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ASYMMETRICALLY SUBSTITUTED CALIX[4]ARENES: A TWO-DIMENSIONAL ^{1}H NMR STUDY OF A TETRAESTER DERIVATIVE IN THE CONE-CONFORMATION

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Abstract: Several new chiral calix[4]arenes with three or four different substituents in the p-position have been prepared by fragment condensation. Standard derivatization procedures always led to the formation of mixtures of various conformational isomers from which the derivative in the cone-conformation could be isolated only by preparative HPLC. For a tetraester derivative it was shown by two-dimensional ^{1}H NMR spectroscopy, that due to the different substituents the cone-conformation is strongly distorted. The sodium complex of this tetraester, however, assumes a regular cone-conformation again.

Calixarenes are cyclic oligomers in which p-substituted phenolic units are linked via methylene bridges in the o-position[1 2)]. Calixarenes are nonplanar and, especially the calix[4]arenes, assume the so-called cone-conformation in which the OH groups are mutually syn with respect to the mean macrocyclic plane, giving the molecule a cup or calix like shape which was also the origin for the name "calixarenes" This nonplanarity offers the possibility of obtaining chiral molecules either by using different phenolic units to build up the molecule[3)] or by the incorporation of m-substituted phenolic units[4 5)]

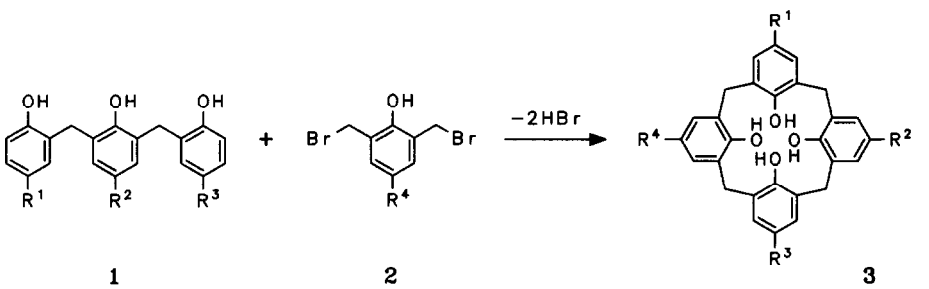
Although in the crystalline state the cone-conformation, having all the hydroxyl groups at one side of the molecule and thus stabilized by a cyclic array of intramolecular hydrogen bonds, was found exclusively for all examples studied[6)], a rapid interconversion cone to cone is observed in solution[7)]. For chiral calixarenes this rapid equilibrium is equivalent to racemization. Therefore, stable enantiomers will not be obtainable, unless this interconversion is completely hindered. Conformational fixation can be achieved by the introduction of suitable residues at the phenolic hydroxyl groups which are bulky enough not to pass through the annulus[8)] According to a recent study, residues larger than ethyl are necessary[9)]

In principle, reactions at the phenolic hydroxyl groups may lead to any of the four possible conformations, but various examples are described in the literature, in which the cone-conformation was formed in high yield[1]. Especially the compounds obtained by etherification with haloacetic acid derivatives or haloketones, are highly interesting neutral ligands for metal cations[10].

If such a derivatization reaction is envisaged with a calix[4]arene possessing four different phenolic units, complete conversion of all four hydroxyl groups with the exclusive formation of the cone-conformation is highly desirable. Otherwise one might end up with an intractable mixture of similar compounds and conformational isomers[11]. This objective turned out to be more difficult than one would have predicted.

Synthesis of asymmetrical calix[4]arenes

The calix[4]arenes 3 were obtained by condensation of a suitable linear trimer 1 with a bisbromomethylated phenol 2 as described already for similar compounds[3]. The p-substituents employed are shown below.



1 2 3

	3a	3b	3c	3d	3e	3f	3g
R^1	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	C_6H_{11}	C_6H_{11}
R^2	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$	$C(CH_3)_3$
R^3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R^4	C_8H_{17}	C_6H_{11}	C_6H_5	$CO_2C_2H_5$	$CH_2CO_2C_2H_5$	C_6H_5	$CO_2C_2H_5$

The yields of pure 3, readily isolated and purified by flash chromatography, were in the range of 13-18% for compounds carrying para-alkyl or aryl substituents only (3a-3c, 3f) and somewhat lower (9-13%) for compounds 3d, 3e, and 3g bearing an ester group (see Table 1). Whether this is caused by a lower reactivity due to the electron withdrawing effect of COOEt or to further side reactions of the ester group is not quite clear.

Since in similar cases yields up to 50% were occasionally obtained, it may be assumed that optimization of the reaction conditions for the individual cases could lead to an increased yield. Recently an improvement of the yields for several calix[4]arenes prepared by an analogous procedure in combination with a slightly different working up procedure was reported[12].

The linear trimers 1 were prepared by stepwise synthesis starting with an o-brominated phenol followed by alternating the bromomethylation and condensation steps[3]. An excess of the p-substituted phenol has to be used in these condensation reactions to avoid substitution of its second o-position. Finally 1 was obtained after eliminating the protecting bromine substituent by hydrogenation under alkaline conditions.

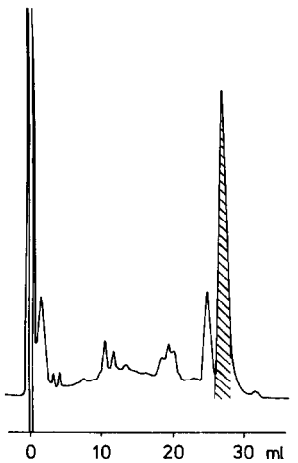
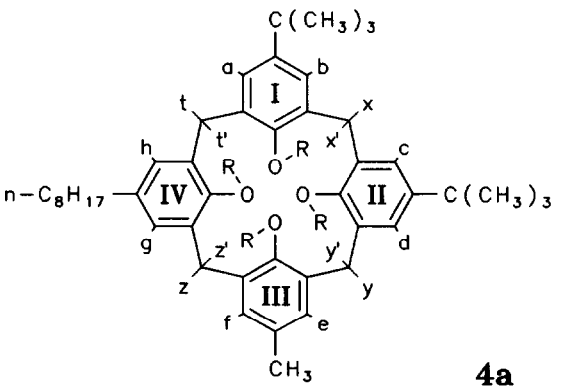


Fig. 1. HPLC of the crude mixture of **4**, showing the fraction used for the following studies.

After many attempts with various compounds of type 3 had failed to produce a single derivative in the cone-conformation by simple purification techniques, we succeeded in isolating a pure fraction by preparative HPLC of the crude product mixture obtained from the reaction of 3a with ethyl bromoacetate (see Figure 1). This product (**4a**), obtained in 51% as a colourless highly viscous oil, was studied by ^{1}H NMR, leading to the results discussed in the following section.



4a

R = CH_2–CO–OEt

2D-NMR Studies

In the following discussion the designations shown in the formula are used. The four aromatic rings are distinguished by Roman numerals I – IV, the aromatic protons in meta-position by letters **a** to **h**, and the protons of the methylene bridge with letters **x**, **y**, **z**, and **t** for the equatorial and **x'**, **y'**, **z'**, and **t'** for the axial ones.

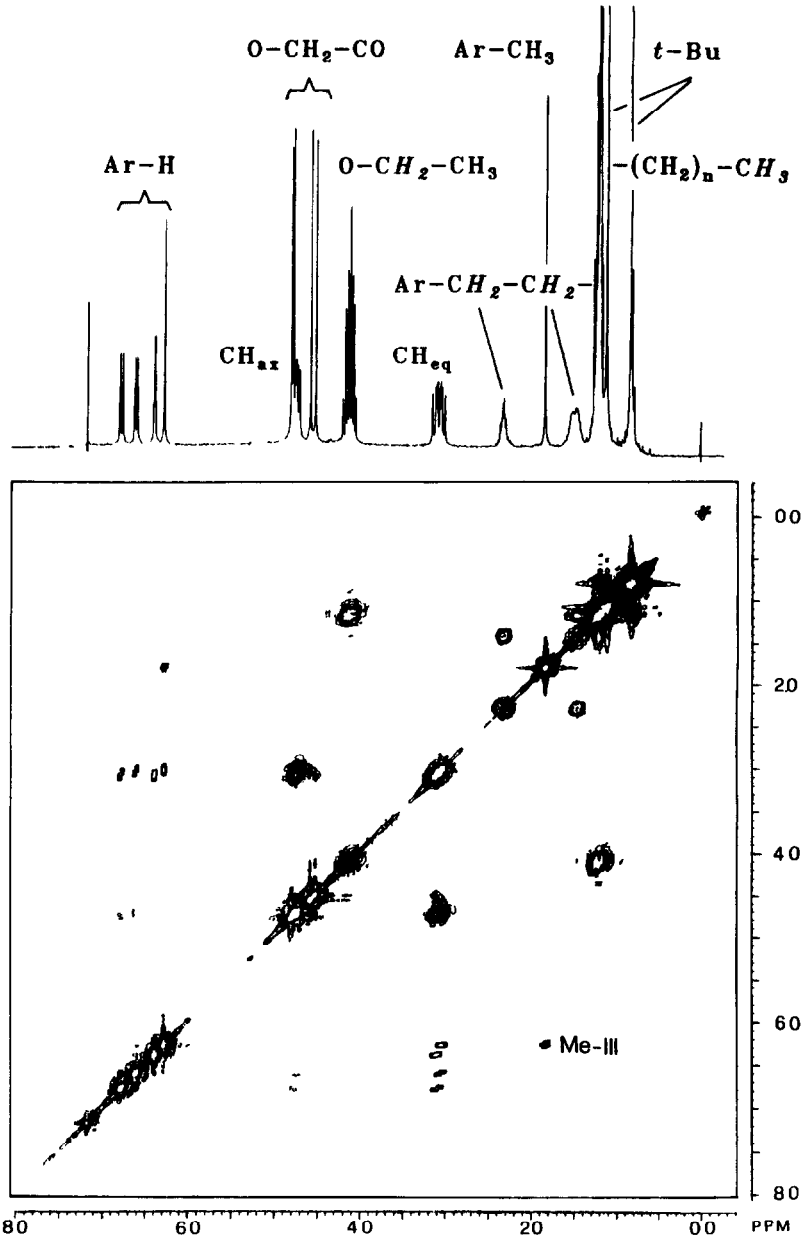


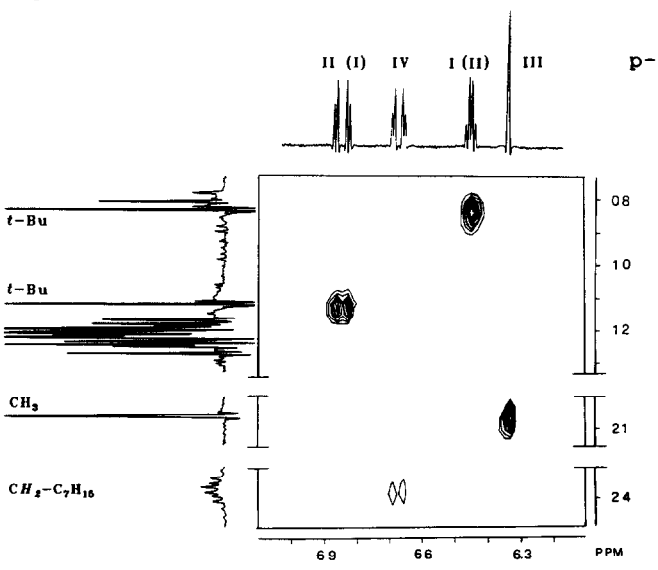
Fig. 2. Complete 2D-COSY spectrum of tetraester **4a** (270 MHz, $CDCl_3$)

Interestingly the ^{1}H NMR spectrum of **4a** shows separate signals for each of the four methylene bridges, for each of the four phenolic units and for each of the four residues attached to the phenolic oxygens. The two singlets for the two *t*-butyl groups, separated by 0.29 ppm, at a first glance, suggest a partial cone-conformation for **4a**, with one of the *t*-butyl groups directed in the opposite direction to the other p-substituents. Remarkably also, four different sets of signals (singlet, quadruplet, triplet) are observed for the residues $O\text{-}CH_2\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_3$. This cannot be explained by the different substituents in the p-positions, since exactly the same values are found for the corresponding mononuclear model compounds.

The 2D-COSY experiment, shown in Figure 2 with all correlations, leads to a first assignment A long range coupling observed between the methyl protons in the p-position of ring III and two aromatic protons, makes it possible to assign the signal at 6.3 ppm to the protons e and f. Starting from this assignment we are able unambiguously to assign all other signals and to prove the cone-conformation on the basis of the NOESY results The 2D-NOESY experiment gives the following connectivities.

a) NOEs between protons of the p-substituents and aromatic protons

The methyl (Me, t-Bu) and methylene (octyl) protons of the para substituents give NOEs to the m-protons (ortho relative to these substituents[1]) of their own aromatic rings Thus, the assignment of ring III is confirmed, ring IV is now assigned, while rings I and II remain in doubt at this stage as summerized in Figure 3.

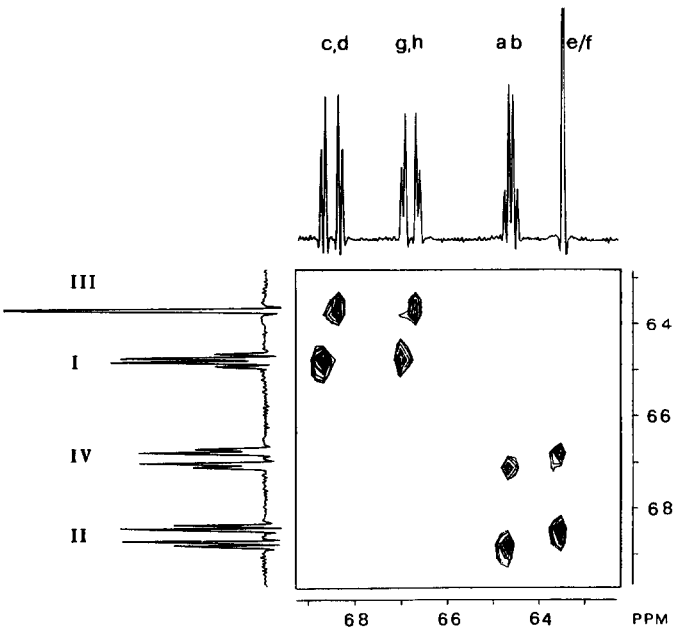


p-substituent	ring	protons
$C(CH_3)_3$	I,	a, b
	(or II,	c, d)
$C(CH_3)_3$	II,	c, d
	(or I,	a, b)
CH_3	III,	e, f
$(CH_2)_7\text{-}CH_3$	IV,	g, h

Fig. 3. NOEs between p-substituents and aromatic protons and assign ments derived from it.

b) NOEs between the aromatic protons of adjacent rings

Among the aromatic resonances only those from protons e and f are degenerate, the other ones show the typical doublets of AB-systems with m-coupling. Due to dipolar interactions protons e and f of ring III show NOEs to the aromatic protons of two adjacent aromatic rings, one of which is the already designed ring IV (proton g). Therefore the other one must be proton d, which enables the assignment of ring II and consequently of ring I. This assignment is further confirmed by the NOEs found between proton h (ring IV) and proton a (ring I) and proton b (ring I) and proton c (ring II).



proton (ring)	
known	assigned
e (III)	d (II)
f (III)	g (IV)
h (IV)	a (I)
b (I)	c (II)

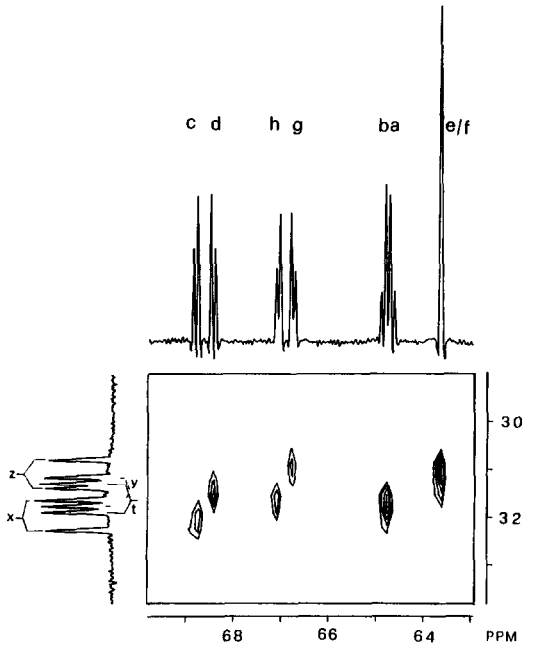
Fig. 4. NOEs between aromatic protons of adjacent rings and assignment derived from it.

Thus, not only are all aromatic rings with their protons now well assigned and confirmed, the fact that all aromatic protons show NOEs to the aromatic protons of the adjacent ring also proves that the molecule must be in the cone-conformation.

c) NOEs between equatorial protons of the methylene bridges and aromatic protons

As shown in Figure 5 NOEs are found between all equatorial methylene protons[13] and two aromatic protons. This allows the assign ment of all methylene protons x - t. It further confirms the assignment of the aromatic protons, since e.g. protons b and c must be in adjacent position to

show a NOE with the same proton x. Finally it proves again the cone-conformation of the molecule, since the second (axial) proton of a given methylene bridge should also show a NOE to the aromatic proton, if one of the aromatic rings would point in the opposite direction.



methylene proton	aromatic protons
x	b and c
y	d and e
z	f and g
t	h and a

Fig. 5. NOEs between equatorial methylene protons and aromatic protons.

d) NOEs between substituents R and aromatic protons

No NOEs are observed from any proton of the residues attached to phenolic oxygen and any aromatic proton. Although the absence of a NOE for itself never is decisive, in connection with the results mentioned above, this is again strong evidence for the cone-conformation.

Figure 6 contains 2D-COSY spectra showing the connectivities between the aromatic protons and the protons of the methylene bridge Interestingly, while all connectivities are observed between aromatic and equatorial protons x to t (Figure 6a), no connectivities are observed between the aromatic protons of ring I (a and b) and the corresponding axial protons x' and t', and only weak connectivities are observed between the aromatic protons of ring III (e and f) and the corresponding axial protons y' and z'(Figure 6b). This suggests that the long range coupling constants between aromatic and axial protons are zero for ring I and very small for ring III, indicating a distortion of ring I, and, to a lesser extent, of ring III.

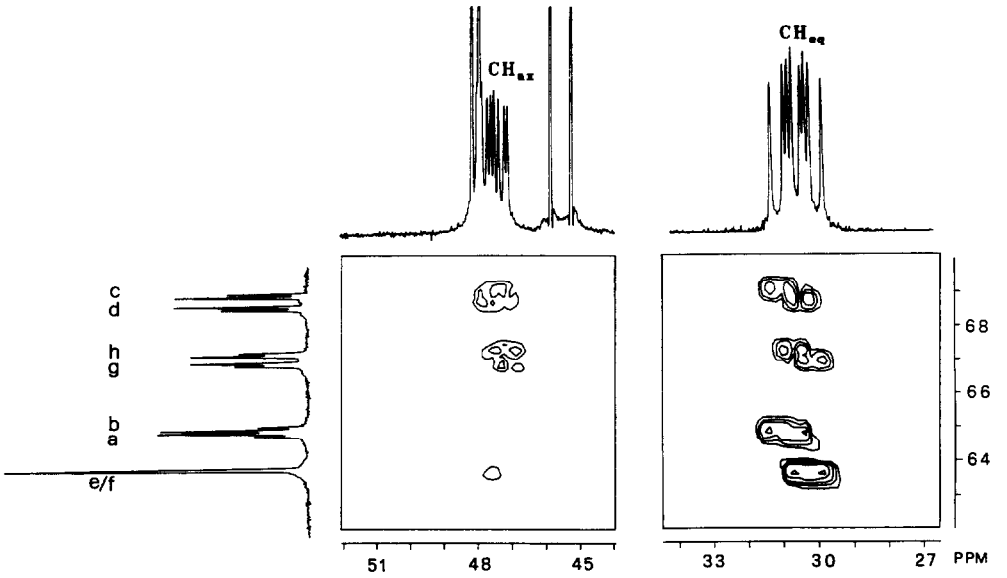


Fig. 6. 2D-COSY spectra, showing the connectivities between aromatic and methylene protons.

If a solution of **4a** in $CDCl_3$ is shaken with NaSCN (or if a stoichiometric amount of a methanolic solution of NaSCN is added) the spectrum of the Na^+-complex of **4a** is observed, as earlier in similar cases.[14] (The formation of a complex is again indicative for the cone-conformation.) The most striking differences between the spectrum of the free ligand and that of the complex are the following:

a) Both *t*-butyl groups now show (roughly) one signal at 1.21 ppm.

b) Only one set of signals is found for the protons of the residues attached to the phenolic oxygens (i.e. one triplet and one quadruplet for the ethyl groups and practically one singlet for the OCH_2CO-protons at 4.61 ppm).

Further differences and changes between the two spectra become evident from Figure 7.

Conclusion

The results obtained by 2D-NMR clearly show that compound **4a** is fixed in the cone-conformation which, however, is rather distorted. This distortion obviously is caused by the different space required by the p-substituents (including their different solvation shell[15]!) It is worth noting that a

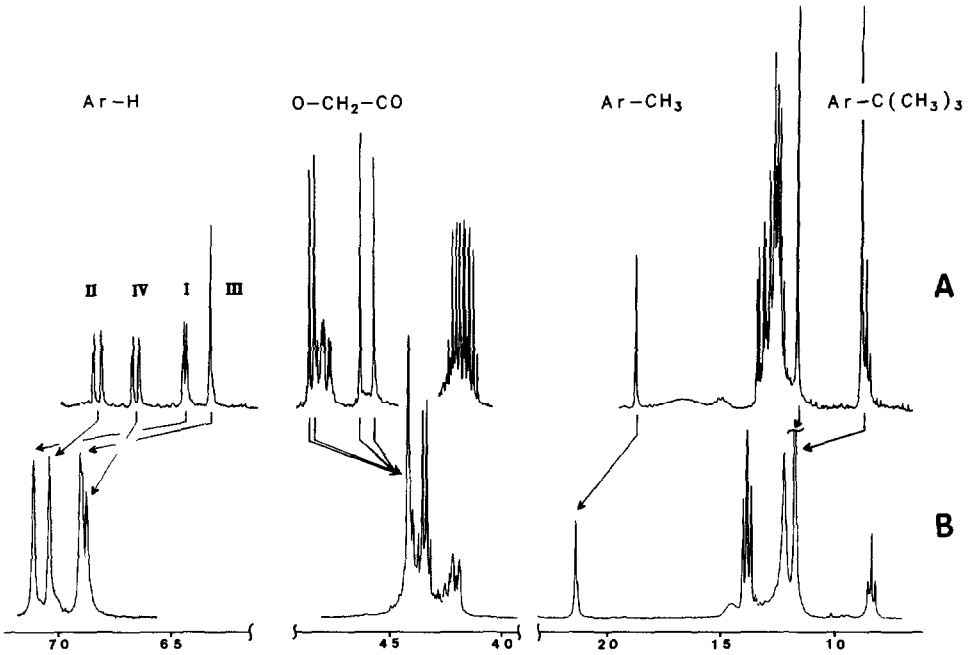


Fig. 7. Comparison of the ^1H NMR spectra of tetraester **4a** (A) and its Na^+-complex (B).

compound with a symmetry plane (and consequently only one kind of *t*-butyl groups) would result, if p-octyl is replaced by p-methyl or vice versa. Thus, the distortion is brought about by the rather small difference in these two substituents.

The complexation of a Na^+ ion, at the other hand, requires a regular arrangement of the ligating functions (ether and carbonyl oxygens)[16], and therefore the whole molecule is conformationally rearranged. The calix[4]-arene part now assumes more or less the regular fourfold symmetry, although it is still chiral due to the asymmetric substitution pattern. While such a regular arrangement of both the ligating functions and the calix part was found for the potassium complex of the tetraamide of *t*-butylcalix[4]arene in the crystalline state[10b] (and tacidly assumed for all the alkali ion complexes of similar derivatives) this is the first experimental proof, that this regular conformation exists also in solution

We may conclude that in calix[4]arenes one side of the molecule communicates conformationally with the other side, or in other words, that there is transfer of information from one side to the other side, from the

"lower rim" of the calix to the "upper rim" and vice versa. These results are closely in line with the abrupt change in the cation extraction properties for tetraester derivatives of para-bridged calixarenes when changing the bridge length from seven to six carbon atoms[17] and with the strong differences found in pK_{a1} for calix[4]arenes containing one p-nitrophenol unit and various substituents in the opposite p-position[18].

The detailed ^1H NMR study of **4a** has provided an interesting insight into the conformational properties of calix[4]arenes and their derivatives. On the other hand our results show that the formation of a mixture of different conformational isomers obviously is an intrinsic problem of asymmetrically substituted calix[4]arenes in contrast to calix[4]arenes consisting of identical phenolic units. Therefore, the synthesis of chiral host molecules in the cone-conformation is not very promising on this way and chiral calix[4]arenes with C_4-symmetry[5] will be a better starting point.

Experimental Part

Preparation of Compounds:

The trinuclear compounds **1** were synthesized in six steps (a-f) as described already in detail for similar cases[3b]:

a) Bromination of p-cyclohexyl- and p-*t*-butylphenol (0.4 mol in 400 mL $CHCl_3$, 0.42 mol bromine, room temperature, purification by distillation in high vacuum).

b) Bromomethylation of these o-bromophenols (acetic acid, molar ratio phenol/paraformaldehyde 1:1.5, gaseous HBr; compare the general procedure for **2**). 2-Bromo-6-bromomethyl-4-cyclohexylphenol ($R^1=C_6H_{11}$): 65% of colourless crystals, mp. 88-89°C, directly from the reaction mixture. 2-Bromo-6-bromomethyl-4-*t*-butylphenol ($R^1=C(CH_3)_3$): 72% of an orange oil.

c) Condensation with excess p-*t*-butylphenol: p-*t*-Butylphenol (1.5 mol) was dissolved in 400 mL toluene at 80°C, the bromomethylated phenol (0.25 mol) was added, and the mixture kept at 90°C for 8 h (argon). Steam distillation and recrystallization of the residue from petroleum ether (80-100°C) gave the dinuclear compounds as colourless crystals. 2-(3-Bromo-5-cyclohexyl-2-hydroxybenzyl)-4-cyclohexylphenol ($R^1=C_6H_{11}$): 58%, mp. 129-130°C. 2-(3-Bromo-5-*t*-butyl-2-hydroxybenzyl)-4-*t*-butylphenol ($R^1=C(CH_3)_3$): 55%, mp. 148-150°C.

d) Bromomethylation of these dinuclear compounds: Gaseous HBr was passed through a mixture of 0.1 mol dinuclear compound, 0.2 mol paraformaldehyde and 90 mL acetic acid. From the orange solution a white crystalline precipitate formed (immediately or after storage in a refrigerator) which was recrystallized from toluene/petroleum ether. 2-(3-Bromo-5-cyclohexyl-2-hydroxybenzyl)-6-bromomethyl-4-cyclohexylphenol ($R^1=C_6H_{11}$): 65%, mp. 154-156°C. 2-(3-Bromo-5-*t*-butyl-2-hydroxybenzyl)-6-bromomethyl-4-*t*-butylphenol ($R^1=C(CH_3)_3$): 63%, mp. 116-118°C.

e) Condensation with excess p-cresol: p-Cresol (0.36 mol) was dissolved in 100 mL toluene at 80°C, the bromomethylated dinuclear compound (0.06 mol) was added, and the mixture kept at 100°C for 6 h (argon). Steam distillation and recrystallization of the residue gave the trinuclear compounds as colourless crystals. 2-(3-Bromo-5-cyclohexyl-2-hydroxybenzyl)-4-cyclohexyl-6-(2-hydroxy-5-methylbenzyl)-phenol (R^1=C_6H_{11}): 93%, mp. 178-180°C. 2-(3-Bromo-5-*t*-butyl-2-hydroxybenzyl)-4-*t*-butyl-6-(2-hydroxy-5-methylbenzyl)-phenol (R^1=$C(CH_3)_3$): 78%, mp. 181-183°C.

f) Elimination of bromine by hydrogenation: The trinuclear compound (0.05 mol) was dissolved in 300 mL methanol containing 11.4 g (0.2 mol) KOH. This solution was added with stirring under hydrogen atmosphere to a slurry of Raney-Ni (1 teaspoon) in 100 mL methanol, and the hydrogenation proceeded at room temperature and normal pressure. The catalyst was filtered off, the filtrate dropped into diluted hydrochloric acid and the precipitate recrystallized from ethanol/water to give colourless crystals of 1. 2-(5-Cyclohexyl-2-hydroxybenzyl)-4-cyclohexyl-6-(2-hydroxy-5-methylbenzyl)-phenol (R^1=C_6H_{11}): 81%, mp. 202-204°C. 2-(5-*t*-Butyl-2-hydroxybenzyl)-4-*t*-butyl-6-(2-hydroxy-5-methylbenzyl)-phenol (R^1=$C(CH_3)_3$): 78%, mp. 181-183°C.

General procedure for the preparation of bisbromomethylphenols 2:

A rapid stream of gaseous HBr was passed through a suspension of p-substituted phenol (0.1 mol) and paraformaldehyde (0.3 mol) in 50-70 mL acetic acid for 15 to 20 min. With warming a yellow-brownish, viscous solution was formed, from which a white crystalline precipitate separated, partly during the reaction, partly after storage in a refrigerator. It was filtered, washed with cold acetic acid, dried over KOH and recrystallized to give colourless crystals of 2.

2,6-Bisbromomethyl-4-octylphenol (R^4=C_8H_{17}): 66%, mp. 76-77°C from hexane. 2,6-Bisbromomethyl-4-cyclohexylphenol (R^4=C_6H_{11}): 52%, mp. 77-79°C from toluene. 2,6-Bisbromomethyl-4-phenylphenol (R^4=C_6H_5): 48%, mp. 175-177°C from toluene. 3,5-Bisbromomethyl-4-hydroxybenzoic acid ethylester (R^4=$COOC_2H_5$): 69%, mp. 153-155°C from toluene. 3,5-Bisbromomethyl-4-hydroxyphenylacetic acid ethylester (R^4=$CH_2COOC_2H_5$): 59%, mp. 113-115°C from toluene; 3,5-Bisbromomethyl-4-hydroxyphenylacetic acid (R^4=CH_2COOH): 66%, mp. 155-157°C from ethylacetate/petroleum ether (80-100°C).

General procedure for the preparation of calix[4]arenes 3:

In a 1-L three necked flask equipped with condenser and mechanical stirrer the trinuclear compound 1 and the bisbromomethylated phenol 2 (7.5 mmol each) were dissolved in 250 mL of dry dioxane. Under argon 5.7 g of $TiCl_4$ (30 mmol) were added together with an additional quantity of 250 mL of dioxane and the reaction mixture was kept in an oil bath at 110°C for 60-90 h. The disappearance of 1 was followed by tlc. The dioxane was evaporated i. vac., the residue dissolved in CH_2Cl_2 (200-250 mL), and after addition of 50 g silica gel, the solvent was evaporated again. The silica gel was extracted over night with CH_2Cl_2 in a Soxhlet apparatus. This procedure to separate oligomeric and polymeric byproducts was repeated once Evaporation of the CH_2Cl_2 finally gave a brownish oil which partly crys-

Table 1. Some properties of asymmetrically substituted calix[4]arenes

	yield (%)	mp. °C	^{1}H NMR data (200 MHz, δ-values, $CDCl_3$) OH	ArH	Ar-CH_2-Ar	CH_3	$C(CH_3)_3$	EI-MS m/z (M^+,%)
3a	18.5	229	10.25	7.03[a]	4.24[b]	2.18		662.6 (46)
				6.86[a]	3.46[b]			
3b	13.1	306	10.28	7.02[a]	4.24[b]	2.16	1.22	632.6 (100)
				6.86[a]	3.46[b]			
3c	13.8	450	10.30	7.45-7.82[c]	4.28[b]	2.13	1.23	626.4 (44)
3d	13.2	292	10.22	7.76[d]	4.25[b]	2.16	1.20	622.4 (71)
				7.02[a]	3.6 [b]			
				6.89[d]				
3e	8.8	228	10.24	7.01[e]	4.2 [b]	2.15	1.22	636.4 (100)
				6.85[d]	3.45			
3f	13.6	290	10.29	7.35[f]	4.26[b]	2.13	1.21	652.4 (100)
				7.04[d]	3.5 [b]			
				6.85[b]				
3g	10.9	288	10.24	7.77[d]	4.25[b]	2.14	1.21	648.3 (100)
				7.03[d]	3.5 [b]			
				6.88[a]				

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[a] (m,4H) [b] (br m,4H) [c] (br m,13H) [d] (m,2H) [e] (m,6H) [f] (br m,7H)

tallized. It was further purified by flash-chromatography. The solid white material thus obtained can be recrystallized from acetone and/or methanol. Further data are given for the individual compounds in Table 1.

Chromatography

All compounds (except the bromomethylated ones) were checked for purity by tlc using silica plates of 0.25 mm thickness (POLYGRAMM SIL G/UV_{254}, Macherey-Nagel).
For flash chromatography silica gel (230-400 mesh ASTM, E. Merck) was used in columns of 20 or 40 mm in diameter filled to a height of about 20 cm. A first purification was always achieved with $CHCl_3$, later $CHCl_3$, CCl_4, mixtures of both or heptane/ethylacetate were used as eluents.
Isolation of **4a** by preparative HPLC was done on a RP_{18} column (E. Merck) with THF/water 70:30. All attempts to separate its enantiomers using various commercial columns with chiral stationary phases failed so far.

Spectroscopic Studies

All 2D-NMR spectra were obtained on a Bruker AM-270 equipped with an Aspect-3000 computer. Additional spectra of **4a** and its Na^+-complex were run on a Bruker AM-400. Solutions with a concentration of 0.02-0.03 M in $CDCl_3$ were used.

The 2D-NOE experiment was performed according to the procedure described by Denk et al.[19], based on the difference method first suggested by Bodenhausen and Ernst[20] in which two scans corresponding to the conventional NOESY are coadded, followed by subtraction of two transients which contain only the contribution from the diagonal peaks. Mixing time was 0.8 s. For both the COSY and NOESY experiments 256 t_1 increments were implemented over 512 data points in t_2 dimension. Spectra were collected in the phase-sensitive mode, using the TPPI sequence. Fourier transform was performed after applying a shifted sine bell routine to the raw data in both dimensions, and zero-filling the data matrix to 1024*512.

References and Footnotes

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(11) Although in principle a *single* residue of sufficient size would be enough to prevent racemization by ring inversion, a complete conversion of all OH-groups is necessary for asymmetric calix[4]arenes not to end up with an untractable mixture of isomeric or similar compounds, since due to the four different phenolic units, four different mono- as well as tri-derivatives and six different di-derivatives are possible in the cone-conformation. Furthermore it is essential, for the same reason, to obtain exclusively the cone-conformation, since for a tetra-derivative four diastereomers in the partial cone and two in the *1,2*- respectively *1,3*-alternate conformation are possible.

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(13) In bridged calix[4]arenes (which are fixed in the cone-conformation by the aliphatic chain connecting two opposite p-positions) we observed NOEs between the phenolic OH and the A-part as well as between the aromatic protons in m-position (relative to OH) and the B-part of the AB doublets found for the methylene bridge protons, showing that the quasi-equatorial protons of the methylene bridge appear at higher field.

(14) The following shifts (ppm) are observed for the Na^+-complex of the analogous tetraester derivative of *t*-butyl calix[4]arene in comparison to the free ligand in $CDCl_3$: ArH 0.34, $O-CH_2CO$ -0.34, $Ar-CH_AH-Ar$ -0.62, $Ar-CHH_B-Ar$ 0.20, $O-CH_2-Me$ 0.16, CH_2-CH_3 0.12, $C(CH_3)_3$ 0.06

(15) In benzene-d_6 the difference between the two singlets for the *t*-butyl groups is only 0.14 ppm instead of 0.29 ppm in $CDCl_3$, and two signals are observed for the $O-CH_2-CO$ groups instead of four.

(16) Compare the X-ray structure reported in reference (10b) for a K^+-complex of a tetraamide derivative.

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