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Homocalixarenes and Homocalixpyridines

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Abstract. A new type of host is introduced: *all*-homocalixarenes. Phane syntheses leading to molecules which may be termed, in the most general sense, homocalixarenes, are outlined in a brief overview. The design, synthesis, conformations and host properties of *all*-homocalixarenes and *all*-homocalixpyridines are described in detail.

Key words: Phane syntheses, *all*-homocalixarenes, *all*-homocalixpyridines, host tailoring, large functionalized cavities, host properties, liquid-liquid-extraction experiments, crystal structures.

1. Introduction

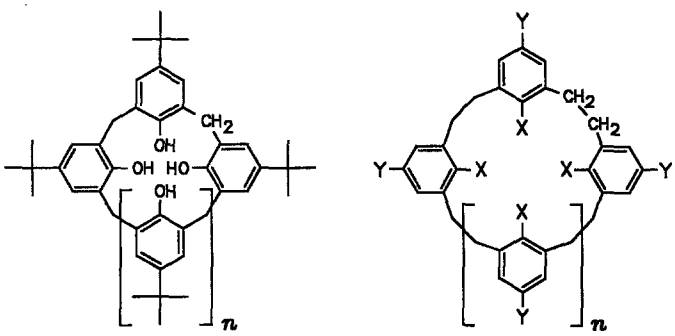
Molecular recognition is a fundamental aspect of biological processes and particular interest is focused on its understanding. One pathway to this understanding is the study of 'model' compounds, the products of 'supermolecular chemistry', wherein specific properties of biomolecules may be considered in isolation. The control of both functional groups and molecular stereochemistry in these synthetic molecules provides numerous insights into the relationship between structure and function, insights which are often obscured within the full complexity of the biological systems.

The calixarenes [1, 2] are a versatile group of 'host' molecules which have indeed been used to probe various aspects of enzyme functions [3]. Nonetheless, it is not to be expected that a single molecular structure could provide a basis for the mimicry of all enzymic behaviour, and thus new molecules with controllable architecture are valuable. This work describes such a group of molecules, closely related to the calixarenes obtained through the syntheses which combine aspects of cyclophane and host/guest chemistry. It defines the group of '*all*-homocalixarenes'.

2. Phane Chemistry as a Tool for Host Tailoring

The field of cyclophane chemistry encompasses the chemistry of a remarkable variety of molecules, so that it is of general importance to survey its current state of development [4]. Molecular stereochemistry has long been a fundamental issue, and it is the wide, known range of partial structures, fixed or conformationally

* This paper is dedicated to the commemorative issue on the 50th anniversary of calixarenes.



1 2

Fig. 1. Structural features of calixarenes (left side) versus homocalixarenes (right side).

flexible, that affords such a rich field for research into molecular design, synthesis, structural analysis, physical properties and, chemical reactions, all the way to supramolecular chemistry! Phanes are ideal model compounds in which benzene and other aromatic rings can be placed relative to one another in a tailor-made fashion. One can introduce into the rings of many cyclophanes substituents which act as ligands towards both cations and neutral molecules. One can achieve a particular arrangement of functional groups and thereby trigger their chemical interaction. The possibility of locating groups precisely in space allows cyclophane chemistry to be used to provide the essential units for specialised structures such as 'nests', hollow cavities, 'multi-floor structures', helices, macropolycycles and long hollow tubes, as well as major ligand systems like the calixarenes and, now, the *all*-homocalixarenes.

Whereas calixarenes contain a $[1_n]$metacyclophane skeleton, the *all*-homocalixarenes are $[2_n]$metacyclophanes in which an additional CH_2 group is present in all their bridges (Figure 1).

2.1. NOMENCLATURE

The close and obvious relationship between these new molecules and the calixarenes justifies the use of a closely related nomenclature. '*all*-Homocalix[n]arene' (*all*-HC) is used as a generic term for those calixarene analogues which contain symmetrically one additional CH_2 group in all their bridges. '*all*-Homocalix[n]pyridine' denotes the group of homocalixarenes with pyridines as the aromatic units, an example being 6,13,20,27-tetramethoxy-*all*-homocalix[4]pyridine (**3**). Whereas the prefix 'homo' indicates the enlargement of the cavity, the prefix '*all*' is intended to indicate that the aliphatic bridges in the macrocycle are enlarged symmetrically, so that it is not necessary to explicitly state the number of additional carbon atoms as in 'di-, tri- ... homocalixarene'

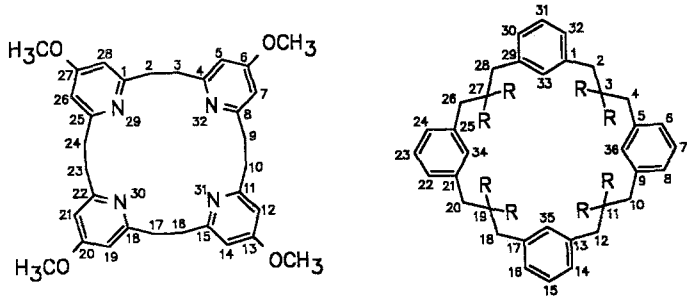


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Fig. 2. Structural features of an *all*-homocalix[4]pyridine (left side) and an *all*-bishomocalix[4]arene (right side).

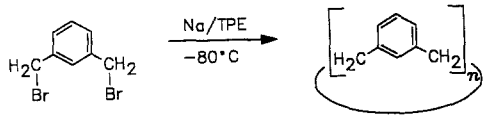
(e.g., **2**: Y = H, X = OH is 29,30,31,32-tetrahydroxy-*all*-homocalix[4]arene). With two additional CH_2 groups in all aliphatic bridges, the molecules are designated '*all*-bishomocalix[n]arenes' (e.g., **4** in Figure 2).

We have chosen the metacyclophane skeleton as a versatile and stable platform for functional units. A critical appraisal of the efficienty of the syntheses of cyclophanes incorporating more than two aromatic units is given below. The specific focus is upon those metacyclophanes which can be considered, in the broadest sense, *all*-homocalixarenes.

2.2. METACYCLOPHANES

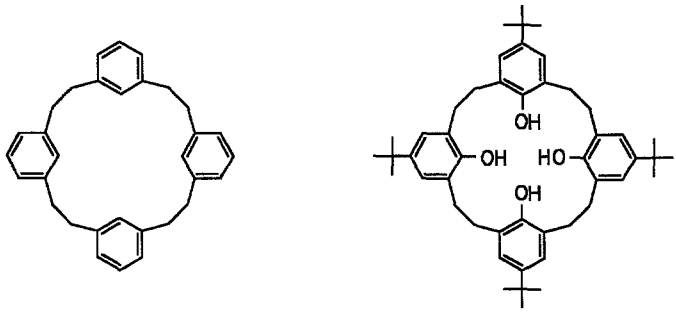
2.2.1. *Müller–Röscheisen Cyclisation*

The first [2.2]metacyclophane was obtained by Pellegrin using the Wurtz reaction [6]. Using a modified Wurtz reaction, Jenny *et al.* were able to obtain higher, 'oligomeric' $[2_n]$metacyclophanes from 1,3-bis(bromomethyl)benzene (**5**) [7], actually by employing Müller–Röscheisen conditions of sodium tetraphenylethene in THF at -80 °C [8]. The reaction mixture yields the full series of oligomeric $[2_n]$metacyclophanes up to the 50-membered $[2_{10}]$metacyclophane. Over a period of three years, all were isolated by various procedures. The first isolated cyclo-oligomer of this series, the first isolated *all*-homocalixarene, was the $[2_4]$metacyclophane (**6**), obtained in 1.7% yield by Burri and Jenny in 1966 [9]. Shortly thereafter they reported the isolation of the $[2_3]$metacyclophane (7.5%) and the other cyclo-oligomers up to the $[2_{10}]$metacyclophane (<1%) [10–13] except the $[2_7]$metacyclophane and the $[2_9]$metacyclophane, which were isolated two years later (<1%) [14].



5 $n = 2–10$

Also, using sodium tetraphenylethene in THF, Tashiro *et al.* prepared disubstituted [2.2]metacyclophanes in 1981 via intermolecular ring closure of the dimeric building block 1,2-bis[5-*tert*-butyl-3-(iodomethyl)-2-methoxyphenyl]-ethane [15]. As a side product of intramolecular reaction, they obtained a methoxy-substituted tetra-*tert*-butyl-[2_4]metacyclophane in 34% yield. Demethylation with BBr_3 gave **7**.



6 **7**

2.2.2. *Samarium (II) Diiodide Coupling*

Coupling of 1,3-bis(bromomethyl)benzenes in the presence of SmI_2 in THF gives cyclic and acyclic oligomers, the distribution depending upon the amount of SmI_2 used. Five equivalents of SmI_2 gave the unsubstituted [2_3]metacyclophane in 10.2% yield and the tetramer **4** in 7.5% yield but no higher oligomers were observed [16].

2.2.3. *Sulfone Extrusion Method*

In 1969, Vögtle [17] first outlined the sulfone route for the preparation of [2.2.0]metacyclophane as one of the rare metacyclophanes containing three aromatic units. In 1981, Vögtle *et al.* prepared the [2.2.2.2]biphenylophane **10** in 48% yield by sulfone pyrolysis at 600 °C/10^{-6} torr [18].

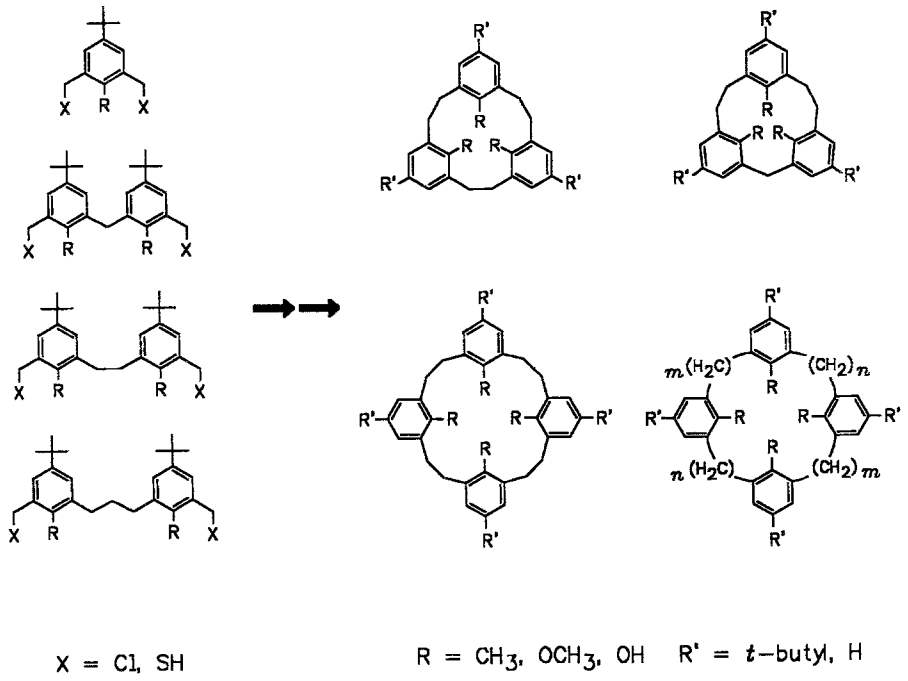
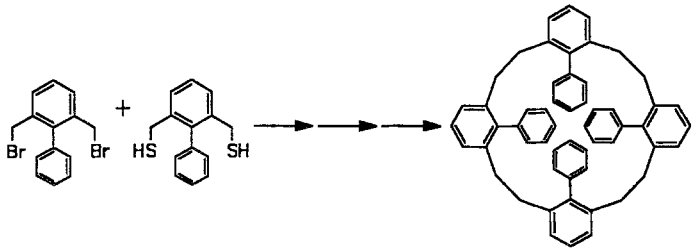


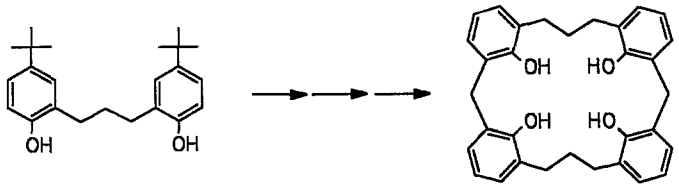
Fig. 3. Conventional sulphur method for synthesis of $[2_n]$- and $[m.n]$metacyclophanes.



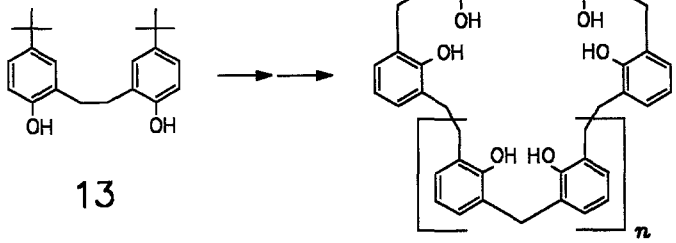
Whereas **7** isolated as a side product, in 1989 Tashiro *et al.* deliberately prepared trimeric and tetrameric metacyclophanes by the conventional sulfone method. Cyclisation of monomeric or dimeric thiol- and chloride-functionalised precursors linked by $(CH_2)_n$ bridges in various combinations, yielded, after ring contraction via sulfone pyrolysis, a multitude of $[2_n]$- and [m.n]-metacyclophanes as shown in Figure 3 [19–24].

2.2.4. *Condensation with Aldehydes*

The base-catalysed condensation of **11** with formaldehyde in *p*-xylene yields, in three steps, the tetrahydroxy[3.1.4.1]metacyclophane **12** [25]. Recently, Yamato *et al.* [26] reported the synthesis of hexa- and octa-hydroxy[2.1]$_n$metacyclophanes **14** and **15** from 1,2-bis(5-*tert*-butyl-2-hydroxy-phenyl)ethane **13** via the same method in 70–90% yield. Interestingly, no dimer was formed.



11 12



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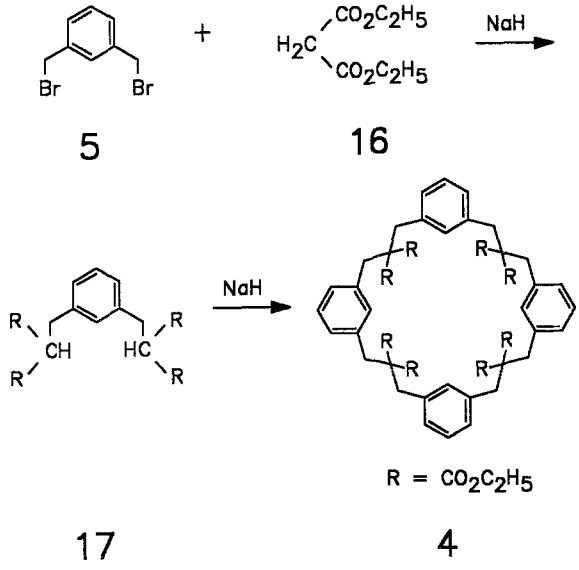
14: n = 1

15: n = 2

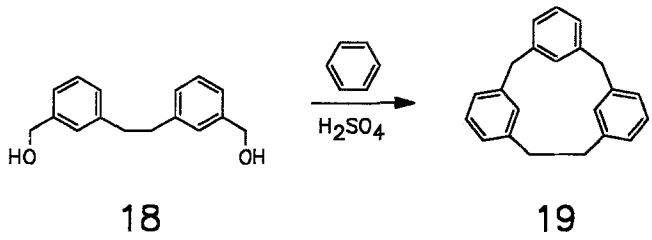
2.2.5. *Malonate Cyclisation*

In 1972, Vögtle *et al.* reported a synthesis for [3$_n$]metacyclophanes via condensation of 1,3-bis(bromomethyl)benzene **5** with malonate **16** [27].



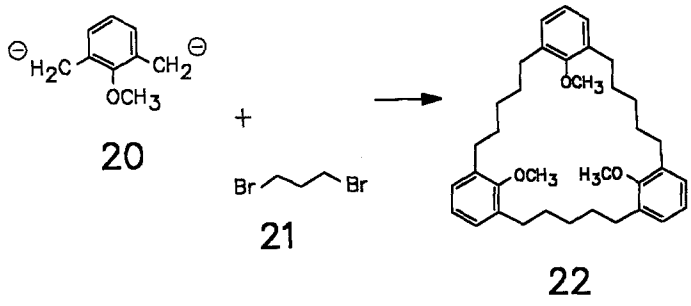
2.2.6. *Cycloalkylation of Benzene by Diols*

Addition of a benzene solution containing 3,3′-bis(hydroxymethyl)bibenzyl **18** to concentrated sulfuric acid yields the [2.1.1]metacyclophane **19** in 17% yield [28].

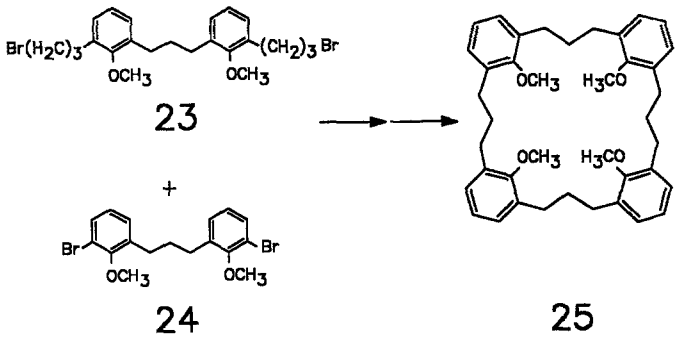


2.2.7. *Via Dianions*

A [5.5.5]metacyclophane **22** was obtained in 1% yield by reacting the dianion of 2,6-dimethylanisole **20** with the α,ω-dihalide **21** [29].

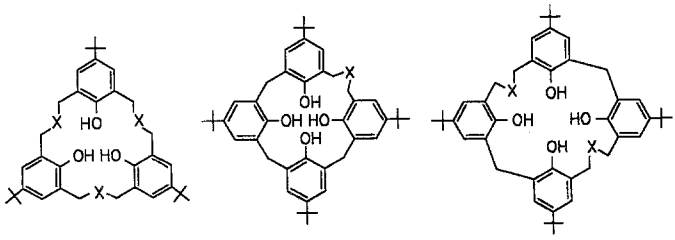


As an alternative to sulfone extrusion, Burns *et al.* [30] recently described a five-step synthesis via the dianion of **24** for the preparation of [3$_4$]metacyclophane **25** in 21% yield.



2.3. HETERAPHANES

As well as those thiaphanes mentioned in Section 2.2 as intermediates in [2$_n$]- and [m.n]phane syntheses, there are oxa- and azaphanes like **26**, **27** and **28**, which are named homooxa- and homoazacalixarenes because they were first obtained through the 'Petrolite' procedure of calixarene synthesis in 1962 [31, 32]. The compounds were first characterised in 1979, and in 1983 Gutsche [35] described detailed syntheses based on inter- or intra-annular thermally-induced dehydration of bis(hydroxymethyl)aromatic building blocks.



26 27 28

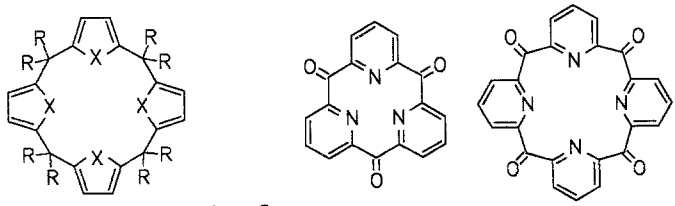
X = O, $NCH_2C_6H_5$

More recently, syntheses of oxacalixarene analogues (azacalixarenes) based on condensation between benzylamine and 2,6-bis(hydroxymethyl)-4-alkylphenol have been described [36].

2.4. HETEROPHANES

[2.2.2](2,5)Thiophenophane has been obtained as a by-product of the synthesis of [2.2](9,10)naphthaleno(2,5)thiophenophane by crossed Hofmann degradation of the corresponding quaternary ammonium hydroxides [37].

Whereas acid-catalysed condensations of furans [38, 40], thiophenes [41–44] or pyrroles [45, 46] provide heterocalixarenes **29** in one step, the introduction of pyridine rings is more difficult. Newkome *et al.* were successful in preparing the triketone **30** and the tetraketone **31** [47, 48].

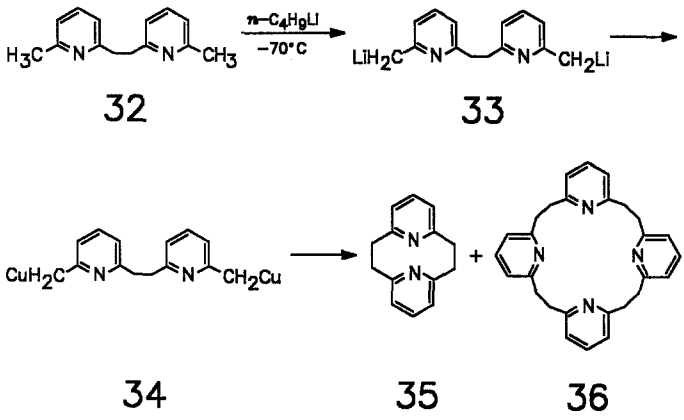


29 X = O, X = S, X = NH 30 31

R = H, CH_3, C_2H_5, C_6H_5

Pyridinophanes with ethano bridges have been synthesised by Jenny *et al.* via Müller–Röscheisen cyclisation of 3,5-bis(bromomethyl)pyridine [49, 50] and 2,6-bis(bromomethyl)pyridine [51, 52], leading to $[2_n](2,6)$pyridinophanes involving

up to six pyridine units. Also, the tetrameric cyclooligomer **36** can be derived from intermolecular reaction of the dimeric copper compound **34** [53].



3. From Phanes to *all*-Homocalixarenes and -calixpyridines

3.1. CONCEPT

In order to meet the objectives mentioned in the introduction, we have developed a versatile host architecture [54], which is expected to comply with the requirements for an effective host listed below:

- adjustable cavity size – for steric host/guest fit;
- conformational flexibility straight into time with preorganisation;
- various easily accessible binding sites providing high selectivity through structural modifications so as to control both the electronic fit to charged or neutral but acidic/basic guests and parameters such as charge, dipole moment, lipophilicity and H-bonding ability;
- good solubility in organic solvents, PVC membranes;
- stability in the reaction environment;
- anchoring groups for immobilising and fixing signal-giving units.

Knowledge gained through the study of calixarene systems should allow these new molecules to be used more effectively and efficiently to achieve even more demanding goals.

A near-planar ring skeleton, intended to enhance solubility relative to that of the calixarenes, should result from the introduction of an alternating arrangement of rigid aromatic and flexible aliphatic moieties. Consequently, this should have the result of avoiding the existence of rigid conformers perhaps unable to enclose

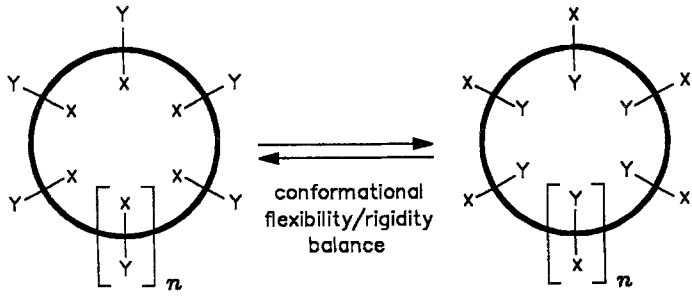


Fig. 4. Schematic carbocyclic *all*-homocalixarenes with variable ring size and functionalities X, Y inside and outside.

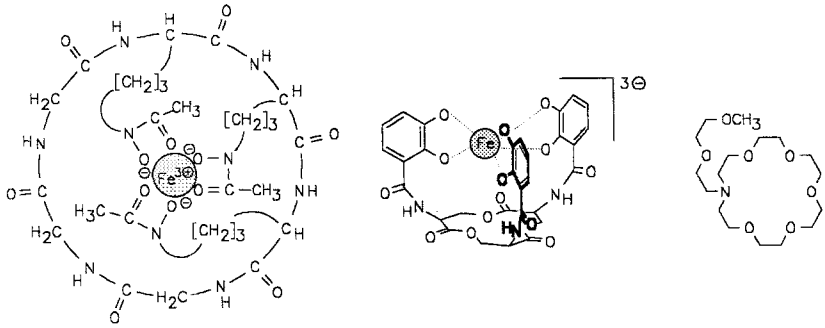


Fig. 5. Ferrichrome (left side) and enterobactin (middle) $Fe^{3\oplus}$ complexes as examples from nature for lariat type complexones (right side).

guests and of stable conformers as mixtures which would have to be separated and characterised. A chemically stable large ring skeleton of adjustable size can be built up and modified by the introduction of functional groups even under vigorous conditions. For tailoring, the host molecule can be endowed with binding sites both inside and outside the cavity (Figure 4).

Although cavity size can be controlled over a wide range by varying the number of aromatic units, ligand arms fixed inside the cavity can be used to assist guest binding by adjusting the steric and electronic host/guest fit, as in natural ionophores (cf. Figures 5, 6).

3.2. SYNTHESIS

Of the multitude of cyclisation methods (Sections 2.2–2.4) possible, the Müller–Röscheisen procedure has the versatility to make it the method of choice. As indicated previously, its application allowed both $[2_n]$metacyclophanes and $[2_n]$pyridinophanes to be obtained for the first time [55].

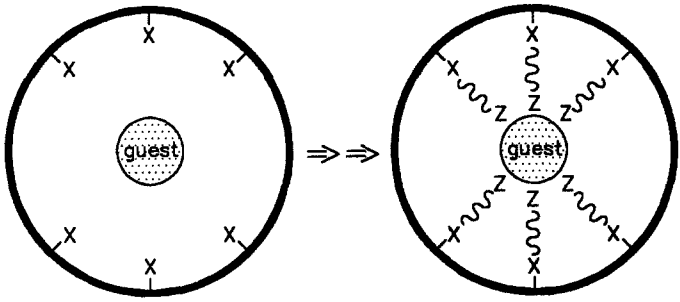


Fig. 6. *all*-Homocalixarenes allow us to adjust the steric and electronic host/guest complementarity.

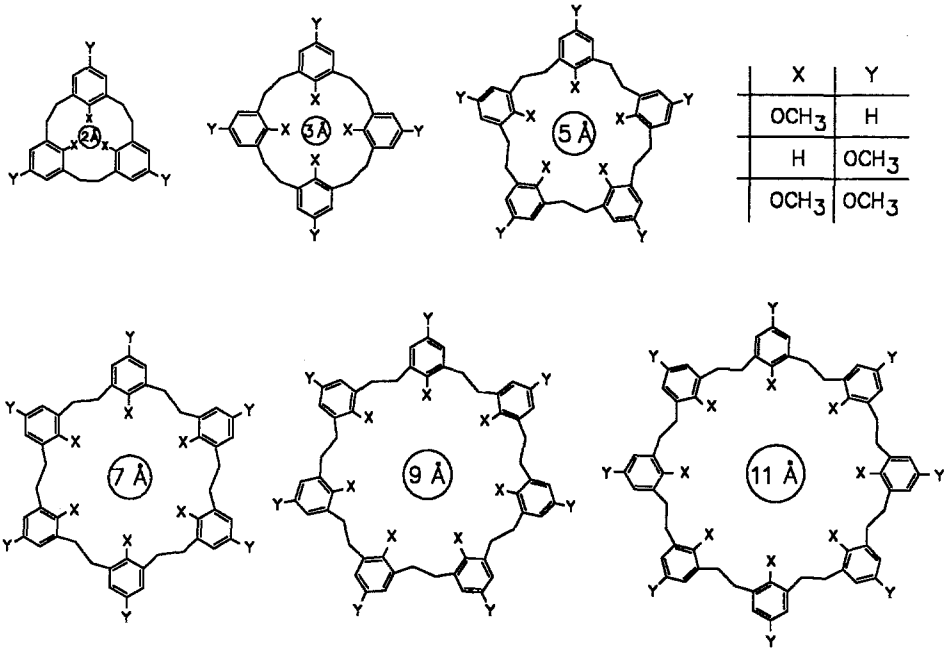


Fig. 7. A spectrum of eligible cavity sizes (longest O-O distances estimated for X = OCH_3, Y = H) feasible by Müller–Röscheisen cyclization.

In order to improve the yield of cyclooligomers, we modified the Müller-Röscheisen method; high dilution conditions can be achieved by using perfusers to add the dibromo compound very gradually. In the case of pyridines, the reaction was conducted at -90 °C to minimise by-product formation. A chromatographic procedure was developed to isolate the complete spectrum of cyclooligomers (Figure 7) obtained in the one-step synthesis.

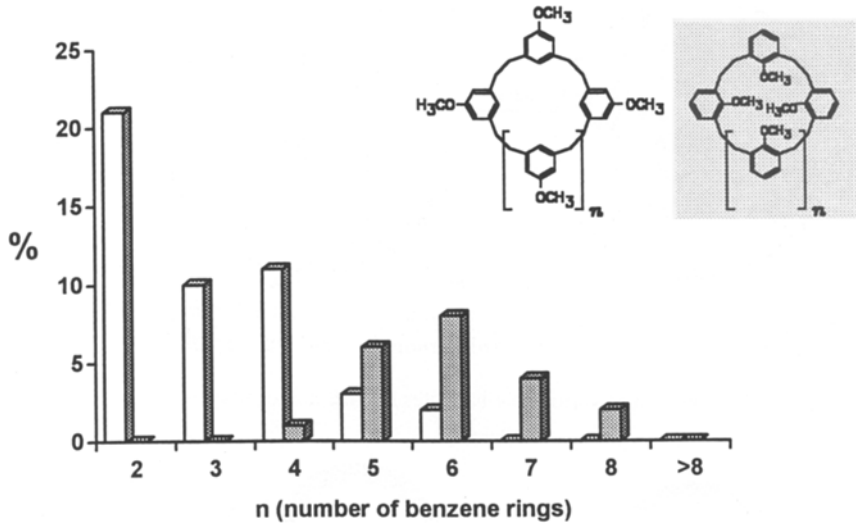


Fig. 8. Steering of oligomer formation in *all*-homocalixarenes synthesis by intraannular substituents.

3.2.1. *Methoxy-Substituted all-Homocalixarenes as Host Precursors*

From different bis(bromomethyl)benzenes, various methoxy-substituted *all*-homocalixarenes were easily obtained (Figure 7) [55]. The intention was to use them as starting materials for the introduction of additional appropriate heteroatoms as individual coordination sites for guest complexation. The control of cavity size was based upon variation in the *endo* and *exo*-annular substituents X and Y (Figure 8).

3.2.2. *Refunctionalisation*

The homocalixarenes can be prepared not only in a wide range of ring sizes (10–80 members cf.: Figure 7) but also with almost any variation in functional groups. Cleavage of the methoxy protective groups in the macrocycles leads to a series of oligophenols, where the hydroxyl groups provide one useful type of binding site. These groups can be alkylated to provide hosts of high denticity with ligand arms such as those of oxapropionic acid, esters, amides and thioamides (Figure 9).

Ether cleavage with BBr_3 proceeds in 67–99% yield [56]. The oligophenols exhibit greatly differing solubilities, e.g., pentamer **44** and octamer **43** (Figure 18) show high solubility in di- or trichloromethane, while the hexamer is only soluble in DMSO and the heptamer in acetone. Refunctionalisation to oxapropionic methyl ester derivatives by reaction with methyl bromoacetate proceeds in 68–87% yields for the exoannular macrocycles and in 63% yield in the case of the endoannular

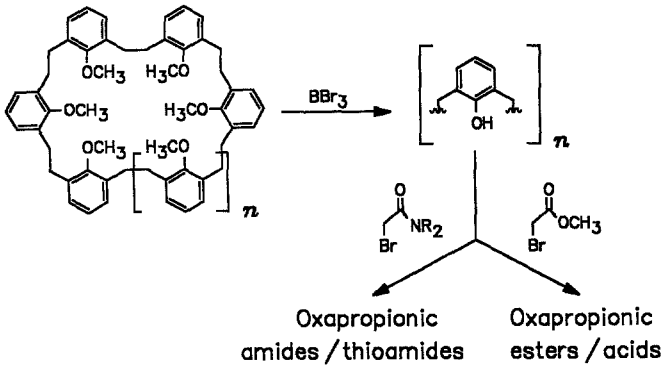


Fig. 9. Introduction of various binding sites into *all*-homocalixarenes.

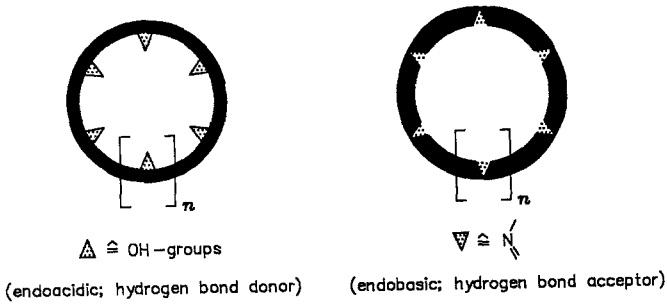


Fig. 10. Schematic diagram of endoreceptors fitted with convergent acidic or basic functional groups/donor sites.

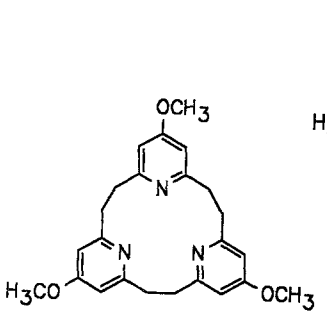
hexaphenol. The exoannular esters can be converted to the acids in 92–96% yields [56]. The hexaethylamide **42** was obtained in 80% yield [57].

3.2.3. *all-Homocalixpyridines*

In contrast to calixarenes, *all*-homocalixarenes may contain either endoacidic or endobasic cavities (Figure 10), because cyclisation of pyridine units is possible, too. The guest-binding strength of pyridine-containing hosts is readily controlled by the addition of OR groups at the 4-position of the pyridine rings.

The distribution of products in the case of the cyclisation of 2,6-bis(bromomethyl)-4-methoxypyridine depends mainly on dilution conditions and the temperature. At temperatures of about -100 to -90 °C, formation of open-chain products is decreased. Use of high-dilution conditions leads to odd-numbered main products like the trimer **37** (12%) and pentamer **38** (2%) [58]. Increase of concentration produces a broader spectrum of cyclooligomers. Although even-numbered conventional calixarenes are readily obtained, improvements in the synthetic yields for odd-numbered calixarenes have been slowly achieved [59, 60].

Recently, Gutsche *et al.* did report a one-step synthesis giving a quite acceptable yield for *p-tert*-butylcalix[5]arene [61].



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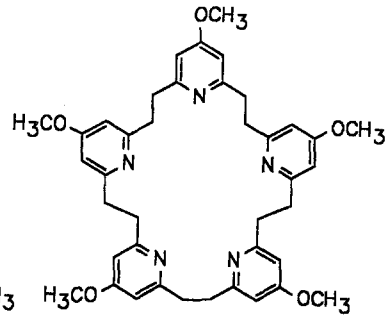

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3.3. PROPERTIES

3.3.1. *Melting Points*

In contrast to calixarenes, which generally melt well above 250 °C, *all*-homocalixarenes (Figure 7) melt below 250 °C and show a characteristic melting point pattern (Figure 11).

- odd-numbered cyclooligomers melt more easily than adjacent even-numbered ones;
- melting points of even-numbered cyclooligomers decrease with increase in ring size;
- there is a minimum for the heptamer explained by its conformational characteristics.

Jenny, among others, concluded that the compounds with an odd number of rings are not completely strain-free [14], a conclusion that is consistent with the yields.

3.3.2. *NMR Spectra*

The aliphatic protons, which appear as an AA′BB′ system in [2.2]metacyclophanes, become a singlet in higher oligomers of homocalixarenes and -calixpyridines (δ = 2.75–2.95). This suggests that they are highly mobile. ^{1}H-NMR singlets are observed at δ 2.78 (ethano protons) and δ 3.60 (methylene protons) even in [2.1.1]metacyclophane [62]. The high-field shift of inner protons in [2.2]metacyclophanes decreases regularly with an increase in ring size (δ = 4.08–6.60). In

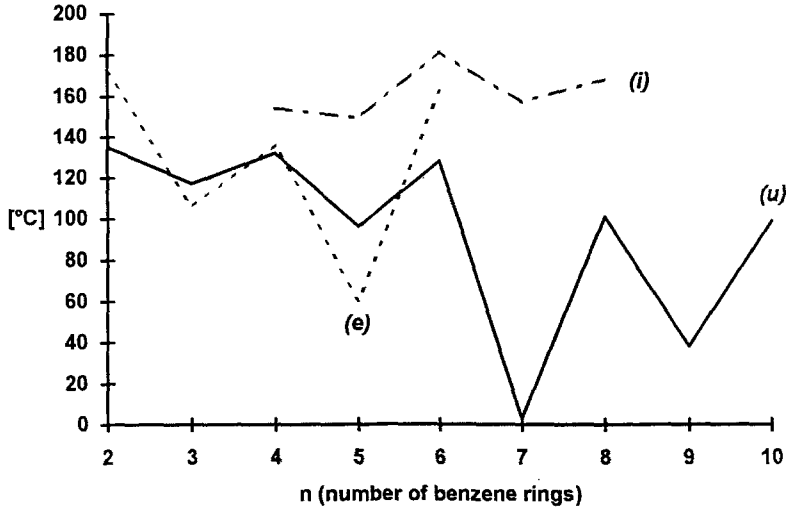


Fig. 11. Melting points of *all*-homocalixarenes (**u**: unsubstituted, **i**: with intraanular OCH_3 groups, **e**: with extraanular OCH_3 groups) in dependence of the number of benzene units.

methoxy-substituted homocalixarenes, the intra-annular methyl proton resonances are also shifted to higher field (trimer: 3.46; tetramer: 3.12).

3.4. CONFORMATIONS

3.4.1. *Flexibility/Rigidity Balance*

Calixarenes have an inherent rigidity which limits the range over which they can be shaped to a particular host. For this reason, attention has gradually focused on homocalixarenes. Shinkai *et al.*, for example, have reported the ion binding selectivity of hexahomotrioxacalix[3]arene [63, 64]. On the one hand, the multitude of calixarene conformations has advantages regarding preorganisation and selectivity (additional shapes for molecular recognition), but on the other hand their separation causes problems. Due to the expanded aliphatic bridges in *all*-homocalixarenes, the host skeleton is flexible and undergoes a fast ring flip process, so that conformational isomerism is markedly simplified (cf. Figure 4). The benefit of this simplification has been demonstrated by Shinkai *et al.* in the case of a hexahomotrioxacalix[3]arene containing ester groups as ionophores, where only two conformers, cone and partial cone, are detected and the molecule shows selectivity towards Na^+. The influence of bulky groups inside the cavity (cf. **10**) of *all*-homocalix[4]arenes on their conformations has been studied by Tashiro *et al.* [65].

3.4.1.1. *Capped all-Homocalixarenes* Although some level of conformational flexibility is desirable, especially for ligands to be used for guest transport where the

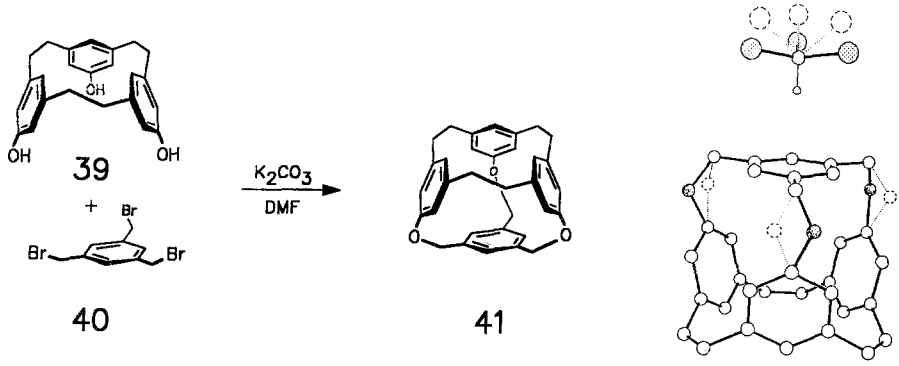


Fig. 12. Preliminary crystal structure of **41**.

kinetics of complexation-decomplexation should be fast, it is possible to envisage situations where greater rigidity of an *all*-homocalixarene could be desirable. One way to achieve this is to form a 'cap' involving ether linkages to a benzene ring. In fact, the capped *all*-homocalixarene **41** can be obtained by reaction under high dilution conditions of the triphenol **39** with the tribromo compound **40** [66]. Preliminary results of an X-ray structural analysis are shown in Figure 12. A trichloromethane molecule is oriented over one of the benzene rings at a distance of 338 pm in the crystal.

3.4.2. *Crystallographic Studies*

X-ray structure analyses are not available for unsubstituted $[2_n]$metacyclophanes and $[2_n]$pyridinophanes. Only NMR data are available as an index of conformational characteristics. For *all*-homocalixarenes and *all*-homoalixpyridines of various ring sizes, however, it has been possible to obtain single crystals suitable for crystallographic studies. In the trimeric exoannular *all*-homocalixarene and -calixpyridine, the aromatic rings do not lie in a single plane (Figure 13). Two methoxy groups are oriented in the same direction, with the third one opposed ('partial cone' conformation). The distances of the nitrogen atoms projecting into the 15-membered ring of **37** are: 408.4 pm (N8,...N16), 356.1 pm (N8...N24) and 395.3 pm (N16...N24).

With increasing ring size, *all*-homocalixarenes become flatter. Methoxy groups of the tetramer (Figure 13) are directed outwards. Facing benzene rings are almost parallel, as is also found in the methyl tetra-ester. In the endo- and exoannular methoxy-substituted *all*-homocalix[5]arene, the five benzene rings are situated in different planes (Figure 14). All endoannular substituents are oriented in the same direction but opposite to the exoannular methoxy groups. In contrast, the pentameric, methoxy-substituted *all*-homocalixpyridine **38** is nearly planar. Five water molecules and one trichloromethane molecule are included inside the cavity. Four of the water molecules form hydrogen bonds with two nitrogen atoms

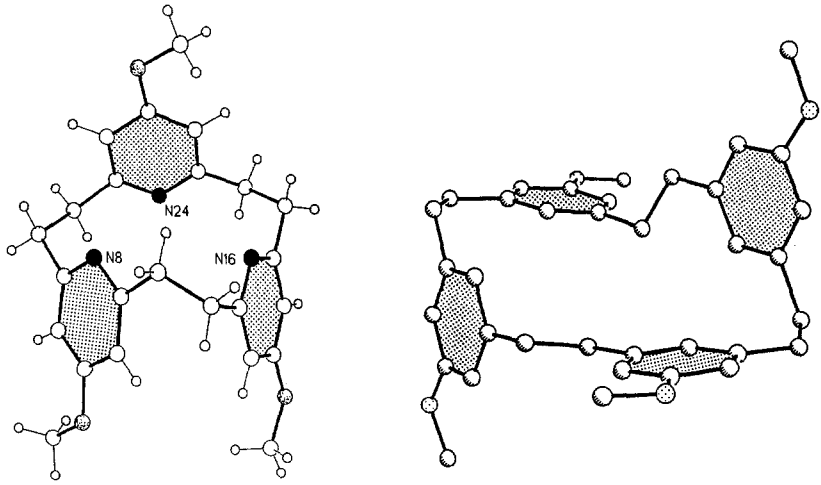


Fig. 13. Crystal structures of **37** (left side), and the *all*-homocalix[4]arene substituted with OCH_3 groups (right side).

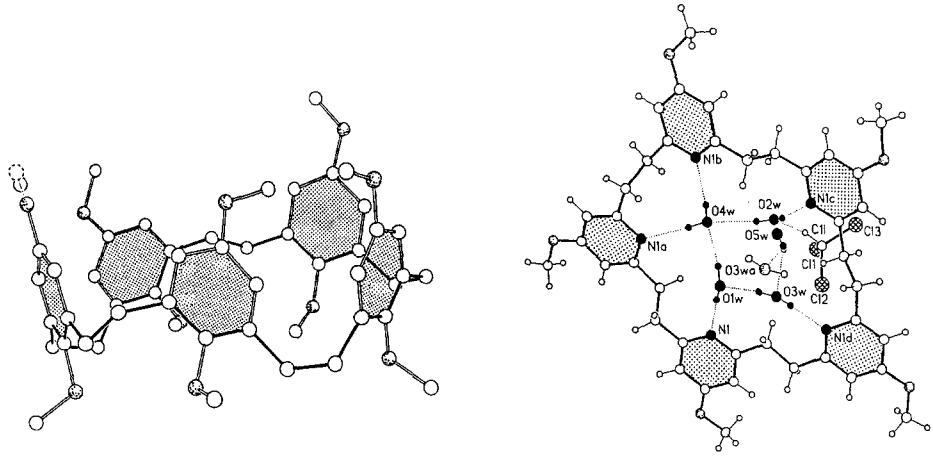


Fig. 14. Crystal structure of the intra- and extraannular methoxy substituted *all*-homocalix[5]arene (left side) compared to **38** (right side).

(N1A...O4w; 290.8 pm; N1B...O4w: 285.2 pm). Other N...O distances range from 284.3 pm (N1...O1w) to 306.7 pm (N1D...O3w). The distance N1A...N1D, 856 pm, is twice as long as the largest distance in trimer **37**.

The near planarity of the macrocyclic ring skeleton, which is not possible in the calixarene series, is also demonstrated by the example of a cyclohexamer, which X-ray structural analysis reveals its acts as a host towards cyclohexane. An endoannularly substituted hexaester, however, shows a very different 'stepped'

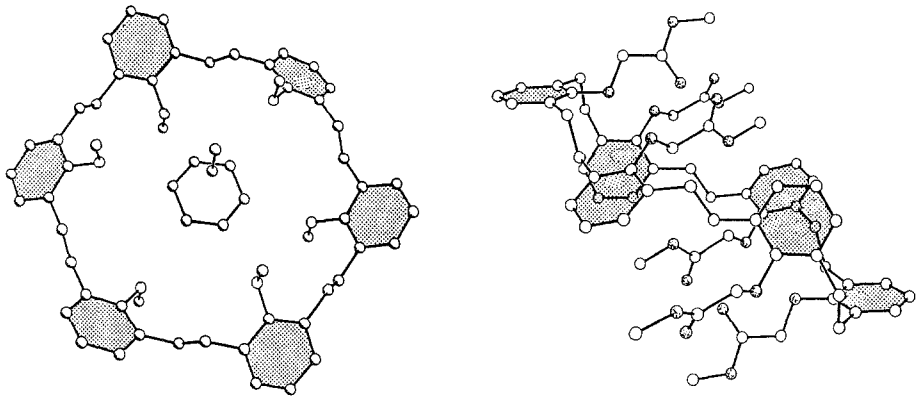


Fig. 15. Crystal structures of a near to planar *all*-homocalix[6]arene and the stepped ester derivative.

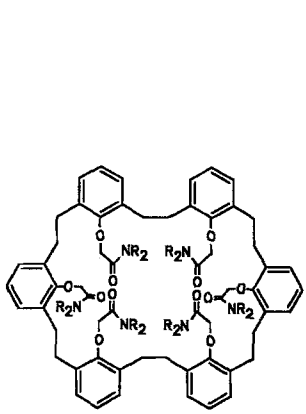
structure in which the benzene rings lie in four different planes and only four of the ester groups project in to the cavity.

In the hexaamide **42**, a three-dimensional cavity is formed in which each benzene ring can be considered to be flanked by two similarly-oriented benzene rings. Presumably because of steric hindrance, the amido groups do not project into the cavity but are bent out of the macrocycle, indicating that the ring is quite flexible. All carbonyl groups of the amido units point in the same direction. The orientations of the amido groups relative to the macroring mean plane can be described as: above, below, within, below, above, within. The homocalixarene molecules are connected to embedded water molecules by hydrogen bonds, forming long chains within the crystal.

Hitherto, no X-ray structural analysis of any heptameric *all*-homocalixarene has been obtained. The highest cyclooligomer for which crystallographic information is now available is the octamer **43**. All hydroxy groups are oriented inwards (Figure 17). Each *all*-homocalixarene molecule encapsulates one ethanol and one cyclohexane molecule. Four of the hydroxyl groups form hydrogen bonds to a disordered ethanol molecule. In the case of the *all*-homocalixpyridines, it is remarkable that all the even-numbered oligomers crystallise as needles unsuitable for X-ray crystallography.

3.5. HOST PROPERTIES

Whereas the unsubstituted parent compounds prepared by Jenny *et al.* (Section 2.2.1) were not considered likely to be able to act as ligands or hosts, some indications of the capacity of *all*-homocalixarenes and -calixpyridines to bind to guests are given by the results of X-ray structure analyses. The cluster type inclusion of water by the pentameric pyridine macrocycle **38** via hydrogen bonds seems



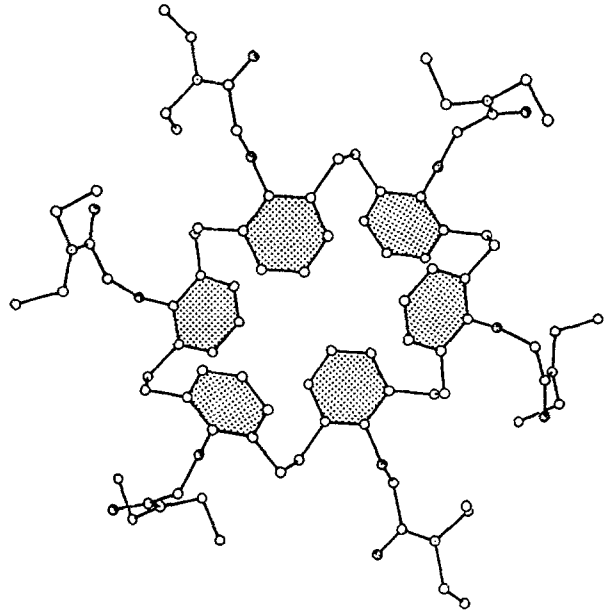


Fig. 16. Crystal structure of **42**.

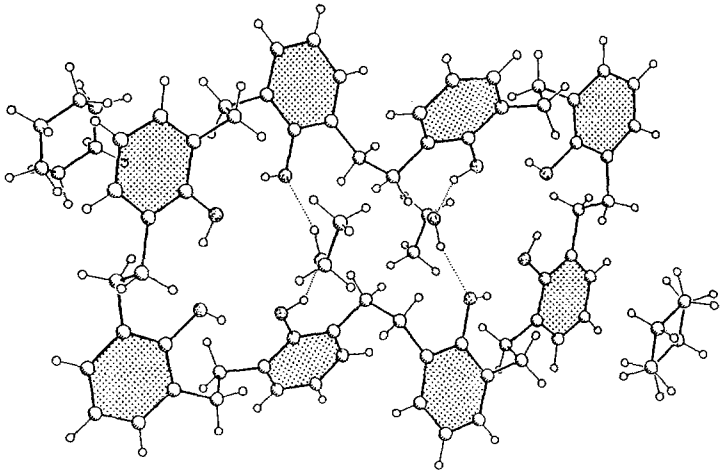


Fig. 17. Crystal structure of **43**.

to be rare and may be an exceptional case. Oligophenol **43** displays guest binding towards ethanol and cyclohexane. Host sensitivities/selectivities and liquid-liquid partition experiments [67–69] have been investigated with regard to the use of

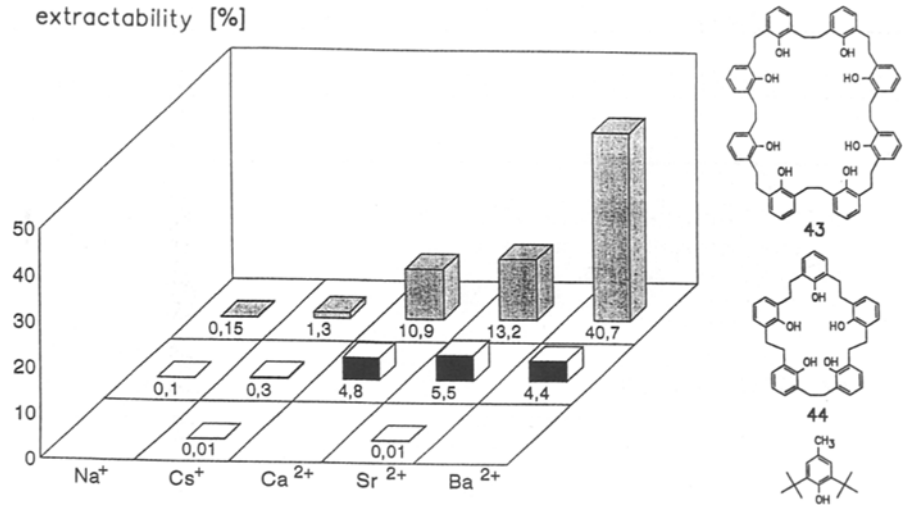


Fig. 18. Extraction properties of **43** and **44**. $[M(NO_3)_n] = 1 \times 10^{-4}$ M; $[NaNO_3] = 0.1$ M; [NaOH] = 0.1 M; [ligand] = 5×10^{-3} in trichloromethane.

the hosts in ion-selective electrodes and transport processes [70–72]. The most relevant results are:

- Pentahydroxy-*all*-homocalix[5]arene **44** discriminates strongly in favour of the alkaline earth metal ions Ca^{2+}, Sr^{2+} and Ba^{2+} over the alkali metal ions, even when the latter are present in as much as a 1000-fold excess [56] (Figure 18).
- Extractibility improves at high pH due to the ionisation of the hydroxyl groups.
- Octaphenol **43** is also selective towards the alkaline earths and more efficient in extraction due to its greater number of hydroxyl groups.
- From calcium, strontium and barium, **43** extracts barium selectively as a 1 : 1 complex.
- Complex formation constants of selected hosts have been measured in water [74] (Figure 19). Some values are extremely high, even in comparison with those of crown ethers.

To favour both selectivity and extractability, amido groups were introduced, eliminating the dependence on hydroxyl group ionisation. With this macrocycle, Ba^{2+} is extracted with a pronounced peak selectivity in contrast to other singly and doubly charged cations [57] (Figure 20). Host properties were examined in different lipophilic phases. Higher extractabilities were obtained in toluene than

	Cation:	$Li^{\oplus}$	$Na^{\oplus}$	$K^{\oplus}$	$Sr^{2\oplus}$	$Ba^{2\oplus}$
42	Log K:	2.03	1.66	1.97	2.70	2.81
44		1.96	1.38	1.07	2.47	

Fig. 19. Complex formation constants of some *all*-homocalixarenes in water, determined UV-spectroscopically as an increase of solubility of the host in water as a function of rising $M^{n+} + Cl_n^-$-concentrations.

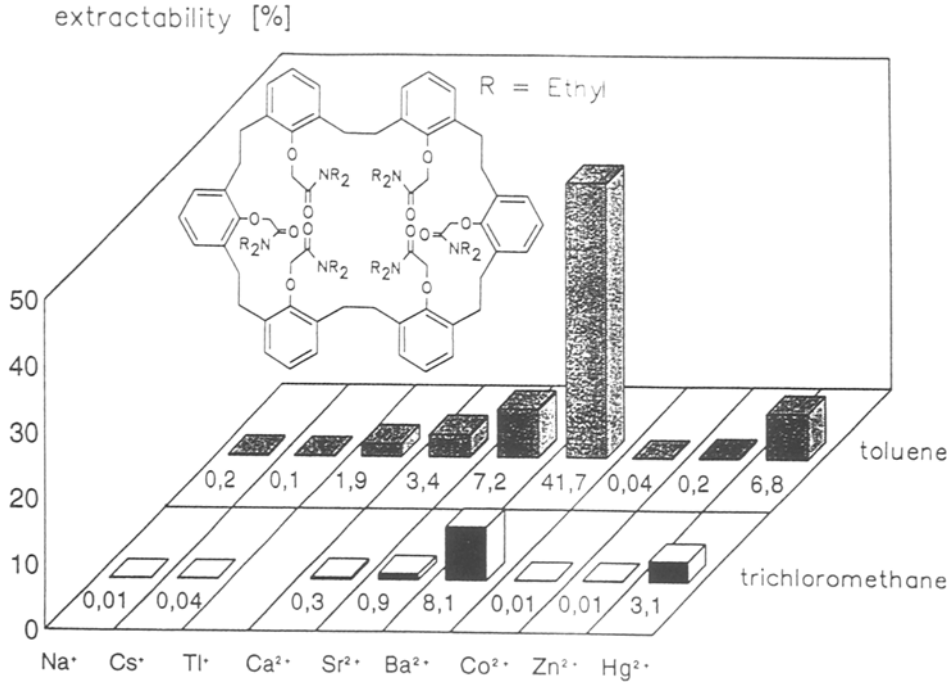


Fig. 20. Extractability of metal ions with *all*-homocalixarene **42**. $[M(NO_3)_n] = 1 \times 10^{-4}$ M; [picric acid] = 5×10^{-3} M; [ligand] = 1×10^{-3} in trichloromethane or toluene.

in trichloromethane because the amido oxygen is blocked as a binding site in the latter solvent, as revealed by infra-red spectroscopy.

It is well known from calixarene chemistry that the introduction of sulfur as a binding site shifts the selectivity from the alkali and alkaline earth metal ions towards the transition metal ions [75]. Recent results have provided evidence of selectivity towards Pd(II) and Hg(II) for a thiomorpholine-substituted hexaamido *all*-homocalixarene.

all-Homocalixpyridines have also been investigated in regard to their host properties. With pyridine nitrogen atoms as preorganised binding sites [76], *all*-homocalixpyridines show an appreciable selectivity towards transition metals, in particular Ag(I), Hg(II), Cu(II) and Pd(II), dependent upon cavity size.

4. Conclusions

A synthetic advance associated with the synthesis of *all*-homocalixarenes is that almost any binding site or functional group can be readily incorporated. These multiple possibilities for structural modification enable the host structure to be optimised for metal cations, anions, and both neutral and charged organic guests. Many applications as analytical sensors can then be envisaged.

Particular prospects are to optimise *all*-homocalixarenes towards environmentally relevant cations with, for example, the objective of removing radioactive and toxic metals from drinking water, and to design new hosts for medical applications such as magnetic resonance imaging based on gadolinium complexes.

Mass spectrometry has revealed [77] that cyclooligomers containing up to 21 aromatic units (i.e., a 105-membered ring host or 'gigantocycle' [78]) can be present in *all*-homocalixarene reaction mixtures. These are possible receptor molecules for larger biologically relevant molecules. Endowed with coordination sites like side arms containing hydrogen-bonding units, sugards, amino acids, peptides and nucleotides might well then be guests. The incorporation of homocalixarenes into nanoscale structures may well be possible by reactions between oligomers endowed with complementary binding sites.

To produce enlarged *all*-homocalixarenes soluble in water and exhibiting very high affinity constants, we have in mind the concept of *all*-bishomocalixarenes in which the aliphatic bridge is functionalised with carboxy substituents.

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