Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Synthesis and inclusion properties of teraazametacyclophanes containing bisphenol A unit

Tyo Sone[a]; Yoshihiro Ohba[a]; Fumiaki Nishino[a]; Shuichi Yamanami[a]
[a] Department of Materials Science and Engineering, Faculty of Engineering, Yamagata University, Yonezawa, Japan

To cite this Article Sone, Tyo , Ohba, Yoshihiro , Nishino, Fumiaki and Yamanami, Shuichi(1993) 'Synthesis and inclusion properties of teraazametacyclophanes containing bisphenol A unit', Supramolecular Chemistry, 2: 1, 47 — 52
To link to this Article: DOI: 10.1080/10610279308027506
URL: http://dx.doi.org/10.1080/10610279308027506

SUPRAMOLECULAR CHEMISTRY, Vol. 2, pp. 47–52
Reprints available directly from the publisher
Photocopying permitted by license only

Synthesis and inclusion properties of teraazametacyclophanes containing bisphenol A unit

TYO SONE*, YOSHIHIRO OHBA, FUMIAKI NISHINO and SHUICHI YAMANAMI

Department of Materials Science and Engineering, Faculty of Engineering, Yamagata University, Yonezawa 992 Japan

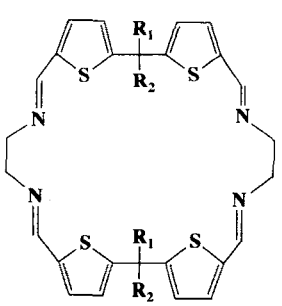
(Received July 30, 1992)

Novel 26-membered, 8b and 10, and 28-membered tetraazametacyclophanes, 9, containing two bisphenol A units were synthesized; 8b and 9 in five steps from bisphenol A via the corresponding macrocyclic tetraimine Schiff bases, while 10 in three steps. The macrocyclic Schiff bases were obtained in high yields (>80%) by [2 + 2] cyclization of the diformyl or bischloromethyl derivatives of bisphenol A dimethyl ether with the corresponding aliphatic α,ω-diamines or piperazine under high dilution conditions, making a remarkable synthetic feature. The macrocycles formed crystalline inclusion compounds with a variety of neutral organic molecules. Complexation studies by Diederich's solid-liquid extraction method revealed that the metacyclophanes formed complexes with phenanthrene, anthracene, pyrene, and acenaphthylene in acidic aqueous solution with association constants K_a up to 1.5×10^5 M^{-1}.

INTRODUCTION

Polyazaparacyclophanes have attracted considerable attention from the viewpoint of molecular recognition.[1] An important characteristic of the azacyclophane molecules is that they can serve as water-soluble hosts with definite structure and are of interest in relation to modeling of biological functions of such as receptor, enzyme, and carrier.

In contrast to its para counterpart, few azametacyclophanes[2] designed for inclusion host have appeared in the literatures. To our knowledge no water-soluble azametacyclophane host has been reported except for the multi-bridged ones. The formation of macrocyclic compounds is, in general, not easy because of unfavorable activation entropy for the cyclization. In many cases cyclophanes are available by cyclization in rather low yields. In connection with other work, we recently found that, without using metal ions as a template, [2 + 2] cyclization between bis(5-formyl-2-thienyl)methane derivatives and 1,2-diaminoethane yielded the corresponding macrocyclic tetraimine Schiff bases **1** in high yields.[3] The successful cyclization suggests an efficient route to the metacyclophanes via macrocyclic Schiff bases which can be reduced. The similar process has been used by Jazwinski et al. for the synthesis of polyazaparacyclophanes containing diphenylmethane skeleton.[4] The efficient cyclization may be due to the favorable position of the CHO groups as well as rigidity of di(2-thienyl)methane units which favor the formation of the macrocycles. Considering that the 2 and 5 positions in thiophene stand geometrically in the meta relationship in benzene, bisphenol A which has structural resemblance to di(2-thienyl)methane is of choice as the building block. Examination of the CPK model indicates the 26-membered metacyclophane **8b** consisting of two bisphenol A and two 1,2-ethylenediimino units as building blocks have hydrophobic cavities large and deep enough to include organic molecules. Further, this system is subject to wide structural modification, phenolic OH as well as NH group(s) in the bridges being useful for functionalization of the metacyclophanes. Based on the idea we decided to investigate the synthesis and inclusion properties of the 26-membered **8** and **10** and 28-membered tetraazametacyclophanes **9** containing bisphenol A units.



1 R_1, R_2 = alkyl

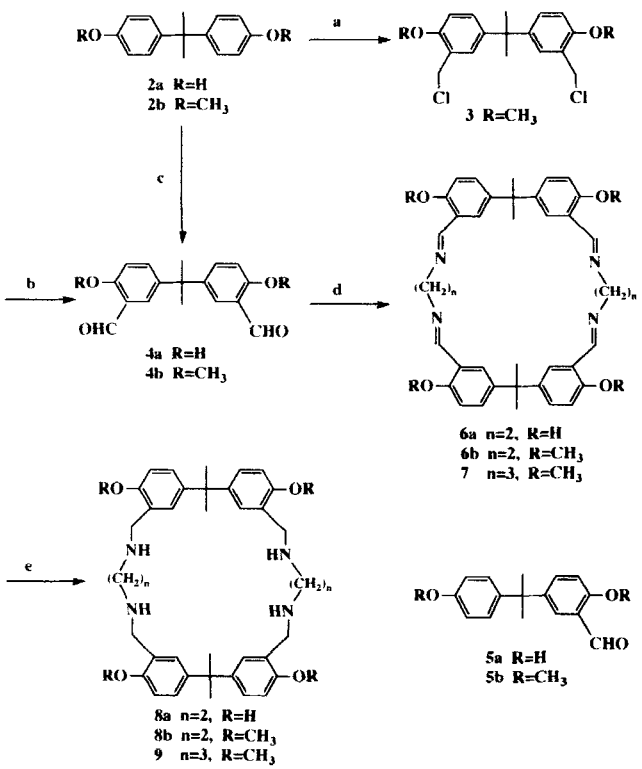
*To whom correspondence should be addressed.

RESULTS AND DISCUSSION

Synthesis of the hosts

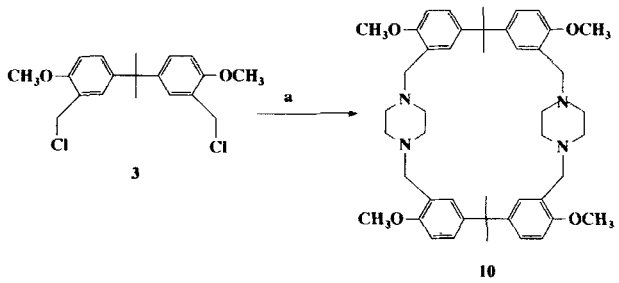
The metacyclophanes **8b** and **9** were synthesized starting from commercially available bisphenol A **2a** in five steps via the corresponding macrocyclic tetraimine Schiff bases **6b** and **7** (Scheme I). The key step of this route is [2 + 2] cyclization between the dialdehyde **4b** and the diamines; the reaction was achieved in high yields as expected. Thus, treatment of bisphenol A dimethyl ether **2b** with paraformaldehyde in a mixture of acetic acid and hydrochloric acid in the presence of H_3PO_4 afforded the bischloromethyl derivative **3** (92%).

Application of the Sommelet reaction (hexamethylenetetramine, $CHCl_3$) to **3** gave the dialdehyde **4b** (65%). Cyclization of **4b** with 1,2-diaminoethane or 1,3-diaminopropane in $CHCl_3$ at room temperature under high-dilution conditions afforded **6b** and **7**, respectively (92 and 83%). The spectral data (^1H NMR, IR, MS) are consistent with the structures of the expected macrocyclic Schiff bases, showing the IR band at 1640 cm^{-1} and the NMR peak at δ 8.75 – 8.80 characteristic for azomethine, but no bands and peaks ascribable to either amino or formyl group. Finally,



(a) $(HCHO)_n$, HCl, H_3PO_4/AcOH, 80°C, 4h, 92% (b) $(CH_2)_6N_4/CHCl_3$, reflux, 8h, then H_2O, reflux, 4h, 65% (c) $CHCl_3$, 50% NaOH, 60-70°C, 4h; 18% (4a), 38% (5a) (d) $H_2N(CH_2)_nNH_2/CHCl_3$, high dilution, room temp., 33h; 81% (6a), 92% (6b), 83% (7) (e) $LiAlH_4$/THF, reflux, 6h; 74% (8b), 90% (9).

Scheme I



(a) piperazine, $Et_3N/CHCl_3$, high dilution, room temp., 26h, 94%

Scheme II

$LiAlH_4$ reduction of the macrocyclic Schiff bases in THF yielded the expected 26-membered **8b** and 28-membered metacyclophanes **9** (74% and 90%).

Similarly, the 26-membered metacyclophanes containing piperazine unit **10** was also synthesized in three steps from bisphenol A by the [2 + 2] cyclization between **3** and piperazine in $CHCl_3$ in 94% yield (Scheme II). The spectral data of **10** support the proposed structure.

The metacyclophanes are soluble in aqueous hydrochloric acid solution as well as in organic solvents such as $CHCl_3$, CH_2Cl_2, CH_3OH, acetone, THF, and dioxane. They form adducts with water on standing in air, which are slightly soluble in most organic solvents.

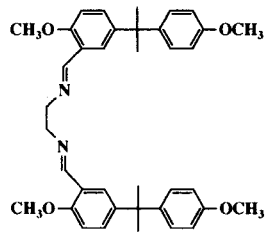
Alternatively, direct formylation of bisphenol A by the Reimer-Tiemann reaction ($CHCl_3$, KOH) yielded the dialdehyde **4a** in low yield (18%), the monoaldehyde **5a** being the main product (38%). Cyclization of **4a** with 1,2-diaminoethane afforded the corresponding macrocyclic Schiff base **6a** in high yield (81%), but attempts ($LiAlH_4$, $NaBH_4$, H_2-Pd/C) to convert **6a** into the metacyclophane **8a** having free phenolic OH group were all unsuccessful.

Inclusion properties

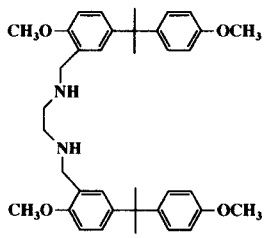
The metacyclophanes **8b**, **9**, and **10** as well as the macrocyclic Schiff bases **6a** and **6b** form crystalline inclusion compounds with a variety of neutral organic molecules. They are similar to each other in guest selectivity; aromatic hydrocarbons, including naphthalene and anthracene, are effectively included, while small molecules such as CH_2Cl_2 and CH_3OH are rather hard to be included (Table 1). It is interesting to note that the macrocyclic Schiff base **6a** having phenolic OH group forms 2:1 complexes with most of the guest examined, while its methoxy analog **6b** forms 1:1 complexes. This is probably attributed to the difference in inclusion lattice between the two hosts; intermolecular hydrogen bonding through phenolic OH groups in the molecule play a role in constructing the inclusion lattice of **6a**.

The complexation properties of the metacyclophanes **8b**, **9**, and **10** in aqueous hydrochloric acid solution (pH 1.0) with anthracene, phenanthrene, pyrene, and acenaphthylene were investigated by means of a solid-liquid extraction method that had been introduced by Diederich.[5] The association constants K_a for the formation of 1:1 host-guest complex were evaluated with host concentrations ($10^{-3} - 10^{-5}$ M) below the critical micelle concentrations (cmc) of the hosts which were determined by ^{1}H NMR spectroscopy.[6] The assumption of 1:1 stoichiometry for the complexes is based on the examination of CPK molecular models and the linear relationships between the concentration of the hosts and that of the guests solubilized in the aqueous solution by complexation. Moreover, the noncyclic reference compound **12** was not effective in solubilizing the guests in the water under the same conditions, suggesting the inclusion of the guest molecules in the cavity of the metacyclophane hosts.

The complexation study showed the ability of the metacyclophanes to form inclusion complexes in water (pH 1.0). The association constants K_a of the three metacyclophanes are in the range of K_a $1.5 \times 10^5 - 1.2 \times 10^2$ M^{-1} (Table 2.) The values compare with those reported in the complexations of cyclotetrachromotropylene,[7] p-(dialkylaminomethyl)calixarenes[8] and p-(carboxyethyl)calixarenes[8]for the same guests. An tetraoxaparacyclophane with four spiro piperidinium bridges has also been found to form inclusion complex with pyrene with higher association constant ($K_a = 1.1 \times 10^6$ M^{-1}).[5]



11



12

CPK model examinations indicated that there was some size complementarity between the aromatic hydrocarbons and the cavities of the metacyclophanes. The low cmc values of the hosts, however, prevented the application of ^{1}H NMR studies to get informations about the geometry of the complexes.

In conclusion, we have synthesized a new class of tetraazametacyclophanes containing two bisphenol A units. The metacyclophanes have an ability to form crystalline inclusion complexes with various sorts of neutral organic compounds. The metacyclophanes also act as hosts for polycyclic aromatic hydrocarbons in acidic water. They provide the first examples of water-soluble metacyclophane hosts. Structural modification of the metacyclophanes to improve the complexation abilities are now in progress.

Table 1 Crystalline inclusion compounds of tetraazametacyclophenes[a]

	Host (H)				
	6a	**6b**	**8b**	**10**	**9**
Guest (G)	*(H:G)*				
acetone	–	+	+	+	+
methanol	–	–	–	–	–
dichloromethane	–	–	1:1	–	–
cyclohexane	2:1[b]	2:1[b]	+[c]	1:1[b]	–[d]
tetrahydrofuran	2:1	1:1	1:1	1:1	–
dioxane	–	–	+	1:1	–
benzene	1:1	1:1	1:1	1:1	+[d]
toluene	–[b]	1:1[b]	+[c]	1:1[b]	–[d]
o-xylene	2:1[b]	1:1[b]	1:1[c]	1:1[b]	1:1[d]
m-xylene	2:1[b]	1:1[b]	1:1[c]	1:1[b]	1:1[d]
p-xylene	2:1[b]	+[b]	+[c]	1:1[b]	1:1[d]
naphthalene	2:1[b]	1:1[b]	+[c]	1:1[b]	1:1[d]
anthracene	1:1[b]	1:1[b]	1:1[c]	1:1[b]	1:1[d]
pyrene	1:1[b]	+[b]	2:1[c]	2:1[b]	+[d]

[a] Determined by ^{1}H NMR integration: + host-guest ratio is not clear; – host-guest complex does not form. As a solvent or co-solvent CH_2CL_2[b], MeOH[c], or THF[d] was used.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 60 MHz in $CDCl_3$, unless otherwise indicated, on a Hitachi R-600 or Hitachi R-90 spectrometer (90 MHz), chemical shifts being reported in δ ppm relative to TMS as an internal standard. IR and mass (70 eV, unless otherwise indicated) spectra were recorded on a Hitachi EPI-S2 and on a Hitachi UMU-6MG spectrometers, respectively.

Table 2 Association constants for 1:1 complexes between tetraazametacyclophanenes and aromatic guests in aqueous solution (pH = 1.0) determined by solid-liquid extraction

	$K_a(M^{-1})$			
Guest	**8b**	**9**	**10**	$G_{max}(M^{-1})$[a]
phenanthrene	$(1.5 \pm 0.1) \times 10^5$	$(1.3 \pm 0.1) \times 10^3$	$(7.0 \pm 0.1) \times 10^3$	6.5×10^{-5}
anthracene	$(1.4 \pm 0.1) \times 10^4$	$(3.5 \pm 0.1) \times 10^3$	$(4.6 \pm 0.1) \times 10^3$	2.7×10^{-6}
pyrene	$(1.2 \pm 0.1) \times 10^4$	$(5.0 \pm 0.1) \times 10^3$	$(3.0 \pm 0.1) \times 10^3$	6.0×10^{-7}
acenaphthylene	$(1.6 \pm 0.1) \times 10^3$	$(2.0 \pm 0.1) \times 10^3$	$(1.2 \pm 0.1) \times 10^2$	7.3×10^{-5}

[a] Maximum solubility of aromatic guest in aqueous solution (pH = 1.0).

2,2-Bis(3-chloromethyl-4-methoxyphenyl)propane (3)
To a solution of 2,2-bis(4-methoxyphenyl)propane **2b** (5.0 g, 20 mmol) in a mixture of acetic acid (25 mL) and concentrated HCl (25 mL) was added paraformaldehyde (1.5 g, 50 mmol) and H_3PO_4 (8 mL) and the mixture was stirred at 80°C for 4 h. Water (100 mL) was added to the reaction mixture and the aqueous mixture was extracted with $CHCl_3$ (4 × 50 mL); combined organic extracts were washed with water (4 × 300 mL), dried over Na_2SO_4, and concentrated in vacuo to a give dark oil. Purification by column chromatography on silica gel (Wako C-200; $CHCl_3$/hexane 1:2), followed by recrystallization from hexane gave **3** (6.3 g, 92%): colorless prisms, mp 101–102 °C; ^{1}H NMR 1.65 (s, 6H), 3.86 (s, 6H), 4.62 (s, 4H), 6.84 (d, J = 8Hz, 2H), 7.18 (dd, J = 8 and 2Hz, 2H), 7.27 (d, J = 2Hz, 2H); IR ($CHCl_3$) 3000, 2840, 1600, 1580, 1500, 1260, 1180 cm^{-1}; MS m/z 352 (M^+, 100%). Anal. Calcd for $C_{19}H_{22}O_2Cl_2$: C, 64.59; H, 6.28. Found: C, 64.89; H, 6.39.

2,2-Bis(3-formyl-4-methoxyphenyl)propane (4b)
A mixture of bischloromethyl derivative **3** (2.0 g, 5.7 mmol) and hexamethylenetetramine (1.6 g, 11.4 mmol) in $CHCl_3$ (25 mL) was heated at reflux for 8 h. The solvent was removed under reduced pressure to afford a pale yellow oil. Water (40 mL) was added to the residual oil and the mixture was refluxed for 4 h. The reaction mixture was extracted with $CHCl_3$, washed with water (2 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatographic separation of the crude product on silica gel (Wako C-200; $CHCl_3$) and recrystallization from a mixture of EtOAc and hexane gave **4b** (1.1 g, 65%): colorless prisms, mp 144–145°C; ^{1}H NMR 1.58 (s, 6H), 3.98 (s, 6H), 6.98 (d, J = 8Hz, 2H), 7.48 (dd, J = 8 and 2Hz, 2H), 7.93 (d, J = 2Hz, 2H), 10.67 (s, 2H); IR ($CHCl_3$) 2940, 2840, 1680, 1500, 1380, 1250, 1080 cm^{-1}; MS m/z 312 (M^+, 30%). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.79; H, 6.38.

13,13,30,30-Tetramethyl-9,17,26,34-tetramethoxy-3,6,20,23-tetraazapentacyclo[29.3.1.1.^{8,12}.1^{14,18}.1^{25,29}]octatriaconta-1(35)2,6,8,10,12(36),14,16,18(37),19,23,25,27,29(38),31,33-hexadecaene (6b)
A solution of the dialdehyde **4b** (1.2 g, 3.9 mmol) in $CHCl_3$ (100 mL) and a solution of 1,2-diaminoethane (0.23 g, 3.9 mmol) in $CHCl_3$ (100 mL) were added simultaneously to CH_3Cl (100 mL) over a period of 9 h with stirring under N_2 atmosphere at room temperature. After the addition the mixture was stirred for another 24 h at room temperature. The reaction mixture was dried over Na_2SO_4 and concentrated. The residue was crystallized from a mixture of $CHCl_3$ and hexane (1:2) to give **6b** (1.2 g, 92%): colorless powder, mp 236–238°C; ^{1}H NMR (90 MHz) 1.72 (s, 12H), 3.75 (s, 12H), 3.95 (s, 8H), 6.50–7.20 (m, 8H), 7.80–8.00 (m, 4H), 8.75 (s, 4H); IR ($CHCl_3$) 2960, 2900, 2840, 1640, 1600, 1500, 1250, 1180, 1130 cm^{-1}; MS m/z 672 (M^+, 100%). Anal. Calcd for $C_{42}H_{48}N_4O_4 \cdot H_2O$: C, 73.01; H, 7.30; N, 8.11. Found: C, 73.19; H, 7.11; N, 7.66.

13,13,30,30-Tetramethyl-9,17,26,34-tetramethoxy-3,6,20,23-tetraazapentacyclo[29.3.1.1.^{8,12}.1^{14,18}.1^{25,29}]octatriaconta-1(35),8,10,12(36),14,16,18(37),25,27,29(38),31,33-dodecaene (8b)
Lithium aluminum hydride (0.38 g, 10 mmol) was added dropwise to a solution of the Schiff base **6b** (0.67 g, 1.0 mmol) in THF (100 mL) under ice-cooling with stirring, and the mixture was refluxed for 6 h. After cooling, benzene, MeOH, and then water were added to the reaction mixture to quench excess $LiAlH_4$. The precipitates were filtered off and the organic solvents were evaporated from the filtrate under reduced pressure. The residue was extracted with $CHCl_3$ (3 × 50 mL). The extracts were washed with water (2 × 100 mL) and saturated NaCl solution (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to leave the crude product, which was purified by recrystallization ($CHCl_3$/hexane 1:2) to afford **8b** (0.5 g, 74%): pale yellow powder, mp 96–101°C; ^{1}H NMR (90 MHz) 1.61 (s, 12H), 2.20–2.90 (broad s, 12H), 3.30–3.90 (broad s, 20H), 6.55–6.80 (m, 4H), 6.85–7.15 (s, 8H); IR ($CHCl_3$) 2960, 2840, 1610, 1500, 1460, 1250, 1150, 1030, 810 cm^{-1}; MS (20 eV) m/z 680 (M^+, 7%). Anal. Calcd for $C_{42}H_{56}N_4O_4 \cdot 1/2H_2O$: C, 73.12; H, 8.33; N, 8.12. Found: C, 73.41; H, 7.92; N, 7.21.

14,14,32,32-Tetramethyl-10,18,28,36-tetramethoxy-3,7,21,25-tetraazapentacyclo[31.3.1.1^{9,13}.1^{15,19}.1^{27,31}]-tetraconta-1(37),2,7,9,11,13(38),15,17,19(39),20,25,27,29,31(40),33,35-hexadecaene (7)
A solution of the dialdehyde **4b** (312 mg, 1 mmol) in $CHCl_3$ (20 mL) and a solution of 1,2-diaminopropane (74 mg, 1 mmol) in $CHCl_3$ (20 mL) were added simultaneously to $CHCl_3$ (20 mL) over a period of 9 h with stirring under N_2 atmosphere at room temperature. After the addition the mixture was stirred for another 24 h at room temperature. After the work-up described for the synthesis of **6b**, recrystallization of the product from a mixture of benzene and hexane (1:2) yielded **7** (290 mg, 83%): pale yellow powder, mp 133–135°C; ^{1}H NMR 1.72 (s, 12H), 1.98–2.42 (m, 4H), 3.45–4.10 (m, 20H), 6.60–7.40 (m, 8H), 7.80–8.19 (m, 4H), 8.80 (s, 4H); IR ($CHCl_3$) 2940, 2840, 1640, 1600, 1500, 1260, 1150, 920, 810 cm^{-1}; MS m/z 700 (M^+, 40%). Anal. Calcd for $C_{44}H_{52}N_4O_4 \cdot 1/2H_2O$:

C, 74.55; H, 7.39; N, 7.91. Found: C, 74.60; H, 7.56; N, 7.54.

14,14,32,32-Tetramethyl-10,18,28,36-tetramethoxy-3,7,21,25-tetraazapentacyclo[31.3.1.1^{9,13}.1^{15,19}.1^{27,31}]-tetraconta-1(37),9,11,13(38),15,17,19(39),27,29,31(40),33,35-hexadecaene (9)

The Schiff base **7** (290 mg, 0.4 mmol) was reduced with $LiAlH_4$ (152 mg, 4 mmol) in THF (100 mL) as described for the synthesis of **8b**. The crude product was recrystallized from a mixture of benzene and hexane (1:2) and dried (50 °C/3 Torr, 5 h) to afford **9** (260 mg, 90%): pale yellow powder, mp 71–74°C; ^{1}H NMR 1.50–1.90 (broad s, 16H), 2.40–2.95 (m, 12H), 3.15–4.26 (m, 20H), 6.50–7.40 (m, 12H); IR ($CHCl_3$) 2900, 2830, 1600, 1500, 1260, 1150, 920, 810 cm^{-1}; MS (20 eV) m/z 708 (M^+, 27%). Anal. Calcd for $C_{44}H_{60}N_4O_4 \cdot 3H_2O$: C, 69.26; H, 8.72; N, 7.34. Found: C, 69.63; H, 8.68; N, 7.31.

Reimer-Tiemann reaction of bisphenol A

Chloroform (15 mL, 80 mmol) was added dropwise to a stirred solution of bisphenol A (4.6 g, 20 mmol) in 50% NaOH (44 mL) over a period of 4.5 h at 60–70°C, and the mixture was stirred for additional 4 h at the same temperature. After cooling the reaction mixture was acidified to pH 3 by adding 50% acetic acid and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was washed with water (3 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo to give a brown oil. Separation and purification of the oil by column chromatography on silica gel (Wako C-200) afforded 2-(3-formyl-4-hydroxyphenyl)-2-(4-hydroxyphenyl)-propane **5a** (1.8 g, 38%) and 2,2-bis(3-formyl-4-hydroxyphenyl)propane **4a** (1.0 g, 18%). **5a**: colorless prisms, mp 103–104°C; ^{1}H NMR 1.73 (s, 6H), 6.63–7.48 (m, 7H), 9.79 (s, 1H); IR ($CHCl_3$) 3600, 3000, 2850, 1660, 1600, 1500, 1280, 1180, 840 cm^{-1}; MS m/z 256 (M^+, 32%). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.08; H, 6.29. **4a**: colorless prisms, mp 74–75°C; ^{1}H NMR 1.73 (s, 6H), 6.94 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 2H), 7.48 (d, J = 2 Hz, 2H), 9.79 (s, 2H); IR ($CHCl_3$) 3600, 3000, 2850, 1660, 1600, 1500, 1280, 1180, 840 cm^{-1}; MS m/z 284 (M^+, 100%). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.80; H, 5.63.

13,13,30,30-Tetramethyl-9,17,26,34-tetrahydroxy-3,6,20,23-tetraazapentacyclo[29.3.1.1.^{8,12}.1^{14,18}.1^{25,29}]octatriaconta-1(35),2,6,8,10,12(36),14,16,18(37),19,23,25,27,29(38),31,33-hexadecaene (6a)

A solution of the dialdehyde **4a** (2.8, 10 mmol) in $CHCl_3$ (100 mL) and a solution of 1,2-diaminoethane (0.6 g, 10 mmol) in $CHCl_3$ (100 mL) were added simultaneously to CH_3Cl (300 mL) over a period of 16 h with stirring under N_2 atmosphere at room temperature. After the addition the mixture was stirred for another 16 h at room temperature. After the work-up described for the synthesis of **6b**. The crude product was recrystallized from benzene and dried (100°C/2 Torr, 3 h) to yield **6a** (2.5 g, 81%): pale yellow powder, mp 231–234°C; ^{1}H NMR 1.55 (s, 12H), 3.82 (s, 8H), 6.7–7.3 (m, 12H), 8.32 (s, 4H); IR (KBr) 3420, 2980, 1630, 1600, 1500, 1370, 1290, 1240, 1190, 830 cm^{-1}; MS m/z 616 (M^+, 7%). Anal. Calcd for $C_{38}H_{40}N_4O_4$: C, 74.01; H, 6.53; N, 9.09. Found: C, 73.78; H, 6.51; N, 8.95.

8,8,25,25-Tetramethyl-4,12,21,29-tetramethoxy-1,15,18,32-tetraazaheptacyclo[30.2.2.2.^{15,18}.1^{3,7}.1^{9,13}.1^{20,24}.1^{26,30}]-dodetetraconta-3,5,7(39),9,11,13(40),20,22,24(42)-dodecaene (10)

A solution of the bischloromethyl derivative **3** (1.1 g, 3.0 mmol) in $CHCl_3$ (100 mL) and a solution of piperazine (0.26 g, 3.0 mmol) in $CHCl_3$ (100 mL) were added simultaneously under N_2 atmosphere to a solution of Et_3N (1.2 g, 12 mmol) in $CHCl_3$ (200 mL) over a period of 9 h at room temperature. Then the mixture was stirred for 17 h. The reaction mixture was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by recrystallization (benzene/hexane 1:3) yielded **10** (1.0 g, 94%): colorless powder, mp 110–115°C; ^{1}H NMR 1.68 (s, 12H), 2.34 (s, 8H), 2.50 (s, 8H), 3.35 (s, 8H), 3.79 (s, 12H), 6.60–6.85 (m, 4H), 6.85–7.25 (m, 8H); IR ($CHCl_3$) 2950, 1600, 1500, 1460, 1260, 1150, 1030, 810 cm^{-1}; MS m/z 732 (M^+, 59%). Anal. Calcd for $C_{48}H_{60}N_4O_4 \cdot 4H_2O$: C, 68.63; H, 8.51; N, 6.96. Found: C, 68.08; H, 8.47; N, 6.21.

2-(3-Formyl-4-methoxyphenyl)-2-(4-methoxyphenyl)-propane (5b)

The monoformyl derivative of bisphenol A **5a** was converted into the dimethoxy derivative **5b** by the action of Me_2SO_4 in aqueous KOH solution. The crude product was purified by column chromatography on silica gel (Wako C-200, AcOEt/hexane 1:8). **5b**: pale yellow oil; ^{1}H NMR 1.68 (s, 6H), 3.81 (s, 3H), 3.95 (s, 3H), 6.77–7.68 (m, 5H), 7.95 (d, J = 2 Hz, 1H), 10.67 (s, 2H); IR (CCl_4) 2970, 2830, 1680, 1500, 1380, 1250, 1080, 820 cm^{-1}; MS m/z 284 (M^+, 38%). Anal. Calcd for $C_{18}H_{20}NO_3$: C, 76.04; H, 7.08. Found: C, 75.95; H, 7.07.

1,6-Bis[2-methoxy-5-[2-(4-methoxyphenyl)propane-2-yl]-phenyl]-2,5-diazahexa-1,5-diene (11)

To a stirred solution of the monoformyl compound **5b** (5.3 g, 18.7 mmol) in CH_2Cl_2 (150 mL) was added

dropwise 1,2-diaminoethane (0.56 g, 9.8 mmol) in CH_2Cl_2 (50 mL) over a period of 80 min at room temperature under N_2 atmosphere, and the mixture was stirred for 5 h. The reaction mixture was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was recrystallized from a mixture of benzene and hexane (1:1) to give **11** (4.6 g, 84%): pale yellow needles, mp 121–123°C; ^{1}H NMR 1.72 (s, 12H), 3.75 (s, 12H), 3.95 (s, 4H), 6.62–7.33 (m, 12H), 8.00 (d, J = 2Hz, 2H), 8.75 (s, 2H); IR (CCl_4) 2960, 2900, 2830, 1680, 1600, 1500, 1460, 1440, 1370, 1250, 1180, 830 cm^{-1}; MS m/z 592 (M^+, 3%). Anal. Calcd for $C_{38}H_{44}N_2O_4$: C, 77.00; H, 7.48; N, 4.73. Found: C, 77.12; H, 7.53; N, 4.67.

1,6-Bis[2-methoxy-5-[2-(4-methoxyphenyl)propane-2-yl]-phenyl]-2,5-diazahexane (12)

The Schiff bbase 11 (3.0 g, 5.1 mmol) was reduced with $LiAlH_4$ (1.0 g, 30 mmol) in THF (100 mL) as described for the synthesis of **8b**. The crude product was purified by column chromatography on alumina (Wako 200, $CHCl_3$) to afford **12** (1.9 g, 63%): pale yellow oil; ^{1}H NMR 1.61 (s, 12H), 2.20–2.90 (broad s, 8H), 3.30–3.90 (broad s, 14H), 6.55–7.23 (m, 14H); IR 3470, 2960, 2900, 2840, 1600, 1500, 1460, 1250, 1150, 830 cm^{-1}; MS m/z 596 (M^+, 53%). Anal. Calcd for $C_{38}H_{48}N_2O_4$: C, 76.48: H, 8.10; N, 4.69. Found: C, 76.96; H, 8.24; N, 4.61.

Preparation of crystalline inclusion compounds (general procedure)

The macrocycle was dissolved in minimum amount of organic solvent (liquid guest) or with solid in MeOH or CH_2Cl_2 by heating and the solution was cooled to room temperature. The precipitates were filtered, where necessary, washed with hexane, and dried at room temperature for 12 h. The host-guest ratio was determined by ^{1}H NMR spectroscopy.

Determination of association constants

The procedure is virtually similar to that described by Diederich and Dick.[5] The association constant K_a for the 1:1 host-guest complexation were calculated according to the equations 1 and 2; [HG], [H], and [G] refer to the concentrations of the complex HG, the uncomplexed metacyclophane H, and the uncomplexed aromatic hydrocarbon G in the system described below, respectively.

$$H + G \rightleftharpoons HG \quad (1)$$

$$K_a = [HG]/[H][G] \quad (2)$$

A suspension of finely ground sample (ca. 100 mg) of the solid guest in an aqueous HCl solution (0.1 N, pH 1.0; 10 mL) of the host ($[H_o]$; total concentration of the host in the range of 10^{-5}–10^{-3} M) was exposed to ultrasonic irradiation in 15 min and shaken mechanically for another 15 min; the exposure to ultrasonic irradiation and shaking were repeated alternatively eight times. The suspension was centrifuged at 3000 rpm for 5 min and filtered. The filtrate was extracted with hexane (4 × 10 mL) and the amount of the guest present in the hexane was measured by UV spectroscopy, giving $[G_o]$($[G_o] = [G_{max}] + [G_c]$; $[G_o]$, $[G_{max}]$, and $[G_c]$ refer to the concentrations of the total guest, the uncomplexed and complexed guests in the aqueous solution, respectively). The value $[G_{max}]$ was obtained by the same procedure in the absence of the host. Thus, the concentrations of the complex [HG]($=[G_c] = [H_c]$; $[H_c]$ refer to the concentration of the complexed host) and the uncomplexed host [H] were calculated by subtractions, $[G_o] - [G_{max}]$ and $[H_o] - [H_c]$($=[H_o] - [HG]$), respectively. The concentration of the uncomplexed guest [G] is equal to the maximum solubility $[G_{max}]$ of the guest in the aqueous HCl solution.

The complexation studies were carried out under critical micelle concentration (cmc) of the hosts which were evaluated by ^{1}H NMR spectroscopy;[6] the cmc of the hosts were ca. 3.0×10^{-2} M for **8b** and **10** and 2.8×10^{-2} M for **9**.

ACKNOWLEDGMENT

The authors thank Mr. Kazuaki Sato for synthetic assistance and elemental analyses.

REFERENCES AND NOTES

1 (a) Diederich, F.; *Cyclophanes*, Royal Society of Chemistry: Cambridge, **1991**. (b) Odashima, K.; Koga, K.; in *Cyclophanes* (Keehn, P.M. and Rosenfield, S.M., eds.), Academic Press, New York, **1983**; Vol. II, pp. 629–678. (c) Murakami, Y.; in *Cyclophanes* (Vögtle, F., eds.), Springer-Verlag, Berlin Heiderberg, **1983**; Vol. II, pp. 107–155. (d) Tabushi, I.; Yamamura, K.; in *Cyclophanes* (Vögtle, F., eds.), Springer-Verlag, Berlin Heiderberg, **1983**; Vol. I, pp. 145–182.

2 (a) Moneta, W.; Baret, P.; Pierre, J.-L.; *J. Chem. Soc. Chem. Commun.* **1985**, 899. (b) Losensky, H.-W.; Spelthann, H.; Ehlen, A.; Vögtle, F.; Bargon, J.; *Angew. Chem. Int. Ed. Engl.* **1988**, 1189. (c) Hunter, C.A.; *J. Chem. Soc. Chem. Commun.* **1991**, 749.

3 Sone, T.; Ohba, Y.; Watanabe, R.; *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1346.

4 Jazwinski, J.; Lehn, J.-M.; Meric, R.; Vigneron, J.-P.; Cesario, M.; Guilhem, J.; Pascard, C.; *Tetrahedron Lett.* **1987**, *28*, 3489.

5 Diederich, F.; Dick, K.; *J. Am. Chem. Soc.* **1984**, *106*, 8024.

6 Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167.

7 Poh, B.-L.; Koay, L.-S.; *Tetrahedron Lett.* **1990**, *31*, 1911.

8 Gutsche, C.D.; Alam, I.; *Tetrahedron* **1988**, *44*, 4689.