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Inherently Chiral Calixarenes *

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Abstract. Due to the nonplanarity of the basic 1_n-metacyclophane system, calixarenes and resorcarenes can be transformed into molecules with inherent chirality. Various attempts to achieve this goal are reviewed. Special emphasis is given to derivatives with C_n-symmetry, including derivatives of spherand calixarenes and other calixarene-like macrocycles.

Key words: Inherent chirality, asymmetric and dissymmetric calixarenes, resorcarenes.

1. Introduction

One of the main reasons for the still increasing interest in calixarenes is their ability to act as host molecules, which is even more pronounced in suitable derivatives that are readily available using calixarenes as starting materials. One of the main features of naturally occurring host molecules is their capacity for enantioselective recognition. Various attempts have therefore been made to obtain chiral host molecules based on calixarenes.

As with any molecule, a calixarene may be converted into chiral derivatives simply by attaching chiral substituents. In principle this can be done at the 'lower rim' (at the phenolic oxygens) or at the 'upper rim' (*p*-positions). Thus, compounds **1** and **2** were obtained by etherification of the corresponding calixarenes with 2-methylbutyl bromide or by Friedel–Crafts acylation with 2-methylbutanoyl chloride [1]. Aminomethylation with chiral amines like proline (**3**) may be mentioned as an example in the resorcarene series [2].

If one uses enantiomerically pure reagents derivatives are obtained in this way directly as pure enantiomers, provided the derivatization reaction proceeds without racemization. Larger quantities thus become available in a quite straightforward way, which is advantageous in comparison to the compounds discussed below.

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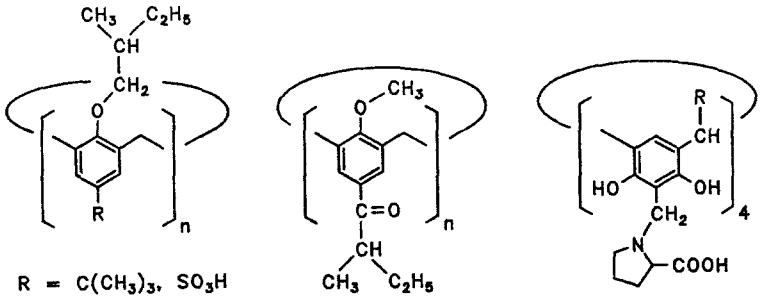
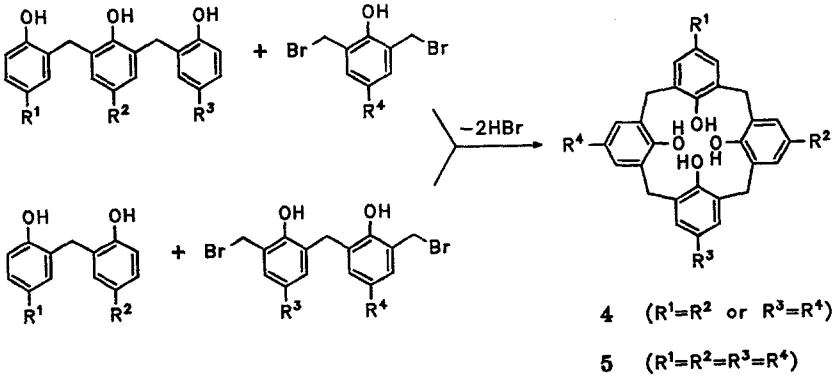


1 2 3

The chirality of compounds like **1–3** is entirely based on the chirality of the derivatizing reagents. However, due to their nonplanar shape, calixarenes offer numerous additional possibilities for producing chiral host molecules, which are not based on a chiral subunit but on the absence of a plane of symmetry or an inversion center in the molecule as a whole. In other words, opening of the macrocyclic structure would lead to an achiral linear molecule. Below we attempt to present a systematic overview of such 'inherently chiral' calixarenes.

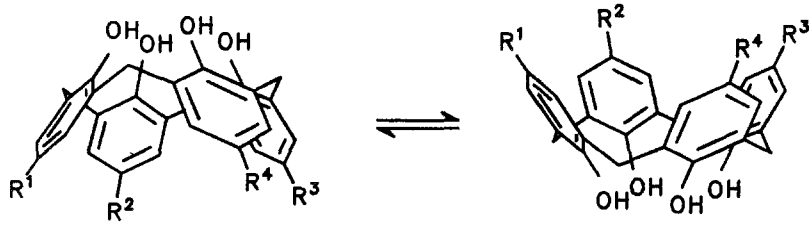
2. Asymmetric Calix[4]arenes with Different Phenolic Units

Early attempts in our group were directed at the preparation of calix[4]arenes with three (order AABC) or four different *p*-substituted phenolic units [3]. Molecules of these types [4] can be obtained in a rational way [3, 5] by fragment condensation of suitable trimers with bisbromomethylated phenols (3+1) or suitable dimers with bisbromomethylated dimers (2+2) [6].



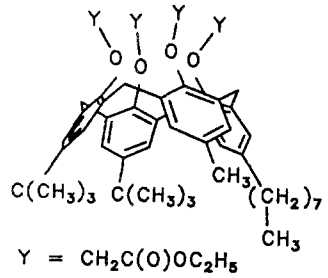
(1)

Various examples with residues such as Me, *t*-Bu, *n*-alkyl, cyclohexyl, phenyl, COOR, CH_2COOR and Cl have been synthesized in this way with yields up to 25–35% in the final cyclization step [3, 5, 7].



(2)

To obtain stable enantiomers, the well-known ring inversion of calix[4]arenes, which is in this case synonymous with racemization, must be made impossible. This can be done, for instance, by the introduction of sufficiently large residues on the phenolic oxygen atoms. Due to the asymmetry of such a calixarene complete conversion of all OH groups to a *cone*-derivative must be achieved in a clean reaction [8]. This conversion, which is standard for many symmetrically substituted calix[4]arenes, caused some problems with compounds like **4** and **5**, probably due to their asymmetry [5]. Thus, the tetraester derivative **6**, fixed in the *cone* conformation, obviously assumes a rather distorted shape. This follows from its ^{1}H-NMR spectrum showing, for instance, two singlets for *t*-butyl groups separated by 0.29 ppm, a difference which completely disappears in its Na^+ complex. Similar distortions may be present already in partially *O*-alkylated intermediates, favoring the formation of conformations different from *cone* in the final tetraether.



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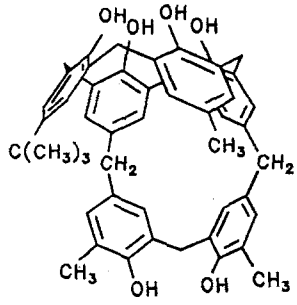
The ring inversion (Equation 2) may also be suppressed by suitable bridges between *p*-positions. An example is given by the annelated calix[4]arene **7** which is asymmetric due to the difference of the residues (Me, *t*-Bu) in the *p*-positions [9]. The existence of stable enantiomers was shown here by splitting of ^{1}H-NMR signals in the presence of Pirkle's reagent. A single crystal X-ray analysis suggests a *cone*-conformation for both calix[4]arene substructures, as indicated in the formula. In solution both calix[4]arene parts may be more or less flexible, undergoing the conformational changes *cone* $\rightleftharpoons$ *partial cone* $\rightleftharpoons$ *1,2-alternate*, but the molecular skeleton does not allow their conversion into the opposite *cone*-conformations.



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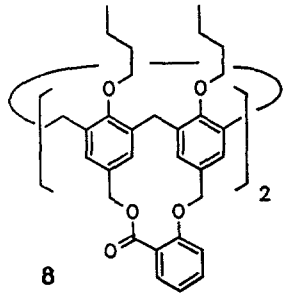
Directional bridges between adjacent *p*-positions represent another possibility for introducing molecular asymmetry or dissymmetry. As a recent example, the macrocyclic ether derivative **8** should be mentioned in this connection [10]. This is obtained from the tetrachloromethylated calix[4]arene-tetrapropylether (already fixed in the *cone* conformation) with salicylic acid. Its two salicylic acid residues cause it to have C_2 symmetry.



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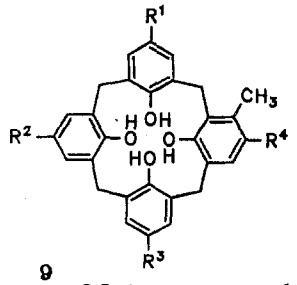
3. Calix[4]arenes with a Single *m*-Substituted Phenolic Unit

Asymmetric calix[4]arenes also result from the incorporation of a single *meta*-substituted phenolic unit (**9**), an idea first realized by Vicens *et al.* [11] and subsequently picked up by Shinkai *et al.* [12]. Again, these compounds have been synthesized by '3+1' fragment condensation.



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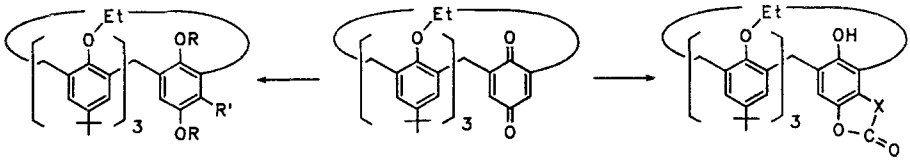
	R^1	R^2	R^3	R^4
a	Me	Me	Me	Me
b	iPr	iPr	iPr	iPr
c	iPr	Phe	iPr	iPr
d	tBu	tBu	tBu	iPr

From **9d** the tetrapropyl ether could be prepared in the *cone* conformation and resolved by chromatography on chiral stationary phases [12]. Thus, the first single enantiomer of an inherently chiral calixarene was obtained.

Examples of this type also comprise compounds with a *meta*-hydroxyl group, i.e. with a single resorcinol unit, incorporated in the 2,6-position [13]. Very recently Gutsche synthesized calix[4]arenes with *meta*-substituted phenolic units [14] from the corresponding monoquinone derivatives by addition of various reagents, some examples being shown in Equation 3.



10 **11**

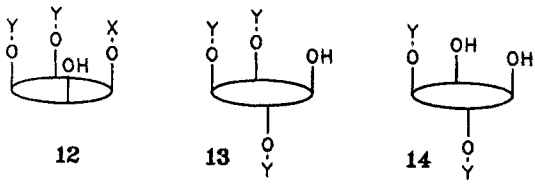
R=H, R'=S–C_6H_4–CH_3
R=Ac, R'=O–Ac

X=S, CHR, SCH_2 (3)

4. Asymmetric Calix[4]arenes by *O*-Alkylation with Achiral Residues

In principle the same asymmetric pattern found in **4** or **5** can also be obtained by *O*-alkylation (or *O*-acylation), adding different residues [15–17] to the phenolic oxygen. This strategy has the additional advantage that (with residues larger than ethyl) simultaneously the conformation is fixed and racemization becomes impossible.

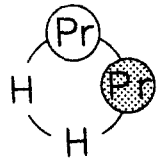
For an *all-syn* arrangement of the *O*-alkyl groups, at least two different residues are necessary (**12**), but additional possibilities exist if the *O*-alkyl groups are in the *anti* position. Thus, compounds **13** and **14** with one kind of *O*-alkyl groups are asymmetric (**13**) or dissymmetric (**14** has effectively C_2 symmetry). Examples of these types have been prepared mainly by Shinkai *et al.* [15] and Pappalardo *et al.* [16], and some of them have been resolved by chromatographic techniques [15, 16b, 16c].



12 **13** **14**

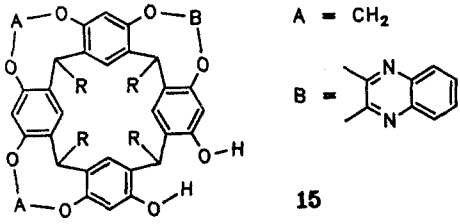
When describing these various *O*-alkylation products the terms *cone*, *partial cone*, *1,2-* and *1,3-alternate* should be used *only* for the tetraethers, where the mutual arrangement of the *O*-alkyl groups unambiguously defines one of these basic conformations. Since the OH group can pass through the annulus a partially *O*-alkylated calixarene can still assume different conformations (at least in principle). This has been demonstrated by the formation of different conformational isomers in subsequent *O*-alkylation steps. For instance for **12** *cone* and *partial*

cone conformations are possible, for **13** *partial cone* and *1,2-alternate*, and for **14** all conformations except the *cone* conformation. Thus the expressions *cone*, etc., should be used here only to assign these *conformations*, while the mutual situation of the *O*-alkyl groups can be described using *syn* and *anti* or the superscripts α and β. For instance **14** (Y = Pr) could be named *anti*-1,2-dipropylether, abbreviated by Pr^{α}, Pr^{β}, H, H or symbolized by



Using different *O*-alkyl residues 34 types of tetraalkylethers, 13 types of trialkylethers and 8 types of dialkylethers are possible, among which 17, 9 and 3 are chiral [18].

Cavitands are more-or-less rigid, bowl shaped molecules with an enforced cavity. Many examples have been prepared from resorcarenes by intramolecular connection of the hydroxyl functions of adjacent resorcinol units [19]. Asymmetric cavitands [20] have been obtained using a similar principle as described above by introducing just two different bridges (A, B) as shown in **15**.



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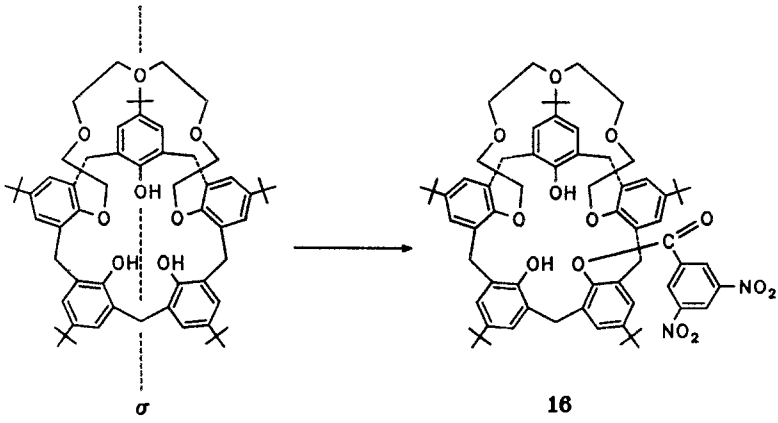
5. *O*-Alkylation or *O*-Acylation Products of Larger Calixarenes

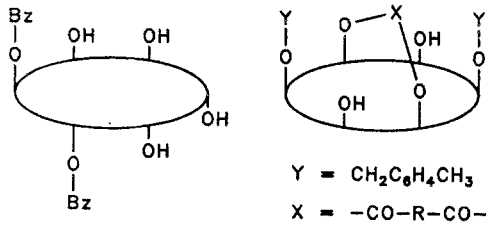
The number of possible *O*-alkylation products of calix[5]arenes is greater than those of calix[4]arenes and consequently there are also more possibilities for constructing asymmetrical substituted derivatives by *O*-alkylation. In general, selective functionalization of calix[5]arenes is not yet very advanced. The crown ether derivatives which we recently obtained are the first examples of selective *O*-alkylation [21a]. Such a 1,3-crown ether (which has C_S symmetry as indicated) can be made asymmetric by further monoalkylation or monoacylation at one of the remaining *proximal* OH groups [21b].



σ **16** (4)

While the structure of a monoester can be easily established by NMR and mass spectrometry, five singlets for *t*-butyl groups and 10 doublets for Ar–H protons (partly superimposed) prove the asymmetry of **16** (Figure 1). This clearly shows that one of the adjacent OH groups has reacted, but it gives no definite information on the orientation (*syn* or *anti*) of the ester group with respect to the crown ether chain. A high field shift of one *t*-butyl singlet indicates at least a rather distorted conformation.

The recent rapid development of selectively functionalized calix[6]arenes also has a large, yet unexplored potential for obtaining inherently chiral derivatives. Two different diastereomeric 1,2-dibenzylethers of *t*-butylcalix[6]arene (*syn* and *anti*) have been obtained, for instance, from which the *anti* isomer (**17**) is chiral (C_2 symmetry) [22]. The free energy barrier for their mutual interconversion (about 27 kcal mol^{-1}) should also be sufficient to isolate the enantiomers of **17**. 1,2,4-Tri-*O*-alkyl or -acylderivatives [23] should be separable into the enantiomers as long as neither the *O*-acyl nor the *p*-substituent can penetrate the annulus. The macrobicyclic 2,5-esters **18** obtained from 1,4-di-*p*-methylbenzylethers are also chiral, having C_2-symmetry in the *all-syn* isomer [24].



17 **18**

6. Chirality in Symmetrically Bridged Calixarenes

It is interesting to note that rigid bridges like the phthaloyl residue, which in principle has a symmetry plane, can impose an asymmetric conformation on the

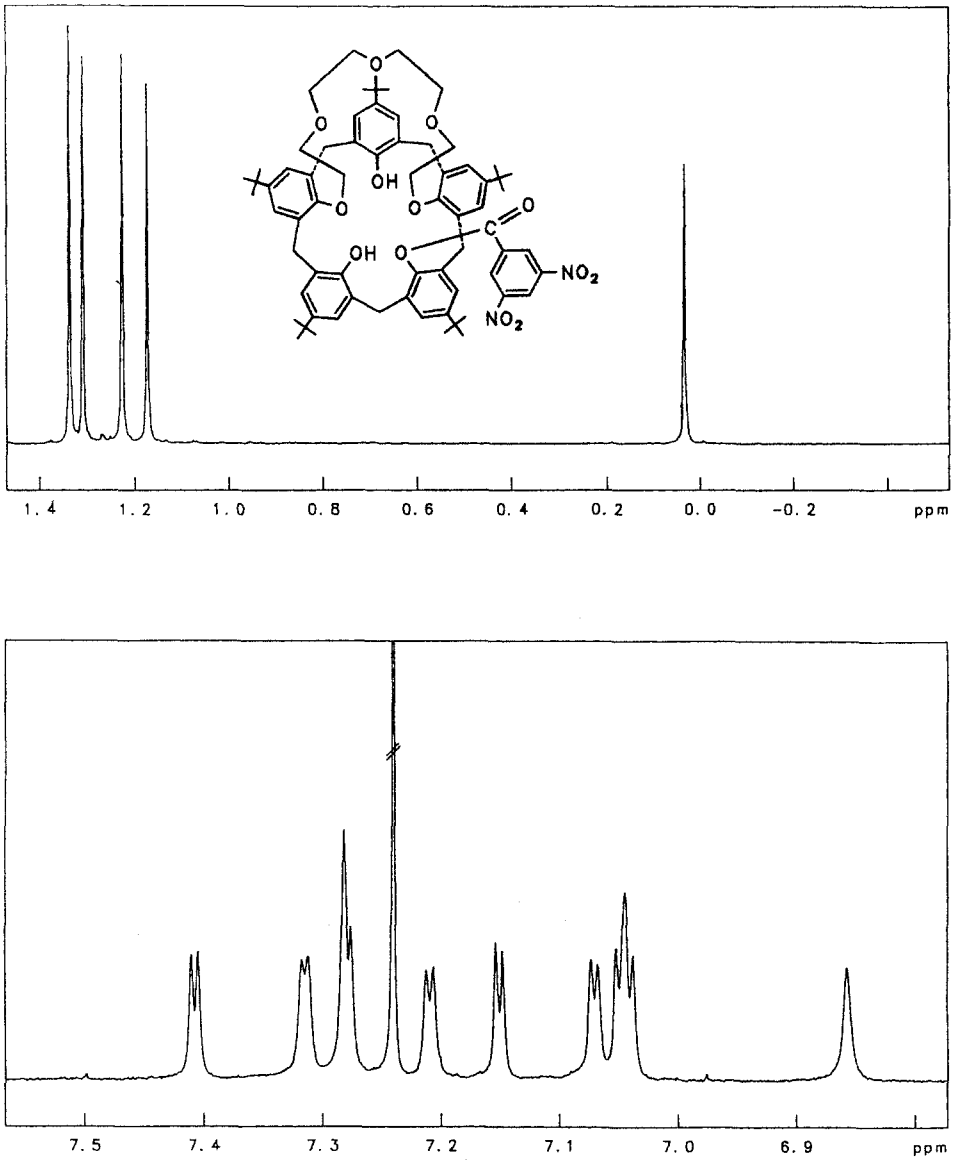


Fig. 1. Sections of the ^{1}H-NMR spectrum of the calix[5]arene derivative **16**.

calixarene skeleton. At room temperature, for instance, the 1,3-phthaloyl-bridged calix[5]arene **19** shows five singlets for the *t*-butyl groups (1.38, 1.30, 1.24, 1.14 and 1.11 ppm), proof of the absence of any symmetry element. At 120°C, however, three singlets (1.26, 1.10 and 1.21 ppm, ratio 2 : 2 : 1) are observed, as with the more flexible crown ether derivatives. A similar observation was made for the 1,2-phthaloyl bridged *t*-butylcalix[6]arene (five *t*-butyl singlets at room temperature and three singlets of equal intensity at 120°C), where the asymmetry was shown

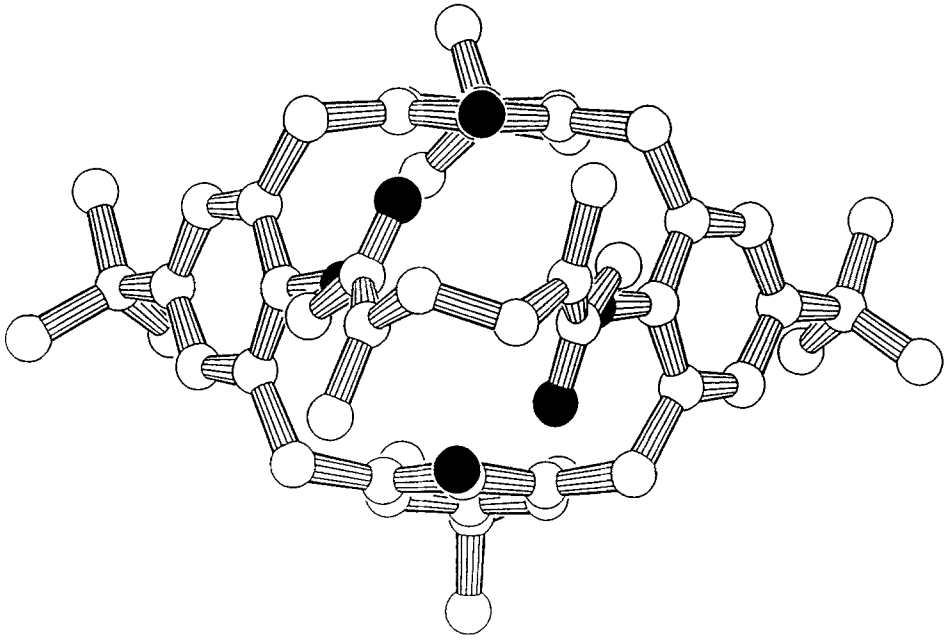
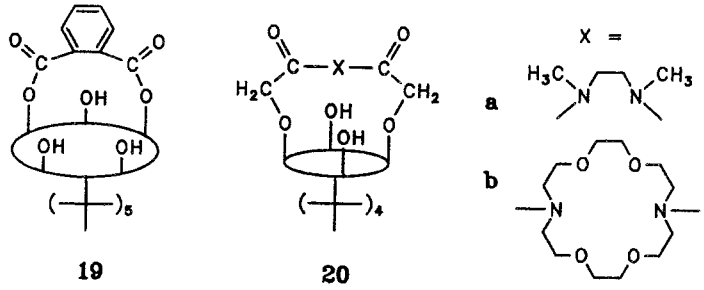


Fig. 2. Single crystal X-ray structure of the macrobicyclic amide **20a**.

also by X-ray structural analysis [25].

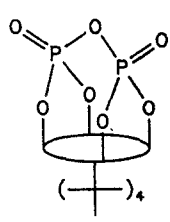


19 **20**

1,3-Bridged calix[4]arenes (e.g. calixcrowns) normally have C_{2V} symmetry. This is also observed for the macrocyclic amides **20** obtained by reaction of *t*-butylcalix[4]arene-1,3-diacidchlorides with various diamines, including ethylenediamine [26]. *N,N'*-Dimethylethylenediamine, however, leads to a cyclic amide with C_2 symmetry, which is obviously caused by the steric demands of this rather rigid bridge.

The structure found in the crystalline state (Figure 2) is also maintained in solution, as shown by ^{1}H-NMR spectroscopy in the presence of Pirkle's reagent. The four doublets (*meta*-coupling) observed for the aromatic protons in the corresponding amide **20b** obtained with diaza-18-crown-6 must be explained in a similar way.

A calix[4]arene bridged via the four phenolic oxygen functions by a pyrophosphate group (**21**) assumes a dissymmetric conformation at low temperature [27]. While the room-temperature ^{1}H-NMR spectrum shows one signal for the *t*-butyl groups and two different aromatic protons, the low-temperature (203 K) NMR spectrum shows two *t*-butyl groups and four different aromatic protons, which is in agreement with a chiral molecule having C_2-symmetry.



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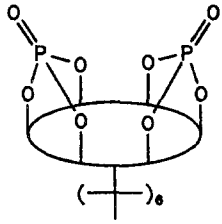

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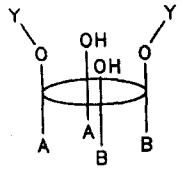
A similar observation was made for the calix[6]arene **22** which is bridged by two phosphate groups where, even at room temperature, the ^{1}H-NMR spectrum shows a dissymmetric conformation with C_2 symmetry.

Inherently chiral derivatives are also known from calix[8]arenes. Dimetalla complexes were obtained with titanium (as well as with Zr, V, Sn) in which the two titanium atoms have a pseudooctahedral environment bonded to all of the eight calixarene oxygens, two of which are bridging, and two isopropoxide oxygens. The C_2 symmetry was proved by single crystal X-ray analysis and in solution by two-dimensional ^{1}H-NMR spectroscopy [28]. Various complexes of *t*-butylcalix[8]arene with lanthanide ions have a similar structure [29].

7. 'Symmetry Breaking' by Di-*O*-Alkylation

Calix[4]arenes consisting of two different *p*-substituted phenolic units are readily prepared by fragment condensation ('2+2' for AABB, '3+1' for ABAB). In the *cone* conformation their molecules possess C_S and C_{2V} symmetry. 1,3-Diethers



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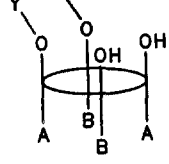

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in *syn*-arrangement are generally readily available from calix[4]arenes [30]. They can also be prepared in high yields from calix[4]arenes of the type AABB, and therefore they represent an attractive type of inherently chiral derivative [31]. The asymmetry here is due to the fact that in **23** the symmetry plane of the calix[4]arene substructure does not coincide with the symmetry planes of the arrangement of the

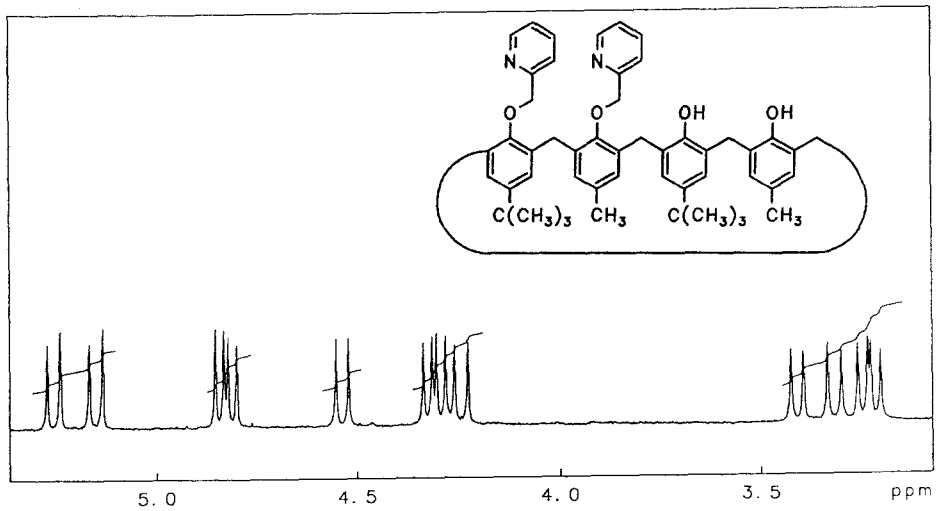
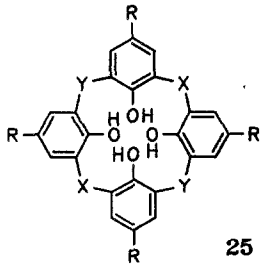


Fig. 3. Methylene protons section of the ^{1}H-NMR spectrum of a 1,2-diether derivative of type **24**.

alkyl groups. In a certain sense this situation is comparable to that encountered in atropisomers of biphenyls, where each aromatic ring usually represents a symmetry plane.

The same symmetry considerations are valid for 1,2-diether derivatives of calix[4]arenes of the type ABAB (**24**). Their synthesis, however, is a rather difficult approach, since 1,2-di-*O*-alkylation is not nearly as selective as 1,3-di-*O*-alkylation [30]. Since two different mono-, 1,3-di- and triether derivatives are possible (neglecting even derivatives with *anti*-arrangement of the *O*-alkyl groups), a rather complex reaction mixture exists, even if these compounds are formed only in small amounts. As one example [32] the section of the methylene protons is shown in Figure 3. Twelve doublets of equal intensity with geminal coupling prove that all six Ar–CH_2–Ar and O–CH_2–Py groups are different, each having two diastereotopic protons [32].

With calix[4]arene-like macrocycles of type **25** having two different bridges X and Y [33–35] *all* mono- and triether derivatives are asymmetric. Their 1,3-diethers have C_2 symmetry, while the two possible 1,2-diethers have a symmetry plane. The first examples of such compounds were mentioned by Nishimura [35].



25

a X=CH_2 Y=CH_2OCH_2

b X=CH_2 Y=$(CH_2)_3$

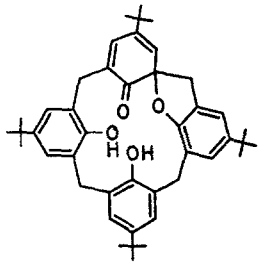
c X=CH_2 Y=1,2-cyclobutano

R–R=$(CH_2)_5$

8. Further Asymmetric Derivatives

t-Butylcalix[4]arene may be converted by mild oxidation ($Me_3PhN^+Br_3^-$/$NaHCO_3$ in CH_2Cl_2) into spirodienones [36] which are extremely interesting examples of chiral derivatives. The structure of the monospirodienone **26** has been established by single crystal X-ray analysis. Two signals for the different OH groups and four AX systems for the methylene bridges are observed in the ^{1}H-NMR spectrum. On the one hand, the chirality of **26** is mainly due to the asymmetrically substituted spirocarbon atom and therefore this compound is not inherently chiral. However, there is also some similarity to a calix[4]arene having three different phenolic units or three different oxygen functions (two hydroxyl groups in proximal positions, a carbonyl and an ether group) in the order AABC (cf. Section 4).

Three of six possible bis-spirodienone derivatives have been obtained in a similar way from *p-tert*-butylcalix[4]arene, one of them (**27**) showing C_2 symmetry. The other two are achiral (C_1 and C_S symmetry). Tris-spirodienones have been obtained meanwhile from *t*-butylcalix[6]arene [36e].



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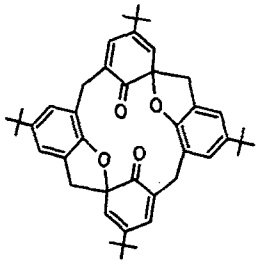


27

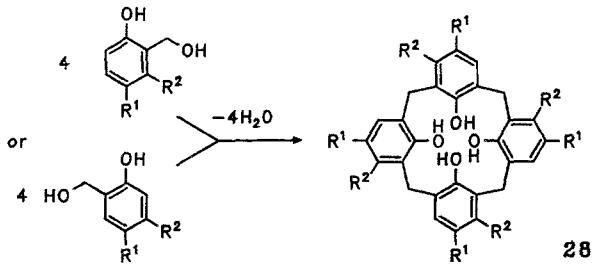
Calix[4]arene ethers, like the tetrapropylethers, can be converted into mono-$Cr(CO)_3$ complexes [37]. Starting with the *cone* or the *1,3-alternate* isomer, these derivatives still have a symmetry plane, while the corresponding derivative of the isomer in the *1,2-alternate* conformation becomes asymmetric. Starting with a *partial cone* conformer, an asymmetric molecule can be obtained only by introducing the $Cr(CO)_3$ at one of the aromatic rings next to the inverted phenol ring.

9. Dissymmetric Calixarenes with C_n Symmetry

Dissymmetric molecules are chiral but still have symmetry elements: a single n-fold axis (C_n symmetry) or, in addition, n two-fold axes perpendicular to it (D_n symmetry). Some derivatives with C_2 symmetry have been already mentioned above in connection with asymmetric compounds of the same type.

Most attractive, and not just from an aesthetic point of view, are dissymmetric calix[n]arenes having an n-fold symmetry axis. Several calix[4]arenes with C_4

symmetry have been obtained from 3,4-disubstituted phenols as shown in Equation (5) with yields up to 30% in the cyclization step [38].



	R¹	R²
a	CH_3	CH_3
b	$CH(CH_3)_2$	CH_3
c	Cl	CH_3
d	$(CH_2)_3$	
e	$(CH_2)_4$	
f	CH=CH−CH=CH	

(5)

The regular incorporation of the phenolic units has been demonstrated not only by their ^{1}H-NMR spectra, but also, for one example, by X-ray analysis. It shows the molecule in a 'pinched' *cone* conformation with (essentially) C_2 symmetry. In solution no deviation from the (average) C_4 symmetry is observed down to temperatures of -100°C. In comparison to calix[4]arenes with *p*-substituted phenolic units a slightly lower energy barrier (13.4 vs. 14.6 kcal mol^{-1}) is found for the ring inversion.

Due to the equivalence of the phenolic units, it is now possible to construct in an unambiguous way all kinds of *O*-alkylation products (from mono- to tetraethers), as with achiral calix[4]arenes. Of course, the symmetry is reduced in partially *O*-alkylated derivatives. Mono- and triether derivatives are asymmetric (C_1) while 1,3-diether derivatives with the usual *syn*-arrangement of the *O*-alkyl groups have C_2 symmetry. An *anti*-1,3-diether (the formation of which is not observed under usual reaction conditions) would have an inversion center in its *1,2-alternate* conformation, hence being achiral.

As an example, Figure 4 shows the ^{1}H-NMR spectrum of a mono-*p*-nitrobenzylether. Eight singlets for the methyl groups or four singlets for the aromatic protons demonstrate that all phenolic units are different. Especially noteworthy is the AB system (two doublets with geminal coupling) for the diastereotopic O–CH_2–Ar protons which has nothing to do with restricted rotation around these σ-bonds but is entirely due to the fact that the benzyl group is attached to a chiral skeleton.

Various *syn*-1,3-diether derivatives were obtained in good yields. Some of them were resolved into pure enantiomeric forms [39] by chromatography with chiral stationary phases. Figure 5 demonstrates that their CD spectra are similar in principle, but show subtle differences, which must be due to small conformational differences. As special examples for 1,3-derivatives the crown ethers **29** should be mentioned (R_1 = R_2 = Me). These were obtained as usual by reaction with tetra- and pentaethyleneglycol ditosylates, respectively, in about 20% yield [40].

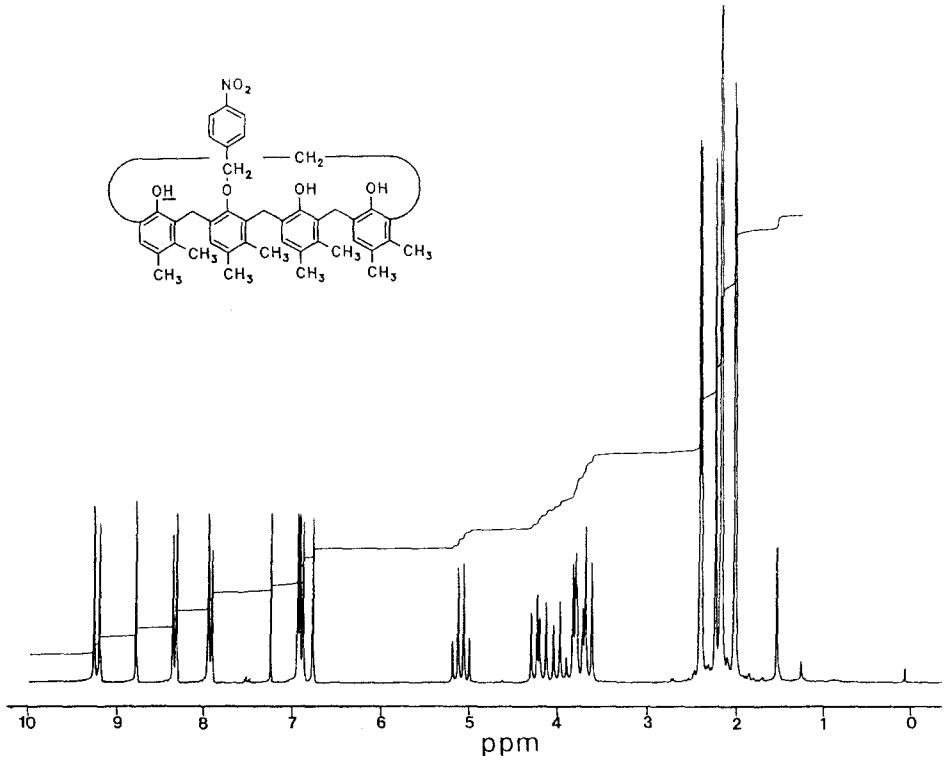
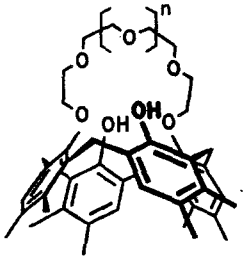


Fig. 4. ^{1}H-NMR spectrum of the mono-*p*-nitrobenzylether of **28a**.



29 **n = 1, 2**

^{1}H-NMR spectral studies show that the tetraether derivatives of **28** assume a 'pinched' *cone* conformation (as in the crystalline state) at moderately low temperatures. This is clearly due to the steric demands of the *meta*-methyl groups. The C_4-symmetry suggested by the structure is observed in solution only at higher temperatures, as the time average of two conformations with C_2 symmetry.

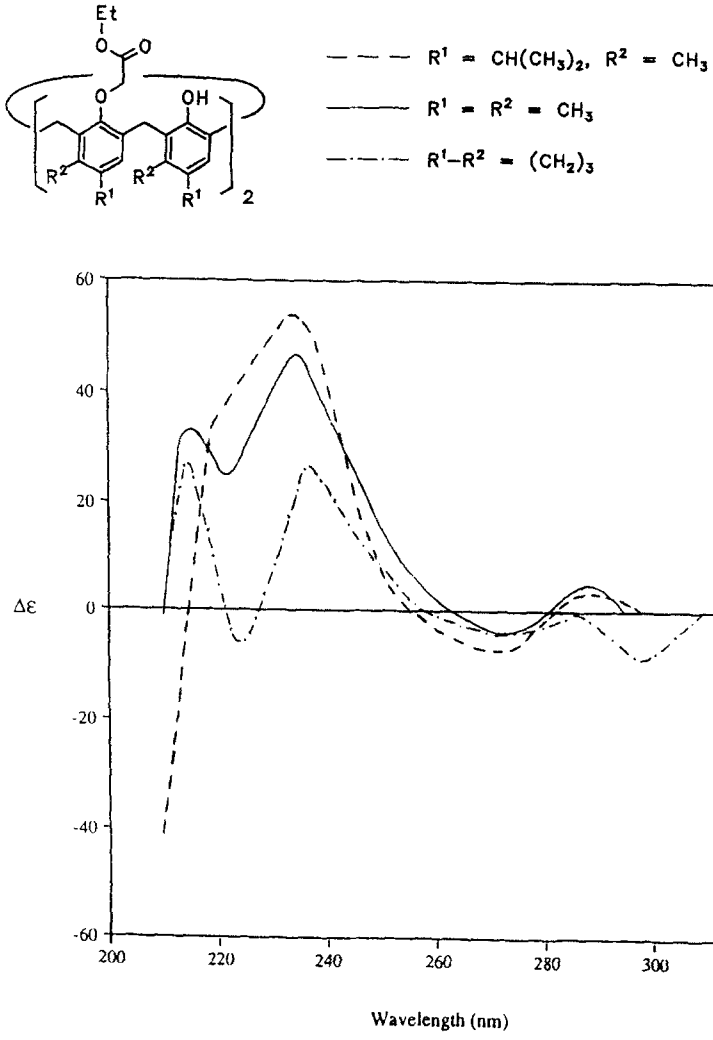
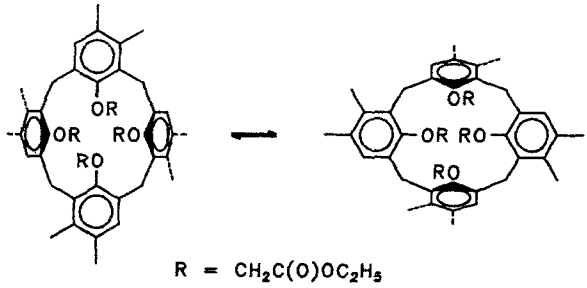


Fig. 5. CD spectra of the 1,3-diether derivatives of **28a**, **b** and **c**.

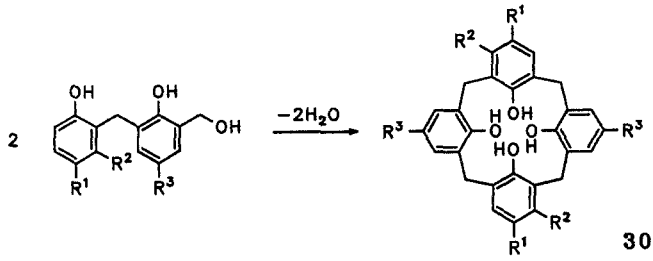


$$C_2 \rightleftharpoons [C_4]^{\ddagger} \rightleftharpoons C_2 \qquad (6)$$

The energy barrier for this 'pseudorotation' process, which most probably has a C_4 symmetrical transition state, is in the range of $\Delta G^{\#} = 13$–14 kcal mol^{-1}. A similar molecular motion (with a much lower energy barrier) was already assumed from relaxation time studies for the corresponding derivatives of *t*-butylcalix[4]arene [41].

The regular incorporation of the β-naphthol units in **28** is determined by the synthetic strategy. The condensation of α-naphthol with formaldehyde has recently allowed calix[4]arenes to be synthesized in which the naphthol units are incorporated via their 2,4-positions. In this way not only the isomer with C_4 symmetry is formed, but simultaneously also the isomers with C_1 and C_S symmetry. It was possible, however, to isolate the C_4 symmetric compound in 9–10% yield, while a fourth isomer with C_{2V} symmetry was not found [42]. Due to the absence of intraannular substituents these molecules are quite flexible.

Calix[*n*]arenes with two *meta*-substituted phenolic units in opposite positions may be chiral (C_2 symmetry) or achiral (C_S symmetry). Addition reactions to 1,3-di-quinone derivatives, in analogy to Equation 3, give a mixture of both isomers, from which for one example the C_2 isomer **30** was isolated. The C_2 isomer is formed in a more rational way according to Equation 7 with 20% yield in the cyclization step [38]. However the five-step synthesis of the dinuclear precursor means that this, too, is not a very attractive alternative.

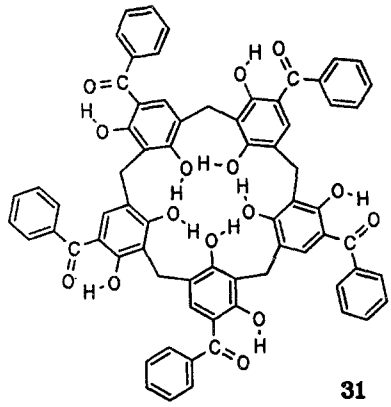


(7)

10. Compounds with Resorcinol Units

Acid catalyzed condensation of 2,4-dihydroxy-3-hydroxymethylbenzophenone in dioxane also leads to a calixarene with regular incorporation of the phenolic units [43]. This was easily proved by the ^{1}H-NMR spectrum which showed just one set of signals for the repeating phenolic unit (e.g. two singlets for OH and one singlet for the Ar–H of the resorcinol units and an AB system for the Ar–CH_2–Ar protons). Mass spectrometry and finally also a single crystal X-ray structure revealed that, surprisingly in this case, the calix[5]arene **31** was formed. This is not only a rare example of a molecule with intrinsic C_5 symmetry, it is also the first example of a calix[5]arene consisting entirely of resorcinol units. In contrast to the 'usual' resorc[4]arenes, however, the resorcinol units are not incorporated via the 4,6-positions but via the 2,6-positions. This shows also that calixarenes (which in a narrow sense are derived from phenols) and resorcarenes should be

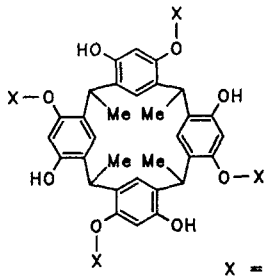
considered together. In a more general sense the name 'calixarene' may be used for *all* 1_n*-metacyclophanes*.



31

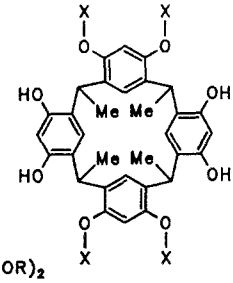
Compound **31** shows another surprising result. While the energy barrier for the cone-to-cone ring inversion in calix[5]arenes is usually lower than in calix[4]arenes (the values for *p*-methylcalix[4]- and -[5]arene are $\Delta G^{\neq}$ = 14.6 and 12.7 kcal mol^{-1}) dynamic NMR gave a comparatively high barrier of $\Delta G^{\neq}$ = 17.3 kcal mol^{-1} for **31**. The reason for this is not yet entirely understood.

Two interesting approaches to C_4 symmetrical derivatives have recently been described in the resorcarene family. Esterification with Cl–P(O)–$(OR)_2$ usually gives the corresponding octaester. For R = Et, *i*-Pr, however, a tetraester was isolated in good yields, to which the authors assign structure **32a** [44]. Two singlets found in the ^{1}H-NMR spectrum for each of the aromatic protons (in 2- and 5-position of the resorcinol units) are explained by a distorted conformation also found for octaesters. However, this would afford two signals for the OH groups and two different phosphorus ester groups, where only a single set of signals is found. Thus the NMR data are in even better agreement with structure **32b**.

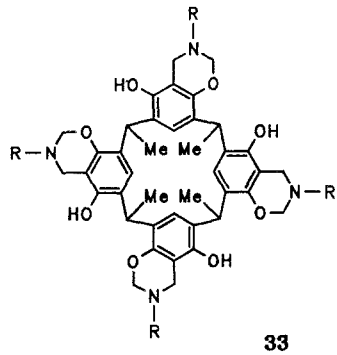


X = P(O)(OR)$_2$

32a



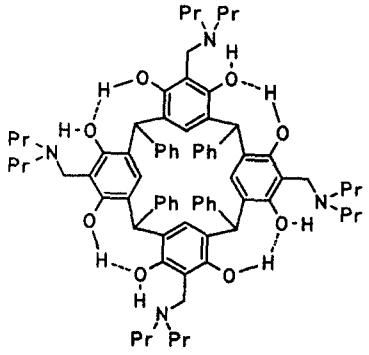
32b



33

Aminomethylation of resorcarenes with several primary amines leads to compounds for which the formula **33** suggests C_4 symmetry [2a]. However, no spectroscopic data have been published for this type of compound, nor do the authors

mention this potential chirality. We recently prepared various compounds of this type for which a single set of signals for all protons of the resorcinol unit was observed, which is comparable only with the C_4 symmetrical formula **33**. Meanwhile this was unambiguously proved for one example (R=p–C_6H_4–NO_2) by single crystal X-ray analysis [45]. C_4 symmetry was found in the crystalline state for product **34** due to the network of intramolecular hydrogen bonds, all of which proceed in the same direction [46a] and a tetralactone with C_4-symmetry derived from a resorcarene has been described by Cram *et al.* [46b]. Finally, in this connection a calixarene-like macrocyclic compound should be mentioned, in which four uracil units are connected in a regular fashion by (en)Pt bridges between their nitrogen atoms. The molecule has C_4 symmetry, but a 1,3-alternate conformation with C_2 symmetry is found in the crystalline state [47].



34

11. Spherand-Type Calixarenes

Condensation of 2,2′-dihydroxy-5,5′-di-*tert*-butyldiphenol with formaldehyde leads to macrocyclic molecules **35** which combine structural features of a calixarene and a spherand [48, 49]. They have three or four methylene groups: less than a calix[6]- or -[8]arene and more than the corresponding spherand. Their ^{1}H-NMR spectrum which shows one singlet for *t*-butyl, methylene and hydroxyl protons and a pair of doublets for the aromatic protons, indicate that these parent macrocycles are either highly symmetrical or rather flexible molecules. The splitting observed at lower temperature for the methylene protons is in favour of the latter explanation, although the exact minimum energy conformation is not yet known.

O-alkylation of the parent spherand calixarenes leads to derivatives in which the biphenyl subunits are fixed in a certain configuration, as in usual atropisomers. Although such a molecule then contains chiral subunits it may nevertheless be regarded as an inherently chiral molecule. Opening of the macrocycle would lead to a linear molecule in which (at least for small residues R) racemization would be

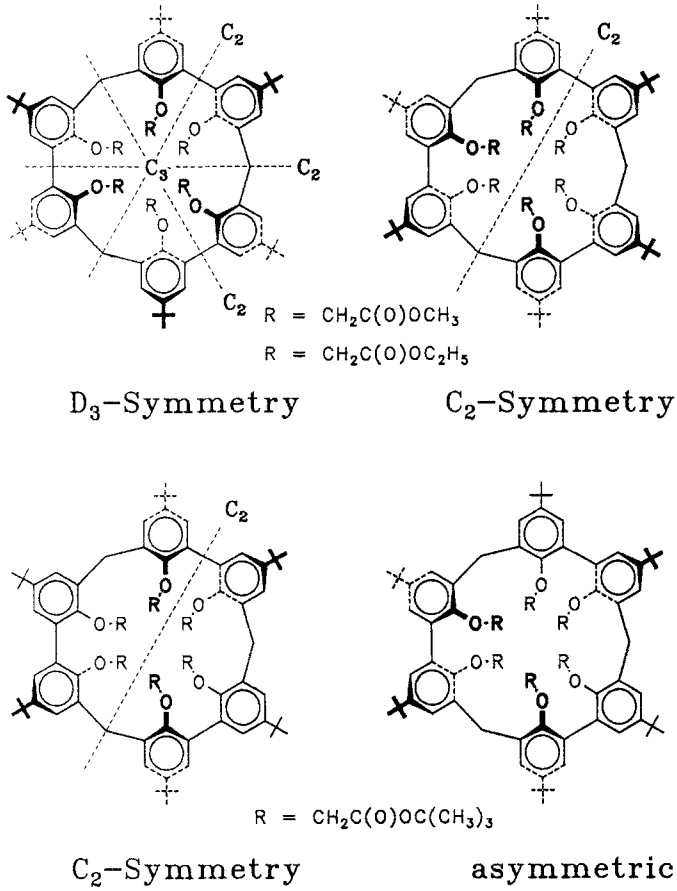
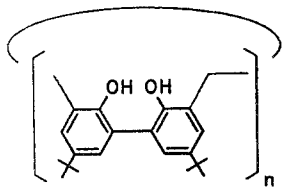


Fig. 6. Possible diastereomeric hexaethers of **35a**.

possible via a transoid transition state, while in the macrocycle the cisoid transition state is the only possibility.



35a n=3 **35b** n=4

Two diastereoisomers are possible for the trimer, both of which are chiral. *R,R,R* or *S,S,S* configuration of the biphenyl units leads to D_3 symmetry and *R,R,S/S,S,R*

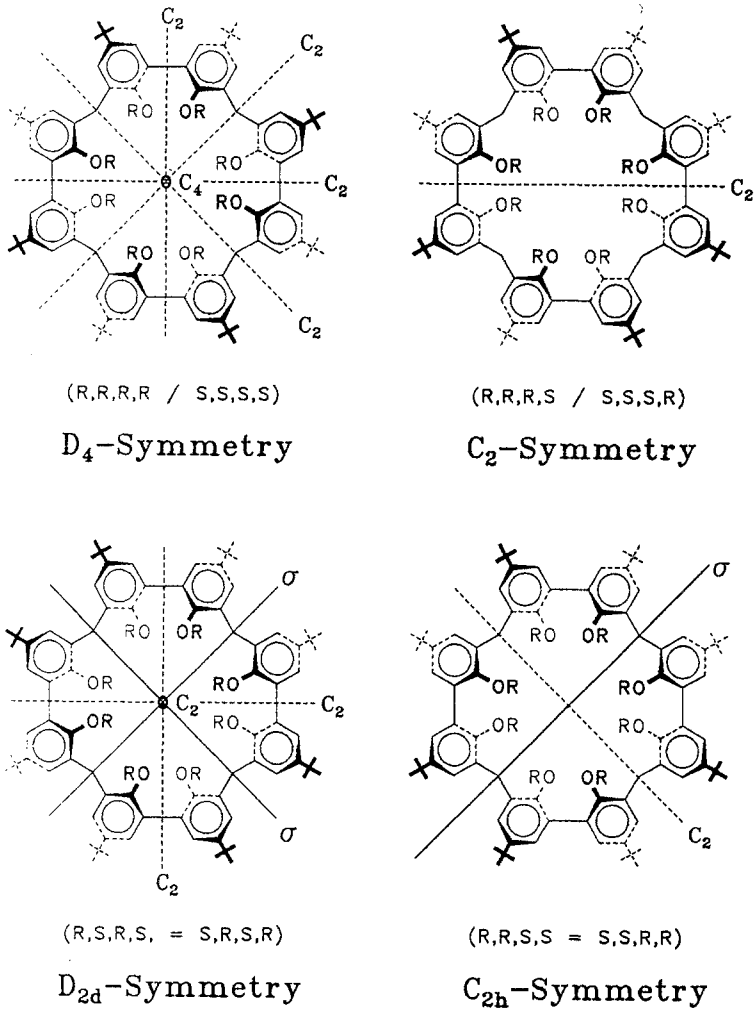
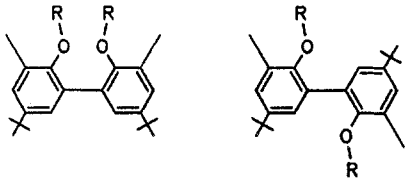


Fig. 7. Possible diastereomeric octaethers of **35b**.

configuration results in C_2 symmetry.



While Yamato *et al.* were able to isolate both hexamethylethers [48] (the D_3 isomer only in low yield and in inpure form), our own attempts at alkylation with ethylbromoacetate gave only the C_2 isomer (in yields up to 92%). In addition to

the ^{1}H-NMR spectroscopic evidence, its structure was also determined by single crystal X-ray analysis [49]. Further chemical modification by hydrolysis or transesterification is possible, without changing the configuration.

If ethylbromoacetate is replaced in the alkylation reaction by *t*-butylbromoacetate, the residues R are bulky enough to hinder not only the rotation around the Ar–Ar bonds but also around the Ar–CH_2–Ar bonds. This means the diphenylmethane subunits become asymmetric (atropisomeric), too. In addition to a C_2 symmetric derivative now also an asymmetric (C_1) derivative exists for the *R,R,S/S,S,R* configuration of the biphenyl units (see Figure 6). Both diastereomers could be isolated in pure form and converted by transesterification into the same (C_2 symmetrical) hexamethylester which was also obtained from the hexaethylester.

Four different octaether derivatives should be available from the cyclic tetramer (Figure 7), two of which are chiral while the other two are meso-forms. However, up to now all our attempts at alkylation have led only to mixtures of these diastereomers, in accordance with the results of the *O*-methylation [48].

12. Conclusion

This survey demonstrates the huge potential which is available in the calixarene family for obtaining inherently chiral host molecules or chiral building blocks for the construction of even larger molecular systems. Clearly the possibilities are not exhausted by the examples discussed above and further strategies will be developed in the future. Although convincing examples have not yet been described, chiral recognition and discrimination will be one of the main topics in calixarene chemistry in the future.

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8. Otherwise an untreatable mixture of isomeric or similar compounds will be obtained. For instance, four different mono- or trialkylated derivatives in *syn* arrangements, or four different tetra-*O*-alkylated derivatives in the *partial cone* conformation are possible.
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