Macrocyclic Ethers and Their Inclusion Complexes

Jari Ratilainen, Karri Airola, Martin Nieger, Marc Böhme, Juhani Huuskonen, and Kari Rissanen*

Abstract: The synthesis and characterisation of eleven new macrocyclic ethers (up to 96-membered [6+6] gigantocycle) with well-defined cavities are described. Syntheses of the macrocycles **M1**–**M7** were performed under high-dilution conditions. A "supramolecular" purification method was used for the small [2+2] macrocycles **M3**–**M7**, which separated selectively from the reaction mixture on recrystallisation from a dichloromethane/diethyl ether solution mixture. This proved to be an excellent method for purifying [2+2] macrocyclic ethers containing 1,1-diphenylmethane moieties, and the separation was nearly quantitative. Molecular inclusion of dichloromethane in the cavities of noncovalently bonded macrocyclic ethers **M2**–**M5** was studied by X-ray diffraction in the solid state. Additionally, clathrate formation was found for macrocycles **M1** (including diethyl ether), **M2** (including water), **M6** (including benzene) and **M7** (including benzene).

Keywords
clathrates · host–guest chemistry · hydrogen bonds · macrocyclic ligands

Introduction

The synthesis of macrocyclic ligands as receptors for ions or uncharged organic molecules is important for the study of complexation abilities and complex formation.[1] In order to achieve high recognition, it is desirable that receptor and substrate be in contact over a large area.[2] This occurs when the host is able to wrap around its guest, establishing numerous noncovalent bonding interactions appropriate to the molecular size, shape and architecture of the guest. Although high recognition may be achieved with rigidly organised receptors, processes of exchange, regulation, cooperativity and allostery require a built-in flexibility, so that the host may adapt and respond to changes.[3]

Macrocyclic compounds have been studied intensively during the last few decades, because their host–guest interactions play an important role in forming and stabilising, for example, rotaxane[4] and catenane[5] structures. The structure and the interaction facilities of the macrocyclic host molecules affect their ability to accommodate different organic[6] or ionic[7] guest molecules. The different possible complexation functions of the host molecules open up a broad research area, which focuses on designing host macrocycles for selective complexation of chosen guest molecules.[8] A large body of experimental information may be gained from using different template effects in macrocycle,[9] rotaxane[10] and catenane[11] syntheses. The discovery that macrocyclic compounds can form channel-type supramolecules including small organic guests[12] has led to the development of supramolecular tubes[13] and cables.[14]

In this paper, we present the detailed syntheses of eleven macrocyclic ether systems by direct cyclisation under high-dilution conditions and the selective separation of [2+2] macrocycles **M3**–**M7** (Figure 1) from the reaction mixtures by forming inclusion complexes with neutral organic guests. Our aim was to investigate catenane formation, but complexation of dichloromethane with **M3**–**M7** was observed instead. It turned out that the selective complexation can be used for purification of the [2+2] macrocyclic ethers containing rigid 1,1-diphenylmethane moieties.

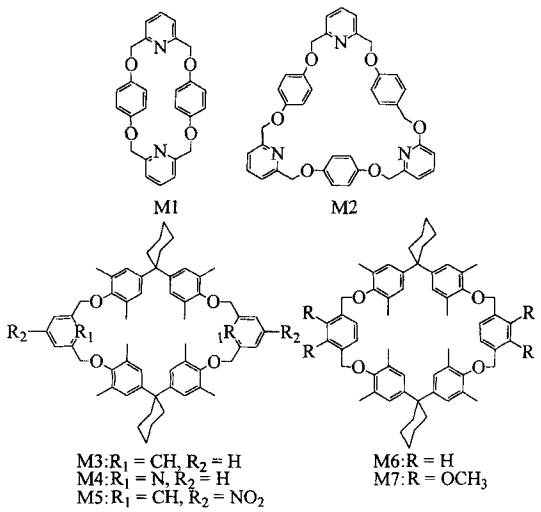

Figure 1. Neutral macrocyclic host molecules **M1**–**M7**.

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Table 1. Crystallographic data for macrocycles **M1** (A), **M2** (B, C), **M3** (D), **M4** (E), **M5** (F), **M6** (G) and **M7** (H).

	A	B	C	D	E	F	G	H
formula	$C_{26}H_{22}N_2O_4 \cdot 0.5\,Et_2O$	$C_{39}H_{33}N_3O_6 \cdot H_2O$	$C_{39}H_{33}N_3O_6 \cdot CH_2Cl_2$	$C_{60}H_{68}O_4 \cdot 2CH_2Cl_2$	$C_{58}H_{66}N_2O_4 \cdot 1.5CH_2Cl_2$	$C_{60}H_{66}N_2O_8 \cdot 2CH_2Cl_2$	$C_{60}H_{68}O_4 \cdot 4C_6H_6$	$C_{64}H_{76}O_8 \cdot 2C_6H_6$
M_r	463.52	657.70	724.61	1023.0	982.52	1113.00	1165.58	1129.46
a (Å)	9.699(2)	10.774(1)	16.268(2)	9.959(1)	6.436(1)	7.683(1)	18.407(2)	8.069(1)
b (Å)	17.017(2)	11.457(2)	11.344(14)	11.387(1)	12.222(2)	23.021(2)	10.205(10)	13.330(2)
c (Å)	15.289(3)	14.701(2)	11.541(2)	13.088(1)	17.705(1)	16.223(1)	19.240(6)	16.740(2)
α (deg)	90	109.08(1)	119.29(1)	66.90(1)	71.70(1)	90	90	110.02(1)
β (deg)	104.73(2)	96.14(1)	97.34(1)	81.64(1)	88.51(1)	92.92(1)	105.81(10)	98.72(1)
γ (deg)	90	94.72(1)	98.61(1)	78.80(1)	86.22(1)	90	90	101.96(1)
V (Å^3)	2440.5(8)	1691.8(4)	1786.0(4)	1335.3(2)	1319.4(3)	2865.6(5)	3477.0(4)	1605.8(4)
Z	4	2	2	1	1	2	2	1
T (K)	293	293	293	200	200	293	293	293
space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
ρ_{calcd} (g cm^{-3})	1.262	1.291	1.347	1.272	1.237	1.290	1.113	1.168
μ (cm^{-1})	0.86	0.89	2.34	23.81	19.46	23.28	5.08	5.81
radiation	$Mo_{K\alpha}$	$Mo_{K\alpha}$	$Mo_{K\alpha}$	$Cu_{K\alpha}$	$Cu_{K\alpha}$	$Cu_{K\alpha}$	$Cu_{K\alpha}$	$Cu_{K\alpha}$
R_{av}	0.0544	0.0694	0.0449	0.0690	0.1059	0.0666	0.0475	0.0660
R_w^2	0.1402	0.1935	0.1330	0.2238	0.3205	0.1872	0.1274	0.2008

Results and Discussion

Crystal Structures: Table 1 summarises the crystallographic data of the investigated inclusion complexes.[15]

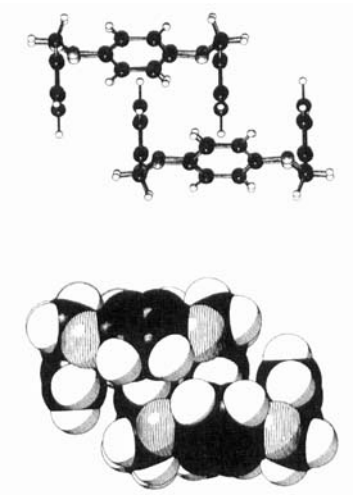

Figure 2. Packing diagram of **M1** showing the dimeric structure in crystalline state.

Macrocycle **M1** seems to contain self-complementary building blocks, since a dimeric packing structure was observed in the crystalline state (Figure 2). The rigid compound **M1** adopts a "cup" conformation, and $\pi-\pi$ interactions of the pyridine moieties, stacked parallel to one another, stabilise the dimeric structure in the solid state. Disordered diethyl ether is found in the crystal lattice of macrocycle **M1**, and water in that of **M2** (Figure 3a). Macrocycle **M2** also forms a 1:1 molecular inclusion complex with dichloromethane in which each hydrogen atom of the guest points towards the centre of one pyridine moiety of the host molecule and π hydrogen bonding stabilises the resulting inclusion complex (Figure 3b). The flexibility of the host macrocycle, along with the lack of space in the cavity owing to the packing of the host molecules in the solid state, does not allow for the inclusion of more than one dichloromethane molecule.

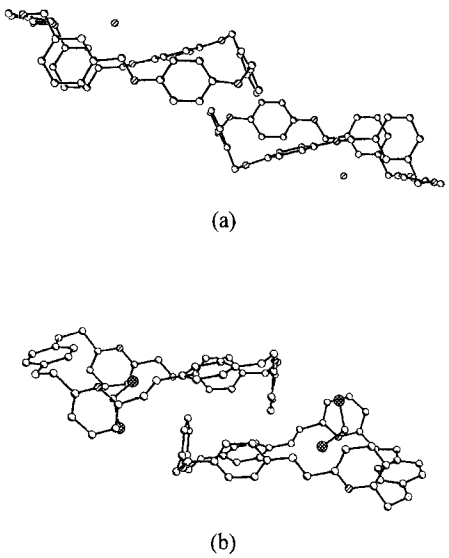

Figure 3. Packing in the crystal lattice inclusion complex of **M2** with water (a) and molecular inclusion complex of **M2** with dichloromethane (b) (hydrogen atoms are omitted for clarity).

Selective dichloromethane inclusion was observed when compounds **M3**–**M5** were crystallised from a dichloromethane/diethyl ether mixture. The crystal structure determinations reveal that macrocycles **M3**–**M5** form 2:1 dichloromethane molecular inclusion complexes. In particular, compound **M3** selectively forms a dichloromethane inclusion complex (Figure 4) in which each guest proton points towards the centre of an aromatic ring belonging to a 1,1-diphenylmethane moiety (with π–H bond lengths of 2.65 and 2.69 Å). The crystal structure shows clear evidence for π hydrogen bonding between the host and the guests, which stabilises the **M3**–dichloromethane molecular inclusion complex in the solid state. In solution, the formation of

Abstract in Finnish: *Työssä kuvataan 11 makrosyklisen eetterimolekyylin (aina 96-jäseniseen [6+6] gigantosykliin asti) synteisointi ja karakterisointi. Makrosyklit **M1**–**M7** syntetisoitiin "high-dilution"-olosuhteissa ja [2+2] makrosyklien **M3**–**M7** eristämisessä käytettiin hyväksi niiden kykyä muodostaa inkluusiokomplekseja dikloorimetaanimolekyylien kanssa. 1,1-difenyylimetaaniosia sisältävät [2+2] makrosyklit kiteytyivät lähes kvantitatiivisesti ulos dikloorimetaani/dietyylieetteri seoksesta. Pienten orgaanisten molekyylien kompleksoitumista makrosyklien kanssa tutkittiin röntgendiffraktion avulla. Makrosyklit **M2**–**M5** muodostivat dikloorimetaani-inkluusiokomplekseja. Tämän lisäksi makrosyklien **M1**, **M2**, **M6** ja **M7** havaittiin muodostavan klatraatteja.*

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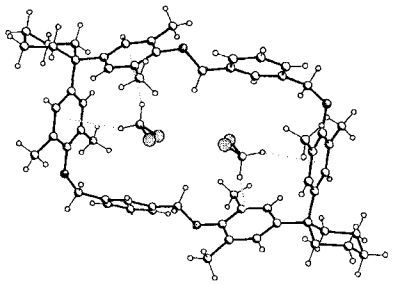

Figure 4. Crystal structure showing the π hydrogen bonding in the inclusion complex of **M3** with dichloromethane (π–H bond lengths: 2.65 and 2.69 Å).

the π hydrogen bonded host–guest complex could not be detected by NMR spectroscopy, because of the fast exchange process caused by the entropy of the molecules.

M4 and **M5** also form 2:1 molecular inclusion complexes with dichloromethane in the solid state, but π hydrogen bonding, similar to that in **M3**, is not observed. Dichloromethane guests are found to be disordered in the cavity of **M4** (Figure 5).

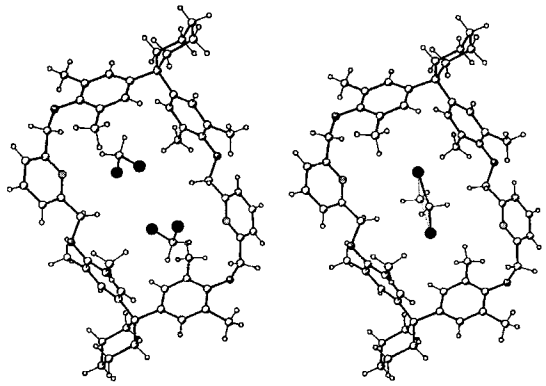

Figure 5. Possible orientations of dichloromethane in the cavity of **M4** in the crystalline state.

Recognition of the guests must have occurred through π hydrogen bonding with the 1,1-diphenylmethane moieties, but other noncovalent interactions must also operate in the final molecular inclusion complex. It is also possible that the nitrogen atoms of the pyridine moieties change the polarity distribution in the host molecule in such a fashion as to lead to a disordering of the guests, or the disorder may be caused by molecular diffusion over a long period of time, while the single crystals were left in the mother liquid.

Figure 6 depicts the molecular inclusion complex of **M5**. Owing to the NO_2-substituted benzene unit, the cavity of **M5** opens up slightly more than the cavity of **M3**. The distances between the dichloromethane hydrogens and the aromatic rings (2.9 and 3.0 Å) are out of the effective π hydrogen bonding range; thus, steric factors play a greater role in determining the way dichloromethane guest molecules fit into the cavity of **M5**.

Clathrate formation was observed when **M6** and **M7** were crystallised from pure benzene. In the crystalline state, **M6** and **M7** lie on a crystallographic symmetry element (centrosymmetric). In the case of **M6**, two clathrated benzene molecules are

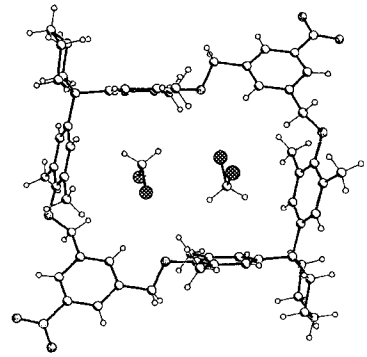

Figure 6. Molecular inclusion complex of **M5** with dichloromethane.

located within the cleft formed by two host molecules and two benzene molecules are in a face-to-edge arrangement with the cyclohexyl moieties (Figure 7a). **M7** has a more tightly packed solid state structure and is able to accommodate benzene guests between the packed channels (Figure 7b). As can be seen from

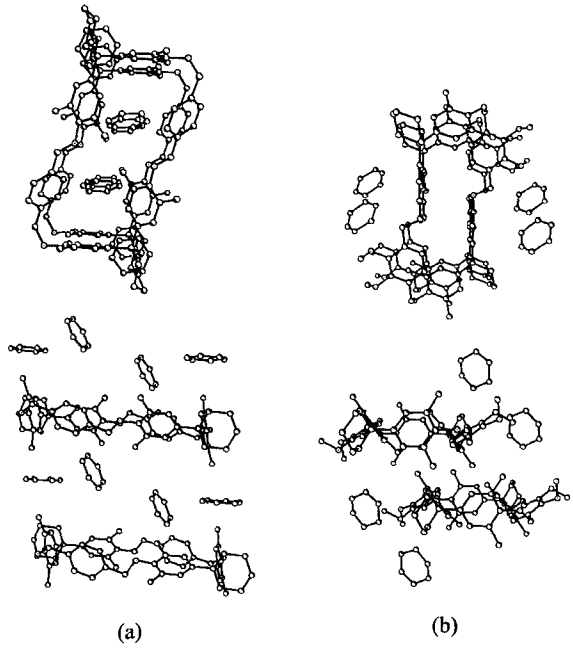

Figure 7. Packing in the crystal lattice of the inclusion complex of **M6** (a) and **M7** (b) with benzene (hydrogen atoms are omitted for clarity).

Figure 7, the cavities of **M6** and **M7** collapse in the crystal structure, because the *para*-substituted spacer molecules are not preorganised (unlike the *meta*-substituted spacer units) and thus give more flexibility to the macrocyclic molecules. This explains why the macrocycles **M6** and **M7** cannot accommodate benzene molecules in their cavities under the conditions described here. In the purification of **M6** and **M7**, some kind of π hydrogen bonded molecular inclusion complex must be formed with dichloromethane, because macrocycles **M3**–**M7** showed very similar behaviours during crystallisation from the dichloromethane/diethyl ether mixture; unfortunately, no single crystals of **M6** or **M7** and dichloromethane were obtained.

Synthesis: Figure 8 depicts the synthesis of the macrocyclic ethers shown in Figure 1. The syntheses of macrocycles **M1**–**M7** were carried out under high-dilution conditions. Solutions of the starting materials were added simultaneously to refluxing

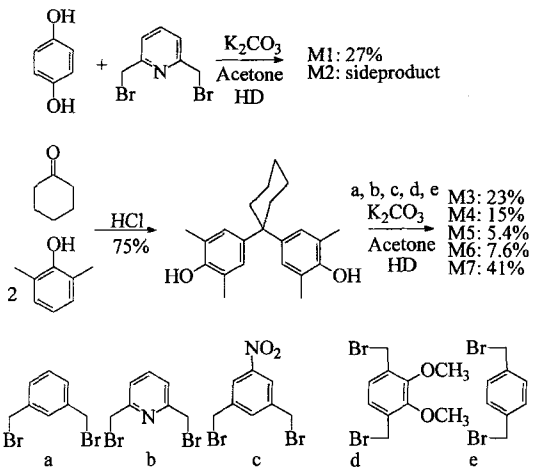

Figure 8. Synthesis of symmetrical macrocyclic host molecules.

acetone, and the resulting mixtures were refluxed for 48 h after the addition was complete. High-dilution syntheses are normally complete shortly after the reactants are added, but aromatic halomethyl compounds were found to be moderately unreactive towards phenolic hydroxyl groups under these conditions, and thus long periods of reflux were needed. The reactions were more readily followed by ^{1}H NMR spectroscopy, rather than by thin-layer chromatography, which proved to be unreliable.

Separation: High-dilution synthesis always gives a mixture of macrocyclic and polymeric compounds. Templating effects and preorganisation of the starting materials usually favor the formation of particular compounds, but in all cases, separation of the different products is needed. In this case, [2+2] macrocycles **M3**–**M7** could be separated selectively from the reaction mixtures by formation of inclusion complexes with dichloromethane in a diethyl ether solution. Under these conditions, the crystallisation of [2+2] macrocycles **M3**–**M7** was nearly quantitative. Figure 9 gives a schematic representation of how crystallisation of **M3**–**M7** is achieved through selective recognition of dichloromethane. NMR spectra showed no signs of impurities. [2+2] Macrocycles **M3**–**M7**, which are fairly rigid, give better separated signals in the ^{1}H NMR spectra (0.05–0.1 ppm more shielded), compared to their larger and more flexible analogues (**M43**–**M46**). In the case of symmetrical macrocyclic products, elementary analysis does not provide any definitive information on the purity of the compounds; in contrast, the NMR spectra show whether the [2+2] products are pure or whether they contain other macrocyclic compounds as impurities.

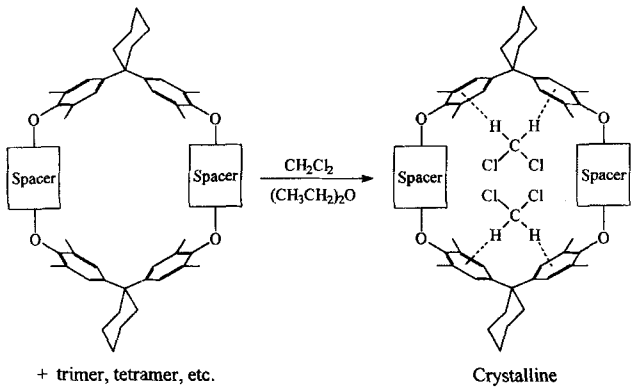

Figure 9. Spontaneous separation of [2+2] macrocycles **M3**–**M7** by selective recognition of dichloromethane.

A dissolved organic compound may crystallise when its solubility is changed, either physically by decreasing the temperature, or chemically by changing the polarity of the solvent. In the case of macrocyclic host molecules, purifications are usually performed chromatographically. Chromatographic methods, although often useful and versatile, are expensive and time-consuming when used in the separation of compounds that behave very similarly. Under particular conditions, it may be possible to quantitatively separate a few milligrams of various products by chromatographic methods, but for the separation of bulk amounts, several chromatographic separation cycles are usually needed.

In this paper, we have described the separation of macrocyclic compounds in organic solvents. This phenomenon has already been applied to separate cyclodextrins in aqueous solutions. If the macrocyclic compound has a cavity that is large enough to include one or several solvent molecules, it can form a supramolecular system. This complexation will not change the physical properties of the macrocyclic compounds. However, if the macrocycle contains a functionality that can selectively complex certain guests in the solvent mixture, crystallisation of the inclusion complex may occur, not because the physical properties of the macrocycle have changed, but because of the physical properties of the supermolecule as a whole. Thus, the purification of macrocyclic compounds from reaction mixtures by making use of host–guest interactions may be an alternative to chromatographic purification in certain cases.

Selective host–guest purification is strongly dependent on the functionalities in the macrocyclic hosts. There are no general rules for the separation of a given macrocycle by using particular solvents, but we are quite confident that, providing the cavity of the macrocyclic compound is designed for selective inclusion complexation, it should be possible to find the right conditions for the supermolecular separation of at least one of the compounds in almost every case. In our system, [2+2] macrocycles **M3**–**M7** could be selectively separated from the reaction mixture by crystallisation from dichloromethane/diethyl ether. Interactions with the 1,1-diphenylmethane functionalities allow dichloromethane molecules to be included selectively in the cavities of the [2+2] macrocycles **M3**–**M7** in diethyl ether solutions. The supermolecules thus formed then crystallise out spontaneously. In comparison, the cavities of macrocycles **M1** and **M2** are quite small, and no obvious functionalities are present for selective host–guest interactions. Both compounds crystallise from the mixture of dichloromethane and diethyl ether, but no selectivity is observed during crystallisation.

There have been many reports on the influence of supramolecular host–guest interactions between two or more mole-

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cules in crystallographic or NMR investigations, or in the synthesis of catenanes and rotaxanes. Here we have described how this physical phenomenon can be used as a tool for the selective separation of certain types of host molecules.

Conclusions

This paper describes a method for the purification of macrocyclic host molecules. Selective complexation of a guest molecule in a solvent mixture can change the physical properties of certain macrocyclic ligands through the formation of a supermolecule, which may then separate spontaneously from the reaction mixture. Thus, supramolecular separation can occur if the host macrocycle contains functional groups that allow selective guest complexation. We have shown that [2 + 2] macrocycles **M3**–**M7** containing 1,1-diphenylmethane moieties can be purified through crystallisation from dichloromethane/diethyl ether solvent mixtures, by slow evaporation of the solvent mixture.

Experimental Section

General: All chemicals and solvents were reagent grade and used as received. 2,6-Bis(bromomethyl)pyridine was prepared according to a published procedure.[16] Other bis(bromomethyl) compounds were prepared from the commercially available starting materials by bromination with *N*-bromosuccinimide.[17] ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM GSX270 FT-NMR spectrometer. All chemical shifts are relative to internal tetramethylsilane. Mass spectra were run on a VG AutoSpec HRMS or a Kratos Concept 1H (FAB-MS) spectrometer. Melting points (uncorrected) were measured with an Electrothermal IA 9200 apparatus. X-ray data were collected on an Enraf-Nonius CAD4 diffractometer.

Structure Determination: Colourless crystals of macrocycles **M1** and **M2** were obtained by slow concentration of a dichloromethane/diethyl ether solution mixture and were used for X-ray diffraction analysis. Additionally, an attempt to obtain a host–guest complex of **M2** with 1,3-dihydroxybenzene from a dichloromethane/methanol/hexane solvent mixture led to the formation of a crystal lattice of the inclusion complex of **M2** with water. Crystallisation of **M3**, **M4** and **M5** from a dichloromethane/diethyl ether (excess) solvent mixture and of **M6** and **M7** from a benzene solution also produced colourless crystals. Suitable crystals were selected and mounted on the diffractometer. The cell parameters were determined by the automatic centring of 25 reflections and refined by the least-squares method. Intensities were collected with graphite-monochromatised $Mo_{K\alpha}$ [$\lambda(Mo_{K\alpha}) = 0.7107$ Å] or $Cu_{K\alpha}$ [$\lambda(Cu_{K\alpha}) = 1.54178$ Å] radiation, using the $\omega/2\theta$ scan technique. The structures were solved by direct methods[18] and subjected to full-matrix refinement.[19] All non H-atoms were refined anisotropically. The hydrogen atoms were calculated in their idealised positions and refined as riding atoms.

Synthesis of 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane: HCl (35%, 30 mL) was added to a stirred solution of cyclohexanone (36.0 mmol) and 2,6-dimethylphenol (72.0 mmol), and the resulting mixture was refluxed for 48 h. After cooling with an ice bath, the reaction mixture was neutralised with 40% NaOH and extracted with $CHCl_3$ (4 × 50 mL). The organic phases were combined and dried with Na_2SO_4. Evaporation of the solvent, followed by sublimation of the unreacted 2,6-dimethylphenol, resulted in the isolation of 8.8 g of a reddish solid; Yield 75%. M.p. 188–190 °C; ^{1}H NMR ($CDCl_3$): δ = 1.50 (brs, 6H, CH_2), 2.18 (s, 16H, CH_3Ar, CH_2), 4.43 (s, 2H, O*H*), 6.85 (s, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 16.3, 23.1, 26.6, 37.5, 44.7, 122.4, 127.3, 140.7, 149.7; MS (EI): 324 [M^+].

General Procedure for Cyclisation: *para*-Hydroquinone or 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane and the desired bis(bromomethyl)-arene (a, b, c, d or e; Figure 8) were each dissolved in 200 mL of acetone, and the resulting solutions were added slowly and simultaneously over a period of 8 h to a refluxing mixture of K_2CO_3 in acetone (400 mL). The mixture was kept at reflux for an additional 48 h and then cooled to room temperature. The inorganic salts were filtered off, acetone was removed in vacuo, and the residue chromatographed through a short column on silica gel to separate the cyclic compounds from the polymers.

Macrocycles M1 and M2: 2,6-Bis(bromomethyl)pyridine (1.9 mmol), hydroquinone (1.9 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. The crude product was chromatographed several times on silica gel (diethyl ether) to yield 110 mg of the pure macrocycle **M1**; Yield 27%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): δ = 5.11 (s, 8H, CH_2), 6.59 (s, 8H, H_{Ar}), 7.14 (d, 4H, H_{Ar}), 7.38 (t, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$): δ = 71.9, 116.1, 121.7, 138.5, 152.6, 158.3; HRMS *m/z* (M^+, $C_{26}H_{22}N_2O_4$): calcd 426.1580, obsd 426.1578. The reaction gave **M2** as a by-product, but it was not possible to purify it completely. Single crystals of **M2** were obtained with water and dichloromethane, and their structures were determined by X-ray diffraction, but no spectroscopic data or physical properties of **M2** are available.

Macrocycle M3: 1,3-Bis(bromomethyl)benzene (1.5 mmol), 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane (1.5 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. Crystallisation from the dichloromethane/diethyl ether solvent mixture yielded 150 mg of **M3**; Yield 23%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): δ = 1.39 (brs, 12H, CH_2), 2.09 (s, 24H, CH_3), 2.17 (brs, 8H, CH_2), 4.81 (s, 8H, CH_2O), 6.62 (s, 8H, H_{Ar}), 7.24 (s, 2H, H_{Ar}), 7.37 (s, 6H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 17.7, 23.7, 27.1, 37.8, 45.8, 74.9, 128.2, 128.3, 128.5, 129.2, 130.7, 138.3, 144.6, 154.1; HRMS *m/z* (M^+, $C_{60}H_{68}O_4$): calcd 852.5118, obsd 852.5133.

Macrocycle M4: 2,6-Bis(bromomethyl)pyridine (1.5 mmol), 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane (1.5 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. Crystallisation from the dichloromethane/diethyl ether solvent mixture yielded 100 mg of **M4**; Yield 15%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): δ = 1.45 (brs, 12H, CH_2), 2.12 (s, 24H, CH_3), 2.16 (brs, 8H, CH_2), 4.88 (s, 8H, CH_2O), 6.79 (s, 8H, H_{Ar}), 7.56 (d, 4H, H_{Ar}), 7.80 (t, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 17.8, 23.7, 27.2, 37.6, 45.6, 76.5, 121.3, 128.1, 130.5, 138.0, 144.8, 155.1, 158.2; HRMS *m/z* (M^+, $C_{58}H_{66}N_2O_4$): calcd 854.5023, obsd 854.5023.

A FAB mass spectrum of the unpurified reaction mixture showed molecular peaks at 855.5 ([*M*+H] for the dimer **M4**) and for molecular masses for higher macrocyclic ethers (up to hexamer, Figure 10). It was possible to determine molecular peaks of 1282.7 ([*M*+H] for the trimer **M43**), 1709.9 ([*M*+H] for the tetramer **M44**), 2138.2 ([*M*+2H] for the pentamer **M45**) and 2565.5 ([*M*+H] for the hexamer **M46**) from the FAB mass spectra (see structures of compounds **M43**–**M46** in Figure 10). From the ^{1}H NMR spectrum it was not possible to distinguish between the signals of macrocycles **M43**, **M44**, **M45** and **M46**, but the simplicity of the NMR spectrum together with the FAB results proved that no catenanes were formed.

Macrocycle M5: 1,3-Bis(bromomethyl)-5-nitrobenzene (1.5 mmol), 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane (1.5 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. Crystallisation from a dichloromethane/diethyl ether solvent mixture yielded 38 mg of **M5**; Yield 5.4%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): δ = 1.55 (brs, 12H, CH_2), 2.25 (s, 24H, CH_3), 2.30 (brs, 8H, CH_2), 4.92 (s, 8H, CH_2O), 6.95 (s, 8H, H_{Ar}), 7.93 (s, 2H, H_{Ar}), 8.30 (s, 4H, H_{ar}); ^{13}C NMR ($CDCl_3$): δ = 17.4, 23.4, 26.8, 37.3, 45.4, 73.1, 121.9, 128.0, 130.2, 132.6, 140.8, 144.9, 148.7, 153.6; HRMS *m/z* (M^+, $C_{60}H_{66}N_2O_8$): calcd 942.4734, obsd 942.4752.

Macrocycle M6: 1,4-Bis(bromomethyl)benzene (1.5 mmol), 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane (1.5 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. Crystallisation from a dichloromethane/diethyl ether solvent mixture yielded 50 mg of **M6**; Yield 7.6%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): δ = 1.48 (brs, 12H, CH_2), 2.04 (s, 32H, CH_3, CH_2), 4.77 (s, 8H, CH_2O), 6.69 (s, 8H, H_{Ar}), 7.05 (s, 8H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 17.1, 23.2, 26.6, 37.3, 45.6, 73.4, 127.8, 128.8, 130.2, 136.9, 144.4, 152.1; HRMS *m/z* (M^+, $C_{60}H_{68}O_4$) calcd 852.5118, obsd 852.5133.

Macrocycle M7: 1,4-Bis(bromomethyl)-2,3-dimethoxybenzene (1.5 mmol), 1,1-bis(3,5-dimethyl-4-hydroxyphenyl)cyclohexane (1.5 mmol) and potassium carbonate (10 g) were used in the cyclisation reaction. Crystallisation

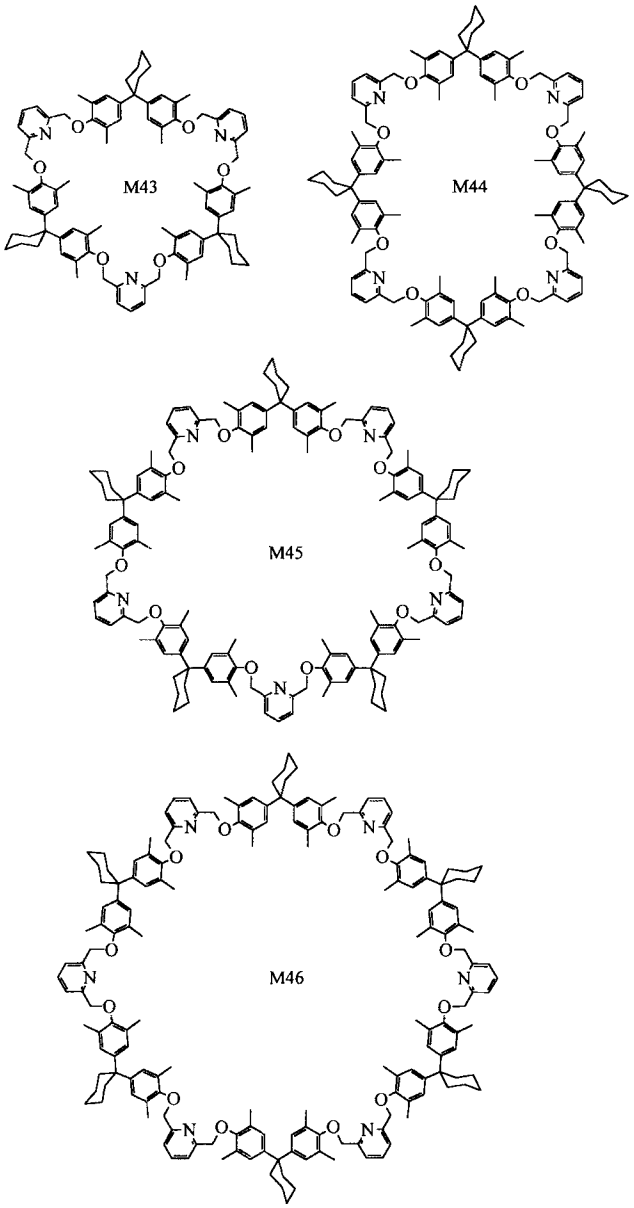

Figure 10. Larger macrocycles detected after cyclisation reaction.

from a dichloromethane/diethyl ether solvent mixture yielded 300 mg of **M7**; Yield 41%. M.p. > 250 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (brs, 12H, CH_2), 2.10 (s, 24H, CH_3), 2.17 (brs, 8H, CH_2), 3.70 (s, 12H, CH_3O), 4.89 (s, 8H, CH_2O), 6.76 (s, 12H, H_{ar}); ^{13}C NMR ($CDCl_3$): $\delta = 17.0$, 23.1, 26.5, 37.1, 45.3, 60.5, 68.3, 125.3, 127.6, 130.3, 131.8, 144.2, 151.2, 152.6; HRMS *m/z* (M^+, $C_{64}H_{76}O_8$): calcd 972.5540, obsd 972.5521.

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