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ORIGINAL ARTICLE

Synthesis of a water-soluble macrocyclic anthracenophane and its size-selective molecular recognition

Kazuhiro Nakamura[1] · Shuhei Kusano[1] · Osamu Hayashida[1]

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Abstract A tetraazacyclophane having two anthracene moieties (**3**) was synthesized by a reaction of nosyl-protected diaminodiphenylmethane with 9,10-bis(bromomethyl)anthracene, followed by removal of the protecting groups. Water-soluble anthraceophane (**1**) was prepared by condensation of **3** with Fmoc-β-alanine, followed by removal of the Fmoc groups. Host **1** showed size-selective guest discrimination in aqueous media. Bis-ANS (4,4′-dianilino-1,1′-binaphthyl-5,5′-disulfonate) having a suitable molecular size was incorporated in the internal cavity of **1** with binding constant (K) of 2.6×10^5 M^{-1}, although slightly smaller guests such as 1,8-ANS (8-anilinonaphthalene-1-sulfonate) were not, as confirmed by fluorescence titration experiments.

Keywords Anthracenophane · Host–guest chemistry · Enhanced guest-binding

Introduction

Current topics of host–guest chemistry are development of synthetic hosts that form host–guest complexes with targeted organic compounds [1–3]. Recently, macrocyclic hosts such as calixarenes [4], pillararenes [5], cyclophanes [6], and the others [7] have been designed and developed. Especially, there is a lot of flexibility in the design of cyclophanes by changing in shape and size of the macrocyclic skeleton. In addition, azacyclophanes [8] are chemically modified by introducing various functional groups [9] into the nitrogen atom. For instance, a tetraaza[6.1.6.1]paracyclophane [10] containing diphenylmethane units, prepared by Koga et al., is frequently used as a macrocyclic skeleton because durene, a guest molecule, was accommodated in its cavity. Moreover, water-soluble azacyclophanes based on the tetraaza[6.1.6.1]-paracyclophane can provide a hydrophobic cavity for inclusion of naphthalene derivatives as a guest molecule in aqueous media [11]. For example, cationic water-soluble cyclophane **2** [12] was found to form 1:1 host–guest complexes with naphthalene derivatives such as 1,8-ANS (8-anilinonaphthalene-1-sulfonate) [13] with binding constant (K) in the order of 10^4 M^{-1} (Figs. 1, 2) [12]. On the other hand, there is very little affinity for **2** to bind larger guest molecules such as Bis-ANS (4,4′-dianilino-1,1′-binaphthyl-5,5′-disulfonic acid) (Fig. 2) [14]. Several approaches have been applied so as to enhance the guest-binding ability [15]. A possible approach for that is multiplying in the macrocycle; i.e., cyclophane oligomers having several macrocyclic binding sites shows multivalent effects in the guest-binding [16]. Alternative approach is rational molecular design of macrocyclic hosts having a suitable internal cavity for the binding of Bis-ANS derivatives. On these grounds, we interested in the development of macrocyclic compounds as a host for Bis-ANS as a guest molecule. Bis-ANS has about two-times larger molecular size than that of 1,8-ANS. Here, we designed water-soluble anthracenophane (**1**) as a water-soluble macrocyclic host having a nano-sized internal cavity (Fig. 1). The host molecule was expected to provide an internal cavity for the binding Bis-ANS and two anthracene

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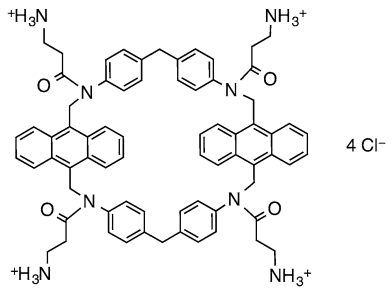
✉ Osamu Hayashida
hayashida@fukuoka-u.ac.jp

[1] Department of Chemistry, Faculty of Science, Fukuoka University, Nanakuma 8-19-1, Fukuoka 814-0180, Japan



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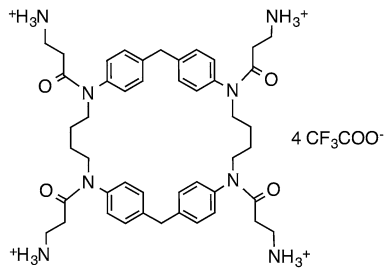

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Fig. 1 Cationic azacyclophanes **1** and **2**

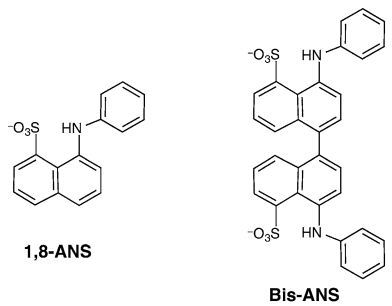


Fig. 2 Hydrophobic guests, 1,8-ANS and Bis-ANS

fluorophore moieties for sensing the guest molecules. In this context, we report synthesis of **1** and its guest-binding behavior with emphasis on the size-selective molecular recognition.

Results and discussion

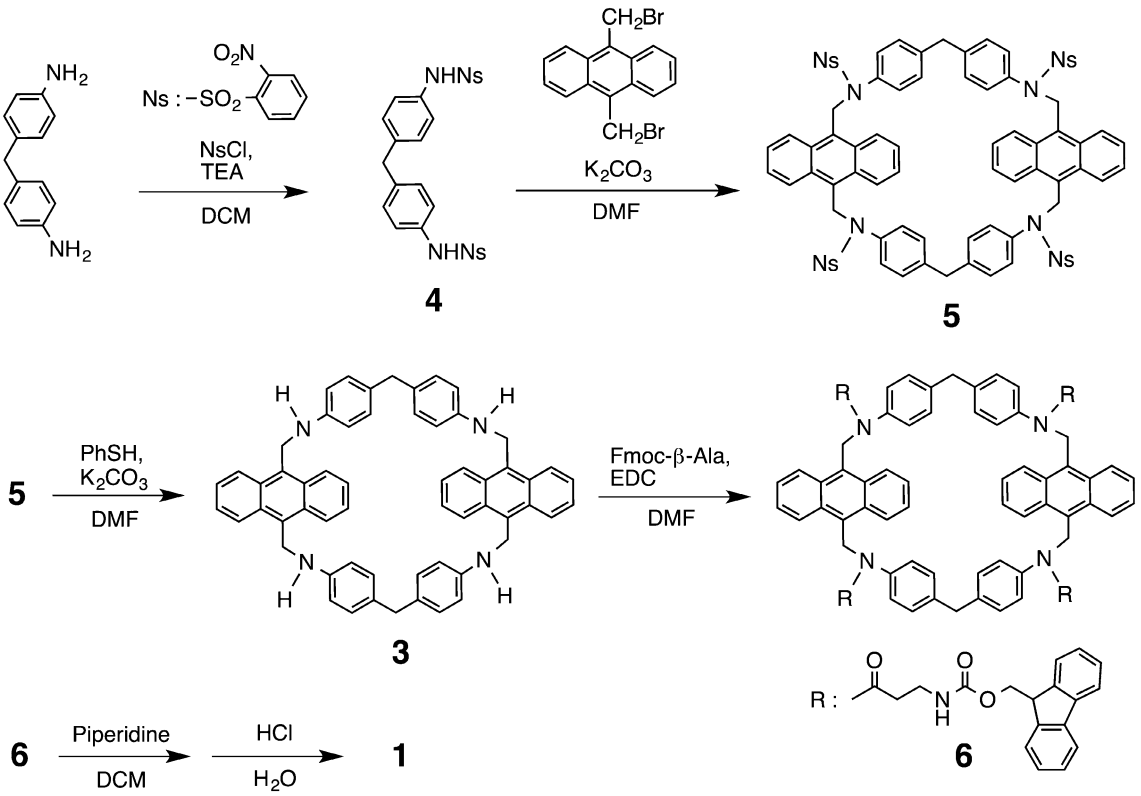
Synthesis of macrocyclic anthracenophane

We designed *N*,*N*′,*N*″,*N*‴-tetrakis(3-aminopropanoyl)-1,18,32,49-tetraaza[2.2.1.2.2.1]paracyclo-(9,10)anthracenophane (**3**) as a water-soluble macrocyclic host having a nano-sized internal cavity. Anthracenophane **3** was synthesized according to Scheme 1. First, 4,4′-diaminodiphenylmethane was protected by nosyl groups [17] using nosyl chloride to give **4** in a 75 % yield. *N*,*N*′,*N*″,*N*‴-nosyl-protected tetraaza-anthracenophane **5** was obtained by a reaction of **4** with 9,10-bis(bromomethyl)anthracene [18] in the presence of K_2CO_3 in dry DMF in a 26 % yield. Then, tetraazaanthracenophane **3** was synthesized by removal of the protecting groups with benzenethiol. On the other hand, the use of tosyl chloride in place of nosyl chloride afforded the corresponding tosyl-protected tetraazaanthracenophane in a manner similar to that applied synthesis of **5**. However, we have not been successful in obtaining **4** by acidic hydrolysis of the tosyl-protected tetraazaanthracenophane, due to an unfavorable decomposition side reaction. Interestingly, it is possible to introduce various functional groups into tetraazaanthracenophane **3** by condensation of the corresponding carboxylic acid derivatives. Actually, anthracenophane having four side-chains **6** was obtained by condensation of **3** with Fmoc-β-alanine in the presence of 1-ethyl-3(3-dimethyl-aminopropyl)carbodiimide (EDC). After removal of the Fmoc groups, anthracenophane having four side-chains with a terminal amino group **1** was synthesized. We fully characterized all the new compounds unambiguously by elemental analysis as well as by MALDI-TOF MS and ^{1}H and ^{13}C NMR spectroscopy (see ESM).

Binding behavior of macrocyclic anthracenophane with Bis-ANS

According to the computer-aided molecular CPK modeling studies [19], macrocyclic anthracenophane **1** provides a nano-sized hydrophobic cavity, which is constructed with two 9,10-disubstituted anthracene derivatives and two diaminodiphenylmethane moieties (see ESM). In addition, four terminal ammonium moieties place at the exterior of the macrocyclic skeleton, which contribute to water-solubility. In actuality, anthracenophane **1** shows good solubility in water (0.04 g/ml).

The guest-binding behavior of **1** was investigated by using hydrophobic guests such as 1,8-ANS and Bis-ANS, with regard to the size-selective molecular recognition (Fig. 2). These guests are fluorescent probes for evaluation of microenvironmental properties of the cyclophane cavity, because their emission of both intensity and wavelength is sensitive to change in microenvironmental polarity of the surrounding medium [13]. As regards a characteristic aspect of anthracenophane, **1** shows fluorescence emission maxima at 403, 427, and 452 nm in aqueous HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) buffer (0.01 M, pH 7.4, 0.15 M with NaCl). Interestingly, upon addition of BisANS to the HEPES buffer containing **1**, the fluorescence intensity originating from **1** at 403, 427, and 452 nm was decreased accompanying an increase of the fluorescence intensity of entrapped Bis-ANS molecules at around 520 nm, as shown in Fig. 3a, indicating a formation



Scheme 1 Preparation of cationic anthracenophane **1**

of host–guest complexes. Such quenching of the anthracene fluorophores of **1** seems to be caused by the energy transfer between the anthracene moieties of **1** and the incorporated Bis-ANS molecules in the host–guest complexes. With increasing concentrations of Bis-ANS, the fluorescence intensity originating from **1** decreased, showing a saturation behavior for the complexation of **1** and Bis-ANS (Fig. 3c). In addition, Job's continuous variation plot revealed that **1** bound Bis-ANS in a 1:1 molar ratio of host to guest (Fig. 4). The 1:1 host:guest binding constant (K) was evaluated by Benesi-Hildebrand analysis [20] applied to the fluorescence titration data under the condition of large excess amount of Bis-ANS ($K = 2.6 \times 10^5$ M^{-1}). Unfortunately, NMR measurements for the complexation of **1** and Bis-ANS were unsuccessful due to a limited solubility of the host–guest complexes at higher concentration for NMR experiments. As regards size-sensitive molecular recognition by the host, the slight fluorescence spectral changes of **1** were observed upon the addition of small guests such as 8-anilinonaphthalene-1-sulfonate (1,8-ANS), as shown in Fig. 3b. In addition, neither 6-anilinonaphthalene-2-sulfonate (2,6-ANS) nor 6-*p*-toluidinonaphthalene-2-sulfonate (TNS) showed the change of fluorescence spectrum of **1** (see ESM). Therefore, the K values of **1** with 1,8-ANS, 2,6-ANS, and TNS were not determined due to the low affinity. These results indicate that the binding affinity of **1** toward Bis-ANS was relatively selective among the adopted guests. In addition, the opposite is true, because host **2** [12] having a slightly small macrocycle (vide supra) bound small guests such as 1,8-ANS, 2,6-ANS, and TNS with K values of 3.6×10^3, 1.4×10^4, and 1.5×10^4 M^{-1}, respectively [12], whereas the K value of **2** toward Bis-ANS was not determined accurately due to weak fluorescence spectral changes (see ESM).

Conclusions

We successfully synthesized cationic anthracenophane having a nano-sized internal cavity **1**. Anthracenophane **1** shows characteristic fluorescence emission maxima at 403, 427, and 452 nm that are capable of sensing the guest-binding in aqueous HEPES. It was found that anthracenophane **1** strongly bounds Bis-ANS with K of 2.6×10^5 M^{-1}, while the fluorescence spectral changes of **1** were almost negligible upon the addition of 1,8-ANS, 2,6-ANS, and TNS, reflecting size-selective guest discrimination. On the other hand, multivalency effect in macrocycles is promising in order to enhance the K value with the guest, because we have previously clarified that effective local concentration in the macrocycles of cyclophane oligomers

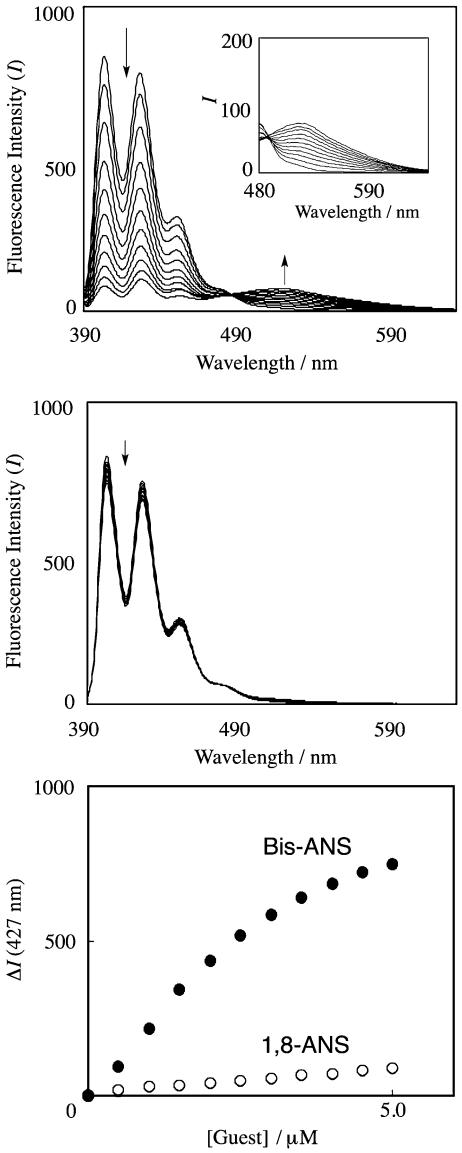


Fig. 3 Fluorescence spectra of **1** (0.05 μM) by adding incremental amounts of Bis-ANS (**a**) and 1,8-ANS (**b**) in a HEPES buffer at 298 K. [Bis-ANS] = [1,8-ANS] = 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 μM. The corresponding titration curves (**c**). Ex. 375 nm

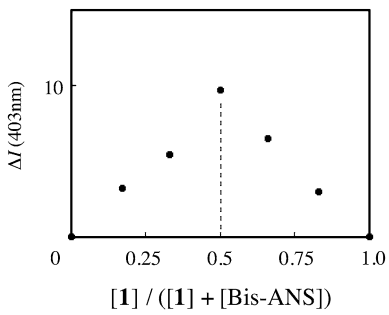


Fig. 4 Job's plot for host–guest complexation of **1** with Bis-ANS. [**1**] + [Bis-ANS] = 0.05 μM. Ex = 375 nm

(dimer, trimer, tetramer, and pentamer) caused favorable decrease in dissociation rate constants by surface plasmon resonance measurements [16]. Currently, the development of multivalent anthracenophane hosts is in progress along this concept.

Experimental section

Materials

HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) buffer (0.01 M, pH 7.4, 0.15 M with NaCl) was purchased from GE Healthcare. The following compounds were obtained from commercial sources and used without further purification: 8-anilinonaphthalene-1-sulfonate (1,8-ANS) and 4,4′-dianilino-1,1′-binaphthyl-5,5′-disulfonate (Bis-ANS) (both from Sigma-Aldrich Japan, Tokyo, Japan). A cationic water-soluble cyclophane (**2**) was prepared after a method reported previously [12].

General methods

Elemental analyses were recorded on a Yanako CHN Corder MT-5. ^{1}H and ^{13}C spectra were taken on Bruker AVANCE III 400 N spectrometer. Fluorescence spectra were recorded on a Perkin Elmer LS55 spectrometer. Fluorescence spectra, IR spectra, and MALDI TOF MS were recorded on Perkin Elmer LS55, Perkin-Elmer spectrum one, and Bruker autoflex speed spectrometers, respectively.

Nosyl-protected 4,4′-diaminodiphenylmethane 4

A solution of 4,4′-diaminodiphenylmethane (5.0 g, 25.2 mmol) and triethylamine (TEA, 7.6 ml) in dry dichloromethane (DCM, 30 ml) was added dropwise to a solution of 2-nitrobenzenesulfonylchloride (NsCl, 17.4 g, 63.0 mmol) in dry DCM (10 ml) at 0 °C, and then the mixture was stirred for 24 h at the same temperature. The solvent was distilled off on a rotatory evaporator to give a pale yellow solid. The solid was washed with hexane, dried *in vacuo* at room temperature to give a pale yellow solid (10.7 g, 75 %): ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.85 (s, 2H), 7.03 (d, J = 8.5 Hz, 4H), 7.10 (d, J = 8.5 Hz, 4H), 7.21(m, 4H), 7.72 (m, 4H), and 7.87 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K) δ 39.8, 121.4, 125.0, 129.8, 130.3, 131.9, 132.9, 134.9, 135.0, 138.1, and 148.3. IR 3299 cm^{-1} (N–H), 1531 cm^{-1} (N=O), 1349, 1163 cm^{-1} (SO_2). Found: C, 50.94; H, 3.57; N, 9.26, Calcd for $C_{25}H_{20}N_4O_8S_2{\cdot}H_2O$: C, 51.19; H, 3.78; N, 9.55. MALDI-TOF MS m/z 591 $[M + Na]^+$, where M shows $C_{25}H_{20}N_4O_8S_2$.

Nosyl-protected tetraazacyclophane 5

A solution of **4** (1.5 g, 2.6 mmol) and 9.10-bis(bromomethyl)anthracene (950 mg, 2.6 mmol) in dry DMF (250 ml) was added dropwise over 4 h to a suspension of potassium carbonate (1.8 g) in DMF (300 ml) at 90 °C, resulting mixture was stirred for overnight at room temperature. The solvent was evaporated to dryness under reduced pressure. Distilled water (1000 ml) was added to the residue. The resulting mixture was then stirred for 1 h at room temperature, insoluble materials were collected by filtration. The residue was chromatographed on a column of silica gel (SiO_2) with chloroform as eluent. The product fraction was evaporated to dryness under reduced pressure to give a pale yellow solid (510 mg, 26 %): ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.32 (s, 4 H), 5.84 (s, 8 H), 6.28 (d, $J = 8.0$ Hz, 8H), 6.58 (d, $J = 8.0$ Hz, 8H), 7.53 (m, 4H), 7.57 (dd, $J = 10.1$ Hz, 8H), 7.69 (m, 4H), 7.74 (m, 8H), and 8.32 (dd, $J = 10.1$ Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 42.4, 46.7, 123.9, 124.8, 125.9, 126.7, 130.6, 130.8, 131.4, 131.6, 132.2, 133.1, 133.7, 143.6, and 148.4. IR 3301 cm^{-1} (N–H), 1539 cm^{-1} (N=O), 1359, 1166 cm^{-1} (SO_2). Found: C, 61.64; H, 4.05; N, 6.81, Calcd for $C_{82}H_{60}N_8O_{16}S_4{\cdot}3H_2O$: C, 61.72; H, 4.17; N, 7.02.

Tetraazacyclophane having anthracene moieties 3

Potassium carbonate (550 mg) was added to a solution of **5** (510 mg, 0.33 mmol) in DMF (4 ml). Benzenethiol (0.29 ml, 2.65 mmol) was added and the mixture was stirred for 6 h at room temperature. The mixture was extracted with dichloromethane (DCM, 100 ml) and washed with saturated aqueous sodium chloride (50 ml). The organic solution was obtained and dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow solid. The residue was chromatographed on a column of silica gel (SiO_2) with chloroform:EtOAc (9:1 v/v) as eluent. The product fraction was evaporated to dryness under reduced pressure to give a pale yellow solid (250 mg, 94 %): ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.22 (s, 4H), 5.34 (s, 8H), 6.16 (s, 16H), 7.28 (m, 4H), 7.54 (dd, $J = 10.1$ Hz, 8H), and 8.30 (dd, $J = 10.1$ Hz, 8H). ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 41.6, 42.9, 118.5, 124.3, 125.0, 126.9, 130.2, 131.5, 131.5, and 144.3. IR 3371 cm^{-1} (N–H). Found: C, 85.31; H, 6.15; N, 6.76, Calcd for $C_{58}H_{48}N_4{\cdot}H_2O$: C, 85.05; H, 6.15; N, 6.84. MALDI-TOF MS m/z 801 $[M + H]^+$, M shows $C_{58}H_{48}N_4$.

Cyclophane having four Fmoc-β-Ala residues 6

A solution of **3** (100 mg, 0.12 mmol) in dry DCM (2 ml) was added dropwise to a solution of Fmoc-β-alanine (Fmoc-β-Ala, 310 mg, 1.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (191 mg, 1.0 mmol) in dry DCM (3 ml), and the mixture was stirred for 24 h at room temperature. The solvent was distilled off on a rotatory evaporator to give a pale yellow solid. The residue was chromatographed on a column of silica gel (SiO_2) with chloroform as eluent. The product fraction was evaporated to dryness under reduced pressure to give a pale yellow solid (243 mg, 98 %): ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 2.50 (t, $J = 10.6$ Hz, 8H), 3.36 (s, 4H), 3.56 (d, $J = 4.4$ Hz, 8H), 4.27 (m, 4H), 4.39 (d, $J = 7.1$ Hz, 8H), 5.74 (s, 8H), 6.36 (d, $J = 8.2$ Hz, 8H), 6.57 (d, $J = 8.2$ Hz, 8H), 7.36 (t, $J = 14.8$ Hz, 8H), 7.44 (t, $J = 14.8$ Hz, 8H), 7.53 (dd, $J = 10.1$ Hz, 8H), 7.76 (d, $J = 7.2$ Hz, 8H), 7.80 (d, $J = 7.2$ Hz, 8H), and 8.08 (dd, $J = 10.1$ Hz, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 35.6, 37.1, 42.2, 44.4, 47.3, 66.8, 120.0, 125.0, 125.0, 125.1, 125.4, 125.6, 127.1, 127.7, 129.3, 130.6, 136.1, 141.3, 143.7, 144.0, 156.4, and 171.8. IR 3300 cm^{-1} (N–H), 1634 cm^{-1} (C=O). Found: C, 76.91; H, 5.60; N, 5.28, Calcd for $C_{130}H_{108}N_8O_{12}{\cdot}3H_2O$: C, 76.98; H, 5.67; N, 5.52. MALDI-TOF MS m/z 1996 $[M + Na]^+$, where M shows $C_{130}H_{108}N_8O_{12}$.

Cationic cyclophane having anthracene moieties 1

To a solution of **6** (610 mg, 0.309 mmol) in dry DCM (2 ml) was added piperidine (1 ml). The mixture was stirred for overnight at room temperature. The solvent was distilled off on a rotatory evaporator to give a pale yellow solid. The residue was chromatographed on a column of silica gel (SiO_2) with chloroform as eluent. The product fraction was evaporated to dryness under reduced pressure to give a pale yellow solid (312 mg, 93 %): ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 2.50 (t, $J = 12.9$ Hz, 8H), 3.00 (t, $J = 12.9$ Hz, 8H), 3.34 (s, 4H), 5.73 (s, 8H), 6.50 (d, $J = 8.5$ Hz, 8H), 6.70 (d, $J = 8.5$ Hz, 8H), 7.58 (dd, $J = 10.1$ Hz, 8H), 8.16 (dd, $J = 10.1$ Hz, 8H). ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 35.7, 39.8, 40.6, 48.2, 128.8, 129.3, 130.7, 130.9, 132.9, 134.3, 139.4, 148.1, and 148.1. IR 3300 cm^{-1} (N–H), 1633 cm^{-1} (C=O). Found: C, 70.23; H, 7.02; N, 9.39, Calcd for $C_{70}H_{68}N_8O_4{\cdot}6H_2O$: C, 70.45; H, 6.76; N, 9.39. MALDI-TOF MS m/z 1107 $[M + Na]^+$, where M shows $C_{70}H_{68}N_8O_4$.

Fluorescence titration experiments

By adding incremental amounts of guests such as Bis-ANS, 1,8-ANS, 2,6-ANS, and TNS to a HEPES buffer (0.01 M, pH 7.4, 0.15 M with NaCl) containing **1** (0.05 μM) at 298 K, the each fluorescence spectra were recorded with employing excitation wavelength at 375 nm. Aqueous stock solution of **1** (0. 1 mM) was prepared after addition of small amount of HCl aq. (4 eq.).

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