Intramolecular Coaggregation Behavior in Novel Cyclotriveratrylenes with Cholic Acid Podants

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Two molecules 1a and 1b consisting of one cyclotriveratrylene (CTV) and three cholic acid podants have been designed and synthesized. Fluorescent studies in water/dimethoxyethane mixtures reveal an intramolecular coaggregation between the CTV and the attached cholic acid moieties. Their fluorescent emission intensity increases and then decreases with the increase of water content, whereas under the same measuring conditions the intensity of CTV derivative 2a, which possesses no similar cholic acid moiety, increases and then reaches a maximum value. The intensity decrease in 1a and 1b has been attributed to the decrease of the microenvironmental polarity in media of increasing polarity because of the shielding effect of the hydrophobic face of the cholic acid moiety.

Keywords CTV, cholic acid, hydrophobic-lipophilic interaction, coaggregation

Introduction

Aggregation and coaggregation brought about by hydrophobic-lipophilic interaction (HLI) are the basis for the formation of assemblies such as aggregates, micelles, vesicles, biomembranes, and living cells.[1-3] Conformational coiling is also a common phenomenon for many biomolecules, especially for peptides, proteins, and lipids. Since Menger's first proposal for rationalization of the rate retardation of the hydrolysis of *p*-nitrophenyl dodecanoate in aqueous medium,[2a] HLI-driven aggregation of organic molecules have been extensively investigated[3,4] and successfully applied to organic synthesis,[5] photochemistry,[1b,6] and photobiology.[7] In addition to aggregation, linear molecules with sufficient chain-length tend to coil like hairpins (self-coiling) in aqueous or acqui-organo solutions. For linear molecules with identical chromophores at the ends, such self-coiling can facilitate the formation of intramolecular excimers and this phenomenon can actually be regarded as intramolecular aggregation for the chromophores. In the past decade, coaggregation, *i. e.*, aggregation of different organic molecules, has also been well established.[8] Surprisingly, although electrostatic and hydrogen bonding-driven conformational change has been extensively investigated,[9] reports about HLI-driven intramolecular coaggregation of different parts of a single molecule are very rare.[10] Considering the importance of HLI-driven aggregation and chain coiling in many biomolecules or systems,[11] it is of importance to develop new models to investigate such an intramolecular coaggregation behavior.

Cycloveratrylenes (CTVs) are a class of cyclic oligomers, which have been widely utilized as building blocks to construct various receptors for recognizing small organic molecules,[12] while cholic acid is a typical amphiphilic molecule possessing a hydroxylated hydrophilic face as well as an all-hydrocarbon hydrophobic face.[13] In order to test the credibility of the above-mentioned concept of intramolecular coaggregation, we have designed one class of model molecules by attaching three amphiphilic steroidal moieties to a CTV scaffold. In this paper, we hope to describe their synthesis and intramolecular coaggregation behavior in water/dimethyl-

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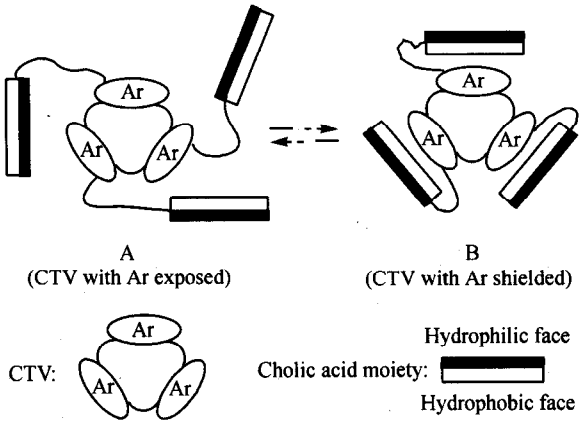
Received August 17, 2000; accepted November 17, 2000.
Project supported by the National Natural Science Foundation of China and Chinese Academy of Sciences.

glycol (DME) mixture, which is shown in Scheme 1. Fluorescent studies have revealed that the molecules adopt random and flexible conformations (Cartoon A) in pure DME, a solvent with no solvent aggregating power (SAgP).[14] However, in solvents with high SAgP, *i.e.*, DME-H_2O mixtures, hydrophobic "cavities" might be formed by the intramolecular aggregation between the three benzenes and the hydrophobic surfaces of the cholic acid podants, as shown by Cartoon B in Scheme 1. In other words, the microenvironmental polarity of this "cavity" would be reduced.

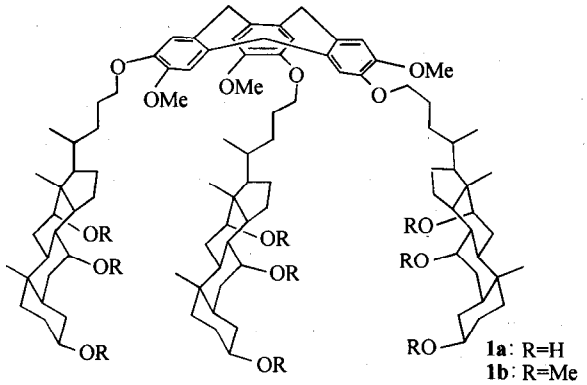
Scheme 1 Intramolecular coaggregation behavior



Results and discussion

Design considerations

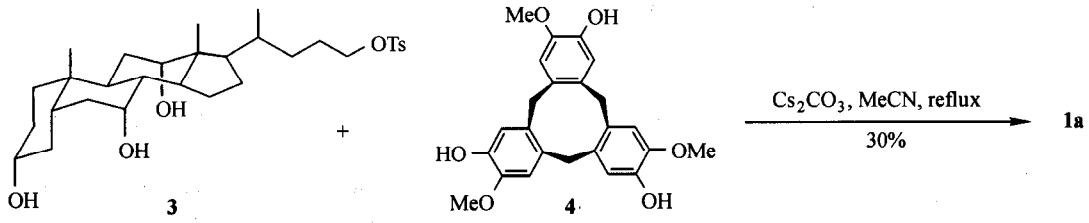
Molecular aggregation and coaggregation have been investigated mainly by the kinetic or fluorescent probe method. We chose the latter for our purpose since no reaction was needed and it is of high sensitivity. We designed two target molecules, *i.e.*, **1a** and **1b**, which consist of one CTV core and three attached cholic acid or trimethylated cholic acid podants respectively. CTV was used as the scaffold not only because of its hydrophobicity and suitable size, which is essential for the expected coaggregation with other large moieties, but also for its low self-aggregating tendency as a result of its bowl-shaped nonplanar structure. The three separated benzenes in CTV were used as fluorescent probes. The amphiphilic feature of the cholic acid moiety would provide the target molecules enough solubility in aqueous-organo binary solvents. In organic solvents, the three cholic acid moieties should be conformationally flexible and the benzenes in the CTV core completely exposed to the solvents. In highly polar solvents, however, intramolecular coaggregation might take place such that the three large hydrophobic faces of the attached steroidals would be forced to approach the hydrophobic benzenes and form pseudo cavities, which might behave as highly sensitive fluorescent probes to changes of microenvironmental polarity. A comparison of their fluorescent properties with **2**, which bears no steroidal podants, might provide evidence for the occurrence of intramolecular coaggregation.



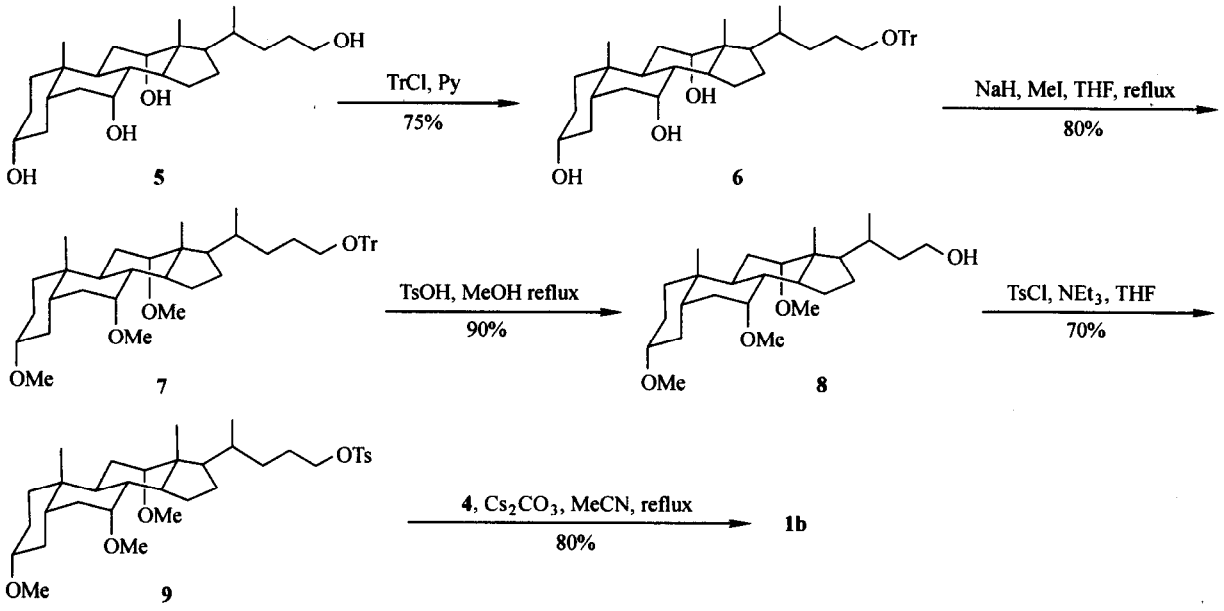
Synthesis

Scheme 2 shows the synthesis of compound **1a** from

Scheme 2

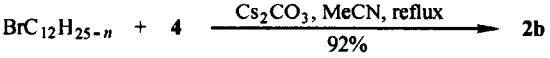


Scheme 3



the reaction of tosylate **3** and CTV **4**. Scheme 3 summarizes the synthetic route, which had been used to prepare compound **1b**. Thus, tetraol **5** was first selectively tritylated with trityl chloride to generate the ether derivative **6**, which was then totally methylated to give compound **7** in good yield. Detritylation and subsequent tosylation with tosyl chloride of **7** afforded tosylate **9**. Compound **9** then reacted with CTV **4** in the presence of cesium carbonate in refluxing acetonitrile, to afford the target compound **1b**. The synthesis of **2b** from the reaction of CTV **4** and lauryl bromide is shown in Scheme 4.

Scheme 4



Monomer concentrations

In order to investigate the dependence of the emission intensity of the fluorescent probe on the polarity of the solvents at a fixed concentration, intermolecular aggregation must be avoided to ensure that the change in the fluorescent intensity in graded aqui-organo solutions only reflects the CTV probes in the monomeric state. Thus, the fluorescent intensity versus substrate concentrations was first plotted in order to find a suitable monomeric concentration. The plot is shown in Fig. 1. Since the substrates exhibited relatively poor solubility in pure water ($\Phi = 0$, Φ is the volume fraction of DME of an aqueous DME), the measure was carried out at $\Phi = 0.1$. It has been found that there exists a good linear relationship between the fluorescent intensity and the concentration of **1a**, **1b**, or **2a** within the measured concentration range (see Fig. 1). Since all the CTV derivatives exhibit much better solubility in pure DME than that in pure water, the substrates should have higher saturated monomer concentration in the binary solvent with a larger Φ value. It was therefore reasonable to assume that the substrates exist as monomers within or below the plotted

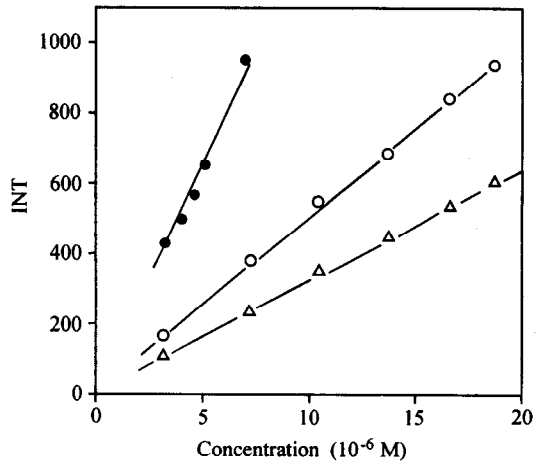


Fig. 1 Fluorescent intensity (INT) at $\Phi = 0.1$ as a function of substrate concentration for **1a** (○), **1b** (△), and **2a** (●). The data point represents an average of three measurements with an error of ± 5%.

concentration range ($< 18.0 \times 10^{-6}$ M for **2a** when $\Phi \leq 0.9$). Compound **2b** is insoluble in the solvent of $\Phi =$ **0.1** and is hardly soluble even at $\Phi =$ **0.4**. Although is emission intensity increased with decreasing Φ value, there was no linear relationship between them within the concentration range in Fig. **1**.

Fluorescent properties

All the fluorescence emission spectra of the above substrates were measured at the fixed concentration of $\mathbf{3.2 \times 10^{-6}}$ M in graded water/DME systems. The spectra of **1a** are shown in Fig. 2. Continuous increase of water content (decrease of Φ) resulted in a continuous increase in fluorescent intensity until a Φ value of 0.6 was reached (Fig. 2A). Further decrease of the Φ value resulted in obvious decrease in fluorescent intensity (Fig. 2B) until it reached a value of 0.2 as shown by Fig. 3. Although the emission intensity changed substantially with the solvent composition, the specific value of λ_{max} was not sensitive to the solvent composition and remained around 320 nm with an uncertainty of ± 3 nm. Similar results were also observed for other substrates (*vide infra*).

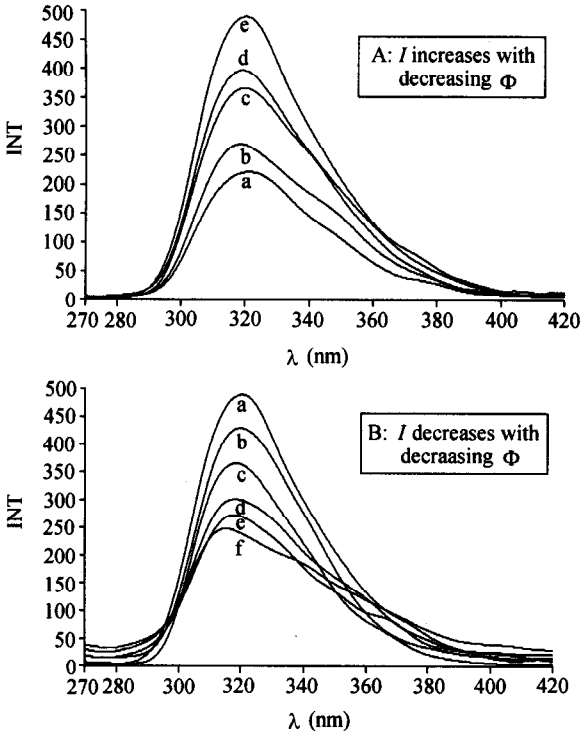


Fig. 2 Fluorescent spectra of **1a** in DME/water solution: (A) Φ = 1.0 (a), 0.9 (b), 0.8 (c), 0.7 (d), 0.6 (e). (B) Φ = 0.6 (a), 0.5 (b), 0.4 (c), 0.3 (d), 0.2 (e), 0.1 (f).

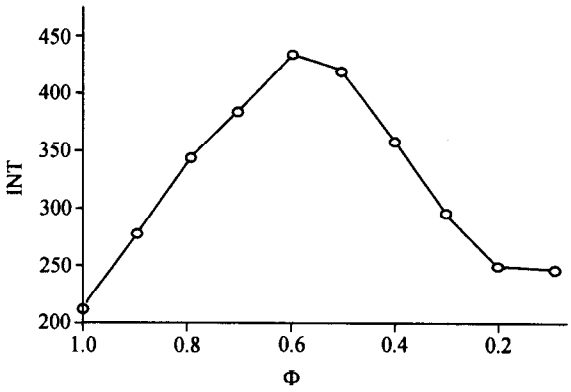


Fig. 3 Relative emission intensity at λ_{max} for **1a** via Φ. The data point represents an average of three measurements with an error of ± 5%.

Compound **1b** exhibited a similar fluorescent be-

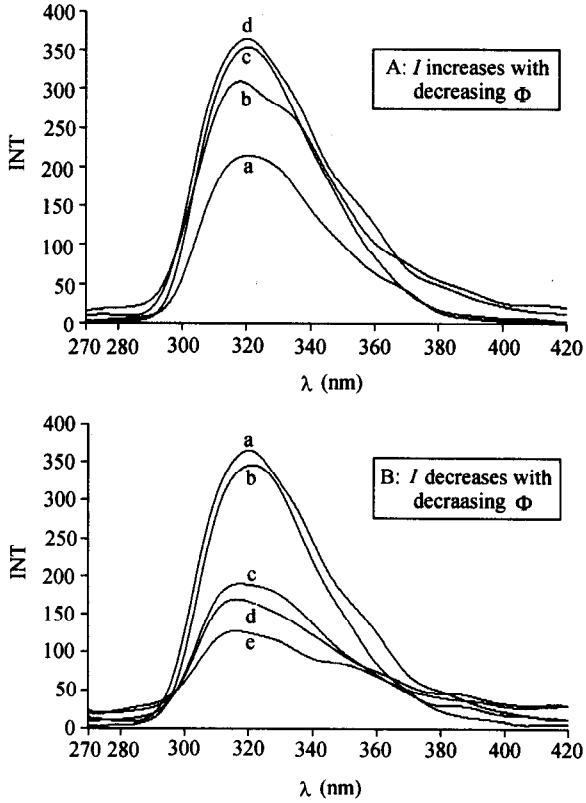


Fig. 4 Fluorescent spectra of **1b** in DME/water solution: (A) Φ = 1.0 (a), 0.9 (b), 0.8 (c), 0.7 (d). (B) Φ = 0.7 (a), 0.6 (b), 0.5 (c), 0.3 (d), 0.1 (e). Some data are not shown for benefit of clarity.

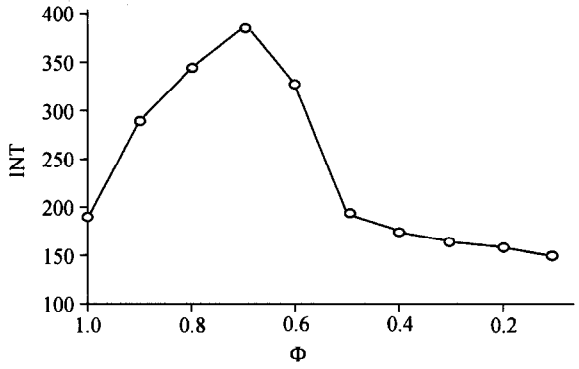


Fig. 5 Relative emission intensity at λ_{max} for **1b** via Φ. The data point represents an average of three measurements with an error of ± 5%.

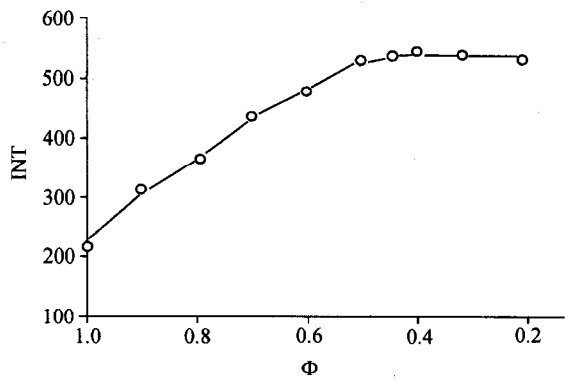


Fig. 7 Relative emission intensity at λ_{max} for **2a** via Φ. The data point represents an average of three measurements with an error of ± 5%.

havior in the water/DME solvent, as shown in Fig. 4 and Fig. 5. However, some significant differences could be observed by comparing **1b** with **1a**. Firstly, the turning point of the emission intensity versus the increase of the water content (decrease of Φ values) occurred earlier at Φ = ca. 0.7. Secondly, its emission intensity underwent a sharper decrease until the Φ value of ca. 0.5 was achieved and, after that, reduced slowly with further increase of the water content, *i. e.*, decreasing Φ values (from 0.5 to 0.1), while the obvious decrease of the emission intensity of **1a** took place within a markedly larger Φ range of ca. 0.6—0.2.

The fluorescent spectra of steroidal-free substrate **2a** in varying water/DME solvents are presented in Fig. 6 and a plot of the related emission intensity at λ_{max} as a function of decreasing Φ values (curves a to e) is shown in Fig. 7. It can be easily seen that **2a** exhibits an obviously different fluorescent emission behavior. Although acontinuous increase in the emission intensity is also observed with decreasing Φ values until a composition of Φ = ca. 0.5 was reached, here no inflexion is observed, as there are for **1a** and **1b**. From Φ = 0.5 on, the emission intensity does not change much with the increasing-water content in the solvent mixture. In the limited range of Φ values from 1.0 to 0.7, it has been observed that the fluorescence emission intensity of substrate **2b** at the same concentration in water/DME solvent also increases with the decreasing Φ values. Unfortunately, poor solubility of **2b** made it impossible to further investigate the fluorescent behavior of monomeric **2b** in solvents of smaller Φ values.

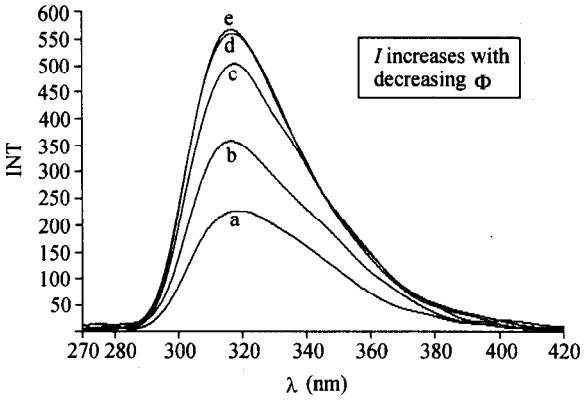


Fig. 6 Fluorescent spectra of **2a** in DME/water solution; Φ = 1.0 (a), 0.8 (b), 0.6 (c), 0.4 (d), 0.2 (e). Some data are not shown for benefit of clarity.

Discussion

The substantial difference of the fluorescence properties of **1a** and **1b** with those of **2a** in graded water/DME mixtures might be rationalized by the hypothetical proposition that intramolecular coaggregation of the CTV core with the hydrophobic face of the steroidal moieties takes place in **1a** and **1b**, but not in **2**, in highly polar aqui-organo media. The increases in the emission intensity of **1a** and **1b** at the first stage reflect the polarity increase of the microenvironment surrounding the benzenes of the CTV core. In this case, very few pseudo hydrophobic "cavities" are formed and most of the **1** molecules take the flexible random conformations as indicated as an extreme case by Cartoon A, Scheme 1. However, when the macroenvironmental polarity increases, more and more of the **1** molecules will be driven by

HLI to participate in imtramolecular coaggregation and take up conformations which lead to the formation of more and more pseudo hydrophobic "cavities" as depicted in Cartoon B, Scheme 1. Under these circumstances, benzene rings will be shielded by the hydrophobic side of the steroidal moieties, in other words, more and more hydrophobic microenvironments would be formed with increasingly polar macroenvironments. With this scenario, emission intensity will decrease with decreasing Φ values. In other words, only the molecules of **1** will be expected to behave in this manner while those of **2**, being not in possession of the cholic-acid moieties, will not be expected to do so. As shown by the curves in Fig. 3, Fig. 5 and Fig. 7, the first two curves possess an inflexion and a maximum while the third has only a platform. The existence of the difference appears to be in harmony with our speculated scenarios.

Previously it had been revealed that chain coiling needs a chain length of more than ten carbons for some linear molecules.[15] In the present study, the relatively rigid CTV configuration, together with large size of the steroidal moiety and its suitable configuration, compensates for the short linking aliphatic chain and makes it possible for the steroidal moiety to reach the CTV moiety. There is also another favorable factor that facilitates the intramolecular coaggregation. Since the CTV core has three separated benzene units, the steroidal moiety could reach the benzene, to which it is not directly attached. Actually, a CPK molecular model investigation also reveals the rationality of intramolecular coaggregation. In principle, the steroidal moiety could reach both the outer and inner sides of the CTV core (Scheme 1 does not indicate this feature). It is not clear if it exclusively approaches the outside of the bowl-shaped CTV core, although a CPK model study showed that this approach is obviously energetically favorable as a result of a smaller spatial hindrance.

Summary

The solvent composition dependence of the emission intensity apparently reveals the occurrence of intramolecular coaggregation of the CTV and steroidal moieties of compounds **1a** and **1b** in aqui-organo mixtures with sufficiently high polarity. Although HLI and other weak interactions-driven cyclodextrin-based intramolecular aggregation or chain coiling has been extensively studied,[16] the present study represents the first example of HLI-driven intramolecular coaggregation of different domains based on specifically designed molecules. Since the CTV core has mainly acted as a hydrophobic fluorescent probe, it is reasonable to envision that other molecules or groups can be incorporated in a similar manner to generate new models. Further study will be focused on the effects of other factors, such as the number of the amphiphilic moieties, chain length, substituting position, and property and size of the probe on the intramolecular aggregation behavior.

Experimental

Methods and materials

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. For mass spectra recorded in the FAB mode, 3-nitrobenzyl alcohol was used as a matrix. Elemental analysis was carried out at the SIOC analytical center. The solvents in the samples were indicated by the ^{1}H NMR spectra. Fluorescence measurements were carried out on a Perking Elmer LS 50 luminescence spectrometer at 35℃. The excitation wavelength was determined by the UV-Vis spectra. The excitation wavelength and spectral band width used in all cases are 235 nm and 2.5 nm, respectively. Unless stated otherwise, all reagents and chemicals were obtained from commercial sources and used without further purification. Deionized water was doubly distilled before use. DME was dried over sodium and doubly distilled under N_2 throughout this work. Triol **6**,[17] CTV **4**,[18] tetraol **5**,[19] Tosylate **3**,[19] and ether **2a**[18] were prepared according to the literature procedures.

Substrate **1a** A suspension of tosylate **3** (1.76 g, 3.20 mmol), CTV **4** (0.41 mg 1.00 mmol), and K_2CO_3 (1.76 g, 3.20 mmol) in dried acetonitrile (150 mL) was stirred at 80℃ for 5 days. The solvent was then removed *in vacuo* and THF (100 mL) added. The insoluble solid was filtered off and washed with THF (5 mL × 2). After the solvent was removed under reduced pressure, the residue was subjected to column chromatography over silica gel (ethyl acetate as the eluent). The crude product was purified again with preparative thin layer chromatography to give pure **1a** (1.20 g, 75%) as a white solid. Mp 197—198℃. ^{1}H NMR ($CDCl_3$) δ: 6.95 (s, 3H), 6.92 (s, 3H), 4.73 (d,

J = 13.6 Hz), 4.05—3.58 (m, 12H), 3.80—3.65 (m, 12H), 3.51 (d, J = 13.3 Hz, 3H), 2.29—0.90 (m, 90H), 0.67 (s, 6H), 0.44 (s, 3H). MS (ESI) m/z(%): 1560 (M^+ + Na). Anal. Cacld. for $C_{96}H_{144}O_{15} \cdot 3H_2O$: C, 72.57; H, 9.59. Found: C, 72.42; H, 9.50.

Compound **7** A solution of compound **6** (4.70 g, 7.30 mmol) and NaH (60%, 10.0 g, 0.25 mmol) in dry THF (200 mL) was refluxed for 30 min under N_2 followed by addition of iodomethane (20.0 mL, 0.32 mmol). After the mixture was stirred at 40℃ for 48 h and then water was added dropwise to quench the reaction. An aqueous hydrogen chloride solution (2 M) was added until the mixture became neutral. The solvent was removed to a volume of 50 mL and the mixture extracted with ether (4 × 50 mL). The combined extract was washed with water and brine, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (chloroform/petroleum ether 2:1) to give compound **7** (4.10 g, 80%) as a pale yellow glass. ^{1}H NMR ($CDCl_3$) δ: 7.46—7.44 (m, 6 H), 7.31—7.19 (m, 9H), 3.36 (s, 1H), 3.32 (s, 3H), 3.22 (s, 3H), 3.21 (s, 3H), 3.14 (s, 1H), 3.01—2.89 (m, 3H), 2.22—0.83 (m, 30H), 0.63 (s, 3H). MS (FAB): m/z(%) 676 (M^+). Anal. Calcd for $C_{46}H_{62}O_4 \cdot 1.5C_6H_{14}$: C, 82.21, H, 10.17. Found: C, 81.71, H, 10.37.

Compound **8** To a solution of **7** (4.00 g, 5.71 mmol) in acetone (100 mL) was added hydrogen chloride solution (0.1 M, 15 mL). The mixture was refluxed for 24 h, then aqueous K_2CO_3 (1 M) was added until the mixture became neutral. The mixture was concentrated to ca. 60 mL and then extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with water and brine, and dried ($MgSO_4$). After removal of solvent *in vacuo*, the residue was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate 1:1), to give compound **8** (2.34 g, 90%) as a white crystal. Mp 140—141℃. ^{1}H NMR ($CDCl_3$) δ: 3.61 (t, J = 6.5 Hz, 2H), 3.59—2.95 (m, 13H), 2.17—0.88 (m, 30H), 0.64 (s, 3H). MS (EI) m/z(%): 389, 285 (95), 253 (100). Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.20; H, 11.42. Found: C, 74.26, H, 11.10.

Compound **9** A solution of **8** (1.00 g, 2.20 mmol), tosyl chloride (1.14 g, 6.00 mmol), Et_3N (1.40 mL, 10.0 mmol) and 4-dimethylaminopyridine (DMAP, 5.0 mg) in THF (80 mL) was stirred under reflux for 16 h. After most of solvent was removed *in vacuo*, water (20 mL) was added. The mixture was then extracted with ether (3 × 50 mL). The combined extracts were washed with water (20 mL × 2), brine (20 mL), and dried ($MgSO_4$). The solvent was then removed to give a residue, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 2:1), to give tosylate **9** (0.90 g, 90%) as a white solid. Mp 32—34℃. ^{1}H NMR ($CDCl_3$): δ: 7.81 (s, 1H), 7.78 (s, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 4.00 (t, J = 6.6 Hz, 2H), 3.33 (s, 3H), 3.23 (s, 3H), 3.21 (s, 3H), 3.14 (s, 1H), 3.13—2.95 (m, 2H), 2.45 (s, 3H), 2.20—0.84 (m, 30H), 0.62 (s, 3H). MS (FAB) m/z(%): 590 (M^+). Anal. Calcd. for $C_{34}H_{54}O_6S$: C, 69.22, H, 9.20. Found; C, 69.10, H, 9.23.

Substrate **1b** A solution of CTV **4** (0.12 g, 0.30 mmol), tosylate **9** (0.64 g, 1.08 mmol), and Cs_2CO_3 (1.05 g, 3.20 mmol) in acetonitrile (50 mL) was stirred at 80℃ for 38 h. The solvent was then distilled off. The mixture was triturated in ether (150 mL). The organic solution was washed with water (20 mL × 2), brine (20 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography (silica gel, ether). Compound **1b** (0.39 g) was obtained in 80% yield as a white powder. Mp 156—157℃. ^{1}H NMR ($CDCl_3$) δ: 6.83 (s, 3H), 6.82 (s, 3H), 4.75 (d, J = 13.6 Hz, 3H), 4.09—4.15 (m, 3H), 3.82 (s, 9H), 3.53 (d, J = 13.6 Hz, 3H), 3.40 (s, 6H), 3.33 (s, 9H), 3.25 (s, 9H), 3.21 (s, 9H), 3.05—2.95 (m, 6H), 2.21—0.89 (m, 90H), 0.64 (d, J = 3.5 Hz, 9H). MS (FAB) m/z(%): 1664 (M^+). Anal. Calcd. for $C_{105}H_{162}O_{15} \cdot 2H_2O$: C, 74.21; H, 9.22. Found: C, 74.17; H, 9.72.

Substrate **2b** This compound was prepared in 92% yield as a white solid from the reaction of CTV **4** and lauryl bromide in refluxing acetonitrile after 48 h, using the procedure described above for compound **1b**. Mp 67—68℃. ^{1}H NMR ($CDCl_3$) δ: 6.84 (s, 3H), 6.82 (s, 3 H), 4.70 (d, J = 13.8 Hz, 3H), 3.96—3.85 (m, 6H), 3.76 (s, 9H), 3.50 (d, J = 13.8 Hz, 3H), 1.76—1.72 (m, 3H), 1.36 (br. s, 6H), 1.20 (s, 54H), 0.85—0.80 (m, 6H). MS (FAB) m/z(%): 913 (M^+). Anal. Calcd. for $C_{60}H_{96}O_6$: C, 78.95; H, 10.59. Found: C, 78.95; H, 10.60.

Acknowledgment

We thank Dr. Chunhong Li of Brigham Young University for help of preparing compound **6**.

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(E200008163 JIANG, X.H.; DONG, L.J.)