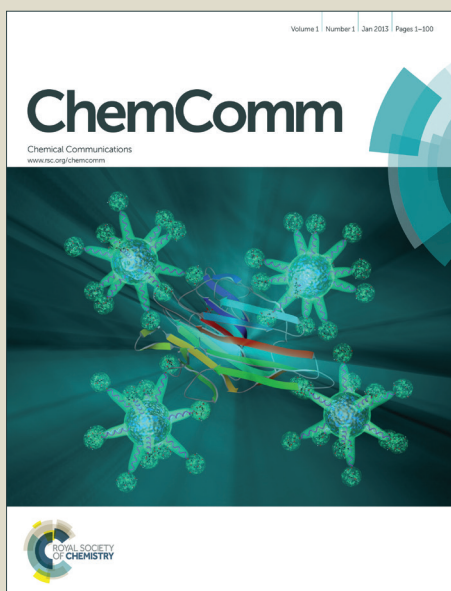


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COMMUNICATION

Chemical-responsive control of lower critical solution temperature behavior by pillar[10]arene-based host–guest interactions†

Xiaodong Chi and Min Xue*

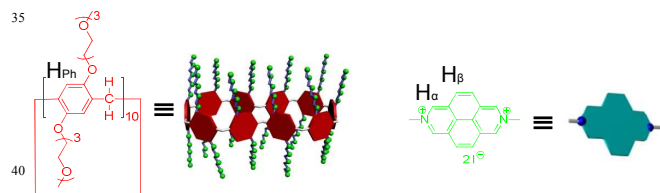
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A new water-soluble thermoresponsive pillar[10]arene with tri(ethylene oxide) groups was synthesized and its clouding point could be reversibly controlled based on a chemical-responsive host–guest system.

Stimuli-responsive materials, which can respond to environmental stimuli, such as light, redox, and temperature-change, have attracted remarkable attention in the field of smart materials due to their various practical applications, including sophisticated drug delivery,¹ biomaterials,² and molecular separation.³ Among them, water-soluble thermoresponsive polymers showing lower critical solution temperature (LCST) behaviour are one of the most appealing stimuli-responsive species due to their potential biomedical applications.⁴ However, some low molecular weight compounds, including pillararenes,⁵ are also able to exhibit LCST-type phase changes upon careful structural design or under well-defined conditions, which have shown potential application in fabricating thermoresponsive materials.

Pillar[*n*]arenes,^{6,7} a new generation of macrocyclic hosts next to crown ethers,⁸ cyclodextrins,⁹ calixarenes,¹⁰ cucurbiturils,¹¹ have developed vigorously thanks to their unique structures and high functionality, bringing along many applications in the fabrication of interesting and functional supramolecular systems, such as chemosensors, supramolecular polymers, drug delivery systems and transmembrane channels.¹² Herein, we prepared a new water-soluble pillar[10]arene bearing triethylene oxide chains (Scheme 1) that shows LCST behavior. We also employed its host–guest complexation with diazapyrenium salt **G** to reversibly tune the LCST behavior (Scheme 1).



Scheme 1 Chemical structures and cartoon representation of pillar[10]arene **1** and guest molecule **G**.

The synthetic method for pillar[10]arene with tri(ethylene oxide) groups **1** is shown in Scheme S1. Pillar[10]arene **1** was prepared by etherification of *per*-hydroxylated pillar[10]arene **2**, which was synthesized according to a previously reported

procedure.⁶¹ After stirring a mixture of **2** and excess triethylene glycol monomethyl ether mono-*p*-tosylate at reflux for 3 days, **1** was obtained as a light yellow liquid.

Like pillar[5,6]arenes with tri(ethylene oxide) groups,¹³ pillar[10]arene **1** also showed LCST behavior in water. As shown in Fig. 1a, a clear aqueous solution of **1** (2.00 mM) turned to be turbid on heating to 50 °C. It became to be clear again as the temperature fell down. The LCST behavior of **1** could be attributed to the introduction of the hydrophilic triethylene glycol chains onto the hydrophobic pillar[10]arene backbone (aromatic and methylene bridges).¹³ When the temperature reached the LCST, the intra/inter triethylene glycol chain interactions increase, and pillar[10]arene aggregation occurred, leading to phase transition. What is more interesting is that the LCST behavior of **1** has concentration dependence feature. As the concentration of **1** increased, T_{cloud} of **1** decreased, which showed the same phenomena with analogous pillar[5,6]arenes.¹³

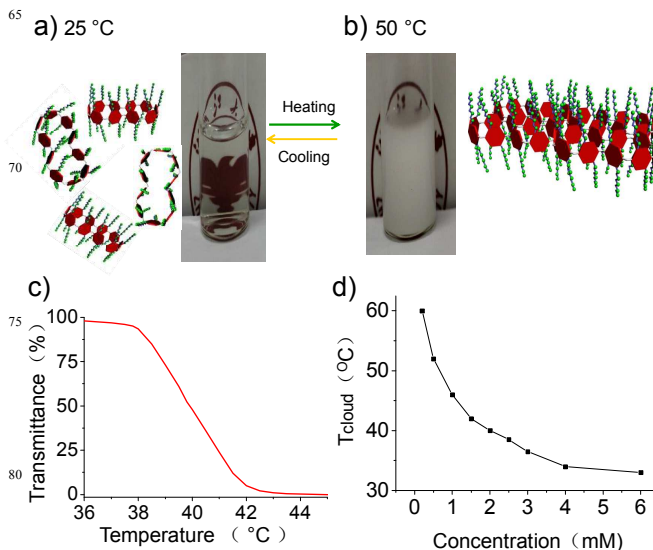


Fig. 1 Photos of an aqueous solution of **1** (2 mM) at (a) 25 and (b) 50 °C. (c) Temperature dependence of light transmittance of **1** in aqueous solution. (d) Concentration dependence of the clouding point (T_{cloud}) of **1** in water.

The host–guest complexation between **1** and **G** was studied by ¹H NMR spectroscopy (Fig. S7). In comparison to the spectrum of free **G** (Fig. S7a, ESI†), the resonance peaks corresponding to the protons on **G** shifted upfield in the

presence of **1** (Fig. S7b, ESI†). Upfield shift changes were observed for the signals related to the protons H_α and H_β ($\Delta\delta = -0.23$ and -0.36 ppm for H_α and H_β , respectively) upon addition of an equivalent amount of **1** (Fig. S7b, ESI†). Moreover, the peaks of the protons on **1** also exhibited slight chemical shift changes in the presence of **G** arising from the interactions between **1** and **G** (Fig. S7b, ESI†).

Further evidence for the formation of a stable host–guest complex **1**⊃**G** was obtained from UV-vis absorption spectroscopy. The spectrum of an aqueous solution containing **1** and **G** (molar ratio = 1:1) exhibited a broad absorption above 460 nm, which corresponded to the characteristic absorption of the charge-transfer complex between electron-rich **1** and electron-deficient **G** (Fig. S5, ESI†).^{6k} Furthermore, the resulting solution had a yellow color when **1** and **G** (molar ratio = 1:1) were mixed in water, indicating the formation of a typical charge-transfer complex (Fig. 3a).^{8f} All these results indicated that the complexation of **1** with **G** took place in solution.

The stoichiometry of the complex between pillar[10]arene **1** and **G** was determined to be 1:1 in aqueous solution by isothermal titration calorimetry (ITC) and the association constant for the complex was $4.2 (\pm 0.3) \times 10^4 \text{ M}^{-1}$.

In the previous work,¹³ Ogoshi et al. reported that host–guest complexation had an effect on T_{cloud} . Hence, we hypothesized that it should be possible to tune the LCST behavior of **1** upon addition of **G**. As the concentration of **G** increased, T_{cloud} gradually increased while maintaining sharp transitions (Fig. S6, ESI†). We demonstrated that T_{cloud} could be successfully controlled by adding different amounts of **G** into the aqueous solution.

It was recently reported by us that the complexation between pillar[10]arene and **G** could be controlled in the presence of diethylamine (DEA) or trifluoroacetic acid (TFA).^{6k} Thus, we used DEA to exclude **G** from the cavity of **1**. When excess DEA was added to a solution containing **1** (1.00 mM) and **G** (1.00 mM), the yellow solution turned to be dark green (Fig. 3a), indicating dissociation of the complex. Subsequently, the complex **1**⊃**G** formed again when enough TFA was added to neutralize DEA. At the same time, the dark green solution gradually reverted to yellow (Fig. 3a). This reversible process was confirmed by proton NMR experiments (Fig. 2). When DEA (10.0 equiv.) was added to a solution of **1** (1.00 mM) and **G** (1.00 mM) in D_2O , the intensity of the aromatic signals of **G** disappeared substantially and the protons of **1** almost returned to their uncomplexed values (Fig. 2b). However, after addition of TFA (10.0 equiv.) to this solution, the complexation between **1** and **G** was recovered; most chemical shift changes corresponding to the protons of **1** and **G** were observed again (Fig. 2c). The reversible process could be repeated over several cycles.

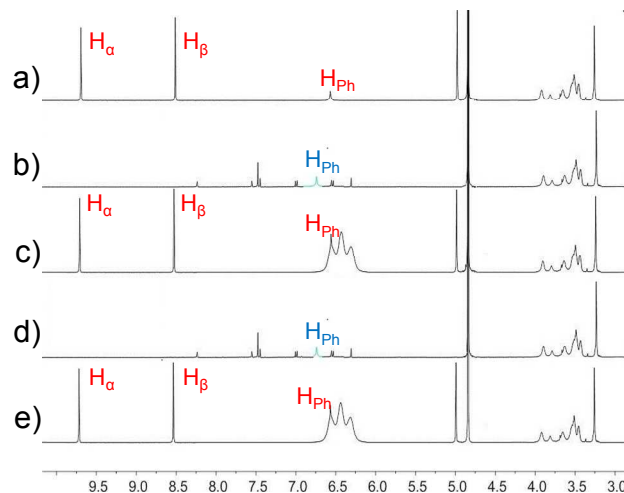


Fig. 2 Partial ^1H NMR spectra (400 MHz, D_2O , 25 $^\circ\text{C}$): (a) 1.00 mM **1** and 1.00 mM **G**; (b) after addition of 10.0 equiv. of DEA to (a); (c) after addition of 10.0 equiv. of TFA to (b); (d) after addition of 10.0 equiv. of DEA to (c); (e) after addition of 10.0 equiv. of TFA to (d).

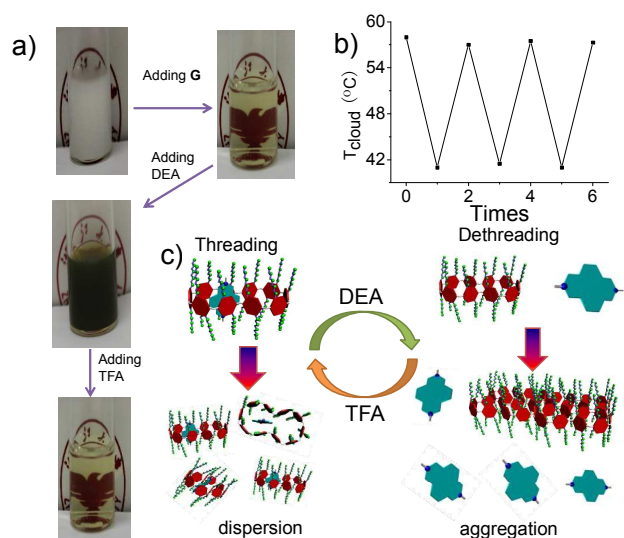


Fig. 3 (a) Photos of a mixture of **1** (2.00 mM) and **G** (3.00 mM) in water at 50 $^\circ\text{C}$ after adding DEA or TFA. (b) Changes of T_{cloud} upon addition of DEA or TFA. (c) Illustration of chemical-responsive control of the LCST behavior by pillar[10]arene-based host–guest interactions.

We further explored the effect of the threading/dethreading that caused the change of T_{cloud} by turbidity measurements (Fig. 3b). By adding 1.5 equiv of **G** to a turbid aqueous solution of **1** at 50 $^\circ\text{C}$, the turbid aqueous solution became clear (Fig. 3a). T_{cloud} increased from 40 $^\circ\text{C}$ to 58 $^\circ\text{C}$, owing to the formation of the host–guest inclusion complex between **1** and **G** that led to the increase of T_{cloud} . When 10.0 equiv. of DEA was added into the clear yellow aqueous solution, the solution became turbid again and the color of the solution became dark green. T_{cloud} decreased from 58 $^\circ\text{C}$ to 41 $^\circ\text{C}$. This was because DEA could form a more stable adduct with **1**, leading to dethreading of **G** from the cavity of the pillar[10]arene (Fig. 3c). Subsequently, the complex **1**⊃**G** could form again when enough TFA was added to neutralize DEA. At the same time, the turbid dark green solution gradually reverted to clear yellow (Fig. 3a).

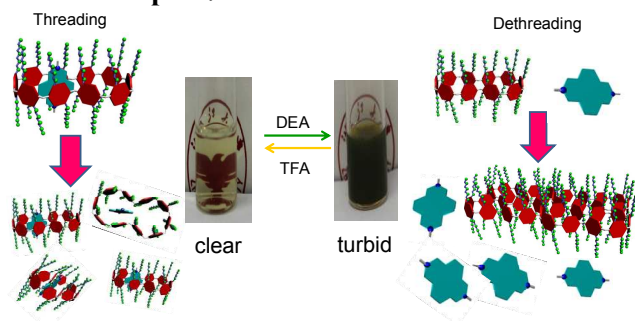
In summary, we have successfully synthesized a water soluble pillar[10]arene with tri(ethylene oxide) groups, which showed excellent LCST behavior. It was found that the T_{cloud} of **1** could be controlled upon addition of different amounts of **G**. Furthermore, owing to the chemical-responsive host–guest complexation between **1** and **G**, its clouding point could be reversibly controlled by adding DEA or TFA. This chemical controllable threading/dethreading led to chemical reversible switching of the LCST behavior. Thanks to the biocompatible oligoethylene oxide moieties on **1** and the tunable thermoresponsive properties, this thermoresponsive material may be applied in many bio-relevant fields, such as smart bioactive surfaces, phase separation immuno-assays, hyperthermia-induced drug delivery and tissue engineering. This work was supported by the National Natural Science Foundation of China (21202145), and the China Postdoctoral Science Foundation (2013M541767).

Notes and references

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China., Fax: +86-571-8795-3189; Tel: +86-571-8795-3189; E-mail: xuemin@zju.edu.cn

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Colour Graphic:**Text:**

5 A new water-soluble thermoresponsive pillar[10]arene with tri(ethylene oxide) groups was synthesized and its clouding point could be reversibly controlled based on a chemical-responsive host-guest system.