JOC The Journal of Organic Chemistry

Article

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Synthesis, Guest-Binding, and Reduction-Responsive Degradation Properties of Water-Soluble Cyclophanes Having Disulfide Moieties

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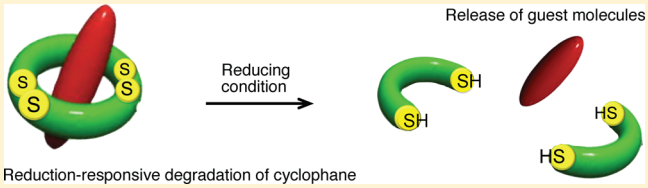
Supporting Information

ABSTRACT: Water-soluble cationic cyclophane having diphenyl disulfide moieties (**1a**) was synthesized as a reduction-responsive degradable host. The stoichiometry for the complex of **1a** with anionic fluorescence guests, such as 4,4′-bis(1-anilinonaphthalene-8-sulfonate) (Bis-ANS) and 4-(1-pyrene)-butanoic acid (PBA), was confirmed to be 1:1 host:guest by a Job plot. The binding constants (K) of **1a** toward Bis-ANS and PBA were evaluated to be 6.7×10^3 and 4.5×10^4 M^{-1}, respectively, as confirmed by fluorescence spectroscopy. Reduction of disulfide bonds of **1a** by dithiothreitol gave its reduced form having poor guest-binding affinity that led to release of the entrapped guest molecules to the bulk aqueous phase. Meanwhile, anionic cyclophane **1b**, which was derived from **1a** by a reaction with succinic anhydride, binds cationic anticancer drugs, such as daunorubicin hydrochloride (DNR) and doxorubicin hydrochloride (DOX), with a K of 2.1×10^3 and 7.5×10^2 M^{-1}, respectively. A similar reduction-responsive guest release feature was observed when DNR and DOX were employed as a guest for complexation with **1b**.



INTRODUCTION

Currently, the development of functionalized host vehicles having stimuli-responsive binding capabilities[1] has attracted much attention for targeted drug delivery[2] and controlled guest release.[3] Among all functionalities, disulfide bonds have been frequently utilized as a reductively degradable linkage.[4] A great number of artificial vehicles, such as disulfide-functionalized polymeric micelles,[5] vesicles,[6] and nanoparticles,[7] have been reported. On the other hand, cyclophanes with a sizable internal cavity[8] are also typical hosts capable of providing hydrophobic binding sites. Moreover, a wide synthetic variation can be achieved by introducing various functional groups into appropriate sites of the cyclophanes.[9] On these grounds, we became interested in the development of well-defined and cleavable cyclophanes based on disulfide linkages. In the preceding paper, we have developed a cleavable cyclophane dimer on the basis of a molecular design that allows connection of two tetraaza[6.1.6.1]paracyclophane[10] skeletons with a disulfide linkage.[11] The host showed enhanced guest binding affinity relative to that by monocyclic cyclophane,[12] as confirmed by fluorescence spectroscopy. Reduction of the disulfide bond of the host gave monocyclic cyclophanes having less guest-binding affinity.[11] In the course of our ongoing research on reduction-responsive degradable cyclophanes, a challenging subject of investigation is the development of functionalized cyclophanes having disulfide moieties within the macrocyclic skeleton. Figure 1 shows our concept on reduction-responsive release of guest molecules. That is, the reduction of disulfide bonds of cyclophanes gave the structural fragments having poor guest-binding affinity and, consequently, showed release of the entrapped guest molecules to the bulk aqueous phase. For the proof-of-principle experiments, we developed a water-soluble cationic cyclophane having disulfide moieties in the macrocyclic skeleton. Furthermore, we also designed an analogous derivative with terminal anionic side chains. We describe herein the synthesis of the water-soluble cyclophanes having disulfide moieties, their guest-binding behavior, and their reduction-responsive degradation properties with an emphasis on the release of guest molecules.

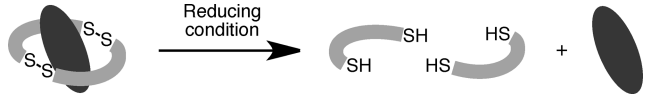


Figure 1. Schematic representation for the reduction-responsive degradation of cyclophanes having disulfide moieties with a concomitant release of guest molecules.

RESULTS AND DISCUSSION

Design and Synthesis of Cyclophanes Having Diphenyl Disulfide Moieties. First, we designed 1,2,21,22-tetrathia-9,14,29,34-tetraaza[6.2.6.2]paracyclophane (**4**) as a reduction-responsive degradable cyclophane. This compound can provide two disulfide moieties responsible for degradation. It is also desirable for water-soluble hosts to provide hydrophobic binding sites that can be desolvated upon guest incorporation. In addition, hydrophobic binding sites must be reasonably separated from hydrophilic groups that are required for giving water solubility to cyclophanes, so that the hydrophobic efficiency is maintained for guest incorporation.[13] We have now designed cationic and anionic cyclophanes having

Received: March 20, 2013
Published: May 16, 2013

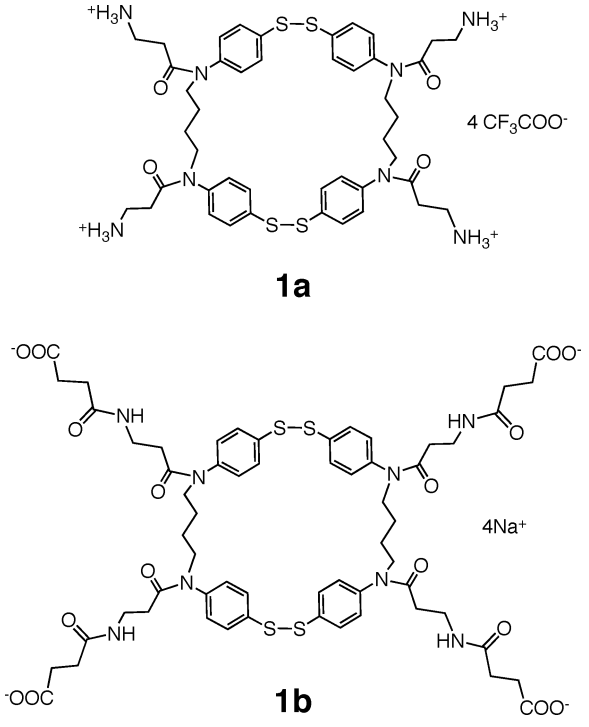


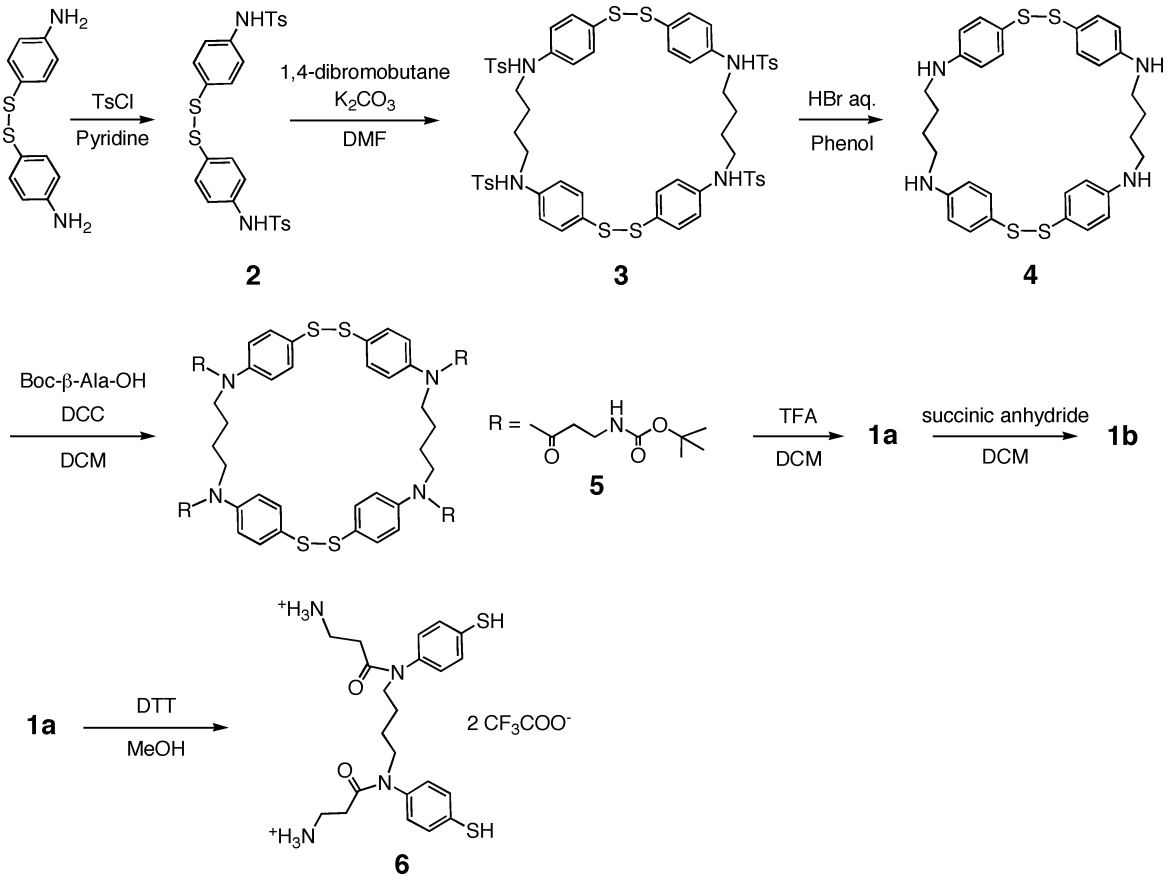
Figure 2. Water-soluble cyclophanes having disulfide moieties **1a** and **1b**.

disulfide moieties by introducing polar side chains with a terminal ammonium and carboxylate residue on the periphery of the macrocyclic skeleton through amide linkages, **1a** and **1b**, respectively (Figure 2).

Water-soluble cyclophanes having diphenyl disulfide moieties **1a** and **1b** were prepared by following the reaction sequence given in Scheme 1. A precursor (**3**) of **4** was synthesized by cyclization of 1,4-dibromobutane with *N*,*N*′-bistosyl-4,4′-dithiodianiline (**2**),[14] which was prepared from dithiodianiline by a reaction with tosyl chloride. Acidic hydrolysis of **3** by hydrobromic acid in phenol gave **4**. Cationic cyclophane **1a** was synthesized by condensation of **4** with boc-*β*-alanine in the presence of dicyclohexylcarbodiimide (DCC), followed by a treatment with TFA. **1a** was then converted to a cyclophane having carboxylic acid residues **1b** by a reaction with succinic anhydride. In addition, a thiol derivative in the reduced form of the cyclophanes (**6**) was also obtained in the reduction of **1a** by using dithiothreitol (DTT). New compounds were fully characterized by means of spectroscopy (IR, ^{1}H and ^{13}C NMR, and TOF-MS) and elemental analysis (see the Supporting Information).

On the basis of the molecular mechanics studies of cyclophane **1a**, followed by molecular dynamics simulations,[15] **1a** was found to provide relatively large internal cavities with inner diameters of ca. 11−12 Å, as shown in Figure 3. Peripheral polar side chains with reasonably separated distances from the cavity were expected to confer the advantage of enhanced solubility in neutral aqueous media. From a practical standpoint, cyclophanes **1a** and **1b** had good H_2O solubilities of 220 and 6.7 mg/mL, respectively. These results indicate that **1a** and **1b** having hydrophobic cavities were expected to act as water-soluble hosts.

Scheme 1. Preparation of Cyclophanes Having Disulfide Moieties 1a and 1b



dx.doi.org/10.1021/jo400591w | J. Org. Chem. 2013, 78, 5463−5469

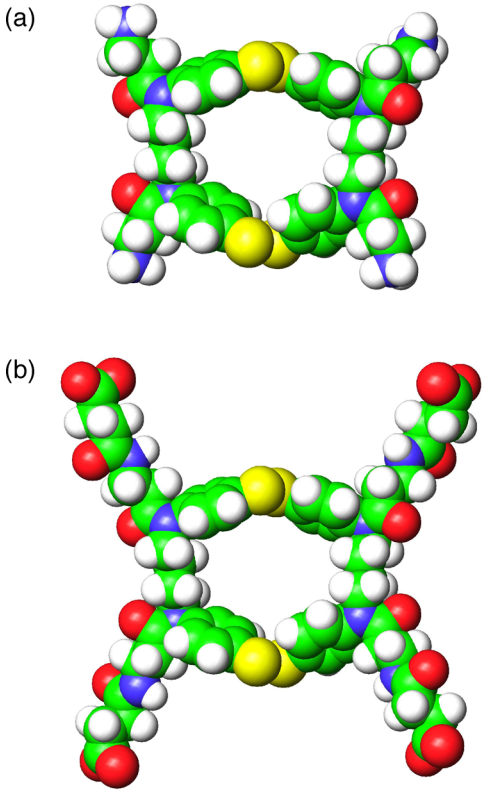


Figure 3. Computer-generated CPK models for **1a** (a) and **1b** (b). Carbon, hydrogen, oxygen, nitrogen, and sulfur atoms are shown in green, white, red, blue, and yellow, respectively.

Guest-Binding of Cyclophanes. The guest-binding affinity of **1a** toward anionic fluorescent guests, such as 4,4′-bis(1-anilinonaphthalene-8-sulfonate) (Bis-ANS)[16] and 4-(1-pyrene)butanoic acid (PBA)[17] (Figure 4), whose emissions are sensitive to change in the microenvironments experienced by molecules,[18] was examined by fluorescence spectroscopy in aqueous HEPES (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) buffer (0.01 M, pH 7.4, 0.15 M with NaCl) at 298 K. The fluorescence intensity that originated from Bis-ANS increased along with a concomitant blue shift of the fluorescence maximum upon addition of a large excess amount of **1a**, as shown in Figure 5. A similar fluorescent character was also observed for the complexation of **1a** with PBA (Figure 5), even though the fluorescence intensity originating from PBA was subject to decrease upon complexation. The present host was found to undergo complexation with the guests in a 1:1 molar ratio of host to guest, as confirmed by the Job's continuous variation method (see the Supporting Information). Binding constants for the formation of inclusion complexes of **1a** with the identical guests in a 1:1 molar ratio (K) were evaluated on the basis of the Benesi–Hildebrand relationship;[19] K = 6.7 × 10^3 and 4.5 × 10^4 M^{-1} for Bis-ANS and PBA, respectively. On the other hand, the fluorescence spectral changes were negligible upon addition of anionic cyclophane **1b** to the aqueous HEPES buffer containing Bis-ANS and PBA. Naturally, these anionic guests were not incorporated into the cavity of anionic cyclophane **1b**, reflecting an electrostatic repulsion.[20] By contrast, cationic fluorescent guests, such as 1-pyrenemethylamine hydrochloride (PMA),[21] were bound to anionic host **1b** (K, 1.5 × 10^4 M^{-1} for complexation with PMA), whereas **1a** showed almost no affinity for PMA. In addition, anionic host **1b** also binds cationic anticancer drugs,[22] such as daunorubicin hydrochloride (DNR) and doxorubicin hydrochloride (DOX), as shown in Figure 6. The K values for complexation of **1b** with DNR and DOX were evaluated to be 2.1 × 10^3 and 7.5 × 10^2 M^{-1}, respectively.

Small fluorescent guests, such as 6-*p*-toluidino-naphthalene-2-sulfonate (TNS), are frequently used as a suitable guest for water-soluble cyclophanes based on a tetraaza[6.1.6.1]paracyclophane skeleton.[18] However, TNS molecules were not incorporated into the large tetrathia-tetraaza[6.2.6.2]paracyclophane skeleton of **1a** (see the Supporting Information). These results suggested that **1a** was capable of performing size-sensitive molecular discrimination originating from the geometry of the hydrophobic cavity.

Reduction-Responsive Guest Release of Cyclophanes. Reduction of **1a** was investigated by ^{1}H NMR spectroscopy in CD_3OD at 298 K. Aromatic proton signals at 7.24 and 7.60 ppm originating from **1a** were disappearing in the presence of an excess amount of DTT (20 equiv) as a reducing agent, as shown in Figure 7. Newly appeared proton signals at 7.07 and 7.38 ppm were attributable to those of the reduced form of **1a**, which was identified with **6** (Figure 7). In addition, ESI-TOF

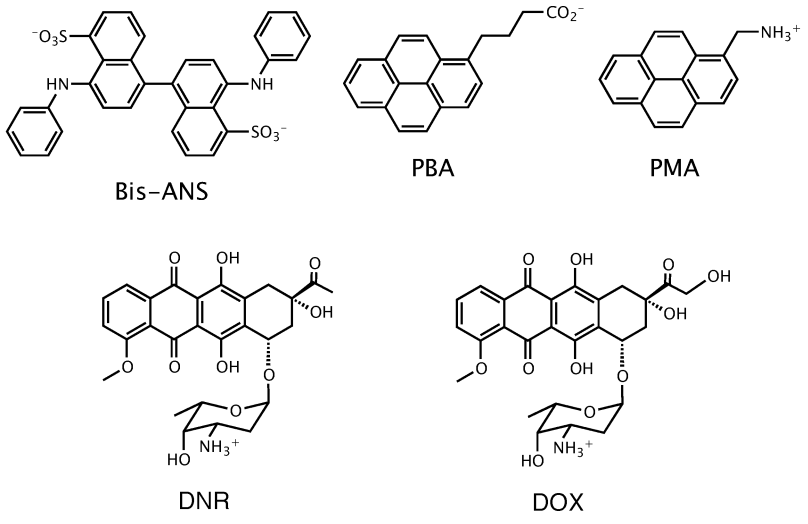


Figure 4. Hydrophobic fluorescent guests.

dx.doi.org/10.1021/jo400591w | J. Org. Chem. 2013, 78, 5463–5469

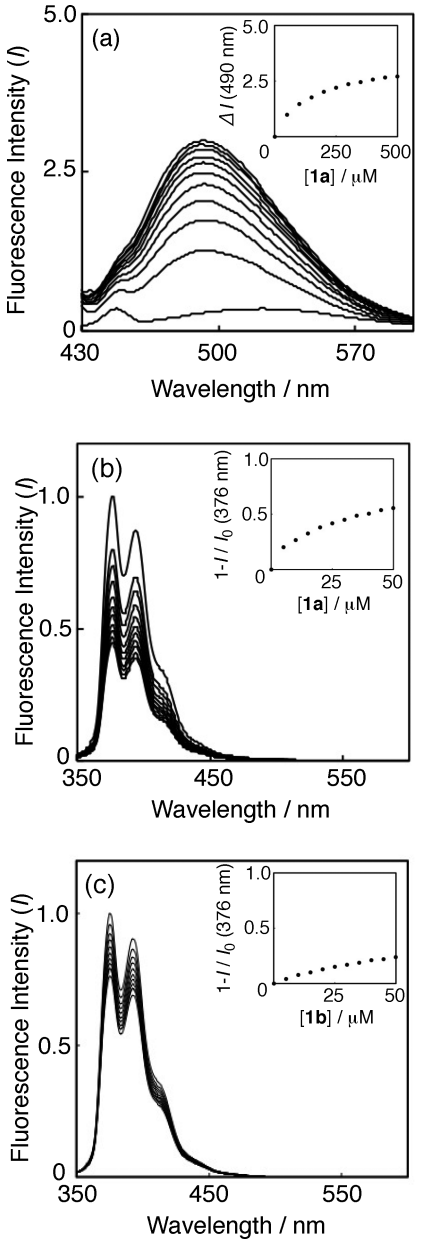


Figure 5. Fluorescence spectral changes for aqueous solutions of **1a** with Bis-ANS (a), **1a** with PBA (b), and **1b** with PMA (c) in HEPES buffer at 298 K. [Bis-ANS] = [PBA] = [PMA] = 1.0 μM. [**1**] (for Bis-ANS) = 0, 50, 100, 150, 200, 250, 300, 350, 400, 450, and 500 μM (from bottom to top). [**1a**] (for PBA) = [**1b**] (for PMA) = 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 μM (from top to bottom). Ex. 390, 322, and 322 nm for Bis-ANS, PBA, and PMA, respectively. Inset: the corresponding titration curves.

MS spectroscopy showed that thiol derivative **6** was predominantly obtained by this procedure, as shown in Figure 8; m/z 447.15 $[M + H]^+$. Similar reduction of **1a** was also observed by using glutathione (GSH) in place of DTT.

The reduction-responsive guest-releasing behavior of **1a** was investigated in a similar manner by fluorescence spectroscopy. Upon addition of DTT to a HEPES buffer solution containing host–guest complexes of **1a** with Bis-ANS, the fluorescence intensity that originated from the guest molecules was subject to decrease, as shown in Figure 9a. These results indicate that **6** has almost no guest-binding affinity[23] generated by the reduction of the disulfide bond of **1a** by DTT. Accordingly,

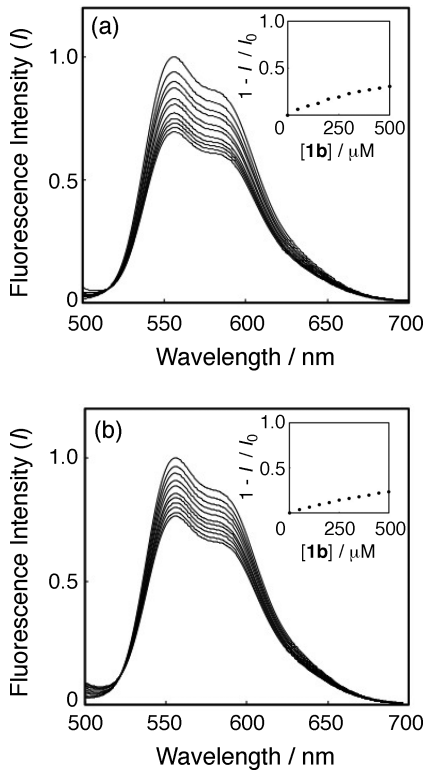


Figure 6. Fluorescence spectral changes for an aqueous solution of DNR (a) and DOX (b) upon addition of **1b** in HEPES buffer at 298 K. [DNR] = [DNR] = 2.5 μM. [**1**] = 0, 50, 100, 150, 200, 250, 300, 350, 400, 450, and 500 μM (from top to bottom). Ex. 460 nm. Inset: the corresponding titration curves.

almost entrapped guest molecules by **1a** were released to the bulk aqueous phase after 160 min of incubation, reflecting the reduction-responsive cleavage of the macrocycle. Similarly, upon addition of GSH (10 mM) to a HEPES buffer solution containing host–guest complexes of **1a** with Bis-ANS, a decrease in fluorescence intensity was also observed, reflecting the release of the entrapped guest molecules (Figure 9b). In addition, similar reduction-responsive guest releasing behavior of **1b** was also observed by using DNR and DOX as a guest (see the Supporting Information).

■ CONCLUSION

Water-soluble cyclophanes **1a** and **1b** having disulfide moieties were successfully synthesized. Cationic host **1a** bound anionic guests, such as Bis-ANS and PBA, whereas anionic host **1b** bound cationic guests, such as DNR and DOX. In addition, the entrapped guest molecules by the hosts were released to the bulk phase by a treatment with DTT. The degradation of the present cyclophanes and the guest release under reducing conditions, such as intracellular environments, is a future subject of interest to be carried out.

■ EXPERIMENTAL SECTION

1,2,21,22-Tetrathia-9,14,29,34-tetratosyl-9,14,29,34-tetraaza[6.2.6.2]paracyclophane (3). A solution of **2**[14] (4.6 g, 8.3 mmol) and 1,4-dibromobutane (1.8 g, 8.3 mmol) in dry *N*,*N*-dimethyl-formamide (DMF, 20 mL) were added dropwise to a solution of K_2CO_3 (5.7 g, 41 mmol) in DMF (40 mL) for 5 h at 90 °C, and the resulting mixture was stirred for 12 h at room temperature. The solution was stirred for overnight at room temperature. The resulting mixture was added to H_2O (300 mL) and stirred for 1 h at

dx.doi.org/10.1021/jo400591w | J. Org. Chem. 2013, 78, 5463–5469

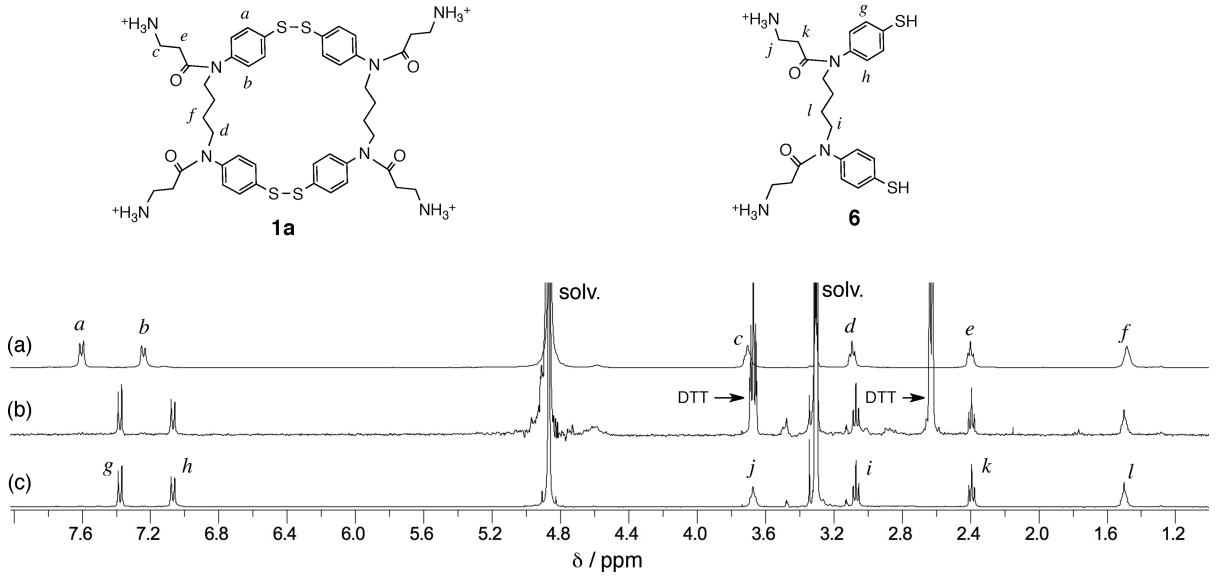


Figure 7. ^{1}H NMR spectra of **1a** (a) and **6** (c) in CD_3OD at 298 K. ^{1}H NMR spectrum of a solution of **1a** (0.5 mM) and DTT (10 mM) in CD_3OD at 298 K (b).

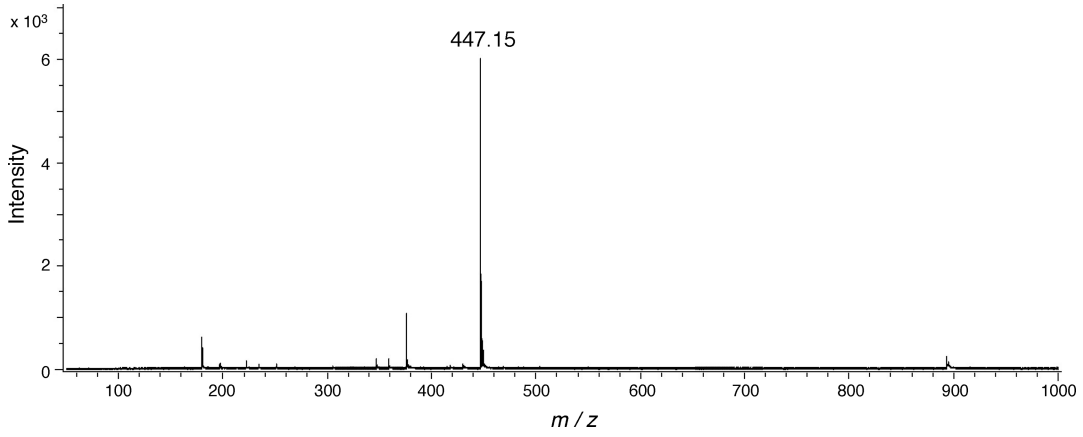


Figure 8. ESI-TOF MS spectra of a solution of **1a** (0.5 mM) and DTT (10 mM) in methanol.

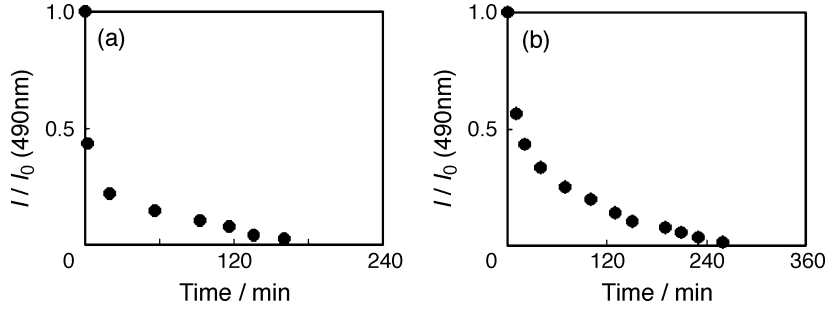


Figure 9. Time course for changes of fluorescence intensity originating from Bis-ANS (1.0 μM) in HEPES buffer in the presence of **1a** (50 μM) upon addition of DTT (5 mM) (a) and GSH (10 mM) (b) at 298 K.

room temperature. Precipitates were recovered by filtration, washed with H_2O, and dried under reduced pressure at room temperature to give a white solid. The mixture of the white solid and ethyl acetate (EtOAc, 100 mL) was refluxed for 1 h and cooled to room temperature. Precipitates were recovered by filtration, washed with EtOAc, and dried under reduced pressure at room temperature to give a white solid. The white solid was added to $CHCl_3$ (60 mL), and the resulting mixture was stirred for 1 h at room temperature. The separated precipitates were collected by filtration, washed with $CHCl_3$, and dried in vacuo to give a white solid. 2.8 g (55%): mp 140−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.40 (s, 8H), 2.41 (s, 12H), 3.52 (t, 8H), 6.83 (d, 8H), 7.23 (d, 8H), 7.37 (d, 8H), and 7.42 (d, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 21.8, 24.3, 49.0, 127.6, 127.9, 129.3, 135.0, 136.4, 138.1, and 143.9. IR 1643 cm^{-1} (SO_2−N). Found: C, 57.89; H, 4.87; N, 4.60. Calcd for $C_{60}H_{60}N_4O_8S_8{\cdot}H_2O$: C, 58.13; H, 5.04; N, 4.52. ESI-TOF MS: m/z 1256.84 $[M + Cl]^-$.

1,2,21,22-Tetrathia-9,14,29,34-tetraaza[6.2.6.2]paracyclophane (4). An aqueous hydrobromic acid solution (47%, 10 mL) was added dropwise to a solution of **3** (1.6 g, 1.3 mmol) and phenol (10 g, 0.12 mmol), and the resulting mixture was stirred for 1 h at 90 °C.

dx.doi.org/10.1021/jo400591w | J. Org. Chem. 2013, 78, 5463−5469

H_2O (200 mL) was added to the mixture, which was then washed with diethyl ether (300 mL). The pH of the solution was adjusted to 11 by adding sodium hydroxide, and extracted with $CHCl_3$ (100 mL × 3). The combined organic phase was washed with 5% aqueous sodium hydroxide (50 mL) and saturated aqueous sodium chloride (50 mL) in this sequence. After being dried (Na_2SO_4), the solution was evaporated to dryness under reduced pressure to give a pale yellow solid. 300 mg (38%): mp 146−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.73 (s, 8H), 3.17 (m, 8H), 3.83 (t, 4H), 6.48 (d, 8H), and 7.27 (d, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 27.1, 43.5, 113.2, 124.3, 134.5, and 148.8. IR 3395 cm^{-1} (N−H). Found: C, 63.57; H, 6.08; N, 9.02. Calcd for $C_{32}H_{36}N_4S_4$: C, 63.54; H, 6.00; N, 9.26. ESI-TOF MS: m/z 639.05 $[M + Cl]^-$.

Cyclophane Bearing Boc-Protected Amines (5). Dicyclohexylcarbodiimide (99 mg, 0.48 mmol) was added to a solution of Boc-β-Ala-OH (91 mg, 0.48 mmol) in dry dichloromethane (DCM, 2 mL) at 0 °C, and the mixture was allowed to stand at the same temperature while being stirred for 20 min. The mixture was added to a solution of **4** (47 mg, 0.08 mmol,) in dry DCM (5 mL), and the resulting mixture was stirred for 3 days at room temperature. Precipitates that formed (*N*,*N*′-dicyclohexylurea) were removed by filtration, the solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc (20 mL). Insoluble materials were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (SiO_2) with EtOAc as an eluent. Evaporation of the product fraction under reduced pressure gave a white solid. 65 mg (63%): mp 100−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 1.42 (s, 44H), 1.46 (s, 8H), 2.12 (m, 8H), 3.26 (m, 8H), 3.65 (m, 8H), 5.26 (m, 4H), 7.02 (d, 8H), and 7.49 (d, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 25.0, 28.7, 35.1, 36.6, 48.7, 79.3, 128.1, 129.2, 137.0, 141.2, 156.1, and 171.6. IR 1645 cm^{-1} (C═O), 3332 cm^{-1} (N−H), 1166 cm^{-1} (C−O, Boc). Found: C, 58.81; H, 6.83; N, 8.63. Calcd for $C_{64}H_{88}N_8O_{12}S_4{\cdot}H_2O$: C, 58.78; H, 6.94; N, 8.63. ESI-TOF MS: m/z 1311.03 $[M + Na]^+$.

Cationic Cyclophane Having Disulfide Moieties (1a). Trifluoroacetic acid (TFA, 0.25 mL) was added to a solution of compound **5** (65 mg, 0.05 mmol) in dry DCM (1.5 mL), and the mixture was stirred for 2 h at room temperature. After the solvent was evaporated off under reduced pressure, DCM (5 mL) was added to the residue, and this procedure was repeated three times to remove remaining TFA. Evaporation of the solvent under reduced pressure gave a pale white solid. The crude product was purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol as an eluent. Evaporation of the product fraction under reduced pressure gave a white solid (triamine derivative of cyclophane as the trifluoroacetic acid salt). 59 mg (88%): mp 118−121 °C. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 1.49 (m, 8H), 2.40 (t, 8H), 3.09 (t, 8H), 3.71 (m, 8H), 7.24 (d, 8H), and 7.60 (d, 8H). ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 24.4, 31.4, 35.7, 118.5, 28.1, 129.2, 137.1, 140.7, 161.6, and 170.1. IR 1634 cm^{-1} (C═O). Found: C, 44.75; H, 4.75; N, 8.13. Calcd for $C_{52}H_{60}F_{12}N_8O_{12}S_4{\cdot}3H_2O$: C, 44.63; H, 4.75; N, 8.01. ESI-TOF MS: m/z 889.32 $[M + H]^+$, where M denotes the tetraamine derivative of cyclophane as the free base.

Anionic Cyclophane Having Disulfide Moieties (1b). Succinic anhydride (119 mg, 1.20 mmol) was added to a solution of **1a** (200 mg, 0.15 mmol) and triethylamine (0.2 mL) in dry DCM (4 mL) at room temperature, and the mixture was stirred for 1 day. The solution was evaporated to dryness under reduced pressure to give a white solid. The crude product was purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol as an eluent. Evaporation of the product fraction under reduced pressure gave a white solid. The resulting sodium salt was converted into the free acid by ion-exchange chromatography on a column of Amberlite IR-120B with methanol as an eluent. Evaporation of the product fraction under reduced pressure gave a white solid. 160 mg (83%): mp 96−98 °C. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 1.47 (s, 8H), 2.20 (t, 8H), 2.38 (t, 8H), 2.52 (t, 8H), 3.67 (m, 8H), 7.17 (d, 8H), and 7.56 (d, 8H). ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 24.6, 29.0, 30.3, 33.9, 35.6, 51.0, 128.3, 129.2, 136.7, 141.4, 171.6 173.3, and 175.0. IR 1727 cm^{-1} (COOH). Found: C, 55.27; H, 5.87; N, 8.65. Calcd for $C_{60}H_{72}N_8O_{16}S_4{\cdot}H_2O$: C, 55.11; H, 5.70; N, 8.57. ESI-TOF MS: m/z 1289.44 $[M + H]^+$.

Reduced Form of 1a (6). Dithiothreitol (18 mg, 0.12 mmol, 12 equiv) was added to a solution of **1a** (15 mg, 0.01 mmol) in methanol (2 mL), and the resulting mixture was stirred for 4 days at room temperature. The solution was evaporated to dryness under reduced pressure. The crude product was purified by gel filtration chromatography on a column of Sephadex LH-20 with methanol as an eluent. Evaporation of the product fraction under reduced pressure gave a white solid. (19 mg, quantitative): mp 60−63 °C. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 1.50 (m, 4H), 2.40 (t, 4H), 3.08 (m, 4H), 3.34 (s, 2H), 3.69 (m, 4H), 7.07 (d, 8H), and 7.38 (d, 8H). ^{13}C NMR (100 MHz, CD_3OD, 298 K) δ 25.6, 31.3, 35.8, 128.1, 128.4, 128.8, 129.2, 129.9, 170.1, and 170.3. IR 1630 cm^{-1} (C═O), 1174 cm^{-1} (N−H). Found: C, 45.24; H, 4.94; N, 7.84. Calcd for $C_{26}H_{32}F_6N_4O_6S_2{\cdot}H_2O$: C, 45.08; H, 4.95; N, 8.09. ESI-TOF MS: m/z 469.10 $[M + Na]^+$, where M denotes the diamine derivative of cyclophane as the free base.

Binding Constants of Cyclophane with Fluorescence Guests. To each solution of a fluorescent guest (1.0 μM) in HEPES buffer were added increasing amounts of the hosts at 298 K, and the guest fluorescence intensity was monitored after each addition by excitation at 390, 322, 322, 460, and 460 nm for Bis-ANS, PBA, PMA, DNR, and DOX, respectively. An aqueous stock solution of **1b** was prepared after addition of NaOH. The binding constants were calculated on the basis of the Benesi−Hildebrand method for titration data.

Computational Procedure. The calculations were carried out on a Pentium 4 3.2 GHz x 2 machine using MacroModel 9.1 molecular modeling software on a Red Hat Enterprise Linux WS 4.3 operating system. Molecular mechanics and molecular dynamics methods were utilized at arriving at the optimized structures. The geometry of **1a** and **1b** was optimized using molecular mechanics employing the OPLS_2005 force field for the simulation of the hosts. The geometry was optimized without any constraints, allowing all atoms, bonds, and dihedral angles to change simultaneously. The dielectric was set to distance dependent with a scale factor of 1. A 1 ps molecular dynamics was carried out in vacuo using the molecular mechanics OPLS_2005 force field under constant temperature conditions (300 K).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for compounds **3**, **4**, **5**, **1a**, **1b**, and **6**; Job plots; and additional fluorescence titration spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The present work is partially supported by a Grant-in-Aid (No. 24550166) from the Ministry of Education, Culture, Science, Sports and Technology of Japan.

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