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CALIX[4]ARENES WITH RESORCINOL UNITS INCORPORATED IN 2,6-POSITION

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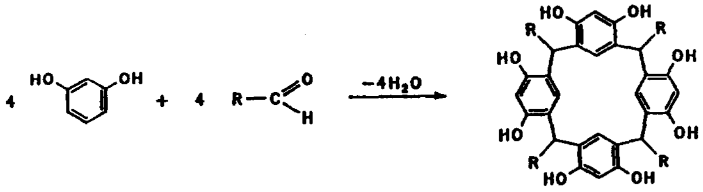
Summary: Calix[4]arenes containing one or two resorcinol units incorporated via their 2,6-positions were prepared by fragment condensation. Due to the cyclic array of intramolecular hydrogen bonds these molecules assume the cone-conformation.

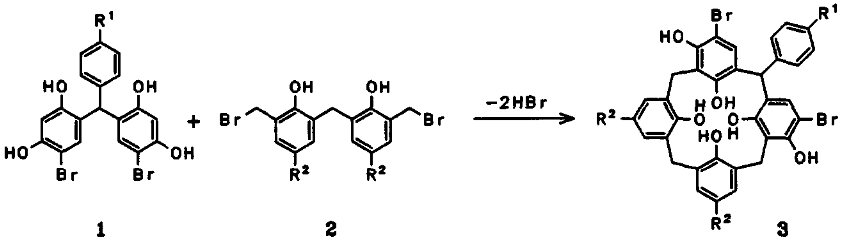
A controlled reaction of resorcinol with higher aldehydes under acidic conditions was first reported by Niederl[1], but the resulting cyclic tetramers were not fully characterized until Högberg[2] established the existence of two diastereomeric compounds. Later Dalcanale[3] isolated a third of four possible diastereomers.



The reaction is now so well understood, that under thermodynamic control with a large variety of aldehydes[4] the all-*cis* isomer can be obtained in high yields[5]; these compounds have been used as starting materials for the preparation of more sophisticated molecules like cavitands[6] and carcerands[7].

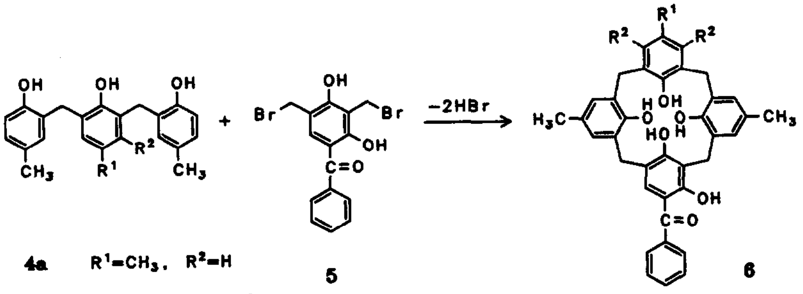
In these resorcinol derived calix[4]arenes all the resorcinol units are connected via alkylidene bridges at the 4,6-positions, which means that all eight OH-groups occupy *exo*-positions relative to the macro ring. In contrast, calixarenes which are obtained by the base induced condensation of p-substituted phenols with formaldehyde have all the OH-groups in *endo*-position, forming a cyclic array of intramolecular hydrogen bonds[8]. We have developed methods which allow the synthesis of calix[4]arenes consisting of different phenolic units[9]. When these methods are applied to suitable resorcinol derivatives calix[4]arenes may be obtained in which the resorcinol units are incorporated via their 2,6-positions. This means, that these compounds have the complete cyclic array of intramolecular hydrogen bonds and one (or more) additional hydroxyl group(s) as substituent(s) in meta-position. Here we report the first examples:

a) 4-Bromoresorcinol reacts with benzaldehyde or p-substituted benzaldehydes (1 h at 75 °C in ethanol with HCl as catalyst) in high yields (80-90%) to afford dinuclear compounds 1. (Similar dinuclear compounds should be available also from other 4-substituted resorcinols and with other aldehydes.) Further condensation with bisbromomethylated dinuclear compounds 2 (dioxane/$TiCl_4$, 120 h at 110 °C) furnishes the calixarenes 3 (ca. 10 % yield) which are easily isolated by flash chromatography.



R^1 = Cl, H, NO_2 R^2 = CH_3, C_6H_5

b) Condensation of 3,5-bisbromomethyl-2,4-dihydroxybenzophenone 5 (readily available in 85 % yield by bromomethylation) with the trinuclear compound 4 gives the corresponding calix[4]arene in 8 % yield.



4a R^1=CH_3, R^2=H

4b R^1=CO-C_6H_5, R^2=OH

As in similar cases the alternative condensation of a bisbromomethylated trimer with a 4-substituted resorcinol gives the calixarenes only in lower yield (1-2%). If **4b** is taken as the trimeric component (easily obtainable in 65% yield by condensation of 5 with an excess of p-cresol), the product calixarene **6b** consists of a mixture of the two possible diastereomers (as indicated in the scheme).

Molecules **6a** are chiral[10]. This can be seen in their ^1H nmr spectra at low temperature where the racemization by interconversion of the opposite cone conformations is slow on the nmr time scale. Here four different methylene groups give rise to four pairs of doublets. Of the 16 possible signals at least 14 are seen in figure 1a and at least one of the doublets is further split in the presence of Pirkles reagent (figure 1b,c), thus confirming the existence of two enantiomeric species.

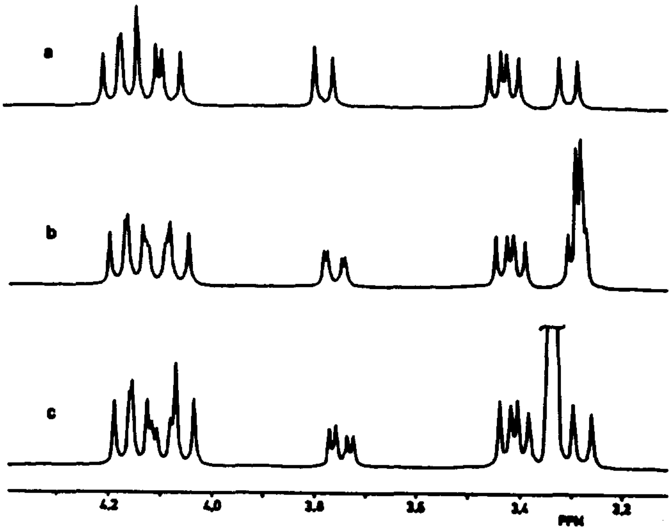


Fig. 1 (a) Section of the ^1H nmr spectra (400 MHz, $CDCl_3$, -40° C) of **6a**; **(b,c)** in the presence of increasing amounts of (S)-(+)-1-(9-anthryl)-2,2,2-trifluoro-ethanol.

In contrast to **6a** the two cone conformations of 3 are diastereomeric, with the substituent $-C_6H_4-R^1$ in either the axial or equatorial position. Each isomer contains two different methylene groups in the ratio 1:2 each giving raise to a pair of doublets. Of the 16 possible signals 14 are again found, with 2 doublets of the A part superimposed (figure 2). Surprisingly the two diastereomers are present nearly to the same extent (ca. 57:43 ratio from nmr integration).

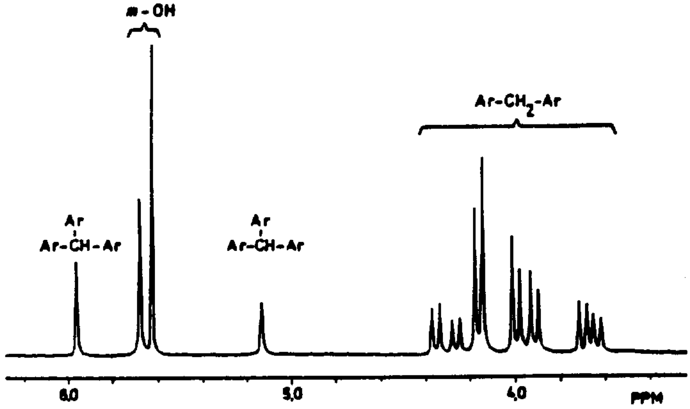


Fig. 2 Section of the ^{1}H nmr spectrum (400 MHz, CDCl$_3$, −40° C) of 3 (R^1 = H, R^2 = C$_6$H$_5$) showing the presence of two diastereomeric cone-conformations.

In summary our results show that 4-substituted resorcinol units can be incorporated via their 2,6-positions into calix[4]arenes in a defined way leading to molecules with the m-hydroxyl groups as additional functional groups close to the cavity. Most probably the yields of the cyclization step can be optimized for individual compounds.

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