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Concave Reagents - 19. Synthesis, Structure, and Basicity of a Calix[6]arene Bridged by an Aniline[1]

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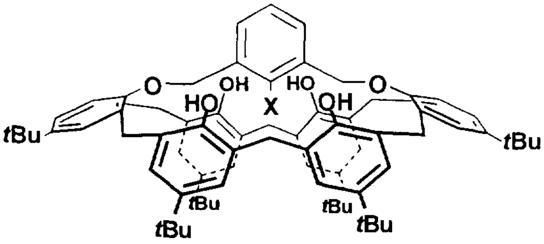
Abstract: The bridged calix[6]arene **2**, the first concave aniline, was synthesized via the nitro compound **1** using iron pentacarbonyl as reducing agent. The basicity of **2** was investigated qualitatively and quantitatively. On the NMR time scale both compounds adopt a C_{2v}-symmetrical conformation but variable temperature NMR measurements reveal that **1** is in a C_s-symmetrical shape at deep temperatures. Copyright © 1996 Elsevier Science Ltd

According to the concept of concave reagents,[2] a variety of bimacrocyclic concave acids and bases such as pyridines, 1,10-phenanthrolines, carboxylic acids and sulfinic acids have been synthesized by incorporation of an appropriate functional group into a concave environment. Many of these concave reagents have been employed in model reactions leading to improved selectivities due to the concave shielding of the functional group. Several synthetic strategies have been applied in order to obtain concave reagents. A new approach to concave pyridines implies the bridging of *p-tert*-butylcalix[6]arene[3] with a bridge which contains the functional group.[1,4] Recently, bridged calix[6]arenes containing functional groups in the bridge were also described by Okazaki et al.[5] Here we report the synthesis and structure of new bridged calixarenes **1** and **2**.



1: X = NO_2
2: X = NH_2
3: X = H
4: X = Br

Scheme 1

The A,D-bridged[6] calixarene **1** was prepared in 64 % yield from *p-tert*-butylcalix[6]arene and 1,3-bis(bromomethyl)-2-nitrobenzene in the presence of sodium hydride in refluxing THF/DMF without high dilution. According to its ^1H NMR spectrum **1** is in a C_{2v}-symmetrical (**u**,u,u,u,u,u)[7] cone-like conformation which has been observed in the case of the pyridine bridged calix[6]arenes[1,4] or the similar *m*-xylylene bridged calix[6]arene **3** possessing the same framework.[8] The spectrum features two singlets in a 2:1 ratio for the *tert*-butyl hydrogen atoms and one broad singlet for the hydroxyl hydrogen atoms. In contrast to the spectra of the pyridine bridged calix[6]arenes or compound **3** pronounced line broadenings are observed in the methylene region. Especially the oxymethylene signal is broadened to such an extent that it nearly cannot be distinguished from the baseline (see figure 1a). The spectrum becomes more lucid upon cooling. Below -50 °C there are three *tert*-butyl resonances (ratio 1:1:1) and two singlets belonging to the hydroxyl groups. The oxymethylene hydrogen atoms appear as two AB doublets at 4.75 and 5.88 ppm (figure 1b). The spectrum indicates a C_s-symmetrical molecule. Apparently at low temperatures the nitro group of the bridge is pointing sideways and not into the cavity. Upon heating the bridge swings from one side to the other in the course of which the nitro group passes the rim of the calixarene cavity. The free enthalpy of activation $\Delta G^{\neq}$ = 14 kcal mol^{-1} for this motion was determined from the coalescence temperature for the *tert*-butyl and the hydroxyl resonances. A similar compound **4** possessing a bromine atom instead of a nitro group is reported to show a similar behavior.[5c] In this case the $\Delta G^{\neq}$ value is 16 kcal mol^{-1} which is consistent with the fact that a nitro group is moderately smaller than a bromine atom.[9]

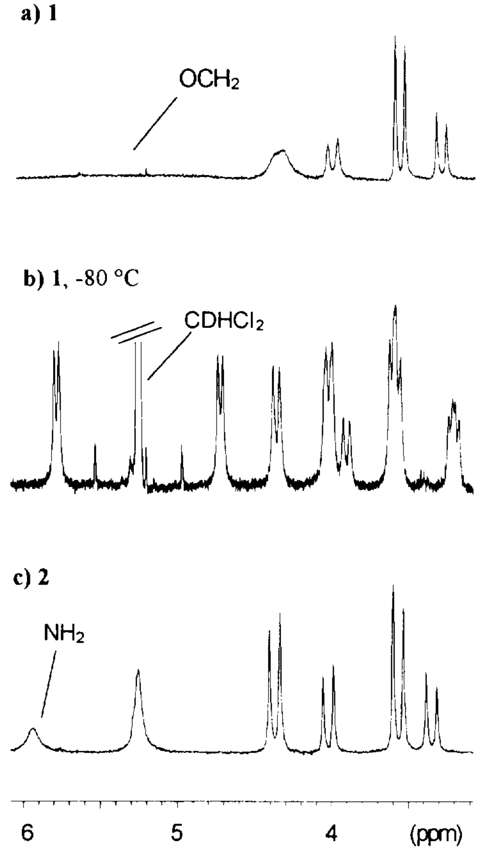


Figure 1. Parts of NMR spectra of **1** and **2**

However, the aim of this work was the synthesis of the aniline **2**. For this purpose **1** was treated with common reducing agents known to be compatible with groups attached to benzylic hetero atoms. But these attempts to reduce the nitro group of **1** to an amino group either failed or resulted in cleavage of the bridge from the calixarene framework. Finally the synthesis of **2** was accomplished by a phase transfer catalyzed reduction with iron pentacarbonyl in the presence of sodium hydroxide.[10] Under these conditions the $[HFe(CO)_4]^-$ anion is formed and the reaction is assumed to proceed via an electron transfer pathway. This method furnished the aniline bridged calix[6]arene **2** in 67 % yield. Hence a new member is added to the family of concave reagents since **2** is the first concave aniline.

The ^1H NMR spectrum of **2** is quite similar to that of **3**[8] or to the pyridine bridged calixarenes.[1,4] It is characteristic of a C_{2v}-symmetrical A,D-bridged calix[6]arene and features sharp signals in the diaryl methylene region, whereas the singlet for the oxymethylene hydrogen atoms at 5.29 ppm is slightly broadened (see figure 1c). According to the NMR data, the bridge of **2** swings faster through the annulus than the bridge of **1** which is plausible since an amino group is sterically less hindered than a nitro group. However, temperature-dependent NMR spectra could not be recorded because of the low solubility of **2** at temperatures below - 25 °C so that $\Delta G^{\neq}$ could not be determined. In the case of the pyridine bridged calix[6]arenes only line broadening but no coalescence was observed down to - 80 °C in dichloromethane. Assuming a similar splitting of the *tert*-butyl singlet (36 H) by 0.06 ppm below - 80 °C as observed in the case of **1**, $\Delta G^{\neq}$ for the swinging of the pyridine bridge must be smaller than 10 kcal mol^{-1}. Therefore $\Delta G^{\neq}$ of the concave aniline **2** must be between 10 and 14 kcal mol^{-1}.

When picric acid is added to a solution of **2** in $CDCl_3$, most signals in the spectrum are not affected, but the two signals of the aniline moiety are shifted significantly to lower magnetic field ($\Delta\delta$ = 0.62 and 0.21 ppm). This is due to the protonation of the amino group which causes a stronger electron-withdrawing effect and proves the basic character of **2**. Another result of the protonation is the fairly broadening of the oxymethylene resonance which can be explained by an inhibited motion of the bridge through the annulus in comparison to the unprotonated species.

A photometrical titration against thymol blue in ethanol was used for quantitative determination of the basicity of 2.[11] This method furnishes relative basicities log K in ethanol for protonation instead of pK_a values in water and has been applied for most concave bases. On the thymol blue scale, log K of the pyridine bridged calixarene is ca. 1.3[1] but log K of **2** is only -0.9. Presumably a stabilization of the protonated species by hydrogen bonds to the lateral hydroxyl groups which has been discussed as an explanation for the increased basicity of the pyridine bridged calixarene does not occur in **2**.

EXPERIMENTAL

Nitro compound **1**: Under nitrogen, 1.95 g (2.00 mmol) of *p-tert*-butylcalix[6]arene[3a] was added to a suspension of 480 mg (ca. 12 mmol) of sodium hydride [the dispersion in mineral oil (60 %) was washed three times with *n*-pentane] in 250 ml of THF/DMF (9:1). A solution of 742 mg (2.40 mmol) of 1,3-bis(bromomethyl)-2-nitrobenzene[9c] in 50 ml of THF/DMF (9:1) was added dropwise to the boiling mixture. After 18 h of refluxing, 20 ml of methanol was added. Most of the solvents was evaporated and the residue was dissolved in 600 ml of diethyl ether. The ethereal solution was washed four times with 75 ml portions of water and dried with magnesium sulfate. The crude product was separated (64 % yield) by chromatography [silica gel, dichloromethane/cyclohexane (1:1), R_f 0.37] from remaining *p-tert*-butylcalix[6]arene (R_f 0.65, 10 % yield) and purified by recrystallization from dichloromethane/methanol, m. p. 222 - 224 °C (dec.). - IR (KBr): $\tilde{\nu}$ = 3341 (OH), 1541 (NO_2), 1362 ($CH_3 + NO_2$). - ^1H NMR (300 MHz, CD_2Cl_2, - 80 °C): δ = 1.10 (s, 18 H, $C(CH_3)_3$), 1.18 (s, 18 H, $C(CH_3)_3$), 1.24 (s, 18 H, $C(CH_3)_3$), 3.10 - 3.17 [m (2 d), 2 H, Ar-CH_2-Ar], 3.50 - 3.58 [m (2 d), 4 H, Ar-CH_2-Ar], 3.88 (d, J = 13.5 Hz, 1 H, Ar-CH_2-Ar), 3.98 - 4.02 [m (2 d), 3 H, Ar-CH_2-Ar], 4.36 (d, J = 12.8 Hz, 2 H, Ar-CH_2-Ar), 4.75 (d, J = 9.8 Hz, 2 H, Ar-CH_2-O), 5.88 (d, J = 9.8 Hz, 2 H, Ar-CH_2-O), 6.97 - 7.13 [m, 12 H, Ar-*H* (calix)], 7.60 [A_2B, J = 7.4 Hz, 1 H, Ar-*H* (bridge)], 7.70 [A_2B, J = 7.4 Hz, 2 H, Ar-H (bridge)], 8.17 (s, 2 H, O*H*), 8.78 (s, 2 H, O*H*). - MS (EI, 70 ev): m/z (%) = 1120 (M^+, 61), 973 (100). - MS (CI, isobutane): m/z (%) = 150 ($C_8H_7NO_2 + H^+$, 100). - $C_{74}H_{89}NO_8$ (1120.5): calcd. C 79.32, H 8.01, N 1.25, found C 79.07, H 7.98, N 1.24.

Amino compound **2**: To a solution of 560 mg (500 µmol) of **1** in 10 ml of benzene, 75 µl (550 µmol) of iron pentacarbonyl, 10 ml of 1 N NaOH and ca. 50 mg of Aliquat 336 were added. The resulting suspension was stirred for 8 h and was then poured into ca. 40 ml of dichloromethane, 15 ml of water was added. The organic layer was separated, washed twice with 15 ml portions of water, and dried with magnesium sulfate.

The crude product was purified by chromatography [silica gel, dichloromethane/cyclohexane (1:1), R_f 0.18] and recrystallization from dichloromethane/methanol yielding 67 % of colorless crystals, m. p. 229 - 231 °C (dec.). - IR (KBr): $\tilde{\nu}$ = 3437, 3374 (OH, NH_2). - ^1H NMR (200 MHz, $CDCl_3$): δ = 1.20 (s, 18 H, $C(CH_3)_3$), 1.25 (s, 36 H, $C(CH_3)_3$), 1.56 ($\approx$ 4 H, H_2O), 3.42 (d, J = 13.8 Hz, 2 H, Ar-CH_2-Ar), 3.56 (d, J = 13.5 Hz, 4 H, Ar-CH_2-Ar), 4.06 (d, J = 13.8 Hz, 2 H, Ar-CH_2-Ar), 4.37 (d, J = 13.5 Hz, 4 H, Ar-CH_2-Ar), 5.29 (s, 4 H, Ar-CH_2-O), 5.93 (br. s, 2 H, NH_2), 6.67 [t, J = 7.5 Hz, 1 H, Ar-H (bridge)], 7.08 [d, J = 2.4 Hz, 4 H, Ar-H (calix)], 7.11 [d, J = 2.4 Hz, 4 H, Ar-H (calix)], 7.14 [s, 4 H, Ar-H (calix)], 7.18 [d, J = 7.5 Hz, 2 H, Ar-H (bridge)], 8.52 (s, 4 H, OH). - MS (EI, 70 ev): m/z (%) = 1090 (M^+, 16), 1073 (M^+ - NH_3, 10), 973 (97), 648 (100). - $C_{74}H_{91}NO_6 \cdot 1.5\ H_2O$ (1090.5 + 9.0): calcd. C 79.53 H 8.48 N 1.25, found C 79.70 H 8.31 N 1.20.

REFERENCES AND NOTES

1. Concave Reagents 18: Ross, H.; Lüning, U. *Liebigs Ann.*, in press.
2. a) Lüning, U. *Liebigs Ann. Chem.* **1987**, 949 - 955. - b) Lüning, U. *Top. Curr. Chem.* **1995**, *175*, 57 - 99.
3. a) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238 - 242. - On calixarenes in general see: b) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989. - c) Vicens, J.; Böhmer, V., Eds. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Dordrecht, 1991. - d) Böhmer, V. *Angew. Chem.* **1995**, *107*, 785 - 818; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713 - 745.
4. Ross, H.; Lüning, U. *Angew. Chem.* **1995**, *107*, 2723 - 2725; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2555 - 2557.
5. a) Tokitoh, N.; Saiki, T.; Okazaki, R. *J. Chem. Soc. Chem. Commun.* **1995**, 1899 - 1900. - b) Saiki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, *61*, 2924 - 2925. - c) Saiki, T.; Goto, K.; Tokitoh, N.; Goto, M.; Okazaki, R. *Tetrahedron Lett.* **1996**, *37*, 4039 - 4042.
6. A,D-bridging is defined as the connection of two opposite phenol rings of a calix[6]arene. The alternative term 1,4-bridging does not correspond to the numbering of the calix[6]arene oxygene atoms (37-42).
7. Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572 - 6579.
8. Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 1542 - 1547.
9. a) Vögtle, F. *Tetrahedron Lett.* **1969**, 3193 - 3196. - b) Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5299 - 5318. - c) Vögtle, F.; Grütze, J.; Nätscher, R.; Wieder, W.; Weber, E.; Grün, R. *Chem. Ber.* **1975**, *108*, 1694 - 1711.
10. des Abbayes, H.; Alper, H. *J. Am. Chem. Soc.* **1977**, *99*, 98 - 101, and ref.
11. a) Lüning, U.; Müller, M. *Liebigs Ann. Chem.* **1989**, 367 - 374. - b) Lüning, U.; Baumstark, R.; Peters, K.; v. Schnering, H. G. *Liebigs Ann. Chem.* **1990**, 129 - 143.

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