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Syntheses, X-ray structures and conformational studies of tetraoxa[*n.n*]metacyclophanes

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New types of macrocyclic ligands with tetraoxa[*n.n*]metacyclophane molecular skeletons have been synthesized. The structures of 14,28-dibromo-1,8,15,22-tetraoxa[8.8]metacyclophane 2a, 16,32-dibromo-1,10,17,26-tetraoxa[10.10]metacyclophane 2b, 14,28-dibromo-2,7,16,21-tetraoxa[8.8]metacyclophane 3a, 16,32-dibromo-2,9,18,25-tetraoxa[10.10]metacyclophane 3c, 18,36-dibromo-2,11,20,29-tetraoxa[12.12]-metacyclophane 3d, 20,40-dibromo-2,13,22,33-tetraoxa[14.14]metacyclophane 3e and 14,28-diiodo-2,7,16,21-tetraoxa[8.8]metacyclophane 9a have been determined by single-crystal X-ray structure analyses. In compounds 2a and 2b, two bromide atoms face each other within the macrocyclic ring while in compounds 3c, 3d and 3e the bromine atoms face in opposite directions, outwards from the macrocyclic ring. In the smaller ring compounds 3a and 9a the structure was intermediate between these two types.

Substitution of the bromine atoms *via* lithiation has been achieved smoothly with iodine and methyl iodide as the electrophiles to afford disubstituted compounds in good yields, while with trimethylsilyl chloride as the electrophile the mono-substituted compound has been obtained.

Tetraoxa[*n.n*]metacyclophanes **1** and their bromides **2** and **3** are important macrocyclic ligands because the hydrogen atom between the two oxygen atoms (for **1**) or the two bromine atoms (for **2** and **3**) have the possibility of being substituted with various heteroatoms *via* lithiation. Thus heteroatoms so introduced are protected from the outer environment by the surrounding alkane chain, while at the same time being forced by the conformational demand of the ring into close proximity. Thus, such compounds have potential in providing a good steric protection,[1] in situations where two heteroatoms may interact in a special way or enter into unstable bonding. At the same time such macrocyclic compounds can work as unique host molecules.[2] Consequently we were interested in the preparation of these tetraoxa[*n.n*]metacyclophanes and accordingly, have studied their conformation. As for the structure of small [*n.n*]metacyclophanes in which *n* is <3, there have been many reports presenting X-ray crystallographic analyses and such structures can be predicted relatively easily.[3] This is not so for larger cyclophanes, where structural predictions are still difficult, both for solid compounds and especially for those in the solution state.

In this paper we describe the syntheses and X-ray crystallographic determination of the structure of tetraoxa[*n.n*]metacyclophanes in the solid state in addition to a theoretical prediction of the conformation by using semi-empirical molecular orbital calculations and molecular mechanics/molecular dynamics calculations. At the same time, we present some examples of the substitution of the inner bromides with heteroatoms and carbon functionalities.

Results and discussion

Attempts to prepare tetraoxa[*n.n*]metacyclophanes **1**, **2** and **3** in a one-step method starting from resorcinol derivatives or the tribromide **4** resulted in complex product mixtures of cyclic and acyclic compounds of various sizes. These compounds were therefore prepared by a two-step method *via* acyclic intermediates such as **5**, **6** or **7**, as shown in Scheme 1. In this way, the tetraoxa[*n.n*]metacyclophanes **1**, **2** and **3** could be prepared in moderate yields (Table 1).

Table 1 Synthesis of tetraoxa[*m.m*]metacyclophanes **1**, **2** and **3**

	Carbon chain length *n*	*m*	Mp (°C)	Yield (%)
1a	6	8	122	14.0
1b	8	10	112	11.6
1c	10	12	107	8.5
1d	12	14	95	4.7
2a	6	8	178	15.7
2b	8	10	168	19
2c	10	12	145	16
2d	12	14	122	22
3a	4	8	137	16.8
3b	5	9	93	17.5
3c	6	10	125	26.8
3d	8	12	115	10.6[a]
3e	10	14	84	13.5[a]
3f	12	16	94	24.5

[a] Overall yields of the two-step reactions from compound **4**.

X-Ray crystallographic structure determinations of the cyclophanes

Some tetraoxa[*n.n*]metacyclophanes crystallized out to give good single crystals which were suitable for X-ray crystallographic analyses. The molecular structures of the dibromides **2a** (tetraoxa[8.8]metacyclophane), **2b** (tetraoxa[10.10]metacyclophane), **3a** (tetraoxa[8.8]metacyclophane), **3c** (tetraoxa[10.10]-metacyclophane), **3d** (tetraoxa[12.12]metacyclophane), **3e** (tetraoxa[14.14]metacyclophane) and diiodide **9a** (tetraoxa[8.8]metacyclophane) in the solid state were determined as shown in Figs. 1–7, respectively. In **2a**, two conformers were included in the unit cell, however since the difference in the structure of these two conformers was not significant, only one of them is depicted in the Figure. In Table 2, the crystallographic parameters are summarized.

In all these tetraoxa[*n.n*]metacyclophanes so far examined, the aromatic rings were essentially parallel to each other, with no overlapping of these rings being observed in projection. The structures are characterized as 'sigmoidal' structures when seen from the side of the aromatic ring plane, as depicted in the

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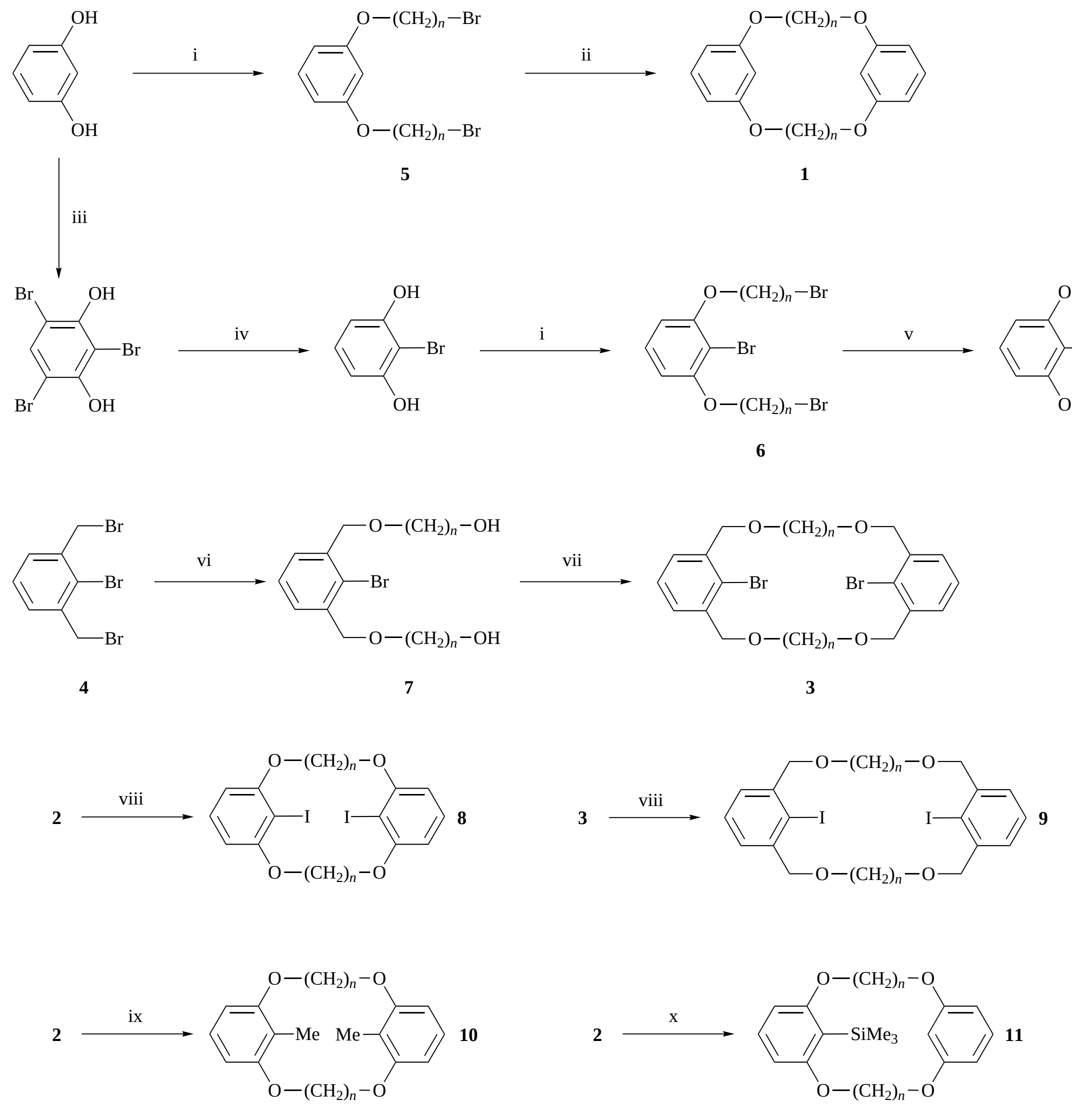

Scheme 1 *Reagents and conditions*: i, $Br(CH_2)_nBr$, K_2CO_3, acetone, reflux 3 days; ii, resorcinol, K_2CO_3, acetone; iii, Br_2, CCl_4; iv, Na_2SO_3, H_2O; v, 2-bromoresorcinol; vi, $HO(CH_2)_nOH$, Na, THF; vii, **4**, NaH, THF, reflux 7 days; viii, BuLi, I_2; ix, BuLi, MeI; x, BuLi, Me_3SiCl

lower sections of Figs. 1–7. The solid-state structures of [*n.n*]paracyclophanes ($n = 7$–11) were reported to have a 'box-like' structure in which the two aromatic rings are parallel with almost complete overlapping in projection.[4] Bis(5-methoxycarbonyl-1,3-phenylene)-($3x + 2$)-crown-x which can be regarded as polyoxa[*n.n*]metacyclophanes ($n = 10$ and 13) also have 'sigmoidal' structures with the aromatic rings essentially parallel to each other, overlap only partially in projection.[5] It may be reasonable to assume that 'large' [*n.n*]metacyclophane type compounds prefer the 'sigmoidal' structure in the solid state.

One distinguishing point in the structures is that in **2a** and **2b**, the two bromine atoms face each other within the macrocyclic ring and the intramolecular distances between them is relatively small; 3.90 and 4.29 Å for **2a** and 3.48 Å for **2b**. For convenience, we named this type of conformation Type **C** as classified in Fig. 8. In contrast, in **3c**, **3d** and **3e** the two bromine atoms face in opposite directions, outwards from the macrocyclic ring, with the intramolecular distances between them being relatively large; 12.03 Å for **3d** and 14.24 Å for **3e**. This type of conformation was named Type **E** (Fig. 8). In the smaller ring compounds **3a** and **9a**, the structures were intermediate between these two types and are designated as Type **D** (Fig. 8). The reason for this extreme difference in the conformation observed in these compounds is not clear at present.

The distance between the two bromine atoms in one conformer of **2a** is the same as the sum of the van der Waals radii of the bromine atom (3.90 Å), while that in **2b** is 3.48 Å, this being shorter than the sum of the van der Waals radii. These results indicate that the two bromine atoms of these compounds can interact strongly, at least in the solid state.

Calculation of the stable conformations of the cyclophanes by semi-empirical molecular orbital and molecular mechanics methods

The structure of a compound in solution is often different from that in the crystal state, the latter not always being the most stable one. In order to estimate the possibility of particular structures occurring in solution and to discuss the structures in the crystal state, energies of possible conformers were calculated by the semi-empirical molecular orbital and molecular mechanics methods.

Possible stable conformations were obtained by repeating molecular dynamics and molecular mechanics calculations (MM2) starting from various initial structures,[6] the resulting conformations being roughly classified as type **A**, **B**, **C**, **D** or **E**, as depicted in Fig. 8. Type **A** represents structures in which two aromatic rings are situated nearly perpendicular to each other. In Type **B**, the two aromatic rings are almost parallel and the bromine atoms face the same direction, known as the '*syn*' structure. In Type **C**, the two aromatic rings are almost parallel and the two bromine atoms face each other within the macrocyclic ring, known as the '*anti*' structure. In Type **E**, the two aromatic rings are almost parallel and the two bromine atoms

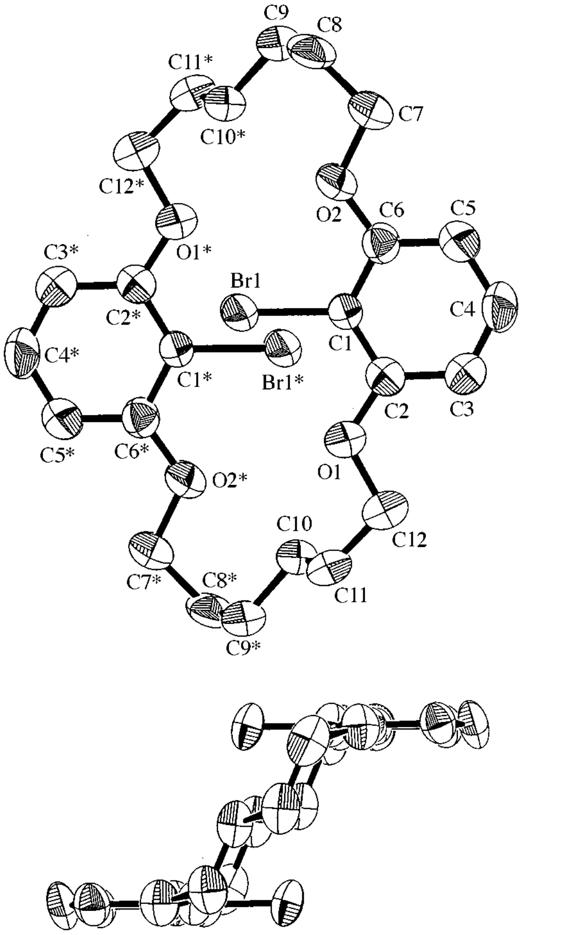

Fig. 1 X-Ray crystal structure of 14,28-dibromo-1,8,15,22-tetraoxa[8.8]metacyclophane **2a**

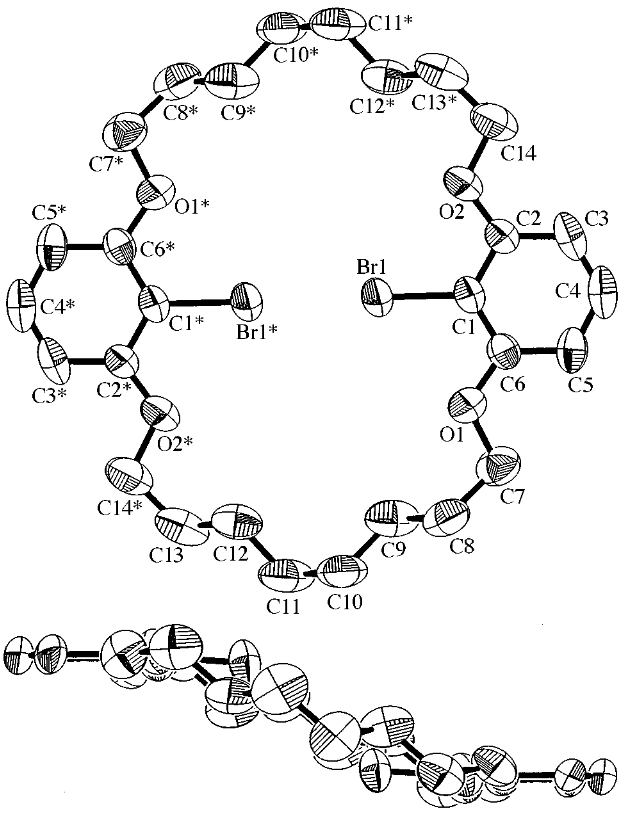

Fig. 2 X-Ray crystal structure of 16,32-dibromo-1,10,17,26-tetraoxa[10.10]metacyclophane **2b**

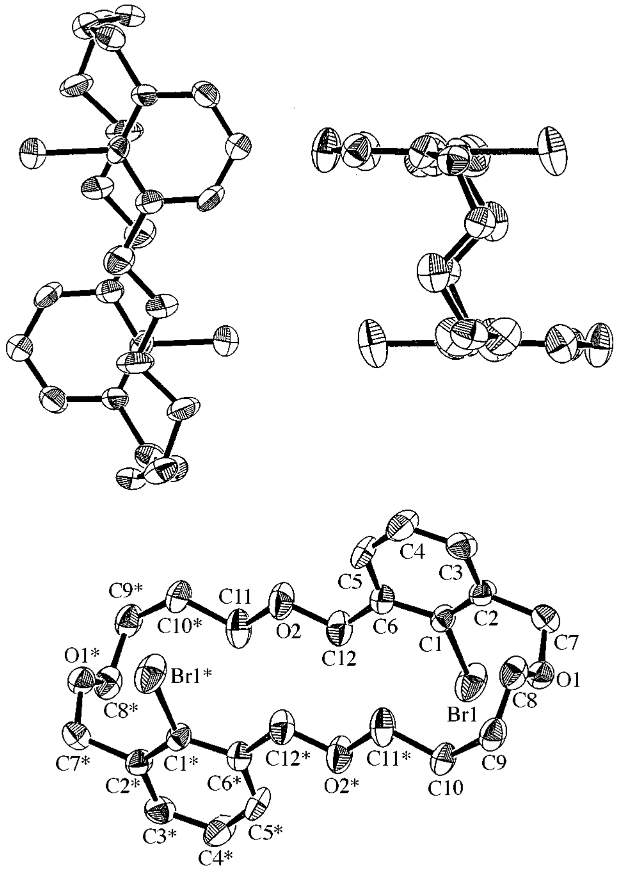

Fig. 3 X-Ray crystal structure of 14,28-dibromo-2,7,16,21-tetraoxa[8.8]metacyclophane **3a**

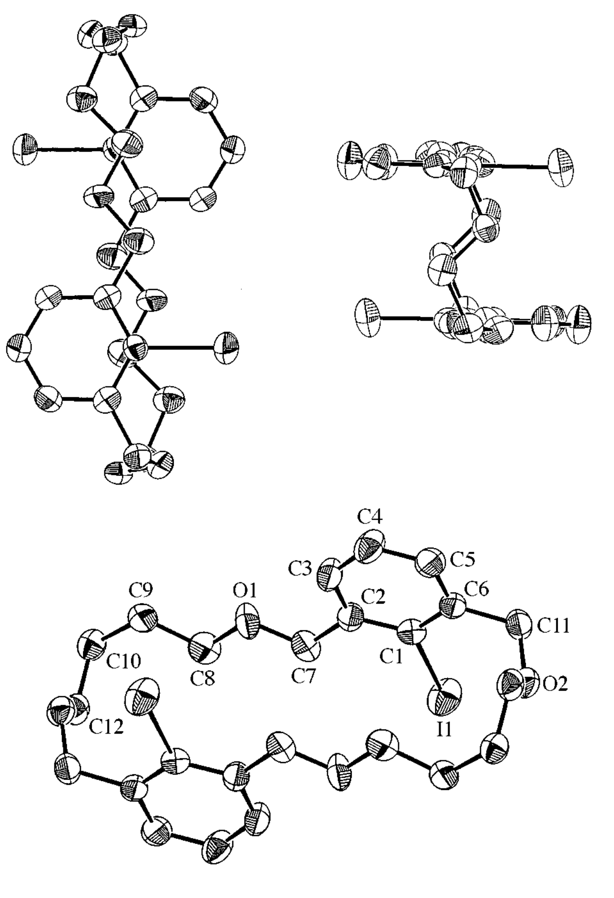

Fig. 4 X-Ray crystal structure of 14,28-diiodo-2,7,16,21-tetraoxa[8.8]metacyclophane **9a**

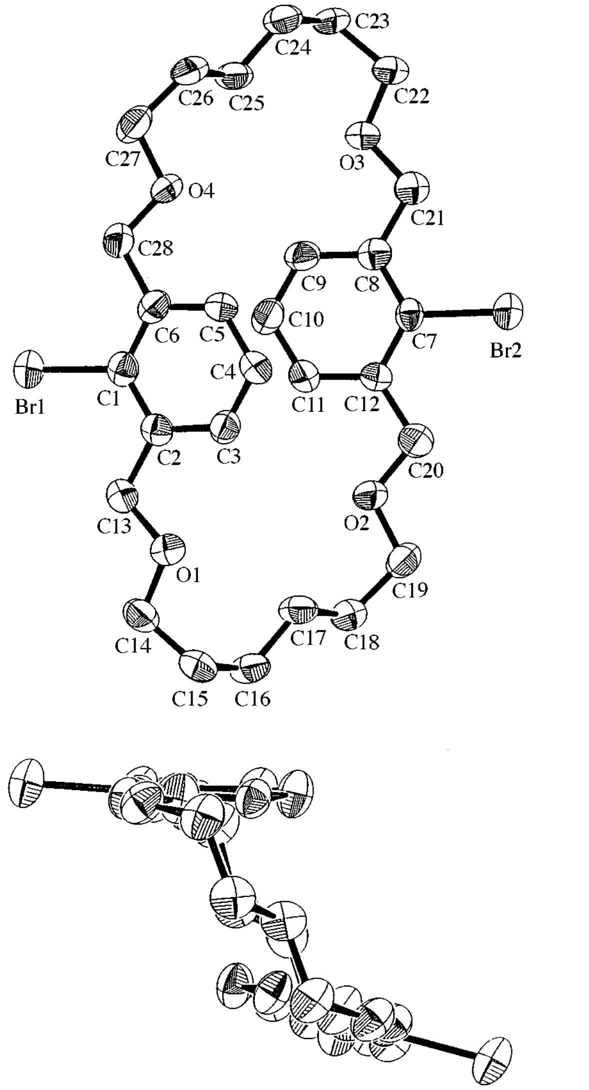

Fig. 5 X-Ray crystal structure of 16,32-dibromo-2,9,18,25-tetraoxa[10.10]metacyclophane **3c**

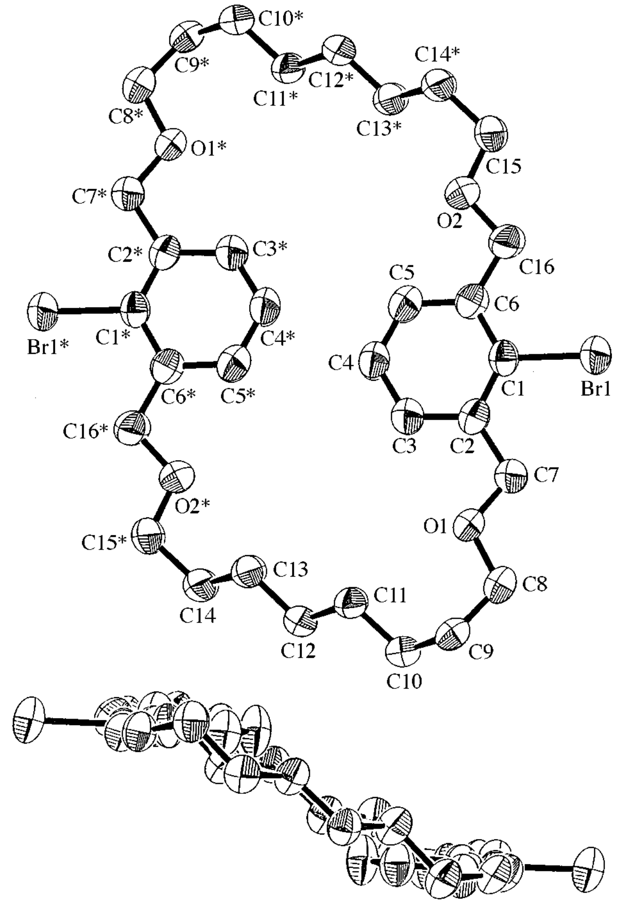

Fig. 6 X-Ray crystal structure of 18,36-dibromo-2,11,20,29-tetraoxa[12.12]metacyclophane **3d**

face opposite directions, outwards from the macrocyclic ring. Type **D** is intermediate between Type **C** and Type **E**.

Molecular orbital calculations (AM1) were performed starting from each of the optimized structures.[7] Although the optimized structures from the molecular orbital method were not the same as those obtained by MM2, the difference was negligible and the essential characteristics of the structure remained the same.

In Figs. 9 and 10, calculated energy differences from the most stable conformers in each compound are summarized. Dark bars present MM2 energy differences, while white bars show AM1 energy differences from the most stable conformers in each compound. Shadowed characters with asterisks indicate the structures observed by X-ray crystallography. In all the compounds the most stable conformers calculated by MM2 corresponded to the structures observed by X-ray crystallography. The agreement of AM1 energies with those of MM2 is poor, and the most stable conformers calculated by AM1 did not reproduce the results obtained by X-ray crystallography in any way at all. It has already been reported by Professor Fukazawa that molecular mechanics calculations provide better geometry for macrocyclic compounds than do semi-empirical MO calculations.[3b] In the present calculations the AM1 method showed the X-ray structure to be the least stable structure for compounds **2b**, **3a** and **9a**. Molecular orbital or molecular mechanics methods essentially calculate the molecular structures in the gas phase. Although the solid-state structure often differs from those in solution or the gas phase, it is unlikely that the structure in the crystal state is the least stable of those calculated in the gas phase. We can therefore conclude that molecular mechanics calculations are more reliable than AM1 to provide the correct geometry for these types of cyclophanes. Moreover, since in all the cases measured here molecular mechanics calculations were able to predict the structure in the crystalline state, it seems reasonable to expect that this method can be generally applied for the prediction of the structures of these types of compounds in the solid state.

Substitution of the bromine atoms with heteroatoms and carbon atoms

An attempt was made to substitute the bromine atoms of these cyclophanes with other functionalities *via* lithiation with butyllithium followed by the addition of electrophiles. When the cyclophanes **2a** and **2b** were lithiated by butyllithium followed by the addition of iodine, the corresponding iodides **8a** and **8b** were obtained in yields of 82.2 and 67.7%, respectively. Compound **3a** also gave the diiodide **9a** in the same way in a yield of 71.7%. Dimethylated compound **10** could be obtained in a yield of 84.5% from **2a** by using methyl iodide as the electrophile. Use of trimethylsilyl chloride as the electrophile in the reaction with **2a**, gave only the mono-trimethylsilylated compound **11** (71.7%), one bromine atom being substituted with hydrogen. Probably because of steric hindrance, the second trimethylsilyl molecule had difficulty in reacting with the other aryllithiums, which reacted with water during the work-up procedure.

Reactions of **2a**–**2d** and **3a**–**3f** with trichlorophosphine and trichlorobismuthine as the electrophiles also afforded debrominated compounds after work-up together with small amounts of some unidentified products, although the mass spectrum of the reaction mixture showed incorporation of these heteroatoms within the molecules.

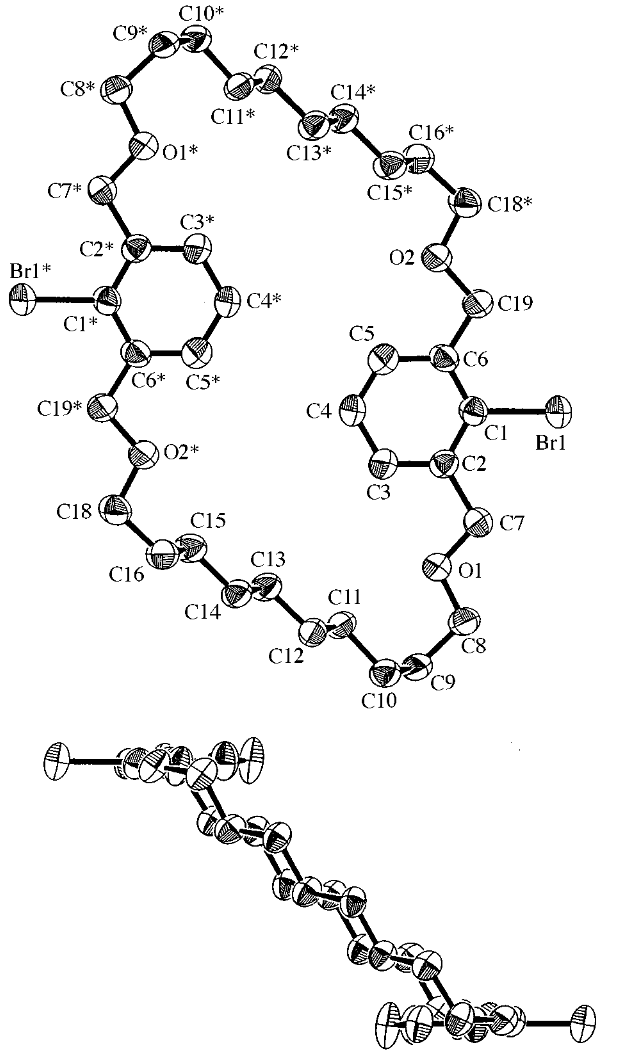

Fig. 7 X-Ray crystal structure of 20,40-dibromo-2,13,22,33-tetraoxa[14.14]metacyclophane **3e**

The van der Waals radii of the iodine group and the methyl group are both 2.00 Å,[8] while the estimated van der Waals radius of the trimethylsilyl group calculated by the sum of the C–Si bond length and the van der Waals radius of the methyl group is 3.86 Å. The estimated van der Waals radius of the dichlorophosphino group is calculated to be 3.91 Å. According to the above results, groups with van der Waals radii not larger than 2.00 Å can undergo substitution of both bromine atoms without difficulty, while those with radii not larger than 3.9 Å can substitute only one bromine atom; groups with radii larger than 3.9 Å seem to have difficulty in substituting these cyclophanes efficiently.

Herein we have shown the syntheses of a series of tetraoxa[*n.n*]metacyclophanes **1**, **2** and **3**. An X-ray crystallographic study of them revealed that compounds **2a** and **2b** had Type **C** structures, compounds **3c**, **3d** and **3e** had Type **E** structures, while compounds **3a** and **9a** had type **D** structures. Whilst molecular mechanics calculations reproduced these structures quite nicely, semi-empirical molecular orbital calculations could not. The substitution of the bromine atoms was achieved smoothly with sterically small electrophiles such as I and Me, while larger electrophiles encountered difficulties in giving the products.

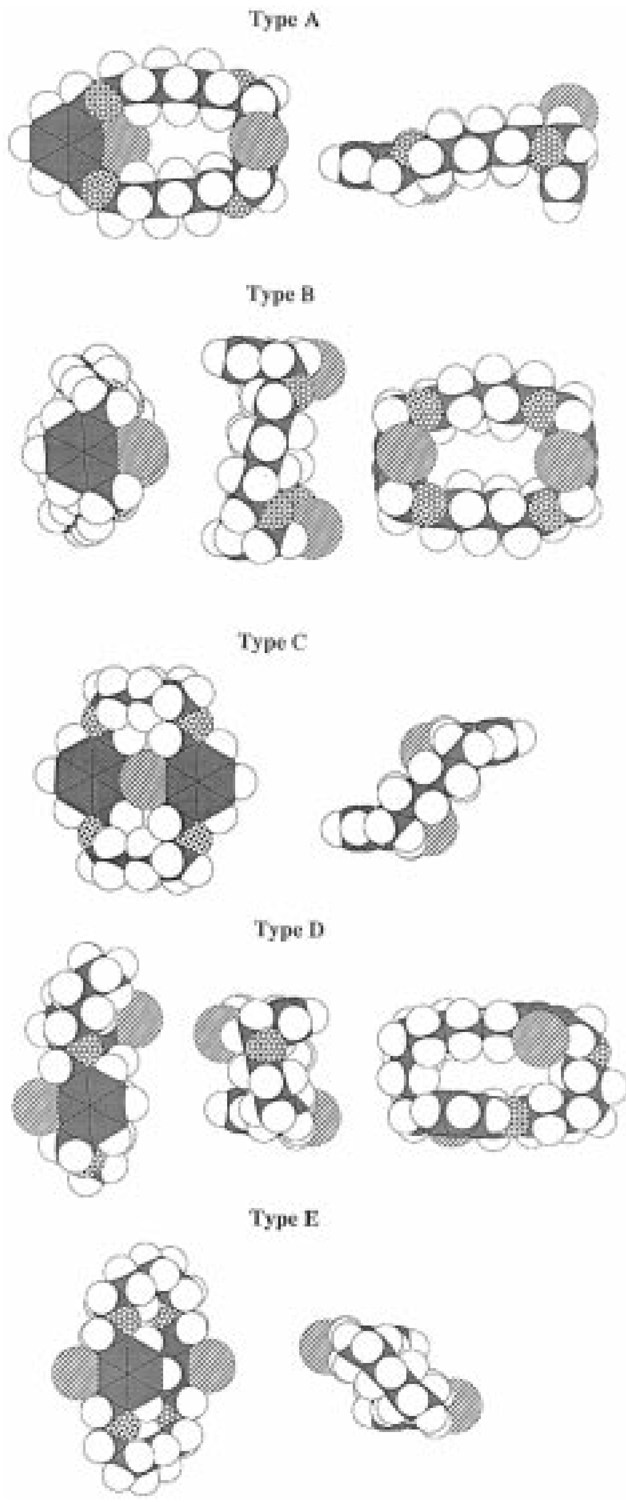

Fig. 8 Conformation type classification as exemplified by **2a**. In Type **A**, the two aromatic rings are situated nearly perpendicular to each other. In Type **B**, the two aromatic rings are almost parallel and the bromine atoms face the same direction. In Type **C**, the two aromatic rings are almost parallel and the two bromine atoms face each other within the macrocyclic ring. In Type **E**, the two aromatic rings are almost parallel and the two bromine atoms face opposite directions outwards from the macrocyclic ring. Type **D** is intermediate between Type **C** and Type **E**.

Experimental

Mps were measured by a Yanako micro-melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a JEOL-JNM-GSX270 or JNM-EX 400 spectrometer and *J* values are given in Hz. IR and UV–VIS spectra were recorded with a Hitachi 270-30 and Shimadzu UV-2200 spectrometer, respectively. Mass spectra were taken on a Hitachi M-80B.

2-Bromoresorcinol was prepared by a reported method.[9]

1,3-Bis(6-bromohexyloxy)benzene 5a

A solution of resorcinol (1.29 g, 11.7 mmol), 1,6-dibromo-

Table 2 X-Ray crystallographic data for compounds **2a**, **2b**, **3a**, **3c**, **3d**, **3e** and **9a**

Compound	**2a**	**2b**	**3a**	**3c**	**3d**	**3e**	**9a**
Formula	$C_{24}H_{30}O_4Br_2$	$C_{28}H_{38}O_4Br_2$	$C_{24}H_{30}O_4Br_2$	$C_{28}H_{38}O_4Br_2$	$C_{32}H_{46}O_4Br_2$	$C_{37.5}H_{56}O_{4.5}Br_2$	$C_{24}H_{30}O_4I_2$
M	542.31	598.41	542.31	598.41	654.52	738.66	636.31
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/a$	*Pbca*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a/Å	12.358(4)	9.268(3)	12.601(3)	11.888(3)	13.005(3)	14.366(7)	7.586(1)
b/Å	12.939(3)	12.644(2)	21.778(2)	12.019(2)	13.819(6)	15.065(6)	23.312(3)
c/Å	15.352(3)	12.478(4)	8.578(2)	10.185(3)	4.799(2)	4.828(2)	7.846(1)
α/°	90	90	90	103.09(2)	92.10(3)	95.79(3)	90
β/°	92.60(2)	101.38(3)	90	95.30(3)	91.53(3)	93.71(4)	116.132(8)
γ/°	90	90	90	104.87(2)	113.67(3)	70.64(4)	90
V/Å^3	2452.2(9)	1433.4(7)	2353.9(7)	1352(1)	788.5(5)	980.3(7)	1245.7(3)
Reflection used for unit cell determination	24	25	25	25	25	17	25
2θ Range/°	29.5–30.0	23.5–25.6	22.9–25.6	22.9–25.6	26.0–30.0	29.6–30.0	24.3–25.9
Z	4	2	4	2	1	1	2
D_c/g cm^{-3}	1.469	1.386	1.530	1.469	1.378	1.251	1.696
F(000)	1104	616	1104	616	340	387	624
μ/cm^{-1}	33.41	28.27	34.35	30.37	26.11	21.09	25.22
Scan mode	ω–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ
Max. θ/°	55.0	55.0	55.0	55.0	55.1	55.0	55.0
Unique data	5856	2915	3097	6192	3366	4471	2937
Obs. Data	$I > 3\sigma(I)$ 2353	$I > 1\sigma(I)$ 1325	$I > 1\sigma(I)$ 1068	$I > 2\sigma(I)$ 2778	$I > 3\sigma(I)$ 1576	$I > 3\sigma(I)$ 2219	$I > 2\sigma(I)$ 1571
No. of variables	272	155	137	308	173	196	136
R, R_w	0.045, 0.067	0.064, 0.100	0.069, 0.086	0.054, 0.071	0.041, 0.054	0.075, 0.115	0.041, 0.042
Goodness of fit	1.31	1.14	1.14	1.05	1.11	1.08	1.21
$\Delta\rho_{max}$/e Å^{-3}	0.45	0.70	1.01	0.45	0.35	1.86	0.45
$\Delta\rho_{min}$/e Å^{-3}	−0.52	−0.53	−0.70	−0.45	−0.32	−0.52	−0.64

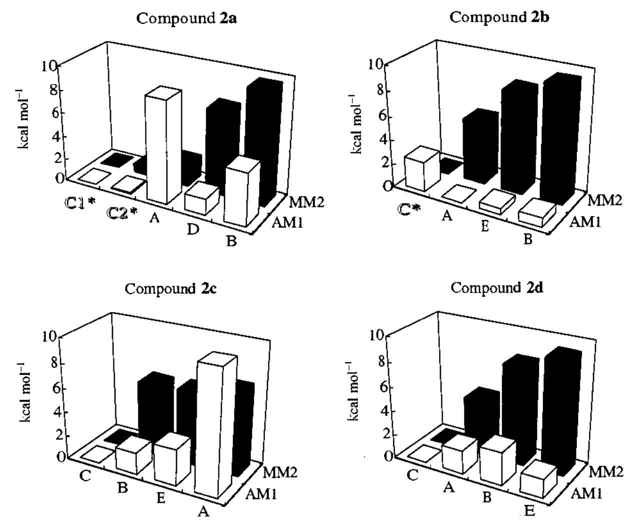

Fig. 9 Energies above the energy of the global minima of metacyclophanes **2**. For each compound, optimization was performed starting from various initial structures, and the final structures were classified as **A**, **B**, **C**, **D** and **E**, as depicted in Fig. 8. When more than two optimized structures in one compound had a similar conformation, the most stable one was selected as the representative one. Dark bars are for MM2 energy differences, while white bars show AM1 energy differences from the most stable conformers of each compound. Shadowed characters with asterisks indicate the structures observed by X-ray crystallography.

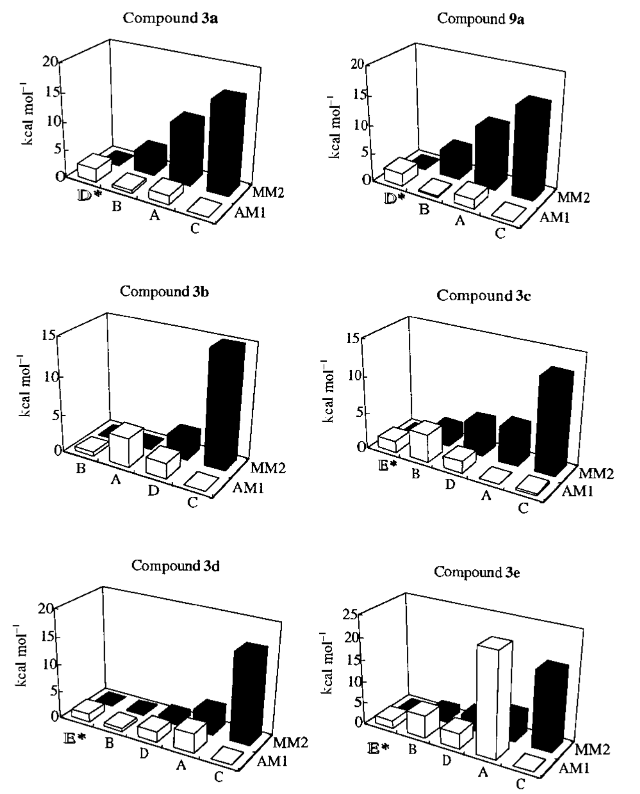

Fig. 10 Energies above the energy of the global minima of metacyclophanes **3** and **9a**. For each compound, optimization was performed starting from various initial structures, and the final structures were classified as **A**, **B**, **C**, **D** and **E**, as depicted in Fig. 8. When more than two optimized structures in one compound had a similar conformation, the most stable one was selected as the representative. Dark bars are for MM2 energy differences, while white bars show AM1 energy differences from the most stable conformers of each compound. Shadowed characters with asterisks indicate the structure observed by X-ray crystallography.

hexane (8.59 g, 35.2 mmol) and K_2CO_3 (4.15 g, 30.0 mmol) in acetone (50 cm^3) was refluxed for 3 days with stirring, after which the solvent was removed *in vacuo*. Water was added to the residue which was then extracted with ethyl acetate. The extract was washed with 10% aqueous NaOH, dried (Na_2SO_4) and evaporated. The residue was purified by passage through a silica-gel column using hexane–CH_2Cl_2 as the eluent; yield 54%; mp 42 °C; δ_H($CDCl_3$) 1.45–1.52 (m, 8H), 1.70–1.92 (m, 8H), 3.40 (t, 4H, *J* 6.8), 3.92 (t, 4H, *J* 6.4), 6.42–6.50 (m, 3H) and 7.10–7.17 (m, 1H); δ_C($CDCl_3$) 25.21, 27.82, 28.99, 32.59, 33.68, 67.55, 101.32, 106.54, 129.68 and 160.17; *m*/*z* (EI) 438 (M + 4, 20%), 436 (M + 2, 48), 432 M$^+$, 20) and 110 (100); ν_{max}(KBr)/cm^{-1} 2935, 1614, 1578, 1464, 1288, 1186, 850 and 650 (Found: C, 49.7; H, 6.7. $C_{18}H_{28}O_2Br_2$ requires C, 49.6; H, 6.5%).

1,3-Bis(8-bromooctyloxy)benzene 5b

By a method similar to that used for the preparation of **5a**, **5b** (41.4%) was obtained, mp 57 °C; δ_H($CDCl_3$) 1.30–1.50 (m, 16H), 1.70–1.92 (m, 8H), 3.40 (t, 4H, *J* 6.9), 3.92 (t, 4H, *J* 6.6), 6.40–6.50 (m, 3H) and 7.10–7.18 (m, 1H); δ_C($CDCl_3$) 25.94, 28.07, 28.66, 29.16, 29.20, 32.75, 33.87, 67.81, 101.40, 106.60, 129.72 and 160.30; *m*/*z* (EI) 494 (M + 4, 7%), 492 (M + 2, 13), 490 (M^+, 7) and 110 (100); ν_{max}(KBr)/cm^{-1} 2932, 1614, 1464 and 1180 (Found: C, 53.7; H, 7.4. $C_{22}H_{36}O_2Br_2$ requires C, 53.7; H, 7.4%).

1,3-Bis(10-bromodecyloxy)benzene 5c

By a method similar to that used for the preparation of **5a**, **5c** (49.9%) was obtained, mp 67 °C; δ_H($CDCl_3$) 1.25–1.52 (m, 24H), 1.70–1.91 (m, 8H), 3.40 (t, 4H, *J* 6.9), 3.92 (t, 4H, *J* 6.6), 6.40–6.50 (m, 3H) and 7.10–7.18 (m, 1H); δ_C($CDCl_3$) 25.86, 27.97, 28.56, 29.09, 29.16, 29.18, 29.27, 32.63, 33.68, 67.61, 101.17, 106.32, 129.46 and 160.13; *m*/*z* (EI) 550 (M + 4, 12%), 548 (M + 2, 22), 546 (M^+, 12) and 110 (100) (Found: C, 57.1; H, 8.1. $C_{26}H_{44}O_2Br_2$ requires C, 56.9; H, 8.1%).

1,3-Bis(12-bromododecyloxy)benzene 5d

By a method similar to that used for the preparation of **5a**, **5d** (38.4%) was obtained, mp 72 °C; δ_H($CDCl_3$) 1.72–1.90 (m, 8H), 3.41 (t, 4H, *J* 6.8), 3.92 (t, 4H, *J* 6.6), 6.44–6.50 (m, 3H) and 7.10–7.20 (m, 1H); δ_C($CDCl_3$) 26.00, 28.13, 28.72, 29.23, 29.34, 29.38, 29.47, 32.80, 33.98, 67.88, 101.36, 106.54, 129.68 and 160.31; *m*/*z* (EI) 607 (M + 4, 8%), 604 (M + 2, 14), 602 (M^+, 8) and 110 (100) (Found: C, 59.6; H, 8.7. $C_{30}H_{52}O_2Br_2$ requires C, 59.6; H, 8.7%).

1,8,15,22-Tetraoxa[8.8]metacyclophane 1a

A stirred solution of resorcinol (2.85 g, 25.9 mmol), compound **5a** (7.54 g, 17.3 mmol) and K_2CO_3 (7.14 g, 51.8 mmol) in acetone (500 cm^3) was refluxed for 7 days after which solvent was removed *in vacuo*. Water was added to the residue which was then extracted with ethyl acetate. The extract was washed with 10% aqueous NaOH, dried (Na_2SO_4) and evaporated. The residue was purified by passage through a silica-gel column using hexane–CH_2Cl_2 as the eluent; yield 6.1%; mp 116 °C (lit.,[10] 114 °C); δ_H($CDCl_3$) 1.50–1.62 (m, 8H), 1.65–1.90 (m, 8H), 3.97 (t, 8H, *J* 6.1), 6.40–6.50 (m, 6H) and 7.10–7.18 (m, 2H); δ_C($CDCl_3$) 25.14, 28.26, 67.35, 101.59, 106.49, 129.74 and 160.31; *m*/*z* (CI) 385 (M + 1, 100%) and 110 (14); ν_{max}(KBr)/cm^{-1} 2940, 1498, 1282, 1184 and 822 (Found: C, 74.7; H, 8.3. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%).

1,10,17,26-Tetraoxa[10.10]metacyclophane 1b

Yield 11.6%; mp 112 °C; δ_H($CDCl_3$) 1.30–1.54 (m, 16H), 1.70–1.82 (m, 8H), 3.95 (t, 8H, *J* 6.2), 6.42–6.50 (m, 6H) and 7.10–7.17 (m, 2H); δ_C($CDCl_3$) 25.14, 28.26, 67.35, 101.59, 106.49, 129.74 and 160.31; *m*/*z* (EI) 440 (M^+, 92%) and 110 (100); ν_{max}(KBr)/cm^{-1} 2900, 2840, 1720, 1582, 1470, 1440, 1390, 1278, 1170, 1140, 1080, 1030, 820 and 780 (Found: C, 76.0; H, 9.2. $C_{28}H_{40}O_4$ requires C, 76.3; H, 9.1%).

1,12,19,30-Tetraoxa[12.12]metacyclophane 1c

Yield 8.5%; mp 107 °C (lit.,[11] 106 °C); δ_H($CDCl_3$) 1.30–1.55 (m, 24H), 1.70–1.85 (m, 8H), 3.94 (t, 8H, *J* 6.2), 6.40–6.50 (m, 6H) and 7.10–7.20 (m, 2H); δ_C($CDCl_3$) 25.87, 29.00, 29.11, 67.77, 101.65, 106.49, 129.72 and 160.32; *m*/*z* (EI) 496 (M^+, 16%) and 110 (100); ν_{max}(KBr)/cm^{-1} 2900, 2820, 1580, 1480, 1460, 1270, 1160, 1140, 1040, 810 and 770 (Found: C, 77.4; H, 9.7. $C_{32}H_{48}O_4$ requires C, 77.4; H, 9.7%).

1,14,21,34-Tetraoxa[14.14]metacyclophane 1d

Yield 4.7%; mp 95 °C; δ_H($CDCl_3$) 1.30–1.55 (m, 24H), 1.70–1.85 (m, 8H), 3.94 (t, 8H, *J* 6.2), 6.40–6.50 (m, 6H) and 7.10–7.20 (m, 2H); δ_C($CDCl_3$) 25.87, 29.00, 29.11, 67.77, 101.65, 106.49, 129.72 and 160.32; *m*/*z* (EI) 496 (M^+, 16%) and 110 (100); ν_{max}(KBr)/cm^{-1} 2900, 2820, 1580, 1480, 1460, 1270, 1160, 1140, 1040, 810 and 770 (Found: C, 77.4; H, 9.7. $C_{32}H_{48}O_4$ requires C, 77.4; H, 9.7%).

1,3-Bis(6-bromohexyloxy)-2-bromobenzene 6a

A stirred solution of 2-bromoresorcinol (18.8 g, 100 mmol), 1,6-dibromohexane (97.58 g, 400 mmol) and K_2CO_3 (41.5 g, 300 mmol) in acetone (600 cm^3) was refluxed for 3 days after which solvent was removed *in vacuo*. Water was added to the residue which was then extracted with ethyl acetate. The extract was washed with 10% aqueous NaOH, dried (Na_2SO_4) and evaporated. The residue was purified by passage through a silica-gel column using hexane–ethyl acetate as eluent; yield 61%; mp 67 °C; δ_H($CDCl_3$) 1.22–1.64 (m, 8H), 1.76–2.00 (m, 8H), 3.43 (t, 4H, *J* 6.7), 4.02 (t, 4H, *J* 6.3), 6.53 (d, 2H, *J* 8.6) and 7.16 (t, 1H, *J* 8.6); δ_C($CDCl_3$) 25.20, 27.79, 28.88, 32.63, 33.75, 68.98, 102.12, 105.71, 127.95 and 156.65; *m*/*z* (EI) 518 (M + 6, 19%), 516 (M + 4, 42), 514 (M + 2, 42), 512 (M^+, 19) and 188 (100); ν_{max}(KBr)/cm^{-1} 2948, 2908, 1594, 1478, 1402, 1254, 1088, 1038, 764, 708 and 646 (Found: C, 42.15; H, 5.2. $C_{18}H_{27}O_2Br_3$ requires C, 42.0; H, 5.3%).

1,3-Bis(8-bromooctyloxy)-2-bromobenzene 6b

Yield 47%; mp 61 °C; δ_H($CDCl_3$) 1.30–1.60 (m, 16H), 1.72–1.94 (m, 8H), 3.41 (t, 4H, *J* 6.9), 4.02 (t, 4H, *J* 6.4), 6.52 (d, 2H, *J* 8.3) and 7.16 (t, 1H, *J* 8.3); δ_C($CDCl_3$) 25.89, 28.05, 28.64, 29.07, 32.76, 33.87, 69.17, 102.17, 105.66, 127.91 and 156.75; *m*/*z* (EI) 574 (M + 6, 4%), 572 (M + 4, 12), 570 (M + 2, 12), 568 (M^+, 4) and 188 (100); ν_{max}(KBr)/cm^{-1} 2940, 1602, 1478, 1438, 1252, 1092, 1036 and 640 (Found: C, 46.3; H, 6.0. $C_{22}H_{35}O_2Br_3$ requires C, 46.3; H, 6.2%).

1,3-Bis(10-bromodecyloxy)-2-bromobenzene 6c

Yield 41%; mp 69 °C; δ_H($CDCl_3$) 1.00–1.90 (m, 36H), 3.40 (t, 4H, *J* 6.9), 4.01 (t, 4H, *J* 6.4), 6.52 (d, 2H, *J* 8.4) and 7.15 (t, 1H, *J* 8.4); δ_C($CDCl_3$) 25.90, 28.10, 28.66, 29.05, 29.18, 29.27, 29.35, 32.76, 33.90, 69.13, 102.08, 105.58, 127.86 and 156.71; *m*/*z* (EI) 630 (M + 6, 6%), 628 (M + 4, 10), 626 (M + 2, 11), 624 (M^+, 5) and 188 (100); ν_{max}(KBr)/cm^{-1} 2920, 1588, 1400, 1216, 1062, 764, 660 and 616 (Found: C, 49.7; H, 6.9. $C_{26}H_{43}O_2Br_3$ requires C, 49.8; H, 6.9%).

1,3-Bis(12-bromododecyloxy)-2-bromobenzene 6d

Yield 40%; mp 76 °C; δ_H($CDCl_3$) 1.20–1.58 (m, 32H), 1.75–1.92 (m, 8H), 3.40 (t, 4H, *J* 6.9), 4.01 (t, 4H, *J* 6.6), 6.52 (d, 2H, *J* 8.2) and 7.15 (t, 1H, *J* 8.2); δ_C($CDCl_3$) 25.95, 28.14, 28.73, 29.10, 29.27, 29.39, 29.47, 32.80, 33.94, 69.25, 102.13, 105.62, 127.87 and 156.76; *m*/*z* (EI) 686 (M + 6, 4%), 684 (M + 4, 12), 682 (M + 2, 11), 680 (M^+, 4) and 188 (100); ν_{max}(KBr)/cm^{-1} 3432, 2844, 1568, 1400, 1250, 1092, 1046, 766, 728, 660 and 616 (Found: C, 52.5; H, 7.5. $C_{30}H_{51}O_2Br_3$ requires C, 52.7; H, 7.5%).

14,28-Dibromo-1,8,15,22-tetraoxa[8.8]metacyclophane 2a

A stirred solution of 2-bromoresorcinol (9.45 g, 50 mmol), the dibromide **6a** (20.5 g, 40 mmol) and K_2CO_3 (17.3 g, 125 mmol) in acetone (2400 cm^3) was refluxed for 8 days after which solvent was removed *in vacuo*. Water was added to the residue which was then extracted with ethyl acetate. The extract was washed with 10% aqueous NaOH, dried (Na_2SO_4) and evaporated. The residue was purified by passage through a silica-gel column using hexane–ethyl acetate as the eluent; yield 15.7%; mp 178 °C; δ_H($CDCl_3$) 1.60–1.76 (m, 8H), 1.76–1.94 (m, 8H), 4.07 (t, 8H, *J* 5.7), 6.50 (d, 4H, *J* 8.3) and 7.12 (t, 2H, *J* 8.3); δ_C($CDCl_3$) 25.51, 28.8, 68.32, 103.02, 105.55, 127.49 and 156.55; *m*/*z* (EI) 544 (M + 4, 20%), 542 (M + 2, 38), 514 (M^+, 19) and 83 (100); ν_{max}(KBr)/cm^{-1} 2940, 2876, 1596, 1478, 1394, 1296, 1232, 1104, 1036, 752 and 664 (Found: C, 53.1; H, 5.6. $C_{24}H_{30}O_4Br_2$ requires C, 53.1; H, 5.6%).

16,32-Dibromo-1,10,17,26-tetraoxa[10.10]metacyclophane 2b
Yield 19.0%; mp 167 °C; δ_H($CDCl_3$) 1.10–1.90 (m, 24H), 4.03 (t, 8H, *J* 5.3), 6.51 (d, 4H, *J* 8.2) and 7.14 (t, 2H, *J* 8.4); δ_C($CDCl_3$) 26.41, 29.41, 29.57, 69.39, 102.75, 105.56, 127.69 and 156.85; *m*/*z* (CI) 601 (M + 5, 28%), 599 (M + 3, 3), 596 (M^+, 28) and 83 (100) (Found: C, 56.0; H, 6.4. $C_{28}H_{38}O_4Br_2$ requires C, 56.2; H, 6.4%).

18,36-Dibromo-1,12,19,30-tetraoxa[12.12]metacyclophane 2c
Yield 16.4%; mp 145 °C; δ_H($CDCl_3$) 1.28–1.44 (m, 16H), 1.44–1.62 (m, 8H), 1.72–1.88 (m, 8H), 4.02 (t, 8H, *J* 5.7), 6.51 (d, 4H, *J* 8.2) and 7.14 (t, 2H, *J* 8.4); δ_C($CDCl_3$) 26.12, 29.11, 29.17, 29.28, 69.09, 102.28, 105.44, 127.79 and 156.82; *m*/*z* (EI) 656 (M + 4, 44%), 654 (M + 2, 78), 652 (M^+, 38) and 83 (100); ν_{max}(KBr)/cm^{-1} 2924, 1592, 1394, 1100 and 762 (Found: C, 58.7; H, 7.1. $C_{32}H_{46}O_4Br_2$ requires C, 58.7; H, 7.1%).

20,40-Dibromo-1,14,21,34-tetraoxa[14.14]metacyclophane 2d
Yield 22.1%; mp 122 °C; δ_H($CDCl_3$) 1.22–1.42 (m, 24H), 1.42–1.60 (m, 8H), 1.72–1.87 (m, 8H), 4.02 (t, 8H, *J* 5.8), 6.51 (d, 4H, *J* 8.2), 7.15 (t, 2H, *J* 8.4); δ_C($CDCl_3$) 26.16, 29.15, 29.34, 29.41, 69.12, 102.31, 105.55, 127.82 and 156.79; *m*/*z* (EI) 712 (M + 4, 62%), 710 (M + 2, 100), 708 (M^+, 42) and 83 (100); ν_{max}(KBr)/cm^{-1} 2924, 1590, 1460, 1296, 1098 and 762 (Found: C, 61.1; H, 7.9. $C_{36}H_{54}O_4Br_2$ requires C, 60.9; H, 7.7%).

14,28-Diiodo-1,8,15,22-tetraoxa[8.8]metacyclophane 8a
A dry THF (75 cm^3) solution of **2a** (0.75 g, 1.5 mmol) in a 100-cm^3 flask, was treated with butyllithium (6 mmol) at −78 °C. The solution was stirred at the same temperature for 3 h, after which iodine (1.65 g, 6.75 mmol) in dry THF (15 cm^3) was added dropwise to it; the solution was then allowed to warm to room temperature after which it was stirred for 12 h. The excess iodine was reduced by the addition of saturated aq. sodium sulfite to the mixture which was then extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated *in vacuo* and the residue was purified by recrystallization from CCl_4–hexane to give colourless crystals (82.2%), mp 202 °C; δ_H($CDCl_3$) 1.60–1.90 (m, 16H), 4.08 (t, 8H, *J* 5.2), 6.42 (d, 4H, *J* 8.2) and 7.15 (t, 2H, *J* 8.2); δ_C($CDCl_3$) 25.20, 28.97, 67.79, 80.44, 104.63, 129.05 and 158.76; *m*/*z* (EI) 636 (M^+, 100%) and 509 (75); ν_{max}(KBr)/cm^{-1} 2950, 1600, 1470, 1400, 1285, 1120, 1080 and 780 (Found: C, 45.2; H, 5.0. $C_{24}H_{30}O_4I_2$ requires C, 45.3; H, 4.75%).

16,32-Diiodo-1,10,17,26-tetraoxa[10.10]metacyclophane 8b
Yield 67.7%; mp 162 °C; δ_H($CDCl_3$) 1.40–1.58 (m, 8H), 1.58–1.75 (m, 8H), 1.75–1.88 (m, 8H), 4.02 (t, 8H, *J* 5.3), 6.43 (d, 4H, *J* 8.2) and 7.16 (t, 2H, *J* 8.2); δ_C($CDCl_3$) 26.29, 29.33, 29.54, 69.20, 79.89, 104.84, 129.24 and 158.97; *m*/*z* (EI) 692 (M^+, 100%), 565 (8), 438 (6) and 236 (62) (Found: C, 48.7; H, 5.6. $C_{28}H_{38}O_4I_2$ requires C, 48.6; H, 5.5%).

14,28-Dimethyl-1,8,15,22-tetraoxa[8.8]metacyclophane 10
A dry THF (5 cm^3) solution of **2a** (54 mg, 0.1 mmol), was treated with butyllithium (0.4 mmol) added at −78 °C. The solution was then stirred at the same temperature for 3 h, after which methyl iodide (0.8 mmol) was added to it. The solution was then allowed to warm to room temperature for 12 h after which it was evaporated, and diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product, which was purified by recrystallization from chloroform–hexane; yield 84.5%, mp 165 °C; δ_H($CDCl_3$) 1.40–1.80 (m, 22H), 3.85–4.00 (m, 8H), 6.47 (d, 4H, *J* 8.2) and 7.07 (t, 2H, *J* 8.2); δ_C($CDCl_3$) 8.12, 26.22, 29.32, 67.33, 103.81, 115.06, 125.74 and 157.75; *m*/*z* (EI) 412 (M^+, 100%), 207 (38) and 124 (95) (Found: C, 75.4; H, 8.7. $C_{26}H_{36}O_4$ requires C, 75.7; H, 8.8%).

20-Trimethylsilyl-1,14,21,34-tetraoxa[14.14]metacyclophane 11
A dry THF (35 cm^3) solution of **2d** (213 mg, 0.3 mmol) was treated with butyllithium (1.2 mmol) added at −78 °C. The solution was then stirred at the same temperature for 3 h after which trimethylsilyl chloride (1.2 mmol) was added to it. The solution was then allowed to warm to room temperature for 12 h, after which it was evaporated, diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product, which was purified by recrystallization from chloroform–hexane; yield 71.7%, mp 111 °C; δ_H($CDCl_3$) 0.32 (s, 9H), 1.25–1.40 (m, 24H), 1.70–1.82 (m, 8H), 3.85–4.00 (m, 8H), 6.42–6.50 (m, 5H) and 7.10–7.25 (m, 2H); δ_C($CDCl_3$) 1.95, 25.91, 26.42, 29.07, 29.13, 29.20, 29.23, 29.27, 29.39, 67.81, 67.91, 101.48, 103.28, 106.55, 113.55, 129.71, 131.06, 160.33 and 164.89; ν_{max}(KBr)/cm^{-1} 2916, 1596, 1476, 1280, 1174, 1092, 1026 and 782 (Found: C, 74.8; H, 10.4. $C_{39}H_{64}O_4Si$ requires C, 74.95; H, 10.3%).

General procedure for the preparation of the diols 7
Sodium metal (3.45 g, 150 mmol) was added to the dried polymethylenediol (1.2 mol) in a 300-cm^3 flask under an argon atmosphere. When all the sodium metal had dissolved, the tribromide **4** (10.3 g, 30 mmol) in dry THF (30 cm^3) was added dropwise to the solution. The mixture was stirred and heated at *ca.* 60 °C for 48 h, after which it was neutralized with concentrated hydrochloric acid and evaporated. Unchanged polymethylenediol was recovered by distillation under reduced pressure and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate (1 : 1) as the eluent to give the product. Since for **7d** (*n* = 8) and **7e** (*n* = 10) the separations from the starting polymethylenediols were difficult because the polarities of the materials are very similar, they were used for the next step reaction without further purification.

1,3-Bis(4-hydroxybutoxymethyl)-2-bromobenzene 7a
Yield 80.9%; yellow crystals, mp 64–65.5 °C; δ_H($CDCl_3$) 1.65–1.76 (m, 8H), 2.37 (s, 2H, OH), 3.59 (t, 4H, *J* 6.0), 3.64 (t, 4H, *J* 6.3), 4.59 (s, 4H), 7.31 (dd, 1H, *J* 8.9 and 5.8) and 7.37–7.42 (m, 2H); δ_C($CDCl_3$) 25.95, 29.22, 61.79, 70.47, 72.06, 122.59, 126.84, 127.65 and 137.64; *m*/*z* (CI) 361 (M + 1, 33%), 345 ($MH^+ - H_2O$, 9) and 271 [$M^+ - O(CH_2)_4OH$, 100]; ν_{max}(KBr)/cm^{-1} 3304, 2950, 2968, 1446, 1360, 1130, 968 and 775 (Found: C, 53.1; H, 6.9. $C_{16}H_{25}O_4Br$ requires C, 53.2; H, 7.0%).

1,3-Bis(5-hydroxypentyloxymethyl)-2-bromobenzene 7b
Yield 72.3%, yellow crystals; mp 49–51 °C; δ_H($CDCl_3$) 1.44–1.80 (m, 14H, alkane and OH), 3.56 (t, 4H, *J* 6.4), 3.63 (t, 4H, *J* 6.4), 4.57 (s, 4H), 7.31 (dd, 1H, *J* 8.5 and 6.1) and 7.36–7.42 (m, 2H); δ_C($CDCl_3$) 21.94, 28.94, 31.84, 61.57, 70.40, 71.84, 122.29, 126.63, 127.36 and 137.57; *m*/*z* (CI) 389 (M + 1, 27%), 285 [$M^+ - O(CH_2)_5OH$, 21], 199 (30), 182 (100) and 105 (23); ν_{max}(KBr)/cm^{-1} 3320, 2940, 2856, 1140, 1030 and 784 (Found: C, 55.4; H, 7.4. $C_{18}H_{29}O_4Br$ requires C, 55.5; H, 7.5%).

1,3-Bis(6-hydroxyhexyloxymethyl)-2-bromobenzene 7c
Yield 69.4%, yellow crystals; mp 45–48 °C; δ_H($CDCl_3$) 1.40–2.02 (m, 18H, alkane and OH), 3.55 (t, 4H, *J* 6.4), 3.63 (t, 4H, *J* 6.6), 4.57 (s, 4H, benzyl), 7.24 (dd, 1H, *J* 8.5 and 6.1) and 7.30–7.35 (m, 2H); δ_C($CDCl_3$) 25.23, 25.62, 29.27, 32.17, 61.87, 70.52, 71.93, 122.40, 126.73, 127.43 and 137.72; *m*/*z* (CI) 417 (M + 1, 31%), 299 [$M^+ - O(CH_2)_6OH$, 32], 199 (28) and 183 (100); ν_{max}(KBr)/cm^{-1} 3324, 2940, 2860, 1360, 1136 and 784 (Found: C, 57.45; H, 7.85. $C_{20}H_{33}O_4Br$ requires C, 57.55; H, 8.0%).

1,3-Bis(12-hydroxydodecyloxymethyl)-2-bromobenzene 7f
Yield 67.1%, pale yellow solid; mp 69–71 °C; δ_H($CDCl_3$) 1.23–1.68 (m, 42H, alkane and OH), 3.54 (t, 4H, *J* 6.6), 3.63 (t, 4H, *J* 6.6), 4.57 (s, 4H, benzyl), 7.31 (dd, 1H, *J* 8.6 and 6.0) and 7.38–7.42 (m, 2H); δ_C($CDCl_3$) 25.46, 25.81, 29.09, 29.13, 29.24, 29.28, 32.26, 61.90, 70.63, 71.87, 122.12, 126.63, 127.23 and

137.71; *m/z* (CI) 585 (M + 1, 11%), 383 [$M^+ - O(CH_2)_{12}OH$, 29], 201 (64), 183 (60) and 105 (100); ν_{max}(KBr)/cm^{-1} 3264, 2920, 2848, 1470, 1130 and 1059 (Found: C, 65.5; H, 9.7. $C_{24}H_{30}O_4Br_2$ requires C, 65.6; H, 9.8%).

General procedure for the preparation of 3

The tribromide **4** (0.69 g, 2.0 mmol) and the diol **7** (2.0 mmol) in dry THF (20 cm^3) were added dropwise to a suspension of sodium hydride (0.4 g, *ca.* 10 mmol) in dry THF (110 cm^3) under an argon atmosphere. The mixture was refluxed for 7 days after which it was concentrated *in vacuo*, neutralized with 10% hydrochloric acid and extracted with chloroform. The organic layer was washed with saturated aq. NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 5% ethyl acetate in hexane as the eluent to give the product.

14,28-Dibromo-2,7,16,21-tetraoxa[8.8]metacyclophane 3a

Yield 16.8%, colourless crystals; mp 135–137 °C; δ_H($CDCl_3$) 1.65–1.75 (m, 8H), 3.53 (t, 8H), 4.46 (s, 8H, benzyl), 7.20 (dd, 2H, *J* 8.7 and 6.0) and 7.27–7.29 (m, 4H); δ_C($CDCl_3$) 25.8, 69.6, 72.0, 123.5, 126.7, 128.1 and 137.9; *m/z* (CI) 545 (M^+ + 5, 39%), 543 (M^+ + 3, 78), 541 (M^+ + 1, 40), 399 (98), 271 (46), 185 (99), 183 (100) and 105 (69); ν_{max}(KBr)/cm^{-1} 2948, 2910, 2864, 1354, 1120, 1086, 1050 and 804 (Found: C, 53.1; H, 5.8. $C_{24}H_{30}O_4Br_2$ requires C, 53.2; H, 5.6%).

15,30-Dibromo-2,8,17,23-tetraoxa[9.9]metacyclophane 3b

Yield 17.5%, colourless crystals; mp 91.5–93 °C; δ_H($CDCl_3$) 1.53–1.63 (m, 12H), 3.52 (t, 8H, *J* 5.8), 4.52 (s, 8H, benzyl), 7.17 (dd, 2H, *J* 8.4 and 7.0) and 7.34 (d, 4H, *J* 7.6); δ_C($CDCl_3$) 22.4, 28.7, 69.9, 72.2, 124.0, 126.9, 128.7 and 138.1; *m/z* (CI) 573 (M^+ + 5, 5%), 571 (M^+ + 3, 12), 569 (M^+ + 1, 5), 467 (36), 367 (34), 285 (29), 183 (100) and 104 (41); ν_{max}(KBr)/cm^{-1} 2950, 2908, 2870, 1136, 1120, 1094 and 780 (Found: C, 54.6; H, 5.9. $C_{26}H_{34}O_4Br_2$ requires C, 54.75; H, 6.0%).

16,32-Dibromo-2,9,18,25-tetraoxa[10.10]metacyclophane 3c

Yield 26.8%, colourless crystals; mp 123–125 °C; δ_H($CDCl_3$) 1.35–1.55 (m, 8H), 1.63–1.67 (m, 8H) 3.52 (t, 8H, *J* 6.1), 4.55 (s, 8H, benzyl), 7.10 (t, 2H, *J* 7.5) and 7.31 (d, 4H, *J* 7.32); δ_C($CDCl_3$) 25.5, 29.3, 70.1, 72.2, 122.9, 126.9, 127.8 and 138.1; *m/z* (CI) 601 (M^+ + 5, 5%), 599 (M^+ + 3, 8), 597 (M^+ + 1, 5), 519 (12), 481 (28), 367 (21), 299 (20), 185 (94), 183 (100) and 104 (46); ν_{max}(KBr)/cm^{-1} 2900, 2856, 1352, 1126 and 780 (Found: C, 56.2; H, 6.5. $C_{28}H_{38}O_4Br_2$ requires C, 56.2; H, 6.4%).

18,36-Dibromo-2,11,20,29-tetraoxa[12.12]metacyclophane 3d

Yield from **4** was 10.6%, colourless crystals; mp 114–115 °C; δ_H($CDCl_3$) 1.34–1.40 (m, 16H), 1.58–1.65 (t, 8H, *J* 6.26), 4.57 (s, 8H, benzyl), 7.24–7.29 (m, 2H) and 7.38 (d, 4H, *J* 7.94); δ_C($CDCl_3$) 25.8, 28.9, 29.5, 70.5, 72.2, 122.6, 127.0, 127.6 and 138.2; *m/z* (CI) 657 (M^+ + 5, 3%), 655 (M^+ + 3, 5), 653 (M^+ + 1, 3), 573 (6), 509 (8), 367 (23), 327 (16), 185 (100) and 183 (98); ν_{max}(KBr)/cm^{-1} 2932, 2908, 2860, 1472, 1394, 1350, 1132 and 774 (Found: C, 58.6; H, 7.2. $C_{32}H_{46}O_4Br_2$ requires C, 58.7; H, 7.1%).

20,40-Dibromo-2,13,22,33-tetraoxa[14.14]metacyclophane 3e

Yield from **4** was 13.5%, colourless crystals; mp 82.5–84 °C; δ_H($CDCl_3$) 1.23–1.39 (m, 24H), 1.55–1.66 (m, 8H), 3.54 (t, 8H, *J* 6.26), 4.56 (s, 8H), 7.28–7.34 (dd, 2H, *J* 6.6 and 8.5) and 7.40 (d, 4H, *J* 6.7); δ_C($CDCl_3$) 26.0, 28.9, 29.0, 29.5, 70.7, 72.2, 122.7, 126.7, 127.7 and 138.2; *m/z* (CI) 762 (M^+ + 2, 7%), 537 (10), 355 (36), 185 (87) and 105 (100); ν_{max}(KBr)/cm^{-1} 2924, 2852, 1368, 1348, 1132, 1024 and 786 (Found: C, 60.85; H, 7.7. $C_{36}H_{54}O_4Br_2$ requires C, 60.4; H, 7.8%).

22,44-Dibromo-2,15,24,37-tetraoxa[16.16]metacyclophane 3f

Yield 24.5%, colourless crystals; mp 93–94 °C; δ_H($CDCl_3$) 1.27–1.43 (m, 32H), 1.59–1.66 (m, 8H), 3.54 (t, 8H, *J* 6.4), 4.56 (s, 8H), 7.28–7.34 (dd, 2H, *J* 6.3 and 8.7) and 7.40 (d, 4H, *J* 6.7); δ_C($CDCl_3$) 26.1, 29.1, 29.18, 29.24, 29.6, 70.7, 72.3, 122.8, 127.0, 127.7 and 138.2; *m/z* (CI) 769 (M^+ + 5, 2%), 767 (M^+ + 3, 12), 765 (M^+ + 1, 5), 685 (6), 565 (6), 485 (5), 383 (33), 285 (19), 185 (91), 183 (100) and 105 (63); ν_{max}(KBr)/cm^{-1} 2924, 2852, 1470, 1360, 1132, 1026 and 790 (Found: C, 62.5; H, 8.35. $C_{40}H_{62}O_4Br_2$ requires C, 62.7; H, 8.15%).

14,28-Diiodo-2,7,16,21-tetraoxa[8.8]metacyclophane 9a

14,28-Dibromo-2,7,16,21-tetraoxa[8.8]metacyclophane **3a** (0.5 mmol, 271 mg) was dried in a 50-cm^3 flask *in vacuo* by heating to *ca.* 100 °C. After the flask had been flushed with dry argon, it was charged with dry THF (25 cm^3) to dissolve compound **3a**; butyllithium (1.5 mmol) was then added at −56 °C to the flask. The mixture was stirred at −56 °C for 4 h after which an excess of iodine (3.9 g, *ca.* 15 mmol) in dry THF (2 cm^3) was added to it. The reaction mixture was allowed to warm to room temperature during about 3 h after which excess of iodine was reduced by the addition of saturated aq. sodium sulfite. The mixture was extracted with chloroform and the extract dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was purified by passage through a silica-gel column with 5% ethyl acetate–hexane as the eluent; yield 71.7%, colourless crystals; mp 134–135 °C; δ_H($CDCl_3$) 1.74–1.78 (m, 8H), 3.52 (t, 8H, *J* 6.0), 4.41 (s, 8H) and 7.22 (s, 6H); δ_C($CDCl_3$) 26.1, 69.7, 76.9, 102.7, 127.7, 128.1 and 141.2; *m/z* (EI) 636 (M^+, 15%), 546 (28), 492 (48), 231 (100) and 104 (74); ν_{max}(KBr)/cm^{-1} 2944, 2904, 2860, 1356, 1130, 1090, 1146 and 800 (Found: C, 45.4; H, 4.9. $C_{24}H_{30}O_4I_2$ requires C, 45.3; H, 4.75%).

Crystallographic analyses of cyclophanes

Intensity data were recorded on a Rigaku AFC5R or a RASA7R diffractometer with graphite-monochromated Mo-Kα radiation and a 12 kW rotating anode generator. Data were corrected for Lorenz polarization and absorption effects. The structure was solved by the Patterson method or direct methods.[12] The non-hydrogen atoms were refined anisotropically. Neutral atom-scattering factors were taken from Crommer and Waber.[13] Anomalous dispersion effects were included in F_c;[14] the values for $D_{f'}$ and $D_{f''}$ were those of Cromer.[15] All the calculations were performed using the TEXSAN[16] crystallographic software package of Molecular Structure Corporation. The ORTEP[17] programs were used to obtain Figs. 1–7. Crystal data and experimental details are listed in Table 2. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://chemistry.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/166.

Details of calculations

Molecular mechanics and molecular dynamics calculations were performed using the Chem3D Plus software package on a Macintosh.[6] Semi-empirical calculations were performed using MOPAC ver. 6.01 on a CONVEX C3440.[7] No assumptions were made concerning the symmetry of the compounds. The results are tabulated in Table 3. Details of the calculations are available as supplementary material (SUPPL. NO. 57336, 92 pp.). For details of the Supplementary Publications Scheme see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors).

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Table 3 Calculated energies and energy differences from the global minima for metacyclophanes **2**, **3** and **9**

Compound	Type[a]	ΔAM1[b]/kcal mol^{-1}	ΔMM2[c]/kcal mol^{-1}	AM1[d]/kcal mol^{-1}	MM2[e]/kcal mol^{-1}
2a	**C1***	0.00	0.00	−121.81	27.04
	C2*	0.15	0.72	−121.66	27.76
	A	8.77	1.88	−113.04	28.92
	D	1.40	7.19	−120.41	34.23
	B	4.54	9.58	−117.27	36.62
2b	**C***	2.54	0.00	−143.68	29.84
	A	0.00	5.19	−146.22	35.03
	E	0.50	8.21	−145.72	38.05
	B	0.73	9.41	−145.49	39.25
2c	**C**	0.00	0.00	−175.30	34.66
	B	1.80	5.88	−173.50	40.54
	E	2.99	5.98	−172.31	40.64
	A	9.99	6.76	−165.31	41.42
2d	**C**	0.00	0.00	−202.08	38.24
	A	1.94	4.52	−200.14	42.76
	B	2.70	7.97	−199.38	46.21
	E	1.49	9.17	−200.59	47.41
9a	**D***	2.31	0.00	−111.59	19.66
	B	0.25	4.59	−113.65	24.25
	A	1.63	10.41	−112.27	30.07
	C	0.00	15.48	−113.90	35.14
3a	**D***	2.43	0.00	−137.02	20.44
	B	0.49	3.64	−138.96	24.08
	A	1.58	10.54	−137.87	30.98
	C	0.00	15.80	−139.45	36.24
3b	**B**	0.56	0.00	−150.91	23.41
	A	3.83	0.02	−147.65	23.43
	D	2.04	2.74	−149.43	26.14
	C	0.00	14.82	−151.47	38.23
3c	**E***	1.55	0.00	−164.65	24.39
	B	3.86	2.09	−162.34	26.48
	D	1.60	4.24	−164.60	28.63
	A	0.00	4.86	−166.20	29.25
	C	0.31	12.72	−165.89	37.11
3d	**E***	1.49	0.00	−193.26	28.42
	B	0.67	0.17	−194.08	28.59
	D	1.89	1.03	−192.86	29.45
	A	3.49	3.82	−191.26	32.24
	C	0.00	15.94	−194.75	44.36
3e	**E***	1.79	0.00	−220.47	30.03
	B	5.21	1.82	−217.05	31.85
	D	3.55	3.11	−218.71	33.14
	A	23.68	5.46	−198.58	35.49
	C	0.00	17.42	−222.26	47.45

[a] Conformational type as depicted in Fig. 8. The asterisks indicate the conformation type observed in the X-ray structure. [b] Energy above the energy of the global minimum for each compounds calculated by AM1 method. [c] Energy above the energy of the global minimum for each compounds calculated by MM2 method. [d] Heat of formation energies calculated by AM1. [e] Total energies calculated by MM2.

References

1 For recent papers concerning steric protections see; K. Toyota, H. Takahashi, K. Shimura and M. Yoshifuji, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 141; F. Luderer, H. Reinke and H. Oehme, *Chem. Ber.*, 1996, **129**, 15; N. Tokitoh, H. Suzuki and R. Okazaki, *Chem. Commun.*, 1996, 125.

2 As a representative paper see; T. Nabeshima, H. Furusawa and Y. Yano, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 1750.

3 (*a*) T. Shinmyozu, T. Hirakawa, G. Wen, S. Osada, H. Takemura, K. Sako and J. M. Rudzinski, *Liebigs Ann.*, 1996, 205; (*b*) Y. Fukazawa, Y. Yang, T. Hayashibara and S. Usui, *Tetrahedron*, 1996, **52**, 2847; (*c*) T. Ishi-i, T. Sawada, S. Mataka, M. Tashiro and T. Thiamin, *Chem. Ber.*, 1996, **129**, 289; (*d*) V. V. Cane, W. H. De Wolf and F. Bickelhaupt, *Tetrahedron*, 1994, **50**, 4575, and references therein.

4 M. Mascal, J.-L. Kerdelhue, A. S. Batsanov and M. J. Begley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1141.

5 Y. Delaviz, J. S. Merola, M. A. G. Berg and H. W. Gibson, *J. Org. Chem.*, 1995, **60**, 516.

6 Molecular mechanics and molecular dynamics calculations were performed using Chem 3D for Macintosh from Cambridge Scientific Computing Inc., Cambridge, MA.

7 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902; MOPAC ver. 6, J. J. P. Stewart, QCPE Bull., 1989, **9**, 10; Revised as 6.01 for CONVEX C3440 by CONVEX Co.

8 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441; L. Pauling, *The Nature of the Chemical Bond*, 3rd edn. Cornell University Press, Ithaca, N. Y., 1961.

9 T. L. Davis and V. F. Harrington, *J. Am. Chem. Soc.*, 1934, **56**, 129.

10 A. Lüttringhaus, *Liebigs Ann. Chem.*, 1937, **528**, 181.

11 A. Lüttringhaus and K. Ziegler, *Liebigs Ann. Chem.*, 1937, **528**, 155.

12 Structure solution methods: PHASE; J. C. Calbrese, PHASE: Patterson Heavy Atom Solution Extractor, Ph. D. Thesis, University of Wisconsin-Madison, 1972; DIRDIF; P. T. Beurskens, DIRDIF: Direct Method for Difference Structures—an automatic procedure for phase extension and refinement of difference structure factors, Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

13 D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, vol. IV, The Kynoch Press, Birmingham, England, 1974, Table 2.2A.

14 J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, 1964, **17**, 781.

15 D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, vol. IV, The Kynoch Press, Birmingham, England, 1974, Table 2.3.1.

16 TEXSAN—TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985.

17 K. K. Johnson, ORTEP II. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

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