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Synthesis of a Novel 1,4-Bridged Calix[8]arene "Host" Cavity

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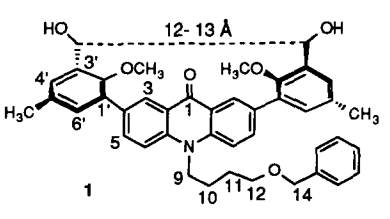
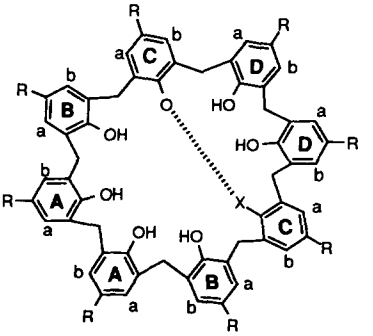
Abstract: A conformationally stable, acridone-based linker (**1**) was synthesized and attached to *p-tert*-butylcalix[8]arene (**2**) to form the novel 1,4-bridged calix[8]arene derivative **3**. The structural assignment of **3** was based on its MS and high-field NMR data and supported by molecular modeling calculations. © 1997 Elsevier Science Ltd.

In recent years, the chemistry of complex formation between calixarene *hosts* and a variety of *guests* has been under extensive investigation.[1] The inclusion properties of both hydrophobic[2] and water soluble[3] calix[8]arenes have been explored and the selective complexation of large aromatic compounds (eg C_{60}), as well as small neutral organic molecules has been observed. In the latter case, the binding of *two* guests for each calix[8]arene host was reported,[3b] suggesting that these conformationally flexible molecules can adopt an induced-fit-type complexation, creating two half-cavities. Thus, immobilization of the conformational freedom of a calix[8]arene cavity, coupled with appropriate molecular recognition elements, should enhance its selective binding of small organic molecules, creating a novel mimic of a biological receptor.[4] Such a molecule might also be useful as a catalyst or in the development of new materials for affinity-type chromatography. In this report, we present the synthesis of the novel 1,4-bridged *p-tert*-butylcalix[8]arene analog **3** and molecular modeling calculations indicating that this molecule adopts an energetically favorable "pinched" conformation with two slightly non-symmetrical host cavities (Fig. 1).



2 R = *t*-Bu, n = 8
4 R = *t*-Bu, n = 4



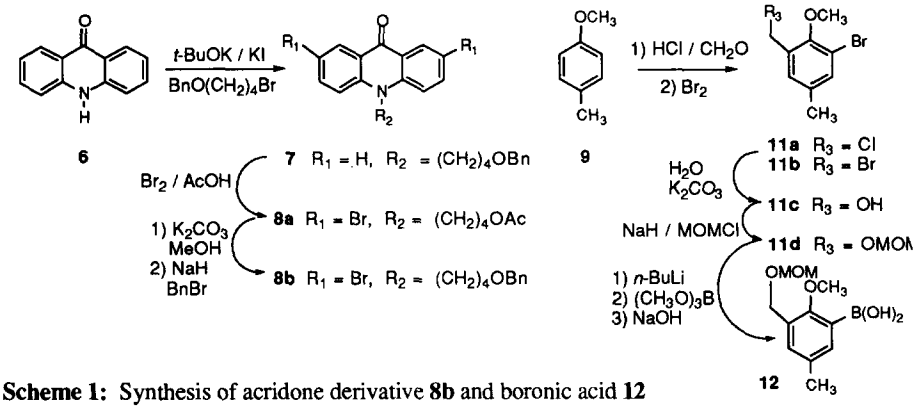
3 R = *t*-Bu, X = O
5 R = *t*-Bu, X = -OH, HO-

The conformational properties of *p-tert*-butylcalix[8]arene (**2**) have been analyzed by solution ^{1}H NMR,[5] ^{13}C (CPMAS) NMR[6] and X-ray crystallography.[7] In all cases the phenol rings within the macrocycle were found to have the same relative orientation giving rise to only one set of NMR resonances. From Gutsche's pioneer studies on these molecules, it is known that the most stable conformation of **2** in the solid state is a flat "pleated-loop" conformation, whereas in solution the cyclic octamer **2** may behave as though it were a dimer of the cyclic tetramer, calix[4]arene **4**, due to a stable "pinched" conformation.[8] A dynamic equilibrium (pseudorotation)

that is fast on the NMR time scale was proposed by Gutsche in order to explain the single set of NMR resonances observed for **2** in nonpolar solvents.[8]

We have examined the static "pinched" conformations of the *p-tert*-butylcalix[8]arene (**2**) cavity using molecular mechanics calculations, based on Allinger's MM2 force field,[9] and found that it has two symmetrical binding pockets (C_2 symmetry) with four distinct environments for the eight aryl units (Fig. 1). Within each four-unit substructure (*A, B, C, D*), the hydroxyl groups belonging to the *A, B* and *C* rings are hydrogen bonded, whereas the fourth aryl group (*D*) is twisted in such a manner that hydrogen bonding is not possible. The distance between the hydroxyl groups (O-O) was calculated to be approximately 6-7 Å along the narrow (pinched) axis of the cavity and 11-12 Å along the long axis. With these values in mind, we subsequently designed the conformationally stable bifunctional linker **1** which could be used to cross-link the 1,4- or 1,5-phenoxy groups of **2** along the long axis of the oval cavity, thus rigidifying the binding pocket (Fig. 1). Although molecular modeling calculations showed that the bridging distance in linker **1** (C3'$\underline{C}H_2OH$ to C3'$\underline{C}H_2OH$) is slightly greater than that of the cavity (~12 Å for the *cis* conformer and ~13 Å for the more stable *trans* conformer shown in **1**), given the flexibility of **2** these variations were not deemed significant.

Preparation of linkers **1** required the synthesis of the dibromo acridone derivative **8b** and the boronic acid **12** (Scheme 1). *N*-alkylation of commercially available acridone (**6**) to the corresponding benzyl derivative **7** was achieved using 4-benzyloxy-1-bromobutane (previously prepared from 1,4-dibromobutane and benzyl alcohol)[10] in the presence of *t*-BuOK and KI. However, subsequent bromination of **7**, using bromine in refluxing acetic acid,[11] led to the acetyl derivative **8a** instead of the desired product.[12] Compound **8b** was finally obtained after hydrolysis of the acetate in base and re-protection of the free alcohol with benzyl bromide (Scheme 1).



Scheme 1: Synthesis of acridone derivative **8b** and boronic acid **12**

Preparation of compound **12** (Scheme 1) involved the initial alkylation of commercially available 4-methyl anisole (**9**) to 2-chloromethyl-4-methyl anisole (**10**) using excess formaldehyde in concentrated HCl and HCl gas.[13] After bromination of **10**, a mixture of 2-bromo-4-methyl-6-chloromethyl anisole (**11a**) and 2-bromo-4-methyl-6-bromomethyl anisole (**11b**) was obtained which was converted to the common hydroxy intermediate **11c** under basic conditions and then protected as the methoxymethyl (MOM) ether (**11d**). Compound **11d** was subsequently converted to the the corresponding boronic acid **12**, upon treatment with *n*-BuLi at -78 °C followed by trimethyl borate and aqueous NaOH.[14] All of the intermediates leading to the synthesis of both **8b** and **12** were obtained in good to excellent yields (65-95%) and characterized by MS, ^1H and ^{13}C NMR.

Palladium catalyzed Suzuki-type coupling[14] between the acridone derivative **8b** and the boronic acid **12**, followed by hydrolysis of the MOM-ethers under mild acidic conditions, led to the isolation of the

bifunctional linker **1** in 60% yield over the two steps.[15] The dibromo derivative of **1** was prepared with PBr_3 and then coupled to *p-tert*-butylcalix[8]arene (**2**) in refluxing THF in the presence of NaH (10 eq). The bridged compound **3** and the singly cross-linked adduct **5** were isolated from the reaction mixture in only 5-10% yield after purification. The formation of other products was also evident by TLC. However, they were formed in very small amounts and their characterization was not pursued.

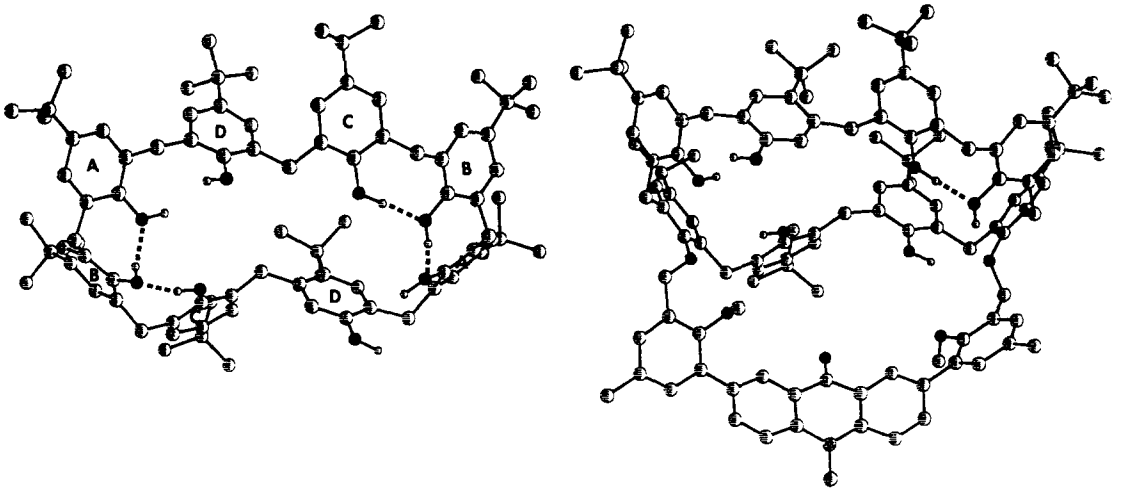


Figure 1: Energy-minimized structures of the conical conformation of calix[8]arene **2** and the 1,4-bridged product **3** (compound **3** was minimized with a N-CH_3 substituent in order to simplify the calculations).

Both the MALDI and ES MS spectra of compounds **3** and **5** were consistent with the molecular formulas $C_{130}H_{151}O_{12}N$ and $C_{130}H_{153}O_{13}N$, respectively [MALDI MS *m/z* 1941.9 and 1959.8 $(M+Na)^+$, ES MS *m/z* 1917.5 and 1935.5 $(M-H)^-$, calculated mass for $C_{130}H_{151}O_{12}N$ 1918.87 and for $C_{130}H_{153}O_{13}N$ 1936.88]. The structural identity of compound **3** was confirmed from detailed analysis of its ^1H, COSY, HMQC and NOESY NMR data.[16] The ^1H NMR spectrum of **3** showed the presence of four different *t*-butylphenol rings [*A*, *B*, *C* and *D*, two different protons in each ring (labeled Ha and Hb)] and five different methylene units connecting these rings (integral ratio 1:2:2:2:1). Molecular modeling calculations of all four possible bridged products indicated that these NMR data could only result from a 1,4- or a 1,2-bridged calix[8]arene product. However, the formation of the latter compound was highly disfavored and it could only be formed by severely distorting the acridone moiety of the linker.[17] Thus, we have assigned the structure of the 1,4-bridged calix[8]arene analog to our product (compound **3**); this assignment is completely consistent with all of the NMR data observed, including the expected NOEs between the methylenes of the linker (C3'-CH_2-O-*C*) and the methylenes linking rings *B* to *C* of the calix[8]arene. A weak NOE was also observed between the H4' protons of the linker and the methylene groups linking rings *C* to *D*. The protons of the *D* rings, as well as the methylene groups between the two *D* rings, gave rise to the broadest signals in the ^1H NMR spectrum of **3**. This broadening may indicate a higher degree in conformational rigidity on one side of the molecule relative to the other. A key structural feature of this novel calix[8]arene derivative (**3**) is that it has an appropriately functionalized "side-arm", the benzyl protected alcohol of the linker, which could serve as an anchor in order to attach **3** to a solid support. A more efficient synthesis of **3** and an investigation of its potential applications in "guest-host" chemistry are currently in progress in our laboratory.

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15. Compound **1:** Rf = 0.16 in 1:3 hex:EtOAc. Mp. 170-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (m, 2H11), 2.03 (m, 2H10), 2.25 (s, 6H, C5'-C<u>H</u>$_3$), 3.28 (s, 6H, C2'-OC<u>H</u>$_3$), 3.56 (t, J = 6.0 Hz, 2H12), 4.38 (t, J = 7.8 Hz, 2H9), 4.47 (s, 2H14), 4.63 (s, 4H, C3'-C<u>H</u>$_2$OH), 7.05 (d, J = 1.8 Hz, 2H4'), 7.14 (d, J = 2.1 Hz, 2H6'), 7.25 (m, 5H, C14-<u>Ph</u>), 7.47 (d, J = 9.0 Hz, 2H6), 7.91 (dd, J = 9.0, 2.1 Hz, 2H5), 8.63 (d, J = 2.1 Hz, 2H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 24.7, 27.1, 46.6, 61.1, 62.1, 70.0, 73.6, 115.0, 122.8, 127.8, 128.0, 128.1, 128.8, 129.3, 131.7, 132.0, 133.3, 134.3, 134.4, 135.3, 138.4, 141.1, 153.8, 178.1. MALDI MS m/z 658 (base peak, $M+H)^+$.

16. Compound **3**: Flash column chromatography using a solvent gradient from 8:1 to 2:1 hex:EtOAc led to partial purification, Rf = 0.28 in 3:1 hex:EtOAc eluting twice. The pure compound was isolated after preparative TLC (200:1 CH_2Cl_2:Et_2O). ^{1}H NMR (500 MHz in $CDCl_3$) linker: (a) N-alkyl substituent δ 1.95 (m, 2H11), 2.18 (m, 2H10), 3.70 (t, J = 11 Hz, 2H12), 4.51 (t, J = 4.6 Hz, 2H9), 4.62 (s, -OC<u>H</u>$_2$-Ph) and 7.26-7.41 (Ph); (b) acridone δ 7.63 (d, J = 9.0 Hz, H6), 7.80 (dd, J = 8.5, 2.0 Hz, H5) and 9.35 (d, J = 2.0 Hz, H3); (c) 4-methyl anisole moiety δ 2.32 (s, C5-C<u>H</u>$_3$), 3.40 (s, -OC<u>H</u>$_3$), 4.62 (m) and 5.66 (br d) (C3'-C<u>HaHb</u>-O-C), 6.86 (H4') and 7.26 (H6'). calix[8]arene moiety: (a) ***A*** rings δ 1.15 (s, *t*-Bu), 7.02 (d, J = 1.8 Hz, Ha), 6.91 (d, J = 1.8 Hz, Hb), 4.18 and 3.46 (2d, J = 13.9 Hz, *A*-C<u>HaHb</u>-*A*), 4.02 and 3.51 (2d, J =15.4 Hz , *A*-C<u>HaHb</u>-*B*); (b) ***B*** rings δ 1.27 (s, *t*-Bu), 7.06 (d, J = 2.2 Hz, Ha), 7.15 (d, J = 2.2 Hz, Hb), 4.40 and 3.72 (2d, J = 14.4 Hz, *B*-C<u>HaHb</u>-*C*); (c) ***C*** rings δ 1.22 (s, *t*-Bu), 7.09 (d, J = 2.0 Hz, Ha), 7.13 (d, J = 2.0 Hz, Hb), 3.35 and 3.98 (2d, J = 14.8 Hz, *C*-CHaHb-*D*); (d) ***D*** rings δ 0.98 (s, *t*-Bu), 6.43 (very broad, Ha), 6.93 (broad, Hb), 4.85 and 4.28 (2d, J = 18.3 Hz, *D*-CHaHb-*D*); OH groups 7.65, 8.18, 8.19 all very broad.

17. Although the relative minimized energies for the 1,3- and 1,5-bridged analogs were within 1-2 kcal/mol of that of the 1,4-bridged analog, the NMR data were not consistent with either a 1,3- or a 1,5-bridged structure.

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