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Solvophobically-Driven Oligo(ethylene glycol) Helical Foldamers. Synthesis, Characterization, and Complexation with Ethane-1,2-diaminium

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Oligo(ethylene glycols) **1a**−**h**, which are incorporated with one to eight 2,3-naphthylene units, respectively, have been synthesized and characterized. The conformational changes of the new oligomers have been investigated in chloroform−acetonitrile binary solvents by the UV−vis, ^{1}H NMR, and fluorescent spectroscopy. It has been revealed that the naphthalene units in hexamer **1f**, heptamer **1g**, and octamer **1h** are driven by solvophobic interaction to stack in polar solvents. As a result, compact helical conformations are formed that give rise to a cavity similar to that of 18-crown-6. Shorter oligomers **1b**−**e** exhibit weaker folding tendency. ^{1}H NMR studies reveal that **1f**−**h** are able to complex ammonium or ethane-1,2-diaminium **19**, but not secondary ammonium compounds. The association constants of complexes **1f·19**, **1g·19**, and **1h·19** in acetonitrile are determined to be $3.5(\pm0.4) \times 10^3$, $1.0(\pm0.12) \times 10^4$, and $2.5(\pm0.4) \times 10^4$ M^{-1}, respectively, with the ^{1}H NMR titration method. For comparison, hexamer **22**, which incorporates six 1,5-naphthylene units, is also prepared. The UV−vis and fluorescent investigations show that **22** is also able to fold in polar solvents, but no helical structure can be produced due to mismatch of the stacking naphthalene units and consequently there is no obvious complexation between **22** with ethane-1,2-diaminium ion. The structures of the longest foldamer **1h** and its complex with **19** have been studied with molecular mechanics calculations. This work represents a new approach to building folding conformations from flexible linear molecules.

Introduction

Biomolecules rely on precise combinations of different noncovalent interactions to produce folded conformations that are responsible for numerous biological functions and processes. In recent years, there has been intense interest in developing foldamers, the synthetic oligomers that fold into well-defined secondary structures.[1] A large number of heterocycles,[2] amino acid derivatives,[3] and oligo(*m*-phenylene ethynylene) derivatives[4] have been employed as molecular backbones to build foldamers. Nevertheless, only a few folding systems have the ability to perform functions, such as molecular recognition,[5] antimicrobial activity,[6] α-helix mimicking,[7] and molecular switching.[8] Therefore, there is still a strong requirement to develop novel folding patterns for further exploring the structure−function relation.

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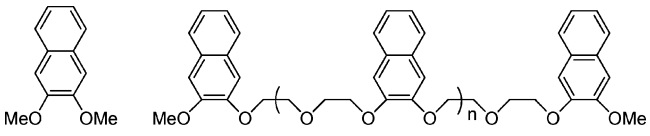
It has been established that in polar solvents nonpolar aromatic units of linear molecules tend to aggregate or stack intermolecularly or intramolecularly as a result of hydrophobic interaction.[9] This kind of hydrophobically driven aromatic stacking is the dominant noncovalent force for the formation of several elegant folding systems. For example, Iverson et al. utilized the hydrophobic interaction to construct a series of peptide-backboned aedamers in aqueous solution.[1f,10] Moore et al. employed such noncovalent force to induce oligo(*m*-phenylene ethynylenes) to fold in polar solvents.[1g,11] Recently, Li et al. also reported that a folded state could be produced for linear phosphoramidites due to intramolecular perylenetetracarboxilic diimide stacking.[12] In this paper, we describe that 2,3-naphthalene-incorporated oligo(ethylene glycols) can spontaneously acquire stable helical conformations in polar solvent. The new solvophobically driven helical foldamers have a cavity similar to that of 18-crown-6 that can complex ammonium or ethane-1,2-diaminium in acetonitrile.

Results and Discussion

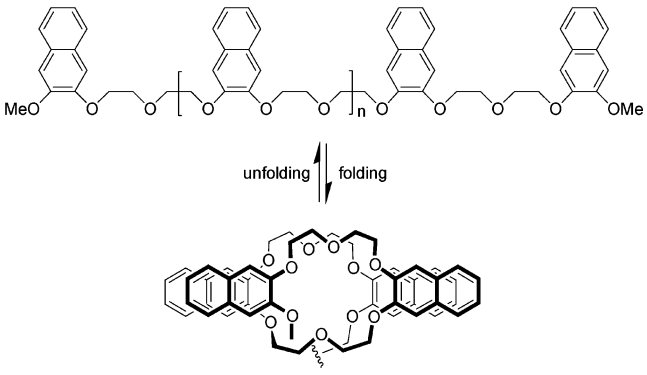
It has been revealed that flexible oligo(ethylene glycols) with two terminal aromatic donors are able to wrap themselves around a cation to acquire a folded conformation in polar solvents.[13] Nevertheless, oligo(ethylene glycols) themselves adopt random, disordered conformations in polar solvents due to their high hydrophilicity. We imagined that introducing hydrophobic aromatic units at suitable positions of the oligo(ethylene glycol) chain might force the skeleton to fold as a result of the formation of $\pi-\pi$ stacking between adjacent naphthalenes. Therefore, a series of naphthalene-incorporated oligo(ethylene glycols) **1b**−**h** were designed and synthesized[14] with compound **1a** as a reference molecule.[15] The



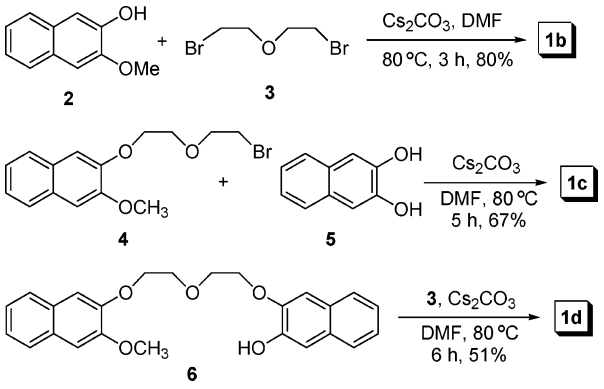
1a **1b:** n = 0, **1c:** n = 1, **1d:** n = 2, **1e:** n = 3 **1f:** n = 4, **1g:** n = 5, **1h:** n = 6

2,3-disubstituted naphthalene unit was chosen, and the adjacent units were separated with a $-OCH_2CH_2OCH_2CH_2O-$ chain because molecular modeling revealed that $\pi-\pi$ stacking between adjacent units would induce the formation of a helical structure, which produces a cavity similar to that of 18-crown-6, as shown in Scheme 1.

SCHEME 1



SCHEME 2



The syntheses of **1b**−**d** are straightforward (Scheme 2). Compound **1b** was prepared in 80% yield from the reaction of **2** and **3** in DMF with cesium carbonate as a base. For preparation of **1c**, bromide **4** was first produced from the reaction of **2** and an excessive amount of **3** under the reaction conditions for **1b**, and subsequent reaction of **4** with **5** produced **1c** in 67% yield. Similarly, **4** was reacted with an excessive amount of **5** to produce **6** in 60% yield. The latter was then reacted with **3** to afford **1d** in 51% yield.

The synthetic routes for **1e** and **1f** are shown in Scheme 3. Thus, tosylate **9** was first prepared in 81% yield from the reaction of **7** and **8** in DMF and then converted into **10** in 80% yield under similar conditions. Palladium-catalyzed hydrogenation of **10** afforded **11** in 89% yield. Subsequent reaction of **11** with **4** in DMF also with cesium carbonate as a base produced **1e** in 51% yield. For the preparation of **1f**, **12** was first produced in 76% yield from the reaction of **6** and **9** and was then deprotected under the catalysis of Pd−C to afford **13** in 86% yield. Treatment of **13** with **3** in hot DMF afforded **1f** in 28% yield.

For the preparation of **1g** (Scheme 4), bromide **14** was first produced in 74% yield from the reaction of **6** and an excessive amount of **3**. Subsequent reaction of **14** with **11** afforded **1g** in 51% yield. The synthesis of **1h** began with the preparation of **15** (Scheme 4). Compound **5** was first treated with an excessive amount of **9** in DMF to produce **15**, which was then reacted with an excessive amount of **3** to afford **16**. Subsequent reaction of **16** with **6**, followed by palladium-catalyzed hydrogenation of intermediate **17**, produced **18** in good yield. Finally, **18** was reacted with **3** in DMF to afford **1h** in 44% yield.

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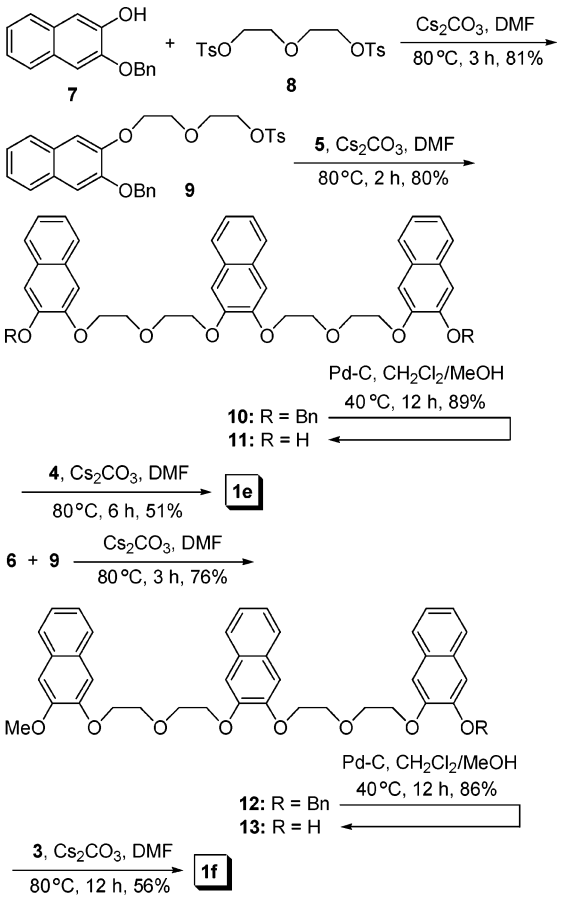
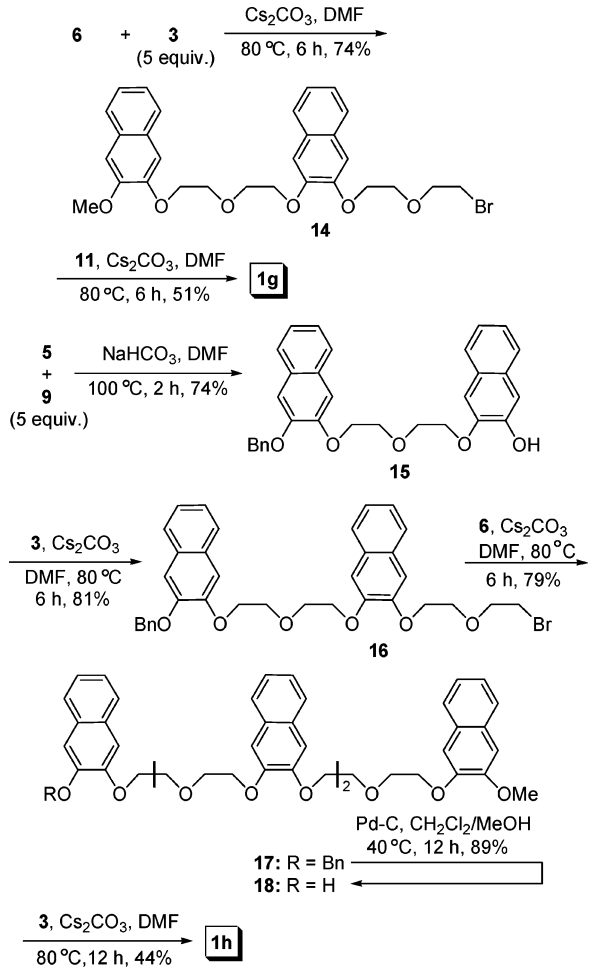
SCHEME 3



SCHEME 4



Compounds **1b**−**h** are soluble in chloroform, a typical nonpolar solvent, and acetonitrile, a typical polar solvent. Therefore, the chloroform−acetonitrile binary solvent systems were chosen for the investigation of the folding behavior of the oligomers. The UV−vis study was first performed to exclude any important intermolecular interaction, the relation of the absorbance with the concentration of the oligomers was first investigated in acetonitrile. The representative results are provided in Figure 1. It can be found that, for all the oligomers, the absorbance is linearly dependent on the concentration within the specific concentration range ((0.45 to 2.4) × 10^{-5} M for **1h**). That is, Beer's law behavior is observed. The experiment ruled out any important intermolecular interactions within or below the concentration range. Similar results were also observed in chloroform. Since it has been well established that chloroform is a "benign" solvent for nonpolar aromatic moieties,[1g,3h,11] it is reasonable to assume that Beer's law should also be observed for the oligomers in mixtures of chloroform and acetonitrile within or below the above concentration range.

The hypochromic effect of the oligomers was then investigated in the chloroform−acetonitrile mixtures. Previous studies have demonstrated that this intramolecularly aromatic stacking-induced effect is a powerful indicator of the folding conformation of the artificial and natural systems.[3h,10−12,16] The UV−vis spectra of all the compounds **1a**−**h** were recorded in the solvents with increasing acetonitrile content at the fixed chromophore (2,3-dioxynaphthalene = Np) concentration of 5.0×10^{-5} M, which corresponds to a concentration of 6.3×10^{-6} M for the longest **1h**. The results are provided in Figure 2. It was found that the hyperchromic effect was first produced and the ϵ_{Np} (apparent molar extinction coefficient for one Np unit of a molecule) is linearly increased with Φ (Φ is volume fraction of acetonitrile in the binary solvent system[9a]) for **1a** in all the solvent systems.[17] This solvent polarity-induced hyperchromic effect became

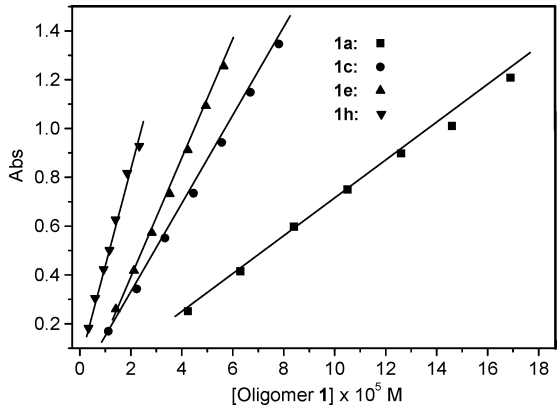


FIGURE 1. Plot of the absorbance (323 nm) vs [**1**] in acetonitrile at 25 °C. Similar linear results were also observed for oligomers **1b**, **1d**, **1f**, and **1g**, which are not shown.

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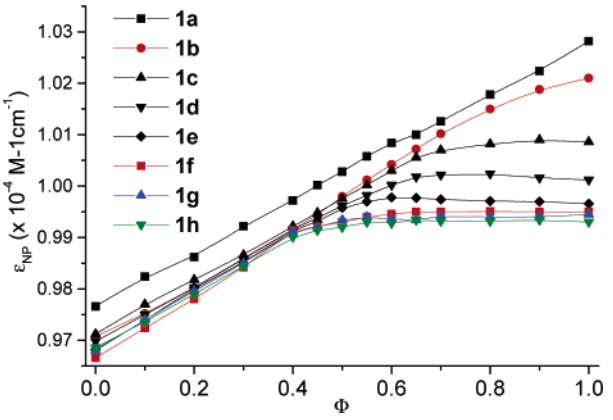

FIGURE 2. Plot of the apparent molar extinction coefficient ϵ_{Np} (323 nm, [Np] = 5.0×10^{-5} M) of oligomers **1** against Φ at 25 °C, highlighting the folding-induced hypochromic effect of the longer oligomers in solvents of high Φ. The curves are drawn only as guides for the eye.

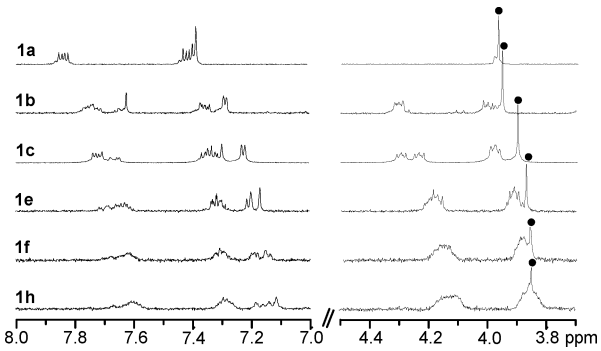

FIGURE 3. Partial ^{1}H NMR spectrum (400 MHz) of oligomers **1** ([Np] = 3.0 mM) in CD_3CN at 25 °C, highlighting the folding-induced upfield shifting of both the aromatic and aliphatic proton signals.

weakened gradually from the short **1b** in solvents of Φ > 0.8 and vanished for the long **1e**−**h** when Φ ≥ 0.5. Because there was no important intermolecular interaction at the low concentration of the oligomers investigated, this ϵ_{Np} derivation, a new hypochromic effect, of oligomers **1b**−**h**, compared to **1a** in solvents of high Φ values, should be generated as a result of the intramolecular stacking between the adjacent naphthalene units, which induced the folding of the linear oligo(ethylene glycol) backbones. The fact that the above hypochromic effect occurred at lower Φ values for the longer oligomers suggests that the longer oligomers have greater folding ability. This observation might be attributed to their increased hydrophobicity and implies that the stacking is cooperative. The terrace exhibited by **1f**−**h** within the area of high Φ values appears to indicate that these longer oligomers adopt completely folding conformation in highly polar solvents.

The UV−vis and fluorescent properties of the oligomers are also investigated in the $CHCl_3$-DMSO binary solvent system. Very similar results are obtained, which show that similar folding conformation could be generated in the more polar solvent system (see the Supporting Information).

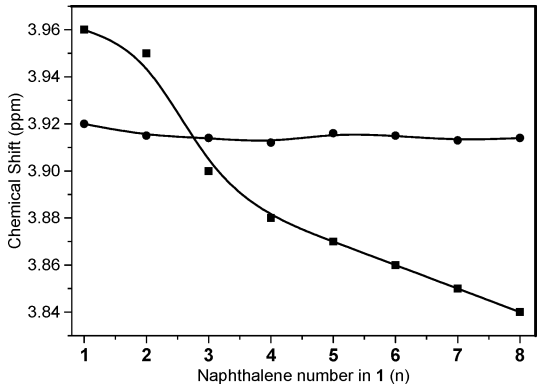

FIGURE 4. Chemical shift of the CH_3 signal vs the Np number of oligomers **1** ([Np] = 3.0 mM) in $CDCl_3$ (●) and CD_3CN (■) at 25 °C. The curves are drawn only as guides for the eye.

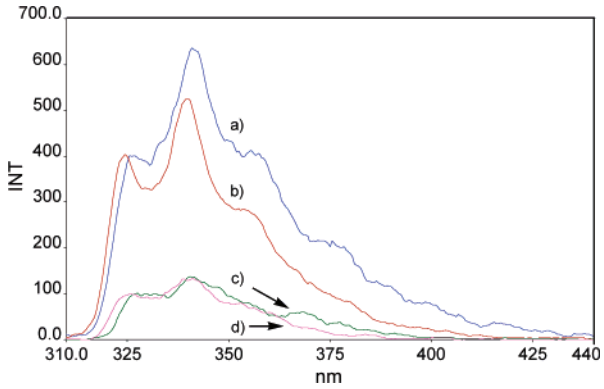

FIGURE 5. Fluorescence spectra of (a) **1h** in MeCN, (b) **1a** in MeCN, (c) **1h** in $CHCl_3$, and (d) **1a** in $CHCl_3$ at 25 °C ([Np] = 2.7×10^{-6} M, λ_{ex} = 280 nm).

^{1}H NMR spectra provide more evidence that longer oligomers **1** adopt folded conformations in polar solvents. Compounds **1g** and **1h** are not soluble in DMSO. However, shorter compounds **1b**−**f** are soluble, and the ^{1}H NMR spectra of these compounds in DMSO-d_6 revealed remarkable upfield shifting for all signals compared to those of **1a** at the identical [Np] (2.0 mM). The spectra of all oligomers **1** in CD_3CN were recorded, and the representative results are presented in Figure 3. It can be seen that pronounced upfield shifting was also exhibited for all the peaks of **1b**−**h** compared to those of **1a**. ^{1}H NMR dilution investigations (3−0.5 mM) revealed no important intermolecular interaction (<0.03 ppm);[18,19] therefore, the upfield shifting should be produced as a result of intramolecular naphthalene stacking and (oligoethylene glycol) skeleton folding. The lowered resolution of the aromatic proton peaks of the longer oligomers also supported the folding state of the skeleton.[20] Al-

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(19) Assuming a 1:1 self-association mode, we determined the K_{assoc} of the longest oligomer **1h** to be approximately 52 M^{-1} by using the ^{1}H NMR dilution method with the sharp methyl signal as probe, which means that <4% of the compound existed as homodimer when [Np] = 3.0 mM.

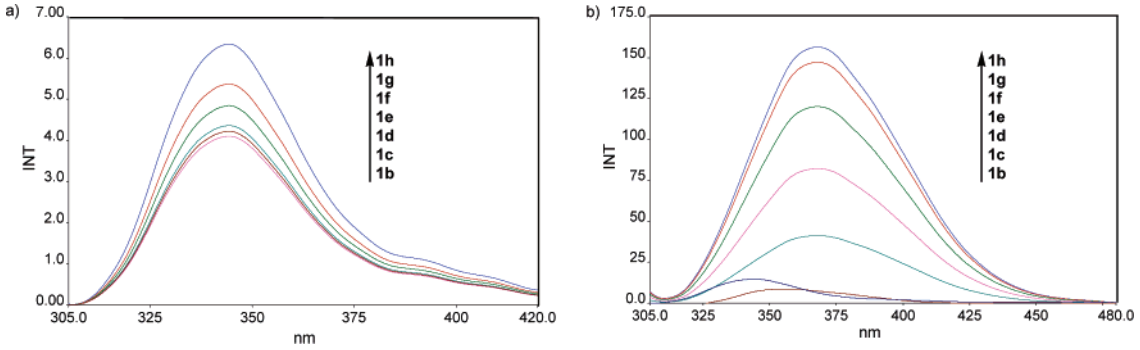


FIGURE 6. Excimer emission spectrum of oligomers **1** (a) in chloroform and (b) in acetonitrile at 25 °C. $\lambda_{ex} = 280$ nm. [Np] = 2.7×10^{-6} M.

though accurate chemical shifts could not be obtained for the naphthalene and methylene signals, the methyl signal of all oligomers was sharp. A plot of the chemical shift of the methyl signal versus the naphthalene number of the oligomers is shown in Figure 4. It can be found that the shifts were nearly unchanged (<0.008 ppm) for **1b**−**h** compared to that of **1a** in $CDCl_3$. However, pronounced upfield shifting was displayed for the oligomers and the shifting was increased with the lengthening of the oligomers (ca. −0.12 ppm for **1h**) in CD_3CN. The increased upfield shifting observed for the longer oligomers should reflect stronger stacking and a correspondingly more compact folding state, which is also consistent with the above UV−vis observations.

The fluorescent study also supports the folded conformations for long oligomers in polar solvents. The fluorescent spectra of **1h** and **1a** in chloroform and acetonitrile at the identical [Np] are shown in Figure 5. It can be seen that in chloroform both compounds exhibited similar spectra with comparable emission strength. In contrast, a remarkable hyperchromic effect was exhibited for **1h** in acetonitrile.[17] A similar hyperchromic effect was also observed for **1b**−**g** at the fixed [Np], which was increased with the lengthening of the oligomers. Because the UV−vis experiments have established that no important intermolecular aggregations exist for all the oligomers at the concentration, the hyperchromic effect should also be attributed to intramolecular aromatic stacking and chain folding.[10] The normalized excimer emission spectra of **1b**−**h** at the identical [Np] in chloroform and acetonitrile, produced by subtracting the spectrum of **1a** from that of **1b**−**h**,[9b] respectively, are given in Figure 6. It can be seen that all the oligomers exhibited a very weak emission band with λ_{max} at ca. 348 nm in chloroform, and the shorter oligomers **1b** and **1c** also displayed weak excimer emission band at $\lambda_{max} = 348$ and 358 nm, respectively, in acetonitrile. In contrast, the longer oligomers **1d**−**h** produced stronger excimer emission in acetonitrile, which was increased with the lengthening of the oligomers. This result also indicates that more compact folding states were generated for the longer oligomers in polar solvent.

The influence of the solvent polarity on the excimer emission of the oligomers was also investigated in chloroform and acetonitrile at the identical [Np] (Figure 7). Within the area of low Φ (≤ ca. 0.2), the excimer intensity of the oligomers was increased linearly with the increase of Φ. However, the excimer emission of the longer oligomers became stronger than the shorter ones and finally unchanged at high Φ (ca. 0.78 for **1h**), while the emission of the shorter compounds **1b** and **1c** exhibited just a slight strengthening even at very high Φ. This is very similar to that revealed by the above UV−vis investigations (Figure 2), supporting that the longer oligomers have greater folding tendency in polar solvents. The terrace observed in Figure 7 for **1f**,**g** within the area of high Φ is also consistent with a completely folding conformation for these oligomers. This is well in accordance with the above UV−vis result.

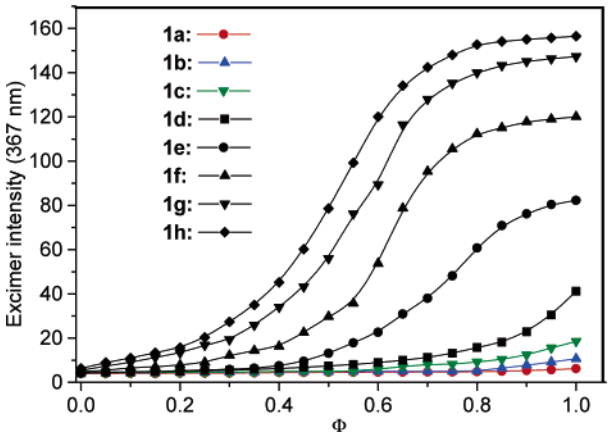


FIGURE 7. Plot of the excimer intensity at 367 nm vs Φ in chloroform and acetonitrile at 25 °C. $\lambda_{ex} = 280$ nm, [Np] = 2.7×10^{-6} M. The curves are drawn as guides for the eye.

Crystals of **1c** suitable for X-ray analysis were grown from DMSO by evaporation of the solution. Figure 8 shows the X-ray structure, in which the two flexible aliphatic chains are pointed away from the central naphthalene. One ending naphthalene is located nearly perpendicular to another ending naphthalene (the angle between the two planes is ca. 84°).

Numerous attempts to crystallize the longer oligomers were not successful. To obtain more insight for the structure of the folding oligomers, molecular mechanics calculation with the compass force field was carried out for the longest **1h**.[21] The structure of the energy-minimized conformation is presented in Figure 9, which reveals a cavity with depth of ca. 10 Å and width of ca. 2.8 Å. The width of the cavity is very close to that of

(20) Extensive intramolecular aromatic stackings usually lead to lowered resolution of the ^{1}H NMR spectra of folding molecules, see refs 10 and 11.

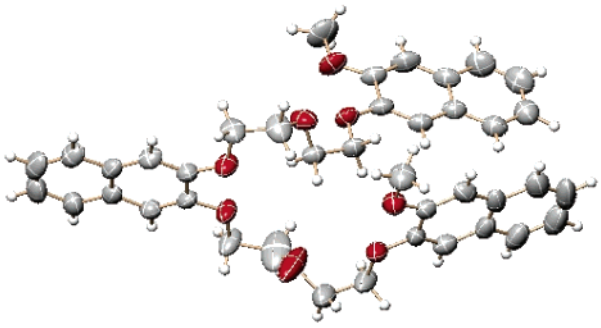


FIGURE 8. X-ray structure of **1c**.

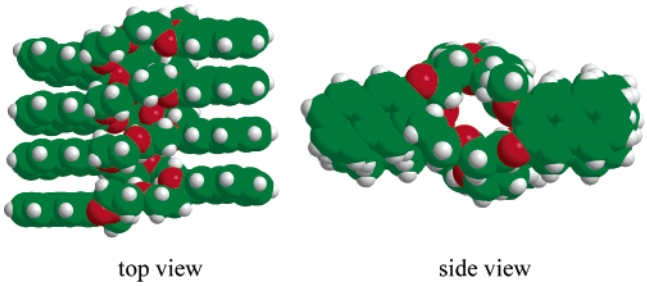


FIGURE 9. Energy-minimized structure of octamer **1h**, showing a cavity similar to that of 18-crown-6.

dibenzo-18-crown-6, the cavity of which has been estimated to be 2.68−2.86 Å.[22,23]

It has been established that dibenzo-18-crown-6 could complex ammonium or alkylammonium.[24] Therefore, a binding study was also carried out between the longer oligomers **1f**−**h** and ammoniums. Adding 2 equiv of ammonium perchlorate to the solution of **1f**−**h** in CD_3CN (1.5 mM) induced important shifting of the signals of the ^1H NMR spectrum of the oligomers. A similar result was not revealed when *n*-Bu_4N^+ ClO_4^- (5 equiv) was added. Therefore, the spectral shifting should result from complexation between the oligomers and ammonium ion but not from the salt effect. Since the ^1H NMR spectrum of the mixtures was of low resolution, quantitative binding study could not be performed. The binding

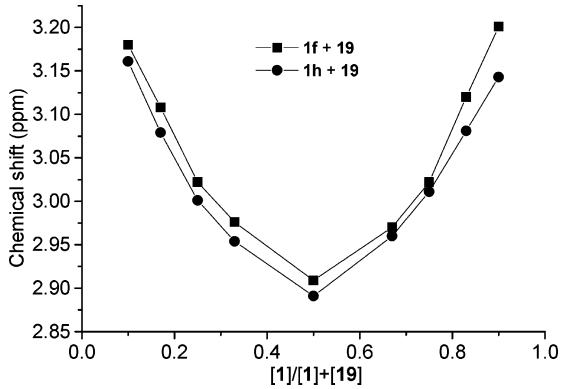


FIGURE 11. Job's plots of the chemical shift of the CH_2 protons of **19** vs [**1**]/[**1**] + [**19**] in CD_3CN at 25 °C ([**1**] + [**19**] = 3.0 mM).

studies between **1f**−**h** and $NH_3^+CH_2CH_2NH_3^+2CF_3SO_3^-$ (**19**) were then performed in CD_3CN. As examples, the results of **1f** and **1h** are provided in Figure 10. It can be found that adding 1 equiv of **19** to the solutions of **1f** and **1h** led to important splitting of the spectrum of the oligomers. The NH signal of **19** disappeared, while its CH_2 signal shifted upfield remarkably (−0.20 and −0.31 ppm, respectively). The upfield shift was obviously generated due to complexation of **19** by the oligomers, the naphthalene units of which produced an important deshielding effect to the CH_2 group of **19**. In addition, the resolution of the resonances of **19** was also moderately increased upon addition of the guest, and the H-1 and H-4 protons of the naphthalene units displayed six identifiable signals, although most of the signals could not be assigned completely (the peak of the aromatic protons adjacent to the MeO group could be assigned with the NOESY experiment). These observations suggest that a more compact conformation was formed for **19** after complexation. Similar result was also observed for **1g**. A Job's plot study revealed a 1:1 binding mode for the complexes (Figure 11).[25a] Quantitative studies were preformed by titrating **19** with the oligomers and observing the changes of the CH_2 signal. The results are provided in Figure 12. By fitting to a nonlinear binding

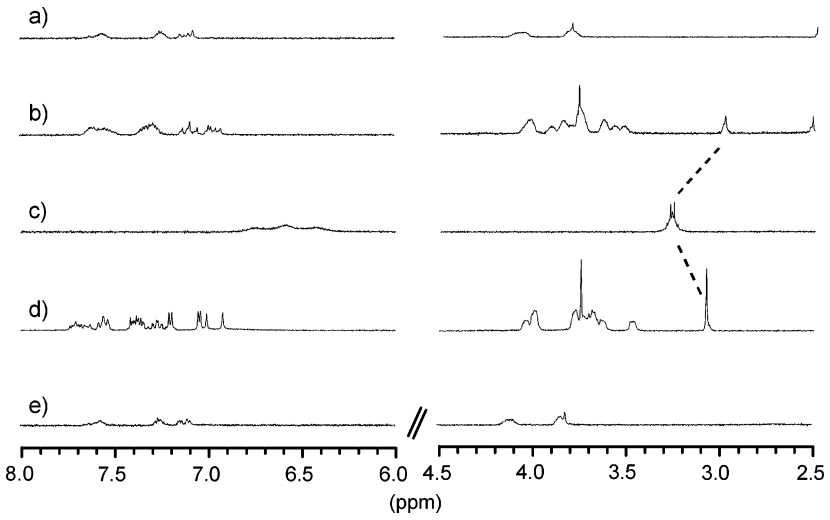


FIGURE 10. Partial ^1H NMR spectrum (400 MHz) of (a) **1h**, (b) **1h** + $NH_3^+CH_2CH_2NH_3^+$ $2CF_3SO_3^-$ (**19**), (c) **19**, (d) **1f** + **19**, and (e) **1f** in CD_3CN at 25 °C (1.5 mM).

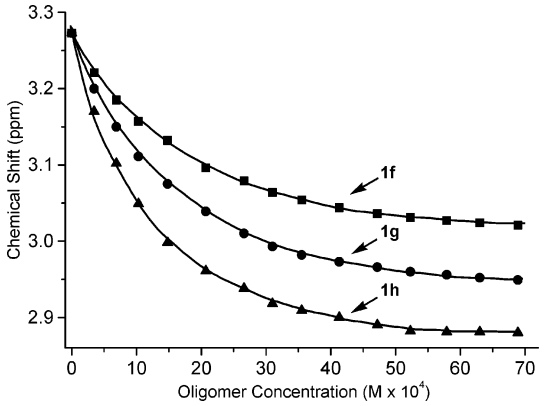


FIGURE 12. Chemical shift changes of the CH_2 proton of **19** (6.9×10^{-4} M) with the concentrations of **1f** (■), **1g** (●), and **1h** (▲) in CD_3CN at 25 °C.

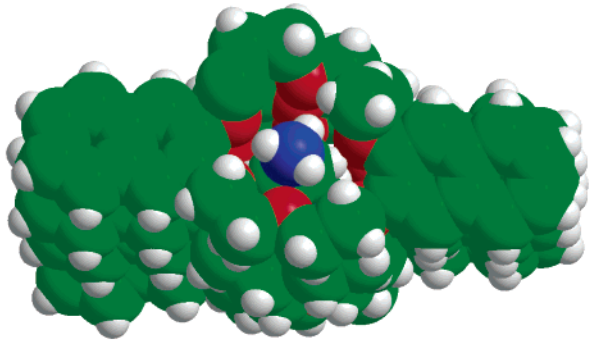
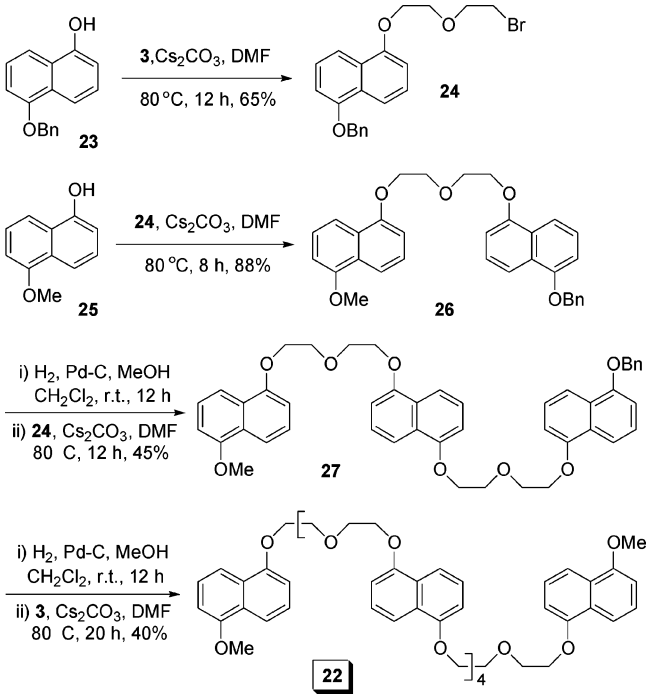


FIGURE 13. Energy-minimized structure of complex **1h·19**.

equation appropriate for a 1:1 binding model,[18,25] association constants (K_{assoc}) of $3.5(\pm0.4) \times 10^3$, $1.0(\pm0.12) \times 10^4$, and $2.5(\pm0.4) \times 10^4$ M^{-1} were determined for complexes **1f·19**×e2 **1g·19**×e2 and **1h·19**, respectively.[26] The binding mode of complex **1h·19** was also investigated by molecular modeling, and an energy-minimized structure was produced (Figure 13), which shows that the dicationic guest is twined by the oligomer.

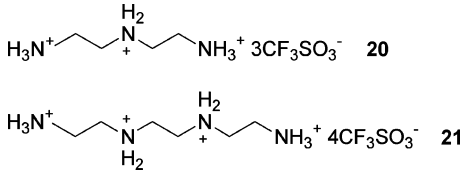
A 2D ^1H NMR experiment in CD_3CN revealed intermolecular NOEs between the ethylene protons of **1f** and the methylene protons of **19**, providing additional evidence that a stable complex **1f·19** was formed in the polar solvent (see the Supporting Information). Strong intramolecular NOEs were also observed between the H-1 and H-4 signals of the naphthalene units and the OCH_2 signals of **1f** in the presence of **19**. These OCH_2 groups should be those directly linked to the naphthalene units. Similar NOEs were remarkably weaker or even not observed at an identical concentration of **1f** in the absence of **19**. These results also indicate that a more compact

SCHEME 5



folding conformation was formed for **1f** in acetonitrile due to its strong complexation toward **19**.

Mixing 1.0 equiv of **20** and **1f**, **1g**, or **1h** in CD_3CN (1.5 mM) did not induce the ^1H NMR signals of both compounds to change notably. Similar results were also observed for the systems of **21** and the oligomers. These observations indicate that the oligomers cannot complex the cationic guests, which are consistent with the fact that 18-crown-6 derivatives could not efficiently complex secondary ammoniums.[27]



To examine if the location of the ethylene glycol chain at the 2,3-positions of the naphthalene unit in the oligomers is indispensable for the formation of the 18-crown-6-like folding state, hexamer **22** was also synthesized (Scheme 5). In brief, **24** was first prepared from the alkylation of **23** and then reacted with **25** to yield **26**. Compound **26** was then converted to **27** by palladium-catalyzed hydrogenation followed by a further alkylation reaction. By repeating the same reaction procedures, **27** was converted to **22** in moderate yield.

UV−vis studies in chloroform and acetonitrile revealed remarkable hypochromic effect, starting from $\Phi = 0.58$, for **22** at $[Np] = 2.7 \times 10^{-6}$ M,[28] while its excimer

(21) Berkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, D.C., 1982.
(22) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, *85*, 271.
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(24) (a) Nagano, O.; Kobayashi, A.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 790. Bovill, M. J.; Chadwick, D. J.; Sutherland, I. O.; Watkin, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1529. (c) Pears, D. A.; Stoddart, J. F.; Fakley, M. E.; Allwood, B. L.; Williams, D. J. *Acta Crystallogr.* **1988**, *C44*, 1426. (d) Trueblood, K. N.; Knobler, C. B.; Lawrence, D. S.; Stevence, R. V. *J. Am. Chem. Soc.* **1982**, *104*, 1355.
(25) (a) Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987. (b) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: New York, 1991; p 123.
(26) Other more complicated binding patterns could not be excluded. Nevertheless, good results were obtained by assuming the simple 1:1 binding mode.
(27) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

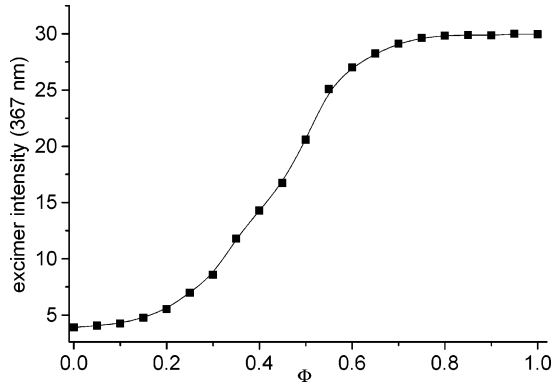

FIGURE 14. Plot of the excimer intensity for compound **22** at 367 nm vs Φ in chloroform and acetonitrile at 25 °C (λ_{ex} = 280 nm, [Np] = 2.7×10^{-6} M).

intensity of the same concentration was increased and reached a platform at Φ = ca. 0.75 (Figure 14). These results are very similar to those observed for **1f**, indicative of a folding conformation and intramolecular stacking taking place for **22**. However, adding up to 10 equiv of ammonium perchlorate or **19** to its solution in CD_3CN did not cause any pronounced shifting of its ^{1}H NMR spectrum (<0.01 ppm). The result reveals that aromatic stacking within **22** did not produce a helical conformation, but might give rise to a folding state similar to that of the "aedamer" reported by Iverson.[10,29] Molecular modeling also revealed that other kinds of isomers of the long oligomers could not produce folding conformations with a cavity through efficient aromatic stacking.

Conclusions

We have demonstrated that structurally flexible 2,3-naphthylene-incorporating oligo(ethylene glycols) can adopt folding conformation in polar solvents as a result of solvophobically driven intramolecular aromatic stacking. The folding conformations of the oligomers have been supported by the UV−vis, ^{1}H NMR, fluorescent spectroscopy, and molecular modeling study. The long oligomers exhibt greater ability to fold and their folding states can produce a cavity with a width similar to that of 18-crown-6, which can complex ammonium or ethane-1,2-diaminium ion.

For a long time, ethylene glycols have been regarded as a kind of disordered oligomers in both polar and nonpolar solvents.[13] The present investigation demonstrates that, by introducing additional functional units at specific positions, the compact and ordered conformation could be induced from the otherwise flexible materials. A noticeable feature of the new kind of foldamers is that a cavity with relatively width could be produced, while the depth of the cavity could be controlled by regulating the length of the oligomers. Further works will focus on introducing chiral side chains to the ethylene glycol chain, which is envisioned to induce the chiral bias of the corresponding oligomers, and constructing longer oligomers or polymers of the same skeleton, which should give rise to nanoscale of tubes.

Experimental Section

Materials and Methods. Melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on a 400 or 600 M Hz spectrometer in the indicated solvents, chemical shifts are expressed in parts per million relative to the residual solvent protons as internal standards. Chloroform (δ = 7.26 ppm) and TMS (δ = 0.00 ppm) were used as an internal standard for $CDCl_3$ and CD_3CN, respectively. Elemental analysis was carried out at the SIOC analytic center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purifications. DMF was dried following standard procedures before use. Silica gel (10−40 μ) was used for all column chromatography. For the ^{1}H NMR titration method, see ref 18b. Compound **1a** was prepared according to the reported method.[15]

Compound 1b. To a stirred suspension of **2**[30] (0.25 g, 1.44 mmol) and cesium carbonate (0.56 g, 1.73 mmol) in DMF (10 mL) was added a solution of **3**[31] (0.17 g, 0.72 mmol) in DMF (2 mL). The mixture was stirred at 80 °C for another 3 h, and the solvent was removed under reduced pressure. The resulting residue was triturated with chloroform (100 mL). The organic phase was washed with water (30 mL × 2) and brine (30 mL) and dried over sodium sulfate. After removal of the solvent in vacuo, the crude product was purified by column chromatography (hexane/CH_2Cl_2 1:3) to afford **1b** as a white powder (0.24 g, 80%). Mp: 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 7.64−7.67 (m, 4 H), 7.34−7.30 (m, 4 H), 7.17 (s, 2 H), 7.10 (s, 2 H), 4.35 (t, J = 5.1 Hz, 4 H), 4.10 (t, J = 5.7 Hz, 4 H), 3.95 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): 149.7, 148.6, 129.3, 129.0, 126.3, 126.2, 124.2, 124.1, 108.0, 106.5, 69.8, 68.2, 55.8. MS (ESI): m/z 436 $[M + NH_4]^+$, 441 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.61; H, 6.27. Found: C, 74.66; H, 6.17.

Compound 4. This compound was prepared from the reaction of **2** and excessive amount of **3** (4.0 equiv) on the basis of the method described for **1b**. The crude product was purified by column chromatography (EtOAc/hexanes 1:15) to give the required product as a white powder (77%). Mp: 55−57 °C. ^{1}H NMR ($CDCl_3$): δ 7.70−7.66 (q, J = 3.5 Hz, 2 H), 7.35−7.32 (m, 2 H), 7.17 (s, 1 H), 7.13 (s, 1 H), 4.32 (t, J = 4.5 Hz, 2 H), 4.02−3.98 (m, 5 H), 3.94 (t, J = 6.6 Hz, 2 H), 3.53 (t, J = 6.6 Hz, 2 H). MS (ESI): m/z 342 $[M + NH_4]^+$, 347 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.75; H, 5.26.

Compound 1c. This compound was prepared as a white powder (67%) from the reaction of 2 equiv of **4** and 1 equiv of **5** on the basis of the method described for **1b**. Mp: 116−120 °C. ^{1}H NMR (CD_3CN): δ 7.72−7.63 (m, 6 H), 7.35−7.20 (m, 12 H), 4.28 (t, J = 4.2 Hz, 4 H), 4.22 (t, J = 4.2 Hz, 4 H), 3.98−3.95 (m, 8 H), 3.89 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.7, 149.0, 148.6, 129.3, 129.0, 126.3, 126.3, 126.2, 124.2, 124.2, 124.0, 108.5, 108.0, 106.4, 69.8, 69.8, 68.5, 68.2, 55.7. MS (ESI): m/z 666 $[M + NH_4]^+$, 671 $[M + Na]^+$. Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.04; H, 6.23. Found: C, 74.06; H, 6.18.

Compound 6. This compound was prepared as a white powder (60%) from the reaction of **4** and an excess amount of **5** (4.0 equiv) on the basis of the method described for **1b**. Mp: 96−99 °C. ^{1}H NMR ($CDCl_3$): δ 7.68−7.63 (m, 4 H), 7.35−7.31 (m, 4 H), 7.25−7.12 (m, 4 H), 6.84 (s, 1 H), 4.39−4.34 (m, 4 H), 4.08−4.06 (m, 4 H), 3.96 (s, 3 H). MS (ESI): m/z 422 $(M + NH_4)^+$, 427 $(M + Na)^+$. Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.15; H, 5.95.

Compound 1d. This compound was prepared as a white powder (51%) from the reaction of 1 equiv of **3** and 2 equiv of **6** on the basis of the method described for **1b**. Mp: 146−148 °C. ^{1}H NMR (acetone-d_6): δ 7.69−7.61 (m, 8 H), 7.28−7.22 (m, 16 H), 4.28−4.21 (m, 12 H), 4.04−3.93 (m, 12 H), 3.88 (s,

(28) At such a low concentration, intermolecular interaction could be ruled out. The concentration is within the concentration range where the Bill's law is observed.

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(31) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 4142.

6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 148.9, 148.6, 129.3, 129.0, 126.3, 126.3, 126.3, 126.2, 124.2, 124.1, 124.0, 108.5, 108.4, 107.9, 106.4, 69.8, 69.8, 69.7, 68.5, 68.4, 68.2, 55.7. MS (ESI): *m/z* 896 $[M + NH_4]^+$, 901 $[M + Na]^+$. HRMS (ESI): *m/z* 901.3531, calcd for $C_{54}H_{54}O_{11}Na$ 901.3558. Anal. Calcd for $C_{54}H_{54}O_{11}$: C, 73.79; H, 6.19. Found: C, 73.50; H, 6.02.

Compound 9. To a stirred suspension of compound **7**[32] (1.00 g, 4.0 mmol) and cesium carbonate (1.43 g, 4.40 mmol) in DMF (40 mL) was added a solution of ditosylate **8**[33] (8.28 g, 20.0 mmol) in DMF (25 mL). The reaction mixture was stirred at 100 °C for 3 h, and the solvent was removed under reduced pressure. The resulting residue was triturated with chloroform (300 mL), and the organic phase was washed with water (50 mL × 3) and brine (50 mL) and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude product was subjected to column chromatography (EtOAc/hexane 1:4) to produce **9** as a white gel (1.60 g, 81%). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2 H), 7.65 (q, J = 4.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2H), 7.38−7.32 (m, 7 H), 7.20 (s, 1 H), 7.13 (s, 1 H), 5.20 (s, 1 H). MS (ESI): *m/z* 493 $[M + H]^+$, 510 $[M + NH_4]^+$. Anal. Calcd for $C_{28}H_{28}O_6S$: C, 68.27; H, 5.73. Found: C, 68.28; H, 5.94.

Compound 10. This compound was prepared as a white powder (80%) from the reaction of 1 equiv of **5** and 2 equiv of **9** (2.0 equiv) on the basis of the method described for **9**. Mp: 120−122 °C. ^{1}H NMR (acetone-d_6): δ 7.70−7.64 (m, 6 H), 7.56−7.53 (m, 4 H), 7.38−7.27 (m, 18 H), 5.21 (s, 4 H), 4.28−4.21 (m, 8 H), 4.02−3.97 (m, 8 H). MS (ESI): *m/z* 818 $[M + NH_4]^+$, 823 $[M + Na]^+$. Anal. Calcd for $C_{52}H_{48}O_8$: C, 77.96; H, 6.05. Found: C, 78.13; H, 6.02.

Compound 11. A suspension of **10** (0.80 g, 1.00 mmol), Pd−C (10%, 0.10 g) in dichloromethane (90 mL), and methanol (10 mL) was stirred under an atmosphere of hydrogen (1 atm) at 40 °C for 12 h. The solid was filtered off, and the filtrate was concentrated in vacuo. The crude product was then purified by column chromatography (CH_2Cl_2/CH_3OH 500:1) to obtain **11** as a white powder (0.56 g, 89%). Mp: 62−63 °C.^{1}H NMR (CD_3OD): δ 7.65−7.61 (m, 2 H), 7.54−7.50 (m, 4 H), 7.27−7.16 (m, 12 H), 7.09 (s, 2 H), 4.24−4.12 (m, 8 H), 3.97−3.91 (m, 8 H). MS (ESI): *m/z* 638 $[M + NH_4]^+$, 643 $[M + Na]^+$. Anal. Calcd for $C_{38}H_{36}O_8$: C, 73.52; H, 5.85. Found: C, 73.52; H, 6.22.

Compound 1e. This compound was prepared as a white powder (51%) from the reaction of **4** and **11** on the basis of the method described for **1b**. Mp: 154−156 °C. ^{1}H NMR (CD_3CN): δ 7.64−7.58 (m, 10 H), 7.29−7.25 (m, 10 H), 7.17−7.13 (m, 10 H), 4.18−4.12 (m, 16 H), 3.87 (m, 16 H), 3.83 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.7, 148.9, 148.6, 129.3, 129.0, 126.3, 126.3, 126.2, 124.2, 124.2, 124.1, 124.0, 108.5, 107.9, 106.4, 69.8, 69.8, 69.8, 68.5, 68.4, 68.2, 55.7. MS (MALDI-TOF): *m/z* 1131 $[M + Na]^+$. Anal. Calcd for $C_{68}H_{68}O_{14}$: C, 73.61; H, 6.19. Found: C, 73.24; H, 6.41.

Compound 12. This compound was prepared as a white gel (76%) from the reaction of **6** and **9** on the basis of the method described for **9**. ^{1}H NMR (acetone-d_6): δ 7.69 (m, 6 H), 7.56 (m, 2 H), 7.36−7.22 (m, 15 H), 5.21 (s, 2 H), 4.26 (m, 8 H), 4.01 (m, 8 H), 3.88 (s, 3 H). MS (ESI): *m/z* 742 $[M + NH_4]^+$, 747 $[M + Na]^+$. HRMS (ESI): *m/z* 747.2930, calcd for $C_{46}H_{44}O_8Na$ 747.2928. Anal. Calcd for $C_{46}H_{44}O_8$: C, 76.22; H, 6.12. Found: C, 76.01; H, 6.20.

Compound 13. This compound was prepared as a white powder (86%) from **12** on the basis of the method described for **11**. Mp: 64−66 °C. ^{1}H NMR (acetone-d_6): δ 7.59−7.47 (m, 6 H), 7.19−7.06 (m, 12 H), 4.21−4.11 (m, 8 H), 3.92−3.84 (m, 8 H), 3.75 (s, 3 H). MS (ESI): *m/z* 652 $[M + NH_4]^+$, 657 $[M + Na]^+$. HRMS (ESI): *m/z* 657.2441, calcd for $C_{39}H_3O_8Na$ 657.2458.

Compound 1f. This compound was prepared as a white powder (56%) from the reaction of 1 equiv of **3** and 2.2 equiv of **13** on the basis of the method described for **1b**. Mp: 170−172 °C. ^{1}H NMR (DMSO-d_6): δ 7.69−7.60 (m, 12 H), 7.31−7.24 (m, 24 H), 4.16 (m, 20 H), 3.88 (m, 20 H), 3.82 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 148.5, 148.3, 128.9, 128.9, 128.7, 126.2, 126.1, 123.9, 123.8, 108.0, 107.9, 107.3, 106.5, 69.0, 68.9, 68.0, 67.7, 55.3. MS (MALDI-TOF): *m/z* 1361 $[M + Na]^+$. HRMS (MALDI): *m/z* 1361.5451, calcd for $C_{82}H_{82}O_{17}$-Na 1361.5444. Anal. Calcd for $C_{82}H_{82}O_{17}$: C, 73.52; H, 6.17. Found: C, 73.19; H, 6.24.

Compound 14. This compound was prepared as a white powder (74%) from the reaction of **6** and an excessive amount of **3** (5.0 equiv) on the basis of the method described for **1d**. Mp: 67−69 °C. ^{1}H NMR ($CDCl_3$): δ 7.63−7.68 (m, 4 H), 7.34−7.30 (m, 4 H), 7.18 (s, 1 H), 7.17 (s, 1 H), 7.13 (s, 1 H), 7.10 (s, 1 H), 4.35−4.31 (m, 4 H), 4.24 (t, J = 4.5 Hz, 2 H), 4.13−4.06 (m, 4 H), 3.95−3.90 (m, 7 H), 3.50 (t, J = 6.0 Hz, 2 H). MS (ESI): *m/z* 572 $[M + NH_4]^+$, 577 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{31}BrO_6$: C, 62.71; H, 5.63. Found: C, 62.38; H, 5.41.

Compound 1g. This compound was prepared as a white solid (51%) from the reaction of **11** (1.0 equiv) and **14** (2.2 equiv) on the basis of the method described for **1b**. Mp: 162−164 °C.^{1}H NMR (DMSO-d_6): δ 7.68−7.59 (m, 12 H), 7.28−7.21 (m, 24 H), 4.13 (m, 24 H), 3.88 (m, 24 H), 3.81 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 148.5, 148.3, 128.9, 128.7, 128.7, 126.2, 126.1, 123.9, 123.8, 107.9, 107.3, 106.5, 69.0, 68.9, 68.0, 67.6, 66.4, 55.3. MS (MALDI-TOF): *m/z* 1591 $[M + Na]^+$. HRMS (MALDI-TOF): *m/z* 1591.6402, calcd for $C_{96}H_{96}O_{20}Na$ 1591.6387. Anal. Calcd for $C_{96}H_{96}O_{20}$: C, 73.45; H, 6.16. Found: C, 73.02; H, 6.32.

Compound 15. A suspension of **5** (0.37 g, 2.32 mmol), **9** (1.14 g, 2.32 mmol), and $NaHCO_3$ (0.20 g, 2.32 mmol) in DMF (40 mL) was stirred at 100 °C for 2 h and then poured into ice (200 g). The precipitate formed was filtered, washed with water thoroughly, and dried in vacuo. After recrystallization from ethyl acetate and hexanes (1:2), the desired compound was obtained as a gray powder (0.83 g, 74%). Mp: 122−124 °C. ^{1}H NMR ($CDCl_3$): δ 7.67−7.62 (m, 4 H), 7.48 (d, J = 6.6 Hz, 2 H), 7.35−7.28 (m, 7 H), 7.22 (s, 1 H), 7.18 (s, 1 H), 7.11 (s, 1 H), 6.74 (s, 1 H), 5.21 (s, 2 H), 4.35 (t, J = 4.2 Hz, 2 H), 4.25 (t, J = 4.2 Hz, 2 H), 4.06−4.03 (m, 4 H). MS (ESI): *m/z* 498 $[M + NH_4]^+$, 503 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{28}O_5$: C, 77.48; H, 5.87. Found: C, 76.91; H, 5.86.

Compound 16. This compound was prepared as a white powder (81%) from the reaction of **15** and **3** (5.0 equiv) on the basis of the method described for **1b**. Mp: 87−89 °C. ^{1}H NMR ($CDCl_3$): δ 7.66−7.64 (m, 4 H), 7.51−7.48 (d, J = 7.8 Hz, 2 H), 7.36−7.31 (m, 7 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 7.12 (s, 1 H), 5.21 (s, 2 H), 4.36 (t, J = 4.5 Hz, 2 H), 4.26−4.21 (m, 4 H), 4.11−4.09 (m, 4 H), 3.92−3.86 (m, 4 H), 3.46 (t, J = 6.3 Hz, 2 H). MS (ESI): *m/z* 648 $[M + NH_4]^+$, 653 $[M + Na]^+$. Anal. Calcd for $C_{35}H_{35}BrO_6$: C, 66.56; H, 5.59. Found: C, 66.59; H, 5.67.

Compound 17. This compound was prepared as a white powder (79%) from **6** and **16** on the basis of the method described for **1b**. Mp: 82−84 °C. ^{1}H NMR (acetone-d_6): δ 7.70−7.20 (m, 29 H), 5.19 (s, 2 H), 4.26−4.19 (m, 12 H), 4.01−3.92 (m, 12 H), 3.86 (s, 3 H). MS (ESI): *m/z* 972 $[M + NH_4]^+$. Anal. Calcd for $C_{60}H_{58}O_{11}$: C, 75.45; H, 6.12. Found: C, 75.31; H, 6.20.

Compound 18. This compound was prepared from **17** on the basis of the method described for **11** as a white powder (89%). Mp: 78−80 °C.^{1}H NMR (acetone-d_6): δ 8.03 (s, 1 H), 7.61−7.66 (m, 8 H), 7.29−7.18 (m, 16 H), 4.28−4.23 (m, 12 H), 4.02−3.95 (m, 12 H), 3.87 (s, 3 H). MS (ESI): *m/z* 882 $[M + NH_4]^+$, 887 $[M + Na]^+$. Anal. Calcd for $C_{53}H_{52}O_{11}$: C, 73.58; H, 6.07. Found: C, 73.34; H, 6.07.

Compound 1h. This compound was prepared as a white powder (44%) from the reaction of **3** and **18** (2.2 equiv) on the basis of the method described for **1b**. Mp: 174−176 °C. ^{1}H NMR (DMSO-d_6): δ 7.64−7.55 (m, 16 H), 7.25−7.17 (m, 32 H), 4.10 (m, 28 H), 3.82 (m, 28 H), 3.78 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.3, 128.8, 128.7, 125.8, 125.6, 123.5, 123.4, 108.6, 108.5, 107.8, 106.7, 68.8, 68.1, 67.8, 55.2. MS

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(MALDI-TOF): *m/z* 1821 $[M + Na]^+$, 1837 $[M + K]^+$. HRMS (MALDI-TOF): *m/z* 1821.7296, calcd for $C_{110}H_{110}O_{23}Na$ 1821.7330.

Compound 24. A solution of **23**[34] (2.50 g, 10.0 mmol) and cesium carbonate (3.90 g, 12.0 mmol) in DMF (100 mL) was stirred at room temperature for 30 min. A solution of **3** (16.6 g, 50.0 mmol) in DMF (100 mL) was then added. The solution was then stirred at 80 °C for 12 h. Upon removal of the solvent under reduced pressure, the resulting residue was triturated with chloroform (200 mL). After normal workup, the crude product was purified by column chromatography (hexane/CH_2Cl_2 1:5) to afford compound **24** as a white powder (2.60 g, 65%). Mp: 74−76 °C. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.55−7.52 (m, 2 H), 7.45−7.34 (m, 5 H), 6.93 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1 H). MS (ESI): *m/z* 401 $[M + H]^+$. Anal. Calcd for $C_{21}H_{21}BrO_3$: C, 62.85; H, 5.27. Found: C, 63.19; H, 5.01.

Comound 26. This compound was prepared as a white powder (88%) from the reaction of **25**[35] and **24** (2.2 equiv) on the basis of the method described for **24**. Mp: 54−56 °C. ^{1}H NMR ($CDCl_3$): δ 7.95−7.82 (m, 4 H), 7.53 (d, J = 6.9 Hz, 2 H), 7.44−7.32 (m, 7 H), 6.93−6.85 (m, 4 H), 5.25 (s, 2 H), 4.37−4.34 (m, 4 H), 4.15 (t, J = 4.5 Hz, 4 H), 4.01 (s, 3 H). MS (ESI): *m/z* 495 $[M + H]^+$. Anal. Calcd for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.90; H, 6.08.

Compound 27. Compound **26** was first subjected to Pd−C-catalyzed hydrogenation in methanol and dichloromethane, a mixture of products was obtained which were difficult to purify and, without purification, treated with dibromide **3** in hot DMF in the presence of cesium carbonate. Compound **27** was obtained after workup and column chromatography (CH_2Cl_2/MeOH 100:1) as a white powder (45% for two steps). Mp: 78−80 °C. ^{1}H NMR ($CDCl_3$): δ 7.92−7.88 (m, 6 H), 7.52 (d, J = 6.9 Hz, 2 H), 7.42−7.28 (m, 9 H), 6.89−6.83 (m, 6 H), 5.24 (s, 2 H), 4.36−4.34 (m, 8 H), 4.17−4.14 (m, 8 H), 3.99 (s, 3 H). MS (ESI): *m/z* 725 $[M + H]^+$. HRMS (ESI): *m/z* 747.2930, calcd for $C_{46}H_{44}O_8Na$ 747.2928.

Compound 22. This compound was prepared as a white powder (40%) by hydrogenation of **27** and treatment of the crude product with **3** by using the procedures described for **27**. Mp: 178−180 °C. ^{1}H NMR ($CDCl_3$): δ 7.78−7.73 (m, 12 H), 7.30−7.24 (m, 12 H), 4.32−4.28 (m, 20 H), 4.09−4.04 (m, 20 H), 3.96 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 148.3, 128.7, 128.8, 128.7, 126.2, 126.1, 123.7, 123.4, 107.9, 107.3, 106.5, 69.1, 68.8, 68.0, 67.5, 55.3. MS (MALDI-TOF): *m/z* 1356 $[M + NH_4]^+$, 1361 $[M + Na]^+$. HRMS-MS (MALDI): *m/z* 1361.5451, calcd for $C_{82}H_{82}O_{17}Na$ 1361.5444.

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Supporting Information Available: The UV−vis and fluorescent experiments of **1a**−**h** in the $CHCl_3$−DMSO binary solvent system, the NOESY spectrum of complex **1f·19** in CD_3CN, and X-ray crystallographic data for **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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