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H_2S-Responsive Lower Critical Solution Temperature of the Host–Guest Complex Based on Oxatub[4]arene with Tri(ethylene oxide) Moieties

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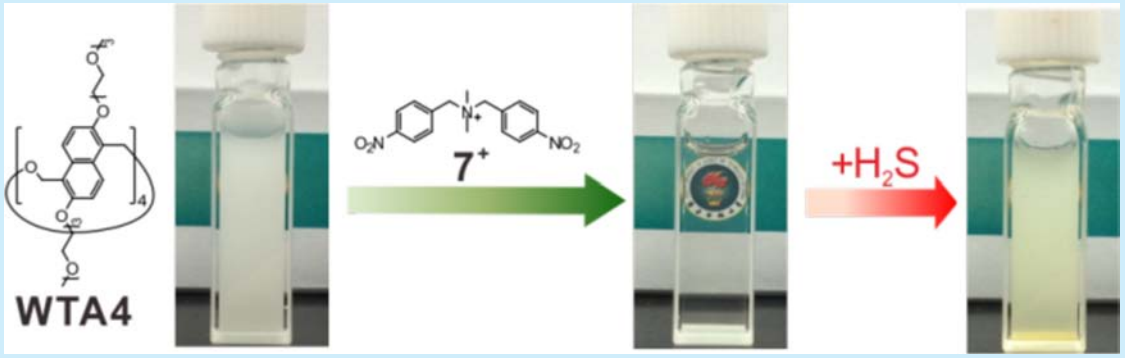
Supporting Information



ABSTRACT: A water-soluble oxatub[4]arene with tri(ethylene oxide) moieties was synthesized. The lower critical solution temperature (LCST) behavior of this macrocyclic receptor was tunable by changing its concentration or by adding an appropriate guest. Most interestingly, the LCST behavior of the host–guest complex showed a response to the presence of the physiological gasotransmitter H_2S through nitro group reduction.

Thermoresponsive materials displaying a lower critical solution temperature (LCST)[1] have attracted extensive attention due to their potential applications in smart surfaces,[2] molecular separation,[3] drug delivery,[4] and sensors.[5] Above the LCST, these materials show a great decrease in solubility, resulting in a sharp drop in the solution transmittance and an observable cloud point. To date, most studies on LCST phase behavior have focused on amphiphilic polymers.[6] LCST behavior has rarely been reported for host–guest systems.[7−9] The advantage of a host–guest system is that the LCST behavior can be reversibly tuned by altering the host–guest binding by added stimulants, such as competitive hosts,[9a] light,[9b] pH,[9c] and oxidizing and reducing agents.[9d] Considering the potential biomedical application of LCST materials, it would be advantageous to use bioactive molecules as stimulants to trigger the LCST behavior. H_2S[10] has been identified as a physiological gasotransmitter that can play diverse roles in human health, and the abnormal production of H_2S is believed to be a signal for a variety of diseases. To the best of our knowledge, there is no LCST system that can respond to H_2S and its related chemicals.

Macrocyclic receptors are the major workhorses in supramolecular chemistry. During the past decade, a number of new macrocyclic receptors have emerged,[11] greatly expanding the toolkit of supramolecular chemistry. Recently, we reported several naphthol-based molecular receptors,[12,13] of which *per*-butyloxatub[4]arene (**TA4**)[13] was particularly interesting. **TA4** has four conformations resulting from the flipping of the naphthalene panels (Figure 1a). These four conformers constitute a complex conformational network and can thus show conformational responses to different guests. Their conformational flexibility and adaptivity enable oxatub[4]arene to recognize a wide range of organic cations. In this work, we report the synthesis and host–guest properties of a water-soluble oxatub[4]arene (**WTA4**) (Figure 1) that shows H_2S-responsive LCST behavior.

WTA4 was synthesized using a different procedure (Figure 1b and SI) from that of **TA4**.[13a] The diol **1** and the dibromide **2** were synthesized starting with 2,6-dihydroxy-1,5-naphthalene-dicarboxaldehyde[14] instead of 2,6-dihydroxynaphthalene, and then macrocyclization between **1** and **2** was performed under a pseudo-high-dilution condition to afford **WTA4** as an oil in a reasonable yield (25%).

WTA4 was very soluble in H_2O at 25 °C and showed reversible LCST-type phase behavior. As shown in Figure 2a, a transparent aqueous solution of **WTA4** (1.0 mM) at room temperature turned milky upon heating to 43 °C and then

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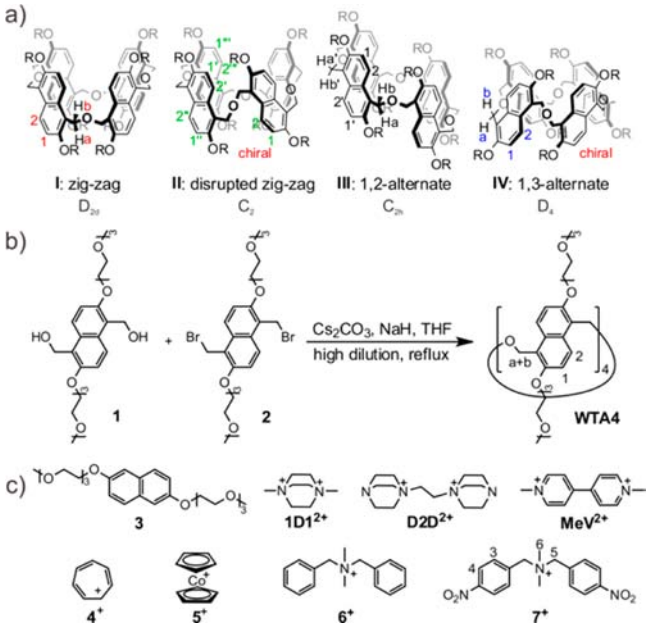

Figure 1. (a) Chemical structures of the four conformers of **TA4** resulting from naphthalene flipping. (b) Synthetic procedure for the water-soluble oxatub[4]arene (**WTA4**). (c) Model compound and all the guests involved in this research. Numbering in the structures is used for the signal assignments in the NMR spectra.

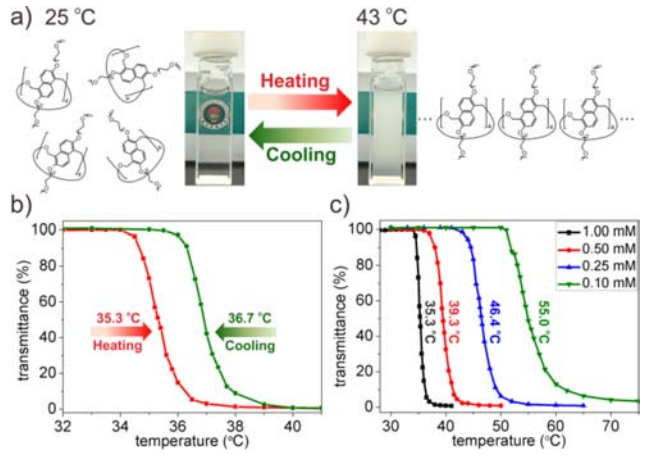

Figure 2. (a) Photographs and structural representations of an aqueous solution of **WTA4** (1.0 mM) at 25 and 43 °C. (b) Temperature dependence of the light transmittance of **WTA4** (1.0 mM) in aqueous solution (red line, heating process; green line, cooling process). (c) Concentration dependence of the light transmittance (heating process) of **WTA4** in aqueous solution.

became clear again when the solution was cooled to 25 °C. This thermal-induced phase-transition phenomenon was not observed for compounds **1** and **3** (Figure S2), suggesting that the oxatub[4]arene skeleton is important for the LCST behavior. Since **WTA4** has no electronic absorption at 650 nm (Figure S1), the cloud-point temperature of the solution can be determined by monitoring the UV−vis transmittance at 650 nm. The decline in transmittance to 50% of the initial value was recorded as the T_{cloud}.[9a] For 1.0 mM **WTA4**, T_{cloud} was estimated to be 35.3 °C. The optical transmittance curves of **WTA4** upon the heating and cooling (Figure 2b) cycles were reversible with 1.4 °C hysteresis, indicating the good thermoresponsive behavior of **WTA4**. Variable-temperature dynamic light scattering experiments (Figures S3 and S4) indicated that **WTA4** formed a larger aggregate at temperatures (45 °C) above T_{cloud} than at temperatures (25 °C) below T_{cloud}. The T_{cloud} of **WTA4** was concentration dependent, and it increased from 35.3 to 55.0 °C when the concentration decreased from 1.0 to 0.1 mM (Figure 2c).

In nonpolar solvent (CD_2Cl_2/CD_3CN = 1:1), **TA4** shows a strong association with organic cations through a variety of noncovalent interactions, including C−H···O hydrogen bonding, C−H···π, and cation···π interactions.[13] We predicted that 1,4-diazabicyclo[2.2.2]octane (DABCO)-based organic cations (**1D1**$^{2+}$, **D2D**$^{2+}$), methyl viologen (**MeV**$^{2+}$), tropylium (**4**$^{+}$), cobaltocenium (**5**$^{+}$), and quaternary ammonium (**6**$^{+}$) should also be good guests for **WTA4** in water. Surprisingly, these guests showed no detectable complexation-induced shifts of the NMR signals of **WTA4** (Figure S5), suggesting that there was no obvious binding between these guests and **WTA4**. This is presumably due to both the heavy solvation of these cations and the hydrophobic cavity of the flexible **WTA4** being concealed in water.

After a careful screening, guest **7**$^{+}$ was found to be a suitable guest for **WTA4** in water even though guest **6**$^{+}$ was not complexed by **WTA4**. The ^{1}H NMR spectra (Figure 3) showed

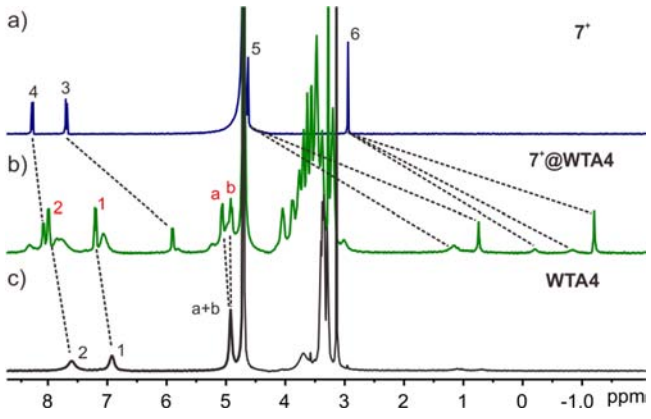

Figure 3. Full ^{1}H NMR spectra (400 MHz, D_2O, 1.0 mM, 25 °C) of (a) **7**$^{+}$, (c) **WTA4**, and (b) their equimolar mixture.

that the signals of both the host and guest undergo very large shifts upon exposure to **7**$^{+}$, indicating that a binding event occurred between these two molecules. Control experiments with excess guest or host (Figure S6) indicate that a slow guest exchange occurred on the NMR time scale. In agreement with ESI mass spectral data (Figure S8), the NMR integrals suggest a 1:1 binding stoichiometry, and the binding constant was determined to be 726 M^{-1} at 25 °C through integration of the NMR signals (Figure S8). The association between **7**$^{+}$ and **WTA4** is probably driven by cation···π interactions, π···π interactions, and the hydrophobic effect since the monocation **7**$^{+}$ is relatively hydrophobic when compared to the dications in Figure 1c.

The association between **7**$^{+}$ and **WTA4** was much stronger in nonpolar organic solvents (Figure 4 and Figure S11). ^{1}H NMR spectra clearly show that **WTA4** existed in three conformations in the presence of **7**$^{+}$. According to our previous experience,[13a,b] the nuclear Overhauser effect (NOE) and peak patterns confirmed that these three conformers were conformers **I**, **II**, and **IV**, occurring in a 1:1:1 ratio (Figures S12 and S13). When they were transferred into water, a similar NMR peak pattern

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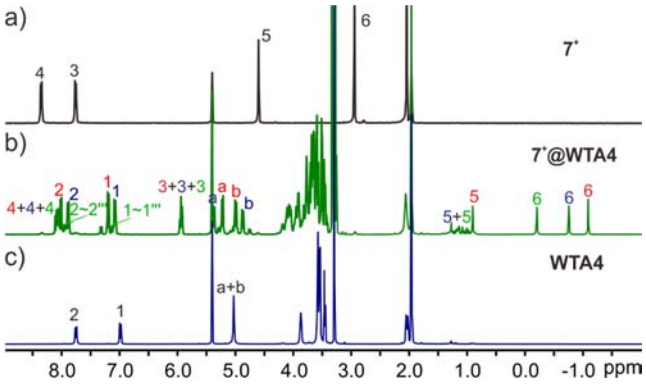

Figure 4. Full ^{1}H NMR spectra (400 MHz, CD_2Cl_2/CD_3CN = 1:1, 2.0 mM, 25 °C) of (a) 7^+, (c) **WTA4**, and (b) their equimolar mixture. The color code for the numbering is the same as in Figure 1a: red, conformer **I**; green, conformer **II**; and blue, conformer **IV**.

was observed (Figure 3b), and the three conformers **I**, **II**, and **IV** also coexisted but in a different ratio (5:2:2) (Figures S14 and S15). This result suggests that **WTA4** shows conformational adaptivity in different solvents even for the same guest.

Host–guest complexation is known to have a significant effect on the T_{cloud} of triethylene oxide substituted pillararenes.[9] Hence, the effect of host–guest complexation on the T_{cloud} was investigated (Figure 5). As the concentration of 7^+ increased

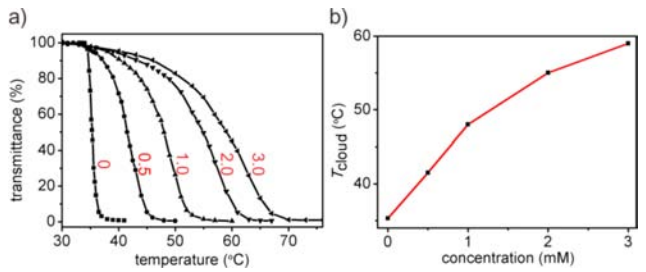

Figure 5. (a) Temperature dependence of the light transmittance of an aqueous solution of **WTA4** (1.0 mM) after the addition of 7^+ (0–3.0 mM). (b) Change in T_{cloud} when the concentration of 7^+ in the solution of **WTA4** (1.0 mM) was increased.

from 0.0 to 3.0 mM, the T_{cloud} of **WTA4** gradually increased from 35.3 to 55.0 °C. Because of the relatively weak binding as well as the decreased association constant upon heating (Figures S9 and S10), the light transmittance declined reluctantly when the temperature increased after the addition of 7^+. However, T_{cloud} was still controlled by varying the amounts of 7^+ in the aqueous solution of **WTA4**.

H_2S-mediated reduction of nitro groups is one of the reaction-based strategies for H_2S detection.[15] Similarly, guest 7^+ may be converted into a neutral molecule[16] through the reduction of the nitro group by H_2S. Through this reaction, guest 7^+ may be expelled from the cavity of **WTA4** when H_2S is added, and thus, the LCST behavior may be affected. NaHS was used as the source of exogenous H_2S. When NaHS was added to the solution of 7^+ and **WTA4**, the ^{1}H NMR signals of the aromatic protons became complicated in the early stages (Figure S16). However, over time, the guest-occupied host was clearly restored to its free state, indicating the dissociation of the host–guest complex (Figure 6b–d). The dynamic change in light transmittance after the addition of 30.0 mM NaHS to a mixture of 7^+ (2.0 mM) and **WTA4** (1.0 mM) at 43 °C was

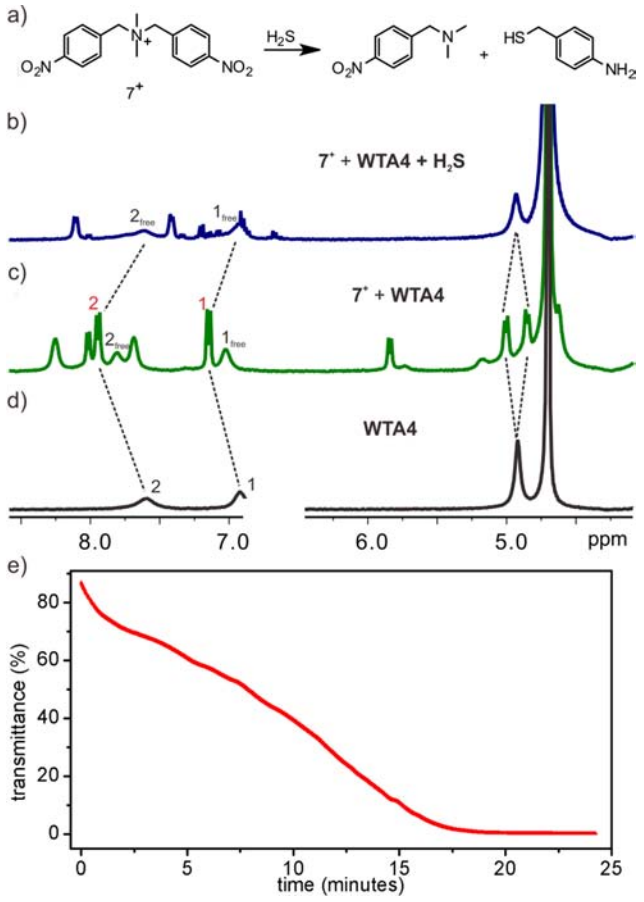

Figure 6. (a) Decomposition of 7^+ through nitro group reduction by H_2S. Partial ^{1}H NMR spectra (400 MHz, D_2O, 25 °C) of (d) **WTA4** (1.0 mM), (c) a 1:2 mixture of **WTA4** (1.0 mM) and 7^+ (2.0 mM), and (b) 1 h after addition of NaHS (30.0 mM) to the mixture. (e) Dynamic changes in the light transmittance of the host–guest complex at 43 °C after the addition of NaHS.

followed over time, and the transmittance gradually decreased to 0% after 25 min (Figure 6e). In addition, NaHS alone has very small effect on the LCST behavior of **WTA4** (Figure S17).

Based on this host–guest system, chemically responsive turbid-to-clear and clear-to-turbid transitions can be achieved (Figure 7). When the solution of **WTA4** (1.0 mM) in water

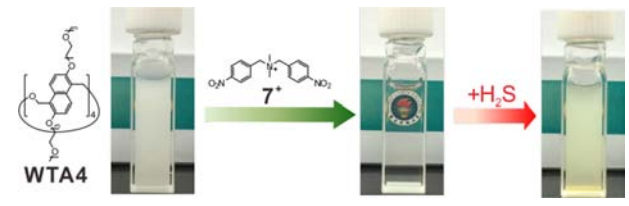

Figure 7. Photos of **WTA4** (1.0 mM) in water before and after addition of 7^+ (2.0 mM) followed by NaHS (30.0 mM) in sequence at 43 °C.

was heated to 43 °C (a temperature above T_{cloud} (35.3 °C)), the solution became turbid (Figure 7a). Addition of 7^+ (2.0 mM) to the solution of **WTA4** at 43 °C caused the solution to become clear (Figure 7b) because the current temperature is below the T_{cloud} (55 °C) of the complex of 7^+ with **WTA4**. After addition of NaHS (30.0 mM) to this mixture at 43 °C, the solution became turbid again because the host–guest

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association between 7^+ and **WTA4** was destroyed through the decomposition of guest 7^+ by nitro reduction.

In summary, a water-soluble oxatub[4]arene with tri(ethylene oxide) moieties, which showed LCST behavior in water, was synthesized. This flexible macrocyclic host showed no obvious binding in water to the organic cations, which are common guests for oxatub[4]arene in nonpolar organic solvents. However, a monocation quaternary ammonium 7^+ with a large hydrophobic surface and nitro groups was shown to be a suitable guest. The T_{cloud} of **WTA4** was well controlled by changing its concentration or by adding different amounts of the hydrophobic quaternary ammonium cation. The LCST behavior of the host−guest complex showed a response to the presence of the physiological gasotransmitter H_2S through nitro reduction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00181.

Experimental details, characterization data, full ^{1}H NMR spectra, and binding constant determination (PDF)

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Notes

The authors declare no competing financial interest.

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