppb),[13c] it should be easily extended to a lower value by coupling to solid-phase extraction.

In summary, we report two water-soluble molecular tubes with endo-functionalized hydrogen-bond donors that are capable of binding highly hydrophilic solvent molecules in water. Hydrogen-bond donors are hidden in a deep cavity and isolated from the bulk solvent, avoiding competition with water. Hydrophobic effects and hydrogen bonds work cooperatively to achieve both high association affinity and high selectivity. In particular, the molecular receptors presented here could achieve selective fluorescent detection of the Group 2B carcinogen and persistent

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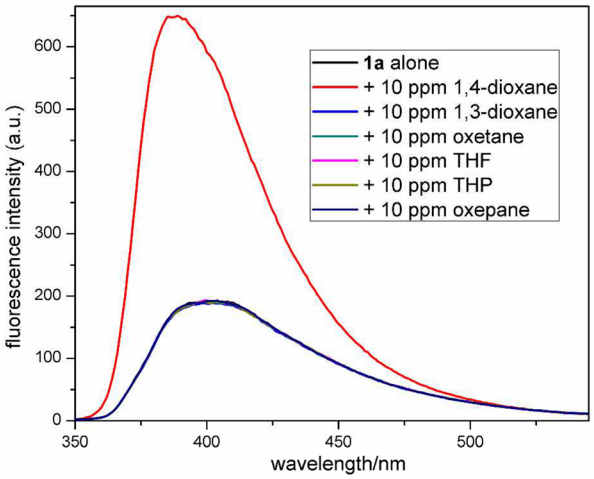

Figure 5. Fluorescence spectra of **1a** (1.0×10^{-5} M, H_2O, 25 °C) in the absence or presence of hydrophilic molecules (10 ppm).

environmental contaminant 1,4-dioxane. We believe that the concepts demonstrated here will lead to synthetic receptors for other environmentally or biologically important neutral hydrophilic molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09472.

Experimental details, synthetic procedures and characterization data for all new compounds, molecular model of the anti isomer, ^{1}H,^{1}H COSY and ^{1}H,^{1}H ROESY NMR spectra of molecular tubes, ^{1}H NMR spectra of the complexes, NMR titration data, fluorescence titration data, single-crystal X-ray data, and ITC data (PDF)

Crystallographic data for 1,4-dioxane@**2a** (CIF)

Crystallographic data for 1,4-dioxane@**2b** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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