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# Biomimetic Studies Using Artificial Systems. V.[1] Design and Synthesis of Novel Water-Soluble Bis-cyclophanes[2]

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**Novel water-soluble bis-cyclophanes (3a—c) with quaternary ammonium nitrogens, composed of two units of QCP44 (2) connected by appropriate bridges, were synthesized as hosts having two discrete hydrophobic cavities to bind two guest molecules simultaneously or a single guest molecule *via* double recognition in neutral water. Glutaryl, terephthaloyl and isophthaloyl groups were used as spacers to bridge the two cyclophane units. The bridge formation was carried out using 5 as an intermediate, in which three of the four nitrogens of CP44 (1) were protected. The details of the synthesis and characterization of duplex hosts (3a—c) as well as of the reference compounds (9—11) are described.**

**Keywords** macrocycle; water-soluble cyclophane; hydrophobic cavity; bis-cyclophane; dual binding sites; duplex host; synthesis; *N*-quaternization

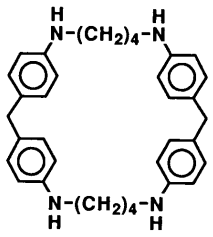
Life is a dynamic process which depends upon recognition (interaction) between inanimate molecules.[4] Such molecular complexation, highly structured, accounts for the high specificities and selectivities observed ubiquitously in biological reactions, such as those between enzymes and substrates, and antigens and antibodies. Accordingly, the design and synthesis of enzyme-mimicking host molecules will be one of the most promising strategies to effect highly efficient reactions in totally artificial systems.[5,6] Host molecules having two hydrophobic cavities as dual binding sites, capable of binding two guest molecules having a single recognizable site or a single guest molecule having two recognizable sites, will be of particular interest. Although some studies had been carried out on such duplex hosts based on cyclodextrins,[7] there has been no example of those based on water-soluble cyclophanes, a class of totally synthetic water-soluble hosts having hydrophobic cavities.[8]

We have designed and synthesized a series of paracyclophanes represented by 1,6,20,25-tetraaza[6.1.6.1]paracyclophane (CP44, **1**),[9] having diphenylmethane units as structural components for hydrophobic cavities. Direct evidence of the formation of 1 : 1 inclusion complexes with organic guests was obtained by an X-ray crystallographic study. Nuclear magnetic resonance (NMR) and fluorescence spectroscopies have confirmed that the inclusion complex formation occurs not only in the crystalline state but also in water (pH below 2).[10a] The complexation by these hosts was found to occur with a particular predominant geometry[10b] and with marked selectivity for aromatic guests.[10c] On the other hand, the complexation with aliphatic guests was negligible.[10c] It has also been shown that the *N*-quaternized derivative of CP44 (QCP44, **2**) retains binding ability and selectivity comparable to those of CP44 (**1**).[10d,e] QCP44 is a versatile modification of CP44 since it is highly soluble in water over the whole pH range.

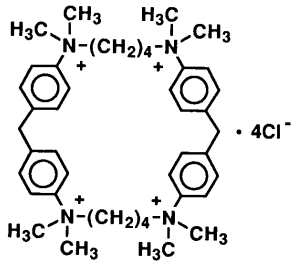
We have recently reported a series of bis-paracyclophanes (**3a—c**) having two QCP44 units connected by appropriate bridges.[2] These compounds were shown to function as duplex hosts, capable of binding two monoaromatic guests or one diaromatic guest with suitable structures to form 1 : 2 or 1 : 1 complexes, respectively. In this paper we describe the details of the synthesis and characterization of duplex hosts (**3a—c**) as well as of the reference compounds (**9—11**). The complexation properties of the duplex hosts toward mono- and diaromatic guests will be described elsewhere.[11]

## Results and Discussion

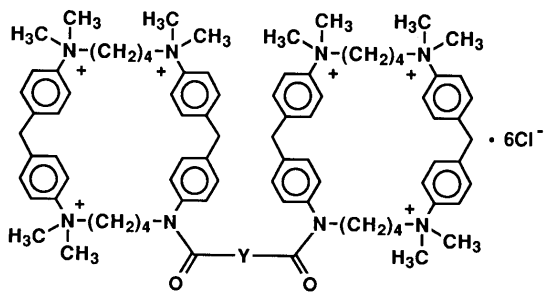
Bis-paracyclophanes (**3a—c**) were synthesized from CP44 (**1**)[10a] as shown in Chart 1. The first attempt to obtain the bridged compounds (**7a—c**) by a direct reaction of diacyl dichloride with an excess of **1** failed, because the reaction under various conditions led to a mixture of several products (intra- and intermolecular diamides) and in addition the products easily decomposed on silica gel column. In order to avoid these problems, the bridge formation was carried out for a CP44 derivative (**5**) in which three of the four nitrogens were protected. Compound **5** was prepared



1 (CP44)



2 (QCP44)



3a: Y = $-(CH_2)_3-$

3b: Y = 

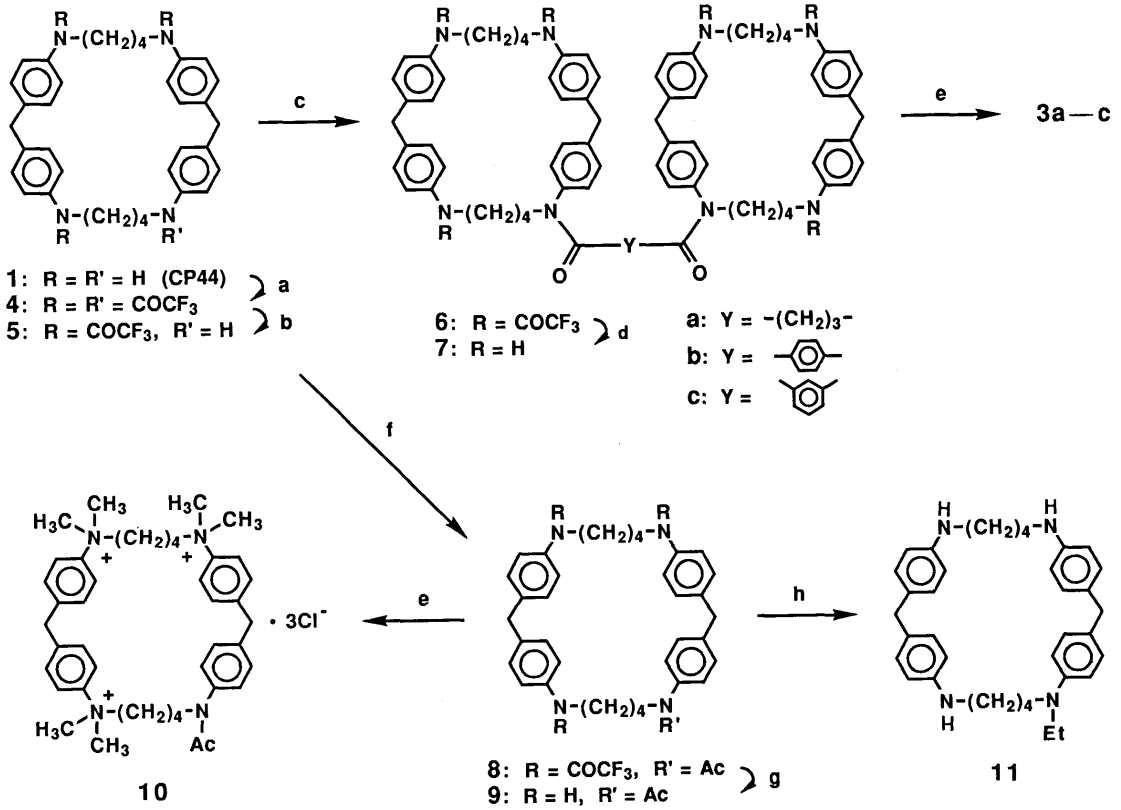
3c: Y = 

by partial hydrolysis of pertrifluoroacetylated CP44 (**4**), using a limited amount of base to avoid hydrolysis of more than one trifluoroacetyl group. Thus, treatment of **4** with 0.5 eq of KOH in tetrahydrofuran (THF)–MeOH gave a mixture containing mostly **4** and **5**. Since these were difficult to separate from each other in a preparative scale, the mixture was reacted directly with diacyl dichlorides. The resulting diamides (**6a—c**), which are stable on silica gel column in contrast to unprotected hexaamines (**7a—c**), were easily separated from the unhydrolyzed pertrifluoroacetylated CP44 (**4**). Hydrolysis of the trifluoroacetyl groups of **6a—c** afforded hexaamines (**7a—c**), which were pure enough to use in the next reaction without purification. The exhaustive *N*-quaternization of **7a—c** was carried out by the procedure of Sommer and Jackson (methyl iodide–tri-*n*-butylamine).[12] The reaction was carefully followed by high performance liquid chromatography (HPLC) using a cation exchange column. The quaternized compounds (iodides) were converted to the chlorides by an ion exchange column (Dowex 1 (Cl)) and purified by repeated reprecipitation from MeOH–$Et_2O$. A series of reference compounds, unquaternized (**9** and **11**) and quaternized (**10**), were also synthesized as shown in Chart 1. Compounds **9** and **10** were synthesized in a similar manner to **7** and **3**, respectively. Compound **11** was prepared by the reduction of **9** with $AlH_3$[13] prepared from $AlCl_3$ and $LiAlH_4$ in THF. Characterization of the target quaternized compounds (**3a—c** and **10**) was done with air-dried samples since they were nonhygroscopic and hence would be suitable for accurate weighing in complexation experiments. The structures of these compounds were confirmed on the bases of infrared (IR) and NMR spectra, and elemental analyses (C, H, Cl, N). All of the quaternized hosts (chlorides) are highly soluble in water, whereas the corresponding iodides are only slightly soluble.

## Experimental

**General** *N*,*N*-Dimethylformamide (DMF) was distilled under reduced pressure from molecular sieves (4A). $CHCl_3$ and $CH_2Cl_2$ were distilled over $P_2O_5$ before use. THF was freshly distilled from sodium–benzophenone ketyl under argon. Melting points were measured on a Buchi 510 melting point apparatus or a Yanaco micromelting point apparatus and are uncorrected. IR spectra were recorded on a JASCO DS-701G diffraction grating infrared spectrophotometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were measured on a JEOL JNM-FX 100 Fourier transform NMR spectrometer (100 MHz). Unless otherwise specified, chemical shifts are reported in $\delta$ values in ppm with tetramethylsilane (TMS) as an internal standard. In the case of using $D_2O$ as a solvent, a TMS capillary was used as an external standard. Coupling constants ($J$) are reported in hertz (Hz). Mass spectra (MS) were recorded on a JEOL JMS-01 SG-2 or a JEOL JMS-DX 300 mass spectrometer. For compounds **6b** and **7b**, ordinary electron impact (EI) and fast atom bombardment (FAB) MS were measured at the Faculty of Pharmaceutical Sciences, Kyushu University. HPLC was conducted with a Hitachi 635 liquid chromatograph, using a RADIAL PAK 8PSC × 10 $\mu$ (Waters Associates) with 0.75—1 M aqueous $Et_3N \cdot HBr$ in 45% $CH_3CN$ (v/v) (pH adjusted to 7) as an eluent. Detection was done at 254 nm. pH measurement was conducted with a Toyo digital pH/mV meter model PT-3D equipped with a glass electrode, using standard solutions of pH 6.88 and 10.02.

**1,6,20,25-Tetrakis(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (4)**[9,14] Trifluoroacetic anhydride (8.6 ml, 61 mmol) was added to a stirred solution of **1** (6.35 g, 12.6 mmol) in $CH_2Cl_2$ (250 ml). Stirring was carried out at room temperature for 5 h, then an additional 8.6 ml (61 mmol) of trifluoroacetic anhydride was added, and the stirring was continued at room temperature overnight. Evaporation of the reaction mixture gave **4** as a white solid (10.75 g, 96%), which was recrystallized from




a, $(CF_3CO)_2O$, $CH_2Cl_2$; b, KOH, THF–MeOH; c, diacyl dichloride, $Et_3N$, $ClCH_2CH_2Cl$; d, KOH, DMF (or THF)–MeOH; e, MeI, $(n\text{-}Bu)_3N$, DMF; f, AcCl, $Et_3N$, $CH_2Cl_2$; g, KOH, THF–MeOH; h, $AlCl_3$, $LiAlH_4$, THF.

Chart 1

$CHCl_3$–EtOH and then $CH_2Cl_2$–hexane to give an analytical sample. Colorless prisms, mp 297—299 °C. IR (KBr) $cm^{-1}$: 1691 ($CF_3\underline{C}ONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.57 (8H, br, $NCH_2C\underline{H}_2$), 3.71 (8H, br, $NC\underline{H}_2CH_2$), 4.01 (4H, s, $ArC\underline{H}_2Ar$), 7.03 and 7.19 (each 8H, two d, $J$=8.3 Hz, Ar$\underline{H}$ (*ortho*, *meta*)). MS *m/z*: 888 ($M^+$). *Anal.* Calcd for $C_{42}H_{36}F_{12}N_4O_4$: C, 56.76; H, 4.08; N, 6.30. Found: C, 57.02; H, 4.33; N, 6.02.

**1,6,20-Tris(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (5)**[14] In a typical experiment, a solution of KOH (111 mg, 1.7 mmol) in THF–MeOH (1 : 1, 84 ml) was added dropwise to a stirred solution of **4** (3.01 g, 3.39 mmol) in THF (420 ml) over a period of 35 min. After stirring at room temperature overnight, the reaction mixture was evaporated. $CH_2Cl_2$ (400 ml) and saturated $NaHCO_3$ (300 ml) were added to the residue, and the organic layer was washed successively with water (300 ml) and brine (300 ml), dried over anhydrous $K_2CO_3$, filtered, and evaporated to give a mixture containing mostly **4** and **5** (2.73 g, **5**:**4**≈1 : 1 by $^1$H-NMR). This mixture was used directly in the next step without purification. An analytical sample of **5** was obtained by repeated column chromatography (silica gel, $CH_2Cl_2$–EtOAc (40 : 1)) and recrystallization from $CH_2Cl_2$–EtOH. White needles, mp 231—232 °C (dec.). IR (KBr) $cm^{-1}$: 3400 (N$\underline{H}$), 1685 ($CF_3\underline{C}ONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.61 (8H, br, $NCH_2C\underline{H}_2$), 3.11 (2H, br, $HNC\underline{H}_2CH_2$), 3.65 (7H, br, $CF_3CONC\underline{H}_2CH_2$ and N$\underline{H}$), 3.84 and 4.00 (each 2H, two s, $ArC\underline{H}_2Ar$), 6.50 (2H, d, $J$= 8.4 Hz, HNAr$\underline{H}$ (*ortho*)), 7.1 (14H, m, the rest of the aromatic protons). MS *m/z*: 792 ($M^+$). *Anal.* Calcd for $C_{40}H_{37}F_9N_4O_3$: C, 60.60; H, 4.70; N, 7.07. Found: C, 60.60; H, 4.79; N, 7.23.

**1,1′-Terephthaloylbis[6,20,25-tris(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane] (6b)** The crude partial hydrolysis product containing mostly **4** and **5**, obtained by the tretment of **4** (3.9 g, 4.4 mmol) with KOH (0.12 g, 1.8 mmol) as described above, was evaporated with benzene to remove water and suspended in 1,2-dichloroethane (100 ml). To this suspension, triethylamine (222 mg, 2.19 mmol) was added with stirring, and then a 0.038 M solution of terephthaloyl dichloride in 1,2-dichloroethane was added dropwise at reflux until the starting material **5** was no longer detectable on thin layer chromatography (TLC) (18 ml of the terephthaloyl dichloride solution (0.68 mmol) was added over a period of 45 min). MeOH (2 ml) was added to the reaction mixture and the stirring was continued at room temperature for 30 min to destroy excess diacyl dichloride. The reaction mixture was evaporated, and the residue was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOAc (10 : 1)) to give **6b** (1.1 g, 63% corrected yield based on the recovery of **4**), which was reprecipitated from $CH_2Cl_2$–$Et_2O$ to give an analytical sample. White powder, mp 240—242 °C (dec.). IR ($CHCl_3$) $cm^{-1}$: 1690 ($CF_3\underline{C}ONR_2$), 1640 ($ArC\underline{O}NR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.56 (16H, br, $NCH_2C\underline{H}_2$), 3.68 (16H, br, $NC\underline{H}_2CH_2$), 3.88 and 3.96 (each 4H, two s, $ArC\underline{H}_2Ar$), 6.5—7.6 (36H, m, Ar$\underline{H}$). MS *m/z*: 1714 ($M^+$). *Anal.* Calcd for $C_{88}H_{76}F_{18}N_8O_8$: C, 61.61; H, 4.47; N, 6.53. Found: C, 61.42; H, 4.35; N, 6.72.

**1,1′-Terephthaloylbis[1,6,20,25-tetraaza[6.1.6.1]paracyclophane] (7b)** A solution of KOH (3.25 g, 49 mmol) in DMF–MeOH (1 : 1, 80 ml) was added to a stirred solution of **6b** (1.90 g, 1.11 mmol) in DMF (40 ml) under argon, and the stirring was continued at room temperature for 6 d. Precipitates appeared after stirring overnight, but the completion of the hydrolysis required additional 5 d. After addition of water (20 ml), the precipitates were collected and washed successively with MeOH and water. The crude product was reprecipitated twice from $CH_2Cl_2$–hexane to give pure **7b** (0.93 g, 71%). White powder, mp 282—284 °C (dec.). IR (KBr) $cm^{-1}$: 3380 (N$\underline{H}$), 1630 ($ArC\underline{O}NR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.66 (16H, br, $NCH_2C\underline{H}_2$), 3.06 (18H, br, $\underline{H}NC\underline{H}_2CH_2$), 3.71 and 3.72 (each 4H, two s, $ArC\underline{H}_2Ar$), 3.79 (4H, br, $CONC\underline{H}_2CH_2$), 6.2—7.3 (36H, m, Ar$\underline{H}$). MS *m/z*: 1138 ($M^+$). FAB-MS *m/z*: 1139 ($M^+$+1). *Anal.* Calcd for $C_{76}H_{82}N_8O_2$: C, 80.11; H, 7.25; N, 9.83. Found: C, 79.80; H, 7.29; N, 9.79.

**1,1′-Terephthaloylbis[6,6,20,20,25,25-hexamethyl-1-aza-6,20,25-triazonia[6.1.6.1]paracyclophane] Hexachloride (3b)** A large excess of methyl iodide (4.4 g, 31 mmol) was added dropwise to a stirred and ice-cooled suspension of **7b** (146 mg, 0.128 mmol) and tri-*n*-butylamine (0.42 ml, 1.8 mmol) in DMF (50 ml), and the stirring was continued at room temperature for 6 d. The progress of quaternization was checked by HPLC using 1.0 M $Et_3N\cdot HBr$ in $CH_3CN$–$H_2O$ as an eluent, as described above in General. The reaction mixture was concentrated under vacuum to *ca.* 20 ml and poured into acetone (500 ml). After standing for *ca.* 2 h, the resulting hygroscopic precipitates were separated by decantation, and applied to an anion exchange column (Dowex 1, Cl form) to exchange the counter anion from iodide to chloride (water as an eluent). After evaporation of the eluate, the residue was reprecipitated from MeOH–$Et_2O$ to give **3b** as a white powder (200 mg, 81%). An analytical sample was obtained by repeated reprecipitation from MeOH–$Et_2O$. The quaternized compound (**3b**) was hygroscopic and hence air-dried until the weight became constant. White powder, mp 155—157 °C (dec.). IR (KBr) $cm^{-1}$: 1622 ($ArC\underline{O}NR_2$). $^1$H-NMR ($D_2O$) $\delta$: 1.73 (16H, br, $NCH_2C\underline{H}_2$), 3.89, 3.95 and 4.00 (each 12H, three s, $N^+(C\underline{H}_3)_2$), 4.22 (16H, br, $NC\underline{H}_2CH_2$), 4.48 and 4.49 (each 4H, two s, $ArC\underline{H}_2Ar$), 7.0—8.3 (36H, m, Ar$\underline{H}$). *Anal.* Calcd for $C_{88}H_{112}Cl_6N_8O_2\cdot 23H_2O$: C, 54.46; H, 8.21; Cl, 10.96; N, 5.77. Found: C, 54.22; H, 8.51; Cl, 10.69; N, 5.87.

**1,1′-Glutarylbis[6,20,25-tris(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1.]paracyclophane] (6a)** The crude partial hydrolysis product containing mostly **4** and **5**, obtained by the treatment of **4** (8.85 g, 9.96 mmol) with KOH (0.28 g, 4.2 mmol) as described above, was evaporated with benzene to remove water and suspended in 1,2-dichloroethane (200 ml). To this suspension, triethylamine (413 mg, 4.08 mmol) was added with stirring, and then a solution of glutaryl dichloride (312 mg, 1.85 mmol) in 1,2-dichloroethane (30 ml) was added dropwise over a period of 2 h. After stirring at room temperature for 1 h, MeOH (4 ml) was added to the reaction mixture and the stirring was continued at room temperature for 30 min. The reaction mixture was evaporated, and the residue was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOAc (10 : 1)) and recrystallization from $CH_2Cl_2$–$Et_2O$ to give **6a** as rosette crystals (1.90 g, 70% corrected yield based on the recovery of **4**), mp 191—194 °C (dec.). IR (KBr) $cm^{-1}$: 1685 ($CF_3\underline{C}ONR_2$), 1650 ($CH_2\underline{C}ONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.52 (18H, br, $NCH_2C\underline{H}_2$ and $COCH_2C\underline{H}_2$), 1.97 (4H, br, $COC\underline{H}_2CH_2$), 3.68 (16H, br, $NC\underline{H}_2CH_2$), 3.99 (8H, s, $ArC\underline{H}_2Ar$), 7.1 (32H, m, Ar$\underline{H}$). *Anal.* Calcd for $C_{85}H_{78}F_{18}N_8O_8$: C, 60.71; H, 4.68; N, 6.66. Found: C, 60.56; H, 4.63; N, 6.95.

**1,1′-Glutarylbis[1,6,20,25-tetraaza[6.1.6.1]paracyclophane] (7a)** A solution of KOH (4.4 g, 67 mmol) in MeOH (20 ml) was added to a solution of **6a** (1.90 g, 1.13 mmol) in THF (26 ml), and the stirring was continued at room temperature overnight. The reaction mixture was concentrated to a half volume and a small amount of water was added. The hexaamine (**7a**) separated as a yellowish white powder (1.1 g, 88%), which was pure enough to be used in the next step, mp 215—216 °C (dec.). IR (KBr) $cm^{-1}$: 3350 (N$\underline{H}$), 1630 ($CH_2\underline{C}ONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.6 (18H, br, $NCH_2C\underline{H}_2$ and $COCH_2C\underline{H}_2$), 1.90 (4H, br, $COC\underline{H}_2CH_2$), 3.08 (12H, m, $HNC\underline{H}_2CH_2$), 3.54 (4H, br, $CONC\underline{H}_2CH_2$), 3.72 and 3.82 (each 4H, two s, $ArC\underline{H}_2Ar$), 4.0 (6H, br, $\underline{H}NCH_2CH_2$), 6.5 (12H, m, HNAr$\underline{H}$ (*ortho*)), 6.9 (20H, m, the rest of the aromatic protons).

**1,1′-Glutarylbis[6,6,20,20,25,25-hexamethyl-1-aza-6,20,25-triazonia[6.1.6.1]paracyclophane] Hexachloride (3a)** This compound was prepared from **7a** (1.1 g, 0.99 mmol) in a manner similar to that described above for **3b**. Reprecipitation from MeOH–$Et_2O$ was repeated twice to give pure **3a** (1.3 g, 74%). White powder, mp 152—154 °C (dec.). IR (KBr) $cm^{-1}$: 1626 ($CH_2\underline{C}ONR_2$). $^1$H-NMR ($D_2O$) $\delta$: 1.69 (18H, br, $NCH_2C\underline{H}_2$ and $COCH_2C\underline{H}_2$), 1.89 (4H, br, $COC\underline{H}_2CH_2$), 3.85, 3.91 and 3.99 (each 12H, three s, $N^+(C\underline{H}_3)_2$), 4.19 (16H, br, $NC\underline{H}_2CH_2$), 4.56 (8H, s, $ArC\underline{H}_2Ar$), 7.19 (4H, d, $J$=8.4 Hz, CONAr$\underline{H}$ (*ortho* or *meta*)), 7.4—8.2 (28H, m, the rest of the aromatic protons). *Anal.* Calcd for $C_{85}H_{114}Cl_6N_8O_2\cdot 15H_2O$: C, 57.91; H, 8.23; Cl, 12.07; N, 6.36. Found: C, 57.99; H, 8.28; Cl, 11.96; N, 6.26.

**1,1′-Isophthaloylbis[6,20,25-tris(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane] (6c)** The crude partial hydrolysis product containing mostly **4** and **5**, obtained by the treatment of **4** (7.75 g, 8.72 mmol) with KOH (0.23 g, 3.5 mmol) as described above, was evaporated with benzene to remove water and suspended in 1,2-dichloroethane (200 ml). To this suspension, triethylamine (440 mg, 4.35 mmol) was added with stirring, and then a solution of isophthaloyl dichloride (310 mg, 1.53 mmol) in 1,2-dichloroethane (40 ml) was added dropwise at reflux over a period of 2 h. After stirring at room temperature for 1 h, MeOH (4 ml) was added to the reaction mixture and the stirring was continued at room temperature for 30 min. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOAc (10 : 1)) to give **6c** (1.8 g, 67% corrected yield based on the recovery of **4**). Recrystallization from $CH_2Cl_2$–$Et_2O$ gave fine white needles, mp 155—158 °C (dec.). IR (KBr) $cm^{-1}$: 1685 ($CF_3\underline{C}ONR_2$), 1640 ($ArC\underline{O}NR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.56 (16H, br, $NCH_2C\underline{H}_2$), 3.71 (16H, br, $NC\underline{H}_2CH_2$), 3.89 and 4.01 (each 4H, two s, $ArC\underline{H}_2Ar$), 6.6—7.6 (36H, m, Ar$\underline{H}$). *Anal.* Calcd for $C_{88}H_{76}F_{18}N_8O_8\cdot 0.8CH_2Cl_2$: C, 59.80; H, 4.39; N, 6.28. Found: C, 59.84; H, 4.10; N, 6.44.

**1,1′-Isophthaloylbis[1,6,20,25-tetraaza[6.1.6.1]paracyclophane] (7c)** This compound was obtained from **6c** (727 mg, 0.424 mmol) in a manner similar to that described above for **7a**, and was used in the next step without purification. Yellowish white powder (330 mg, 68%), mp 140—145 °C (dec.). IR (KBr) $cm^{-1}$: 3380 (N$\underline{H}$), 1630 ($ArC\underline{O}NR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.62 (16H, br, $NCH_2C\underline{H}_2$), 2.4 (6H, br, $\underline{H}NCH_2CH_2$), 3.08

(12H, br, $HNCH_2CH_2$), 3.67 and 3.70 (each 4H, two s, $ArCH_2Ar$), 3.78 (4H, br, $CONCH_2CH_2$), 6.2—7.3 (36H, m, ArH).

**1,1′-Isophthaloylbis[6,6,20,20,25,25-hexamethyl-1-aza-6,20,25-triazonia-[6.1.6.1]paracyclophane] Hexachloride (3c)** This compound was prepared from **7c** (81 mg, 0.071 mmol) in a manner similar to that described above for **3b**. Reprecipitation from MeOH–$Et_2O$ was repeated twice to give pure **3c** (106 mg, 79%). White powder, mp 152—154 °C (dec.). IR (KBr) $cm^{-1}$: 1626 ($ArCONR_2$). $^1$H-NMR ($D_2O$) $\delta$: 1.74 (16H, br, $NCH_2CH_2$), 3.88, 3.93 and 3.96 (each 12H, three s, $N^+(CH_3)_2$), 4.21 (16H, br, $NCH_2CH_2$), 4.44 and 4.55 (each 4H, two s, $ArCH_2Ar$), 6.8—8.4 (36H, m, ArH). *Anal.* Calcd for $C_{88}H_{112}Cl_6N_8O_2 \cdot 20H_2O$: C, 56.02; H, 8.12; Cl, 11.27; N, 5.94. Found: C, 56.35; H, 7.97; Cl, 11.44; N, 6.12.

**1-Acetyl-6,20,25-tris(trifluoroacetyl)-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (8)** The crude product containing mostly **4** and **5**, obtained by partial hydrolysis of **4** (1.78 g, 2.00 mmol) as described above, was reacted with acetyl chloride in a manner similar to that described for **6a—c** except that $CH_2Cl_2$ was used as a solvent. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, $CH_2Cl_2$) to give **8** as white needles (420 mg, 75% corrected yield based on the recovery of **4** (1.1 g, 60%)). This product was recrystallized from $CH_2Cl_2$–$Et_2O$ to give an analytical sample. White needles, mp 263—264 °C (dec.). IR (KBr) $cm^{-1}$: 1680 ($CF_3CONR_2$), 1650 ($CH_3CONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.54 (8H, br, $NCH_2CH_2$), 1.74 (3H, s, $COCH_3$), 3.70 (8H, br, $NCH_2CH_2$), 4.00 (4H, s, $ArCH_2Ar$), 7.2 (16H, m, ArH). MS *m/z*: 834 ($M^+$). *Anal.* Calcd for $C_{42}H_{39}F_9N_4O_4$: C, 60.43; H, 4.71; N, 6.71. Found: C, 60.18; H, 4.71; N, 6.90

**1-Acetyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (9)**[14] This compound was obtained from **8** (120 mg, 0.144 mmol) in a manner similar to that described above for **7a**. The crude product was used in the next step without purification. White powder (67 mg, 85%), mp 203—205 °C (dec.). IR (KBr) $cm^{-1}$: 3350 (NH), 1640 ($CH_3CONR_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.53 (6H, br, $HNCH_2CH_2$), 1.72 (2H, br, $CONCH_2CH_2$), 1.80 (3H, s, $COCH_3$), 1.8 (3H, br, NH), 3.1 (6H, br t, $HNCH_2CH_2$), 3.6 (2H, br, $CONCH_2CH_2$), 3.75 and 3.85 (each 2H, two s, $ArCH_2Ar$), 6.3—7.3 (16H, m, ArH). MS *m/z*: 546 ($M^+$).

**1-Acetyl-6,6,20,20,25,25-hexamethyl-1-aza-6,20,25-triazonia[6.1.6.1]-paracyclophane Trichloride (10)** This compound was prepared from **9** (36 mg, 0.066 mmol) in a manner similar to that described above for **3b**. The reaction was faster and was completed within 4 d. The HPLC check was made with 0.75 M $Et_3N \cdot HBr$ in $CH_3CN$–$H_2O$. Reprecipitation from MeOH–$Et_2O$ was repeated twice to give pure **10** as white powder (31 mg, 52%), mp 131—132 °C (dec.). IR (KBr) $cm^{-1}$: 1623 ($CH_3CONR_2$). $^1$H-NMR ($D_2O$) $\delta$: 1.65 (3H, s, $COCH_3$), 1.75 (8H, br, $NCH_2CH_2$), 3.75, 3.92 and 4.04 (each 6H, three s, $N^+(CH_3)_2$), 4.0 (8H, br, $NCH_2CH_2$), 4.59 and 4.61 (each 2H, two s, $ArCH_2Ar$), 7.05 (2H, d, $J$=8 Hz, CONArH (*ortho* or *meta*), 7.5—8.4 (14H, m, ArH). *Anal.* Calcd for $C_{42}H_{57}Cl_3N_4O \cdot 9H_2O$: C, 55.90; H, 8.38; Cl, 11.79; N, 6.21. Found: C, 56.09; H, 8.61; Cl, 11.78; N, 6.05.

**1-Ethyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (11)** A mixture of $AlCl_3$ (1.33 g, 10 mmol) and $LiAlH_4$ (1.14 g, 30 mmol) in THF (100 ml) was stirred at room temperature for 40 min. To the resulting suspension containing $AlH_3$, a solution of **9** (200 mg, 0.366 mmol) in THF (10 ml) was added dropwise over a period of 40 min, and the stirring was continued at room temperature for 80 min. Next, a mixture of THF and $H_2O$ (1 : 1, 8 ml) was added slowly, and then aqueous NaOH (3 g in 30 ml) was added dropwise, with ice-cooling throughout. The supernatant was separated by decantation, and the precipitates were washed with $CH_2Cl_2$ (25 ml × 2). After combining the supernatant and the washings, the organic layer was separated, dried over anhydrous $K_2CO_3$, and evaporated. The solid residue was recrystallized from $CH_2Cl_2$–MeOH to give a white powder (0.15 g, 77%), mp 129—132 °C (dec.). IR (KBr) $cm^{-1}$: 3360 (NH). $^1$H-NMR ($CDCl_3$) $\delta$: 1.13 (3H, t, $J$=7.1 Hz, $NCH_2CH_3$), 1.63 (11H, br, $NCH_2CH_2$ and NH), 3.15 (8H, br, $NCH_2CH_2$), 3.34 (2H, q, $J$=7.1 Hz, $NCH_2CH_3$), 3.72 and 3.78 (each 2H, two s, $ArCH_2Ar$), 6.5 (8H, m, ArH (*ortho*)), 6.9 (8H, m, ArH (*meta*)). $^1$H-NMR (0.25 N DCl–$D_2O$)) $\delta$: 1.50 (3H, t, $J$=7 Hz, $NCH_2CH_3$), 2.0 (8H, br, $NCH_2CH_2$), 3.4—4.2 (10H, m, $NCH_2CH_2$ and $NCH_2CH_3$), 4.53 (4H, s, $ArCH_2Ar$), 7.73 and 7.85 (each 8H, two d, $J$=8 Hz, ArH (*ortho*, *meta*)). MS *m/z*: 532 ($M^+$). *Anal.* Calcd for $C_{36}H_{44}N_4$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.33; H, 8.42; N, 10.49.

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