Calix[4]arenes, bridged at the upper rim

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Abstract

Calix[4]arenes, in which two opposite p-positions are linked by an aliphatic chain, and their derivatives show transport or complexation properties strongly dependent on the length of this chain. Bicyclo-calix[4]arenes, a special case of *1,3*-bridged calix[4]arenes, and annelated calix[4]arenes, a special case of *1,2*-bridged calix[4]arenes, are also described.

Although the preferred conformation of calix[4]arenes is the cone-conformation due to its stabilization by a cyclic array of hydrogen bonds between the phenolic hydroxyl goups, these molecules are flexible, with a cone to cone inversion rate of about $150 \ s^{-1}$ for a calix[4]arene at 47°C (ref. 1). The cone (or any other) conformation may be fixed by derivatisation of the phenolic oxygens. Another possibility is, to connect two p-positions of opposite (1) or adjacent (3) phenolic units by a suitable bridge. Although partial cone or alternate conformations still are possible in these compounds, the complete ring inversion is entirely prevented by the bridge.

Compounds of type 1 with $(CH_2)_n$-bridges are available by reaction of suitable diphenols with bisbromomethylated phenols in dioxane in the presence of $TiCl_4$ (ref. 2).
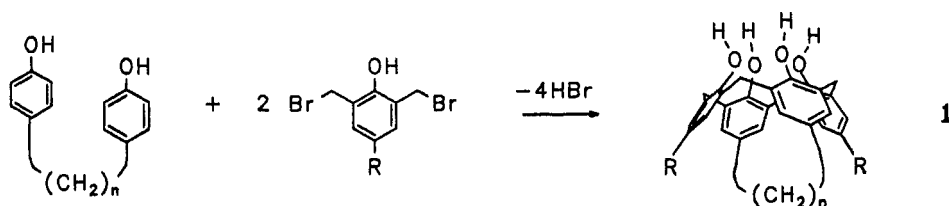
The yields of pure products usually range between 5-25 %, occasionally reaching 35-40 %. The lower limit for n in this synthesis seems to be n=5, but the analogous double calix[4]arenes (compare ref. 3) may be obtained also in other cases as side products.

The X-ray conformational analysis for many of these compounds (ref. 2,4) shows, that the cone conformation, which is always found, is distorted by shorter bridges, leading to two phenolic units being more or less parallel and two units more or less perpendicular. Thus, while the array of intramolecular hydrogen bonds is slightly distorted, the average O-O-distance increases from 2.65 to 2.93 A in going from n=8 to n=5. This weakening of the intramolecular hydrogen bonds can be followed in solution by IR-spectroscopy with ν_{OH}=3179 cm^{-1} for n=14, compa-

rable to the value of 3164 cm^{-1} found for an analogous calix[4]arene, and ν_{OH}=3395 cm^{-1} found for n=5. It becomes evident also from the chemical shift of the OH protons in their ^{1}H-NMR-spectra (Fig. 1). Two different OH groups are found for shorter bridges. The p-substituent in the unbridged units (here Me or t-Bu) has a slight but distinct influence on the OH-resonance in these compounds with a shorter bridge.

Calixarenes are able to transport alkali ions from a basic source phase through a liquid membrane (CH$_2$Cl$_2$/CCl$_4$) to a neutral aqueous receiving phase, with a preference for Cs$^+$ ions, which are most selectively transported by t-butyl calix[4]arene, while the calix[8]arene showed the highest transport rate (ref. 5). When analogous experiments were carried out with a series of compounds 1 (n=5-16, R=Me) (ref. 2), a pronounced maximum for n=8 was found in comparison with n=5,6 or n=9,10. Although the OH-region is somewhat deformed for shorter bridges, the decrease in the ion flux for n=9,10 is better understood by Cs$^+$ ions being held within the calixarene cavity.

This explanation was recently strongly supported by the X-ray structure of the caesium salt of t-butyl calix[4]arene (ref. 6), where the Cs$^+$ ion resides within the cavity formed by the calixarene anion with its negative charge statistically distributed over all four aromatic units. That the caesium-aryl interaction remains stable also in CDCl$_3$ solution, was shown by ^{133}Cs-NMR spectroscopy with a single sharp resonance at -233 ppm, while Cs-t-butylphenolate shows a peak at -34 ppm. When a series of 1 was reacted in a similar fashion with CsF or Cs$_2$CO$_3$ the main Cs-resonance for the compounds with n=7-10 appeared at -161, -190, -209 and -217 ppm in agreement with the complexation of Cs$^+$ within the cavity, while for n=5,6 a peak at 90 or 91 ppm could be interpreted by Cs-oxygen interaction (ref. 7). (Some additional smaller peaks for n=6,7,9,10 are not yet entirely understood.)

Tetraester derivatives of calix[4]arenes, easily available by alkylation with ethyl bromoacetate (or similar esters), are strong neutral ligands which show among the alkali cations a pronounced selectivity for Na$^+$ ions (ref. 1). We have prepared an analogous series 1' derived from bridged calixarenes 1 (n=5-10, R=t-Bu) and determined their complexation constants with Na$^+$, K$^+$ and Ag$^+$ ions in methanol (ref. 8). While the compounds with n=8-10 show the same or even a better complexation behaviour than t-butylcalix[4]arene, a strong decrease in log β is found for shorter chains (Fig. 2). For Na$^+$ for instance, β changes by more than 10^5 in going from n=8 to n=5 and the strongest effect is observed between n=7 and n=6.

To understand this drastic change it is interesting to look at the conformational change reflected in the ^{1}H-NMR spectra of such compounds when complexing a sodium cation (Tab. 1). While the free ligand obviously has C$_2$-symmetry, shown, for example, by two different aromatic protons and two different ether methylene groups, these signals (nearly) coincide for the Na$^+$-complex, showing a fourfold symmetry for the calixarene part. (It may be supposed, that the C$_4$ symmetry shown by corresponding free ligands of unbridged calixarenes in solution is due to a rapid interconversion of the two equivalent conformations with C$_2$-symmetry).

In ligands of this type the alkali ion is held between the phenolic and the carbonyl oxygens, and the optimum arrangement of these ligating
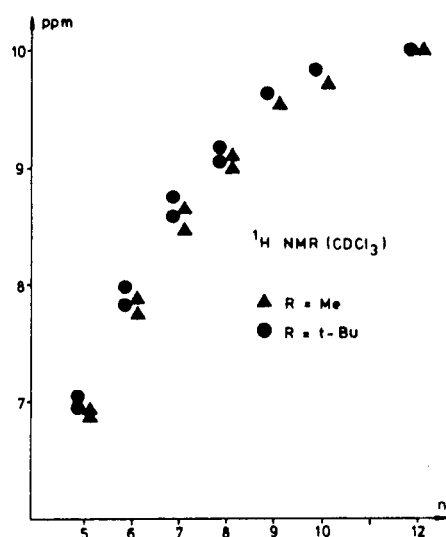
Fig. 1. Chemical shift of
OH-protons in 1 as function
the chain length n.

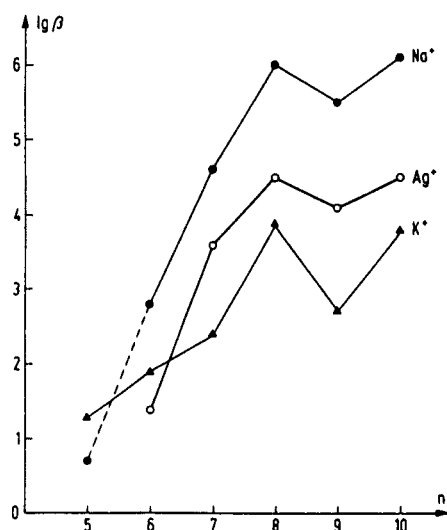Fig. 2. Complexation constants
in tetraesters 1' derived from
1 (R=t-Bu) as function of the
chain length n.

TABLE 1. ^{1}H-NMR spectra of 1' (n=9, R=CH$_3$,
R'=CH$_2$-CO-O-Et) and its Na$^+$-complex (CDCl$_3$,
400 MHz, δ-values in ppm).

Proton	free ligand			Na$^+$-complex		
Ar-H	6.901	(s,	4H)	6.925	(s,	4H)
	6.181	(s,	4H)	6.912	(s,	4H)
O-CH$_2$-CO	5.032	(s,	4H)	4.427	(s,	4H)
	4.428	(s,	4H)	4.423	(s,	4H)
Ar-CH$_2$-Ar	4.786	(d,	4H)	4.168	(d,	4H)
	3.120	(d,	4H)	3.311	(d,	4H)
O-CH$_2$-CH$_3$	4.231	(q,	4H)	4.346	(q,	8H)
	4.114	(q,	4H)			
Ar-CH$_3$	2.315	(s,	6H)	2.084	(s,	6H)
Ar-CH$_2$-	2.05	(m,	4H)	2.40	(m,	4H)
CH$_2$-CH$_3$	1.292	(t,	6H)	1.388	(t,	12H)
	1.229	(t,	6H)			
-(CH$_2$)$_7$-	1.25	(m,	8H)	1.30	(m,	6H)
	1.15	(m,	6H)	0.55	(p,	4H)
				0.41	(p,	4H)

The formula at the right
hand side indicates the
conformational changes
induced by the complexa-
tion.

R' = CH$_2$-CO-O-C$_2$H$_5$
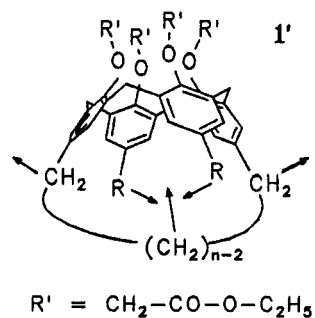
functions obviously requires an overall conformation with fourfold sym-
metry for the calix[4]arene part. The necessary conformational rearran-
gement is obviously possible for longer chains, where the middle of the
chain is pulled into the cavity (which is demonstrated by the upfield
shift of the corresponding methylene signals of the chain), but impos-
sible for the shorter chains n=5 and 6. This is nicely illustrated by
the X-ray structure of such a tetraester, shown in Fig. 3.

Bridged calix[4]arenes with various additional functional groups
within the bridge may be synthesized in a similar manner. Especially
interesting is the -CH$_2$-CH$_2$-CO-CH$_2$-CH$_2$- bridge, which by double aldol
condensation with nitro-malondialdehyde can be converted to a p-nitro-
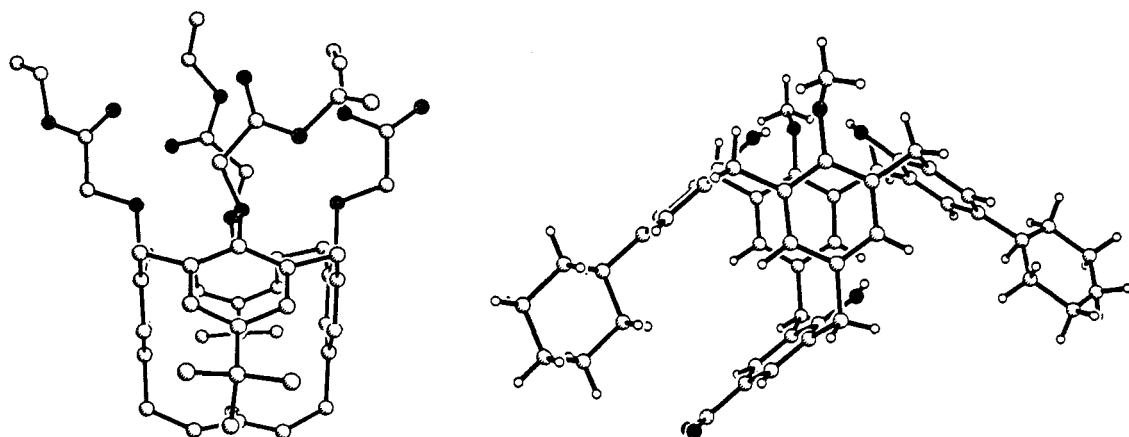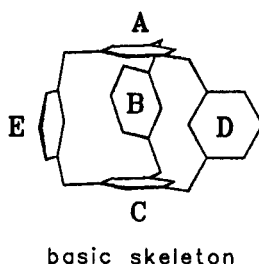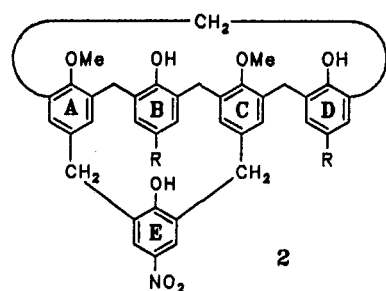phenol unit. This reaction was not succesful up to now with the free

Fig. 3. X-Ray structures of a tetraester derivative of a bridged ca-
lix[4]arene (left) and of a bicyclo-calix[4]arene (right).

calixarene but only with
its dimethyl ether. The
additional phenolic unit
E is linked via methy-
lene bridges to the ad-
jacent phenolic units A
and C, thus creating new
calix[4]arene   systems
(ABCE and ADCE). These
macrobicyclic   molecules
2 may be named "bicyclo-
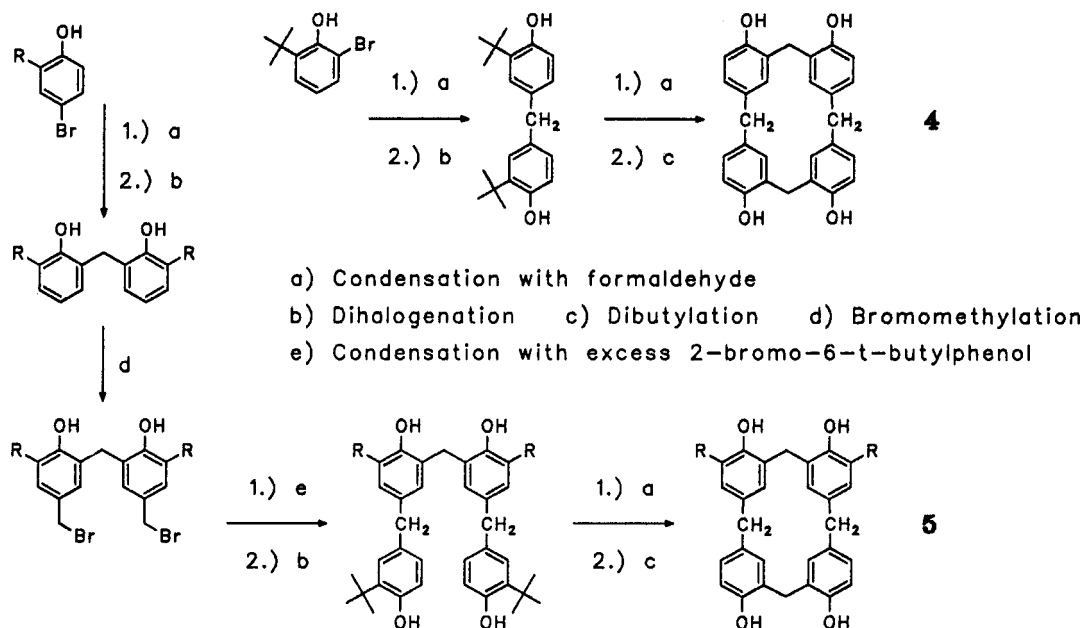calix[4]arenes" for ob-
vious reasons (ref. 9).

An interesting question with these molecules concerns their confor-
mation. Temperature dependent ^{1}H-NMR spectroscopy suggests a rigid cone
conformation for the original calix[4]arene part ABCD, having two OH
and two OCH₃ groups in "endo"-position. This can be deduced from a sin-
gle pair of doublets found for the four methylene bridges. Obviously
two intramolecular hydrogen bonds OH···OCH₃ are sufficient to stabilize
the cone-conformation. The remaining two methylene groups appear as a
singlet, indicating a rapid interconversion between partial cone and
1,3-alternate conformation for the calixarene parts ABCE and ADCE,
where the two OH-groups are in "endo" and the two OCH₃ groups in "exo"
position. The remainder of the spectrum (one singlet for R=t-Bu, three
singlets for the aromatic protons, two singlets for OH with the ratio
2:1) is also in agreement with this interpretation. The rapid movement
of the p-nitrophenol unit (like the clapper in a bell) is frozen on the
^{1}H-NMR time scale between -50°C and -70°C and at -90°C the spectrum is
consistent with the conformation which is found also in the crystalline
state by X-ray analysis (Fig. 3).

Another interesting problem is the reactivity of the p-nitrophenol
unit, the OH-group of which is pointing into the cavity of the calix-
arene ABCD. In agreement with this fact and in contrast to the model
compound (2,6-(4-hydroxybenzyl)-4-nitrophenol) hydrogen bonded comple-
xes with amines are not found. The proton may be abstracted, however,
by bases like LiOH or KOH in methanol. The stronger bathochromic shift
in comparison to the model compound suggests a "poorly" solvated nitro-
phenolate oxygen.

Bridged calix[4]arenes of type 3, in which two adjacent phenolic units are linked by the bridge can be obtained by reaction of a bridged dinuclear compound with a suitable bisbromomethylated dimer (compare ref. 10).
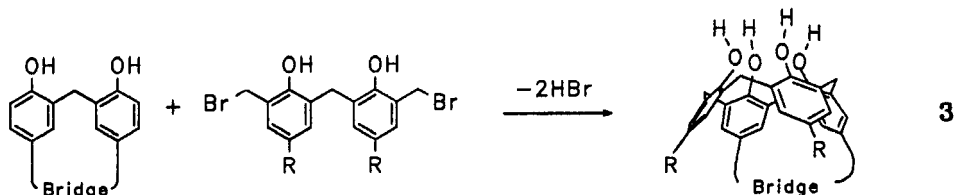
It seemed again most interesting, to make the bridged dimer a calix-[4]arene itself. Such calix[4]arenes with four "exo" OH-groups and two (5) or four (4) free o-positions can be synthesized using bromine and t-butyl as two independent protective groups as outlined in the following scheme.

a) Condensation with formaldehyde

b) Dihalogenation   c) Dibutylation   d) Bromomethylation

e) Condensation with excess 2-bromo-6-t-butylphenol

Condensation of 4 with a bisbromomethylated dimer according Eq. 2 then leads to the annelated calix[4]arenes 6 and 7 in which two or three calix[4]arene substructures are combined in a way analogous to that in which aromatic rings are fused in hydrocarbons like naphthalene, anthracene and so on (ref. 11). An extension of this construction principle to five annelated macrocycles will be possible by the reaction of bisbromomethylated 5 with 4.

Temperature dependent ^{1}H-NMR spectroscopic studies easily show, that the calix[4]arene systems with the OH groups in "endo" position (ABFE and CDGH) assume a "rigid" cone conformation (Fig. 4), while the calix-[4]arene ABCD with "exo" OH groups is in the 1,2-alternate conformation. For type 7 this conformation is required already by large residues (e.g. R=phenyl), but a simultaneous cone conformation of all calix[4]arene systems should be possible for smaller (and mutually attracting) substituents. In molecules of type 6 the 1,2-alternate con-
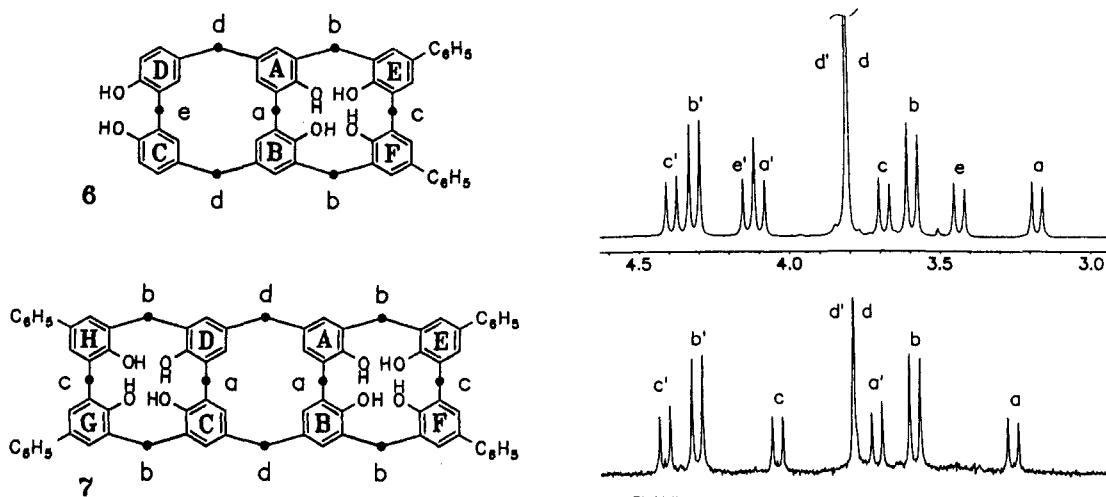
Fig. 4.   Annelated calix[4]arenes and a section of their ¹H-NMR spectra

formation is deduced from NO-effects. Molecular models show, however, that both calix[4]arene substructures should be flexible enough, to allow a cone ⟶ 1,2-alternate inversion, while a complete inversion cone ⟶ cone seems impossible. The latter fact allows the synthesis of inherently chiral calix[4]arenes with free OH groups, when the substituents in the phenolic units C and D or in E and F are different. In first experiments this chirality could be shown by the doubling of NMR-signals in the presence of Pirkle's reagent. At the other hand, the cone conformation for ABCD should be favoured in compounds where four "endo" OH groups are present also in this calixarene part.

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