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THE SYNTHESIS OF DOUBLE-CALIXARENES

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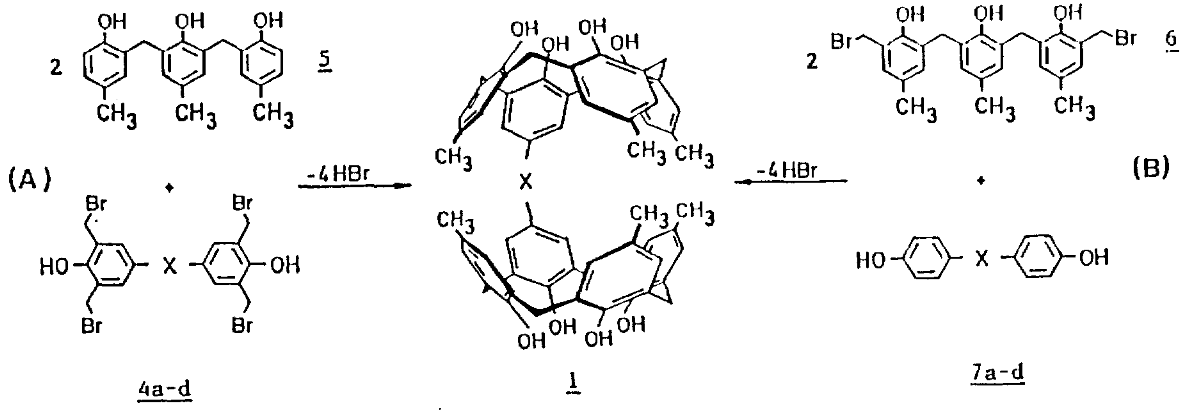
Summary. Macrocyclic molecules consisting of two calix[4]arene moieties linked via their p-positions by one 1, two 2 or four 3 aliphatic chains were synthetized for the first time.

The fact that calix[4]arenes are able to include neutral molecules in their cavity has been shown for several examples in the solid state[1]. However, since the binding forces are weak, in solution those "endo-calix-complexes" are found only in special cases[2]. More efficient binding properties usually are found for ditopic receptor molecules. These are macrocyclic compounds containing two subunits able to encapsulate guest molecules in a cooperative action[3].

In the present note we report our first results on the synthesis of new ditopic receptors made of calix[4]arene[4] moieties connected in p-position by one 1, two 2 or four 3 aliphatic chains with various lengths.

Monolinked double-calixarenes

Double-calixarenes of type 1 were prepared by condensations of either tetrabromomethylated diphenols 4a-d with linear trimer 5 (pathway A) or bis-bromomethylated trimer 6 with diphenols 7a-d (pathway B) performed in refluxing dioxane in the presence of titanium tetrachloride ($TiCl_4$)[5].

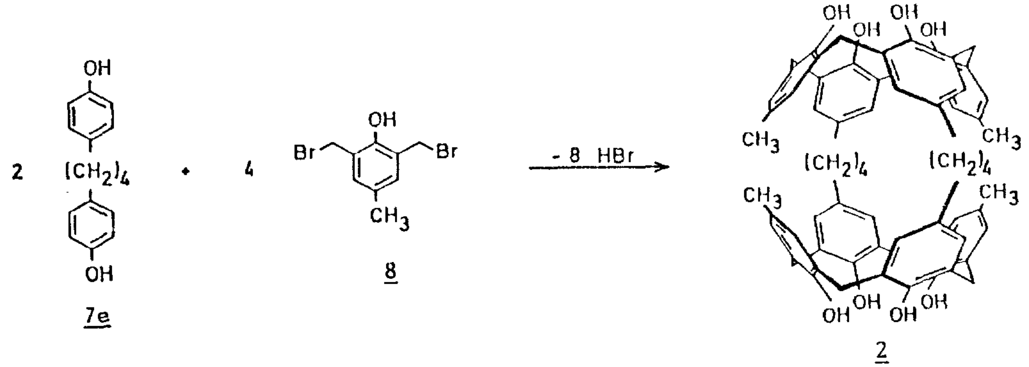


X = CH_3-C-CH_3	$(CH_2)_5$	$(CH_2)_8$	$(CH_2)_{12}$
a	b	c	d

Pathways A and B were used to synthetize 1c and to confirm its structure by independent routes. Pathway A appeared to give higher yields (10-13 % for 1a and 1c) than pathway B (1 % for 1b-d). Despite the low yields all products were readily isolated and purified by flash chromatography[5]. Double-calixarenes 1a-d show the usual ring inversion of calix[4]arenes[4]. For instance, the temperature of coalescence of 1c is 50°C in $CDCl_3$ with a calculated $\Delta G^{\ddagger}$ value[6] of 63.6 $kJ.mol^{-1}$.

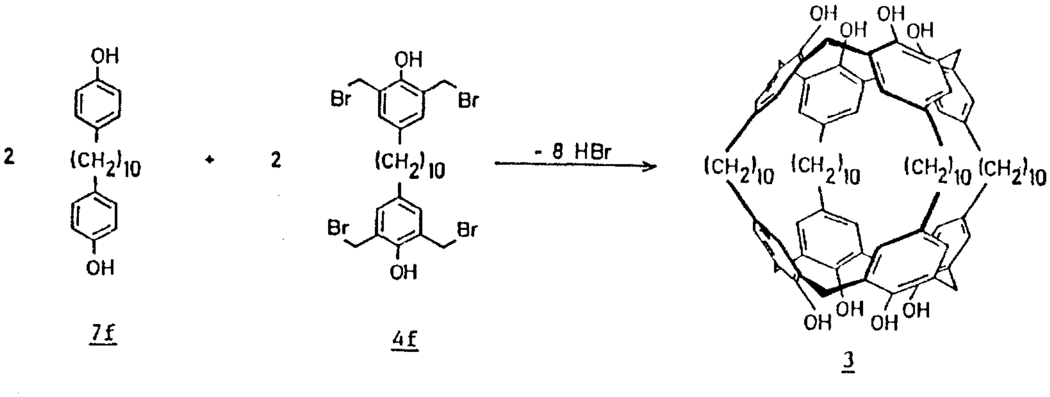
Two-linked double-calixarene

By a similar procedure, 2 was obtained in very low yield by condensation of 2,6-bis-bromomethyl-4-methylphenol 8 with the diphenol 7e (n =4). It is noticed elsewhere that for n > 4 bridged calix[4]arenes are obtained[7]. Although 2 was confirmed by the molecular ion in the mass spectrum, its structure follows already unambigously from the ^1H NMR spectrum[5]. A singlet at 9.93 ppm for the OH-groups shows the strongly hydrogen bonding cyclic array of hydroxyl groups of an undistorted calix[4]arene systems, while the OH-protons are high field shifted in the distorted cone conformation of a bridged calix[4]arene. As expected, the benzylic protons show a stable AB-system at all temperatures.



Four-linked double-calixarene

Similar the double-calixarene 3 was obtained in very low yield by condensation of the tetrabromomethylated diphenol 4f (n = 10) with the parent diphenol 7f (n = 10).



Here again the structure was definitively proved by the temperature independent AB-system of benzylic methylene protons. The undistorted calix[4]arene parts in cone conformation are also shown by the singlet for the OH-protons at 10.04 ppm. The structure of 3 is reminiscent of the structure of cryptophanes made of two cycloveratrylene units[8].

To conclude, double-calixarenes of type 1 are readily available by pathway A. Work is in progress to improve the reaction conditions of preparation of 2 and 3 as well as to disclose other strategies for their synthesis. According to the designed conformation of 1, the cavity formed by the two calix[4]arene subunits can be described as face-to-face cavity. A very similar face-to-face cavity has been observed during the inclusion of anisole by p-tert-butyl calix[4]arene in the solid state[9]. Attempts are under investigation to form similar complexes by crystallization of 1c in appropriate solvents.

References

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4. For general reviews on calixarenes see C.D. Gutsche, Acc. Chem. Res., 1983, 16, 161 ; C.D. Gutsche, Top. Curr. Chem., 1983, 123, 1.
5. 4,4'-Isopropylidenediphenol 7a was purchased from Aldrich Company. Diphenols 7b-f, trimer 5 and tetrabromoderivatives 4 were prepared according to V. Böhmer, F. Marschollek and L. Zetta, J. Org. Chem. 1987, 52, 3200 ; V. Böhmer, L. Merkel and U. Kunz, J. Chem. Soc., Chem. Commun. 1987, 896 ; H. Casablanca, J. Royer, A. Satrallah, A. Taty-C. *and J. Vicens,* Tetrahedron Lett. 1987, 6595 ; H. Goldmann, W. Vogt, E. Paulus and V. Böhmer, J. Am. Chem. Soc. 1988, 110, 6811. The following experimental procedure for preparation of 1a is representative : in a 1L three-necked flask equipped with condenser, dropping funnel and mechanical stirrer a mixture of 400 mL of freshly distilled dioxane and of 2 mL (18.3 mmol) of $TiCl_4$ was refluxed. During 8 h a solution of 2.00 g (3.3 mmol) of tetrabromomethylated diphenol 4a and 2.29 g (6.6 mmol) of trimer 5 in 200 mL of dioxane was added. The reaction was continued for 80 h and then the solvent was removed in vacuum. The residue was directly separated by flash chromatography on silica with $CHCl_3$ to yield double-calixarene 1a as a white solid (420 mg). mp > 300°C. Yield 13 %. ^1H NMR ($CDCl_3$, 80 MHz) δ *10.10 (s, 8, ArOH), 6.66-7.00 (m, 16, aromatics), 4.21, 3.43 (s large, 16,* Ar-CH_2-Ar), 2.19 (s, 18, Ar-CH_3) 2.07 ppm (s,6, CH_3-C-CH_3).

   All compounds were characterized by ^1H-NMR-spectra :
   1c : ($CDCl_3$, 200 MHz) δ 10.13 (s, ArOH), 6.83, 6.81 (s, ArH), 4.16, 3.43 (br d, Ar-CH_2-Ar), 2.39 (t, Ar-CH_2-), 2.14, 2.12 (s, Ar-CH_3), 1.54, 1.27 ppm (m, -$(CH_2)_6$-).

2 : ($CDCl_3$, 200 MHz) δ 9.93 (s, ArOH), 6.84, 6.48 (s, ArH), 4.16 (d, Ar-CH_2-Ar, J_{AB} = 13.8 Hz), 3.35 (d, Ar-CH_2Ar, J_{AB} = 13.8 Hz), 2.57 (br t, Ar-CH_2-), 1.55 (m, -$(CH_2)_2$-), 1.17 ppm (s, Ar-CH_3).

3 : (C_6D_5Br, 400 MHz) δ 10.04 (s, ArOH), 6.56 (s, ArH), 4.11 (d, AR-CH_2-Ar, J_{AB} = 14.3 Hz), 3.22 (d, Ar-CH_2-Ar, J_{AB} = 14.3 Hz), 2.16 (br t, Ar-CH_2-), 1.22, 1.02 ppm (m, -$(CH_2)_8$-).

All analytical data were in agreement with the proposed structures.

6. $\Delta G^{\ddagger}$ was calculated according to H. Günther "NMR Spektroskopie" Georg Thieme Verlag. Stuggart New York, 1983.

$$\Delta G^{\ddagger} = 19.13\, T_c\, (9.97 + \log T_c - \log(\nu_A - \nu_B))$$

with T_c = 323 K and ν_A = 836.03 and ν_B 681.26 Hz

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