Articles

Synthesis and Guest Binding Properties of Cyclophanes Containing Two Benzo[*b*]furan Rings†

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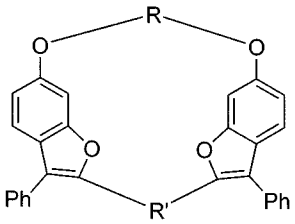
The cyclophanes **1a-d** containing two benzo[*b*]furan rings connected by various bridges have been prepared and their binding behaviors with *N*-benzylphenethylammonium cation **2** were examined by NMR titration method. The successive alkylation reactions of 4-hydroxyl groups and then 2-hydroxyl groups of 2,4-dihydroxybenzophenonse gave macrocycles **5a-c**. Photoirradiation of the macrocycles **5a-c** with 350 nm mercury lamp followed by dehydration afforded the cyclophanes **1a-c**. Hydrolysis of two ester groups pendant on a bridge of **1b** produced the carboxyl group-containing cyclophane **1d**. The cyclophane **1a** having a *p*-xylene bridge showed 1 : 1 binding with **2** with the binding constant of 36 ± 6 M^{-1} in 3 : 1 $CDCl_3$/methanol-d_4 solvent, while **1b** and **1c** which have neutral flexible bridges exhibited no appreciable binding with **2**. The disodium salt of **1d** showed much higher binding affinity for **2** forming 1 : 1 and 1 : 2 complexes.

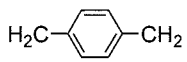
Key Words : Benzo[*b*]furan, Cyclophane, Guest binding

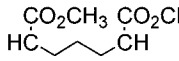
Introduction

Cyclophanes are macrocyclic organic host molecules containing aromatic rings and bind both neutral and cationic guests through π-π, electron donor-acceptor, or cation-π interactions. It is well recognized that cyclophanes have a wide range of applicability in emerging technology as synthetic receptors in molecular recognition, sensors, and molecular motors or their elements.[1,2] Because of this, the design and synthesis of novel cyclophanes and studies on the guest binding properties have become a fascinating branch of organic and supramolecular chemistry.[1,2] However, bridged aromatic groups in the cyclophanes are mostly carbocyclic rings such as benzene and naphthalene derivatives. Heteroaromatic ring-containing cyclophanes are usually limited to pyrrole- and pyridine-containing ones. We consider that the main reason for this is lack of versatile methods to prepare appropriately bridged heterocyclic aromatic systems. Recently, we reported simple synthetic routes to various benzofuran- or benzodifuran ring-containing cyclophanes via photocyclization technique.[3,4] Here, we describe the synthesis of the cyclophanes **1a-d** containing two benzo[*b*]furan rings linked by various bridges and their complexation behaviors with *N*-benzylphenethylammonium cation **2**. The cyclophanes **1a-d** were chosen since the polyether unit in **1a** and **1c** is generally known to exhibit good binding affinity for ammonium cations, and the carboxyl groups in **1d** are expected to increase the interaction with the cations.

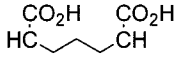


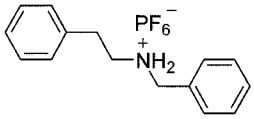
1a-d

a : R =  R' = $CH_2(OCH_2CH_2)_2OCH_2$

b : R =  R' = $(CH_2)_{10}$

c : R = $CH_2(CH_2OCH_2)_3CH_2$ R' = $CH_2(OCH_2CH_2)_2OCH_2$

d : R =  R' = $(CH_2)_{10}$



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†This paper is dedicated to Prof. Yong Hae Kim on the occasion of his retirement from the Department of Chemistry, KAIST

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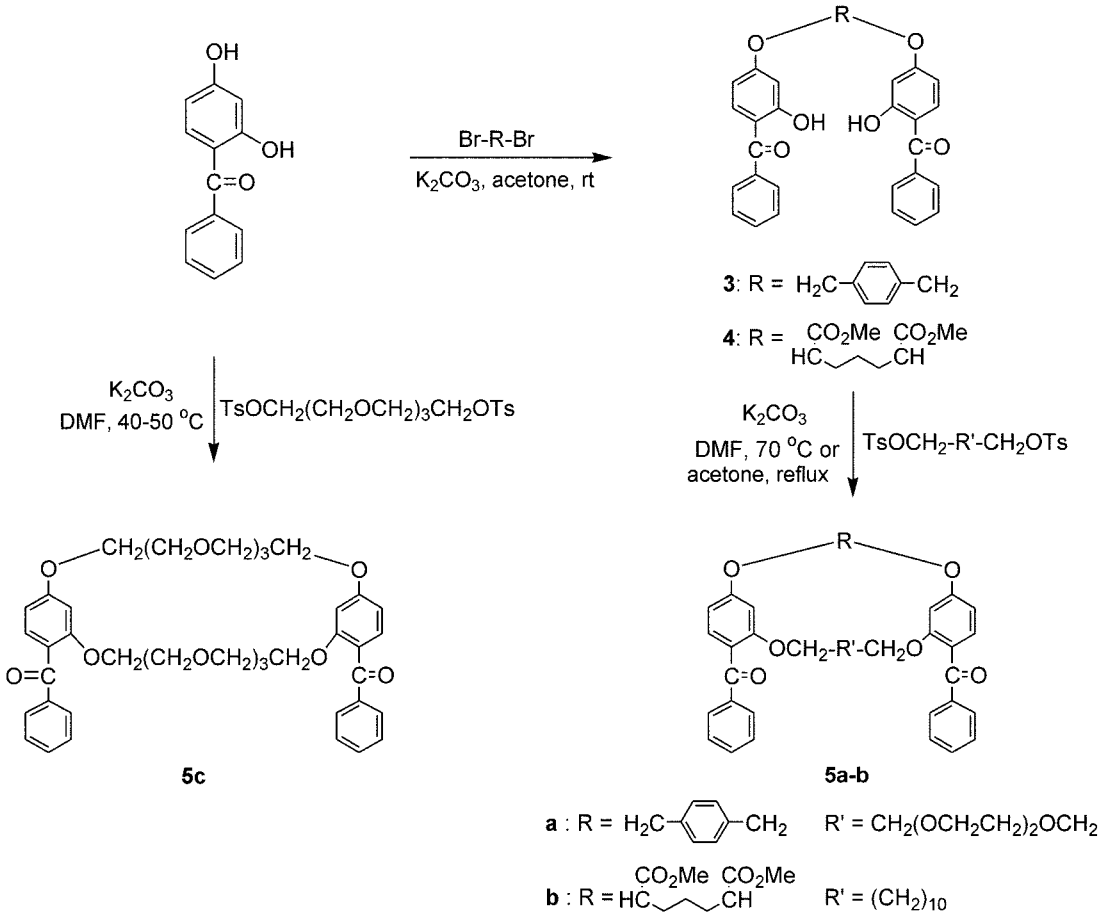
Results and Discussion

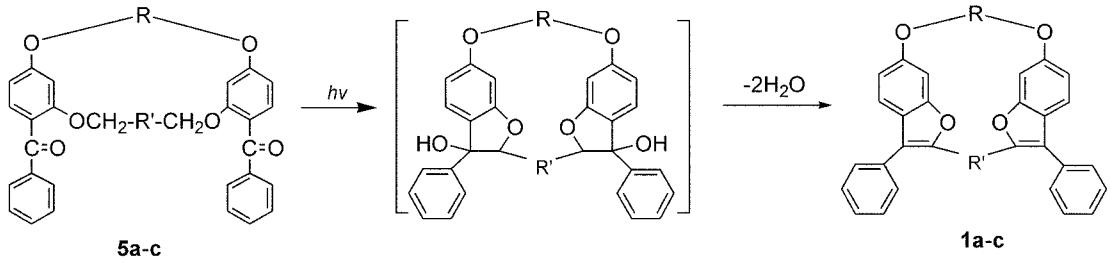
The precursor macrocycles **5a-c** were prepared by successive alkylation reactions of 4-hydroxyl groups and then 2-hydroxyl groups of 2,4-dihydroxybenzophenones, utilizing differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone (Scheme 1).[3] Reaction of 2,4-dihydroxybenzophenone with 0.6 molar ratio of α,α-dibromo-*p*-xylene or dimethyl 2,6-dibromoheptanedioate in acetone at room temperature in the presence of potassium carbonate resulted in selective alkylations at the 4-hydroxyl groups to afford **3** and **4** in 95% and 71% yield, respectively. Further reaction of the compounds **3** and **4** with tetra(ethylene glycol) di-*p*-tosylate or 1,12-dibromododecane in acetone at reflux in the presence of potassium carbonate provided the macrocycles **5a** and **5b** with 34% and 44% yields, respectively. The macrocycle **5c** was prepared in one step from 2,4-dihydroxybenzophenone in 49% yield by reacting with a slight molar excess of tetra(ethylene glycol) di-*p*-tosylate.

It is well known that *o*-alkoxybenzophenones photocyclize readily to benzofuranols *via* δ-hydrogen abstraction.[3-7] The photocyclization of two *o*-alkoxybenzophenone moieties of **5a-c** followed by dehydration produced the cyclophanes **1a-c**: after irradiating a 1 mM benzene[8] solution of **5a-c** with a 350 nm light for 5-6 h, the reaction mixture showed virtually no starting material remaining. Without attempting the isolation and separation of the intermediates, a dehydration reaction was carried out by treating the concentrated reaction mixture with a few drops of 1 M HCl in acetone (Scheme 2). Silica gel column chromatography afforded the desired cyclophanes **1a-c** with 36, 49, and 58% yields, respectively. Hydrolysis of the ester groups of **1b** using aqueous ethanolic solution of NaOH gave the disodium salts of the cyclophane **1d** with 98% yield.

We envisioned that the newly prepared cyclophanes **1a-d** could bind aromatic ring-containing cations through π-π and/or cation-π interactions. In addition, the cyclophanes **1a** and **1c** having polyether moiety and the cyclophane **1d** having two carboxyl groups are expected to bring increased interactions with ammonium ions by coordination and electrostatic interaction, respectively. Thus, we studied complexation behaviors of the cyclophanes **1a-d** with *N*-benzylphenethylammonium cation **2** by NMR titration method. A series of NMR spectra of **2** were taken with varying concentration ratios of the cyclophane to **2**, $[\text{host}]_o/[\mathbf{2}]_o = \gamma$, at fixed concentration of **2**. Figure 1 shows a typical change of ^{1}H NMR peaks of **2** upon the addition of the cyclophanes. It is clearly seen that the chemical shifts of **2** moved upfield upon addition of the cyclophane **1a**. The magnitudes of the complexation-induced-chemical shift $\Delta\delta$ (δ value of the guest in the presence of the cyclophane $-\delta$



Scheme 1. Synthetic pathway for the macrocycles **5a-c**.



a: R = *p*-xylylene; R' = $CH_2(OCH_2CH_2)_2OCH_2$

b: R = $HC(CO_2Me)CH(CO_2Me)(CH_2)_3CH$; R' = $(CH_2)_{10}$

c: R = $CH_2CH_2(OCH_2CH_2)_3$; R' = $CH_2(OCH_2CH_2)_2OCH_2$

d: R = $HC(CO_2H)CH(CO_2H)(CH_2)_3CH$; R' = $(CH_2)_{10}$

Scheme 2. The synthesis of the cyclophanes **1a-d**.

value of the free guest) are measured. Assuming 1:1 complexation between the cyclophane and **2**, $\Delta\delta$ is related to the concentration ratio γ and the binding constant of **2** with the cyclophane K by the equation (1).[9]

$$\Delta\delta = 0.5\,\Delta\delta_c\,[1 + \gamma + 1/K[\mathbf{2}]_o - \{(\gamma - 1 + 1/K[\mathbf{2}]_o)^2 + 4/K[\mathbf{2}]_o\}^{1/2}] \quad (1)$$

where $\Delta\delta_c$ is the chemical shift change expected when all of the guest molecules form the complex.

We followed the chemical shift of the singlet peak for the methylene protons (N-CH_2Ph) of **2**. Figure 2 shows the dependence of $\Delta\delta$ of the methylene protons of **2** on the initial concentration ratio of $[\text{cyclophane}]_o/[\mathbf{2}]_o$. The experimental data of **1a**/**2** system fit well to the equation (1) and the binding constant K in 49 : 1 $CDCl_3$/DMSO-d_6 solvent (Figure 2a) is found to be $27 \pm 2\ M^{-1}$ and the $\Delta\delta_c$ value is 0.42 ± 0.02. The similar NMR titration results of **2** with **1a** in 3 : 1 $CDCl_3$/methanol-d_4 (Figure 2b) gave similar K and $\Delta\delta_c$ values as $36 \pm 6\ M^{-1}$ and 0.46 ± 0.03. On the contrary to the significant upfield shift of **2** in the presence of **1a**, the cyclophanes **1b** and **1c** resulted in no appreciable changes of the chemical shifts of **2** suggesting little binding tendency of **2** with the cyclophanes. The bridges of **1b** and **1c** might be too flexible to form the entropically disfavored complexes with **2**.

The addition of disodium salt of the cyclophane **1d**, **1d**·2Na also shifted ^{1}H NMR peaks of **2** upfield. Variation of the chemical shift of the singlet peak for methylene protons (N-CH_2Ph) of **2** depending upon the concentration ratio of

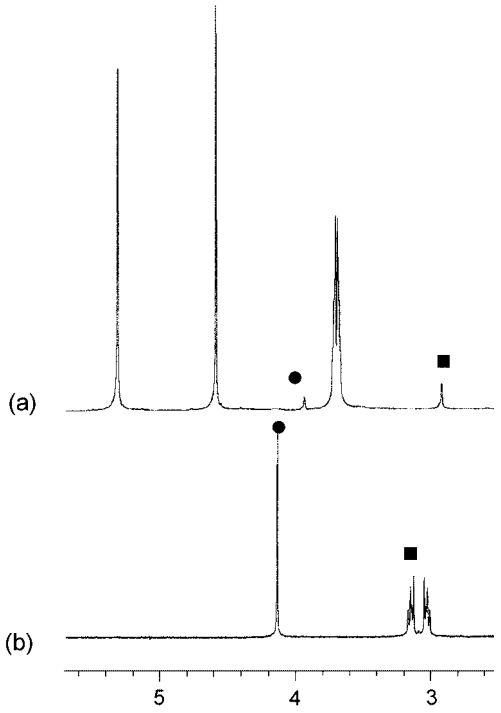


Figure 1. Partial ^{1}H NMR spectra (400 MHz, 49 : 1 $CDCl_3$/DMSO-d_6, 25 °C) of (a) **2** (6.0 mM), (b) **2** (6.0 mM) + **1a** (43 mM): ● and ■ are the peaks from N-CH_2Ph and N-CH_2CH_2Ph of **2**, respectively.

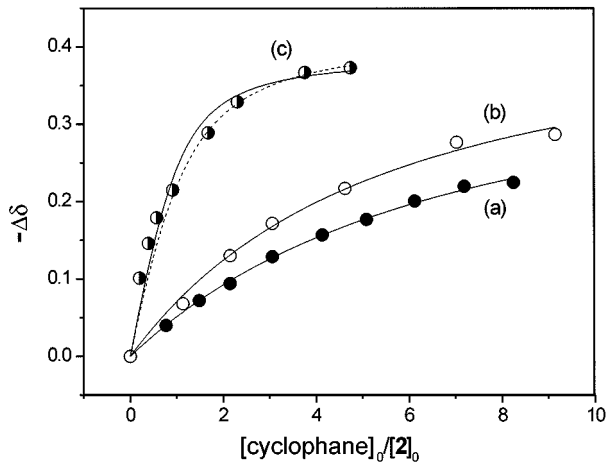


Figure 2. Variation of the complexation-induced chemical shift, $\Delta\delta$ of the methylene protons (N-CH_2Ph) of **2** with the ratios of $[\text{cyclophane}]_o/[\mathbf{2}]_o$. The concentration of **2** was fixed at 6.0 mM. (a, ●), **1a** in 49 : 1 $CDCl_3$/DMSO-d_6; (b, ○), **1a** in 3 : 1 $CDCl_3$/methanol-d_4; (c, ◑), **1d**·2Na in 3 : 1 $CDCl_3$/methanol-d_4. The solid lines are fitted lines to the equation (1) and the dotted line in (c) is the fitted line using only four data points above $[\mathbf{1d}\cdot 2\text{Na}]_o/[\mathbf{2}]_o = 1$.

[**1d**·2Na]$_o$/[**2**]$_o$ in 3 : 1 $CDCl_3$/methanol-d_4 solvent are also shown (Figure 2c). As can be seen from the Figure 2, the dependence of $\Delta\delta$ on the [cyclophane]$_o$/[**2**]$_o$ ratio is much greater for the cyclophane **1d**·2Na than **1a**. This indicates stronger binding of **2** to **1d**·2Na than to **1a**. The data of **1d**·2Na/**2** system fit poorly to the equation (1): a large uncertainty is found in the fitted parameters, K = 730 ± 350 M^{-1} and $\Delta\delta_c$ = 0.39 ± 0.03.

Since the equation (1) is derived on the assumption that 1 : 1 complex is formed between the cyclophane and **2**, we thought that the poor fitting to equation (1) might be due to the formation of 1 : 2 complex between **1d**·2Na and **2**. The formation of the 1 : 2 complex is well expected from electrostatic point of view as the cyclophane bears two carboxylate groups, while the guest is monocationic. To see that **1d**·2Na and **2** really form 1 : 2 complex, Job plot was attempted by following the chemical shift of the methylene protons (N-*CH*$_2$Ph) of **2** in the mixtures of various initial concentration ratio of **1d**·2Na to **2** keeping the total concentration ([**1d**·2Na]$_o$+ [**2**]$_o$) constant.[9a] The shape of Job plot (not shown) of $\Delta\delta$[**2**]$_o$/([**1d**·2Na]$_o$ + [**2**]$_o$) *vs*. [**2**]$_o$/([**1d**·2Na]$_o$ + [**2**]$_o$) was different from that of a typical 1 : 2 complexation:[9a] the maximum was shown near [**2**]$_o$/([**1d**·2Na]$_o$ + [**2**]$_o$) = 0.6 instead of 0.67 and $\Delta\delta$[**2**]$_o$/([**1d**·2Na]$_o$ + [**2**]$_o$) value was higher than the expected value when [**2**]$_o$/([**1d**·2Na]$_o$ + [**2**]$_o$) is less than 0.6. Considering that Job plot works best when only a single complex species is present, the failure of a typical bell-shaped curve indicates that the system forms 1 : 1 complex as well as 1 : 2 complex from following two equilibria:

$$\textbf{1d}\cdot 2Na + \textbf{2} \rightleftharpoons C1 \qquad K_1 = [C1]/([\textbf{1d}\cdot 2Na][\textbf{2}]) \qquad (2)$$

$$C1 + \textbf{2} \rightleftharpoons C2 \qquad K_{12} = [C2]/([C1][\textbf{2}]) \qquad (3)$$

where C1 and C2 denote the 1 : 1 and 1 : 2 complexes, respectively.

Analysis of NMR data by the multiple equilibria is highly complicated as any one of the interacting species is not in far excess of the other due to the experimental limitations. However, the binding constants can be reasonably estimated from the titration data using the following method. As negative cooperativity is expected in the successive binding of **2** to **1d**·2Na, the K_1 value should be greater than K_{12}. Therefore, the 1 : 2 complex C2 would be the predominant complexed species when the concentration ratio of [**1d**·2Na]$_o$/[**2**]$_o$ << 1, while the 1 : 1 complex C1 is the major complexed species when [**1d**·2Na]$_o$/[**2**]$_o$ > 1. For the former case, we can assume a simple 1 : 2 complexation with the binding constant of K_2, which is equivalent to K_1K_{12}. Close examination of the NMR titration results of **2** with **1d**·2Na (Figure 2c) reveals a biphasic pattern divided near [**1d**·2Na]$_o$/[**2**]$_o$ = 1. Fitting of the data of [**1d**·2Na]$_o$/[**2**]$_o$ > 1 to equation (1) gave the K_1 and $\Delta\delta_c$ values as 400 ± 35 M^{-1} and 0.42 ± 0.01, respectively. The K_1 value is about one order of magnitude greater than that of **1a**/**2** binding, presumably due to contribution from electrostatic interaction. Neither K_{12} nor K_2 could be obtained analytically. However, the lower limit of the value is estimated numerically by assuming a simple 1 : 2 complexation equilibrium when [**1d**·2Na]$_o$/[**2**]$_o$ is less than 0.5. Taking a trial $\Delta\delta_c$ value, the fraction of complexed **2** was evaluated from $\Delta\delta$, and then the concentrations of uncomplexed **2** and **1d**·2Na were calculated. Using these values, the 1 : 2 complexation constant K_2 was estimated. The trial $\Delta\delta_c$ was varied until reasonably consistent K_2 value from the first three data points in Figure 2c is obtained. The best consistency was found with $\Delta\delta_c$ = 0.39 and the K_2 value was estimated as about 8×10^4 M^{-2}: this gives the second binding constant K_{12} of **2** to **1d**·2Na defined in the equation (3) as 200 M^{-1} from $K_2 = K_1K_{12}$ relationship.

In summary, we prepared novel cyclophanes **1a-d** containing two benzo[*b*]furan rings and studied their binding behaviors with *N*-benzylphenethylammonium cation **2** by NMR titration method. The cyclophane **1a** having a *p*-xylylene bridge forms 1 : 1 complex with **2** with the binding constant of 36 ± 6 M^{-1} in 3 : 1 $CDCl_3$/methanol-d_4 solvent. The cyclophanes **1b** and **1c** which have flexible bridges exhibit no appreciable binding with **2**. The disodium salt of the dianionic cyclophane, **1d**·2Na, binds two molecules of **2** with the first binding constant of 400 ± 35 M^{-1} and the second binding constant of about 200 M^{-1}. We attribute the higher binding affinity of **1d**·2Na than those of other cyclophanes to the electrostatic interaction and the more favorable interaction of **1a** than **1c** to rigid cavity of **1a**.

Experimental Section

All reagents were purchased from Aldrich Chemical Co. and used as received. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400/100 MHz using tetramethylsilane as an internal standard. High-field NMR measurements and elemental analyses were performed at the Central Research Facilities of Chungnam National University.

1,4-Bis(4-benzoyl-3-hydroxyphenoxymethyl)benzene, 3. The compound **3** was prepared with 95% yield by a method described previously.[3] The spectroscopic data were identical with the previous report,[3] but the melting point (mp 220 °C) is higher than the reported value,[3] mp 175-176 °C.

Dimethyl 2,6-bis(4-benzoyl-3-hydroxyphenoxy)heptanedioate, 4. To the suspension of 2,4-dihydroxybenzophenone (3.00 g, 14.0 mmol) and K_2CO_3 (7.74 g, 56.0 mmol) in acetone (100 mL) was added a solution of dimethyl 2,6-dibromoheptanedioate (2.42 g, 7.00 mmol) in acetone (20 mL) very slowly under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 75 h. After K_2CO_3 was removed by filtration, the reaction mixture was concentrated. Water (50 mL) was added to the concentrated filtrate and extracted with dichloromethane three times. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (eluent: 2 : 1 hexane/ethyl acetate) gave the compound **4** (3.06 g, 71% yield), together with the unreacted starting material (0.55 g, 18% recovery): mp 61-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.80 (m, 2H), 2.01-2.09 (m, 4H), 3.78 (s, 6H), 4.73 (t, 2H, J = 6 Hz),

6.38-6.43 (m, 4H), 7.45-7.64 (m, 12H), 12.60 (s, 2H).

Macrocycle 5a. To a suspension of **3** (1.38 g, 2.60 mmol) and potassium carbonate (2.16 g, 15.6 mmol) in DMF (220 mL) at 70 °C was added a solution of tetra(ethylene glycol) di-p-tosylate (1.33 g, 2.65 mmol) in DMF (50 mL) very slowly over 10 h using a syringe pump under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 48 h and then the solvent was removed under reduced pressure. To the residue, water (10 mL) was added and extracted with dichloromethane three times. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (eluent: 2 : 1 dichloromethane/ethyl acetate) gave the compound **5a** (0.61 g, 34% yield): mp 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35-3.39 (m, 8H), 3.45-3.48 (m, 4H), 3.89 (t, 4H, *J* = 5 Hz), 5.20 (s, 4H), 6.52 (d, 2H, *J* = 3 Hz), 6.69 (dd, 2H, *J* = 9 & 2 Hz), 7.36-7.43 (m, 10H), 7.49 (t, 2H, *J* = 8 Hz), 7.72 (dd, 4H, *J* = 8 & 1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.22, 69.11, 69.97, 70.49, 70.62, 101.12, 108.11, 122.01, 127.65, 127.91, 129.43, 132.01, 132.12, 136.68, 139.11, 158.86, 162.15, 195.60. Anal. Calcd for $C_{42}H_{40}O_9$: C, 73.24; H, 5.85; Found: C, 73.06; H, 6.13.

Macrocycle 5b. The reaction mixture of **4** (1.00 g, 1.63 mmol), 1,12-dibromododecane (0.80 g, 2.45 mmol) and potassium carbonate (1.35 g, 9.78 mmol) in acetone (200 ml) was heated at reflux for 42 h under nitrogen atmosphere. The reaction mixture was worked-up in the same way as described in the synthesis of **4** to afford **5b** (0.56 g, 44% yield): mp 98-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-1.25 (m, 16H), 1.42 (quintet, 4H, *J* = 7 Hz), 1.68-2.15 (m, 6H), 3.78 & 3.79 (two s, 6H), 3.84 (t, 4H, *J* = 7 Hz), 4.74-4.78 (m, 2H), 6.39 & 6.40 (two dd, 2H, *J* = 8 & 2 Hz), 6.59 & 6.60 (two d, 2H, *J* = 2 Hz), 7.36-7.43 (m, 6H), 7.48-7.53 (m, 2H), 7.72-7.75 (m, 4H). Anal. Calcd for $C_{47}H_{54}O_{10}$: C, 72.47; H, 6.99; Found: C, 72.30; H, 6.79.

Macrocycle 5c. To the suspension of 2,4-dihydroxybenzophenone (3.00 g, 14.0 mmol) and K_2CO_3 (9.62 g, 70 mmol) in DMF (300 ml) was added a solution of tetra(ethylene glycol) di-p-tosylate (8.45 g, 16.8 mmol) in DMF (50 mL) at 40-50 °C very slowly under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 40 h and then worked-up in the same way as described in the synthesis of **5a** to afford **5c** (2.54 g, 49% yield) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58-3.63 (m, 16H), 3.70-3.73 (m, 4H), 3.85 (t, 4H, *J* = 5 Hz), 4.13 (t, 4H, *J* = 5 Hz), 4.35 (t, 4H, *J* = 5 Hz), 6.60 (dd, 2H, *J* = 8 & 2 Hz), 7.21 (d, 2H, *J* = 2 Hz), 7.35-7.43 (m, 6H), 7.51 (t, 2H, *J* = 7 Hz), 7.75-7.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.73, 69.41, 69.89, 70.64, 70.72, 70.75, 70.77, 70.82, 102.98, 109.86, 122.08, 127.88, 129.51, 131.39, 132.12, 139.06, 159.63, 162.87, 195.85. Anal. Calcd for $C_{42}H_{48}O_{12}$: C, 67.73; H, 6.50; Found: C, 67.44; H, 6.79.

Photocyclization/dehydration reaction of 5a-c to 1a-c. 1.0 mM Benzene[8] solution of the compound **5a-c** contained in Pyrex glass vessel was purged with nitrogen for 1 h and then irradiated under nitrogen with 350 nm mercury lamps using RPR-100 photochemical reactor (Sourthern New England Ultraviolet Company). After 5-8 h of irradiation, the reaction mixture was concentrated and the residue was dissolved in 5 mL of acetone. The acetone solution was treated with a few drops of 1 M HCl and stirred for 1-2 h. Water was added to the reaction mixture, and extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (eluent: 40 : 1 dichloromethane/ethyl acetate for **1a**; 2 : 1 hexane/ethyl acetate for **1b**; 1 : 1 hexane/ethyl acetate for **1c**) gave the desired cyclophanes **1a-c**.

1a. 36% yield: mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 3.64-3.70 (m, 8H), 4.55 (s, 4H), 5.30 (s, 4H), 6.86 (d, 2H, *J* = 2 Hz), 7.00 (dd, 2H, *J* = 8 & 2 Hz), 7.34-7.39 (m, 2H), 7.36 (s, 4H), 7.43-7.52 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6) δ 63.41, 68.87, 69.50, 70.01, 96.17, 113.48, 120.21, 120.40, 120.67, 125.75, 127.03, 128.33, 128.45, 131.40, 136.33, 148.60, 154.64, 156.48. Anal. Calcd for $C_{42}H_{36}O_7$: C, 77.28; H, 5.56; Found: C, 76.94; H, 5.77.

1b. 49% yield: mp 65-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.31 (m, 12 H), 1.67-2.12 (m, 10H), 2.83 (t, 4H, *J* = 6 Hz), 3.77 & 3.78 (two s, 6H), 4.62-4.68 (m, 2H), 6.80 & 6.81 (two dd, 2H, *J* = 8 & 2 Hz), 7.04 & 7.05 (two d, 2H, *J* = 2 Hz), 7.31-7.36 (m, 2H), 7.38 & 7.39 (two d, 2H, *J* = 8 Hz), 7.43-7.46 (m, 8H). Anal. Calcd for $C_{47}H_{50}O_8$: C, 75.99; H, 6.78. Found: C, 76.00; H, 6.79.

1c. 58% yield: mp 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 3.08 (t, 4H, *J* = 5 Hz), 3.17 (t, 4H, *J* = 5 Hz), 3.23 (t, 4H, *J* = 5 Hz), 3.50 (t, 4H, *J* = 5 Hz), 3.72-3.74 (m, 4H), 4.37-4.39 (m, 4H), 4.71 (s, 4H), 6.94 (dd, 2H, *J* = 8 & 2 Hz), 7.40 (tt, 2H, *J* = 7 & 2 Hz), 7.45-7.54 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6) δ 63.00, 66.48, 68.94, 69.10, 69.43, 70.43, 72.75, 101.93, 115.15, 119.29, 121.43, 121.79, 127.07, 128.39, 128.45, 131.39, 149.09, 154.87, 156.47. Anal. Calcd for $C_{42}H_{44}O_{10}$: C, 71.17; H, 6.26; Found: C, 71.29; H, 6.40.

Hydrolysis of 1b to 1d. The mixture of **1b** (0.10 g, 0.067 mmol), 2 N aqueous NaOH solution (2 mL), and ethanol (2 mL) was stirred at 65 °C for 0.5 h and then concentrated to *ca* 1 mL. The solid contained in the concentrated reaction mixture was separated by a centrifuge, washed with cold distilled water and then ethyl acetate, and then dried under vacuum to give **1d** as disodium salt (0.096 g, 98% yield). Diacid form of **1d** was obtained by adding a few drops of 6 N aqueous HCl to an aqueous solution of disodium salt of **1d** followed by filtration.

1d (diacid): mp 115-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.31 (m, 12H), 1.65-1.76 (m, 4H), 1.77-1.93 (m, 2H), 2.03-2.15 (m, 4H), 2.79-2.85 (m, 4H), 4.68-4.76 (m, 2H), 6.82 (d, 2H, *J* = 8 Hz), 7.06 (d, 2H, *J* = 2 Hz), 7.30-7.36 (m, 2H), 7.39 (d, 2H, *J* = 9 Hz), 7.42-7.44 (m, 8H). Anal. Calcd for $C_{45}H_{46}O_8$: C, 75.61; H, 6.49; Found: C, 75.82; H, 6.71.

1d·2Na **(**disodium salt of **1d**): mp 275 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 1.04-1.25 (m, 12H), 1.60-1.79 (m, 4H), 1.81-1.90 (m, 2H), 1.97-2.06 (m, 4H), 2.77-2.90 (m,

4H), 4.45-4.51 (m, 2H), 6.81 & 6.82 (two dd, 2H, J = 8 & 2 Hz), 6.98 (d, 2H, J = 2 Hz), 7.24-7.34 (m, 4H), 7.38-7.46 (m, 8H).

Synthesis of 2. To a vigorously stirred mixture of phenethylamine (3.83 g, 31.6 mmol) and sodium carbonate (1.00 g, 9.48 mmol) in water (10 mL) at 90-95 °C, benzyl chloride (1.00 g, 7.90 mmol) was added slowly over an hour. After 4 h, the reaction mixture was saturated with NaCl and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (eluent: ethyl acetate) gave *N*-benzylphenethylamine (1.05 g, 63% yield). The phenethylamine hydrochloride salt was obtained as precipitates by treating the chloroform solution of the amine with conc. HCl. The hydrochloride salt was transformed into hexafluorophosphate salt by adding dropwise a saturated aqueous ammonium hexafluorophosphate solution to a solution of the phenethylamine hydrochloride salt in hot water. Filtration and drying of the precipitates provided the hexafluorophosphate salt of *N*-benzylphenethylamine: mp 207 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 2.98-3.03 (m, 2H), 3.15-3.20 (m, 2H), 4.11 (s, 2H), 7.21 (d, 2H, J = 8 Hz), 7.24-7.29 (m, 1H), 7.31-7.36 (m, 2H), 7.42-7.47 (m, 5H), 8.70 (broad s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6) δ 31.80, 48.07, 51.12, 126.80, 128.22, 128.47, 128.67, 129.24, 129.44, 130.31, 135.70. Anal. Calcd for $C_{15}H_{18}F_6NP$: C, 50.43; H, 5.08; N, 3.92; Found: C, 50.17; H, 4.73; N, 4.11.

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