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Synthesis of Water-Soluble Cyclophane Hexamers Having a Triphenylene Core and Their Enhanced Guest-Binding Behavior

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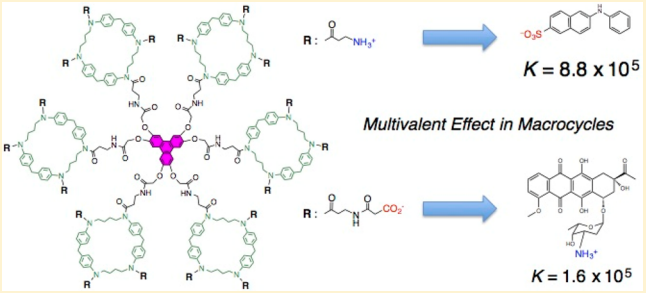
Supporting Information

ABSTRACT: A key compound, a precursor of water-soluble cyclophane hexamer, was prepared via Williamson ether synthesis of tetraaza[6.1.6.1]paracyclophane derivatives bearing a bromoacetamide moiety with triphenylene-2,3,6,7,10,11-hexaol as a core. A cationic cyclophane hexamer (**1**) was obtained by removing the protecting groups from the precursor. Fluorescence titration experiments proved that cationic cyclophane hexamer **1** showed macrocyclic multivalency effects; i.e., 1:1 host/guest binding constants (K) of **1** with anionic guests, 6-anilinonaphthalene-2-sulfonate and 6-*p*-toluidinonaphthalene-2-sulfonate, were increased about 63- and 62-fold, respectively, relative to those of monomeric cyclophane. Similarly, anionic cyclophane hexamer **2**, which was easily prepared from **1**, showed macrocyclic multivalency effects in K values with cationic guests such as hydrochlorides of doxorubicin and daunorubicin as an anticancer drug.



INTRODUCTION

Macrocyclic compounds such as cyclophanes, calixarenes, and cavitands play a leading part in molecular recognition, host–guest chemistry, and supramolecular chemistry.[1−3] Efforts at developing cyclophane derivatives as hosts proved successful.[4] Their host properties have been vigorously investigated; however, shortcomings of simple-monomeric cyclophanes are moderately binding with guest molecules.[5] A feasible approach is to multiply in the macrocycles so as to increase the binding abilities toward guest molecules.[6] Recently, we reported the development of liner-type cyclophane oligomers such as dimers, trimers, tetramers, and pentamers, which are constructed with several macrocyclic skeletons and peptide backbones.[7] Such liner-type cyclophane oligomers having several macrocyclic binding sites show increased guest-binding behavior due to multivalent effects of macrocycles.[7] Additionally, we demonstrated that the considerable decrease in rate constants of host–guest dissociation caused the increase of guest-binding affinity.[8] That is, effectual local concentrations in the macrocycles are thought to be key to the macrocyclic multivalent effects of the cyclophane oligomers.[8] On the other hand, we have also developed divergent-type cyclophane pentamers by connecting four macrocycles on the macrocyclic skeleton as a core.[9] Although these cyclophane pentamers showed enhanced guest-binding ability, the four external macrocyclic moieties are nonequivalent to the internal one. Therefore, there was no choice but to evaluate multivalent effects in macrocycles as an average. In addition to that, these linear and divergent-type cyclophane oligomers do not have a fluorescent moiety.[7−9] Hence, fluorescence sensing of the bind of guest molecules is somewhat inconvenient. In this report, we designed water-soluble triphenylene-based cyclophane hexamers that were constructed with six macrocycles having cationic and anionic moieties as side chains and fluorescent triphenylene-2,3,6,7,10,11-hexaol[10] as a core (**1** and **2**, respectively, Figure 1). Six macrocycles located in the exterior of the cyclophane hexamers are considered to be equivalent for the guest-binding behavior, which is good for accurate analysis. In addition, the fluorescent triphenylene core of the cyclophane hexamers is expected to be useful for detecting host–guest interactions. We report here the synthesis of cationic and anionic cyclophane hexamers having a triphenylene core, **1** and **2**, respectively, and their fluorescence-based binding study toward anionic molecular guests and cationic anticancer drugs in aqueous media.

RESULTS AND DISCUSSION

Synthesis of Cationic and Anionic Cyclophane Hexamers Having a Triphenylene Core. Triphenylene-based cyclophane hexamers **1** and **2** were synthesized in accordance with Scheme 1. First, Boc- and Fmoc-protected tetraamine derivatives of tetraaza[6.1.6.1]paracyclophane **3** were synthesized according to the methods reported previously.[11] Then, the Boc-protected cyclophane derivative having a bromoacetamide moiety **4** was obtained via a dicyclohexylcarbodiimide (DCC) condensation of bromoacetic acid with a cyclophane monoamine derivative, which was synthesized from **3** by a treatment with piperidine. A precursor (**5**) of **1** was synthesized by Williamson ether synthesis of **4**

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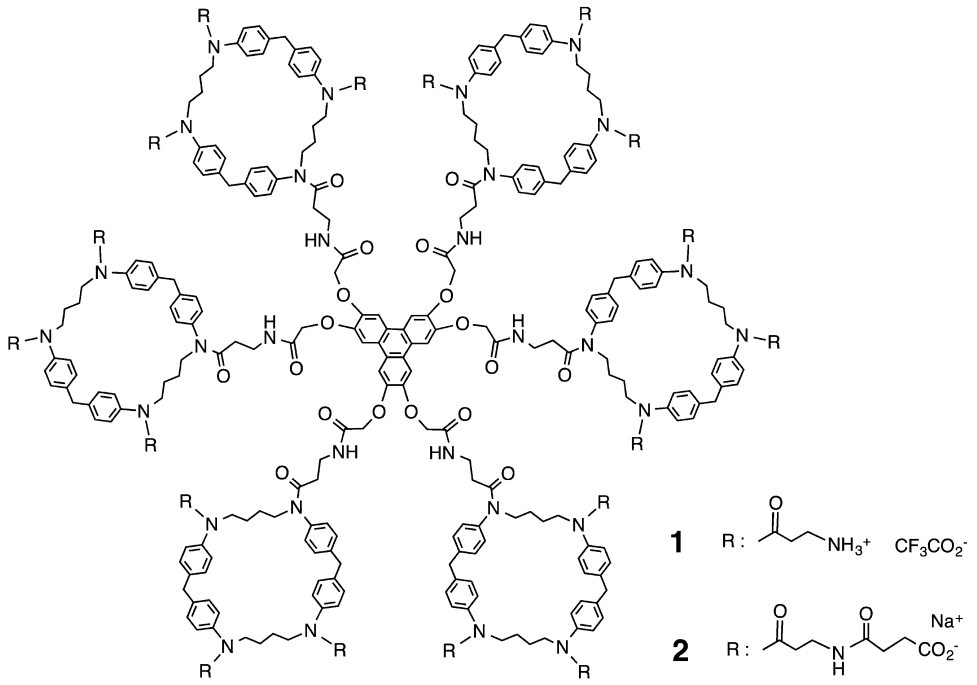

Figure 1. Cationic and anionic cyclophane hexamers **1** and **2**.

with triphenylene-2,3,6,7,10,11-hexaol in acetone by using potassium carbonate as a base in a good yield (97%). Triphenylene-based cyclophane hexamers **1** having cationic side chains were prepared from **5** after removal of the Boc groups by trifluoroacetic acid (TFA), while anionic triphenylene-based cyclophane hexamers **2** were obtained by an aminolysis of succinic anhydride with **1**. As for characterization data, compounds (**1**, **2**, **4**, and **5**) were fully identified unambiguously by elemental analysis as well as by ^{1}H and ^{13}C NMR and MALDI-TOF MS spectroscopy (see the SI).

Binding Behavior of Triphenylene-Based Cyclophane Hexamers with 2,6-ANS and TNS. According to the computer-aided molecular CPK modeling studies,[12] cationic triphenylene-based cyclophane hexamer **1** provides six external cavities as a guest-binding site, which are in all directions (see the SI). In addition, 18 terminal ammonium moieties are placed at the exterior of the macrocyclic skeleton, which play a role in water solubility. In fact, cationic cyclophane hexamer **1** shows good solubility in water (0.3 g/mL). On the other hand, 6-anilinonaphthalene-2-sulfonate (2,6-ANS) and 6-*p*-toluidinonaphthalene-2-sulfonate (TNS) are both well-known anionic fluorescent probes (Figure 2).[13] These fluorescent probes show strong fluorescence intensity in a hydrophobic environment of the surrounding medium, while their fluorescence is almost negligible in aqueous media.[13] We examined the guest-binding behavior of cationic host **1** toward anionic guests, 2,6-ANS and TNS, by fluorescence titration experiments in aqueous HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) buffer (pH 7.4).

As for a characteristic aspect of triphenylene-based cyclophane hexamer, **1** shows fluorescence emission maxima at 377 and 382 nm in aqueous HEPES buffer. Addition of 2,6-ANS to the aqueous solution of host **1** caused the decrease in fluorescence intensity originating from **1** in a short wavelength range as well as the strong increase in fluorescence intensity of 2,6-ANS at around 420 nm (Figure 3a). These results indicate that host **1** binds a 2,6-ANS molecule to form a host−guest complex. The observed decrease in the fluorescence intensity originating from **1** seems to arise from the energy transfer between the triphenylene fluorophore of **1** and the incorporated 2,6-ANS molecules in the host−guest complexes. In addition, the incorporated 2,6-ANS showed strong fluorescence at around 420 nm, reflecting the microenvironmental properties of the hydrophobic cyclophane cavity. With increasing large excess amounts of 2,6-ANS, the fluorescence intensity originating from the incorporated 2,6-ANS increased with a saturation behavior, indicating the formation of host−guest complexes of **1** with 2,6-ANS (Figure 3a). In addition, **1** bound 2,6-ANS in a (1:1) host−guest stoichiometry, which was revealed by a Job's plot (see SI). By using Benesi−Hildebrand analysis[14] for fluorescence titration data, the (1:1) host to guest binding constant (K) of **1** with 2,6-ANS was evaluated to be 8.8×10^5 M^{-1}, as summarized together with the corresponding value for the monomeric cyclophane **6**[15] (Table 1, Figure 4). A similar fluorescence titration behavior, that is, decrease in a short wavelength range of **1** and increase at around 420 nm, was also observed for TNS ($K = 9.3 \times 10^5$ M^{-1}, Figure 3b, Table 1). The K values of **1** with 2,6-ANS and TNS were 63 and 62 times larger than those of **6** with identical guests, respectively (Table 1), reflecting macrocyclic multivalent effects. In regard to electrostatic interaction between the hosts and the guest molecules, the K values for −/− of host/guest pairs between anionic cyclophane hexamer **2** and anionic 2,6-ANS and TNS were smaller by 1 order of magnitude than the corresponding values of cationic **1** (Table 1). About the host−guest complexation of water-soluble cyclophanes, hydrophobic interaction is a generally most important driving force.[11b,16] In addition to the hydrophobic interactions, electrostatic interactions of +/− or −/+ of host/guest pairs become effective for the enhancement of the K values.[11b,16] Similar molecular recognition behavior through hydrophobic and electrostatic interactions was observed in this research.

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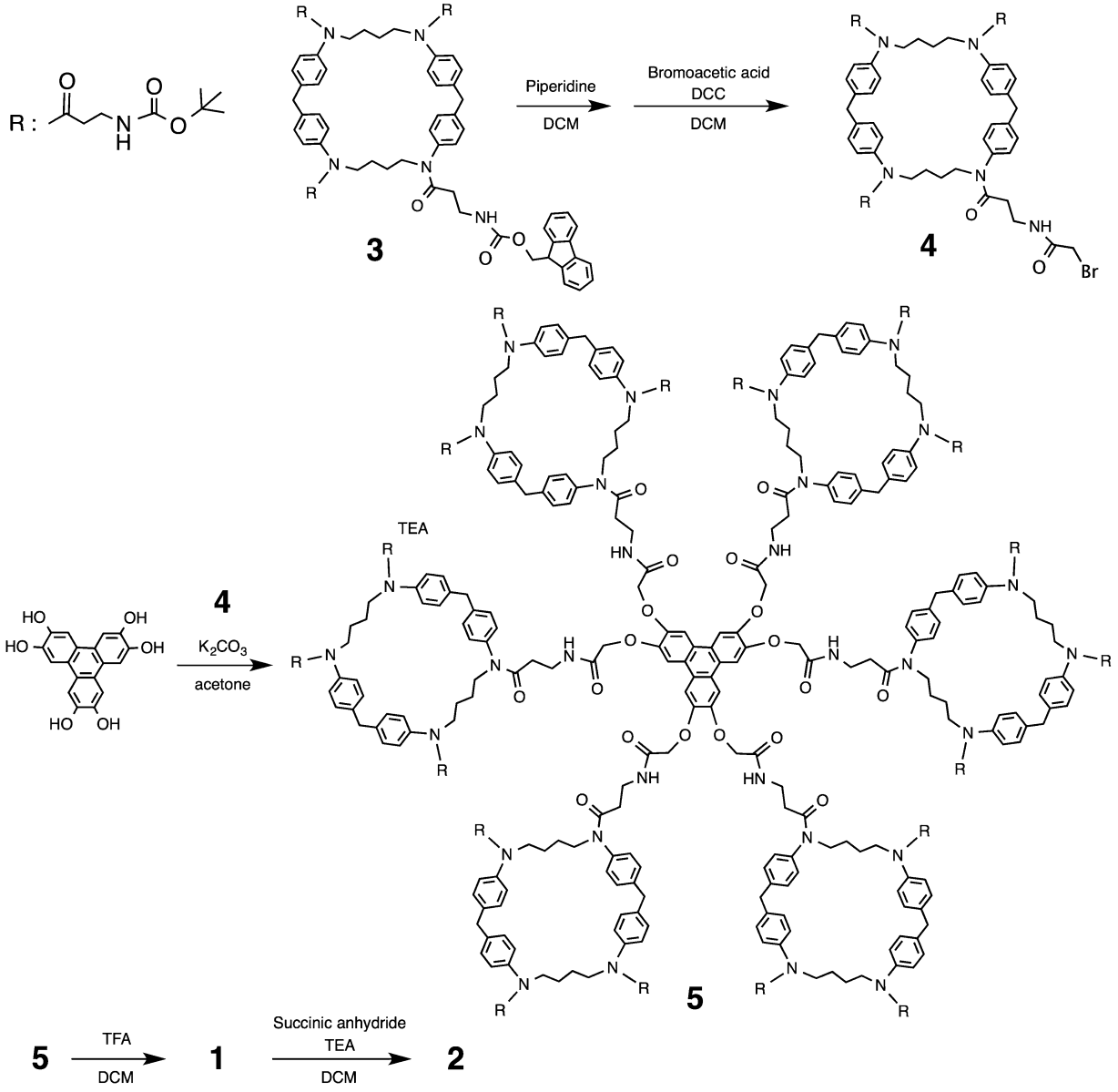
Scheme 1. Synthesis of Cationic and Anionic Triphenylene-Based Cyclophane Hexamers 1 and 2



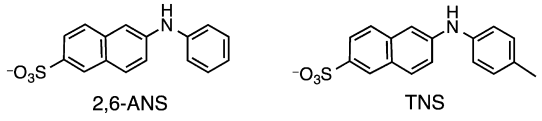


Figure 2. Hydrophobic fluorescent guests 2,6-ANS and TNS.

Even though cyclophane hexamers **1** and **2** have six single-valent binding sites, the stoichiometry is 1:1 host to guest, which was supported by the Job's plots. Not limited to **1** and **2**, other cyclophane oligomers such as tetramer and pentamer also showed 1:1 host to guest stoichiometry.[8] In addition, favorable decrease in dissociation rate constants was confirmed for the tetramer and pentamer by surface plasmon resonance measurements, indicating effective local concentration in the macrocycles (binding sites).[8] From this point of view, we suppose here that entrapped guest molecule by **1** and **2** is moving around *rapidly* between six single-valent binding sites without running away (see the SI). In such a case, the second guest molecule may neither approach nor simultaneously occupy binding sites owing to electrostatic repulsion between the anionic guest molecules.

Binding Behavior of Cyclophane Hexamers with Daunorubicin and Doxorubicin. Microenvironmentally responsible fluorescent probes such as 2,6-ANS and TNS are especially useful for evaluating the host−guest interactions by fluorescence spectroscopy, as mentioned above. Actually, the fluorescent intensity originating from 2,6-ANS and TNS was much enhanced when they were bound to the hydrophobic macrocyclic sites provided by the cyclophane oligomers.[13] It is not the case, however, for the other fluorescent guests lacking such microenvironmental responsibility. For example, both hydrochlorides of daunorubicin and doxorubicin are fluorescence compounds (DNR and DOX, respectively, Figure 5),[17] which show poor microenvironmental responses in fluorescence spectra. Therefore, fluorescent titration experiments by monitoring the fluorescent intensity of DNR and DOX are unfavorable for studying the host−guest interactions.[15] On the other hand, cyclophane hexamers **1** and **2** have a triphenylene core as a fluorescent moiety. We investigated binding behavior

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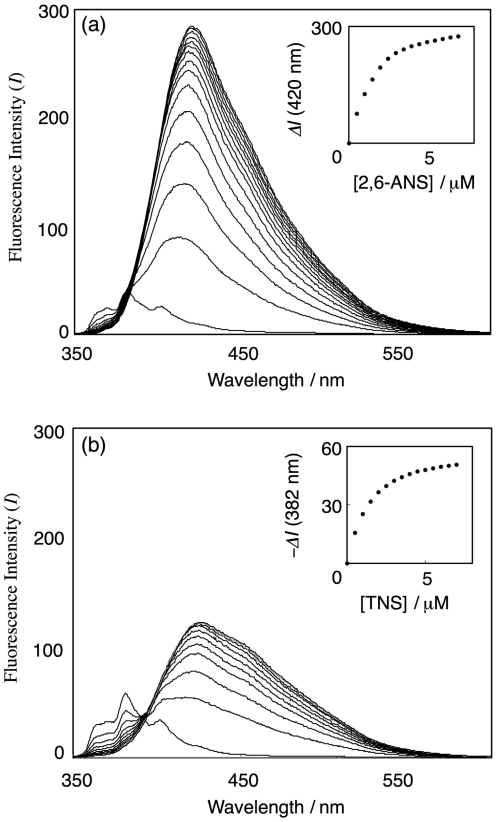

Figure 3. Fluorescence spectra of **1** (0.5 μM) by addition of incremental amounts of 2,6-ANS (a) and TNS (b) in a HEPES buffer at 298 K. [2,6-ANS] = [TNS] = 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, and 7.0 μM. Insets: the corresponding titration curves. Excitation: 305 nm.

Table 1. Binding Constants for Host–Guest Complexes of Cyclophane Hexamers 1 and 2 with 2,6-ANS and TNS in HEPES Buffer at 298 K[a]

	K (M^{-1})		$K/K(6)$	
host	2,6-ANS	TNS	2,6-ANS	TNS
1	8.8×10^5	9.3×10^5	63	62
2	3.5×10^4	7.4×10^4	3	5
6[b]	1.4×10^4	1.5×10^4		

[a]Excitation: 305 nm. [b]Reference 15.

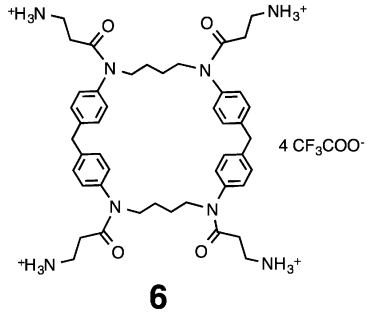

Figure 4. Monocyclic cyclophane **6**.

of **1** and **2** with ordinary and cationic anticancer drugs such as DNR and DOX and found that anionic host **2** was utilized for the fluorescent sensing these guests. That is, the fluorescence intensity of anionic cyclophane hexamer **2** at 382 nm decreased

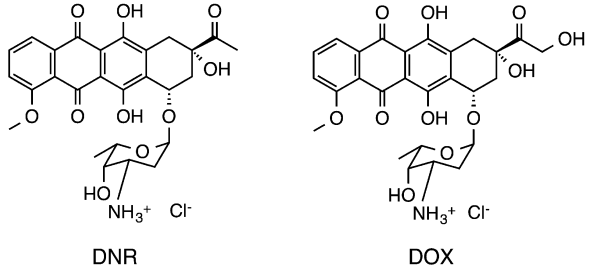

Figure 5. Anticancer drugs as a guest (DNR and DOX).

showing a saturation behavior when cationic DNR was added (Figure 6a). By Benesi–Hildebrand analysis[14] for the

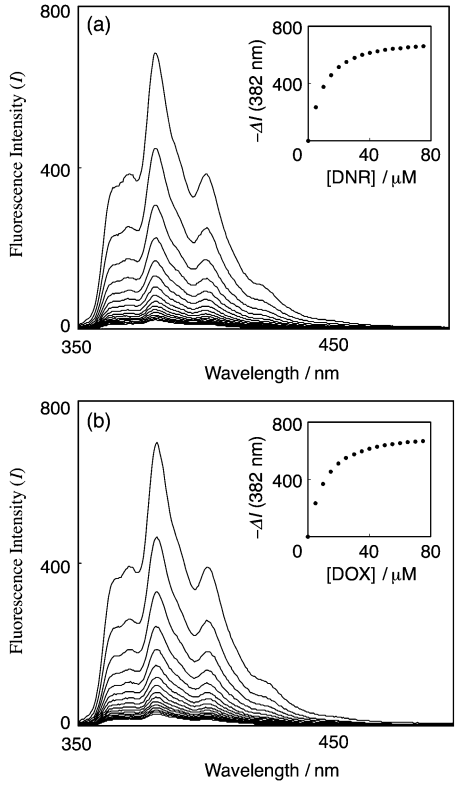

Figure 6. Fluorescence spectral changes of **2** (5.0 μM) by addition of incremental amounts of DNR (a) and DOX (b) in a HEPES buffer at 298 K. [DNR] = [DOX] = 0, 5.0, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, and 75 μM. Insets: the corresponding titration curves. Excitation: 305 nm.

fluorescence titration data, the K value for the complexation of **2** with DNR was calculated to be 1.6×10^5 M^{-1}, as summarized in Table 2. A similar fluorescence titration and

Table 2. Binding Constants for Host–Guest Complexes of Cyclophane Hexamers 1 and 2 with DNR and DOX in HEPES Buffer at 298 K[a]

	K (M^{-1})		$K/K(6)$	
host	DNR	DOX	DNR	DOX
1	2.8×10^4	1.9×10^4	90	58
2	1.6×10^5	1.3×10^5	520	390
6[b]	3.1×10^2	3.3×10^2		

[a]Excitation: 305 nm. [b]Reference 15.

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guest-binding behavior of **2** was also confirmed for DOX by the identical method ($K = 1.3 \times 10^5$ M^{-1}, Figure 6b, Table 2). The K values of **2** with DNR and DOX were ca. 520 and 390 times, respectively, larger to those of monomeric cyclophane **6** with the identical guests,[15] reflecting multivalent effects of macrocycles (Table 2). In regard to electrostatic interactions between the hosts and the anticancer drugs, the K values for cationic cyclophane hexamer **1** with DNR and DOX were smaller by 1 order of magnitude than the corresponding values of anionic **2** (Table 2). The inherent binding ability of **2** toward these anticancer drugs seems to be promising for the use of drug delivery systems.[18]

CONCLUSION

Cationic cyclophane hexamer **1** was successfully prepared by Williamson ether synthesis of Boc-protected cyclophane derivatives bearing a bromoacetamide moiety with triphenylenehexaol as a fluorescent core, followed by a TFA treatment. By reflecting multivalency effects of macrocycles, cationic host **1** showed increased guest-binding affinities with anionic fluorescent guests such as 2,6-ANS and TNS in comparison with those of monomeric cyclophane. Similarly, anionic cyclophane hexamer **2**, which was easily prepared from **1**, showed macrocyclic multivalency effects in K values with cationic anticancer drugs such as DNR and DOX. Characteristic sensing aspect of the triphenylene-based cyclophane hexamers on the fluorescence emission maxima at 382 nm was found to be useful for evaluating the host−guest interactions. By combining the strong binding and good fluorescence responsibility for the guests, these triphenylene-based cyclophane hexamers are promising as a carrier and molecular sensor for anticancer drugs.

EXPERIMENTAL SECTION

Bromoacetamide Derivative of Tetraaza[6.1.6.1]paracyclophane 4. Compound **4** was synthesized from cyclophane **3**[11] (485 mg, 0.37 mmol), 397 mg (88%). The synthetic procedure is described in the SI. Characterization of **4**: mp 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.44 (m, 35H), 2.11 (m, 8H), 3.27 (m, 6H), 3.44 (m, 2H), 3.65 (m, 8H), 3.84 (s, 2H), 3.97 (s, 4H), 5.33 (m, 3H), 6.97 (m, 8H), 7.22 (m, 8H), and 7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 24.8, 28.6, 29.0, 33.8−36.3, 41.0, 48.6, 78.8, 128, 130, 140, 156, 166, and 171; IR (ATR) 1695 cm^{-1} (C═O); MALDI-TOF MS m/z 1232 and 1234 $[M + Na]^+$, where M shows $C_{63}H_{85}BrN_8O_{11}$. Anal. Calcd for $C_{63}H_{85}BrN_8O_{11}\cdot 2H_2O$: C, 60.71; H, 7.20; N, 8.99. Found: C, 61.00; H, 6.92; N, 8.97.

Precursor of Cyclophane Hexamer 5. Compound **5** was synthesized from cyclophane **4** (282 mg, 0.24 mmol) (159 mg, 97%). The synthetic procedure is described in the SI. Characterization of **5**: mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.41 (m, 210H), 2.06 (m, 36H), 2.28 (s, 12H), 3.25 (m, 36H), 3.62 (m, 60H), 3.95 (m, 24H), 4.82 (s, 12H), 5.35 (m, 18H), 6.92 (m, 48H), 7.20 (m, 48H), 7.96 (s, 6H), and 8.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 24.9, 28.4, 34.8−36.4, 41.1, 48.7, 75.2, 79.0, 117−130, 141, 148, 149, 156, 167, 171, and 190; IR (ATR) 1636 cm^{-1} (C═O); MALDI-TOF MS m/z 7121 $[M + Na]^+$, where M shows $C_{396}H_{516}N_{48}O_{72}$. Anal. Calcd for $C_{396}H_{516}N_{48}O_{72}\cdot 5H_2O$: C, 66.14; H, 7.37; N, 9.35. Found: C, 66.00; H, 7.33; N, 9.13.

Cationic Cyclophane Hexamer 1. Compound **1** was synthesized from cyclophane **5** (224 mg, 0.032 mmol) (207 mg, 89%). The synthetic procedure is described in the SI. Characterization of **1**: mp 199−200 °C; ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 1.31−1.45 (m, 48H), 2.19 (m, 12H), 2.33−2.41 (m, 36H), 2.88 (m, 36H), 3.49 (m, 12H), 3.59−3.66 (m, 48H), 3.94 (s, 12H), 4.02 (s, 12H), 4.95 (m, 12H), 7.06−7.33 (m, 96H), and 8.17 (m 6H); ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 28.3, 35.2−39.6, 44.3, 51.6, 122, 132, 134, 143, 145, 152, 166, and 174; IR (ATR) 1635 cm^{-1} (C═O); MALDI-TOF MS m/z 5321 $[M + Na]^+$, M shows $C_{306}H_{372}N_{48}O_{36}$. Anal. Calcd for $C_{342}H_{390}F_{54}N_{48}O_{72}\cdot 5H_2O$: C, 55.20; H, 5.42; N, 9.04. Found: C, 55.05; H, 5.64; N, 8.84.

Anionic Cyclophane Hexamer 2. Compound **2** was synthesized from cyclophane **1** (52 mg, 7.1 μmol) (43 mg, 80%). The synthetic procedure is described in the SI. Characterization of **2**: mp 161−162 °C; ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 1.31−1.40 (m, 48H), 2.10 (m, 36H), 2.41 (m, 36H), 2.54 (m, 48H), 3.29 (m, 48H), 3.50 (m, 12H), 3.63 (m, 48H), 3.93−3.99 (m, 24H), 6.96 (m, 48H), 7.27 (m, 48H), and 8.21 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, 298 K) δ 29.8, 34.0−35.1, 38.9−40.4, 53.3, 56.4, 129, 133, 135, 145, 146, 153, 173, 176, 178, and 179; IR 1632 cm^{-1} (C═O); MALDI-TOF MS m/z 7123 $[M + Na]^+$, where M shows $C_{378}H_{444}N_{48}O_{90}$. Anal. Calcd for $C_{378}H_{444}N_{48}O_{90}$: C, 63.95; H, 6.30; N, 9.47. Found: C, 64.15; H, 6.56; N, 9.23.

Fluorescence Titration Experiments. By adding incremental amounts of guests such as 2,6-ANS and DNR to a HEPES buffer (0.01M, pH 7.4, 0.15 with NaCl) containing cyclophane hexamers at 298 K, each fluorescence spectrum was recorded at an excitation wavelength at 305 nm. An aqueous stock solution of **2** (0. 1 mM) was used after neutralization by small amount of NaOH aq.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00558.

NMR spectra for **1**, **2**, **4**, and **5**; computer-generated CPK models for **1**; Job's continuous variation plot and additional fluorescence titration experiments (PDF)

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Notes

The authors declare no competing financial interest.

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