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-dihydroxybenzophenone gave macrocycles 5a-c. Photocyclization 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 CDCl₃/methanol-d₄ 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.

† 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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![Diagram of cyclophane 1a-d]
Results and Discussion

The precursor macrocycles 5a-c were prepared by successive alkylation reactions of 4-hydroxy groups and then 2-hydroxy groups of 2,4-dihydroxybenzophenones, utilizing differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone (Scheme 1). Reaction of 2,4-dihydroxybenzophenone with 0.6 molar ratio of α,α-dibromo-p-xylene or dimethyl 2,6-dibromohexanediol 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. The photocyclization of two o-alkoxybenzophenone moieties of 5a-c followed by dehydration produced the cyclophanes 1a-c: after irradiating a 1 mM benzene 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, [host]/[2] = γ, at fixed concentration of 2. Figure 1 shows a typical change of 1H 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 ∆δ (δ value of the guest in the presence of the cyclophane − δ
value of the free guest) are measured. Assuming 1:1 complexation between the cyclophane and 2, \( \Delta \delta \) is related to the concentration ratio \( \gamma \) and the binding constant of 2 with the cyclophane \( K \) by the equation (1).\(^9\)

\[
\Delta \delta = 0.5 \Delta \delta_0 \left[ 1 + \gamma + \frac{1}{K} \right] - \left[ \left( \gamma - 1 + \frac{1}{K} \right)^2 \right]
\]

where \( \Delta \delta_0 \) 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\(_2\)Ph) of 2. Figure 2 shows the dependence of \( \Delta \delta \) of the methylene protons of 2 on the initial concentration ratio of [cyclophane]/[2]. 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 \( \Delta \delta \) value is 0.42 \( \pm \) 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 \( \Delta \delta \) values as 36 \( \pm \) 6 M\(^{-1}\) and 0.46 \( \pm \) 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\(_3\)Ph) of 2 depending upon the concentration ratio of

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

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**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\(_3\)Ph and N-CH\(_2\)CH\(_2\)Ph of 2, respectively.

**Figure 2.** Variation of the complexation-induced chemical shift, \( \Delta \delta \) of the methylene protons (N-CH\(_3\)Ph) of 2 with the ratios of [cyclophane]/[2]. 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 [1d·2Na]/[2] = 1.
[1d-2Na]/[2], in 3 : 1 CDCl3/methanol-d4 solvent are also shown (Figure 2c). As can be seen from the Figure 2, the dependence of Δδ on the [cyclophane][/2] 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 Δδ = 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 the concentration ([2]), 2Na⁻ of 1d-2Na is estimated as about 8 x 10⁻² M⁻¹; this gives the second binding constant K12 of 2 to 1d-2Na defined in the equation (3) as 200 M⁻¹⁻¹ from K12/K12₁₂ relationship.

In summary, we prepared novel cyclophanes 1a-d containing two benzofuran rings and studied their binding behaviors with N-benzylphenethylammonium cation 2 by NMR titration method. The cyclophane 1a having a p-xylene bridge forms 1 : 1 complex with 2 with the binding constant of 36 ± 6 M⁻¹ in 3 : 1 CDCl3/methanol-d4 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. H NMR and 13C 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-hydroxyphenoxy)benzene, 3. The compound 3 was prepared with 95% yield by a method described previously. The spectroscopic data were identical with the previous report, but the melting point (mp 220 °C) is higher than the reported value, mp 175-176 °C.

Dimethyl 2,6-bis(4-benzoyl-3-hydroxyphenoxy)heptanediode, 4. To the suspension of 2,4-dihydrobenzophenone (3.00 g, 14.0 mmol) and K₂CO₃ (7.74 g, 56.0 mmol) in acetonitrile (100 mL) was added a solution of dimethyl 2,6-dibromohexane (2.42 g, 7.00 mmol) in acetonitrile (20 mL) very slowly under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 75 h. After K₂CO₃ 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; 1H NMR (400 MHz, CDCl₃) δ 1.67-1.80 (m, 2H), 2.01-2.09 (m, 4H), 3.78 (s, 6H), 4.73 (t, 2H, J = 6 Hz),
Macrocyle 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: 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.

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 diosodium 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 diosodium salt of 1d followed by filtration.

**Photocyclization/dehydration reaction of 5a-c to 1a-c.** 1.0 mM Benzene 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 (Southern 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.
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\(_6\)) \( \delta \) 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\(_6\)) \( \delta \) 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\(_6\)NP: C, 50.43; H, 5.08; N, 3.92; Found: C, 50.17; H, 4.73; N, 4.11.

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**References**

8. Benzene is a toxic solvent and should be handled with appropriate care.