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DESIGN AND SYNTHESIS OF A NOVEL CYCLOPHANE AS HOST FOR ARYL PHOSPHATE

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Abstract- A novel Tröger base derived cyclophane bearing mercaptoimidazole groups on the alkyl chains as blanches of 6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine skeleton was synthesized in order to investigate the ability as macrocyclic enzyme models to incorporate phosphotyrosine in future.

The design and synthesis of macrocyclic ring systems play an important role in host-guest chemistry.[1] In particular, cyclophanes, macrocycles containing 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (Tröger base derived)[2] skeleton, represent the central role of synthetic receptors in molecular recognition due to the strong hydrophobicity and π-stacking interactions of their aromatic ring groups. A 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine unit was chosen for this purpose, it is a rigid and chiral molecule which has a C_2 axis of symmetry. The possibility of using this unit to synthesize a variety of host molecules has been studied extensively.[3]

The reversible phosphorylation of tyrosine residues on the surfaces of cellular proteins plays an important role in many signal transduction pathways.

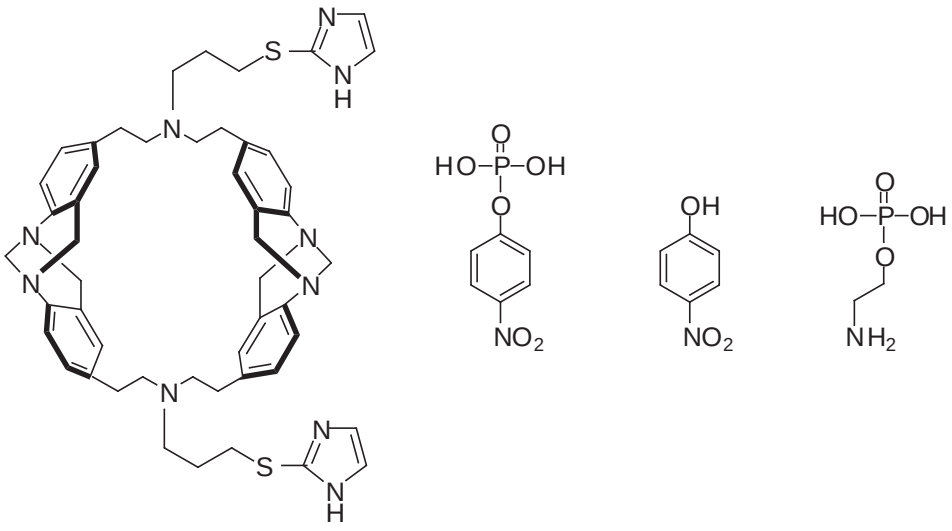


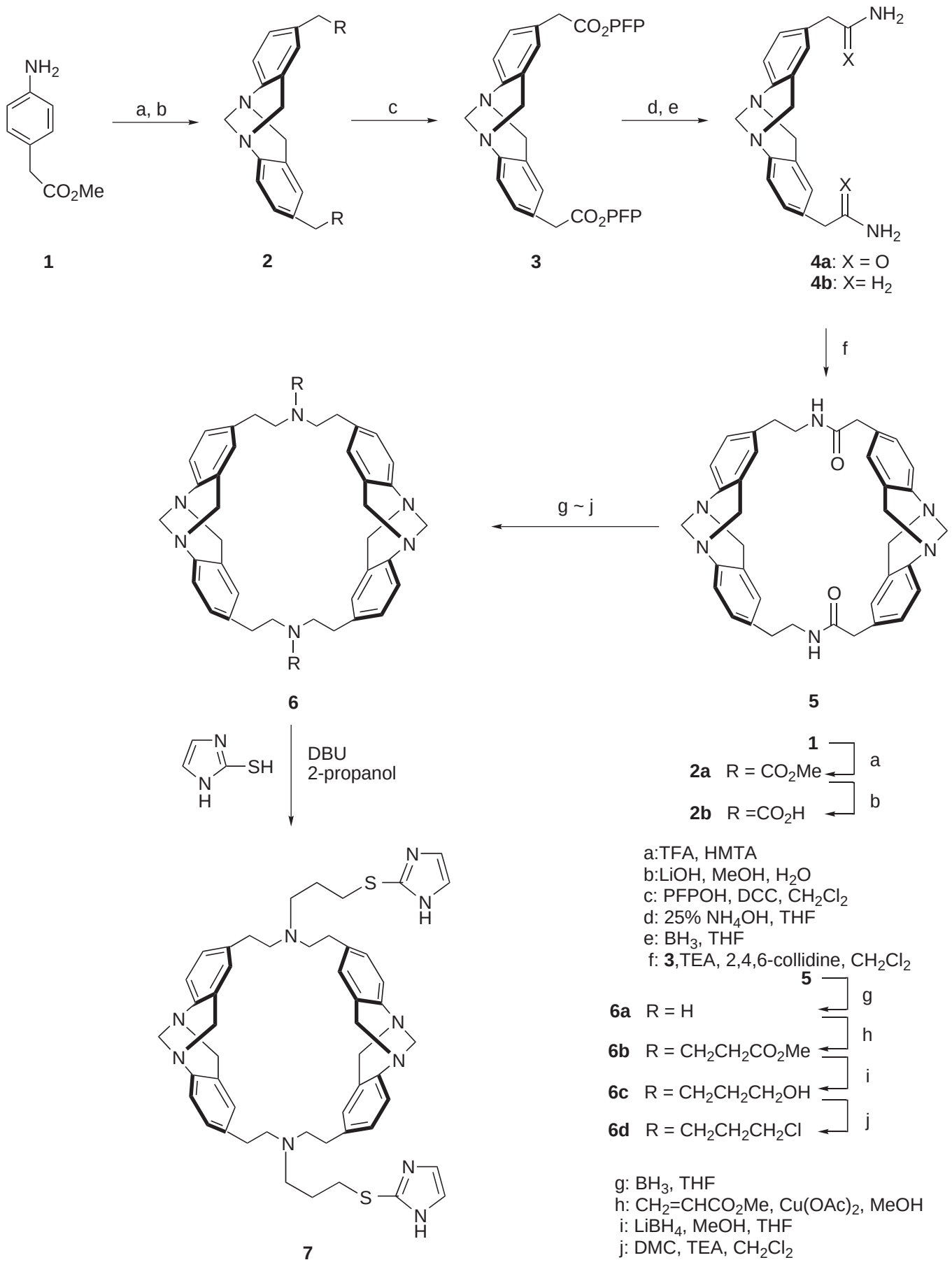
Figure 1. Structures of cyclophane host and guests.

In this paper we report the synthesis of a novel Tröger base derived cyclophane bearing mercaptoimidazole groups on the alkyl bridge as blanches of the 6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine skeleton in order to characterize this artificial host as a receptor for biologically relevant phosphates in their natural environment. It is probable that introduction of mercaptoimidazole groups will be able to bind to the phosphate group by electrostatic interaction and lead to remedy the solubility of cyclophane. The synthesis of the novel cyclophane is shown in Scheme 1.

The synthesis of Tröger base skeleton by treatment of methyl 4-aminophenylacetate (**1**) with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) furnished the methyl ester (**2a**) in 81% yield, followed by hydrolysis of **2a** with LiOH in aqueous methanol to provide dicarboxylic acid (**2b,** 95%) which underwent smooth esterification on treatment with DCC and pentafluorophenol (PFPOH) to give pentafluorophenyl ester (**3**) in 97% yield. The pentafluorophenyl ester function in compound (**3**) was converted to carboxamide (**4a,** 94%) by treatment of pentafluorophenyl ester with 25% NH_4OH in THF, followed sequentially by reduction with BH_3 to corresponding primary amine(**4b,** 100%). The coupling reaction of compounds (**3**) with **4b** gave macrocycle (**5**) as a 1:1 mixture of *meso*-and *dl*-isomers in 70% yield in the presence of TEA and 2,4,6-collidine as base in CH_2Cl_2 under high dilution conditions. The mixture was perfectly separated by silica gel column chromatography eluted with $CHCl_3$:MeOH:25% NH_4OH (100:7:1). Interestingly, when the coupling reaction was carried out in the presence of TEA or 2,4,6-collidine, **5** was obtained in the 23 and 40% yields, respectively, but, with the coexistence of 2,4,6-collidine and TEA in the coupling reaction, the yield of **5** was improved about 1.75 - 3 times. However the effect of employing 2,4,6-collidine is not investigated in detail. The *meso* isomer of compound (**5**) underwent conversion to aminomacrocycle (**6a,** 96%) by reduction with BH_3. A Michael addition between (**6a** (*meso* form)) and methyl acrylate took place smoothly in the presence of $Cu(OAc)_2$ as catalyst in refluxing methanol and gave corresponding methyl ester (**6b**) in 83% yield, the methoxycarbonyl function underwent reduction with $LiBH_4$ in the presence of small amount of methanol in THF to give a primary alcohol (**6c**) in 94% yield, followed sequentially by chlorination with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) to **6d**. Finally, treatment of **6d** with 2-mercaptoimidazole by use of DBU as dehalogenating reagent in 2-propanol resulted in the formation of Tröger base derived cyclophane (**7**) in 86% yield.

The structure of the cyclophane (**7**) was confirmed by ^{1}H NMR and MS spectra. The two 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine skeletons of the novel cyclophane (**7**) serve as suitable structural units to construct a hydrophobic cavity of well-defined structure. The characteristic features of the 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine skeleton is that the two benzene rings are fixed at a definite angle because there are two intervening asymmetric nature of trivalent nitrogen atom.

Examinations on the complex formation of **7** with *O*-phosphorylethanolamine, 4-nitrophenol and 4-nitrophenyl phosphate were made by ^{1}H NMR spectrometry in 0.1M KCl-DCl buffer solution at pD 1.4 below the critical micelle concentration (CMC) of **7**.[4] Marked upfield shifts of 4-nitrophenol aromatic protons were observed. Signals of the protons ($\Delta\delta$) at C-2 and C-3 are shifted upfield in the magnitudes of 1.21 and 1.54 ppm, respectively.[5] The phenomena can be ascribable to a strong intermolecular shielding effect due to the aromatic rings of **7**, and suggest the formation of a 1:1 inclusion complex


NH2
CO2Me
a, b
R
R
c
CO2PFP
CO2PFP
d, e
NH2
X
X
NH2
1
2
3
4a: X = O
4b: X= H2
f
H
N
O
O
N
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g ~ j
R
N
R
6
5
N
SH
N
H
DBU
2-propanol
S
N
H
7
1
2a R = CO2Me
2b R =CO2H
a
b
a:TFA, HMTA
b:LiOH, MeOH, H2O
c: PFPOH, DCC, CH2Cl2
d: 25% NH4OH, THF
e: BH3, THF
f: 3,TEA, 2,4,6-collidine, CH2Cl2
5
6a R = H
6b R = CH2CH2CO2Me
6c R = CH2CH2CH2OH
6d R = CH2CH2CH2Cl
g
h
i
j
g: BH3, THF
h: CH2=CHCO2Me, Cu(OAc)2, MeOH
i: LiBH4, MeOH, THF
j: DMC, TEA, CH2Cl2

Scheme 1.

between **7** and 4-nitrophenol. Dissociation constant (Kd) was calculated on the basis of Benesi-Hildebrand equation[6] using the host-induced upfield shifts of the guest proton signals. The Kd value of the complex was 0.015 M. On the other hand, in the case of using 4-nitrophenyl phosphate as guest instead of 4-nitrophenol, signals of the protons (Δδ) at C-2 and C-3 are shifted upfield in the magnitudes of 1.59 and 2.07 ppm, respectively (Figure 2).[5] The Kd value[6] was 0.0012 M and the 1:1 inclusion complex was confirmed by Job's method of continuous variations (Figure 3).[7] In case of using *O*-phosphorylethanolamine as guest, however, chemical shift changes were not observed under same condition. It was concluded that **7** works as host that form complexes selectively with aromatic phosphates as guests and 4-nitrophenyl phosphate has stronger interactions with 2-mercaptoimidazole groups than 4-nitrophenol.

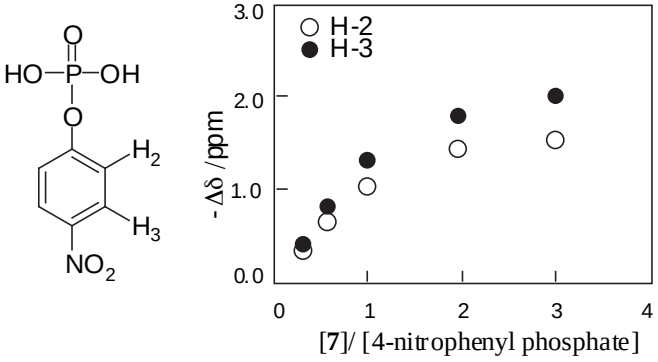

Figure 2. Relationship between Δδ and **7**/4-nitrophenyl phosphate

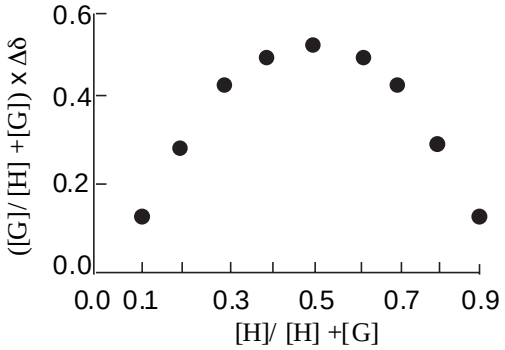

Figure 3. Job plot for the formation of a complex between host **7** and 4-nitrophenyl phosphate in 0.1 M KCl-DCl buffer (pD 1.4) at 303 K.

EXPERIMENTAL

Melting points were determined using a Yanagimoto Melting point Apparatus Yanaco MP and were uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX 400 spectrometer containing tetramethylsilane as standard. MS spectra were taken on a HITACHI M-2000 double-focusing spectrometer.

2, 8-Bis(methoxycarbonylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (2a)

A solution of methyl 4-aminophenylacetate (**1**) (1.62 g, 9.8 mmol) and HMTA (1.39 g, 9.8 mmol) in TFA (60 mL) was stirred at rt. After 2 d, TFA was removed by lyophilization. The residue was taken up in H_2O (50 mL) and made basic to pH 11 by the addition of 25% NH_4OH (100 mL). The aqueous solution was extracted with CH_2Cl_2 (50 mL x 3). The combined organic phases were washed with brine and dried over $MgSO_4$, and evaporated under reduced pressure to afford a yellow oil, which was chromatographed on silica gel column with EtOAc:MeOH (9:1) as an eluent to give a yellow solid (1.46 g, 81%). An analytical sample was obtained by recrystallizing this material from EtOAc-hexane, pale yellow needles. mp 122-123℃. ^{1}H NMR ($CDCl_3$) δ: 3.49 (s, 4H), 3.66 (s, 6H), 4.14 (d, 2H, *J* =16.7 Hz), 4.28 (s, 2H), 4.67 (d, 2H, *J* =16.7 Hz), 6.82 (s, 2H), 7.08 (s, 4H). MS (EI) (*m/z*) 366 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{21}H_{22}N_2O_4$: 366.1579. Found 366.1596. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.71; H, 5.85; N, 7.74.

2, 8-Bis(hydroxycarbonylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (2b)

A mixture of **2a** (1.252 g, 3.4 mmol) and $LiOH \cdot H_2O$ (0.33 g, 7.86 mmol) in 32 mL of 3:1 (v:v) MeOH/H_2O was stirred at rt. After 24 h, the mixture was concentrated under reduced pressure. The concentrate was diluted with H_2O (10 mL). The solution was then acidified by the addition of 0.6N HCl (final pH 2.0). The pale yellow precipitate was collected by filtration (1.09 g, 95%). An analytical sample was obtained by recrystallizing this material from MeOH, pale yellow fine needles. mp 300°C (decomp). ^{1}H NMR (DMSO-d_6) δ: 3.36 (s, 4H), 4.01 (d, 2H, *J* =16.8 Hz), 4.16 (s, 2H), 4.54 (d, 2H, *J* =16.8 Hz), 6.76 (s, 2H), 6.96 (d, 2H, *J* =9.0 Hz), 7.00 (d, 2H, *J* =9.0 Hz), 12.20 (brs, 2H). MS (EI) (*m/z*) 338 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{19}H_{18}N_2O_4$: 338.1266. Found 338.1254. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.59; H, 5.57; N, 8.18.

6*H*, 12*H*-5,11-Methanodibenzo[*b,f*][1,5]diazocine-2,8-diylacetic acid pentafluorophenyl ester (3)

A suspension of **2b** (2.37 g, 7 mmol), pentafluorophenol (2.58 g, 14 mmol) and DCC (2.90 g, 14 mmol) in CH_2Cl_2 (350 mL) was stirred at rt. After 12 h, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc:hexane (1:1) as an eluent to give a colorless solid (4.55 g, 97%). An analytical sample was obtained by recrystallizing this material from EtOAc-hexane, colorless fine needles. mp 140-141°C. ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 4H), 4.19 (d, 2H, *J* =16.8 Hz), 4.32 (s, 2H), 4.72 (d, 2H, *J* =16.8 Hz), 6.91 (s, 2H), 7.16 (s, 4H). MS (EI) (*m/z*) 670 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{31}H_{16}N_2O_4F_{10}$: 670.0944. Found 670.0950. Anal. Calcd for $C_{31}H_{16}F_{10}N_2O_4$: C, 55.53; H, 2.41; N, 4.18. Found: C, 55.68; H, 2.46; N, 4.14.

2, 8-Bis(carbamoylmethyl)-6*H*,12*H*-5,11-methanodibenzo[b,f][1,5]diazocine (4a)

To a solution of **3** (2.41 g, 3.59 mmol) in THF (15 mL) was added 25% NH_4OH (7 mL, 54 mmol) at rt. After stirring for 1 h, sat. $NaHCO_3$ (200 mL) was added to the reaction mixture. The precipitate was collected by filtration, washed with H_2O, ether and dried under vacuum to give a colorless powder (1.12 g, 93%). An analytical sample was obtained by recrystallizing this material from MeOH, colorless fine needles. mp 300°C (decomp). ^{1}H NMR (DMSO-d_6) δ: 3.18 (s, 4H), 4.02 (d, 2H, *J* =16.8 Hz), 4.17 (s, 2H), 4.55 (d, 2H, *J* =16.8 Hz), 6.76 (s, 4H, arom-H and NH_2), 6.97 (d, 2H, *J* =8.4 Hz), 7.00 (d, 2H, *J* =8.4 Hz), 7.35 (s, 2H, NH_2). MS (EI) (*m/z*) 336 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{19}H_{20}N_4O_2$: 336.1586. Found 336.1588. Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.77; H, 6.16; N, 16.52.

2, 8-Bis(2-aminoethyl)-6*H*,12*H*-5,11-methanodibenzo[b,f][1,5]diazocine (4b)

A suspension of **4a** (52 mg, 0.155 mmol) in THF (2 mL) was stirred at 0°C under N_2 atmosphere. $BH_3 \cdot SMe_2$ (0.19 mL, 1.97 mmol) was added. The reaction mixture was stirred for 24 h at 80°C, then was cooled to rt. 0.7 M hydrogen chloride-MeOH solution (1 mL) was added, and the reaction mixture was refluxed for 1 h, and evaporated under reduced pressure. The residue was made basic to pH 11 with excess 25% NH_4OH. The mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded a yellow oil, which was chromatographed on a silica gel column with $CHCl_3$:MeOH:25% NH_4OH (100:40:4) as an eluent to give yellow oil (47 mg, 100%). ^{1}H NMR (CD_3OD) δ: 2.61 (t, 4H, *J*

=7.1 Hz), 2.76 (t, 4H, *J* =7.1 Hz), 4.12 (d, 2H, *J* =16.7 Hz), 4.29 (s, 2H), 4.62 (d, 2H, *J* =16.7 Hz), 6.79 (s, 2H), 7.00 (d, 2H, *J* =8.2, 1.6 Hz), 7.05 (d, 2H, *J* =8.2 Hz). MS (EI) (*m/z*) 308 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{19}H_{24}N_4$: 308.2000. Found 308.2012. Anal. Calcd for $C_{19}H_{24}N_4$: C, 73.99; H, 7.84; N, 18.17. Found: C, 74.09; H, 7.65; N, 18.26.

Macrocycle (5)

A solution of **3** (456 mg, 0.68 mmol) in CH_2Cl_2 (20 mL) and a mix solution of **4b** (210 mg, 0.68 mmol) and TEA (0.95 ml, 6.8 mmol) in CH_2Cl_2 (20 mL) were added dropwise over a period of 3 h to a stirred solution of collidine (824 mg, 6.8 mmol) in CH_2Cl_2 (250 mL) at 60°C under N_2, and the stirring was continued at the same temperature for 36 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with $CHCl_3$:MeOH:25% NH_4OH (100:7:1) as an eluent to give 290 mg (70% (*meso*:*dl* =1:1)) of a colorless powder. mp 295°C (*meso* -isomer) (decomp). ^1H NMR (*meso*-isomer) ($CDCl_3$) δ: 2.52-2.58 (m, 4H), 3.18 (2H, d, *J* =15.7 Hz), 3.25 (d, 2H *J* =15.7 Hz), 3.31-3.37 (m, 4H), 4.04 (d, 2H, *J* =11.4 Hz), 4.10 (d, 2H, *J* =11.4 Hz), 4.30 (s, 2H), 4.32 (s, 2H), 4.68 (d, 4H, *J* =16.5 Hz), 5.42 (brs, 2H), 6.53 (s, 2H), 6.59 (s, 2H), 6.83 (d, 2H, *J* =8.1 Hz), 6.90 (d, 2H, *J* =8.1 Hz), 7.04 (d, 2H, *J* =8.7 Hz), 7.07 (d, 2H, *J* =9.0 Hz). MS (EI) (*m/z*) 610 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{38}H_{38}N_6O_2$: 610.3056. Found 610.3064. Anal. Calcd for $C_{38}H_{38}N_6O_2$: C, 74.77; H, 6.27; N, 13.77. Found: C, 74.52; H, 6.30; N, 13.93. ^1H NMR (*dl*-isomer) ($CDCl_3$) δ: 2.18-2.53 (m, 4H). 3.10 (d, 2H, *J* =15.8 Hz), 3.28 (d, 2H, *J* =15.8 Hz), 3.32-3.42 (m, 4H), 4.07 (d, 4H, *J* =16.5), 4.27 (s, 4H), 4.66 (d, 4H, *J* =16.5 Hz), 5.31 (t, 2H, *J* =5.6 Hz), 6.60-6.67 (m, 6H), 6.78 (dd, 2H, *J* =8.3 and 1.8 Hz), 6.98 (d, 2H, *J* =8.1 Hz), 7.04 (d, 2H, *J* =8.1 Hz). mp 240°C (*dl* -isomer) (decomp). Anal. Calcd for $C_{38}H_{38}N_6O_2$: C, 74.77; H, 6.27; N, 13.77. Found: C, 74.50; H, 6.30; N, 13.95.

Macrocycle (*meso*-isomer) (6a)

A suspension of **5** (*meso*-isomer) (277 mg, 0.45 mmol) in THF (5 mL) was stirred at 0°C under N_2 atmosphere. $BH_3{\cdot}SMe_2$ (0.53 mL, 5.49 mmol) was added. The reaction mixture was stirred for 24 h at 80°C, then was cooled to rt. 0.7 M hydrogen chloride-MeOH solution was added, and the reaction mixture was refluxed for 0.5 h, and evaporated under reduced pressure. The residue was made basic to pH 11 with excess 25% NH_4OH. The mixture was extracted with CH_2Cl_2 (100 mL x 3). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded a colorless foam, which was purified by column chromatography on silica gel with $CHCl_3$:MeOH:25% NH_4OH=100:10:1) as an eluent to give 254 mg (96%) of a white powder. An analytical sample was obtained by recrystallizing this material from MeOH, colorless needles. mp 293°C (decomp). ^1H NMR ($CDCl_3$) δ: 2.54-2.77 (m, 16H), 3.99 (d, 4H, *J* =16.6 Hz), 4.28 (s, 4H), 4.60 (d, 4H, *J* =16.6 Hz), 6.62 (d, 4H, *J* =1.5 Hz), 6.91 (dd, 4H, *J* =8.2, 1.5 Hz), 6.97 (d, 4H, *J* =8.2 Hz).^{13}C NMR ($CDCl_3$) δ: 34.7, 50.0, 58.9, 67.1, 124.8, 127.1, 127.7, 128.0, 136.0, 146.0. MS (EI) (*m/z*) 582 $[M]^+$. HRMS (EI) (*m/z*) Calcd for $C_{38}H_{42}N_6$: 582.3471. Found 582.3442. Anal. Calcd for $C_{38}H_{42}N_6$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.39; H, 7.33; N, 14.24.

Macrocycle (6b)

A mixture of **6a** (*meso*-isomer) (58 mg, 0.1 mmol), methyl acrylate (52 mg, 0.6 mmol) and

$Cu(OAc)_2 \cdot H_2O$ (2 mg, 0.01 mmol) in MeOH (1 mL) was stirred for 24 h at 100℃ under N_2 atmosphere. The mixture was filtered through Celite and washed with $CHCl_3$:MeOH (2:1) and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with $CHCl_3$:MeOH (10:1) as an eluent to give 70 mg (93%) of a pale yellow amorphus powder. ^1H NMR ($CDCl_3$) δ: 6.94 (d, 4H, *J* =8.4 Hz), 6.83 (d, 4H, *J* =8.4 Hz), 6.53 (d, 4H, *J* =1.4 Hz), 4.59 (d, 4H, *J* =16.4 Hz), 4.28 (s, 4H), 4.00 (d, 4H, *J* =16.4 Hz), 3.69 (s, 6H), 2.81-2.89 (m, 4H), 2.44-2.48 (m, 12H), 2.26-2.37 (m, 8H). MS (FAB) (*m/z*) 755 $[M+1]^+$. HRMS (FAB) (*m/z*) Calcd for $C_{46}H_{55}N_6O_4$: 755.4284. Found 755.4325. Anal. Calcd for $C_{46}H_{54}N_6O_4$: C, 73.17; H, 7.21; N, 11.14. Found: C, 73.06; H, 7.08; N, 11.29.

Macrocycle (6c)

A mixture of **6b** (120 mg, 0.16 mmol), $LiBH_4$ (32 mg, 1.45 mmol), MeOH (1 mL), and THF (3 mL) was refluxed for 18 h and was then cooled to rt. Water (2 mL) and 1N HCl (0.5 mL) were added to quench the reaction with ice-cooling, then the mixture was made basic to pH 11 with 25% NH_4OH. The mixture was extracted with CH_2Cl_2 (20 mL), the extract was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel with $CHCl_3$:MeOH:25% NH_4OH (100:10:1) as an eluent afforded 105 mg (94%) of a colorless amorphus powder. ^1H NMR ($CDCl_3$) δ: 1.57 (br s, 2H), 1.65-1.72 (m, 4H), 2.39-2.41 (m, 8H), 2.48-2.52 (m, 8H), 2.68 (t, 4H, *J* =5.6 Hz), 3.78 (t, 4H, *J* =5.4 Hz), 4.02 (d, 4H, *J* =16.6 Hz), 4.29 (s, 4H), 4.59 (d, 4H, *J* =16.6 Hz), 6.55 (d, 4H, *J* =1.5 Hz), 6.85 (dd, 4H, *J* =8.3, 1.7 Hz), 6.98 (d, 4H, *J* =8.3 Hz). MS (FAB) (*m/z*) 699 $(M+1)^+$. HRMS (FAB) (*m/z*) Calcd for $C_{44}H_{55}N_6O_2$: 699.4386. Found 699.4403. Anal. Calcd for $C_{44}H_{54}N_6O_2$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.51; H, 7.85; N, 11.97.

Macrocycle (6d)

A mixture of **6c** (78 mg, 0.11 mmol), DMC (45 mg, 0.27 mmol) and TEA (48 μL, 0.34 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 24 h under N_2 atmosphere. The mixture was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel with $CHCl_3$:MeOH (10:1) as an eluent afforded 80 mg (100%) of a colorless powder, which was used for the next reaction without further purification. mp 165-166°C. ^1H NMR ($CDCl_3$) δ: 1.60-1.72 (m, 4H), 2.21-2.28 (m, 4H), 2.31-2.37 (m, 4H), 2.41-2.58 (m, 12H), 3.37-3.44 (m, 4H), 4.02 (d, 4H, *J* =16.6 Hz), 4.30 (s, 4H), 4.29 (s, 4H), 4.60 (d, 4H, *J* =16.6 Hz), 6.44 (s, 4H), 6.86 (dd, 4H, *J* =8.3, 1.7 Hz), 6.97 (d, 4H, *J* =8.3 Hz). MS (FAB) (*m/z*) 735$[M+1]^+{}^{35}Cl$, 737 $[M+1]^+{}^{37}Cl$, 739 $[M+1]^+{}^{39}Cl_2$. HRMS (FAB) (*m/z*) Calcd for $C_{44}H_{53}N_6Cl_2$:735.3708. Found 735.3707. Anal. Calcd for $C_{44}H_{52}N_6Cl_2$: C, 71.82; H, 7.12; N, 11.42. Found: C, 71.85; H, 7.02; N, 11.44.

Cycrophane (7)

A mixture of **6d** (66 mg, 0.09 mmol), 2-mercaptoimidazole (20 mg, 0.2 mmol) and DBU (61 mg, 0.4 mmol) in 2-PrOH (3 mL) was stirred at 100℃ for 18 h under N_2 atmosphere. The mixture was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (20 mL), and the extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel with $CHCl_3$:MeOH:25% NH_4OH(100:10:1) as an

eluent afforded 67 mg (86%) of a colorless amorphous powder. ^{1}H NMR ($CDCl_3$) δ: 1.62-1.71 (m, 4H), 2.45-2.46 (m, 8H), 2.51-2.54 (m, 8H), 2.58 (t, 4H, *J* =6.4 Hz), 2.83-2.90 (m, 4H), 4.01 (d, 4H, *J* =16.6 Hz), 4.32 (s, 4H), 4.60 (d, 4H, *J* =16.6 Hz), 6.53 (d, 4H, *J* =1.7 Hz), 6.50-6.82 (br, 2H), 6.83 (dd, 4H, *J* =8.3, 1.7 Hz), 6.95 (d, 4H, *J* =8.3 Hz), 7.26 (s, 4H). MS (FAB) (*m/z*) 863 $[M+1]^+$. HRMS (FAB) (*m/z*) Calcd for $C_{50}H_{59}N_{10}S_2$: 863.4365. Found 863.4418. Anal. Calcd for $C_{50}H_{58}N_{10}S_2$: C, 69.57; H, 6.77; N, 16.23. Found: C, 69.40; H, 6.61; N, 16.20.

Determination of Kd Values of the Complexes

The Kd values of the host-guest complexes were determined by ^{1}H NMR spectra using the host-induced upfield shifts of the guest proton signals in 0.1M KCl-DCl (pD 1.4) at 303 K on the basis of the Benesi-Hildebrand equation.[5] The concentration of the guest (4-nitrophenol and 4-nitrophenyl phosphate) was 6×10^{-3} M and 5×10^{-3} M, respectively, while those of the host **7** ranges from 1.25×10^{-3} M to 1.5×10^{-2} M (5 points). The non-linear curve fitting procedure with the least squares method was applied.

Job Plots

Equimolar solutions (10^{-2} M) of host and guest were prepared (0.1M KCl-DCl (pD 1.4)) and mixed in various amounts. ^{1}H NMR spectra of the mixture were recorded at 303 K, and the chemical shifts were analyzed by Job's method for NMR results.

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4. ^{1}H NMR spectra of the solutions of **7** in 0.1M KCl-DCl (pD 1.4) were measured. Chemical shifts of all the protons did not change in concentration range of **7** from 1.25×10^{-3} M to 5.0×10^{-2} M. Therefore, the critical micelle concentration (CMC) of **7** was found to be not less than 5.0×10^{-2} M and all experiments were carried out below 5.0×10^{-2} M.
5. $\Delta\delta = \delta$(host + guest) – δ (guest). The magnitudes of Δδ values are dependent on the ratio of the host to the guest.
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