Serial synthesis of oxa[3.$_n$]cyclophanes and homooxacalix[n]arenes *via* reductive coupling of arenedialdehydes, and their X-ray structures †

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Received (in Cambridge, UK) 5th March 2001, Accepted 15th May 2001
First published as an Advance Article on the web 11th June 2001

A wide range of oxa[3.$_n$]cyclophanes and homooxacalix[n]arenes is prepared from the corresponding arenedialdehyde *via* reductive homocoupling reaction in a one-pot fashion. Heterocoupling reaction of arenedialdehyde with bis(trimethylsilyloxymethyl)benzene provides a series of macrocyclic ethers including a new type of oxacalixarene, which consists of the moieties of oxa[3.$_n$]cyclophane and homooxacalix[n]arene; *m*- or *p*-phenylene, and 5-substituted 2-methoxy-*m*-phenylene are tethered by CH_2OCH_2 linkages. A series of macrocycles are separated with gel permeation chromatography (GPC) and identified with NMR (^{1}H, ^{13}C) and mass (MALDI-TOF) spectra. Their solid-state conformations are elucidated by X-ray crystallographic analyses.

Introduction

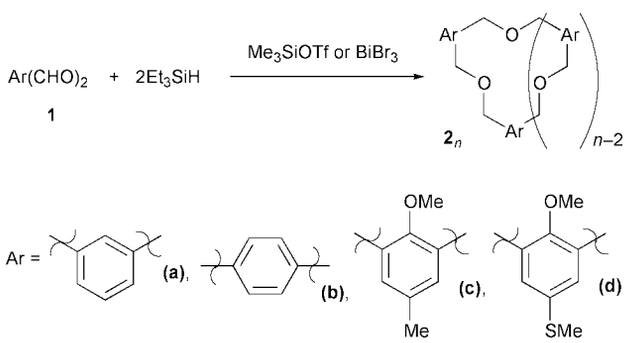
Oxacyclophanes represent an important class of host molecules due to the dual characteristics of cyclophanes and crown ethers. Among them, homooxacalix[n]arenes are the most promising receptors following calixarenes. Actually, hexahomotrioxacalix[3]arenes [1] and octahomotetraoxacalix[4]arenes [1d,2] with or without *O*-protection exhibit characteristic affinities for alkali and alkaline-earth metal cations,[3] ammonium ions,[2a,3c,4] lanthanide ions,[5] and buckminsterfullerene, C_{60}.[6] Although such macrocycles with relatively small ring size (n = 3, 4) have been studied extensively, larger ones still remain unexplored despite the potential of the inclusion properties of neutral molecules [7] and cationic organic guests.[2a,4b,8] This is because no methods to supply these molecules have been reported so far in contrast to calix[n]arenes.[9] As an extension of our study utilizing reductive coupling reactions [10] for the preparation of oxacyclophanes,[1a,10a] we have found that a series of oxa[3.$_n$]cyclophanes and *O*-protected homooxacalix[n]arenes can be prepared from the corresponding arenedialdehydes *via* reductive homo- and heterocoupling reactions. In this report, we describe serial syntheses and X-ray structures of these macrocyclic ethers.

Results and discussion

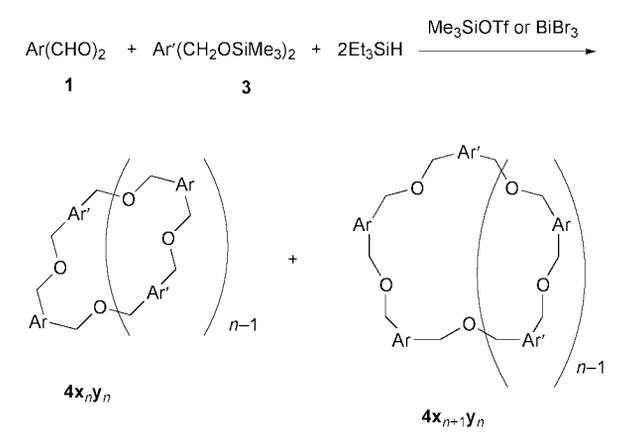
2-Methoxy-5-methylisophthalaldehyde **1c** [11] and 2-methoxy-5-(methylthio)isophthalaldehyde **1d** were prepared from the corresponding 4-substituted phenols *via* diformylation [12] followed by methylation. *m*- and *p*-Bis(trimethylsilyloxymethyl)benzenes were prepared from the corresponding alcohols with Me_3SiCl and Et_3N in diethyl ether.[13] The reductive coupling reactions were carried out in the presence of Et_3SiH and a catalytic amount of a Lewis acid, Me_3SiOTf [10b,c] or $BiBr_3$,[10a] to give a series of macrocyclic ethers (Schemes 1 and 2). After separation using GPC, the mass of the macrocycles was determined by MALDI-TOF-MS spectra.

Homocoupling reaction (Scheme 1, Table 1)

A wide range of macrocyclic ethers, oxa[3.$_n$]metacyclophanes



Scheme 1



Scheme 2

(**2a**$_n$, n = 3–8), oxa[3.$_n$]paracyclophanes (**2b**$_n$, n = 4–11), *p*-methylhomooxacalix[n]arenes (**2c**$_n$, n = 3–9),[2] and *p*-(methylthio)homooxacalix[n]arenes (**2d**$_n$, n = 4–7), were prepared in the yields summarized in Table 1. Total yields of the homologues of oxa[3.$_n$]metacyclophanes were 60–68% (runs 1–3), and the trimer (**2a**$_3$) was obtained in 35–39% yield as a major product. On the other hand, total yields of other macrocycles (**2b**$_n$, **2c**$_n$ and **2d**$_n$) were decreased to 13–46% (runs 4–13), and pentamer (**2b**$_5$), tetramer (**2c**$_4$) and tetramer (**2d**$_4$) were major homologues in series of the products, **2b**$_n$, **2c**$_n$ and **2d**$_n$, respectively. The

† Electronic supplementary information (ESI) available: full details of physical data for all new compounds. See http://www.rsc.org/suppdata/p1/b1/b102031p/

 DOI: 10.1039/b102031p

Table 1 Serial synthesis of oxa[3.$_n$]cyclophanes and homooxacalix[*n*]arenes *via* a reductive homocoupling reaction

Run	Ar (mmol)	Catalyst (mol%)	Solvent (ml)	React. temp. (t/°C)	React. time (t/h)	Yield (%)[a]									Total
						2$_3$	**2**$_4$	**2**$_5$	**2**$_6$	**2**$_7$	**2**$_8$	**2**$_9$	**2**$_{10}$	**2**$_{11}$	
1	**a** (2.0)	Me_3SiOTf (5)	CH_2Cl_2 (40)	0	2	39	12	6	2	2	1				62
2	**a** (2.0)	Me_3SiOTf (5)	CH_2Cl_2 (20)	0	2	35	11	6	4	2	2				60
3	**a** (2.0)	$BiBr_3$ (5)	MeCN (20)	rt	1.5	35	13	8	7	2	3				68
4	**b** (5.0)	Me_3SiOTf (5)	CH_2Cl_2 (50)	0	2.5		3	9	6	4	2	1			25
5	**b** (2.0)	Me_3SiOTf (5)	CH_2Cl_2 (40)	0	2.5		5	15	8	5	5	3	2	1	44
6	**b** (2.0)	Me_3SiOTf (5)	CH_2Cl_2 (30)	0	2		5	14	8	5	5	3	3	3	46
7	**b** (2.0)	Me_3SiOTf (5)	CH_2Cl_2 (20)	0	2		3	12	7	5	3	3	2	3	38
8	**b** (10)	$BiBr_3$ (5)	MeCN (100)	0–rt	2		3	15	5	1					24
9	**b** (5.0)	$BiBr_3$ (5)	MeCN (50)	rt	2.5		2	7	3	2					14
10	**c** (1.0)	Me_3SiOTf (5)	CH_2Cl_2 (30)	0	2	3	16	8	6	6	3	4			46
11	**c** (4.0)	$BiBr_3$ (8)	MeCN (16)	0	1	3	5	4	3	3	2	1			21
12[b]	**d** (2.5)	Me_3SiOTf (10)	CH_2Cl_2 (100)	0	5		7	3	2	1					13
13[c]	**d** (1.0)	Me_3SiOTf (30)	CH_2Cl_2 (50)	−78	9		13[d]	10[d]	8[d]	6[d]					37

[a] Isolated yields unless otherwise noted. [b] Et_3SiH was added over a period of 2 h. [c] Et_3SiH in 20 ml of CH_2Cl_2 was added over a period of 2 h. [d] Yields were determined by ^1H NMR using DMF as internal standard.

products other than macrocycles were thought to be linear polyethers which were removed by column chromatography on silica gel (1 : 3 or 1 : 2 ethyl acetate–hexane). From the viewpoint of reaction pathways, these results suggest that the linear trimer and tetramer from terephthalaldehyde (**5** and **11** in Scheme 3, where Ar = Ar′ = **b**) preferred chain elongation to cyclization (runs 4–9) as compared with the linear pentamer **7** and that the linear trimers derived from **1c** and **1d** (**5** in Scheme 3, where Ar = Ar′ = **c** or **d**) was harder to cyclize than were the linear tetramer **11** because of the presence of the methoxy group (runs 10–13) while trimer was produced mainly from isophthalaldehyde (runs 1–3). As for the Lewis acid used, Me_3SiOTf and $BiBr_3$ gave similar product distributions for synthesis of **2a**$_n$, while Me_3SiOTf afforded a wider range of macrocycles in better yields than did $BiBr_3$ for **2b**$_n$ and **2c**$_n$.

In runs 1 and 2, the concentration did not affect the total yields, but slightly changed the product distribution; the higher the concentration employed, the lower the yield of the small-ring compounds, and *vice versa*. For the preparation of oxa[3.$_n$]paracyclophanes (**2b**$_n$), the best yield was obtained in the substrate concentration of 0.067 M in run 6. Higher concentration (0.10 M) and temperature were needed for the homocoupling reaction catalyzed by bismuth bromide to proceed (runs 8 and 9). In this case, degradation of the products was clearly observed, resulting in lower yields. The largest macrocycle obtained, **2b**$_{11}$, was a 77-membered ring which consisted of eleven *p*-phenylene units with CH_2OCH_2 tethers. The oxa[3.$_n$]-meta- and -paracyclophanes (**2a**$_n$ and **2b**$_n$) have not been prepared previously, while the regioisomers (n = 4),[14] and sulfur and nitrogen analogues of oxa[3.$_n$]cyclophanes (n = 3, 4)[15] as well as oxa[3.$_n$]heterocyclophanes[16] have been prepared. As compared with the synthesis of metacyclophanes (**2a**$_n$), a wider range of homooxacalix[*n*]arenes (**2c**$_n$) was obtained in lower total yields (runs 10 and 11). Me_3SiOTf (run 10) gave a much better yield than did $BiBr_3$ (run 11), as was the case for **2b**$_n$. In the preparation of **2d**$_n$, lower temperature and slow addition of Et_3SiH in the presence of a greater amount of Me_3SiOTf (run 13) were found to be effective in obtaining a much better yield than that in run 12 where similar conditions to run 10 were adopted.

Heterocoupling reaction (Scheme 2, Table 2)

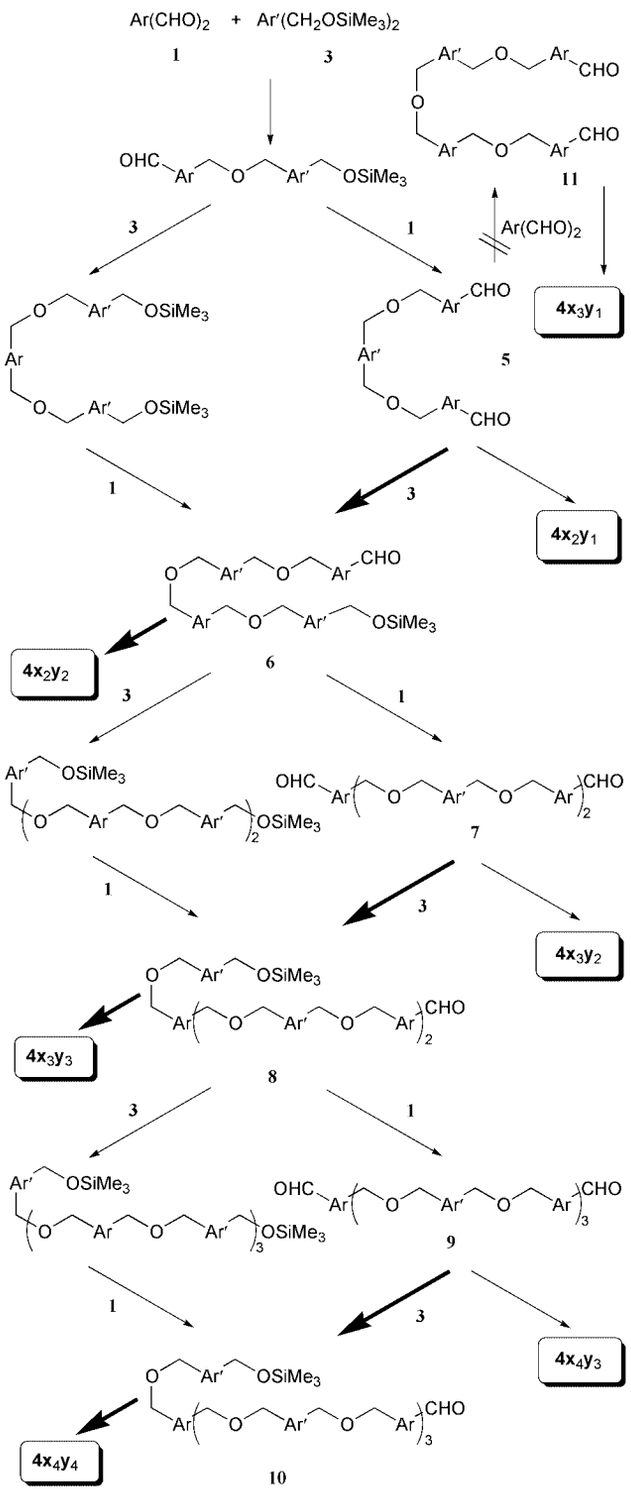
The reductive heterocoupling reaction of an arenedialdehyde **1** with a bis(trimethylsilyloxymethyl)benzene **3** also provided a series of macrocyclic ethers (Scheme 2). Results and conditions of the reactions are summarized in Table 2. The heterocoupling reactions gave only **4x**$_n$**y**$_n$ and **4x**$_{n+1}$**y**$_n$ as macrocycles; no other macrocycles, such as **4x**$_{n+2}$**y**$_n$, were obtained. In the product distribution, **4x**$_n$**y**$_n$ was produced much more than was **4x**$_{n+1}$**y**$_n$, and **4x$_2$y$_2$** was obtained as a major product in each series except for **4b$_3$b$_3$** (= **2b$_6$**) in the preparation of oxaparacyclophanes in runs 3–5.

Although the total yields of the products were similar in runs 1 and 2, the distribution of products was different; $BiBr_3$ tends to produce larger macrocycles, **4x$_4$y$_4$** and **4x$_5$y$_5$**, than Me_3SiOTf, as was observed in the homocoupling reaction (runs 1–3 in Table 1). These facts may imply the occurrence of a template effect of the bismuth atom.[17] $BiBr_3$ was not used for the heterocoupling reactions of other substrates because it was less effective than Me_3SiOTf in the homocoupling reaction. In comparison of runs 3 and 4, a slightly better yield was obtained in lower concentration. A similar relation between concentration and the total yield was observed in the homocoupling reaction (runs 6 and 7 in Table 1). Almost the same results were reproduced in runs 4 and 5 in spite of the different reaction time, indicating that no degradation of the macrocyclic ethers occurred under these conditions. In runs 6–12, novel oxacalixarenes were successfully prepared, which consist of the moieties of oxa[3$_n$]-cyclophane and homooxacalix[*n*]arene; *m*- or *p*-phenylene and

5-substituted 2-methoxy-*m*-phenylene were tethered by CH_2-OCH_2 linkages. By changing the concentrations of substrates and catalyst, the conditions in runs 6 and 10 proved to be the best of all conditions examined in the preparation of calixmeta- and paracyclophanes, respectively.

Reaction pathways (Scheme 3)

Plausible reaction pathways for the reductive heterocoupling reaction are illustrated in Scheme 3, where the reactions



Scheme 3

between linear oligomers are omitted because of their low concentration. The product distribution in heterocoupling reactions suggests the following three points; 1) intermolecular homocoupling reaction of linear dialdehydes **5**, **7** and **9** with arenedialdehyde **1** did not take place, which is supported by the facts that $\mathbf{4x}_{n+2}\mathbf{y}_n$ was not obtained at all and that the coupling reaction of an aldehyde in the presence of an equimolar amount of a silyl ether generally gives heterocoupling products exclusively;[10] 2) linear dialdehydes **5**, **7** and **9** preferred intermolecular heterocoupling with a bis(trimethylsilyloxymethyl)-arene **3** to intramolecular homocoupling because cyclized products, $\mathbf{4x}_{n+1}\mathbf{y}_n$, were obtained in quite low yields; 3) intramolecular heterocoupling reactions of trimethylsilyloxyaldehydes **6, 8** and **10**, that is, cyclization to $\mathbf{4x}_n\mathbf{y}_n$, were easier than were intramolecular homocoupling reactions of **5**, **7** and **9** because more $\mathbf{4x}_n\mathbf{y}_n$ was produced than $\mathbf{4x}_{n+1}\mathbf{y}_n$.

X-Ray structures (Fig. 1)

In order to confirm the structures and elucidate their solid-state conformations, at least one compound of each series of the macrocyclic ethers was subjected to X-ray crystallographic analysis. The ORTEP drawings of $\mathbf{2a}_6$, $\mathbf{2b}_6$, $\mathbf{2c}_4$, $\mathbf{2c}_6$, $\mathbf{2d}_4$, $\mathbf{4c}_2\mathbf{a}_2$ and $\mathbf{4c}_2\mathbf{b}_2$ are shown in Fig. 1. The X-ray structures reveal that the repeat (asymmetric) units are one half in all the molecules except $\mathbf{2a}_6$, in which six-fold symmetry exists. The letters A–D in Fig. 1 refer to the corresponding aromatic rings in each structure, and A′–D′ mean the planes of the repeat units. Two individual conformations were observed in the solid-state structure of $\mathbf{2d}_4$ (Fig. 1e-1 and -2). For homooxacalixarenes ($\mathbf{2c}_4$, $\mathbf{2c}_6$, $\mathbf{2d}_4$, $\mathbf{4c}_2\mathbf{a}_2$ and $\mathbf{4c}_2\mathbf{b}_2$), the dihedral angles between each aromatic ring (A–D) and the mean plane formed by the dibenzyl ethereal oxygen atoms, and distances between faced aromatic rings (A–A′ ~ D–D′) are summarized in Table 3.

In Fig. 1a, $\mathbf{2a}_6$ includes a water molecule inside the circular cavity. The distance between the centers of O2 and C8 is 4.8 Å. Several other oxa[3_n]cyclophanes and homooxacalix[*n*]arenes of larger size also had one-half to two equivalents of water or one equivalent of dichloromethane in the solid state, judging from the results of elemental analysis. These results show that the larger macrocyclic ethers are also considered to hold the small molecules within the cavity and are expected to work as receptors for some neutral organic molecules. Indeed, macrocyclic ethers analogous to $\mathbf{2a}_6$ and $\mathbf{2b}_6$ were reported to form equimolar complexes with benzene and dichloromethane in the solid state.[7]

Rectangular molecular structures, 16.4 × 8.1 Å and 16.5 × 9.5 Å, are observed in $\mathbf{2b}_6$ and $\mathbf{2c}_6$, respectively (Fig. 1b and 1d). The homooxacalix[6]arene ($\mathbf{2c}_6$) adopts a 1,2,3-alternate conformation, in which the methoxy groups on rings A, A′, C and C′, and the methyl substituents on rings B and B′ point toward the interior of the macrocycle so as to fill the cavity as shown in Fig. 1d. Ring C is orientated in a perpendicular fashion (85.0°), while rings A and B are more flattened with angles of 39.2 and 39.4°, respectively.

Both homooxacalix[4]arenes ($\mathbf{2c}_4$ and $\mathbf{2d}_4$, Figs. 1c and 1e) adopt 1,2-alternate conformations, and all the methoxy groups orientate toward the cavity with dihedral angle of between 23.3 and 86.2°. In the packing structure of $\mathbf{2d}_4$, the planes A and B in one conformer (Fig. 1e-1) are parallel to the planes C and D in the other conformer (Fig. 1e-2), respectively, indicating that the positions of oxygen atoms comprising the reference mean planes are different in these two conformers of $\mathbf{2d}_4$. All the distances between the opposite-faced aromatic rings in $\mathbf{2c}_4$ and $\mathbf{2d}_4$ are around 8 Å, and the four aromatic rings in each conformer form nearly a square cavity. Although several crystal structures of hexahomotrioxacalix[3]arenes with or without *O*-protection have been elucidated so far,[1b,5a,18] those of larger homologues are the first to be disclosed here, for compounds $\mathbf{2c}_4$, $\mathbf{2c}_6$ and $\mathbf{2d}_4$.

The calixarenes, $\mathbf{4c}_2\mathbf{a}_2$ and $\mathbf{4c}_2\mathbf{b}_2$, also make square-shaped cavities, with across-cavity distances of 7.30 and 8.10, and 7.70 and 9.25 Å, respectively. Similarly, the cavities are filled with the methoxy groups on rings A and A′ (Fig. 1f and 1g). As

Table 2 Serial synthesis of oxa[3.$_n$]cyclophanes and homooxacalix[*n*]arenes *via* reductive heterocoupling reaction

Run	**x** (Ar) (mmol)	**y** (Ar′) (mmol)	Catalyst (mol%)	Solvent (ml)	React. temp. (θ/°C)	React. time (t/h)	Yield (%)[a]							
							$\mathbf{4x_2y_1}$	$\mathbf{4x_2y_2}$	$\mathbf{4x_3y_2}$	$\mathbf{4x_3y_3}$	$\mathbf{4x_4y_3}$	$\mathbf{4x_4y_4}$	$\mathbf{4x_5y_5}$[b]	Total
1	**a** (1.0)	**a** (1.0)	Me_3SiOTf (5)	CH_2Cl_2 (30)	0	2	4	30	1	9	0	5	2	51
2	**a** (2.0)	**a** (2.0)	$BiBr_3$ (5)	MeCN (20)	rt	2.5	5	17	4	10	0	7	6	49
3	**b** (1.0)	**b** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (30)	0	1		4	3	13	1	5	5	31
4	**b** (1.0)	**b** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (20)	0	1.5		3	2	13	1	4	3	26
5	**b** (1.0)	**b** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (20)	0	4		3	3	12	2	4	3	27
6	**c** (1.0)	**a** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (30)	0	1		25	3	7	1	4		40
7	**c** (1.0)	**a** (1.0)	Me_3SiOTf (5)	CH_2Cl_2 (30)	0	3		27	2	4	2	2		37
8	**c** (1.0)	**a** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (60)	0	4		17	3	4	2	2		28
9	**c** (1.0)	**a** (1.0)	Me_3SiOTf (20)	CH_2Cl_2 (60)	0	2		21	3	6	2	2		34
10	**c** (1.0)	**b** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (40)	0	4		11	4	4	2	3		24
11	**c** (1.0)	**b** (1.0)	Me_3SiOTf (20)	CH_2Cl_2 (40)	0	4		9	3	5	2	3		22
12	**c** (1.0)	**b** (1.0)	Me_3SiOTf (10)	CH_2Cl_2 (20)	0	4		9	3	3	1	2		18

[a] Isolated yields. [b] Although these compounds were not fully identified, they were highly expected to be $\mathbf{4x_5y_5}$ from ^{1}H NMR spectra and retention time in GPC.

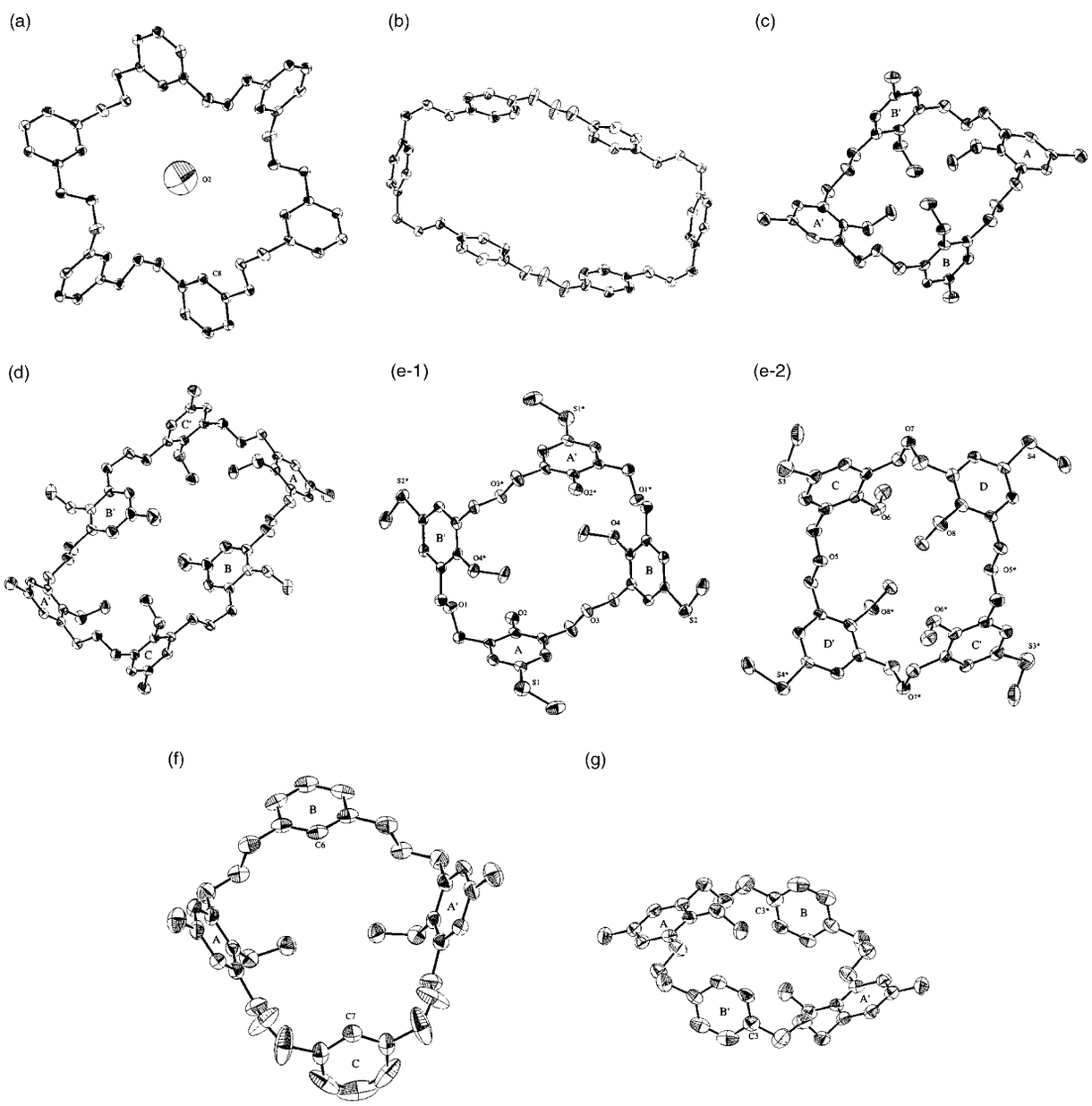


Fig. 1 ORTEP drawings for $\mathbf{2a_6}$ (a), $\mathbf{2b_6}$ (b), $\mathbf{2c_4}$ (c), $\mathbf{2c_6}$ (d), $\mathbf{2d_4}$ (e-1, -2), $\mathbf{4c_2a_2}$ (f) and $\mathbf{4c_2b_2}$ (g). Hydrogen atoms are omitted for clarity.

compared with the structures of octahomotetraoxacalix[4]arenes, $\mathbf{2c_4}$ and $\mathbf{2d_4}$, the cavity of $\mathbf{4c_2a_2}$ is narrower, probably due to the lack of substituents on rings B and C. In $\mathbf{4c_2b_2}$, the lack of substituents on rings B and B′ makes the distance of A–A′ shorter than that in $\mathbf{2c_4}$, resulting in the longer distance for B–B′ in spite of their similar conformations.

Table 3 Dihedral angles and distances between aromatic rings (A–D, A′–D′) in homooxacalixarenes

Compound	Dihedral angle (°)[a]				Distance (Å)[b]				Conformation
	A	B	C	D	A–A′	B–B′	C–C′	D–D′	
2c$_4$	23.3	83.2			8.36	8.14			1,2-alternate
2c$_6$	39.2	39.4	85.0		14.6	9.27	13.5		1,2,3-alternate
2d$_4$	86.2	50.1	53.9	54.1	8.65	7.90	7.42	8.35	1,2-alternate
4c$_2$**a**$_2$	58.7	74.4	14.3		7.30	8.10[c]			1,3-alternate[d]
4c$_2$**b**$_2$	33.7	80.5			7.70	9.25[e]			alternate

[a] Between each aromatic ring and mean plane defined by dibenzylic ethereal oxygen atoms. [b] Between methoxy-bearing carbons in oppositely faced aromatic rings unless otherwise noted. [c] Distance between C6 in ring B and C7 in ring C in Fig. 1f. [d] C6 and C7 in rings B and C orientate upward, while methoxy groups in ring A and A′ orientate downward in Fig. 1f. [e] Distance between C3 and C3* in Fig. 1g.

Table 4 Crystal data of **2a**$_6$, **2b**$_6$, **2c**$_4$, **2c**$_6$, **2d**$_4$, **4c**$_2$**a**$_2$ and **4c**$_2$**b**$_2$

	2a$_6$	**2b**$_6$	**2c**$_4$	**2c**$_6$	**2d**$_4$	**4c**$_2$**a**$_2$	**4c**$_2$**b**$_2$
Formula	$C_{48}H_{50}O_7$	$C_{48}H_{48}O_6$	$C_{40}H_{48}O_8$	$C_{60}H_{72}O_{12}$	$C_{40}H_{48}O_8S_4$	$C_{36}H_{40}O_6$	$C_{36}H_{40}O_6$
Formula weight	738.92	720.90	656.81	985.22	785.05	568.71	568.71
Crystal system	trigonal	monoclinic	monoclinic	triclinic	triclinic	orthorhombic	monoclinic
a (Å)	26.833(1)	15.226(2)	10.770(5)	8.982(1)	13.210(3)	23.388(2)	14.301(9)
b (Å)		6.357(2)	11.260(4)	17.865(2)	14.508(3)	17.227(2)	7.608(1)
c (Å)	4.955(2)	21.079(2)	15.146(7)	8.8358(7)	13.117(2)	7.655(1)	15.421(1)
α (°)				101.254(7)	100.26(2)		
β (°)		110.961(7)	105.77(4)	92.355(9)	107.11(2)		113.25(5)
γ (°)				93.19(1)	116.99(1)		
V (Å^3)	3089.9(10)	1905.1(5)	1767(1)	1386.5(2)	1992.3(8)	3084(1)	1541.7(2)
Temperature/°C	20	20	20	25	22.5	25	20
Space group	R-3 (No. 148)	P21/a (No. 14)	P21/a (No. 14)	P-1 (No. 2)	P-1 (No. 2)	Cmc21 (No. 36)	P21/a (No. 14)
Z-value	3	2	2	1	2	4	2
μ/cm^{-1}	0.79 (Mo-Kα)	0.81 (Mo-Kα)	0.85 (Mo-Kα)	6.57 (Cu-Kα)	2.89 (Mo-Kα)	6.61 (Cu-Kα)	6.61 (Cu-Kα)
No. of observations	952 [$I > 3.00\sigma(I)$]	1511 [$I > 3.00\sigma(I)$]	721 [$I > 3.00\sigma(I)$]	2438 [$I > 3.00\sigma(I)$]	3603 [$I > 2.00\sigma(I)$]	881 [$I > 3.00\sigma(I)$]	1532 [$I > 3.00\sigma(I)$]
No. of variables	86	245	217	326	469	196	191
R	0.055	0.058	0.047	0.048	0.059	0.057	0.061
R_w	0.086	0.093	0.060	0.078	0.088	0.085	0.110
GOF	1.19	1.38	1.22	1.39	1.34	1.40	1.76

Experimental

1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were obtained with a Varian Gemini-200 for solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ and the coupling constants (are in Hz. MALDI-TOF-MS analyses were performed by a Shimadzu/Kratos KOMPACT MALDI II. EI mass spectra were recorded on a Shimadzu GCMS QP5000 spectrometer. GPC separation was carried out by LC908 liquid chromatography (Japan Analytical Industry) equipped with Jaigel 1H and 2H columns (polystyrene gels). Mps were determined with a Yanaco MP-J3 apparatus and are uncorrected. Flash chromatography was performed with Wakogel C-300. CH_2Cl_2 was freshly distilled from CaH_2 under argon. Reagents were used as commercially received. 2-Hydroxy-5-methylisophthalaldehyde was purchased from TCI. *m*- and *p*-Bis(trimethylsilyloxymethyl)benzene were prepared by the reaction of the corresponding xylene-α,α′-diol with trimethylsilyl chloride in the presence of triethylamine in diethyl ether.[13]

Synthesis of 2-methoxyisophthalaldehydes (1c and d)

2-Methoxy-5-methylisophthalaldehyde 1c.[11] To a solution of 2-hydroxy-5-methylisophthalaldehyde (1.0 g, 6.1 mmol) in DMF (10 ml)–acetone (50 ml) were added MeI (6.2 ml, 0.10 mol) and K_2CO_3 (1.0 g, 7.2 mmol). After being stirred at rt for 21 h, the suspension was added to saturated aq. $NaHCO_3$ (100 ml) and extracted with diethyl ether (100 ml) twice. The combined organic layer was washed with saturated aq. NaCl (100 ml) once, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was recrystallized from hexane to afford **1c** (0.99 g, 86%).

2-Hydroxy-5-(methylthio)isophthalaldehyde.[12] Mp 105–106 °C; δ_H 2.52 (3H, s, SCH_3), 7.88 (2H, s, Ar-H), 10.21 (2H, s, CHO), 11.45 (1H, s, OH); δ_C 17.2, 123.6, 130.0, 136.7, 161.6, 191.6 (Found: C, 55.00; H, 4.11. Calc. for $C_9H_8O_3S$: C, 55.09; H, 4.11%).

2-Methoxy-5-(methylthio)isophthalaldehyde 1d. The synthesis was identical to that of **1c**, but starting from 2-hydroxy-5-(methylthio)isophthalaldehyde, to give **1d** (88% yield), mp 130–131 °C; δ_H 2.54 (3H, s, SCH_3), 4.06 (3H, s, CH_3), 7.94 (2H, s, Ar-H), 10.39 (2H, s, CHO); MS (EI) *m*/*z* 211 ([M + H]$^+$) (Found: C, 57.10; H, 4.85. Calc. for $C_{10}H_{10}O_3S$: C, 57.11; H, 4.80%).

General synthesis of oxacyclophanes *via* reductive homocoupling reaction

(The reaction conditions are also given in Table 1.)

To a stirred solution of arenedialdehyde **1** and a Lewis acid catalyst, Me_3SiOTf or $BiBr_3$, in dichloromethane was added triethylsilane (2.2 equiv.) under argon. After being stirred for the time listed in Table 1, the mixture was poured into aq. $NaHCO_3$ and the water layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was subjected to stepwise isolation with flash column chromatography on silica gel (1 : 3 or 1 : 2 ethyl acetate–hexane) followed by GPC. In the first step, the macrocycles **2**$_n$ were separated from $Et_3SiOSiEt_3$ and linear polymers. Each macrocycle was isolated through the second step with GPC. The size of macrocycles (degree of oligomerization) was determined by MALDI-TOF-MS spectra using an ethanol–water (1 : 1) solution of 2,5-dihydroxybenzoic acid or α-cyano-4-hydroxycinnamic acid including 0.1% trifluoroacetic acid as matrix. Physical data of **2a**$_n$, **2b**$_n$, **2c**$_n$ and **2d**$_n$ are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b1/b102031p/.

General synthesis of oxacyclophanes *via* reductive heterocoupling reaction

(The reaction conditions are also given in Table 2.)

To a stirred solution of arenedialdehyde **1**, bis(trimethylsilyl) ether **3** and Lewis acid catalyst, Me_3SiOTf or $BiBr_3$, in dichloromethane was added triethylsilane (2.2 equiv.) under argon. After being stirred for the time listed in Table 2, the mixture was subjected to similar work-up, stepwise isolation, and characterization to those of the homocoupling reaction. Physical data of $\mathbf{4c}_n\mathbf{a}_n$, $\mathbf{4c}_{n+1}\mathbf{a}_n$, $\mathbf{4c}_n\mathbf{b}_n$ and $\mathbf{4c}_{n+1}\mathbf{b}_n$ are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b1/b102031p/.

X-Ray crystallographic analyses of $\mathbf{2a}_6$, $\mathbf{2b}_6$, $\mathbf{2c}_4$, $\mathbf{2c}_6$, $\mathbf{2d}_4$, $\mathbf{4c}_2\mathbf{a}_2$ and $\mathbf{4c}_2\mathbf{b}_2$ ‡

The crystal data and experimental parameters are listed in Table 4. The crystal data were collected on a Rigaku AFC7S four-circle diffractometer with a graphite monochromator. The structures were solved by direct methods using SIR92. The non-hydrogen atoms were refined anisotropically. All calculations were performed using the TEXSAN crystallographic software package (Molecular Structure Corporation).

Acknowledgements

We thank Professor Hitomi Suzuki of Kwansei Gakuin University, and Professor Keiji Maruoka and Professor Atsuhiro Osuka of Kyoto University, for their suggestions and encouragement. We are also grateful to Dr Motoo Shiro of the Rigaku corporation and Dr Hideki Yamochi of Kyoto University for their valuable advice on the X-ray crystallographic analyses.

‡ CCDC reference number(s) 163703–163706. See http://www.rsc.org/suppdata/p1/b1/b102031p/ for crystallographic files in .cif or other electronic format.

References

1 (*a*) N. Komatsu, *Tetrahedron Lett.*, 2001, **42**, 1733; (*b*) K. Tsubaki, T. Otsubo, K. Tanaka and K. Fuji, *J. Org. Chem.*, 1998, **63**, 3260; (*c*) P. D. Hampton, Z. Bencze, W. Tong and C. E. Daitch, *J. Org. Chem.*, 1994, **59**, 4838; (*d*) P. Zerr, M. Mussrabi and J. Vicens, *Tetrahedron Lett.*, 1991, **32**, 1879.

2 (*a*) B. Masci, M. Finelli and M. Varrone, *Chem. Eur. J.*, 1998, **4**, 2018; (*b*) B. Masci and S. Saccheo, *Tetrahedron*, 1993, **49**, 10739.

3 (*a*) H. Matsumoto, S. Nishio, M. Takeshita and S. Shinkai, *Tetrahedron*, 1995, **51**, 4647; (*b*) K. Araki, N. Hashimoto, H. Otsuka and S. Shinkai, *J. Org. Chem.*, 1993, **58**, 5958; (*c*) K. Araki, K. Inada, H. Otsuka and S. Shinkai, *Tetrahedron*, 1993, **49**, 9465.

4 (*a*) K. Araki, K. Inada and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 72; (*b*) B. Masci, *Tetrahedron*, 1995, **51**, 5459; (*c*) M. Takeshita, F. Inokuchi and S. Shinkai, *Tetrahedron Lett.*, 1995, **36**, 3341; (*d*) M. Takeshita and S. Shinkai, *Chem. Lett.*, 1994, 1349; (*e*) M. Takeshita and S. Shinkai, *Chem. Lett.*, 1994, 125.

5 (*a*) C. E. Daitch, P. D. Hampton, E. N. Duesler and T. M. Alam, *J. Am. Chem. Soc.*, 1996, **118**, 7769; (*b*) F. Arnaud-Neu, *Chem. Soc. Rev.*, 1994, **23**, 235.

6 S. D.-M. Islam, M. Fujitsuka, O. Ito, A. Ikeda, T. Hatano and S. Shinkai, *Chem. Lett.*, 2000, 78; A. Ikeda, S. Nobukuni, H. Udzu, Z. Zhong and S. Shinkai, *Eur. J. Org. Chem.*, 2000, 3287; J. L. Atwood, L. J. Barbour, P. J. Nichols, C. L. Raston and C. A. Sandoval, *Chem. Eur. J.*, 1999, **5**, 990; A. Ikeda, T. Hatano, M. Kawaguchi, H. Suenaga and S. Shinkai, *Chem. Commun.*, 1999, 1403; A. Ikeda, Y. Suzuki, M. Yoshimura and S. Shinkai, *Tetrahedron*, 1998, **54**, 2497; K. Tsubaki, K. Tanaka, T. Kinoshita and K. Fuji, *Chem. Commun.*, 1998, 895; A. Ikeda, M. Yoshimura and S. Shinkai, *Tetrahedron Lett.*, 1997, **38**, 2107.

7 P. G. Jones and P. Kuś, *J. Inclusion Phenom.*, 1999, **34**, 267; J. Ratilainen, K. Airola, M. Nieger, M. Böhme, J. Huuskonen and K. Rissanen, *Chem. Eur. J.*, 1997, **3**, 749; E. Weber, H.-J. Köhler and H. Reuter, *J. Org. Chem.*, 1991, **56**, 1236; G. R. Brown, S. S. Chana, J. F. Stoddart, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1989, 211; G. R. Bower, A. M. Z. Slawin, D. J. Williams, G. R. Brown, S. S. Chana and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1989, 212; F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 362; K. Saigo, R.-J. Lin, M. Kubo, A. Youda and M. Hasegawa, *J. Am. Chem. Soc.*, 1986, **108**, 1996; F. Vögtle, H. Puff, E. Friedrichs and W. M. Müller, *J. Chem. Soc., Chem. Commun.*, 1982, 1398.

8 J. C. Ma and D. A. Dougherty, *Chem. Rev.*, 1997, **97**, 1303; G. D. Iasi and B. Masci, *Tetrahedron Lett.*, 1993, **34**, 6635; D. A. Dougherty and D. A. Stauffer, *Science*, 1990, **250**, 1558.

9 *tert*-Butylcalix[*n*]arenes ($n = 4$–20) have been prepared so far; C. D. Gutsche, *Calixarenes Revisited*, The Royal Society of Chemistry, Cambridge, 1998, ch. 3. Quite recently dihomooxa- and tetrahomodioxacalix[6]arenes, and hexahomotrioxacalix[9]arene have been reported; see B. Masci, *J. Org. Chem.*, 2001, **66**, 1497.

10 (*a*) N. Komatsu, J. Ishida and H. Suzuki, *Tetrahedron Lett.*, 1997, **38**, 7219 and references cited therein; (*b*) S. Hatakeyama, H. Mori, K. Kitano, H. Yamada and M. Nishizawa, *Tetrahedron Lett.*, 1994, **35**, 4367; (*c*) M. B. Sassaman, K. D. Kotian, G. K. S. Prakash and G. A. Olah, *J. Org. Chem.*, 1987, **52**, 4314.

11 K. E. Koenig, G. M. Lein, P. Stuckler, T. Kaneda and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 3553; B. Morgan and D. Dolphin, *J. Org. Chem.*, 1987, **52**, 5364.

12 L. F. Lindoy, G. V. Meehan and N. Svenstrup, *Synthesis*, 1998, 1029.

13 E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.

14 F. Vögtle and M. Zuber, *Tetrahedron Lett.*, 1972, 561.

15 O. Hayashida, T. Hirohashi, Y. Hisaeda and Y. Murakami, *Tetrahedron Lett.*, 1995, **36**, 8051; I. Tabushi, K. Yamamura, H. Nonoguchi, K. Hirotsu and T. Higuchi, *J. Am. Chem. Soc.*, 1984, **106**, 2621; I. Tabushi, Y. Kimura and K. Yamamura, *J. Am. Chem. Soc.*, 1981, **103**, 6486.

16 N. Komatsu, A. Taniguchi and H. Suzuki, *Tetrahedron Lett.*, 1999, **40**, 3749 and references cited therein.

17 Y. Habata, F. Fujishiro and S. Akabori, *J. Chem. Soc., Perkin Trans. 1*, 1996, 953; T. Ogawa, A. Yoshikawa, H. Wada, C. Ogawa, N. Ono and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1995, 1407.

18 P. J. Cragg, M. G. B. Drew and J. W. Steed, *Supramol. Chem.*, 1999, **11**, 5; P. D. Hampton, C. E. Daitch and E. N. Duesler, *New J. Chem.*, 1996, **20**, 427; C. E. Daitch, P. D. Hampton and E. N. Duesler, *Inorg. Chem.*, 1995, **34**, 5641; S. Khrifi, A. Guelzim and F. Baert, *Acta Crystallogr., Sect. C*, 1995, **51**, 153; K. Suzuki, H. Minami, Y. Yamagata, S. Fujii, K. Tomita, Z. Asfari and J. Vicens, *Acta Crystallogr., Sect. C*, 1992, **48**, 350.