$C_{15}H_{16}O_2S$ 260.0872, found 260.0876; MS m/z (relative intensity) 260 (28.1, M^+), 173 (100), 129 (19.1), 109 (54.1), 86 (56.0), 77 (69.4), 65 (58.2), 53 (29.2), 42 (40.2).

Methyl 6-Oxobicyclo[2.2.1]hept-2-ene-2-carboxylate Ethylene Ketal (32). *tert*-Butyllithium (1.80 mL, 1.5 M in pentane, 2.70 mmol) was added to a stirring solution of bromide **26** (250 mg, 1.80 mmol) in anhydrous THF (5 mL) at -78 °C under argon over 15 min. After the mixture was stirred for an additional 15 min, bone-dry CO_2 gas was bubbled through the reaction mixture, which was then allowed to come to room temperature. Then the solvent was removed with a rotary evaporator. The crude carboxylic acid thus obtained was dissolved in water (5 mL), acidified with aqueous citric acid (2 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (3 × 1 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator. The carboxylic acid **31** thus obtained was dissolved in CH_2Cl_2 (5 mL). (Dimethylamino)pyridine (25 mg, 0.2 mmol) and methanol (125 μL, 99 mg, 3.09 mmol) were added, and the mixture was cooled to 0 °C. Dicyclohexylcarbodiimide (300 mg, 1.45 mmol) was added. The mixture was warmed to room temperature and stirred for 8 h. Dicyclohexylurea which formed was filtered off, and the filtrate was concentrated on the rotavapor. The residue thus obtained was purified by flash chromatography (30% ethyl acetate in hexanes) to give **32**, which was crystallized from hexanes: yield 200 mg (88%); mp 75-70 °C; ^1H NMR δ 7.16 (d, J = 3.2 Hz, H), 3.87-4.08 (m, 4 H), 3.74 (s, 3 H), 3.12 (br s, H), 2.98 (br s, H), 2.02 (dd, J = 4.0 and 14.0 Hz, H), 1.82 (br s, 2 H), 1.60 (m, H); ^{13}C NMR δ 38.20 (+, t), 41.84 (-, d), 48.39 (-, d), 48.57 (+, t), 51.36 (-, q), 64.18 (+, t), 64.70 (+, t), 117.15 (+, s), 139.19 (+, s), 149.32 (-, d), 165.05 (+, s); HRMS calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0897; MS m/z (relative intensity) 210 (10.2, M^+), 135 (3.5), 119 (2.6), 86 (100), 65 (17.7), 42 (52.7).

Reaction of 31 with Diazomethane. The carboxylic acid **31** was methylated with an ether solution of CH_2N_2. After the usual workup the residue thus obtained was purified by flash chromatography (30% ethyl acetate, in hexane) to give pyrazoline **33**, which was crystallized from ethyl acetate-hexanes: yield 218 mg (80%); mp 101-3 °C; ^1H NMR δ 4.78 (m, H), 4.31 (m, H), 3.83-4.07 (m, 4 H), 3.78 (s, 3 H), 3.10 (br s, H), 2.49 (d, J = 9.0 Hz, H), 2.02 (br s, H), 0.70 (d, J = 11.6 Hz, H); ^{13}C NMR δ 32.91 (+, t), 38.94 (-, d), 40.90 (-, d), 42.50 (+, t), 85.32 (+, t), 107.71 (+, s), 114.50 (+, s), 168.44 (+, s); HRMS calcd for $C_{12}H_{16}N_2O_4$ 252.1111, found 252.1114; MS m/z (relative intensity) 252 (0.3, M^+), 218 (0.3), 149 (3.4), 112 (4.3), 91 (6.5), 86 (100), 77 (9.5), 42 (11.2).

6-Methylbicyclo[2.2.1]hept-5-en-2-one (3). A solution of ethylene ketal **6** (83 mg, 0.5 mmol), *p*-toluenesulfonic acid (0.5 mg), and water (0.1 mL) in THF (5 mL) was boiled 8 h under reflux with stirring. The reaction mixture was diluted with *n*-pentane (15 mL), extracted with aqueous $NaHCO_3$ solution (1 × 0.5 mL) and brine (2 × 1 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator at ~20 °C to give **3** (58 mg, 95%).

Acknowledgment. This research was assisted financially by Grant CA-31595 from the National Cancer Institute of the National Institutes of Health. We thank Dr. Swadesh Raychaudhuri for helpful suggestions.

Registry No. **3**, 19740-15-9; **6**, 119595-31-2; **7**, 119619-05-5; **10a**, 119595-33-4; **10b**, 119595-30-1; **14**, 18310-60-6; **16a**, 119678-61-4; 3-epi-**16a**, 119677-59-7; 3-epi-**16a** methyl ester, 119677-60-0; **17**, 119595-36-7; **18a**, 119595-37-8; **18a** dimethyl ester, 119595-32-3; **21a**, 119595-38-9; **21b**, 119595-34-5; **21c**, 119595-35-6; **22**, 119595-39-0; **23**, 694-98-4; **24**, 83205-20-3; **25**, 119677-61-1; **26**, 119595-40-3; **27**, 31444-18-5; **29**, 119595-41-4; **30**, 119595-42-5; **31**, 119595-43-6; **32**, 119595-44-7; **33**, 119595-45-8; PhSeSePh, 1666-13-3; diphenyl disulfide, 882-33-7; methylcyclopentadiene, 26519-91-5; methyl bromoacetate, 96-32-2; benzeneselenyl bromide, 34837-55-3.

Supplementary Material Available: Experimental details for ethylene ketalization of **3**, as well as preparation of **7**, **10a**, **10b**, **16a**, **21a**, **21b**, **21c**, and **22** and oxidative decarboxylation of **18a** and **21c** (8 pages). Ordering information is given on any current masthead page.

Metacyclophanes and Related Compounds. 24. Preparation and Reaction of Trimethyl[2.2.2]- and Tetramethyl[2.2.2.2]metacyclophane[1]

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8,16,24,32-Tetramethyl[2.2.2.2]- and 8,16,24-trimethyl[2.2.2]metacyclophane (**9** and **10**) were prepared by using the *tert*-butyl group as a positional protective group. Friedel-Crafts acylation of **9** and **10** afforded the corresponding ketones, **12** and **13**, respectively. ^1H NMR spectra indicate that, to avoid the unfavorable steric repulsion among three internal methyl groups, [2.2.2]metacyclophane **10** and its derivatives take a folded form rather than a stepped one.

Host-guest chemistry has been developing in the last two decades.[2] Many macrocyclic compounds were employed as host molecules, especially cyclodextrins and calixarenes, which have attracted major interest, since they form inclusion complexes with various hydrophobic guests in aqueous solution. Also, up to now, there has been much work on the syntheses and inclusion properties of macrocyclic cyclophanes[3] in which, the designing of artificial cavities of various sizes is possible; thus, insight into the relationship between the size of a guest molecule and that of the cavities of a host molecule may be obtained. In this context, it is of interest to modify the cyclophane cavities by introducing functional group(s) into macrocyclophanes. Such chemical modification has been limited, however, because the preparation of large quantities of macrocyclophanes is not easy.

Previously, we developed convenient preparative routes for a series of [2.2]metacyclophanes using the *tert*-butyl

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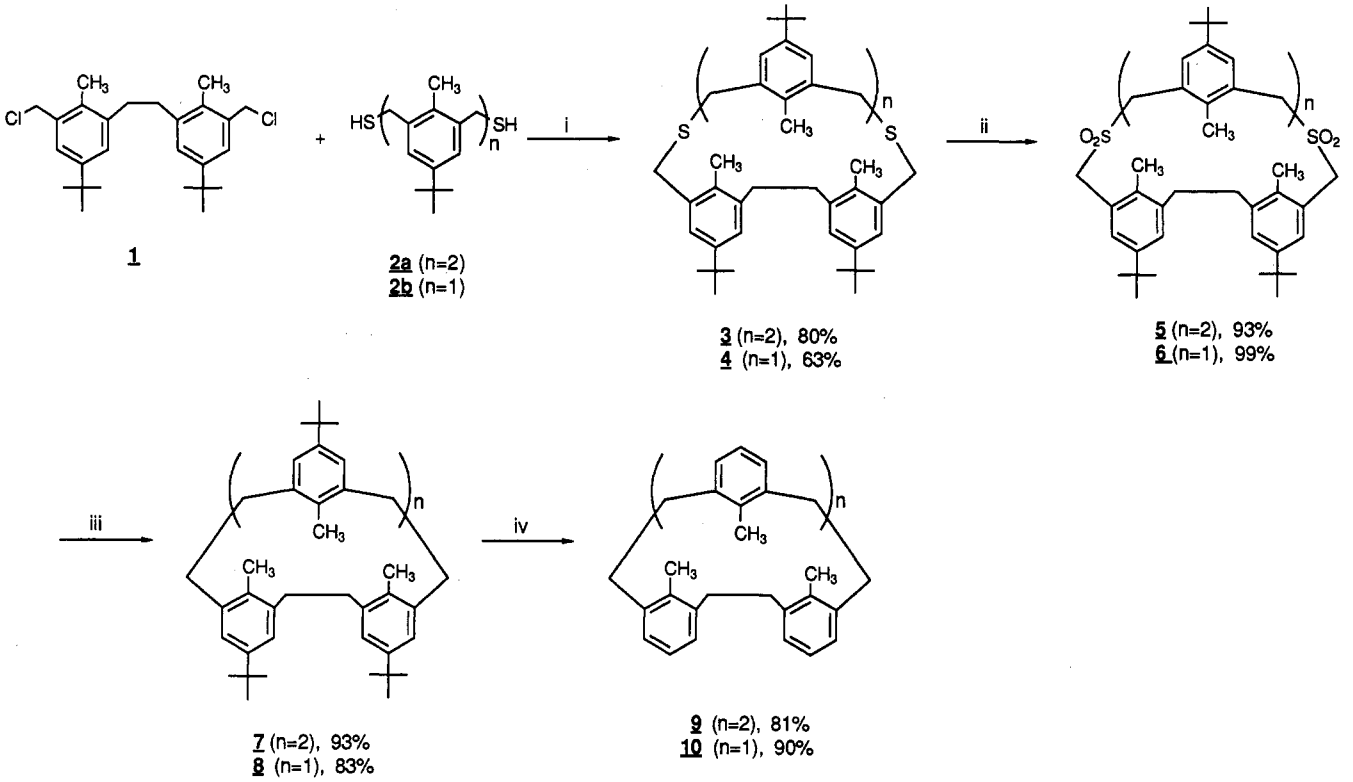
(2) (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.

(3) Odashima, K.; Koga, K. *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vol. II, Chapter 11, p 629.

0022-3263/89/1954-2632$01.50/0

Scheme I[a]



[a] (i) CsOH, $NaBH_4$, EtOH; (ii) MCPBA; (iii) 500 °C/0.04–0.05 Torr; (iv) $AlCl_3$–CH_3NO_2, toluene.

function as a positional protective group.[4-6] We describe here the synthesis of macrocyclic cyclophanes such as the titled metacyclophanes (MCPs) using the above method, as well as studies of their conformation and chemical properties.

Results and Discussion

Preparation. Preparative routes to tetramethyl[2.2.2.2]- and trimethyl[2.2.2]MCP, **9** and **10** are shown in Scheme I.

Cyclization of **1**[4] with **2** under highly dilute conditions with 10% ethanolic CsOH gave the disulfide **3**. Oxidation of **3** with *m*-chloroperbenzoic acid (MCPBA) afforded the corresponding disulfone **5**. Pyrolysis of **5** carried out at 500 °C under reduced pressure (0.4–0.5 Torr) afforded the expected cyclophane **7**, which was treated with $AlCl_3$–CH_3NO_2 in toluene to afford the desired **9**. Cyclophane **10** was prepared via **4**, **6**, and **8**. As shown in Scheme I, the yields of each of these reactions are very good, and the procedures are simple and suitable for large-scale operation.

Reactions. Although bromination[5] of 8,16-dimethyl[2.2]MCP with bromine afforded 5-bromo- and 5,13-dibromo-8,16-dimethyl[2.2]MCP and bromination[5] with NBS afforded 8,16-bis(bromomethyl)[2.2]MCP, bromination of **9** and **10** gave an inseparable mixture of unidentified products. Cyclophanes **9** and **10** afforded only resinous materials in nitration with fuming HNO_3, chloromethylation with chloromethyl methyl ether, and formylation with dichloromethyl methyl ether in the presence of $TiCl_4$.

Table I. Acylation of Tetramethyl[2.2.2.2]metacyclophane (9) and Trimethyl[2.2.2]metacyclophane (10)

entry	MCP	11	catalyst	solvent	product (yield, %)
1	9	11a	$FeCl_3$	CH_2Cl_2	**12a** (42), **12b** (14)
2	9	11a	$AlCl_3$	CS_2	**12c** (71)
3	9	11b	$AlCl_3$	CS_2	**12c** (74)
4	9	11b	$AlCl_3$	$ClCH_2CH_2Cl_2$	no reaction
5	10	11a	$FeCl_3$	CH_2Cl_2	**13a** (27), **13b**, **13c**
6	10	11b	$AlCl_3$	$ClCH_2CH_2Cl$	**13a** (66)
7	10	11a	$AlCl_3$	CS_2	**13c** (13)
8	10	11b	$AlCl_3$	CS_2	**13c** (81)
9	9	11c	$AlCl_3$	CS_2	**12d** (26)
10	9	11c	$AlCl_3$–CH_3NO_2	CS_2	**12d** (21)
11	9	11d	$AlCl_3$	CS_2	**12d** (35)
12	9	11d	$AlCl_3$–CH_3NO_2	CS_2	**12d** (69)
13	10	11c	$AlCl_3$	CS_2	complex mixture
14	10	11c	$AlCl_3$–CH_3NO_2	CS_2	**13d** (45)
15	10	11d	$AlCl_3$	CS_2	**13d** (9)
16	10	11d	$AlCl_3$–CH_3NO_2	CS_2	**13d** (55)
17	9	11e	$AlCl_3$–CH_3NO_2	CS_2	**12e** (42)
18	10	11e	$AlCl_3CH_3NO_2$	CS_2	**13e** (67)

In contrast, acylation of **9** and **10** was successful and gave the expected ketones as summarized in Scheme II and Table I.

The $FeCl_3$-catalyzed acetylation of **9** with acetic anhydride in CH_2Cl_2 afforded a mixture of monoacetyl **12a** and diacetyl **12b** in 42% and 14% yield, respectively. Unfortunately, it is not yet known which structure, **12b-1** or **12b-2**, is the correct one. Acetylation of **9** with **11a** or acetyl chloride (**11b**) in CS_2 in the presence of $AlCl_3$ afforded tetraacetyl **12c** in a good yield. The $AlCl_3$-catalyzed

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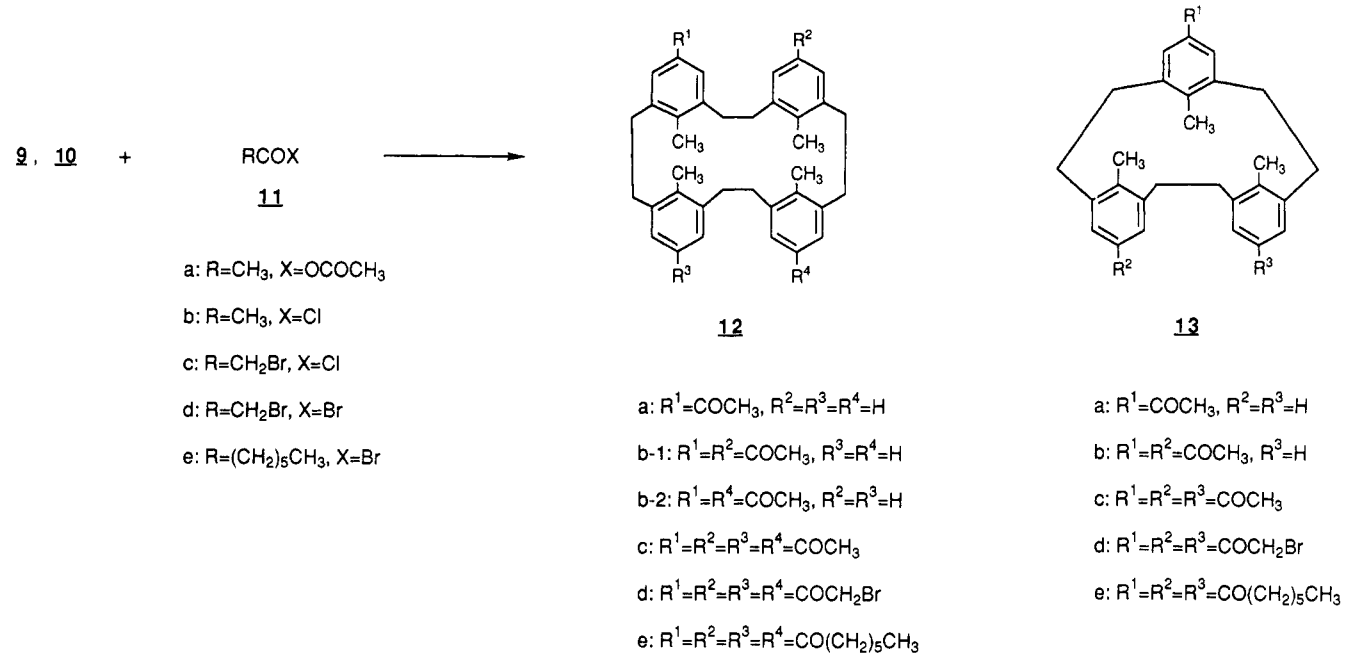
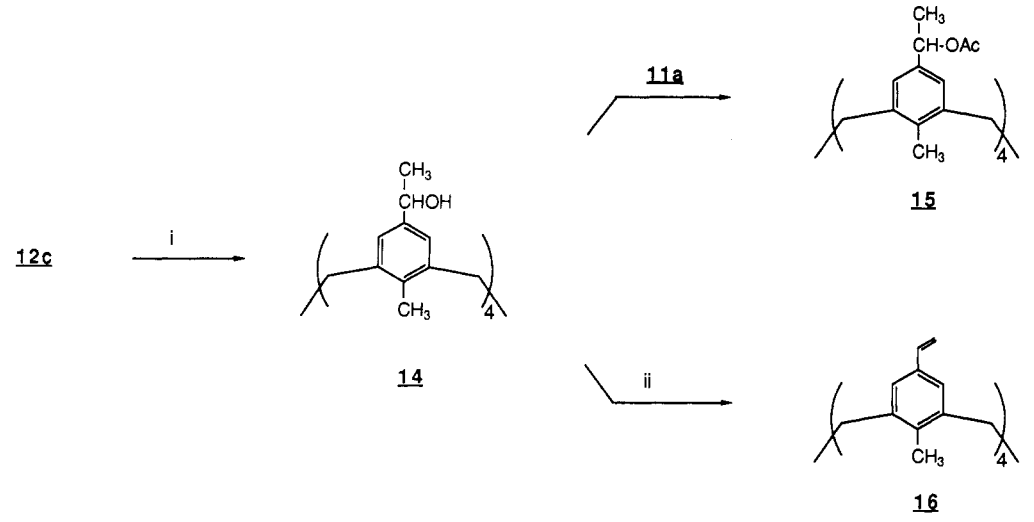
(5) Tashiro, M.; Yamato, T. *J. Org. Chem.* **1981**, *46*, 1543.
(6) (a) Tashiro, M.; Yamato, T. *J. Am. Chem. Soc.* **1982**, *104*, 3701. (b) Tashiro, M.; Koya, K.; Yamato, T. *J. Am. Chem. Soc.* **1982**, *104*, 3707. (c) Tashiro, M.; Yamato, T. *J. Org. Chem.* **1983**, *48*, 1461. (d) Tashiro, M.; Koya, K.; Yamato, T. *J. Am. Chem. Soc.* **1983**, *105*, 6650. (e) Tashiro, M.; Yamato, T.; Kobayashi, K. *J. Org. Chem.* **1984**, *49*, 4724.

Scheme II



Scheme III[a]



[a] (i) $LiAlH_4$; (ii) $ZnCl_2$, CF_3COOH, DMSO.

acetylation of **10** with **11b** in 1,2-dichloroethane afforded monoacetyl **13a** as a sole product in 66% yield, while the reaction in CS_2 gave only triacetyl **13c** in 81% yield. Use of $FeCl_3$ catalyst in CH_2Cl_2 afforded a mixture of **13a**, diacetyl **13b**, and **13c**.

Bromoacetylation of **9** and **10** with **11c** or **11d** was carried out in CS_2 by using $AlCl_3$ or $AlCl_3$–CH_3NO_2 as a catalyst. Tetrakis- and tris(bromomethyl) derivatives, **12d** and **13d**, were obtained as shown in Table I. Generally, $AlCl_3$–CH_3NO_2 catalyst gave better yields in these reactions than $AlCl_3$. Reactions with bromoalkanoyl chlorides having a long carbon chain such as 4-bromobutanoyl chloride and 8-bromooctanoyl chloride gave complex mixtures of unknown products. [2.2.2.2]MCP and [2.2.2]MCP, **12e** and **13e**, with C_7 chains were obtained in the acylation with heptanoyl chloride (**11e**) in CS_2 with $AlCl_3$–CH_3NO_2 catalyst.

In contrast, the reaction of **9** and **10** with benzoyl chloride or succinic anhydride gave only resinous materials.

It was found that the acetyl groups of the above-prepared tetraacetyl- and triacetylcyclophanes, **12c** and **13c**, are unreactive toward various reagents: haloform reaction, oxidation by MCPBA, reactions with hydroxy amine and glycine gave no product but the starting materials were recovered. Benzaldehyde or *p*-nitrobenzaldehyde reacted with **12c** and **13c**, but only inseparable mixtures of unidentified products resulted.

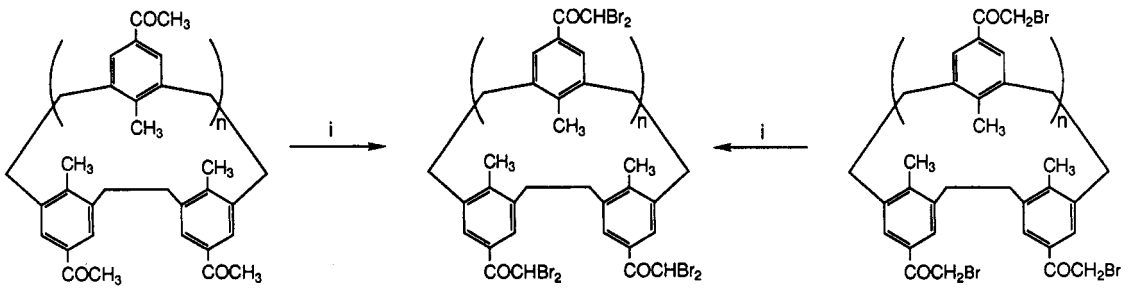
Reduction of **12c** with $LiAlH_4$ afforded the expected alcohol **14**, but $NaBH_4$ did not reduce **12c**. The treatment of **14** with **11a** afforded the tetracetate **15** in 48% yield (Scheme III).

The dehydration of **14** with $ZnCl_2$ and CF_3CO_2H in DMSO afforded the corresponding vinyl derivative **16** in 53% yield.

When **12c** and **13c** were treated with benzyltrimethylammonium tribromide (**19**),[7] tetrakis(dibromomethyl) **17** and tris(dibromomethyl) **19** were formed in 80 and 70%

(7) (a) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Chem. Lett.* **1987**, 627. (b) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2667.

Scheme IV[a]



12c: n=2
13c: n=1

n=2 (80%)
n=1 (70%)

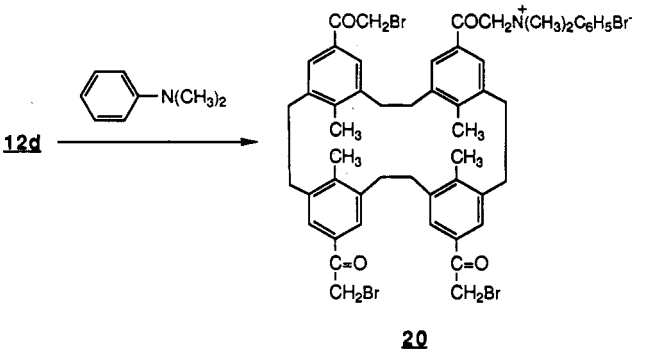
17: n=2
18: n=1

n=2 (29%)
n=1 (13%)

12d: n=2
13d: n=1

[a] (i) $C_6H_5CH_2N^+(CH_3)_3Br^-$ (19).

Scheme V



20

21 22

Figure 1.

yield, respectively (Scheme IV). However, the same reaction with **12d** and **13d**, which may be an intermediate in the above reactions, with **19** afforded **17** and **18** in 29 and 13% yield, respectively.

In order to obtain water-soluble MCPs, **12d** and **13d** were treated with various amines, but a complex mixture of products was formed and the expected ammonium salt of the cyclophanes was obtained in pure form only in the reaction of **12d** with *N,N*-dimethylaniline; **20** was isolated in 80% yield (Scheme V).

^{1}H NMR Spectra of Tetramethyl[2.2.2.2]MCPs and Trimethyl[2.2.2]MCPs. Relatively little is known about the conformation[8] of mobile [2.2.2]- and [2.2.2.2]metacyclophanes. Voegtle et al.[9] prepared tetraphenyl-[2.2.2.2]metacyclophane (**21**) (Figure 1) with an internal phenyl group and studied the restricted rotation of the phenyl substituent by dynamic ^{1}H NMR spectral investigation. Protons of the internal phenyl of **21** appeared at lower field (δ = 5.33, 5.60, 6.40).

All the bridge protons of the above-prepared [2.3.2.3]-MCPs, **3** and **5**, and [2.2.2.2]MCPs, **7**, **9**, **12a**, **12c**, **12d**, **14**, **15**, **16**, and **17**, are observed as a singlet in ^{1}H NMR spectra at 25 °C. Thus, [2.2.2.2]MCPs having four internal methyl groups are mobile. Signals of the internal methyl groups

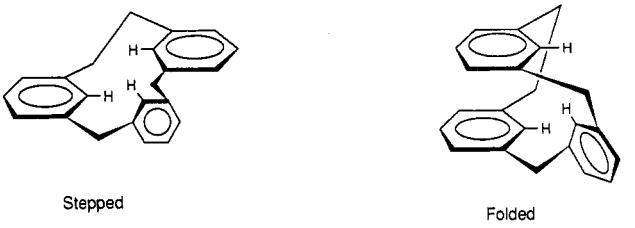


Figure 2. Conformation of [2.1.1]metacyclophane.

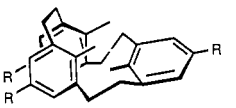


Figure 3. Conformation of trimethyl[2.3.3]metacyclophanes **4** and **6** and trimethyl[2.2.2]metacyclophanes **8**, **10**, **13**, and **18**.

appear in the normal region of 1.20–1.84 ppm. However, the spectrum of **12e** with a C_7 chain is curious; the signal for the internal methyl protons appears at 0.86 ppm as a singlet, while the one for the terminal methyl group of the C_7 chain at δ 2.72 ppm is a triplet. This fact suggests that the internal methyl groups are shielded and the terminal methyl is deshielded by the aromatic ring, but the conformation of **12e** is not known at the present time. The bridge protons of **12e** were observed as a broad singlet.

The ^{1}H NMR spectrum of parent [2.2.2]MCP (**22**)[10] shows the bridge methylene as a singlet and the signals of the internal aromatic protons appear at δ 6.14 ppm, owing to the shielding effect of the aromatic rings.

The signals of the bridge protons of [2.3.3]MCPs, **4** and **6**, appear as a singlet, but those of trimethyl[2.2.2]MCPs, **8**, **10**, **13c**, **13d**, **13e**, and **18**, appear as a complex set of multiple peaks. As summarized in Table II, the signals of three internal methyl protons are observed as a pair of singlets in ^{1}H NMR spectra of the above [2.3.3]- and [2.2.2]MCPs. The intensity ratio of the signal at the higher field and the one at the lower is 2:1, suggesting that one of the three internal methyl groups is shielded. The observed shielding of the methyl group is more pronounced in [2.3.3]- than in [2.2.2]MCPs. This indicates that the steric repulsion between the shielded methyl group and shielding phenyl rings is smaller and they must be closer to each other in [2.3.3]- than in [2.2.2]MCPs.

Previously, two conformers, the stepped and folded forms, were postulated for [2.1.1]MCPs and Sato et al.[11] favored the stepped one on the basis of the shielded aryl protons at δ 6.27 and 6.49 ppm (Figure 2).

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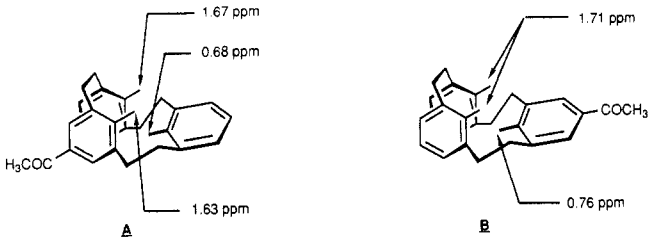

Figure 4. Conformers of [2.2.2]metacyclophane **13a**.

Table II. Chemical Shift (δ ppm) of Internal Methyl Group of MCPs

MCP	compd	shift, δ
[2.3.2.3]	**3**	1.72 (12 H)
	5	1.78 (12 H)
[2.2.2.2]	**7**	1.20 (12 H)
	9	1.52 (12 H)
	12a	1.52 (12 H)
	12c	1.60 (12 H)
	12d	1.74 (12 H)
	12e	0.86 (12 H)
	14	1.34 (12 H)
	15	1.24 (12 H)
	16	1.48 (12 H)
	17	1.84 (12 H)
[2.3.3]	**4**	0.27 (3 H), 2.16 (6 H)
	6	0.20 (3 H), 2.10 (6 H)
[2.2.2]	**8**	0.60 (3 H), 1.93 (6H)
	10	0.72 (3 H), 1.68 (6 H)
	13a	0.68 and 0.76 (total 3 H)
		1.44 and 1.66 (total 6 H)
	13c	0.74 (3 H), 1.67 (6 H)
	13d	0.84 (3 H), 1.74 (6 H)
	13e	0.72 (3 H), 1.66 (6 H)
	18	0.84 (3 H), 1.76 (6 H)

These ^{1}H NMR spectra are consistent with folded conformations for trimethyl[2.3.3]- and trimethyl[2.2.2]MCPs (Figure 3). The ^{1}H NMR spectrum of monoacetyl-[2.2.2]MCP, **14a**, indicates the presence of two folded conformers, **14a-1** and **14a-2**, in the ratio of 2:1 (Figure 4). The stepped conformer is unfavorable because all three internal methyl groups come into close proximity.

As described above, a low-field shift of the terminal methyl protons of the C_7 chain of [2.2.2.2]MCP **12e** is observed. In the ^{1}H NMR spectrum of the corresponding [2.2.2]MCP **13e**, the signal of the terminal methyl groups appears also at low field (δ 2.34 ppm). The above observations seem to be anomalous because the terminal methyl groups usually are not shielded by the aromatic rings of **12e** and **13e**.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 100 MHz in $CDCl_3$. Column chromatography was carried out on silica gel (Wako gel, C-300).

Preparation of 1,2-Bis[5-*tert*-butyl-3-(mercaptomethyl)-2-methylphenyl]ethane (2a). After a solution of 10.0 g (24 mmol) of **1** and 4.60 g (60 mmol) of thiourea in 200 mL of DMSO was stirred at 40–45 °C for 16 h under a nitrogen stream, it was poured into 250 mL of cold 10% aqueous NaOH. The mixture was then stirred for 1 h, acidified with 10% hydrochloric acid, and extracted with CH_2Cl_2 (100 mL × 3). The extract was dried over $MgSO_4$ and evaporated in vacuo to afford a residue, which, on recrystallization from hexane, gave 8.90 g (90%) of **2a** as colorless needles, mp 122–124 °C: ^{1}H NMR δ 1.26 (18 H, s), 1.66 (2 H, t, J = 7 Hz), 2.28 (6 H, s), 2.88 (4 H, s), 3.76 (4 H, d, J = 7 Hz), 7.00 (2 H, d, J = 2 Hz), 7.10 (2 H, d, J = 2 Hz); MS m/z 414 (M^+). Anal. Calcd for $C_{26}H_{38}S_2$: C, 75.30; H, 9.24. Found: C, 75.44; H, 9.35.

Cyclization. Typical Procedure. 5,14,22,31-Tetra-*tert*-butyl-8,17,25,34-tetramethyl-10,27-dithia[2.3.2.3]metacyclophane (3). A solution of 8.40 g (20 mmol) of **1** and 8.30 g (20 mmol) of **2a** in 300 mL of benzene was added dropwise from a Hershberg funnel with stirring to a solution of 9.00 g (59 mmol) of CsOH and 1.50 g (40 mmol) of $NaBH_4$ in 3 L of EtOH. When the addition was completed (addition time 100 h), solvents were evaporated and the residue was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and condensed. The condensate was recrystallized from a mixture of hexane and benzene, giving 12.1 g (80%) of cyclophane **3** as colorless prisms, mp 151–152 °C: ^{1}H NMR δ 1.16 (36 H, s), 1.72 (12 H, s), 2.88 (8 H, s), 3.58 (8 H, s), 6.68 (4 H, d, J = 2 Hz), 6.98 (4 H, d, J = 2 Hz); MS m/z 760 (M^+). Anal. Calcd for $C_{52}H_{72}S_2$: C, 82.02; H, 9.53. Found: C, 82.18; H, 9.52.

5,14,23-Tri-*tert*-butyl-8,17,26-trimethyl-10,19-dithia[2.3.3]metacyclophane (4) was prepared by the reaction of **1** with **2b** under the same conditions as previously described: colorless prisms (hexane–benzene), mp 229–231 °C; ^{1}H NMR δ 0.27 (3 H, s), 1.20 (9 H, s), 1.28 (18 H, s), 2.16 (6 H, s), 3.25 (4 H, s), 3.46 (4 H, s), 3.64 (4 H, s), 6.90 (2 H, d, J = 2 Hz), 6.96 (2 H, s), 7.26 (2 H, d, J = 2 Hz); MS m/z 586 (M^+). Anal. Calcd for $C_{39}H_{54}S_2$: C, 79.80; H, 9.27. Found: C, 79.76; H, 9.23.

Oxidation. Typical Procedure. 5,14,22,31-Tetra-*tert*-butyl-8,17,25,34-tetramethyl-10,27-dithia[2.3.2.3]metacyclophane 10,10,27,27-Tetraoxide (5). After a solution of 12.1 g (16 mmol) of **3** and 17.5 g (81 mmol) of MCPBA in 500 mL of CH_2Cl_2 was stirred at room temperature for 25 h, it was washed with 10% aqueous K_2CO_3 and water, dried over $MgSO_4$, and evaporated in vacuo to give 12.2 g (93%) of disulfone **5** as a colorless crystalline powder, mp 340–343 °C dec: ^{1}H NMR δ 1.16 (36 H, s), 1.78 (12 H, s), 2.96 (8 H, s), 4.14 (8 H, s), 6.74 (4 H, d, J = 2 Hz), 7.06 (4 H, d, J = 2 Hz); MS m/z 824 (M^+). Anal. Calcd for $C_{52}H_{72}O_4S_2$: C, 75.68; H, 8.79. Found: C, 75.84; H, 8.67.

5,14,23-Tri-*tert*-butyl-8,17,26-trimethyl-10,19-dithia[2.3.3]metacyclophane 10,10,19,19-tetraoxide (6) was prepared in the same manner: colorless prisms (hexane–benzene); mp 166–168 °C; ^{1}H NMR δ 0.20 (3 H, s), 1.29 (9 H, s), 1.30 (18 H, s), 2.10 (6 H, s), 3.24 (4 H, s), 4.18 (12 H, br s), 7.30 (2 H, d, J = 2 Hz), 7.40 (2 H, s), 7.48 (2 H, J = 2 Hz); MS m/z 650 (M^+). Anal. Calcd for $C_{39}H_{54}O_4S_2$: C, 71.96; H, 8.36. Found: C, 72.04; H, 8.21.

Pyrolysis. Typical Procedure. After 1.00 g (1.20 mmol) of **5** was pyrolyzed at 500 °C under reduced pressure (0.4–0.5 Torr) according to the reported method,[8] the crude product was dissolved in CH_2Cl_2 and chromatographed over silica gel with hexane as an eluant, giving 783 mg (93%) of **5,13,21,29-tetra-*tert*-butyl-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (7)** as colorless needles (EtOH–EtOAc): mp 209–211 °C; ^{1}H NMR δ 1.20 (12 H, s), 1.30 (36 H, s), 2.80 (16 H, s), 7.08 (12 H, m); MS m/z 696 (M^+). Anal. Calcd for $C_{52}H_{72}$: C, 89.60; H, 10.40. Found: C, 89.50; H, 10.45.

5,13,21-Tri-*tert*-butyl-8,16,24-trimethyl[2.2.2]metacyclophane (8) was also obtained by this method: colorless needles (EtOH–EtOAc); mp 242–244 °C; ^{1}H NMR δ 0.60 (3 H, s), 1.24 (18 H, s), 1.34 (9 H, s), 1.63 (6 H, s), 2.60–3.40 (12 H, m), 6.86 (2 H, d, J = 2 Hz), 7.00 (2 H, d, J = 2 Hz), 7.12 (2 H, s); MS m/z 522 (M^+). Anal. Calcd for $C_{39}H_{54}$: C, 89.59; H, 10.41. Found: C, 89.45; H, 10.48.

Trans-*tert*-butylation. Typical Procedure. To a solution of 1.50 g (2.2 mmol) of **7** in 200 mL of toluene was added a solution 5.70 g (43 mmol) of $AlCl_3$ in 8 mL of nitromethane. After the reaction mixture was stirred at room temperature overnight, it was poured into ice–water. The organic layer was extracted with $CHCl_3$ (100 mL × 3). The extract was washed with water (50 mL × 2), dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallized from a mixture of hexane and CCl_4, giving 830 mg (81%) of **8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (9)** as colorless needles, mp 261–263 °C: ^{1}H NMR δ 1.52 (12 H, s), 2.84 (16 H, s), 6.78–7.04 (12 H, m); MS m/z 472 (M^+). Anal. Calcd for $C_{36}H_{40}$: C, 91.47; H, 8.53. Found: C, 91.44; H, 8.56.

Compound **8,16,24-trimethyl[2.2.2]metacyclophane (10)** was prepared in the same manner: colorless prisms (hexane–CCl_4), mp 220 °C dec; ^{1}H NMR δ 0.72 (3 H, s), 1.68 (6 H, s), 2.68–3.38 (12 H, m), 6.80–7.16 (9 H, m); MS m/z 354 (M^+). Anal. Calcd for $C_{27}H_{30}$: C, 91.47; H, 8.53. Found: C, 91.47; H, 8.53.

Acylation. Typical Procedures. (a) Reaction of 9 with Acetic Anhydride (11a). To a mixture of 189 mg (1.2 mmol)

of $FeCl_3$ in 0.1 mL of **11a** and 5 mL of CH_2Cl_2 was gradually added in 30 min a solution of 100 mg (0.21 mmol) of **9** in 5 mL of CH_2Cl_2. After the reaction mixture was stirred for 12 h, it was poured into dilute hydrochloric acid. The organic layer was extracted with CH_2Cl_2 (30 mL × 2) and the extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed over silica gel using $CHCl_3$ as an eluant to give 45 mg (42%) of **12a** and 16 mg (14%) of **12b.**

5-Acetyl-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (12a): pale yellow prisms (benzene/hexane = 1/1); mp 258–260 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR δ 1.52 (12 H, s), 2.44 (3 H, s), 2.84 (16 H, s), 6.60–7.00 (9 H, m), 7.46 (2 H, s); MS m/z 514 (M^+). Anal. Calcd for $C_{38}H_{42}O$: C, 88.67; H, 8.23. Found: C, 88.67; H, 8.31.

5,13(or 26)-Diacetyl-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (12b): pale yellow prisms (benzene/hexane = 1/1); mp 172–174 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR δ 1.56 (6 H, s), 1.64 (6 H, s), 2.40 (3 H, s), 2.44 (3 H, s), 2.84–2.90 (16 H, m), 6.60–7.00 (6 H, m), 7.40 (2 H, s), 7.46 (2 H, s); MS m/z 556 (M^+). Anal. Calcd for $C_{40}H_{44}O_2$: C, 86.28; H, 7.97. Found: C, 86.61; H, 7.97.

(b) Reaction of 9 with Acetyl Chloride (11b). To a solution of 200 mg (0.42 mmol) of **9** in 60 mL of CS_2 was gradually added 678 mg (5.1 mmol) of $AlCl_3$. After the reaction mixture was refluxed 4 h, it was poured into water and the organic layer was extracted with $CHCl_3$ (50 mL × 2). The extract was washed with water (20 mL × 2), dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallized from a mixture of benzene and hexane to give 201 mg (74%) of **5,13,21,29-tetraacetyl-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (12c)** as colorless prisms, mp 219–222 °C: IR (KBr) 1670 cm^{-1}; ^1H NMR δ 1.60 (12 H, s), 2.40 (12 H, s), 2.92 (16 H, s), 7.44 (8 H, s); MS m/z 640 (M^+). Anal. Calcd for $C_{44}H_{48}O_4$: C, 91.47; H, 8.53. Found: C, 91.40; H, 8.69.

(c) Reaction of 9 with 11d in the Presence of $AlCl_3$–CH_3NO_2. To a solution of 250 mg (0.53 mmol) of **9** in 65 mL of CS_2 was added a solution of 1.70 g (12.7 mmol) of $AlCl_3$ in 0.9 mL of CH_3NO_2. To the mixture was added 0.4 mL (4.3 mmol) of **11d.** After the reaction mixture was refluxed for 3 h, it was poured into ice–water. The organic layer was extracted with $CHCl_3$ (100 mL × 3). The extract was washed with 20 mL of water, dried over $MgSO_4$, and condensed. The residue was recrystallized from a mixture of benzene and hexane to yield 347 mg (69%) of **5,13,21,29-tetrakis(bromomethyl)-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (12d)** as colorless prisms, mp 126–129 °C: IR (KBr) 1670 cm^{-1}; ^1H NMR δ 1.74 (12 H s), 2.96 (16 H, s), 4.20 (8 H, s), 7.42 (8 H, s). Anal. Calcd for $C_{44}H_{44}O_4Br_4$: C, 55.25; H, 4.64. Found: C, 55.27; H, 4.64.

(d) Reaction of 10 with 11b in the Presence of $AlCl_3$ in CH_2Cl_2. To a solution of 80 mg (0.23 mmol) of **10** in 10 mL of CH_2Cl_2 was added in 1 h under nitrogen a solution of 0.1 mL (1 mmol) of **11b** and 340 mg (2.5 mmol) of $AlCl_3$ in 20 mL of CH_2Cl_2. The reaction mixture was poured into 500 mL of ice–water. The organic layer was extracted with CH_2Cl_2 (100 mL × 3). The extract was washed with water (20 mL × 2), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed using $CHCl_3$ to afford 59 mg (66%) of **5-acetyl-8,16,24-trimethyl-[2.2.2]metacyclophane (13a)** as colorless prisms (hexane–CCl_4): mp 189–192 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR δ 0.68 and 0.76 (total 3 H, each s), 1.63, 1.67, and 1.71 (total 6 H, each s), 2.52 and 2.61 (total 3 H, each s), 2.66–3.40 (12 H, m), 6.80–7.16 (6 H, m), 7.48, 7.58, and 7.72 (total 2 H, d with J = 2 Hz, d with J 2 Hz, and s); MS m/z 396 (M^+). Anal. Calcd for $C_{29}H_{32}O$: C, 87.83; H, 8.13. Found: C, 87.52; H, 8.15.

The reactions shwon in runs 3, 5, 7, and 9 in Table I and 2, 4, 6, and 8 in Table II were carried out according to procedure **b**. The reaction shown on run 3 in Table II was carried out by procedure **a**. The reactions shown on runs 6 and 8 in Table I and runs 5, 7, and 9 in Table II were carried out according to procedure *c*.

5,13,21,29-Tetraheptanoyl-8,16,24,32-tetramethyl[2.2.2.2]-metacyclophane (12e): pale yellow prisms (hexane); mp 90–91 °C; IR (KBr) C=O 1680 cm^{-1}; ^1H NMR δ 0.86 (12 H, s), 1.28–1.58 (40 H, m), 2.72 (12 H, t, J = 7 Hz), 2.90 (16 H, s), 7.40 (8 H, s). Anal. Calcd for $C_{64}H_{88}O_4$: C, 83.43; H, 9.63. Found: C, 83.34; H, 9.51.

5,13,21-Triacetyl-8,16,24-trimethyl[2.2.2]metacyclophane (13c): colorless prisms (hexane–benzene); mp 173–176 °C; IR (KBr) C=O 1670 cm^{-1}; ^1H NMR δ 0.74 (3 H, s), 1.68 (6 H, s), 2.54 (6 H, t, J = 7 Hz), 2.62 (3 H, s), 2.76–3.40 (12 H, m), 7.57–7.60 (8 H, m), 7.74 (2 H, s); MS m/z 480 (M^+). Anal. Calcd for $C_{33}H_{36}O_3$: C, 82.46; H, 7.55. Found: C, 82.63; H, 7.80.

5,13,21-Tris(bromomethyl)-8,16,24-trimethyl[2.2.2]metacyclophane (13d): colorless prisms (hexane–benzene); mp 81–83 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR δ 0.84 (3 H, s), 1.74 (6 H, s), 2.70–3.40 (12 H, m), 4.24–4.56 (6 H, m), 7.58–7.60 (4 H, m), 7.77 (2 H, s). Anal. Calcd for $C_{33}H_{33}O_3Br_3$: C, 55.25; H, 4.64. Found: C, 55.57; H, 4.78.

5,13,21-Triheptanoyl-8,16,24-trimethyl[2.2.2]metacyclophane (13e): colorless oil; IR (NaCl) C=O 1680 cm^{-1}; ^1H NMR δ 0.72 (3 H, s), 0.88–1.32 (30 H, m), 1.66 (6 H, s), 2.34 (3 H, t, J = 7 Hz), 2.80–3.16 (18 H, m), 7.52–7.56 (4 H, m), 7.70 (2 H, s); MS m/z 690 (M^+). Anal. Calcd for $C_{48}H_{66}O_3 \cdot H_2O$: C, 81.36; H, 9.60. Found: C, 81.33; H, 9.28.

Reduction of 12c. To a suspension of 59 mg (1.6 mmol) of $LiAlH_4$ in 15 mL of THF was added under nitrogen a solution of 100 mg (0.16 mmol) of **12c** in 15 mL of THF. After the reaction mixture was heated in a after bath (90 °C) for 1 h, to it was added a small amount of NaF hydrate. The solid products were filtrated and the filtrate was dried over $MgSO_4$ and then evaporated in vacuo. The residue was chromatographed over silica gel using $CHCl_3$ as an eluent to afford 101 mg (100%) of **5,13,21,29-tetrakis(1-hydroxyethyl)-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (14)** as colorless prisms (hexane-EtOAc); mp 130–133 °C; IR (KBr) ν OH 3350 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (12 H, s), 1.50 (12 H, d, J = 6 Hz), 1.94 (4 H, br s), 2.80 (16 H, s); 4.80 (4 H, d, J = 6 Hz), 7.00 (8 H, s); MS m/z 576 ($M^+ - 4H_2O$). Anal. Calcd for $C_{44}H_{56}O_4 \cdot 0.5H_2O$: C, 80.32; H, 8.73. Found: C, 80.54; H, 8.93.

Acetylation of 14. After a solution of 20 mg (0.031 mmol) of **14**, 57 mg (0.47 mmol) of 4-(dimethylamino)pyridine, and 0.1 mL (0.47 mmol) of **11a** in 4 mL of CH_2Cl_2 was stirred at room temperature for 12 h, it was poured into ice–water (200 mL). The organic layer was extracted with $CHCl_3$ (50 mL × 2). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which was recrystallized from hexane to afford 12 mg (48%) of **5,13,21,29-tetrakis(1-acetoxyethyl)-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (15)** as pale yellow prisms, mp 52–54 °C: IR (KBr) ν C=O 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (12 H, s), 1.51 (12 H, d, J = 6 Hz), 2.04 (12 H, s), 2.80 (16 H, s), 5.81 (4 H, q, J = 6 Hz), 7.00 (8 H, s). Anal. Calcd for $C_{52}H_{64}O_8$: C, 76.44; H, 7.90. Found: C, 76.22; H, 8.18.

Dehydration of 14. After a mixture of 15 mg (0.023 mmol) of 14 and a small amount of $ZnCl_2$ and CF_3CO_2H in 3 mL of DMSO was heated at 165 °C for 5 min, it was poured into water. The organic layer was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which was chromatographed over silica gel using a 2:1 mixture of hexane and benzene as eluent to afford 7 mg (53%) of **5,13,21,29-tetra(2-propenyl)-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (16)** as colorless needles (hexane), mp >300 °C: NMR ($CDCl_3$) δ 1.48 (12 H, s), 2.84 (16 H, s), 5.12 (4 H, dd, J = 12 and 1 Hz), 5.59 (4 H, dd, J = 18 and 1 Hz), 6.62 (4 H, dd, J = 18 and 12 Hz), 7.00 (8 H, s); MS m/e 576 (M^+). Anal. Calcd for $C_{44}H_{48}$: C, 91.61; H, 8.39. Found: C, 91.56; H, 8.37.

Bromination of 12c and 13c with Benzyltrimethylammonium Tribromide (19). A solution of 40 mg (0.063 mmol) of **12c**, 366 mg (0.94 mmol) of **20** in 2 mL of MeOH, and 5 mL of CH_2Cl_2 was stirred at room temperature for 18 h. The mixed solvents were evaporated in vacuo. The residue was extracted with ether. The ether extract was washed with aqueous $NaHSO_3$ and water, dried over $MgSO_4$, and evaporated in vacuo to leave the residue, which was recrystallized from a 1:1 mixture of hexane and benzene to afford 64 mg (80%) of **5,13,21,29-tetrakis(dibromomethyl)-8,16,24,32-tetramethyl[2.2.2.2]metacyclophane (17)** as colorless prisms, mp 153–154 °C: IR (KBr) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.84 (12 H, s), 3.00 (16 H, s), 6.38 (4 H, s), 7.58 (8 H, s). Anal. Calcd for $C_{44}H_{40}O_4Br_8$: C, 41.55; H, 3.17. Found: C, 41.77; H, 3.24.

Compound **5,13,21,29-tetrakis(dibromomethyl)-8,16,24,32-tetramethyl[2.2.2]metacyclophane (18)** was also prepared by the previously described method: colorless crystalline powder (hexane–benzene); mp 110–112 °C; IR (KBr) 1680 cm^{-1}; NMR

($CDCl_3$) δ 0.84 (3 H, s), 1.76 (6 H, s), 2.68–3.40 (12 H, m), 6.64 (2 H, s), 6.72 (1 H, s), 7.62 (2 H, d, J = 2 Hz), 7.74 (2 H, d, J = 2 Hz), 7.86 (2 H, s). Anal. Calcd for $C_{33}H_{30}O_3Br_6$: C, 41.55; H, 3.17. Found: C, 41.21; H, 3.42.

Reaction of 12d with *N,N*-Dimethylaniline. After a solution of 25 mg (0.026 mmol) of **12d** and 0.5 mL of *N,N*-dimethylaniline in 4 mL of EtOAc was stirred at room temperature for 2 h, the solvent was evaporated in vacuo. The residue was washed with a small amount of EtOAc to give 23 mg (80%) of ***N*-benzyl-*N,N*-dimethyl-*N*-{2-oxo-2-[5′-{13′,21′,29′-tris(bromoacetyl)-8′,16′,24′,32′-tetramethyl[2.2.2.2]metacyclophano}]ethyl}ammonium bromide (20)** as a colorless powder, mp 129–134 °C dec: IR (KBr) ν C=O 1680 cm^{-1}. Anal. Calcd for $C_{52}H_{55}O_4NBr_4$: C, 57.96; H, 5.14; N, 1.30. Found: C, 58.19; H, 5.08; N, 1.31.

Registry No. **1**, 67691-33-2; **2a**, 119877-85-9; **2b**, 77180-45-1; **3**, 119877-86-0; **4**, 119877-87-1; **5**, 119877-88-2; **6**, 119877-89-3; **7**, 119877-90-6; **8**, 119877-91-7; **9**, 119877-92-8; **10**, 119877-93-9; **11a**, 108-24-7; **11b**, 75-36-5; **11c**, 22118-09-8; **11d**, 598-21-0; **11e**, 18255-47-5; **12a**, 119877-94-0; **12b**, 119878-09-0; **12c**, 119877-95-1; **12d**, 119877-96-2; **12e**, 119877-97-3; **13a**, 119877-98-4; **13b**, 119877-99-5; **13c**, 119878-00-1; **13d**, 119878-01-2; **13e**, 119878-02-3; **14**, 119878-03-4; **15**, 119878-04-5; **16**, 119878-05-6; **17**, 119878-06-7; **18**, 119878-07-8; **20**, 119878-08-9; *N,N*-dimethylaniline, 121-69-7.

Synthesis and Vesicle Formation of Identical- and Mixed-Chain Di-*n*-alkyl Phosphate Amphiphiles

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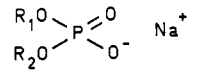
The synthesis of identical-chain and mixed-chain di-*n*-alkyl phosphate amphiphiles $(C_nH_{2n+1}O)(C_mH_{2m+1}O)PO_2^-Na^+$ (**1–13**) is described (n = 10, 12, 14, 16, m = 10, 12, 14, 16; n = 10, 12, 14, m = 18). Despite large differences in the hydrocarbon chains, these amphiphiles, when suspended in an aqueous solution, all form bilayer vesicles as revealed by electron microscopy. With 1,6-diphenylhexatriene as a hydrophobic fluorescent probe, fluorescence polarization values were determined over a range of temperatures. Phase-transition temperatures (T_m) for the transition from a gellike to a liquid-crystalline phase were derived, except for the vesicles formed from the most asymmetric phosphates (n = 10, 12, m = 18). The T_m values decrease with decreasing chain lengths and increasing asymmetry of the alkyl chains. The temperature dependence of the linewidth of the ^{31}P NMR resonance of the vesicles is briefly discussed.

Introduction

Important aspects of the chemistry of biological cell membranes can be successfully mimicked by using bilayer vesicles formed from naturally occurring or synthetic phospholipids.[1] Subsequent pioneering work by Kunitake[2] and others[3] has shown that simple, synthetic double-chain amphiphiles also aggregate to form vesicular assemblies with properties very similar to those of phospholipid vesicles. These developments provide challenging possibilities for investigating the effects of structural variations in the amphiphile on the structural and functional properties of the vesicle bilayers. Therefore, these vesicles offer attractive model systems for analyzing fundamental processes that may be of relevance to a detailed understanding of the properties of biological membranes. These processes include morphological changes,[4,5] lateral and flip-flop movement of amphiphiles in the bilayer,[6,7] osmotic activity,[8,9] and, as demonstrated recently, membrane fusion.[10,11] Herein, we describe the synthesis and phase behavior of a series of saturated di-*n*-alkyl phosphate amphiphiles in which the alkyl chains are equal in length (**1, 6, 10, 13**) or differ in carbon number (**2–5, 7–9, 11, 12**). We find that all amphiphiles readily form vesicles despite the obviously large differences in the total free energy of chain packing in the bilayer as a consequence of the large differences in lengths of both *n*-alkyl chains. The phase-transition temperatures (T_m) for the transition from the



1: $R_1 = R_2 = n\text{-}C_{10}H_{21}$
2: $R_1 = n\text{-}C_{10}H_{21}$; $R_2 = n\text{-}C_{12}H_{25}$
3: $R_1 = n\text{-}C_{10}H_{21}$; $R_2 = n\text{-}C_{14}H_{29}$
4: $R_1 = n\text{-}C_{10}H_{21}$; $R_2 = n\text{-}C_{16}H_{33}$
5: $R_1 = n\text{-}C_{10}H_{21}$; $R_2 = n\text{-}C_{18}H_{37}$
6: $R_1 = R_2 = n\text{-}C_{12}H_{25}$
7: $R_1 = n\text{-}C_{12}H_{25}$; $R_2 = n\text{-}C_{14}H_{29}$
8: $R_1 = n\text{-}C_{12}H_{25}$; $R_2 = n\text{-}C_{16}H_{33}$
9: $R_1 = n\text{-}C_{12}H_{25}$; $R_2 = n\text{-}C_{18}H_{37}$
10: $R_1 = R_2 = n\text{-}C_{14}H_{29}$
11: $R_1 = n\text{-}C_{14}H_{29}$, $R_2 = n\text{-}C_{16}H_{33}$
12: $R_1 = n\text{-}C_{14}H_{29}$; $R_2 = n\text{-}C_{18}H_{37}$
13: $R_1 = R_2 = n\text{-}C_{16}H_{33}$

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