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COMMUNICATION

Reversible and Contrasting Changes of the Cloud Point Temperature of Pillar[5]arenes with One Quinone Unit and Tri(ethylene oxide) Chains Induced by Redox Chemistry and Host-Guest Complexation

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A new water-soluble redox-active pillar[5]arene was synthesized by incorporation of one benzoquinone unit. The pillar[5]arene showed redox-responsive reversible lower critical solution temperature changes in aqueous solution.

Amphiphilic molecules and polymers, which show lower critical solution temperatures (LCSTs), are very important thermo-responsive materials in the fields of chemical biology and materials science because they can be used in controlled drug release, molecular separation, and gene delivery.¹⁻²⁸ Poly(*N*-isopropylacrylamide) is a well-known thermo-responsive polymer; it has a clouding point (T_{cloud}) at 32 °C in aqueous solution.¹⁻¹⁷ However, its T_{cloud} cannot be tuned by external stimuli. The design of new thermo-responsive materials with LCSTs that can be tuned by external stimuli is an important challenge.¹⁸⁻²⁸ The T_{cloud} values of thermo-responsive materials are determined by their chemical compositions, i.e., the ratio of the hydrophobic and hydrophilic parts. As the hydrophobic content increases, T_{cloud} decreases. Stimulus-responsive thermo-responsive materials can therefore be produced by changing the ratio of the hydrophobic and hydrophilic components.^{25,26}

Pillar[5]arenes, which were first reported by our group in 2008,²⁹ are important macrocyclic hosts in supramolecular chemistry.²⁹⁻³⁶ Recently, we reported tunable LCSTs triggered by host-guest complexation of pillar[5]arene with tri(ethylene oxide) chains (**Fig. 1, H1**).²⁵ Pillar[5]arene **H1** has a T_{cloud} at 42 °C because it consists of a hydrophobic pillar[5]arene core and hydrophilic tri(ethylene oxide) chains. The inclusion of a cationic guest, didecylviologen bromide (**Fig. 1, G1**), triggers an increase in T_{cloud} from 42 to 60 °C because inclusion of a hydrophilic guest changes the hydrophilic to hydrophobic ratio.²⁵ There are previous examples of thermo-responsive materials where LCST occurs using chemical,^{5-7,21-23,25} pH,⁸ redox,^{9,10} light²⁶ as a stimulus. But, it is difficult to create

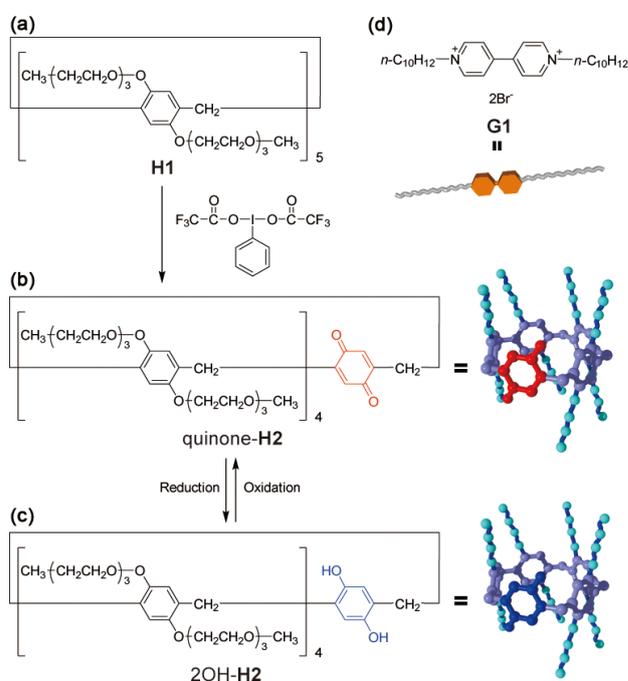


Fig. 1 Chemical structures of pillar[5]arenes (a) with tri(ethylene oxide) chains (**H1**), (b) containing one benzoquinone unit (**quinone-H2**), (c) containing one hydroquinone unit (**2OH-H2**), and (d) viologen guest (**G1**).

multi-responsive thermo-responsive materials owing to complicated designs and syntheses.^{11,12} In the present study, we developed a dual-stimulus, redox- and host-guest complexation-responsive tunable LCST based on a tri(ethylene oxide)-substituted pillar[5]arene containing one benzoquinone unit (**Fig. 1, quinone-H2**). Benzoquinone is easily converted to hydroquinone by reduction, and hydroquinone is converted back to benzoquinone by oxidation. Tri(ethylene oxide)-substituted pillar[5]arene containing one benzoquinone unit (**Fig. 1, 2OH-H2**) can therefore be formed by addition of a

reducing agent, and 2OH-H2 is reversibly converted back to quinone-H2 on addition of an oxidant. Benzoquinone is more hydrophobic than hydroquinone because benzoquinone lacks hydrophilic hydroxyl moieties. A redox reaction is therefore triggered and induces a change in the hydrophobic/hydrophilic ratio. In this study, we demonstrated reversible and contrasting LCST changes using a combination of redox and host-guest complexation systems.

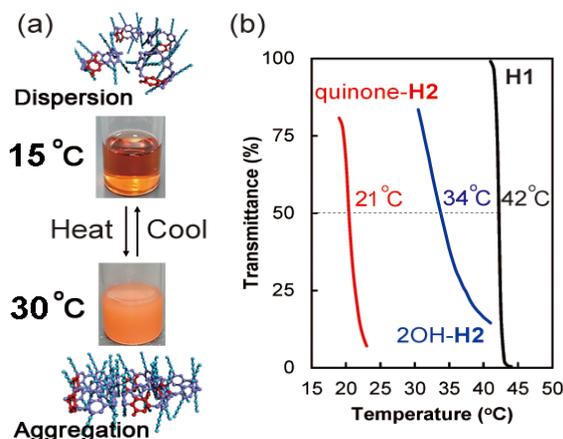


Fig. 2 (a) Photographs of aqueous solution of quinone-H2 (2 mM) at 15 and 30 °C. (b) Temperature dependence of light transmittance of 2 mM aqueous solutions of H1 (black solid line), quinone-H2 (red solid line), and 2OH-H2 (blue solid line).

Quinone-H2 was synthesized by partial oxidation of tri(ethylene oxide)-substituted pillar[5]arene H1 with hypervalent iodine (Fig. 1); this has already been established as a method for the synthesis of di-functionalized pillar[5]arenes.³⁶ An aqueous solution of quinone-H2 was clear at 15 °C, turbid at 30 °C (Fig. 2a), and then clear again when the solution was cooled to 15 °C. Quinone-H2, like H1, therefore has an LCST. T_{cloud} was determined by monitoring the change in transmission at 650 nm using a temperature-controlled UV-vis spectrometer. The transmittance of the solution rapidly decreased at 21 °C on heating, indicating that T_{cloud} of quinone-H2 is 21 °C. 2OH-H2 was prepared by reduction of the benzoquinone unit in quinone-H2 with NaBH₄. T_{cloud} of 2OH-H2 was detected at 34 °C, which is 13 °C higher than that of quinone-H2. This is because hydroquinone is more hydrophilic than benzoquinone. T_{cloud} of H1 is 42 °C,²⁵ which is 21 °C higher than that of quinone-H2 and 8 °C higher than that of 2OH-H2, indicating that the tri(ethylene oxide)-substituted unit in H1 is more hydrophilic than the hydroquinone and benzoquinone units.

Pillar[5]arenes can form host-guest complexes with electron-poor cationic viologen salts because pillar[5]arene has an electron-rich cavity. H1 forms stable 1:1 host-guest charge-transfer (CT) complexes with G1 in aqueous solution. The association constant (K) of the H1 G1 complex determined from the CT band, is $(4.3 \pm 0.5) \times 10^3 \text{ M}^{-1}$ at 25 °C.²⁵ We investigated the host-guest complexation ability of quinone-H2 with G1. An aqueous solution of quinone-H2 is red (Fig. 2a) as a result of formation of an intramolecular CT complex between the dialkoxybenzene and benzoquinone units in quinone-H2. The CT band of quinone-H2 changed on addition of G1 (Fig.

S2a), indicating complexation. The K value of the quinone-H2

G1 complex, determined by UV-vis titration was $(7.5 \pm 0.9) \times 10^3 \text{ M}^{-1}$ at 25 °C (Fig. S2b), which is about twice that of the H1 G1 complex. The strong binding of G1 by quinone-H2 can be explained by the favorable ion-dipole interaction between the positive charge of G1 and the oxygen atom of C=O in quinone-H2; a similar ion-dipole interaction was also observed in the host-guest complexes of viologen salts with cucurbit[7]uril.³⁷ Formation of the quinone-H2 G1 complex was confirmed by ¹H NMR spectroscopy (Fig. S3). The proton signals of G1 showed up-field shifts with quinone-H2, indicating complexation. The effect on T_{cloud} of the formation of a stable host-guest complex between quinone-H2 and G1 was investigated. When G1 was added to an aqueous solution of quinone-H2, T_{cloud} of the mixture increased from 21 to 54 °C (Fig. 3a, red lines and Fig. 3b, red squares).

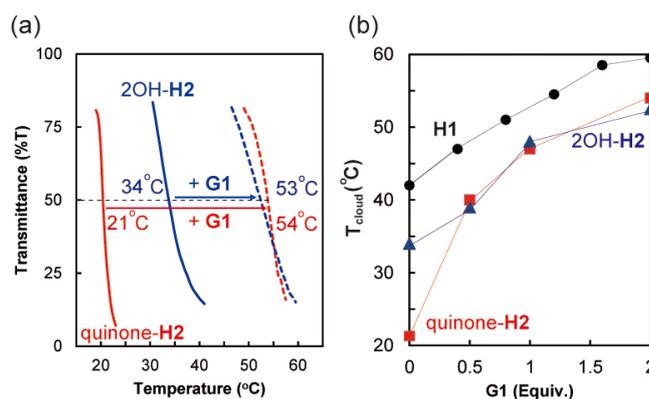


Fig. 3 (a) Temperature dependence of light transmittance of aqueous solutions of quinone-H2 (2 mM, red solid line), a mixture of quinone-H2 (2 mM) and G1 (4 mM, red dash line), 2OH-H2 (2 mM, blue solid line), and a mixture of 2OH-H2 (2 mM) and G1 (4 mM, blue dash line). (b) Change in T_{cloud} on addition of G1 to aqueous solutions of H1 (black circles), quinone-H2 (red squares), and 2OH-H2 (blue triangles).

A similar T_{cloud} change was observed for an aqueous solution of H1 with G1 (Fig. 3b, black circles).²⁵ Host-guest complexation between 2OH-H2 and G1 was also investigated. The solution color changed from colorless to yellow on mixing 2OH-H2 and G1 in aqueous media; aqueous solutions of 2OH-H2 and G1 were both colorless. The yellow color produced a new band at 400 nm in the UV-vis spectrum of a mixture of the host and guest solutions, indicating formation of the CT host-guest complex (Fig. S4a). The K value of the 2OH-H2 G1 complex, determined by UV-vis titration, was $(1.3 \pm 0.1) \times 10^3 \text{ M}^{-1}$ at 25 °C (Fig. S4b), which is about three times smaller than that of the H1 G1 complex, and about six times smaller than that of the quinone-H2 G1 complex. In the ¹H NMR spectrum, an up-field shift of the proton signals from G1 was observed on mixing with 2OH-H2 (Fig. S5); this also supports host-guest complexation. The effect of complexation on T_{cloud} was investigated. Addition of G1 to an aqueous solution of 2OH-H2 increased T_{cloud} from 34 to 53 °C.³⁸

Four states can be produced using a combination of redox and host-guest complexation systems: quinone-H2, 2OH-H2, and quinone-H2 G1 and 2OH-H2 G1 complexes. The ratios of

their hydrophilic and hydrophobic parts are different, and therefore they have different T_{cloud} values. Based on the different T_{cloud} values of the four states, we were able to control the LCST by a combination of redox reactions and host-guest complexation (Fig. 4). For quinone-**H2**, T_{cloud} was observed at 21 °C. When the reducing agent NaBH_4 was added (i), T_{cloud} increased from 21 to 31 °C as a result of the reduction of quinone-**H2** to 2OH-**H2**. Addition of the oxidizing agent NaIO_4 (ii) caused T_{cloud} to decrease from 31 to 21 °C because of oxidation 2OH-**H2** to quinone-**H2**.³⁹ The increases and decreases in T_{cloud} could be reversibly switched by alternating additions of reducing and oxidizing agents (i-iv). Addition of **G1** to the reduced form 2OH-**H2** increased T_{cloud} from 31 to 43 °C (ii'). In contrast, addition of an oxidizing agent to the reduced form 2OH-**2H** decreased T_{cloud} from 31 to 21 °C (ii). Different T_{cloud} changes, i.e., increases and decreases in T_{cloud} for 2OH-**2H**, can therefore be achieved by adding suitable chemicals. We achieved reversible and contrasting LCST changes based on a combination of redox and host-guest complexation systems.

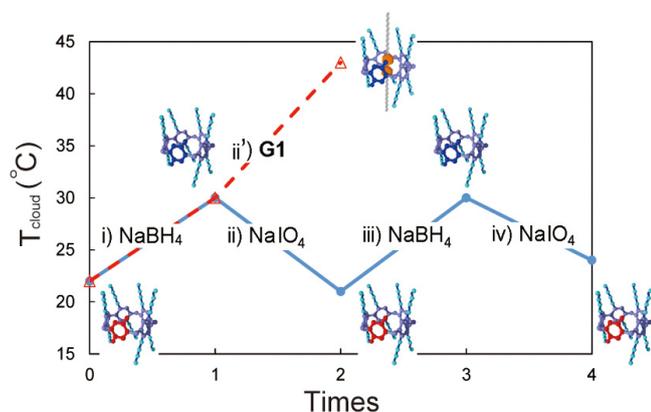


Fig. 4 (i-iv) Reversible T_{cloud} changes for quinone-**H2** (2 mM) by alternating addition of NaBH_4 (0.5 mM) and NaIO_4 (4 mM).⁴⁰ (ii and ii') Contrasting T_{cloud} changes on addition of NaIO_4 (4 mM) or **G1** (4 mM) to reduced form 2OH-**H2**.

In conclusion, we demonstrated dual-tunable LCST changes using a combination of a redox-responsive switching system, i.e., hydroquinone/benzoquinone, **H2**, and host-guest complexation of **H2** with **G1**. The excellent thermo-responsive properties demonstrated in this study are based on new switchable hydroquinone/benzoquinone redox and host-guest systems of **H2**. To the best of our knowledge, contrasting LCST change induced by adding suitable chemicals is first example. Quinone-**H2** consists largely of oligo(ethylene oxide) moieties and benzoquinone moieties. Oligo(ethylene oxide) moieties are biocompatible. Benzoquinones are important compounds in biological systems because they act as antioxidants, and are useful for treatment of heart disease and cancer. We therefore believe that quinone-**H2** has great potential as a drug-delivery system.

Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental section, characterization data, ¹H NMR and UV-vis spectra of mixtures of quinone-**H2** or 2OH-**H2** with **G1**, and UV-vis titrations. See DOI: 10.1039/c000000x/

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- 38 After complexation, the clouding points 2OH-H2 and quinone-H2 are almost identical. This phenomenon is because the final molecular structure, including hydrated water, was very similar between the two complexes.
- 39 2OH-H2 was oxidized by oxygen in the air. But, the oxidation did not complete by oxygen in the air and it took long time. Addition of the oxidant is necessary to complete the oxidation.
- 40 We employed excess oxidant NaIO₄ because the oxidizing ability of NaIO₄ was weaker than NaBH₄.