Biomimetic Studies Using Artificial Systems. VI.[1] Design and Synthesis of Novel Cyclophanes Having Eight Carboxyl Groups on the Aromatic Rings[2]

Muneharu MIYAKE,[a] Makoto KIRISAWA,[a] and Kenji KOGA*,[b]

College of Pharmacy, Nihon University,[a] Narashinodai, Funabashi-shi, Chiba 274, Japan and Faculty of Pharmaceutical Sciences, University of Tokyo,[b] Hongo, Bunkyo-ku, Tokyo 113, Japan. Received December 4, 1992

Novel cyclophanes (9a, b) having eight carboxyl groups on the aromatic rings were designed and synthesized. Macrocyclization of 7a and 7b with 6 was carried out under a high dilution condition to give the corresponding 8a and 8b in 23% and 28% yields, respectively.

Keywords anionic cyclophane; hydrophobic cavity; charge interaction; macrocyclization; carboxyl group

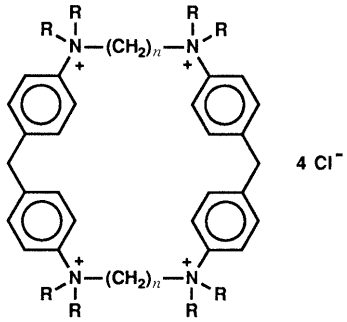
Molecular recognition by host–guest complex formation is known to play a central role in biological processes, such as enzyme catalysis and inhibition, replication, immunological response, transport, drug action, *etc.* Little is known about artificial processes involving such recognition, but this type of complex formation in model systems using man-made hosts is expected to provide a novel basis for selective and efficient artificial processes. Organic compounds usually have hydrophobic moieties, and therefore, hosts capable of forming complexes with organic guests by hydrophobic interactions are of interest. In this regard, water-soluble cyclophanes having a hydrophobic cavity are potential candidates as artificial hosts.[3]

We have previously reported that water-soluble cationic cyclophanes (**1**), having two diphenylmethane units and two bridging chains that are connected *via* four positively charged nitrogens, form inclusion complexes in aqueous solution with anionic and neutral aromatic compounds, but not with cationic aromatic compounds.[3e] Cyclophanes capable of forming complexes selectively with cationic aromatic compounds were not known. Since charge interactions in addition to hydrophobic interactions between the host and the guest are considered to be important for complex formation,[3e] we expected that cyclophanes having similar structures but negative charges at the periphery of the cavity should be soluble in water and should work as selective hosts for cationic aromatic guests. Based on the fact that cationic cyclophanes (**1**) provide a cavity by the face conformation[4] where all aromatic rings are perpendicular to the macrocyclic ring, introduction of negatively charged groups on the aromatic rings should not interfere with the expected cavity. Anionic cyclophanes (**2a, b**) designed in the present study have two diphenylmethane units and two bridging chains that are connected *via* four oxygens, and have eight carboxylate groups on the armatic rings as shown.

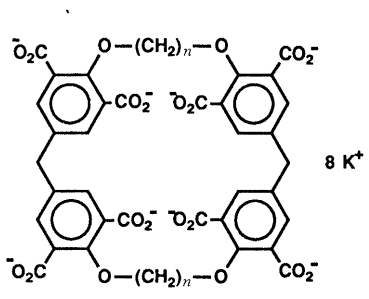
We have recently reported that these anionic cyclophanes (**2a, b**) form inclusion complexes selectively with cationic aromatic compounds as guests in alkaline water.[2] We describe here the details of the synthesis and characterization of **9a** and **9b**,[5] which exist as **2a** and **2b** in aqueous KOH. The complexation properties will be described elsewhere.[6]

As shown in Chart 2, **9a** and **9b** were synthesized from the known benzophenone derivative (**3**),[7] which is readily accessible from phenol. Reduction of the carbonyl group of **3** with triethylsilane in trifluoroacetic acid (TFA)[8] gave the corresponding diphenylmethane derivative (**4**). Treatment of **4** with boron tribromide gave the acid (**5**), which was converted to the corresponding tetraethyl ester (**6**). The reaction of **6** with excess tetramethylene dibromide or hexamethylene dibromide in dimethylformamide (DMF) in the presence of potassium carbonate afforded the corresponding dibromides (**7a, b**).

Macrocyclization of **7a** and **7b** with **6** was carried out under a high dilution condition. The desired **8a** and **8b** were isolated in 23% and 28% yields, respectively, after purification by column chromatography followed by recrystallization. Hydrolysis of **8a** and **8b** gave the objective octacarboxylic acids (**9a, b**).[9] The cyclized structures of **8a**, **8b**, **9a**, and **9b** were confirmed on the basis of the molecular ion peaks in their mass spectra (MS).



1 R = H or Me



2 a : $n=4$
b : $n=6$

Chart 1

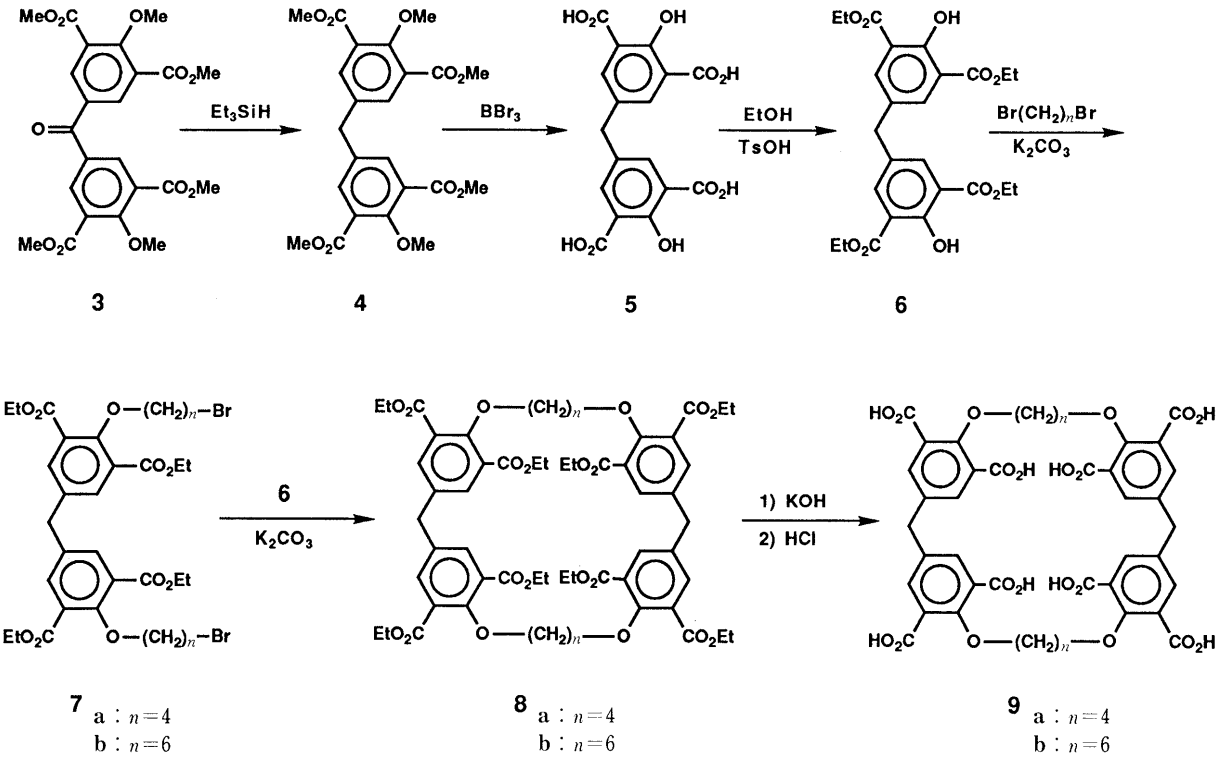


Chart 2

Experimental

General All melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 400 Fourier transform NMR spectrometer. Chemical shifts are reported in δ values using tetramethylsilane (TMS) as an internal standard except for **9a** and **9b**, which were measured in a solution of KOD–D_2O (pD 12.0) using TMS as an external standard. Coupling constants (J) are reported in hertz. MS were recorded on a JEOL JMS-01 SG-2 mass spectrometer.

5,5′-Methylenebis[2-methoxy-1,3-benzenedicarboxylic Acid] Tetramethyl Ester (4) Triethylsilane (5 ml, 31.3 mmol) was added to a solution of **3** (mp 161—163 °C, reported[7] mp 158 °C) (4.74 g, 10 mmol) in TFA (15 ml), and the whole was stirred at room remperature for 20 h. Cold water (200 ml) was added to the reaction mixture, and the precipitates deposited were collected by filtration. Purification by column chromatography (silica gel, $CHCl_3$) followed by recrystallization from acetone–hexane afforded **4** (4.50 g, 98%) as colorless needles of mp 84—85 °C. IR ($CHCl_3$): 1730 cm^{-1}. MS m/z: 460 (M^+). ^{1}H-NMR ($CDCl_3$): 3.92 (18H, s, Ar-COOC$\underline{H}_3$, Ar-OC$\underline{H}_3$), 3.95 (2H, s, Ar-C$\underline{H}_2$-Ar), 7.72 (4H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{23}H_{24}O_{10}$: C, 59.99; H, 5.25. Found: C, 59.81; H, 5.21.

5,5′-Methylenebis[2-hydroxy-1,3-benzenedicarboxylic Acid] (5) A solution of BBr_3 (1.0 ml, 10.8 mmol) in CH_2Cl_2 (6 ml) was added dropwise to a solution of **4** (2.30 g, 5 mmol) in CH_2Cl_2 (20 ml) at −78 °C during 30 min, and the whole was stirred at −78 °C for 2 h and then at room temperature for 24 h. Water (50 ml) was added to the reaction mixture, and precipitates deposited were collected by filtration, and dissolved in AcOEt (500 ml). The AcOEt solution was extracted with 5% aqueous Na_2CO_3, and the aqueous extracts were combined. Acidification with 10% aqueous HCl to pH 1 deposited precipitates, which were collected by filtration and dried. Recrystallization from acetone–$CHCl_3$ gave **5** (1.60 g, 85%) as colorless needles of mp 298 °C (dec.). IR (KBr): 3070, 1717, 1677 cm^{-1}. ^{1}H-NMR (DMSO-d_6-D_2O): 3.89 (2H, s, Ar-C$\underline{H}_2$-Ar), 7.81 (4H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{17}H_{12}O_{10}\cdot H_2O$: C, 51.82; H, 3.58. Found: C, 51.67; H, 3.26.

5,5′-Methylenebis[2-hydroxy-1,3-benzenedicarboxylic Acid] Tetraethyl Ester (6) A solution of **5** (5.0 g, 13.3 mmol) and p-toluenesulfonic acid monohydrate (4.0 g, 21.0 mmol) in ethanol (60 ml) and benzene (40 ml) was heated under reflux for 8 h. Evaporation of the solvent gave a residue, which was dissolved in AcOEt. After washing with 8% aqueous $NaHCO_3$ and water, the AcOEt layer was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography (silica gel, AcOEt) followed by recrystallization from AcOEt–hexane to give **6** (4.4 g, 68%) as colorless needles of mp 84—85 °C. IR ($CHCl_3$): 1720, 1675 cm^{-1}. MS m/z: 488 (M^+). ^{1}H-NMR ($CDCl_3$): 1.40 (12H, t, J=7, COOCH$_2$C$\underline{H}_3$), 3.91 (2H, s, Ar-C$\underline{H}_2$-Ar), 4.41 (8H, q, J=7, COOC$\underline{H}_2$CH$_3$), 7.84 (4H, s, Ar-$\underline{H}$). 11.75 (2H, s, Ar-O$\underline{H}$). *Anal.* Calcd for $C_{25}H_{28}O_{10}$: C, 61.47; H, 5.78. Found: C, 61.22; H, 5.62.

5,5′-Methylenebis[2-(4-bromobutyl)oxy-1,3-benzenedicarboxylic Acid] Tetraethyl Ester (7a) A solution of **6** (2.44 g, 5 mmol) in DMF (100 ml) was added dropwise to a stirred suspension of 1,4-dibromobutane (10.8 g, 50 mmol) and K_2CO_3 (6.9 g, 50 mmol) in DMF (200 ml) at 60 °C during 3 h, and the whole was stirred at 60 °C for 1 h and then at room temperature for 12 h. The reaction mixture was filtered using Celite. The filtrate was mixed with saturated aqueous NaCl (1 l), and the whole was extracted with ether. The ethereal extracts were combined, washed with water, dried over $MgSO_4$, and then evaporated to dryness. The residue was purified by column chromatography (silica gel, ether–hexane) to give **7a** (2.84 g, 75%) as a colorless oil. IR (neat): 1720 cm^{-1}. MS m/z: 756, 758, 760 (1 : 2 : 1) (M^+). ^{1}H-NMR ($CDCl_3$): 1.39 (12H, t, J=7, COOCH$_2$C$\underline{H}_3$), 1.9—2.1 (8H, m, OCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$), 3.51 (4H, t, J=6, C$\underline{H}_2$Br), 3.97 (2H, s, Ar-C$\underline{H}_2$-Ar), 4.03 (4H, t, J=6, OC$\underline{H}_2$CH$_2$), 4.37 (8H, q, J=7, COOC$\underline{H}_2$CH$_3$), 7.68 (4H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{33}H_{42}Br_2O_{10}$: C, 52.24; H, 5.58. Found: C, 51.98; H, 5.41.

5,5′-Methylenebis[2-(6-bromohexyl)oxy-1,3-benzenedicarboxylic Acid]-Tetraethyl Ester (7b) This compound was prepared from **6** (2.44 g, 5 mmol) and 1,6-dibromohexane (12.2 g, 50 mmol) in DMF (500 ml) in the presence of K_2CO_3 (6.9 g, 50 mmol) by a similar procedure to that described above for the synthesis of **7a**. After column chromatography (silica gel, ether–hexane), **7b** (2.25 g, 55%) was obtained as a colorless oil. IR (neat): 1720 cm^{-1}. MS m/z: 812, 814, 816 (1 : 2 : 1) (M^+). ^{1}H-NMR ($CDCl_3$): 1.39 (12H, t, J=7, COOCH$_2$C$\underline{H}_3$), 1.4—1.9 (16H, m, OCH$_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$), 3.42 (4H, t, J=7, CH$_2$C$\underline{H}_2$Br), 3.97 (2H, s, Ar-C$\underline{H}_2$-Ar), 3.99 (4H, t, J=7, OC$\underline{H}_2$CH$_2$), 4.36 (8H, q, J=7, COOC$\underline{H}_2$CH$_3$), 7.66 (4H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{37}H_{50}Br_2O_{10}\cdot H_2O$: C, 53.37; H, 6.30. Found: C, 53.61; H, 6.11.

7,12,22,27-Tetraoxa[6.1.6.1]paracyclophan-5,14,20,29,32,33,36,37-octacarboxylic Acid Octaethyl Ester (8a) A solution of **6** (0.488 g, 1.0 mmol) and **7a** (0.758 g, 1.0 mmol) in DMF (40 ml) was added dropwise to a stirred suspension of K_2CO_3 (1.38 g, 10 mmol) in DMF (60 ml) at 80 °C during 3 h, and the whole was stirred at 80 °C for 6 h and then at room temperature for 12 h. The reaction mixture was filtered using Celite. The filtrate was mixed with saturated aqueous NaCl (1 l), and the whole was extracted with AcOEt. The AcOEt extracts were combined, washed with water, dried over $MgSO_4$, and then evaporated to dryness. The

residue was purified by column chromatography (silica gel, AcOEt–hexane) followed by recrystallization from AcOEt–hexane to give **8a** (0.247 g, 23%) as colorless needles of mp 156—157 °C. IR (Nujol): 1725 cm^{-1}. MS *m/z*: 1084 (M^+). ^1H NMR ($CDCl_3$): 1.34 (24H, t, $J=7$, $COOCH_2C\underline{H}_3$), *ca.* 1.9 (8H, m, $OCH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.86 (2H, s, Ar-$C\underline{H}_2$-Ar), *ca.* 3.9 (8H, m, $OC\underline{H}_2CH_2$), 4.31 (16H, q, $J=7$, $COOC\underline{H}_2CH_3$), 7.66 (8H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{58}H_{68}O_{20}\cdot H_2O$: C, 63.15; H, 6.40. Found: C, 63.24; H, 6.21.

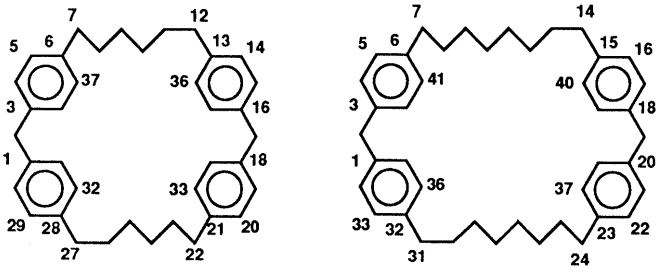
7,14,24,31-Tetraoxa[8.1.8.1]paracyclophan-5,16,22,33,36,37,40,41-octacarboxylic Acid Octaethyl Ester (8b) This compound was prepared from **6** (0.244 g, 0.5 mmol) and **7b** (0.407 g, 0.5 mmol) in DMF (50 ml) in the presence of K_2CO_3 (0.345 g, 2.5 mmol) by a similar procedure to that described above for the synthesis of **8a**. After column chromatography (Fluorisil, AcOEt and then silica gel, AcOEt–hexane) followed by recrystallization from $CHCl_3$–hexane, **8b** (0.16 g, 28%) was obtained as colorless prisms of mp 162—163 °C. IR (KBr): 1715 cm^{-1}. MS *m/z*: 1140 (M^+). ^1H-NMR ($CDCl_3$): 1.3—1.5 (8H, m, $OCH_2CH_2C\underline{H}_2$), 1.30 (24H, t, $J=7$, $COOCH_2C\underline{H}_3$), *ca.* 1.8 (8H, m, $OCH_2C\underline{H}_2CH_2$), *ca.* 3.9 (12H, m, $OC\underline{H}_2CH_2$, Ar-$C\underline{H}_2$-Ar). 4.31 (16H, q, $J=7$, $COOC\underline{H}_2CH_3$), 7.64 (8H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{62}H_{76}O_{20}\cdot H_2O$: C, 64.23; H, 6.79. Found: C, 64.44; H, 6.65.

7,12,22,27-Tetraoxa[6.1.6.1]paracyclophan-5,14,20,29,32,33,36,37-octacarboxylic Acid (9a) A warm solution of **8a** (0.95 g, 0.88 mmol) in MeOH (30 ml) was mixed with a solution of 5 N KOH in MeOH (12 ml) and water (30 ml), and the whole was heated under reflux for 4 h. The reaction mixture was concentrated to half its initial volume under reduced pressure. Under ice-cooling, the resulting solution was acidified with 1 N aqueous HCl to pH 1. The precipitates deposited were collected by filtration, washed with water, and dried. Recrystallization from MeOH–H_2O gave **9a** (0.56 g 74%) as a colorless powder of mp > 300 °C. IR (KBr): 1718 cm^{-1}. MS *m/z*: 860 (M^+). ^1H-NMR (KOD–D_2O): *ca.* 1.6 (8H, m, $OCH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.4—3.5 (12H, m, $OC\underline{H}_2$ and Ar-$C\underline{H}_2$-Ar), 6.87 (8H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{42}H_{36}O_{20}$: C, 58.61; H, 4.22. Found: C, 58.33; H, 4.18.

7,14,24,31-Tetraoxa[8.1.8.1]paracyclophan-5,16,22,23,36,37,40,41-octacarboxylic Acid (9b) This compound was prepared from **8b** (0.57 g) by a similar procedure to that described above for the synthesis of **9a**. Recrystallization from MeOH–H_2O gave **9b** (0.33 g, 72%) as a colorless powder of mp > 270 °C. IR (KBr): 1700 cm^{-1}. MS *m/z*: 916 (M^+). ^1H-NMR (KOD–D_2O): *ca.* 1.0 (8H, m, $OCH_2CH_2C\underline{H}_2C\underline{H}_2CH_2$), *ca.* 1.4 (8H, m, $OCH_2C\underline{H}_2CH_2$), 3.6—3.7 (12H, m, $OC\underline{H}_2$, $ArC\underline{H}_2$-Ar), 7.02 (8H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{46}H_{44}O_{20}\cdot H_2O$: C, 59.10; H, 5.31. Found: C, 58.75; H, 4.67.

References and Notes

1) Part V: C.-F. Lai, K. Odashima, and K. Koga, *Chem. Pharm. Bull.*, **37**, 2351 (1989).
2) A part of this work was published as a communication: M. Miyake, M. Kirisawa, and K. Koga, *Tetrahedron Lett.*, **32**, 7295 (1991).
3) *a*) K. Odashima and K. Koga, "Cyclophanes," Vol. 2, ed. by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, 1983, Chapter 11; *b*) I. Tabushi, *Top. Curr. Chem.*, **113**, 145 (1983); *c*) Y. Murakami, *ibid.*, **115**, 107 (1983); *d*) F. Diederich, *Angew. Chem. Int. Ed. Engl.*, **27**, 362 (1988); *e*) K. Koga and K. Odashima, *J. Incl. Phenom.*, **7**, 53 (1989); *f*) F. Diederich, "Cyclophanes," The Royal Society of Chemistry, London, 1991.
4) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Org. Chem.*, **50**, 4478 (1985).
5) For convenience, a conventional cyclophane nomenclature is used in the experimental section according to the numbering of the parent skeletons (i, ii) shown below, which are named [6.1.6.1]paracyclophane and [8.1.8.1]paracyclophane, respectively. See: D. J. Cram and J. Abell, *J. Am. Chem. Soc.*, **77**, 1179 (1955). The *Chemical Abstracts* name of **9a**, for example, is 7,12,22,27-tetraoxapentacyclo-[26.2.2.$2^{3,6}$.$21^{3,16}$.$2^{18,21}$]octatriaconta-3,5,13,15,18,20,28,30,31,33,-35,37-dodecaen-5,14,20,29,32,33,36,37-octacarboxylic acid.



i ii

6) M. Miyake, M, Kirisawa, and K. Koga, *Heterocycles*, in press.
7) F. Seebach, *Chem. Ber.*, **72**, 1635 (1939).
8) *Cf.* D. N. Kursanov, L. M. Loim, V. A. Baranova, L. V. Moiseeva, L. P. Zalukaev, and Z. N. Parnes, *Synthesis*, **1973**, 420.

9) By treating **8a** with potassium hydroxide in methanol, the corresponding potassium salt was obtained as colorless precipitates (mp > 300 °C) in almost quantitative yield. Although elemental analyses gave results consistent with the corresponding octapotassium salt (**2a**) oligohydrate, it was not possible to get constant results due to the hygroscopic nature of this compound.