°C), m/e (relative intensity) 262 (7), 247 (4), 220 (20), 209 (87), 208 (67), 207 (51), 180 (49), 177 (49), 152 (80), 76 (43), 57 (67), 41 (100). Anal. Calcd for $C_{33}H_{40}O_4$: C, 79.16; H, 8.05 (M = 500). Found: C, 79.06; H, 8.19.

In accordance with its structure, pyrolysis of **20** (10 mg) at 200 °C during 2 min gave a mixture whose constituents, separated by TLC on silica gel (CH_2Cl_2), were as follows: 2,6-di-*tert*-butylbenzoquinone[17] (3 mg, 20%); **10** (2 mg, 40%); **12** (2 mg, 45%).

With Hydroquinone (HQ). In CD_2Cl_2–CD_3OD. To 60 mg (0.22×10^{-3} mol) of crystalline ozonide **7e** in 1 mL of CD_2Cl_2 at −60 °C was added 48 mg (0.44×10^{-3} mol) of hydroquinone dissolved in 1 mL of CD_3OD cooled to −60 °C. The residue obtained after reaction and evaporation of the solvents was extracted with CH_2Cl_2. Insoluble black crystals of quinhydrone (QH) (23 mg, 24%), mp 171 °C, were isolated, and separation by TLC of the soluble fraction gave the following: **10** (3.2 mg, 7%); **8e** (12 mg, 23%); **9** (4 mg, 9%); **12** (24 mg, 48%).

The possible reduction of hydroperoxide **2a** by QH was checked as follows: To 15 mg of **2a** in 1 mL of CH_2Cl_2 was added a solution of 20 mg of QH in 1 mL of CH_3OH; usual separation afforded **12** (12 mg, 82%).

In CH_2Cl_2–CH_3CN. To 64 mg (0.24×10^{-3} mol) of crystalline ozonide **7e** in 1 mL of CH_2Cl_2 at −60 °C was added 53 mg (0.48×10^{-3} mol) of hydroquinone in 1 mL of acetonitrile cooled to 60 °C. As the temperature was raised to ambient, black crystals of quinhydrone (QH) precipitated out and were filtered (42 mg, 40%). Usual separation led to the following: **10** (2 mg, 4%); *p*-benzoquinone, mp 116 °C (3.6 mg, 7%); **2a** (47 mg, 82%).

Decomposition of ozonide **7e** in the mixture CH_2Cl_2–CH_3CN without added HQ led to the results given in Table III.

Decomposition of Ozonide 7e in the Presence of $^1O_2$ Traps. The principle of the method reported in the case of 1-phospha-2,8,9-trioxaadamantane[18] has been followed.

For example, to a solution of 60 mg (0.22×10^{-3} mol) of crystalline ozonide **7e** in 1 mL of CD_2Cl_2 at −70 °C was added 30 μL of 1,2-dimethylcyclohexene, and the ^1H NMR spectrum of the mixture was recorded. After return to ambient temperature, the ^1H NMR spectrum showed no traces of the olefinic hydroperoxides derived from 1,4-dimethylcyclohexene. Further separation led to the following: **10** (5 mg 10%); **8e** (18 mg, 34%); **9** (14 mg, 30%); **2a** (6 mg, 11%); **12** (1 mg, 2%).

The same procedure applied to 80 mg (0.3×10^{-3} mol) of ozonide **7e** and 30 μL (0.3×10^{-3} mol) of cyclohexene led to an identical finding, and separation gave the following: **10** (5 mg, 8%); **8e** (25 mg, 35%); **9** (16 mg, 26%); **2a** (19 mg, 27%); **12** (6 mg, 9%). The increase noted on the yields of **2a** and **12** seems to result from the H-donor ability of cyclohexene.

Registry No. **2a**, 17526-22-6; **6e**, 21992-33-6; **6f**, 24165-83-1; **6g**, 98612-70-5; **6h**, 98612-71-6; **6i**, 2395-96-2; **6j**, 2395-97-3; **6k**, 17803-79-1; **7e**, 98612-72-7; **7f**, 98612-73-8; **7g**, 98612-74-9; **7h**, 98612-75-0; **7i**, 98612-76-1; **7j**, 71955-40-3; **7k**, 98612-77-2; **8e**, 17104-31-3; **8f**, 98612-79-4; **8i**, 14629-83-5; **8j**, 40628-58-8; **8k**, 25548-89-4; **9**, 98612-78-3; **10**, 84-65-1; **12**, 17104-31-3; **13k**, 98612-80-7; **19**, 732-26-3; **20**, 98612-81-8; **21**, 1975-14-0; HQ, 123-31-9; 1,2-dimethylcyclohexene, 1674-10-8; cyclohexene, 110-83-8; 10-methyl-9-anthrone, 73653-01-7; 2-acetyl-2′-hydroxybenzophenone, 17526-21-5; 2,6-di-*tert*-butylbenzoquinone, 719-22-2.

(17) Cook, C. D.; Woodworth, R. C.; Fianu, P. *J. Am. Chem. Soc.* **1956**, *78*, 4159.

(18) Schaap, A. P.; Kees, K.; Thayer, A. L. *J. Org. Chem.* **1975**, *40*, 1185.

(19) The financial assistance given to one of us (G.C.) by CERCHAR is gratefully acknowledged.

Biomimetic Studies Using Artificial Systems. 3.[1,2] Design, Synthesis, and Inclusion Complex Forming Ability of a Novel Water-Soluble Paracyclophane Possessing Diphenylmethane Skeletons[3]

Kazunori Odashima, Akiko Itai, Yoichi Iitaka, and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Received June 24, 1985

A novel water-soluble paracyclophane, CP44 (1), was designed and synthesized as a host molecule possessing a hydrophobic cavity to capture organic guests in water. X-ray crystallographic study revealed the formation of a 1:1 *inclusion* complex, and not a simple stacked complex, between protonated CP44 and durene. This is the first *direct* evidence showing the ability of a water-soluble cyclophane to form an inclusion complex. The inclusion of hydrophobic guests *in water* (acidic condition) was also evidently observed by several kinds of spectra (^1H and ^{13}C NMR, fluorescence).

From the viewpoint of synthetic organic chemistry, the most significant aspects of biological reactions—such as those between enzymes and substrates—are their extremely high speed and selectivity that originate from the prior formation of specific molecular complexes, i.e., *host–guest complexes*.[4,5] These complexes are characteristic in that they are stoichiometric inclusion complexes formed by macromolecular biological hosts, e.g., enzymes, antibodies, and receptors. In such complexes the guest (substrate) is strongly captured and tightly fixed in the inclusion cavity of its specific host, resulting in the formation of a highly structured molecular complex. The highly structured nature of the complex is essential to effect high speed and selectivity in the intracomplex chemical conversion, which is the step subsequent to the guest inclusion (eq 1). If the style of such biological

$$H + G \rightleftharpoons H{\cdot}G \rightarrow H{\cdot}P \rightarrow H + P \qquad (1)$$

H = host, G = guest (substrate), P = product

reactions could be mimicked with simpler organic systems,

(1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

(2) Part 2 of this series: Sasaki, S.; Kawasaki, M.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 4247-4266.

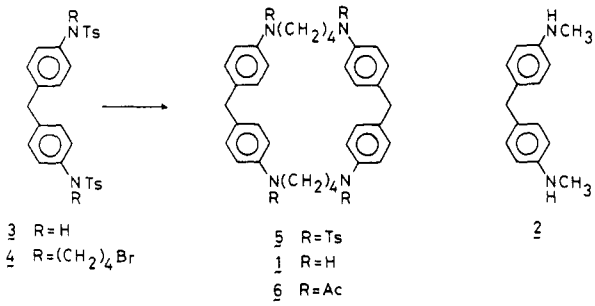
(3) A part of this work was published as a communication: Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504-2505.

(4) (a) Cram, D. J.; Cram, J. M. *Science (Washington, D.C.)* **1974**, *183*, 803-809; (b) *Acc. Chem. Res.* **1978**, *11*, 8-14.

(5) Vögtle, F. *Top. Curr. Chem.* **1981**, *98*; **1982**, *101*; **1984**, *121*.

0022-3263/85/1950-4478$01.50/0

Scheme I



3 R=H
4 R=$(CH_2)_4$Br

5 R=Ts
1 R=H
6 R=Ac

2

especially with artificial host compounds, there might arise a novel and effective approach to the control of chemical reactivities to effect highly efficient organic reactions. With this concept we have initiated studies aiming at the development of artificial systems that exhibit biomimetic functions.[2]

As frequently seen in biological systems, the formation of inclusion complexes by hydrophobic interaction in water plays a significant role in the capture and discrimination of organic guests, since most of the organic compounds have nonpolar moieties. Water-soluble cyclophanes constitute a versatile system to mimic this aspect, first because they may confer hydrophobic cavities of well-defined structure and sufficient depth and second because they are totally artificial hosts that can be designed and synthesized arbitrarily.[6] Particularly the second feature is of great significance as compared with cyclodextrins that are nonsynthetic hosts. Although cyclodextrins have been most widely and systematically studied,[7] their cavity structures are already defined and therefore are not subject to wide modifications.

Water-soluble cyclophanes have focused attention as artificial hosts since the beginning of the 1970's, and several spectral[8a-c] and kinetic[8d,9a-d] studies have suggested that they form inclusion complexes rather than simple stacked complexes with hydrophobic guests in water. However it was not until recently that the inclusion complex forming ability of water-soluble cyclophanes was firmly established by our X-ray study of a crystalline host–guest complex of protonated CP44 with durene, which afforded the *first direct evidence of inclusion* by a water-soluble cyclophane.[3] In this paper we report the details and some additional data that further confirm the inclusion complex formation by this type of hosts.

Results and Discussion

Design and Synthesis. We intended to design and synthesize novel macrocyclic compounds as hosts that have the following properties. The macrocyclic compound is

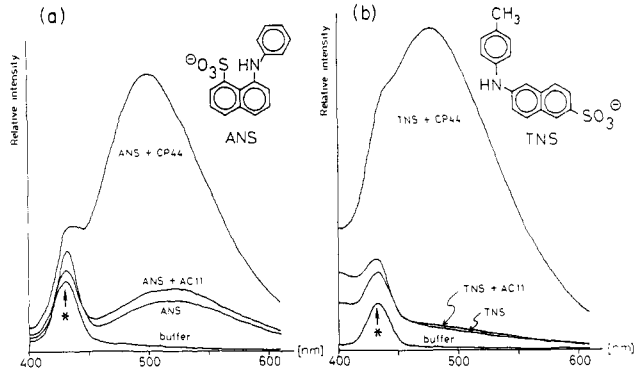
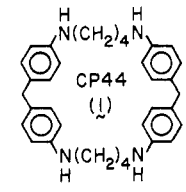


Figure 1. Fluorescence spectra of (a) ANS and (b) TNS in the presence of CP44 or AC11. Conditions: [ANS] = 2×10^{-6} M, [TNS] = 4×10^{-6} M, [CP44] = 5×10^{-5} M, [AC11] = 1×10^{-4} M; in KCl–HCl buffer (pH 1.95); 25.0 ± 0.1 °C; excited at 375 nm. These emission spectra are not corrected for the wavelength-dependent sensitivity of the photomultiplier. The arterisks indicate Raman scattering of water.

soluble in water and has a hydrophobic cavity inside capable of forming a host–guest complex by hydrophobic interactions. This hydrophobic cavity should be sufficiently rigid to effect selectivity by the fit between host and guest, which means molecular recognition at complexation. It is highly desirable that cavities of various sizes are available.

1,6,20,25-Tetraaza[6.1.6.1]paracyclophane[10] (CP44, 1) was designed as a novel type of water-soluble cyclophane,



which is composed of two diphenylmethane skeletons bridged by two tetramethylene chains via four nitrogens. This system was chosen for the following four reasons: (i) The fixed angle of Ar–CH_2–Ar is expected to make the cavity of **1** reasonably rigid. At the same time, the conformation in which all the benzene rings are perpendicular to the macrocyclic ring ("face" conformation[11]) is expected to make the cavity deep. (ii) The amino nitrogens in **1** are expected to make this compound soluble in (acidic) water. (iii) Substitution of two tetramethylene units with other units of various lengths is expected to give cavities of various sizes. (iv) Chemical modification of **1** seems to be possible in various ways.

The synthesis of **1** was carried out as shown in Scheme I. Commercially available 4,4′-diaminodiphenylmethane was tosylated to give the ditosylate **3**.[12] The 2:2 cyclization between **3** and tetramethylene dibromide in the presence of K_2CO_3 in DMF under a high dilution condition gave the cyclic tetratosylate **5** in 25% purified yield. Alternatively, U-shaped dibromide **4**, prepared from **3** and excess tetramethylene dibromide, was cyclized with **3** to give **5** in 73% yield.[13] Detosylation of **5** with 48% aqueous

(6) (a) Odashima, K.; Koga, K. In "Cyclophanes", Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vol. 2, Chapter 11. (b) Tabushi, I., Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145–182. (c) Murakami, Y. *Ibid.* **1983**, *115*, 107–155. (d) Vögtle, F.; Sieger, H.; Müller, W. M. *Ibid.* **1981**, *98*, 107–161.

(7) (a) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: New York, 1978. (b) "Cyclodextrins and Their Inclusion Complexes"; Szejtlli, J., Ed.; Akademiai Kiadó: Budapest, 1982.

(8) (a) Tabushi, I.; Kuroda, Y. *Shokubai* **1974**, *16*, 78–80. (b) Tabushi, I.; Kuroda, Y.; Kimura, Y. *Tetrahedron Lett.* **1976**, 3327–3330. (c) Tabushi, I.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727–5728. (d) Tabushi, I.; Kimura, Y.; Yamamura, K. *Ibid.* **1978**, *100*, 1304–1306.

(9) (a) Murakami, Y.; Sunamoto, J.; Kano, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1238–1244. (b) Murakami, Y.; Sunamoto, J.; Okamoto, H.; Kawanami, K. *Ibid.* **1975**, *48*, 1537–1544. (c) Sunamoto, J.; Kondo, H.; Okamoto, H.; Murakami, Y. *Tetrahedron Lett.* **1977**, *50*, 1329–1332. (d) Murakami, Y.; Sunamoto, J.; Kondo, H.; Okamoto, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2420–2427. (e) Murakami, Y.; Aoyama, Y.; Kida, M.; Nakano, A. *Ibid.* **1977**, *50*, 3365–3371.

(10) For convenience the conventional nomenclature is used throughout. See: Cram, D. J.; Abell, J. *J. Am. Chem. Soc.* **1955**, *77*, 1179–1186. The *Chemical Abstracts* name of this compound is 7,12,22,27-tetraazapentacyclo[26.2.2.$2^{3,6}$.$2^{13,16}$.$2^{18,21}$]octatriaconta-3,5,13,15,18,20,28,30,31,33,35,37-dodecaene.

(11) Tabushi, I.; Yamada, H.; Kuroda, Y. *J. Org. Chem.* **1975**, *40*, 1946–1949.

(12) (a) Kuhn, R.; Jacob, P.; Furter, M. *Justus Liebigs Ann. Chem.* **1927**, *455*, 254–271. (b) Ray, F. E.; Soffer, L. S. *J. Org. Chem.* **1950**, *15*, 1037–1042.

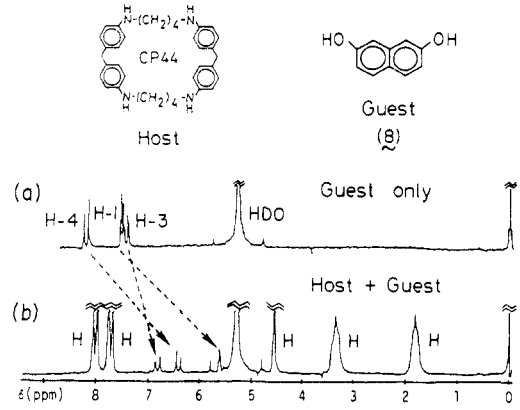


Figure 2. ^{1}H NMR spectra of (a) guest 8 and (b) CP44 + guest 8 in acidic D_2O. Conditions: [8] = 2.5×10^{-2} M, [CP44] = 5.0×10^{-2} M; in DCl–D_2O (pD 1.2); 28 ± 2 °C; Me_4Si as an external standard. H's refer to the signals of the host.

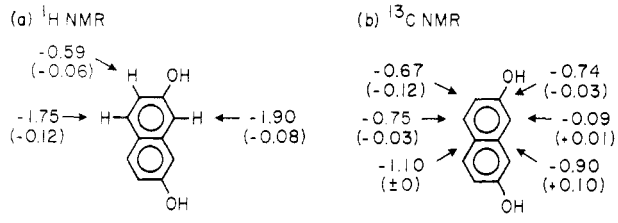


Figure 3. Shifts of the ^{1}H and ^{13}C NMR signals of guest 8 induced by CP44 and AC11 (parentheses) in acidic D_2O. (a) ^{1}H NMR, (b) ^{13}C NMR. See Figure 2 and Table I for the conditions.

HBr/phenol[14] gave CP44 (1). The cyclic structure was evident from the mass spectra of 5 and 1 and also from the tetraacetamide derivative 6 obtained in a quantitative yield. The acyclic compound AC11 (2)[15] was prepared as a reference compound.

Inclusion Complex Formation in Water. As CP44 is soluble in water below pH 2 as an amine salt, its inclusion complex forming ability was examined in acidic water by comparing the spectral changes of hydrophobic guests induced by CP44 with those induced by the acyclic reference compound AC11.

I. Fluorescence Spectra. The guests used were 1-anilinonaphthalene-8-sulfonate (ANS) and 2-toluidinonaphthalene-6-sulfonate (TNS), which are hydrophobic probes employed widely in the area of protein and membrane research.[16] As shown in Figure 1, CP44 induced marked emission enhancement and a blue shift in the fluorescence spectra of both guests in acidic water. These spectral changes indicate the transfer of these guests into a nonpolar environment, as when bound to the cavities of cyclodextrins and proteins, or when dissolved in less polar solvents.[16,17] For both guests the Benesi–Hildebrand plot[18] of the fluorescence intensity in an appropriate concentration range gave a straight line, indicating the formation of a 1:1 host–guest complex. The stability constants (K_s) were calculated to be 6.3×10^3 and 9.6×10^4 M^{-1} for the 1:1 complexes with ANS and TNS, respectively. These K_s values are comparable with the reported values for the known water-soluble cyclophanes.[8b,c,9e,19a,20a,c,21]

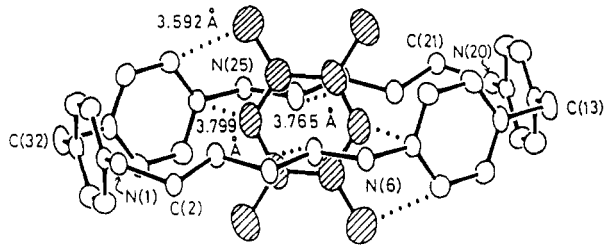


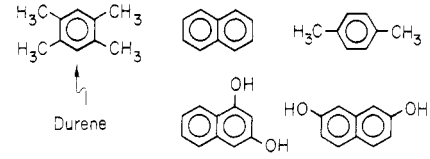
Figure 4. Perspective view of the host–guest complex of CP44·4H$^+$ with durene drawn by one ORTEP program. The carbon atoms of the guest are shaded. The hydrogen atoms of the host and guest, the chloride ions, and the water molecules are not shown. The closest contacts (<3.80 Å) between the carbon atoms of the host and guest are shown with dotted lines.

Table I. Shifts of ^{1}H and ^{13}C NMR Signals of Guest 8 Induced by CP44 or AC11 in Acidic D_2O[a-c]

atom	δ(8)	δ(CP44 + 8)	Δδ(CP44)	δ(AC11 + 8)	Δδ(AC11)
H-1	7.50	5.60	−1.90	7.42	−0.08
H-3	7.40	6.81	−0.59	7.34	−0.06
H-4	8.16	6.41	−1.75	8.04	−0.12
C-1	109.00	108.91	−0.09	109.01	+0.01
C-2	155.12	154.38	−0.74	155.09	−0.03
C-3	116.61	115.94	−0.67	116.49	−0.12
C-4	130.89	130.14	−0.75	130.86	−0.03
C-9	136.86	135.96	−0.90	136.96	+0.10
C-10	124.83	123.73	−1.10	124.83	±0

[a] Conditions: [8] = 2.5×10^{-2} M, [CP44] = 5.0×10^{-2} M, [AC11] = 1.0×10^{-1} M; in DCl–D_2O (pD 1.2); 28 ± 2 °C; Me_4Si as an external standard. [b] Δ(host) = δ (host + 8) − δ(8) (ppm). δ(host + 8) and δ(8) refer respectively to the chemical shifts (ppm) of the signals of guest 8 in the presence and in the absence of CP44 or AC11. The negative values indicate upfield shifts. [c] The assignment of the carbon signals is based on Ernst, L. *Chem. Ber.* **1975**, *108*, 2030–2039.

Chart I



II. ^{1}H NMR Spectra. As shown in Table I and Figures 2 and 3a, CP44 induced marked upfield shifts (~1.9 ppm) of the ^{1}H NMR signals of hydrophobic guest 2,7-dihydroxynaphthalene (8) in acidic D_2O. Concerning ^{1}H NMR spectra, such marked upfield shifts can be ascribed to a strong ring current effect from the aromatic rings of the host.[22a] A similar trend was also observed with some other hydrophobic guests.[23]

(13) We are indebted to Kazuhiko Mori, Atsushi Miwa Hajime Kawakami, and Chung-Fang Lai for this procedure.
(14) Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006–2009.
(15) v. Braun, J. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2145–2156.
(16) Brand, L.; Gohlke, J. R. *Annu. Rev. Biochem.* **1972**, *41*, 843–868.
(17) (a) Cramer, F.; Saenger, W.; Spatz, H.-C. *J. Am. Chem. Soc.* **1967**, *89*, 14–20. (b) Kondo, H.; Nakatani, H.; Hiromi, K. *J. Biochem. (Tokyo)* **1976**, *79*, 393–405. (c) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100–7102.
(18) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
(19) (a) Adams, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 1602–1611. (b) Whitlock, B. J.; Whitlock, H. W., Jr. *Ibid.* **1983**, *105*, 838–844.
(20) (a) Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167–3170; (b) Angew. *Chem., Int. Ed. Engl.* **1983**, *22*, 715–716; *Angew. Chem. Suppl.* **1983**, 957–972. (c) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024–8036. (d) Diederich, F.; Griebel, D. *Ibid.* **1984**, *106*, 8037–8046.
(21) Winkler, J.; Coutouli-Argyropoulou, E.; Leppkes, R.; Breslow, R. *J. Am. Chem. Soc.* **1983**, *105*, 7198–7199.
(22) See for example: (a) Bergeron, R.; Rowan, R., III. *Bioorg. Chem.* **1976**, *5*, 425–436. (b) Bergeron, R.; Channing, M. A. *Ibid.* **1976**, *5*, 437–449.

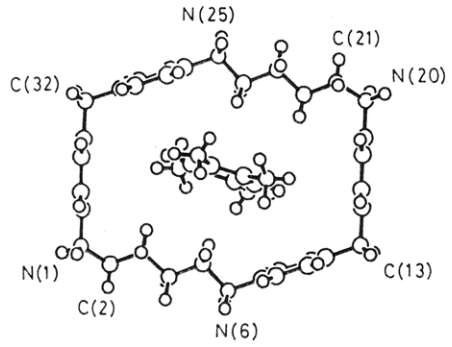


Figure 5. Rectangularly shaped open end of the inclusion cavity of CP44·4H$^+$.

III. ^{13}C NMR Spectra. Table I and Figure 3b show marked shifts induced by CP44 on the ^{13}C NMR signals of guest **8** in acidic D_2O. The marked upfield shifts in this case may reflect mainly the intimate contact between CP44 and **8** in acidic D_2O.[22b]

In contrast to the marked changes induced by CP44 in the above three kinds of spectra (Figures 1 and 3a,b), only small changes were induced by the acyclic reference AC11 (**2**) in all of the corresponding spectra. These observations strongly support the formation of *inclusion* complexes rather than of simple stacked complexes by protonated CP44 in water. In addition the natures of all these spectral changes can be reasonably interpreted by assuming the inclusion of the guests into the cavity of the host.

Direct Evidence of Inclusion (X-ray). Crystal structure determination of a host–guest complex affords *direct evidence of inclusion*. Thus efforts were made to prepare crystals of the host–guest complexes from aqueous solutions, applying a variety of guests having hydrophobic moieties. Crystalline complexes were obtained with several aromatic guests shown in Chart I. A detailed X-ray crystallographic study was carried out for the 1:1 complex with durene (1,2,4,5-tetramethylbenzene), which was characterized as CP44·4HCl·durene·4H_2O.[3,24]

I. Crystal Structure of the Complex. As shown in Figure 4, a typical *host–guest complex*[4] is formed, in which the guest molecule, durene, is fully included in the cavity of the host molecule, CP44·4H$^+$. The whole 1:1 complex sits on a center of symmetry, indicating clearly that the guest molecule is located exactly at the middle of the cavity. The guest molecule is fixed tightly in close contact with the host molecule, and the closest contacts between the host and guest (<3.80 Å) are shown in Figure 4 with dotted lines.

II. Conformation of the Host Molecule. Two characteristic points that are essential to the formation of the inclusion cavity are found in the conformation of the host molecule. (i) The four benzene rings of the host are perpendicular to the mean plane of the macroring, facing one another to adopt the "face" conformation. (ii) The two bridging methylene chains adopt the transplanar conformation except for the gauche conformation about the N(1)–C(2) and N(20)–C(21) bonds. As a result a hydrophobic cavity is formed that has rectangularly shaped open ends (~3.5 × 7.9 Å) and a depth of 6.5 Å (Figure 5).

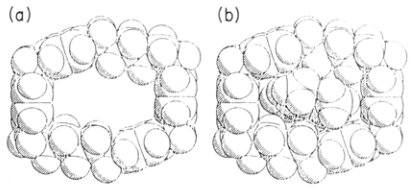


Figure 6. Spatial shape of CP44·4H$^+$–durene complex. (a) Only the spatial shape of the host and (b) the spatial shape of the whole complex are drawn, respectively, showing the close fit between the host and guest. The hydrogen, nitrogen, and sp^3 and sp^2 carbon atoms are drawn with the van der Waals radii of 1.2, 1.5, 1.6 and 1.7 Å, respectively.

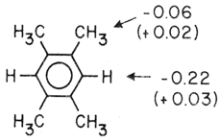


Figure 7. Shifts of the ^{1}H NMR signals of durene induced by CP44 and AC11 (parentheses). Conditions: [durene] = 6.6 × 10^{-3} M, [CP44] = 5.0 × 10^{-3} M, [AC11] = 1.0 × 10^{-2} M; in DCl–D_2O (pD 1.2)/CD_3OD = 3:7; 28 ± 2 °C; Me_4Si as an external standard.

III. Inclusion Geometry of the Guest Molecule. The mode of inclusion of the guest molecule is as follows. The benzene ring fits well to the cavity, being nearly parallel to the inner wall, and the methyl groups which are oriented outside protrude partly from the cavity. The primary basis of the intimate interaction between the host and guest seems to be a good fit between the thickness of the aromatic ring (3.4 Å) and the shorter width of the cavity open ends (~3.5 Å) (Figure 6). However there are some other possible factors for the intimate interaction, such as (i) charge transfer interaction between the aromatic rings of the host and guest and (ii) CH-π interaction between the aliphatic bridges of the host and the aromatic ring of the guest.[25]

Thus, the formation of an inclusion complex as well as the adoption of the "face" conformation.[26] was shown directly through the X-ray study. This is the first direct evidence that confirms the inclusion complex formation by water-soluble cyclophanes as artificial hosts.

^{1}H NMR study as described above was also carried out with durene. Although the insolubility of durene in water forced the experiment to be carried out in acidic D_2O–CD_3OD (3:7), upfield shifts (~0.2 ppm) were observed for the guest proton signals upon an addition of CP44, in contrast with the negligible shifts observed upon an addition on the acyclic reference AC11 (Figure 7). It is therefore reasonable to conclude that the inclusion of durene occurs not only in a crystalline state but also in solution.

Crystal Structures of the Complexes with Other Guests and of the Uncomplexed Host. Crystal structure determination was also carried out for the complexes with naphthalene and with 1,3-dihydroxynaphthalene. It was found that both of these complexes are inclusion complexes in which the host molecule adopts a similar conformation as that in the crystalline complex with durene. The characteristic conformation with the rectangularly shaped

(23) Marked upfield shifts (0.6–1.4 ppm) were also observed for some other guests having aromatic rings as hydrophobic moieties, e.g., 1,3-dihydroxynaphthalene, benzyl alcohol, and 1,4-benzenedimethanol.

(24) Details on X-ray analysis: Itai, A.; Watanabe, A.; Odashima, K.; Koga, K.; Iitaka, Y., to be published. Also, see Supplementary Material with ref 3.

(25) No evidence has been obtained at present that clearly shows strong participation of either of these factors. The details will be reported in a forthcoming paper of this series.

(26) For the ^{1}H NMR studies concerning the conformation of cyclophanes in solutions, see: ref 11 and 19 and references cited therein. Predominance of the "face" conformation in organic solvents was suggested for a series of unsubstituted paracyclophanes.[11]

open ends as shown in Figures 4–6 seems to be the general one that protonated CP44 adopts upon the inclusion of guests. However, an X-ray study further revealed that the conformation of the uncomplexed host is quite different from that of the complexed host. This finding indicates the possibility that the inclusion of a guest occurs with conformational reorganization of the host molecule, as is frequently seen with simple artificial hosts.[27] The detailed crystal structures and discussions concerned with the three host–guest complexes and the uncomplexed host will appear elsewhere.[24]

Diphenylmethane Skeletons as Structural Units. The present results show that the two diphenylmethane skeletons of CP44 serve as suitable structural units to construct a hydrophobic cavity of well-defined structure. One of the characteristic features of the diphenylmethane skeleton is that the two benzene rings are fixed at a definite angle because there is only one intervening methylene unit. In addition, Cram has demonstrated a transannular electronic coupling between the π-electrons of the two benzene rings of a diphenylmethane unit.[28] Such a transannular coupling would tend to decrease the distance between the benzene rings and increase the population of molecules with the π-orbitals of C(1) and C(1′) pointing toward each other.[28a] This interaction, being marked in cyclic systems, may favor the "face" conformation to afford a deep cavity suitable for the inclusion of guests. Empirical force field and molecular orbital calculations of the molecular structure of diphenylmethane also predict that the "face (gable)" conformation is the ground state for the isolated molecules.[29]

Although there had been several examples of paracyclophanes containing diphenylmethane units,[30,31] CP44 (protonated form) afforded the first example that exhibits guest inclusion ability.[32,33] Recently Diederich[20] and Lehn[34] have also observed the inclusion ability of some related compounds, confirming further the utility of diphenylmethane skeleton as a structural unit for this class of hosts.

Conclusion

A novel water-soluble paracyclophane, CP44 (1), was shown to form an inclusion complex, and not a simple stacked complex, on the basis of an X-ray study of the 1:1 crystalline host–guest complex of CP44·4HCl with durene; this is the first direct evidence showing guest inclusion ability of water-soluble cyclophanes as a promising class of artificial hosts. The formation of inclusion complexes in (acidic) water was also clearly observed by fluorescence and NMR (^{1}H and ^{13}C) spectra.

Combination of the direct nature of the evidence by X-ray and the solution-state evidence by spectral methods firmly confirms the inclusion complex forming ability of protonated CP44. This is the first comprehensive study that establishes the guest inclusion ability of water-soluble cyclophanes and that confers a reliable basis for the application of this calss of artificial water-soluble hosts in various fields.

The diphenylmethane skeleton was shown to be a suitable unit to construct a hydrophobic cavity of well-defined structure. The strategy of bridging two diphenylmethane skeletons with two appropriate units has been shown to be versatile for the design of this calss of hosts,[35] as also shown in recent reports by other groups.[20,21,34]

Experimental Section

N,*N*′-Dimethylformamide (DMF) was distilled under reduced pressure from CaH_2. $CHCl_3$ was distilled before use. Melting points were measurd on a Büchi 510 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO DS-701G diffraction grating infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured either on a JEOL JNM-PS 100 NMR spectrometer (^{1}H, 100 MHz) or a JEOL JNM-FX 100 Fourier transform NMR spectrometer (^{1}H, 100 MHz; ^{13}C, 25 MHz). Chemical shifts are reported in δ values in ppm with tetramethylsilane (Me_4Si) as an internal standard, unless otherwise specified. Coupling constants (*J*) are reported in hertz. Mass spectra (MS) were recorded on a JEOL JMS-01 SG-2 mass spectrometer. Fluorescence measurements were conducted with a Hitachi MFP-4 fluorescence spectrophotometer. pH (pD) measurements were made with a Toyo digital pH/mV meter Model PT-3D equipped with a glass electrode, using standard solutions of pH 6.88 and 1.68. High performance liquid chromatography (HPLC) was conducted with a Hitachi 635 liquid chromatograph.

***N*,*N*′-Bis(4-bromobutyl)-*N*,*N*′-ditosyl-4,4′-diaminodiphenylmethane (4).** To a stirred and heated (60 °C) mixture of tetramethylene dibromide (213 g, 0.986 mol) and anhydrous K_2CO_3 (150 g, 1.09 mol) in DMF (2 L) was added dropwise over a period of 0.5 h a solution of **3** (mp 188–188.5 °C (EtOH) (lit. mp 164 °C (AcOH),[12a] mp 186–187.5 °C (aqueous EtOH)[12b])) (50.0 g, 98.7 mmol) in DMF (500 mL), and the whole was stirred for 2 h to room temperature. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was mixed with AcOEt (300 mL), and the whole was washed with brine (300 mL × 3). The AcOEt layer was dried over $MgSO_4$ and evaporated to dryness in vacuo to give black viscous oil. Purification by column chromatography (silica gel, benzene–AcOEt (99:1)) afforded **4** (55.2 g, 72.1%) as a pale purple powder. Recrystallization from $CHCl_3$–ether afforded colorless prisms: mp 110.5–111.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–2.1 (m, $NCH_2CH_2CH_2CH_2Br$, 8 H), 2.43 (s, $ArCH_3$, 6 H), 3.41 and 3.53 (two t, J = 6, $NCH_2CH_2CH_2CH_2Br$, 8 H), 3.96 (s, $ArCH_2Ar$, 2 H), 6.98 (d, J = 8, NAr*H* (ortho), 4 H), 7.10 (d, J = 8, NAr*H* (meta), 4 H), 7.26 (d, J = 8, SAr*H* (meta), 4 H), 7.46 (d, J = 8, SAr*H* (ortho), 4 H); IR (KBr) 1348, 1160 cm^{-1}. Anal. Calcd for $C_{35}H_{40}Br_2N_2O_4S_2$: C, 54.13; H, 5.19; N, 3.61. Found: C, 54.03; H, 5.15; N, 3.41.

***N*,*N*′,*N*″,*N*‴-Tetratosyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (5).** (a) To a stirred and heated (90 °C) suspension of anhydrous K_2CO_3 (138 g, 1.00 mol) in DMF (1 L) was added dropwise over a period of 10 h a solution of **3** (101 g, 199 mmol) and tetramethylene dibromide (43.5 g, 201 mmol) in DMF (1 L), and tetramethylene dibromide (43.5 g, 201 mmol) in DMF (1 L), and the stirring was continued at room temperature overnight. The reaction mixture was poured slowly into stirred water (3 L),

(27) (a) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106. (b) Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177–1183.
(28) (a) Cram, D. J.; Antar, M. F. *J. Am. Chem. Soc.* **1958**, *80*, 3103–3109. (b) Cram, D. J.; Singer, L. A. *Ibid.* **1963**, *85*, 1084–1088.
(29) Barnes, J. C.; Paton, J. D.; Damewood, J. R., Jr.; Mislow, K. *J. Org. Chem.* **1981**, *46*, 4975–4979.
(30) (a) Inazu, T.; Yoshino, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 652–655. (b) Kawato, T.; Inazu, T.; Yoshino, T. *Ibid.* **1971**, *44*, 200–203. (c) Urushigawa, Y.; Inazu, T.; Yoshino, T. *Ibid.* **1971**, *44*, 2546–2547.
(31) (a) Sergheraert, C.; Marcincal, P.; Cuingnet, E. *Tetrahedron Lett.* **1977**, 2879–2880; (b) *Ibid.* **1978**, 4785–4786.
(32) It should also be noted that Stetter has earlier reported a compound related to CP44, which has two 4,4′-diaminobiphenyl (*p*,*p*′-benzidine) units in place of the two 4,4′-diaminodiphenylmethane units.[33] Although crystalline complexes of this compound with dioxane and with benzene have been reported,[33] the latter crystalline complex turned out to be a simple stacked complex (and not an inclusion complex) by a recent X-ray study. See: Hilgenfeld, R.; Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 787–788; *Angew. Chem. Suppl.* **1982**, 1690–1701.
(33) Stetter, H.; Roos, E.-E. *Chem. Ber.* **1955**, *88*, 1390–1395.
(34) Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097–1099.
(35) (a) Odashima, K.; Itai, A.; Iitaka, Y.; Arata, Y.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4347–4350. (b) Soga, T.; Odashima, K.; Koga, K. *Ibid.* **1980**, *21*, 4351–4354. (c) Odashima, K.; Soga, T.; Koga, K. *Ibid.* **1981**, *22*, 5311–5314. (d) Odashima, K.; Koga, K. *Heterocycles* **1981**, *15*, 1151–1154. (e) Takahashi, I.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 973–976.

and the stirring was continued at room temperature for 30 min. The resulting precipitates were isolated by filtration, washed with water (300 mL × 3), air-dried, and stirred with EtOAc (400 mL) at reflux for 1 h. The residual solid was collected by filtration, washed with EtOAc (100 mL × 2), and purified by column chromatography (SiO_2, $CHCl_3$). Addition of EtOAc to the eluate and concentration gave pure **5** (26.6 g, 24%) as colorless needles: dec pt 311 °C; ^1H NMR (CD_2Cl_2) δ 1.4 (m, NCH_2CH_2, 8 H), 2.42 (s, $ArCH_3$, 12 H), 3.5 (br, NCH_2CH_2, 8 H), 3.95 (s, $ArCH_2Ar$, 4 H), 6.79 and 7.04 (two d (AB-type), J = 8, NAr*H* (ortho, meta), 16 H), 7.27 (d, J = 8, SAr*H* (meta), 8 H), 7.42 (d, J = 8, SAr*H* (ortho), 8 H); IR (KBr) 1341, 1160 cm^{-1}; FDMS, m/e 1121 (M^+ + 1). Anal. Calcd for $C_{62}H_{64}N_4O_8S_4$: C, 66.40; H, 5.75; N, 5.00. Found: C, 66.49; H, 5.83; N, 4.83.

(b) To a stirred and heated (100–110 °C) suspension of anhydrous K_2CO_3 (12.75 g, 92 mmol) in DMF (800 mL) was added dropwise over a period of 2 h a solution of **3** (9.0 g, 17.8 mmol) and **4** (13.9 g, 17.8 mmol) in DMF (1.2 L), and the whole was stirred at the same temperature for 1 h. The reaction mixture was filtered, and the filtrate was concentrated to about 100 mL. Crystals deposited were collected by filtration and washed with water to give **5** (14.6 g, 73%) as colorless needles. This sample was found to be identical with that obtained in (a) above.

1,6,20,25-Tetraaza[6.1.6.1]paracyclophane (1, CP44). To a heated solution of **5** (14.4 g, 12.8 mmol) in phenol (30 g, 0.32 mol) was added 47% aqueous HBr (225 mL, 2.0 mol), and the mixture was stirred at reflux for 2 h.[14] After being cooled to room temperature, the reaction mixture was diluted with water (1 L) and washed with Et_2O (500 mL × 2). The aqueous layer was made alkaline with NaOH and extracted with CH_2Cl_2 (1 L × 2). The combined extracts were washed successively with 5% NaOH (1 L), water (1 L × 2), and brine (1 L), dried over anhydrous $MgSO_4$, filtered, and evaporated to give a crystalline residue, which was recrystallized twice from $CHCl_3$ to give pure **1** as white opaque needles (4.34 g, 67%): mp 230–231 °C dec;[36] ^1H NMR (CD_2Cl_2) δ 1.65 (m, NCH_2CH_2, 8 H), 3.08 (m, NCH_2CH_2, 8 H), 3.2 (br, NH, 4 H), 3.67 (s, $ArCH_2Ar$, 4 H), 6.41 (d, J = 8, NAr*H* (ortho), 8 H), 6.87 (d, J = 8, NAr*H* (meta), 8 H); ^{13}C NMR ($CDCl_3$) δ 26.3 (NCH_2CH_2), 40.1 ($ArCH_2Ar$), 43.6 (NCH_2CH_2), 113.0 and 129.5 (NAr*C* (ortho, meta)), 131.1 (NAr*C* (para)), 146.1 (NAr*C* (ipso)); IR (KBr) 3380, 3340 cm^{-1}; MS, m/e 504 (M^+). Anal. Calcd for $C_{34}H_{40}H_4$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.62; H, 7.92; N, 10.98.

Recrystallization of **1** from 2.5 N HCl gave **1**·4HCl as colorless transparent plates.[24] Drying in vacuo of these crystals at 80 °C for 48 h gave white opaque plates: mp 244.5–245 °C dec (sealed under argon); ^1H NMR (DCl–D_2O (pD 1.2)/external Me_4Si) δ 2.05 (br, NCH_2CH_2, 8 H), 3.78 (br, NCH_2CH_2, 8 H), 4.51 (s, $ArCH_2Ar$, 4 H), 7.76 and 7.84 (two d (AB-type), NAr*H* (ortho, meta), 16 H); ^{13}C NMR (DCl–D_2O (pD 1.2)/external Me_2Si) δ 23.0 (NCH_2CH_2), 41.2 ($ArCH_2Ar$), 51.4 (NCH_2CH_2), 124.0 and 131.7 (NAr*C* (ortho, meta)), 133.2 (NAr*C* (para)), 144.2 (NAr*C* (ipso)); IR (KBr) 3200–2100 cm^{-1}. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·H_2O: C, 61.08; N, 6.94; N, 8.38; Cl, 21.21. Found: C, 61.14; H, 7.19; N, 8.59; Cl, 20.95.

***N,N',N'',N'''*-Tetraacetyl-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (6).** To a stirred suspension of **1**·4HCl (112 mg, 0.17 mmol) in CH_2Cl_2 (30 mL) were added successively triethylamine (181 mg, 1.8 mmol) in CH_2Cl_2 (1 mL) and acetyl chloride (140 mg, 1.8 mmol) in CH_2Cl_2 (1 mL) at room temperature, and the stirring was continued at room temperature overnight. Usual workup and purification by column chromatography (silica gel, $CHCl_3$/MeOH = 95:5) gave **6** (107 mg, 92%). Recrystallization from $CHCl_3$–Et_2O gave pure **6** as colorless prisms (hygroscopic): mp 292–293 °C; ^1H NMR ($CDCl_3$) δ 1.5 (br, NCH_2CH_2, 8 H), 1.73 (s, $COCH_3$, 12 H), 3.6 (br, NCH_2CH_2, 8 H), 3.96 (s, $ArCH_2Ar$, 4 H), 6.88 and 7.12 (two d (AB-type), J = 8, NAr*H* (ortho, meta), 16 H); IR (KBr) 1650 cm^{-1}; MS, m/e 672 (M^+). Anal. Calcd for $C_{42}H_{48}N_4O_4$·H_2O: C, 73.02; H, 7.29; N, 8.11. Found: C, 72.86; H, 7.06; N, 7.89.

***N,N'*-Dimethyl-4,4'-diaminodiphenylmethane (2).** Methylation of **3** (MeI/K_2CO_3/Amberlite IRA-410 (Cl form)/DMF), followed by detosylation (47% aqueous HBr/phenol),[14] gave **2**: mp 55.5–56 °C (Et_2O–hexane) (lit.[15] mp 56 °C).

Measurement of Fluorescence Spectra and Determination of K_s Values. Materials. 1-Anilinonaphthalene-8-sulfonate (ANS; purchased as an ammonium salt from Eastman Kodak) was recrystallized 4 times from water and dried in vacuo overnight at 100–110 °C with P_2O_5: mp 236.5–237 °C dec; R_f 0.7 (SiO_2, *n*-BuOH saturated with 20% aqueous AcOH),[37a] 0.85 (Al_2O_3, *n*-BuOH/EtOH/28% aqueous NH_3/H_2O = 66:16:1:29).[37b] 2-Toluidinonaphthalene-6-sulfonate (TNS; purchased as a free acid from Eastman Kodak) was recrystallized from water (charcoal) and dried in vacuo at room temperature overnight with P_2O_5: mp 242–243.5 °C dec (sealed under argon); R_f 0.5 (SiO_2, *n*-BuOH saturated with 20% aqueous AcOH),[37a] 0.2 (SiO_2, *i*-BuOH saturated with 3% aqueous NH_3),[37c] 0.3 (SiO_2, *s*-BuOH saturated with 1% aqueous NH_3).[37d] Redistilled water (from a glass vessel) was used for the fluorescence measurement. Inorganic salts for the buffer were the purest grade reagents available from Wako Pure Chemicals.

Measurement: ratio mode; excitation and emission slit width, 14 nm; excited at 375 nm (ANS, TNS); measured at 505 nm (ANS) and 495 nm (TNS); 25.0 ± 0.1 °C; in KCl–HCl buffer (pH 1.95). Sample solutions were prepared by mixing the stock solutions of the host and of the guest, and the measurements were carried out within 1 h after preparation. Preparation of the sample solutions and the fluorescence measurements were repeated at least twice. The measured fluorescence intensities were corrected on the basis of a standard solution of 1-(dimethylamino)-naphthalene-5-sulfonate (DNS) in 0.1 M $NaHCO_3$.[38] The reproducibility was within ±3%.

Determination of K_s Values. The K_s values of the 1:1 host–guest complexes were determined on the basis of the Benesi–Hildebrand equation,[18] plotting $C_H \cdot C_G/\Delta E$ against $C_H + C_G$ with varying C_H. C_H, C_G, and ΔE refer respectively to the total concentrations of the host and of the guest and the net increase of the fluorescence intensity on mixing the host and guest. The concentrations of the host and guests were as follows: C_G = 2.09 × 10^{-6} M and C_H = 1.39–13.9 × 10^{-5} M (10 points) for ANS, and C_G = 2.11 × 10^{-6} M and C_H = 5.27–31.6 × 10^{-6} M (6 points) for TNS. These concentration ranges were chosen so that the following requirements would be satisfied: (i) The total concentration of the guests (C_G) would be within the ranges in which a linear relationship is observed between the concentration and the fluorescence intensity. These ranges were found to be $C_G < 5 \times 10^{-6}$ M for ANS and $C_G < 1 \times 10^{-5}$ M for TNS. (ii) Absorption of the sample solutions at the excitation wavelength would not exceed 0.02. (iii) The Benesi–Hildebrand plot would give a straight line. (In the higher concentrations of the host, however, the plots deviated from the straight line, indicating the formation of a remarkable amount of the complexes other than the 1:1 type.) The K_s value for each guest was calculated from the slope and intercept of the straight line deduced by the least-squares methods.

Measurement of ^1H and ^{13}C NMR Spectra. Preparation of Samples. In general an appropriate amount of guest was dissolved in a DCl–D_2O solution (pD 1.2) of CP44. As for durene, a CD_3OD solution of the guest was mixed with a DCl–D_2O solution (pD 1.2) of CP44. pD was adjusted according to Glasoe and Long[39] on the basis of the equation: pD = pH meter reading + 0.40.

Measurement of ^1H NMR spectra: 100 MHz; pulse angle, 46°; pulse repetition, 7.0 s; data points, 8 K; spectral width, 1000 Hz; sample tube diameter, 5 mm; temperature, 28 ± 2 °C. Me_4Si (neat) was used as an external standard.[40] The reproducibility was within ±0.02 ppm.

Measurement of ^{13}C NMR spectra: 25 MHz; pulse angle, 42°; pulse repetition, 2.4 s; data points, 16 K; spectral width, 5000 Hz; sample tube diameter, 10 mm; temperature, 28 ± 2 °C. Me_4Si

(36) In a few cases, white needles with mp 182.5–184 °C dec were obtained from the same recrystallization solvent.

(37) (a) Turner, D. C.; Brand, L. *Biochemistry* **1968**, *7*, 3381–3390. (b) Penzer, G. R. *Eur. J. Biochem.* **1972**, *25*, 218–228. (c) McClure, W. O.; Edelman, G. M. *Biochemistry* **1966**, *5*, 1908–1919. (d) Beyer, C. F.; Craig, L. C.; Gibbons, W. A. *Ibid.* **1972**, *11*, 4920–4926.

(38) Himel, C. M.; Mayer, R. T. *Anal. Chem.* **1970**, *42*, 130–132.

(39) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.

(40) Since the chemical shift of HDO as based on the external Me_4Si was constant (δ 5.27 ± 0.01) for every sample, it had served as an internal standard. For a relevant paper, see: Ono, S.; Mitsumori, F.; Arata, Y.; Fujiwara, S. *Bunseki Kagaku* **1977**, *26*, 766–772; *Chem. Abstr.* **1978**, *88*, 56763k.

(neat) was used as an external standard. The reproducibility was within ±0.03 ppm.

Preparation of Crystalline Host-Guest Complexes. Preparation of the crystalline complexes was carried out by employing a modification of the method reported for cyclodextrins by Cramer.[41] Method A: for water-soluble guests, the crystalline complexes were obtained by slow cooling of a heated solution of an appropriate molar ratio of CP44 and guest in 1–2 N HCl. Method B: for water-insoluble liquid guests, the crystalline complexes were obtained by vigorous shaking of the guest (excess) with a solution of CP44 in a small amount of 1–2 N HCl, followed by deliberate recrystallization of the resulting precipitate from a small amount of 0.1 N HCl. Method C: for water-insoluble solid guests, the crystalline complexes were obtained by vigorous shaking of a solution of the guest (excess) in hexane and a solution of CP44 in a small amount of 1–2 N HCl, followed by deliberate recrystallization of the resulting precipitate from a small amount of 0.1 N HCl.

CP44·4HCl·Durene·4H_2O. The crystalline complex was obtained by method C as colorless transparent prisms which, after air-drying for 30 min, were characterized as CP44·4HCl·durene·4H_2O: HPLC (LiChrosorb RP-2 (5 μm), CH_3CN/MeOH/H_2O/28% aqueous NH_3 = 55:10:34:1, detected at 280 nm) CP44/durene = 1.0:1.0.[42] Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_{14}$·4H_2O: C, 61.68; H, 7.76; N, 6.54; Cl, 16.55. Found: C, 61.47; H, 7.48; N, 6.70; Cl, 16.50. This crystal was applied to the X-ray analysis.[3,24] Drying in vacuo of these crystals at 60 °C for 40 h gave white opaque prisms (hygroscopic), which were not suitable any more for X-ray analysis: mp 245–245.5 °C dec (sealed under argon); HPLC host/guest = 1.0:1.0. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_{14}$·1.5H_2O: C, 65.10; H, 7.57; N, 6.90. Found: C, 65.32; H, 7.12; N, 7.28.

CP44·4HCl·(Naphthalene)$_n$·4H_2O. The crystalline complex was obtained by method C as colorless transparent prisms which, after air-drying for 30 min, were analyzed by HPLC (LiChrosorb RP-2 (5 μm), CH_3CN/MeOH)H_2O/28% aqueous NH_3 = 50:15:34:1, detected at 280 nm): CP44/naphthalene = 1.0:1.4.[24,42] Drying in vacuo of these crystals at 60 °C for 4 h gave white opaque prisms: mp 253.5–254 °C dec (sealed under argon);[43] HPLC host/guest = 1.0:1.0. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·$C_{10}H_8$: C, 67.86; H, 6.73; N, 7.19. Found: C, 67.99; H, 6.77; N, 7.13.

CP44·4HCl·(1,3-Dihydroxynaphthalene)$_2$. The crystalline complex was obtained by method A from 1.8 N HCl solution (host/guest = 1:2) as faint brown transparent needles which, after drying in vacuo at 80 °C for 20 h, were characterized as CP44·4HCl·(1,3-dihydroxynaphthalene)$_2$:[24] mp 238.5–239.5 °C dec; ^1H NMR (D_2O) host/guest = 1:2. Anal. Calcd for $C_{34}H_{40}N_4$·4HCl·($C_{10}H_8O_2$)$_2$: C, 66.80; H, 6.23; N, 5.77; Cl, 14.61. Found: C, 66.70; H, 6.26; N, 6.00; Cl, 14.61. In IR spectrum (KBr) the characteristic bands of the guest at 3300 and 1275 cm^{-1} shifted to 3160 and 1260 cm^{-1}, respectively.

CP44·4HBr·(1,3-Dihydroxynaphthalene)$_2$. The crystalline complex was obtained similarly as above from 2.2 N HBr solution as faint brown transparent needles which, after drying in vacuo at 80 °C for 20 h, was characterized as CP44·4HBr·(1,3-dihydroxynaphthalene)$_2$:[24] ^1H NMR (D_2O) host/guest = 1:2. Anal. Calcd for $C_{34}H_{40}N_4$·4HBr·($C_{10}H_8O_2$)$_2$: C, 56.46; H, 5.26; N, 4.88; Br, 27.83. Found: C, 56.33; H, 5.18; N, 5.01; Br, 28.34.

Crystalline Complex with *p*-Xylene. The crystalline complex was obtained by method B as colorless transparent plates, which was found to be a 1:1 complex by HPLC under the same conditions as for the complex with naphthalene. However, this complex could not be characterized by X-ray analysis due to its fast decomposition.

Acknowledgment. This work was supported by the Ministry of Education, Science and Culture, Japan (Grant-in-Aids 56209005).

Registry No. 1, 74043-83-7; 1·4HCl, 74043-85-9; 2, 1807-55-2; 3, 74043-79-1; 4, 98587-50-9; 5, 74043-80-4; 6, 74043-82-6; CP44·4HCl·durene, 98587-51-0; CP44·4HCl·naphthalene, 98587-52-1; CP44·4HCl·(1,3-dihydroxynaphthalene)$_2$, 98587-53-2; CP44·4HBr·(1,3-dihydroxynaphthalene)$_2$, 98587-55-4; CP44·4HCl·*p*-xylene, 98611-61-1; CP44·ANS, 74043-84-8; CP44·TNS, 77929-42-1; 1,4-dibromobutane, 110-52-1.

(41) Cramer, F.; Henglein, F. M. *Chem. Ber.* **1957**, *90*, 2561–2571.

(42) For each lot of the crystals obtained from separate experiments, the host/guest ratio was determined for several *single* crystals. The ratio was always found to be constant for the crystals within the same lot. As to the complex with durene, the ratio was found to be 1.0:1.0 regardless of the lot. As to the complex with naphthalene, however, the ratio was found to be varied from 1.2 to 1.4 depending on the lot.

(43) This value (253.5–254 °C) is remarkably higher than the melting point (dec) of the free host CP44·4HCl (244.5–245 °C when sealed under argon). When sealed under vacuum, however, the melting point (dec) of the complex dropped to the value (240–241 °C), which is close to the melting point (dec) of the free host (242–243 °C when sealed under vacuum). This may indicate the sublimation of naphthalene from the complex when heated to higher temperatures under vacuum.

Oxygen-17 Nuclear Magnetic Resonance Chemical Shifts of Dialkyl Peroxides: Large Conformational Effects

Michael G. Zagorski, David S. Allan, and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Edward L. Clennan,* Poh Choo Heah, and Robert P. L'Esperance

Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071

Received July 15, 1985

^{17}O NMR chemical shifts are reported for 17 dialkyl peroxides including 2,3-dioxabicyclo[2.2.1]heptane (**3a**), the bicyclic peroxide nucleus of prostaglandin endoperoxides such as PGH_2 (**1**). The ^{17}O resonance for **3a** occurs at extraordinarily low field compared to homologous but less rigid and strained bicyclic peroxides. The chemical shifts, δ_O, of the ^{17}O resonances of seven bicyclic secondary dialkyl peroxides including **3a** show a fair linear correlation with those, δ_C, of the corresponding carbons of the hydrocarbon analogues with O replaced by CH_2 according to the equation $\delta_O = 12.9\delta_C - 75.7$ with $r = 0.95$. An excellent correlation ($r = 0.99$) was found for a series of four homologous bicyclic peroxides **3a–d** and the corresponding bicyclic hydrocarbons **9a–d**. A remarkably different correlation, $\delta_O = 1.00\delta_C - 220$ ($r = 0.93$), is observed for four acyclic peroxides and the corresponding hydrocarbons. For the acyclic peroxides, ROOR, and the corresponding hydrocarbons, RCH_2CH_2R, both δ_O and δ_C occur at lower field as R varies from primary to secondary to tertiary in accord with the dominance of a paramagnetic over a diamagnetic contribution to the total screening constant.

Many systematic investigations document the influence of molecular structure on the ^{17}O NMR spectra of organic oxygen-containing functional groups.[1] However, with the sole exception of di-*tert*-butyl peroxide,[1j,2] the ^{17}O NMR

0022-3263/85/1950-4484$01.50/0