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PAPER

Effect of carboxylic acid on micelles of a neutral amphiphilic dendro-calix[4]arene†

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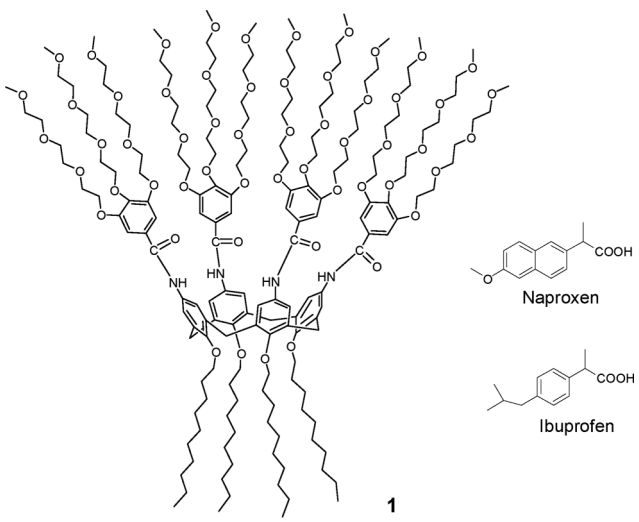
An amphiphilic calix[4]arene bearing branched 3,4,5-tris(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)benzamide groups at the upper rim was synthesized and could increase the solubility of naproxen and ibuprofen in water through hydrogen bonding and π–π stacking interactions. The interactions between amphiphilic calix[4]arene and carboxylic acids such as naproxen and ibuprofen could reverse the direction of the branched substituents and change the shape and size of calixarene micelles from solid to hollow or linear ones.

1. Introduction

Amphiphilic calixarenes, like other amphiphiles, have attracted interest from a range of fields due to their potential in molecule and ion delivery,[1] as drug carriers[2] and self-assembling organic nanomaterials,[3] and as inorganic nanomaterial templates and stabilizer,[4] in protein and DNA recognition,[5] as enzyme mimics,[6] in cell fluorescence imaging,[7] and so on. Reverse micelles composed of twelve *β*-acyl calix[4]arenes could encapsulate 46 water molecules.[8] The introduction of branched hydrophilic substituents instead of linear ones into either rim of the calixarene increases its solubility in water by increasing the size of the hydrophilic head. This also increases the curvature of the hydrophilic head group domain which leads to smaller and more stable micelles or vesicles.[9–11] Conveniently, the size of the vesicles can be tuned by the length of the branched hydrophilic substituents.[9] Although these changes are beneficial for the encapsulation of hydrophobic molecules in an aqueous solution, the effect on the load capacity and location of the guest molecules in the aggregates of the amphiphilic calixarenes has not been investigated. Also, little is known about the effect of the guest molecules on the morphology and size of the calixarene aggregates. Moreover, as a host, such as a drug carrier, charged amphiphilic calixarenes rather than neutral ones are usually used.[1,2,9–11] Here we report that a neutral amphiphilic calix[4]arene bearing branched 3,4,5-tris(2-(2-(2-methoxyethoxy)ethoxy)ethoxy) benzamide (3,4,5-TMEEE benzamide) groups at the upper rim can increase the solubility of naproxen and ibuprofen in water by 84 and 272-fold, respectively, due to hydrogen bonding and π–π stacking interaction. The intermolecular interactions lead to the change in shape and size of the calixarene micelles.

2. Results and discussion

Amphiphilic calix[4]arene **1** (Scheme 1) was synthesized by the reaction of *p*-aminocalix[4]arene decyl ether in cone conformation and 3,4,5-TMEEE benzoyl chloride in good yield and was fully characterized by ^{1}H and ^{13}C NMR, HRMS, IR, and Mp. It is easily soluble in water as well as in conventional organic solvents such as methanol, acetone, THF, chloroform, and benzene *etc.*



Scheme 1 Structure of calixarene **1**, naproxen and ibuprofen.

As shown in Fig. 1, calix[4]arene **1** had one strong emission band at 450 nm and one weak band at 358 nm when it was excited by a light of 284 nm in water. According to the literature,[12] the strong

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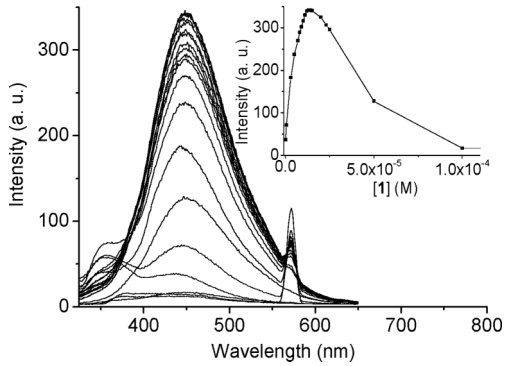


Fig. 1 Change in fluorescence spectra of **1** with its concentration in water. λ_{ex} = 284 nm, em/ex slits = 5/5 nm; inset, curve of fluorescence intensity *vs.* concentration at λ_{max} = 450 nm.

emission band at 450 nm is ascribed to the intramolecular proton and charge transfer fluorescence of benzanilide groups while the weak band at 358 nm is the normal fluorescence of the benzanilide groups. The fluorescence intensity at 450 nm increased when increasing the concentration in the range less than 1.3×10^{-5} M, but it decreased when the concentration was larger than 1.3×10^{-5} M (inset in Fig. 1). A similar result was also observed for the emission band at 358 nm. Aggregation of **1** causes this fluorescence quenching, indicating the critical micelle concentration of **1** is 1.3×10^{-5} M.[10b]

In addition, just like other nonionic surfactants, a solution of **1** in water turned turbid upon heating. The cloud point increased from 46 °C to 60 °C as the concentration decreased from 1.0×10^{-3} to 5.0×10^{-5} M (Fig. 2). When the concentration was less than 1.0×10^{-5} M, the solution did not become turbid even after it was boiling, demonstrating that **1** does not aggregate until the concentration is larger than 1.0×10^{-5} M.

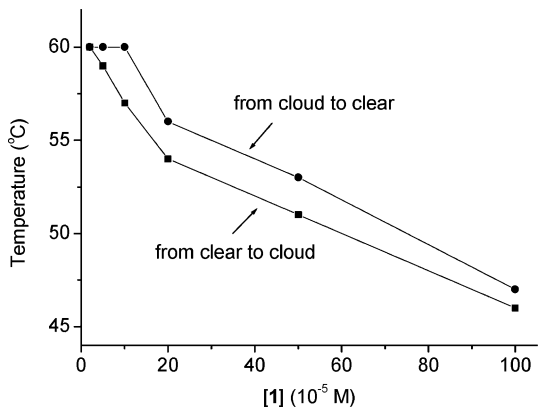


Fig. 2 Change of cloud point with concentration of **1** in water.

Importantly, **1** could increase the solubility of non-steroidal anti-inflammatory hydrophobic drugs naproxen and ibuprofen (Scheme 1) in water. In 1.0 mL of water containing 10 mM of **1**, 2.1 mg of naproxen could be dissolved to give a clear solution. Compared with the solubility 0.025 mg mL^{-1} of naproxen in pure water,[13] the solubility in the aqueous solution of **1** has been increased 84 fold. The molar ratio of 0.91 naproxen : **1** is much higher than the literature value of 0.17 obtained with monoalkyl polyethylene glycol ether ($C_{16}H_{33}$-$(OCH_2CH_2)_{20}OH$).[13] Similarly, a solubility of 3.0 mg mL^{-1} of ibuprofen in the presence of **1** was 272 times larger than 0.011 mg mL^{-1} in pure water.[14] It has been reported[15] that the increased solubility will not only make these drugs easier to use but also have a potential for promoting the potency of the drugs.

The micelle formation of **1** was studied with TEM. Thanks to the gallic groups, the aggregates could be clearly observed by TEM because the four aromatic substituents not only made **1** fluorescence emitting but also gave a high contrast in TEM images. As shown in Fig. 3, **1** could form irregular nanoparticles that had a large diameter distribution from 15 to 100 nm in water. It was clearly observed that the nanoparticles were composed of nano micelles about 5 nm in diameter. The high resolution TEM images also showed the discrete micelles that randomly packed into a nanoparticle with about 80 nm diameter. Interestingly, after naproxen was dissolved into the solution of **1** in water, the diameter of the micelles increased to about 12 nm. Moreover, unlike micelles formed by pure **1**, the micelles were hollow instead of solid, indicating naproxen was not included in the interior of the micelles. The shell width of the hollow micelles was 4 nm, which was much larger than the radius (2.5 nm) of the micelles formed by pure **1**. The round hollow micelles also tended to form larger aggregates, and even aggregated into hollow rod-like micelles. When ibuprofen was dissolved in a solution of **1** in water, the resultant micelles also tended to randomly aggregate into bigger nanoparticles. Similarly, the micelles with a diameter of about 10 nm were much larger than the ones formed by pure **1**.

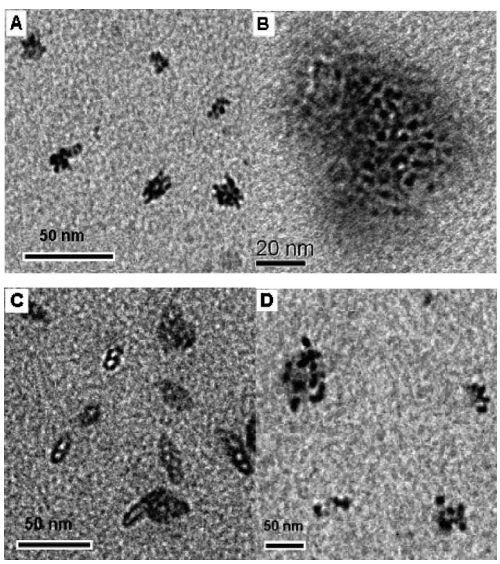


Fig. 3 (A) TEM image of **1**; (B) HR TEM image of **1**; (C) TEM image of a mixture of **1** and naproxen; (D) TEM image of **1** and ibuprofen. Concentration of all compounds in water = 0.5 mM.

Cryo-TEM analysis also confirmed these results. As shown in Fig. 4, **1** formed micelles with a diameter of 5 nm (Fig. 4A), which had a tendency to aggregate into bigger particles about 50 nm in diameter (Fig. 4B). When naproxen was added, large hollow micelles 10–80 nm in diameter were obtained. The shell width of the hollow micelles was 4 nm, which was again much larger than the radius of the micelles formed by pure **1**. When ibuprofen was added to the aqueous solution of **1**, the discrete micelles were more dispersed. The micelles were solid and had a diameter of

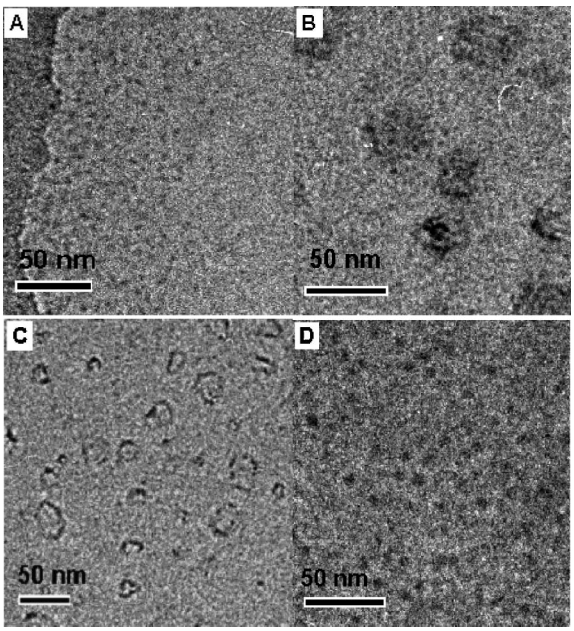


Fig. 4 (A, B) Cryo-TEM image of **1**; (C) Cryo-TEM image of the mixture of **1** and naproxen; (D) Cryo-TEM image of **1** and ibuprofen. Concentration of all compounds in water = 1.0 mM.

7.5 nm, which was also much larger than the micelles resulting from pure **1**.

In order to further study the effect of carboxylic acids on the micelles of **1**, more acids such as alkanoic acid, dodecanoic acid, aromatic acid, and benzoic acid were used. As shown in Fig. 5A, hollow micelles with a diameter of 10–20 nm were obtained when dodecanoic acid was added to an aqueous solution of **1**. The shell was 3.8 nm thick, which was much larger than the radius (2.5 nm) of the micelles formed by pure **1** but was close to the size of micelles from a mixture of **1** and naproxen. Unexpectedly, benzoic acid even gave linear micelles 50–400 nm in length and 7.5 nm wide in addition to some solid micelles 7.5 nm in diameter (Fig. 5B). The width of the linear micelles was again much larger than the diameter of the micelles of pure **1**.

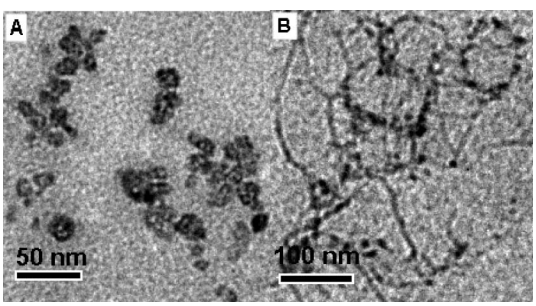


Fig. 5 (A) TEM image of the mixture of **1** and dodecanoic acid; (B) TEM image of the mixture of **1** and benzoic acid. Concentration of all compounds in water = 0.5 mM.

The aggregation of **1** with and without the carboxylic acids in water was also investigated by dynamic light scattering (DLS). **1** in water aggregated into very small particles with a mean diameter of 3.5 nm (Fig. 6A). After equal molar amounts of naproxen, ibuprofen, dodecanoic acid and benzoic acid were added, the

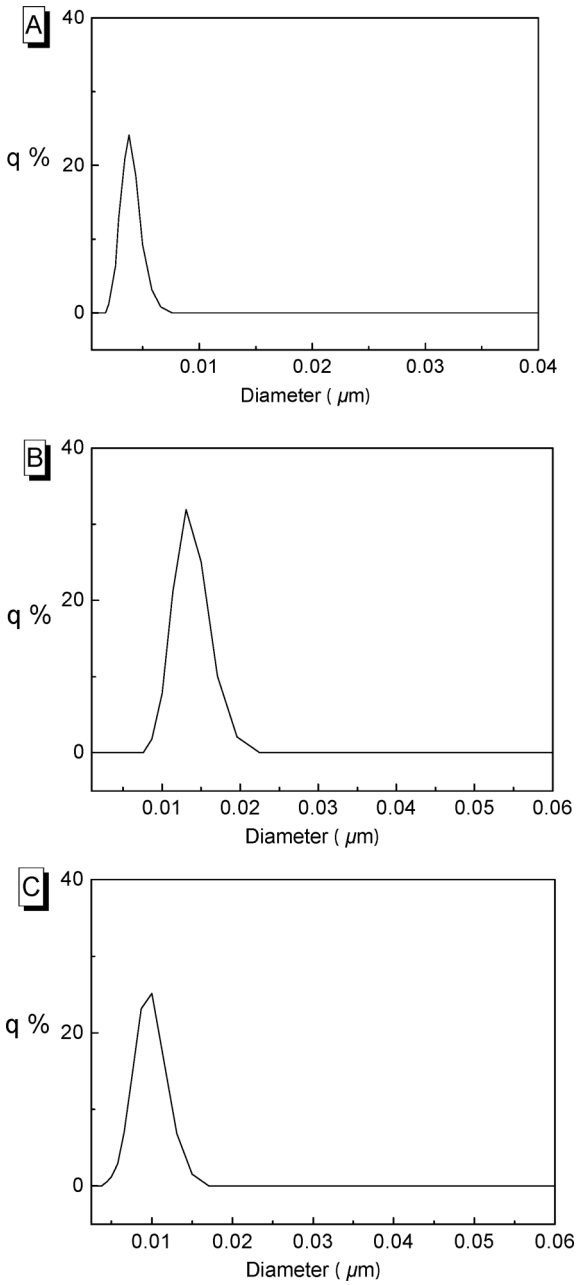


Fig. 6 Dynamic light scattering (DLS) diagram of solutions of (A) **1**, (B) a mixture of **1** and naproxen, (C) a mixture of **1** and ibuprofen in water at 20 °C ([**1**] = [naproxen] = [ibuprofen] = 5.0×10^{-5} M, measured as soon as the solution was prepared).

resultant particles were 13.4, 7.9, 12.2 and 220 nm in diameter, respectively (Fig. 6B–C and Fig. S16†), indicating that the added carboxylic acid could increase the size of aggregates formed by **1** in water.

A fluorescence titration of naproxen (1.0×10^{-6} M) with **1** from 1.0×10^{-7} M to 1.0×10^{-4} M showed that there was a strong interaction between **1** and naproxen (Fig. 7–9). When the concentration of **1** was less than 2.6×10^{-6} M, the fluorescence intensity of naproxen at 357 nm increased a little due to an increase in the fluorescence intensity of calixarene **1** at this position. After 2.6×10^{-6} M, with increasing concentrations of **1**, the fluorescence intensity of naproxen exponentially decreased. The linear increase

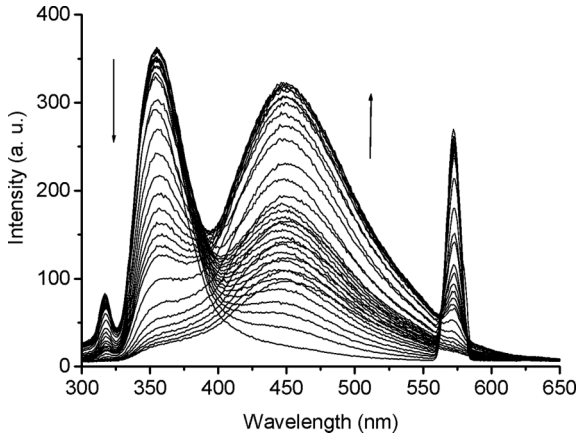


Fig. 7 Change in the fluorescence spectra of naproxen with concentration of added **1**. [Naproxen] = 1.0×10^{-6} M; [**1**] = 2.0×10^{-7}–1.0×10^{-3} M; λ_{ex} = 284 nm, em/ex slits = 5/5 nm. The emission band of naproxen is at about λ_{max} = 357 nm; the main emission band of **1** is at about λ_{max} = 450 nm.

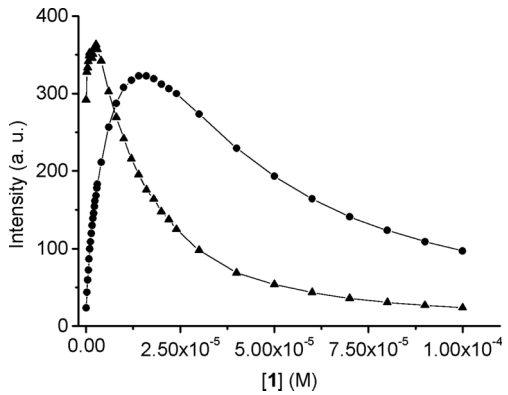


Fig. 8 Change in the fluorescence intensity of naproxen at λ_{max} = 357 (▲) and of **1** at λ_{max} = 450 nm (●) with concentration of added **1**. [Naproxen] = 1.0×10^{-6} M; [**1**] = 2.0×10^{-7}–1.0×10^{-3} M; λ_{ex} = 284 nm, em/ex slits = 5/5 nm.

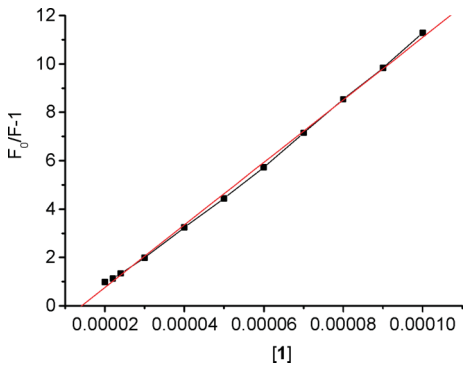


Fig. 9 $F_0/F-1$ value changes with concentration of added **1**. The red straight line is a fitting result using the Stern–Volmer equation. [Naproxen] = 1.0×10^{-6} M; [**1**] = 2.0×10^{-7}–1.0×10^{-3} M; λ_{ex} = 284 nm, em/ex slits = 5/5 nm.

of the fluorescence intensity ratio F_0/F (the intensity of pure naproxen *vs.* that of naproxen mixed with **1**) with the concentration of **1** at concentrations more than 2.0×10^{-5} M was well in agreement with the Stern–Volmer equation.[16] A large quenching constant ($K_{sv} = 1.29 \times 10^5$ L mole^{-1}; relative coefficient 0.999) was obtained, demonstrating that there was a strong interaction between **1** and naproxen.

When 3,4,5-TMEEE benzoic acid (2.0×10^{-4} M) and naproxen (2.0×10^{-4} M) in water were mixed, the former also quenched the fluorescence emission of naproxen. Therefore, the interaction between **1** and naproxen occurred primarily through 3,4,5-TMEEE benzoyl substituents of **1**. It could be inferred that, in addition to forming oxonium salts between the carboxylic acid groups of naproxen and the oxygen atoms of the ethoxyl groups of 3,4,5-TMEEE benzoyl substituents, a π–π stacking interaction between naproxen and the substituents of **1** was also key. Due to the strong electron-donating alkoxyl groups, the benzene ring of 3,4,5-TMEEE benzoyl substituent is also a strong electron-donator. Therefore, electron communication between the benzene ring of the 3,4,5-TMEEE benzoyl substituent and the naphthalene ring of naproxen could be carried out by π–π stacking interactions. Usually, π–π stacking results in fluorescence quenching.[17] It is well known that polyphenolic acids, such as tannic acid and gallic acid,[18] especially 3,4,5-trimethoxybenzoic acid,[18d] are effective in quenching the fluorescence of proteins through π–π stacking interactions between the aromatic rings of the polyphenolic acids and tryptophan in the protein. Our results agree with these reports.

From the ^{1}H NMR spectra, all proton signals from naproxen or ibuprofen changed from sharp and well resolved peaks to broad peaks upon mixing with **1**, indicating that the molecular motion slowed down due to combination with **1** (Fig. 10–11). The aromatic proton signal of naproxen at the lowest downfield in D_2O appeared at 7.79 ppm while the signal in the mixture of **1** and naproxen appeared at 7.52 ppm, indicating an upfield shift of 0.27 ppm. For the aromatic proton of ibuprofen, an upfield shift of 0.21 ppm was also produced. This confirmed that there was a π–π stacking interaction between aromatic rings of **1** and that of naproxen or ibuprofen. NMR titration gave a 1 : 1 association ratio and association constants of 6.3×10^4 M^{-1} and 3.0×10^5 M^{-1}, respectively for **1**–naproxen and **1**–ibuprofen complexes.

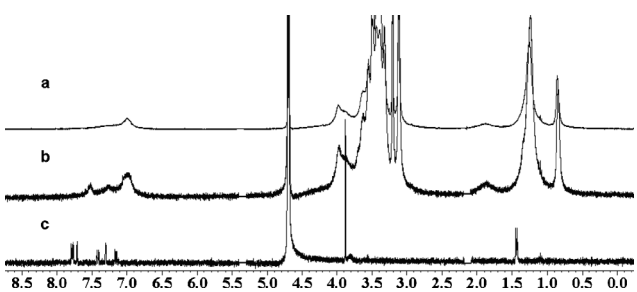


Fig. 10 ^{1}H NMR spectra of **1**, naproxen, and **1**–naproxen mixture in D_2O. (A) Spectrum of **1**; (B) spectrum of **1**–naproxen mixture; (C) spectrum of naproxen. [**1**] = [naproxen] = 1.0×10^{-4} M in all tests.

Due to their flexibility, the branched substituents of calixarene could fold toward the lower rim (Fig. 12, conformer A), point out horizontally (Fig. 12, conformer B) or stretch over the upper rim of the calixarene framework (Fig. 12, conformer C). Molecular mechanic calculations[19] gave a length/width/height of 2.1/1.7/2.6 nm for A, 3.6/2.8/2.6 nm for B and 3.2/1.7/3.5 nm for

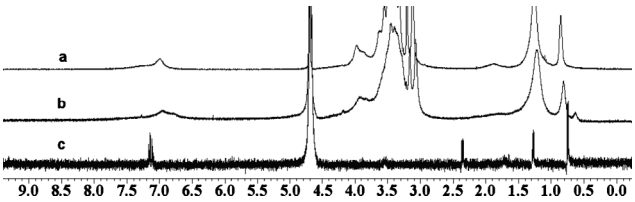


Fig. 11 ^{1}H NMR spectra of **1**, ibuprofen, and **1**–ibuprofen mixture in D_2O. (A) Spectrum of **1**; (B) spectrum of **1**–ibuprofen mixture; (C) spectrum of ibuprofen. [**1**] = [ibuprofen] = 1.0×10^{-4} M in all tests.

C. Only conformer A could form micelles with a diameter as small as 5 nm, therefore, **1** mainly exists as conformer A. The conformer A, formed due to steric repulsion and hydrophilicity of the branched substituents, has been reported in literature.[3a,10] After carboxylic acid was added, the branched substituents pointed horizontally or stretched upward due to strong hydrogen bonds between the carboxylic group and oxygen atom of the 3,4,5-TMEEE substituents as well as through π–π stacking interactions. The resultant complex (Fig. 12D) had a length/width/height of 2.8/1.7/3.8 nm, which is consistent with the 4 nm shell of the hollow micelles and 7.5 nm thickness of the solid and linear micelles (which matches a double height of the conformer D) after acids were added. The conformer D also has the possibility of stretching the branched substituents further up to look more like a cuboid rather than like a wedge. This would allow it to form even bigger hollow micelles and even give linear micelles.

3. Conclusion

In conclusion, a novel amphiphilic dendro-calix[4]arene was synthesized and could increase the solubility of naproxen and ibuprofen in water. It was found for the first time that the solid micelles formed by neutral amphiphilic **1** could be changed into hollow, linear micelles as well as bigger solid ones when the direction of the branched substituents changed with the addition of a carboxylic acid. This finding provides a new way for the design of host compounds and control of the size and shape of micelles by guests.

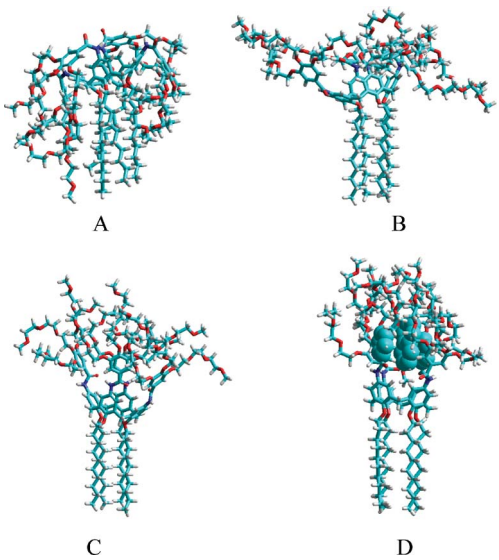


Fig. 12 (A, B, C) Possible conformers of calixarene **1** in water; (D) possible conformer of the complex of **1** and naproxen in water.

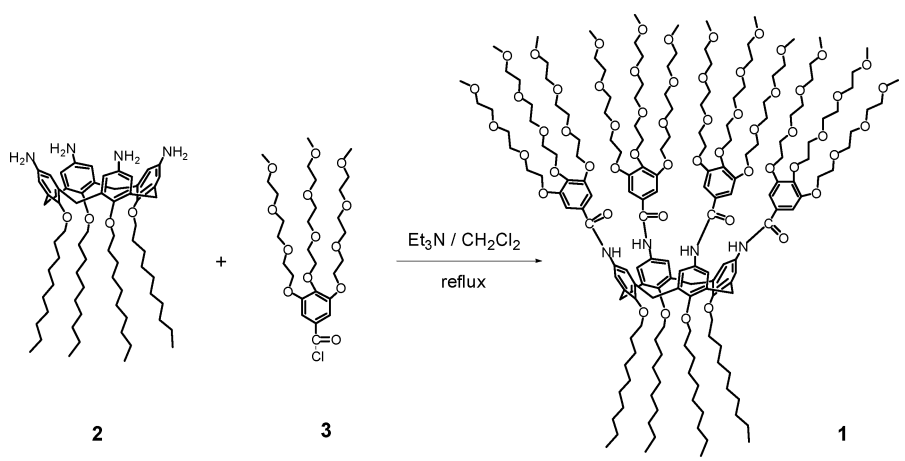
4. Experimental section

Materials

All reagents and solvents were chemical pure (CP) grade or analytical reagent (AR) grade and were used as received unless otherwise indicated. Calix[4]arene amine and acyl chloride were synthesized according to the literature (see ESI†).

Synthesis of compound 1 (Scheme 2)

To the solution of acyl chloride **3**[20] (1.0 g, 1.6 mmol) in CH_2Cl_2 (10 mL), cooled with an ice bath, was dropped a solution of calix[4]arene amine **2**[21] (0.3 g, 0.29 mmol) and redistilled triethylamine (0.3 mL, 2.2 mmol) in CH_2Cl_2 (5 mL). After addition, the ice bath was removed and the mixture was refluxed for about 3 h. The mixture was evaporated to dryness using a rotary evaporator under reduced pressure. The residue was purified by flash column chromatography (silica gel, $CHCl_3/CH_3OH$, 80 : 1) to give a colorless sticky solid (0.45 g, 46%). Mp 43–44 °C; ^{1}H



Scheme 2

NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 4H, CON*H*), 7.20–7.0 (br s, 16H, Ar*H*), 4.49 (d, J = 13.2 Hz, 4H, ArCH_2Ar), 4.20–3.40 (m, 152H, CH_2O), 3.36, 3.31 (2 s, 36H, OCH_3), 3.21 (d, J = 13.2 Hz, 4H, ArCH_2Ar), 1.96 (s, 8H, ArOCH$_2$CH_2CH$_2$), 1.45–1.20 (m, 56H, OCH$_2$CH$_2$(CH_2)$_7$CH$_3$), 0.89 (t, J = 6.4 Hz, 12H, CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 153.5, 152.4, 141.7, 135.2, 132.4, 129.8, 121.3, 107.6, 75.5, 72.4, 72.0, 71.9, 70.68, 70.66, 70.60, 70.56, 70.5, 70.4, 69.8, 69.2, 59.0, 58.9, 32.0, 31.4, 30.3, 30.0, 29.8, 29.5, 26.4, 22.7, 14.1); IR (KBr) ν 3308, 2925, 1663, 1584, 1536, 1495, 1468, 1426 cm^{-1}; $^+$TOF HRMS m/z calcd for ($C_{180}H_{294}N_4O_{56}$)/2 1704.0140 [M+2H$^+$]$^{2+}$/2, found [M+2H$^+$]$^{2+}$/2 1704.0179.

Measurements

^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz spectrometer at 298 K in $CDCl_3$. Mass spectra were measured on a TOF-MS instrument. Absorption spectra were recorded on a UV–vis spectrophotometer. Infrared spectra were recorded on an EQUINAX55 spectrometer. Transmission electron micrographs (TEM) were recorded on a G2 20 electron microscope at 200 kV. HR-TEM was measured on a JEM-2010FEF electron microscope. The micelle suspension was dropped onto a copper grid covered with a thin carbon film on filter paper and air dried. Fluorescent emission spectra were collected on a fluorophotometer at 298 K. Dynamic light scattering (DLS) was measured on a Horiba LB-550 particle size analyzer. Fluorescent emission spectra were collected on a fluorophotometer at 298 K.

For the cryo-TEM experiment, the specimen were prepared in a controlled environment vitrification system (CEVS) at 22 °C and 100% relative humidity to avoid loss of volatiles. A 3.5 μL drop of solution was placed on a GiG 300 mesh holey carbon film and blotted with filter paper (4 s) to form a thin liquid film of the sample. The thin film sample was plunged into liquid ethane at its freezing temperature (–183 °C) to get vitrified and then transferred to liquid nitrogen (–196 °C) for storage. The vitrified specimens were examined in an FEI Tecnai 20 TEM operating at an accelerating voltage of 200 kV. A Gatan CT3500 cryoholder that maintained the specimens below –180 °C during sample transfer and observation was used. The specimens were observed and imaged at low dose mode with a dose of 20e$^-$ A^{-2}.

Fluorescent titration was carried out by addition of a concentrated solution of **1** into a solution of naproxen in H_2O. To keep a constant concentration of naproxen and account for dilution effects during titration, the solution of **1** was prepared with the solution of naproxen at its initial concentration as a solvent. The quenching constant was calculated using the following Stern–Volmer equation[16]:

$$F_0/F = 1 + K_{SV}[Q],$$

where F_0 is the fluorescence intensity of naproxen; F is the fluorescence intensity of naproxen upon addition of **1**; [Q] is the molar concentration (mole L^{-1}) of **1**; and K_{SV} is the quenching constant (L mole^{-1}).

Acknowledgements

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