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# An Amphiphilic Molecular Basket Sensitive to Both Solvent Changes and UV Irradiation

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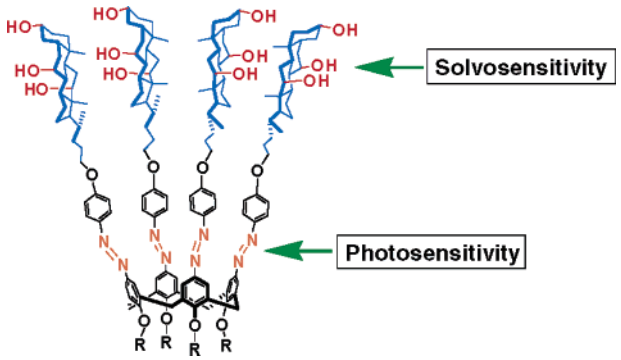


A molecular basket was obtained by linking four cholate units to a cone-shaped calix[4]arene scaffold through azobenzene spacers. The molecule turns its polar faces inward in nonpolar solvents to bind polar molecules such as sugar derivatives. In polar solvents, the nonpolar faces turn inward, allowing the binding of hydrophobic guests such as pyrene. The molecule can also respond to UV irradiation by *trans*−*cis* isomerization of the azobenzene spacers. Response toward both solvents and UV light is fully reversible.

Conformational control is a powerful approach to environmentally responsive materials because the conformation of a molecule dictates many of its properties, including size, shape, and distribution of functional groups, and yet may be altered easily by environmental stimuli. Interest in conformationally controllable molecules is highlighted in foldamer research, which aims at creating synthetic analogues of biopolymers that can adopt well-defined, compact conformations.[1] A benefit in creating responsive materials based on conformational changes is the possibility to integrate conformational responsiveness with other responsive mechanisms so that materials sensitive to multiple stimuli may be rationally designed.

We have been interested in using cholic acid as a building block to construct conformationally controllable foldamers[2] and nonfoldamers.[3] We reported a "molecular basket" (**1**) that can reversibly switch between a micelle-like conformation (with the hydrophilic faces of cholates pointing outward) in polar environments and a reversed-micelle-like conformation in nonpolar environments.[3a,4] As a result of the conformational change, the molecule can act as a tunable supramolecular host to bind polar guests in nonpolar solvents and nonpolar ones in polar solvents.[3b] As the ordered, micelle- or reversed-micelle-like conformations originate from intramolecular aggregation of the cholates, we reasoned that insertion of azobenzene[5,6] linkers would create a molecular basket (**2**) sensitive to both solvents and photoirradiation. The idea is that aggregation should be promoted by the straight *trans* azobenzene spacers but deteriorated by the kinked *cis*-isomers. Complete *cis*-isomerization is probably unnecessary, as mixed *trans*/*cis* spacers may be even worse for the alignment of the cholates than all-*cis* ones. A similar concept also has been employed recently by the groups of Hecht[7] and Parquette[8] to prepare foldamers sensitive to both solvents and UV irradiation.

Azobenzene-derived calixarenes have attracted considerable interest of supramolecular chemists[9] ever since Shinkai and coworkers discovered the autoaccelerative diazo coupling of calix[4]arene. Many calixarenes with azobenzene at the upper rim

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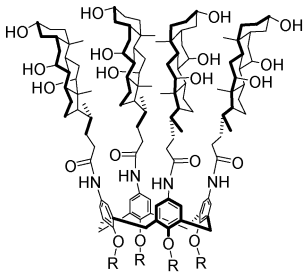
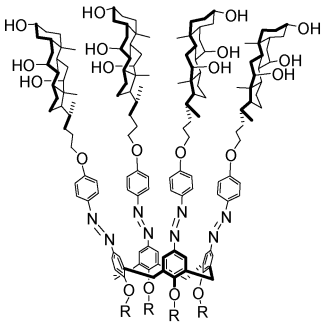


**1**, R = *n*-$C_6H_{13}$



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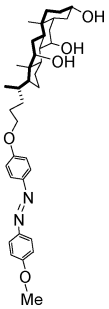


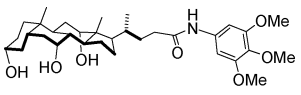
**3**

have been prepared according to Shinkai's method.[11] To ensure a basket-like conformation, we prefer to have the calix[4]arene scaffold preorganized into the cone conformation by alkyl substitution at the lower rim.[3a] However, with one exception,[11e] nearly all previously reported azocalixarenes have unsubstituted hydroxyl groups *para* to the azobenzene groups.

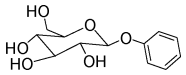
The synthesis of **2** is illustrated in Scheme 1. Tetraaminocalix[4]arene **4** was prepared according to literature procedures.[12] It was diazotized by nitrous acid at 0 °C in aqueous THF to afford the tetradiazonium intermediate **5**, which was reacted directly with an excess of phenol in THF and pyridine. Considering the instability of a highly crowded tetradiazonium salt, the yield of this reaction was remarkably high−over 70% if the reaction condition was properly controlled. Precooling of all solutions (i.e., both **4**/$NaNO_2$ in aqueous THF and the aqueous HCl solution added to the first mixture) was extremely important. A slight increase in reaction temperature during diazotization could reduce the yield from >70% to <10%. The tetraphenol intermediate **6** was generally used in the next step without much purification. Alkylation with brominated cholate derivative **7** occurred smoothly in about 60% yield. In addition, compound **3** with a single cholate unit was prepared as a control. We did attempt an alternative route and prepared compound **8**.[13] Its alkylation to cone-shaped calixarene, however, was unsuccessful.

The aromatic protons of **1** *ortho* to the amido groups appeared as a single peak when the molecule adopted random conformation but split into two peaks as the molecule assumed either the micelle- or reversed-micelle-like conformation.[3a,c] Such a change was not observed in **2**, but the result was expected. Splitting of the aromatic peaks probably originated from hindered rotation of N-Ar bonds[14] during intramolecular aggregation of the cholates[3a] and was previously found to be absent whenever spacers were inserted in between the cholates and the (calixarene or noncalixarene) scaffold.[3c]

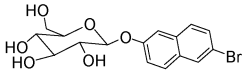
Another way of studying the conformation of these baskets is to monitor the chemical shifts of OH (or NH for **1**) protons during solvent titration. When the changes in chemical shifts of OH are plotted as a function of DMSO percentage in $CCl_4$, the curves for the compounds capable of adopting the reversed-micelle-like conformation show distinct downward deviation from the control curve for a monomeric cholate such as **9**.[3c] Such a deviation indicates a local concentration of DMSO near the OH protons higher than that in the bulk and is a consequence of the reversed-micelle-like conformer, which enriches DMSO from the solvent mixture by its inwardly facing polar groups. Although not as significant as in compound **1** (△, Figure 1a), downward deviation was clearly visible for **2** below 20% DMSO (□).



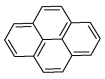
**9**



**10**



**11**



**12**

We also studied the conformation of **2** through its guest-binding properties. In 5% $CD_3OD/CCl_4$, a mostly nonpolar mixture, **2** could bind phenyl $\beta$-D-gluocopyranoside (**10**) with an association constant ($K_a$) of 380 ± 130 $M^{-1}$. Over the range of concentrations used for the NMR titration, the proton signals of the host showed no sign of broadening, indicating lack of self-association. Binding was confirmed to be 1:1 by the Job plot (Figure 1b). This binding constant was essentially the same as that between **1** and **10** ($K_a$ = 340 ± 60 $M^{-1}$).[3b] With extensive aromatic components (i.e., azobenzene) in the structure, binding by **2** should benefit from additional $\pi-\pi$ interactions. Indeed, the binding constant ($K_a$ = 700 ± 150 $M^{-1}$) almost doubled for guest **11**, which had an aromatic group larger than that of **10** but otherwise shared the same hydrophilic substructure.

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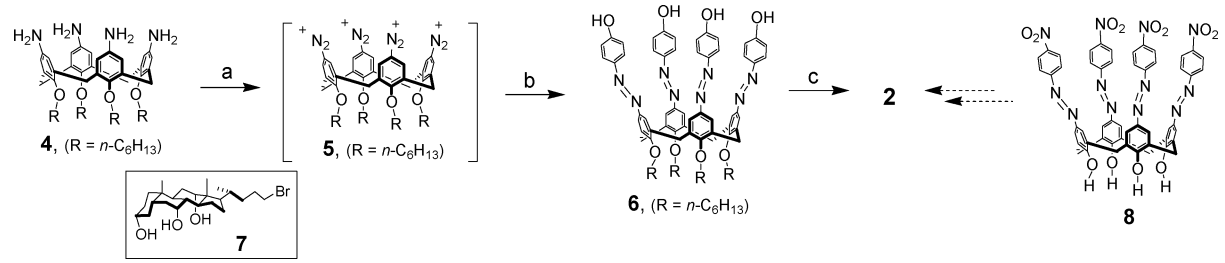
(13) The idea is to alkylate **8** first to afford a cone-shaped azocalixarene with alkoxy groups at the lower rim, followed by reduction of nitro to amine and finally amide coupling to cholic acid.

(14) Rotation of the CONH-aryl bond is hindered already by conjugation; see: Huc, I. *Eur. J. Org. Chem.* **2004**, *69*, 17−29 and references therein.

**SCHEME 1. Synthesis of Compound 2**[a]




[a] Reagents and conditions: (a) $NaNO_2$, HCl, $H_2O$, THF; (b) phenol, pyridine, THF; (c) **7**, $K_2CO_3$, $Bu_4NI$, DMF.

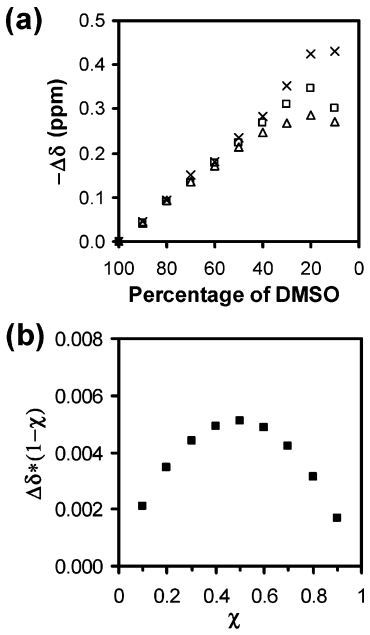



**FIGURE 1.** (a) Changes in $^1$H NMR chemical shifts of OH3 as a function of solvent composition in mixtures of DMSO-$d_6$/$CCl_4$ for compounds **1** (△), **2** (□), and **9** (×). OH3 is the hydroxyl group on the A-ring of the steroid backbone. (b) Job plots for the binding between **2** and phenyl $\beta$-D-glucopyranoside **10**, in which $\chi$ is the molar fraction of the guest. The chemical shift changes ($\Delta\delta$) are for the *para* proton of **10**.

Binding of polar molecules in a nonpolar mixture indicated that, similar to the parent basket **1**, azobasket **2** could adopt reversed-micelle-like conformations.

Pyrene (**12**) was found to be a suitable guest for the micelle-like conformer.[3b] Its binding by **2** was evidenced by upfield shifts of the methyl protons on the hydrophobic faces of the cholates. Even though $K_a$ was quite low, only about 5−10 $M^{-1}$ in methanol for both **2** and **1**, binding with pyrene through the hydrophobic faces of cholates did support the formation of micelle-like conformations in polar solvents. Previously, it was shown that much stronger binding could be obtained once the basket was made water-soluble to create a higher hydrophobic driving force.[3b]

Azobasket **2** displayed a $\pi-\pi^*$ transition near 350 nm and a very weak n$-\pi^*$ band at 450 nm in the UV spectrum. With **2** irradiated by 360 nm UV light for 5 min, the $\pi-\pi^*$ band lost about 40% of the initial intensity while the n$-\pi^*$ band grow stronger (Figure 2a), indicative of *trans*−*cis* isomerization.[5,6] Similar changes could be observed for the control **3**, but the extent of isomerization was much higher in this compound, as its $\pi-\pi^*$ band almost completely disappeared and was replaced

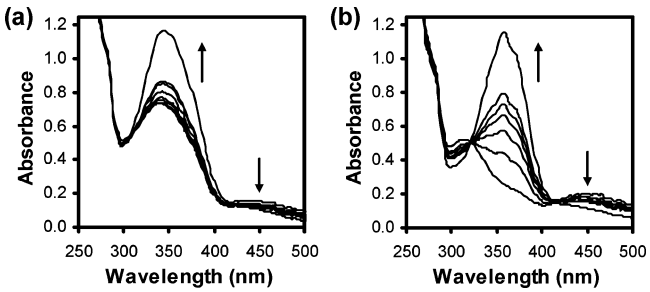



**FIGURE 2.** UV spectra of compounds (a) **2** and (b) **3** recorded at 0, 10, 20, 30, 40, 50, 60 min and then at 24 h after UV irradiation. The spectra at 24 h were nearly identical to those before irradiation. [Azobenzene] = 0.15 mM. Solvents = 5% MeOH/$CCl_4$ in both cases.

by a peak near 310 nm assigned to the *cis*-isomer (Figure 2b).[5,6] Lower conversion in **2** probably did not come from its conformational preference because similar situations occurred in other solvents (i.e., 50/50 or 95/5 methanol/$CCl_4$) that favored the random and micelle-like conformations. It seems that solvophobic forces were not strong enough to significantly influence the much higher energy photochemical process. Both compounds completely revert back to all-*trans* configurations after 24 h in the dark. Recovery is again slower in **2** than in the monomeric control. Since solvophobic interactions should help the all-*trans* structure of **2**, its slower kinetics must be caused by factors (e.g., steric crowdedness) other than its conformational property.

We also monitored the photoisomerization by $^1$H NMR spectroscopy. Portions of the spectra for **2** are shown in Figure 3. Before irradiation, the aromatic region showed two doublets at ca. 6.7 and 7.5 ppm for the protons on the top aromatic rings and a single peak at 7.3 ppm for the bottom calixarene aromatic protons. The aromatic protons became extremely complex after UV irradiation (Figure 3b). At the same time, (part of) the AB quartet for the calixarene methylene bridge ($ArCH_2Ar$) at 4.6 ppm disappeared completely. It is unlikely for UV irradiation to change the preorganized cone conformation of calix[4]arene. Disappearance of the $ArCH_2Ar$ signals probably happened as numerous configurational isomers were generated by partial conversion of the *trans*- to the *cis*-azobenzene. Importantly, the original spectrum recovered completely after 24 h in the dark, demonstrating reversibility of the process.

In summary, we combined photoisomerization of azobenzene with solvent-induced conformational change and synthesized a molecular basket (**2**) that showed dual responsive properties. Much improvement is still needed before it can be used as a "smart" delivery vehicle. The result, nonetheless, demonstrates that it is feasible to integrate conformational control with other

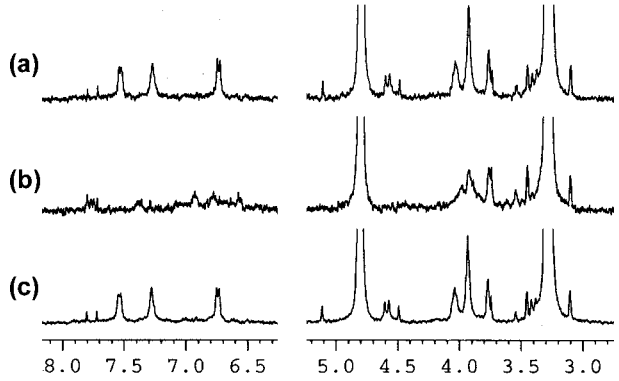



**FIGURE 3.** Portions of $^1$H NMR spectra of compound **2** (a) before, (b) immediately after, and (c) 24 h in dark after irradiation. The peaks between 3.3−4.1 ppm are from protons adjacent to OH and O in **2**. The large peaks at 3.3 and 4.8 ppm come from undeuterated solvents. Solvent = 5% $CD_3CD/CCl_4$.

switching mechanisms and rationally design materials responsive to multiple signals.

## Experimental Section

**General Method.** See Supporting Information.

**Compounds 1, 7, and 4.** See Supporting Information.

**Compound 6.** An aqueous HCl solution (3%, 1 mL) was added to a solution of **4** (101 mg, 0.12 mmol) in THF (4 mL) at 0 °C. A solution of $NaNO_2$ (43 mg, 0.61 mmol) in $H_2O$ (3 mL) precooled to 0 °C was added slowly via a syringe. The reaction mixture was stirred at room temperature for 1 h. A solution of phenol (115 mg, 1.22 mmol) in pyridine (2 mL) and THF (4 mL) was added slowly via a syringe at 0 °C. After 12 h at room temperature, the reaction mixture was poured slowly into $H_2O$ (100 mL). The precipitate formed was collected by suction filtration and washed with water (2 × 10 mL). The product was dried in vacuo and used in the next step without further purification (108 mg, 0.087 mmol, 73% yield). $^1$H NMR (300 MHz, $CDCl_3$, $\delta$): 7.48 (d, 8H, $J$ = 8.7 Hz), 7.28 (s, 8H), 6.68 (d, 8H, $J$ = 8.7 Hz), 4.56 (d, 4H, $J$ = 13.2 Hz), 4.00 (t, 8H, $J$ = 7.2 Hz), 3.33 (d, 4H, $J$ = 9.3 Hz), 1.98 (m, 8H), 1.48−1.39 (m, 24H), 0.96 (t, 12H, $J$ = 6.6 Hz).

**Compound 2.** Compound **6** (108 mg, 0.087 mmol), compound **7** (199 mg, 0.44 mmol), $K_2CO_3$ (122 mg, 0.88 mmol), and $Bu_4NI$ (10 mg, 0.028 mmol) were mixed with anhydrous DMF (5 mL). After 6 h at 50 °C, the reaction mixture was poured slowly into $H_2O$ (100 mL). The precipitate was collected by suction filtration and washed with water (2 × 10 mL). The product was purified by column chromatography over silica gel using $CHCl_3$/methanol as the eluents to give a yellowish powder (148 mg, 62% yield). $^1$H NMR (300 MHz, $CD_3OD/CCl_4$, $\delta$): 7.49 (d, 8H, $J$ = 8.7 Hz), 7.28 (s, 8H), 6.69 (d, 8H, $J$ = 9.0 Hz), 4.58 (d, 4H, $J$ = 6.9 Hz), 4.02 (t, 8H, $J$ = 7.2 Hz), 3.94 (s, 4H), 3.78 (m, 4H), 3.39 (m, 16H), 2.22−0.90 (m, 120H), 0.70 (s, 12H). $^{13}$C NMR (75 MHz, $CD_3OD/CCl_4$, $\delta$): 161.2, 159.2, 148.3, 146.9, 135.6, 124.3, 123.1, 114.6, 75.8, 73.1, 71.7, 68.8, 68.3, 58.7, 47.4, 46.5, 41.8, 39.6, 39.3, 35.8, 35.4, 34.9, 34.7, 32.2, 30.5, 30.0, 28.3, 27.8, 26.5, 26.2, 23.8, 23.3, 23.0, 22.5, 19.7, 17.5, 14.0, 13.4, 12.5. MALDI-TOFMS (m/z): calcd for $C_{172}H_{249}N_8O_{20}$ $[M + H]^+$ 2748.9, found 2744.5.

**Compound 3.** Compound **14** (50 mg, 0.22 mmol), compound **7** (100 mg, 0.22 mmol), and $K_2CO_3$ (151 mg, 1.10 mmol) were dissolved in anhydrous THF (10 mL). The reaction mixture was heated to reflux for 12 h. Solvent was evaporated in vacuo. The product was purified by column chromatography over silica gel using $CHCl_3$/methanol as the eluents to give a yellowish powder (82 mg, 0.14 mmol, 62% yield). $^1$H NMR (400 MHz, $CD_3OD/CDCl_3$, $\delta$): 7.85 (d, 2H, $J$ = 3.0 Hz), 7.82 (d, 2H, $J$ = 3.0 Hz), 7.06 (d, 2H, $J$ = 5.7 Hz), 7.03 (d, 2H, $J$ = 5.7 Hz), 4.04 (t, 2H, $J$ = 6.3 Hz), 3.97 (s, 1H), 3.88 (s, 3H), 3.80 (m, 1H), 3.37 (m, 1H), 2.21 (m, 3H), 1.97−0.92 (m, 30H), 0.73 (s, 3H). $^{13}$C NMR (75 MHz, $CD_3OD/CDCl_3$, $\delta$): 161.6, 161.3, 146.9, 146.7, 124.3, 124.3, 114.7, 114.2, 73.0, 71.5, 68.8, 68.3, 55.5, 47.2, 46.3, 41.6, 41.3, 39.3, 39.2, 35.5, 35.2, 34.7, 34.4, 32.0, 29.8, 28.0, 27.6, 26.3, 25.9, 23.2, 22.4, 17.5, 12.4. MALDI-TOFMS ($m/z$): $[M + H]^+$ calcd for $C_{37}H_{53}N_2O_5$ 605.8, found 605.8.

**Job Plot.** Two stock solutions (1.43 mM) of **2** and phenyl-$\beta$-D-glucopyranoside **10** in $CCl_4/CD_3OD$ (v/v = 90/10) were prepared separately. In 11 separate NMR tubes, portions of the two solutions were added such that their ratios changed from 0 to 1 while maintaining a total volume of 0.6 mL. $^1$H NMR spectrum was recorded for each sample. The changes in the chemical shifts of the *ortho*-, *meta*-, and *para*-protons of the phenyl in phenyl-$\beta$-D-glucopyranoside were monitored. Maximum at 0.5 molar fraction indicated a 1:1 binding stoichiometry.

**$^1$H NMR Titrations.** For the binding of **10** and **11**, the guest was titrated with different amounts of the host, and the chemical shifts of the aromatic protons in the guest were monitored. A typical procedure is as follows. Stock solutions of **2** (0.050 M) and phenyl-$\beta$-D-glucopyranoside **10** (0.010 M) in $CH_3OH$ were prepared. To 12 separate vials was added 60 $\mu$L of the phenyl-$\beta$-D-glucopyranoside solution, followed by 11, 14, 17, 20, 24, 29, 34, 39, 46, 54, 63, 74, 88, 106, and 130 $\mu$L of **2**. Solvent in each vial was completely evaporated. Then 600 $\mu$L of $CCl_4/CD_3OD$ (v/v = 90/10) was added to each vial. The samples were gently shaken for 1 h in the dark and then transferred to 12 separate NMR tubes. $^1$H NMR spectrum was recorded for each sample, and the chemical shifts of the phenyl protons of phenyl-$\beta$-D-glucopyranoside were monitored. The binding constants ($K_a$) were obtained by nonlinear least-squares curve fitting of the titration data.

**Supporting Information Available:** General method of the experiments, synthetic procedures, $^1$H NMR titration data, and $^1$H NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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