Conformational Freezing of *p-tert*-Butylcalix[6]arene in the Cone Structure by Selective Functionalization at the Lower Rim: Synthesis of New Preorganized Ligands

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The selective and symmetrical 1,3,5-methylation of *p-tert*-butylcalix[6]arene **1** is achieved for the first time; subsequent introduction of ester and amide binding groups on the trimethoxy-*p-tert*-butylcalix[6]arene **2** fixes the calix in the cone conformation giving new preorganized cation ligands.

Calixarenes are becoming increasingly important in supramolecular chemistry as useful building blocks for new receptor molecules.[1]

In calixarene chemistry much attention has been devoted to the selective functionalization of calix[4]arenes, both at the phenolic OH groups (lower rim) or at the aromatic nuclei (upper rim). The former has allowed the synthesis of very efficient and selective cation receptors and carriers.[1]

p-tert-Butylcalix[6]arene **1** has been totally functionalized at the lower rim to build up ionophores selective for uranyl,[2] alkali metal[3] and ammonium[4] cations. Very few partially *O*-substituted calix[6]arenes have been synthesized and, with the exception of the 1,2,4,5-tetra-*p*-nitrobenzoate of *p-tert*-butylcalix[6]arene reported by Gutsche *et al.*,[5] most of these derivatives have an undefined structure.[6]

We report for the first time the synthesis of a symmetrically substituted 1,3,5-trimethyl ether of *p-tert*-butylcalix[6]arene, which has been also transformed in new ionophores **3–5** having a C_3 symmetry.[7]

By treating *p-tert*-butylcalix[6]arene **1** with K_2CO_3 (3 equiv.) and CH_3I (4 equiv.) in refluxing dry acetone for 18 h the trimethoxycalix[6]arene **2**, m.p. 273–274 °C was isolated in 30% yield by flash chromatography on silica gel.[†]

Compound **2** has a mobile structure in $CDCl_3$ solution at room temperature as inferred from the ^1H NMR spectrum which shows a sharp singlet at δ 3.87 for the bridging methylenes ($ArCH_{ax}H_{eq}Ar$). The high symmetry of the spectrum and the fact that around −70 °C the coupling between the axial (H_{ax}) and the equatorial (H_{eq}) protons of the bridge appears, point for a 1,3,5-substitution pattern for this trimethoxy derivative of *p-tert*-butylcalix[6]arene.

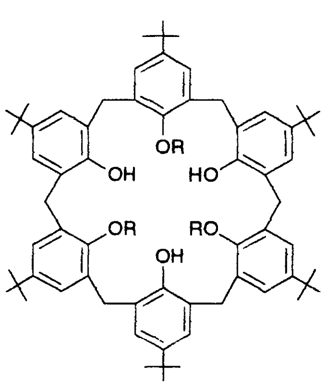
Treatment of compound **2** with sodium hydride and an excess of *tert*-butylbromoacetate or α-chloro-*N*,*N*-diethylacetamide in tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) solution gives the triester **3**, m.p. 230–233 °C and the triamide **4**, m.p. 278–280 °C, in 80 and 60% isolated yield, after precipitation of the crude reaction mixture with methanol.

The two neutral ligands **3** and **4** show ^1H and ^{13}C NMR spectra in accord with a cone structure (Fig. 1).

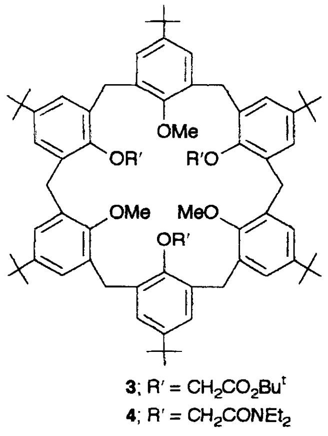
Particularly significant is the simple *AB* quartet observed for the twelve protons of the methylene bridges, with the high-field doublet around δ 3.4 (H_{eq}) far removed from the low-field doublet (H_{ax}) present at δ 4.5.

Other evidence comes from the ^{13}C NMR spectra of these two compounds which show only one triplet for the bridging $ArCH_2Ar$ methylene carbon at δ 30.0, which suggests a *syn* orientation of the aromatic nuclei according to the recently proposed single rule for the determination of calix[4]arene conformations.[8] 2D-NOESY experiments on compound **3** and **4** show correlation of the aromatic protons among themselves and with the equatorial protons (H_{eq}) and not with the distant axial protons, which rule out the possible 1,3,5-alternate conformation for these compounds. Finally, the preliminary X-ray crystal structure determination of compound **4** is in agreement with the proposed cone structure.

The spectra remain unchanged between ±70 °C, indicating that the cone structure for compounds **3** and **4** is stable in this temperature range. The high field shift experienced by the methoxy groups, which absorb at around δ 2.2, indicates that these groups point inside the apolar cavity of the calix experiencing shielding by the π cloud of the aromatic rings. Therefore, the structure of compounds **3** and **4** resembles a flattened cone structure (up–out–up–out–up–out), according to Gutsche's nomenclature.[1a]



1; R = H
2; R = Me



3; R' = $CH_2CO_2Bu^t$
4; R' = CH_2CONEt_2
5; R' = CH_2CO_2H

[†] Satisfactory elemental analyses were obtained for all new compounds. **2**: MS (FAB), *m/z* 1015 (M^+, 100%); ^1H NMR (200 MHz, $CDCl_3$), δ 0.99 [27H, s, $C(CH_3)_3$]; 1.19 [27H, s, $C(CH_3)_3$]; 3.46 (9H, s, OCH_3); 3.87 (12H, s, $ArCH_2Ar$); 6.77 (3H, s, OH); 6.89 (6H, s, ArH); 6.99 (6H, s, ArH). **3**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 [27H, s, $C(CH_3)_3$]; 1.32 [27H, s, $C(CH_3)_3$]; 1.47 [27H, s, $OC(CH_3)_3$]; 2.23 (9H, s, OCH_3); 3.39 (6H, d, *J* 16.1 Hz, $ArCH_{eq}$-Ar); 4.52 (6H, d, $ArCH_{ax}$-Ar); 4.43 (6H, s, OCH_2CO); 6.56 (6H, s, ArH); 7.28 (6H, s, ArH). **4**: MS (EI), *m/z* 1353.5 (M^+, 30%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 [27H, s, $C(CH_3)_3$]; 1.18 (9H, t, *J* 8 Hz, NCH_2CH_3); 1.32 (9H, t, NCH_2CH_3); 1.38 [27H, s, $C(CH_3)_3$]; 2.21 (9H, s, OCH_3); 3.43 (6H, d, *J* 16.0 Hz, $ArCH_{eq}$-Ar); 3.45 (6H, q, NCH_2CH_3); 3.58 (6H, q, NCH_2CH_3); 4.53 (6H, d, $ArCH_{ax}Ar$); 4.59 (6H, s, OCH_2CO); 6.67 (6H, s, ArH); 7.27 (6H, s, ArH). **5**: MS (EI), 1189.9 (M^+, 3.5%) ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 [54H, s, $C(CH_3)_3$]; 3.72 (9H, s, OCH_3), 3.4–4.0 (18H, bs, $ArCH_2Ar$ and OCH_2CO); 6.90 (6H, s, ArH); 7.00 (6H, s, ArH); 7.00 (3H, bs, COOH).

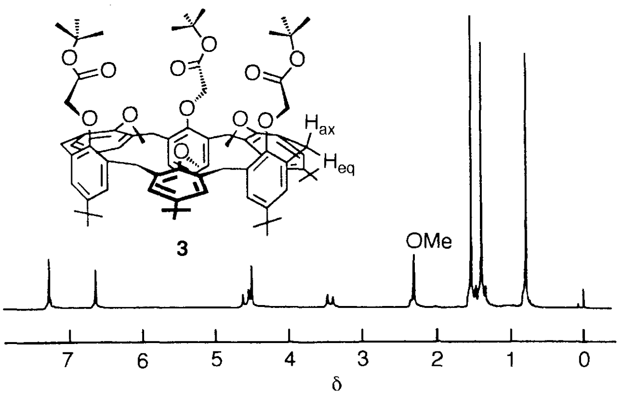


Fig. 1 200 MHz ^{1}H NMR spectrum of compound **3**

Although the functionalization of calix[6]arenes at the phenolic OH groups sometimes results in conformationally rigid derivatives (see *e.g.*[5,6]), compounds **3** and **4** represent the first examples of calix[6]arenes frozen in the cone conformation by simple etherification at the lower rim. This result is particularly significant since most of the fully alkylated calix[6]arene derivatives known so far are conformationally mobile in solution. Steric effects of the bulky *tert*-butyl ester and *N,N*-dialkylamide groups at the lower rim together with some more specific weak interaction between methoxy groups, which point into the cavity (*self*-inclusion), and the aromatic nuclei of the calix can be responsible for this unexpected conformational behaviour.

Treatment of triester **3** with CF_3CO_2H at room temperature gives the triacid **5**, m.p. 292–294 °C, in 60% yield. Compound **5** is conformationally mobile and its ^{1}H NMR spectrum in $CDCl_3$ shows a broad singlet for the methylene bridge Ar–CH_2–Ar.

The two neutral ligands **3** and **4** are not particularly effective in complexing alkali metal picrates in $CDCl_3$ ($K_{ass} < 10^5$ dm^3 mol^{-1})[9] but the triamide **4** complexes guanidinium cation very strongly ($K_{ass} > 10^7$ dm^3 mol^{-1});[9] on the other hand, the triacid **5** should be very effective in extracting trivalent metal cations in organic media.

This work was supported by CNR (Consiglio Nazionale delle Ricerche) and MURST (Ministero dell'Università e della Ricerca Scientifica e Technologica). We are grateful to Centro Interfacoltà di Misure of Parma University for NMR measurements.

Received, 22nd May 1991; Com. 1/02403E

References

1 (*a*) C. D. Gutsche, *Calixarenes. Monograph in Supramolecular Chemistry*, vol. 1; ed. J. F. Stoddart, RSC, Cambridge 1989; (*b*) *Calixarenes, a Versatile Class of Macrocyclic Compounds*, eds. J. Vicens and V. Böhmer, Kluwer, Dordrecht, 1990; (*c*) R. Ungaro and A. Pochini, '*Flexible and Preorganized Molecular Receptors Based on Calixarenes*,' in *Frontiers in Supramolecular Organic Chemistry and Photochemistry*, H.-J. Schneider and H. Dürr, VCH, Weinheim, 1991, 57.

2 T. Nagasaki, S. Shinkai and T. Matsuda, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2617 and references cited therein.

3 F. Arnaud Neu, E. McCollins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Longh, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681.

4 S. K. Chang, H. S. Hwang, M. Sau, J. Youk and S. Kang, *J. Chem. Soc., Chem. Commun.*, 1991, 217.

5 C. D. Gutsche, J. S. Rogers, D. Stewart and K. A. See, *Pure Appl. Chem.*, 1990, **62**, 485.

6 (*a*) Y. Aoyama, Y. Nonaka, Y. Tanaka, H. Tai and M. Ogashi, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1025; (*b*) I. Alam and C. D. Gutsche, *J. Org. Chem.*, 1990, **55**, 4487.

7 Only one example of calix[6]arenes with C_3 symmetry has been reported so far: J. de Mendoza, P. M. Nieto, P. Prados and C. Sánchez, *Tetrahedron*, 1990, **46**, 671, but this compound has free phenolic OH groups and two different substituents at the upper rim of the calix.

8 C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto and C. Sánchez, *J. Org. Chem.*, 1991, **56**, 3372.

9 K_{ass} were evaluated according to the Cram's extraction method, G. M. Lein and D. J. Cram, *J. Am. Chem. Soc.*, 1985, **107**, 448.