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Regioselective *O*-Substitution of *p-tert*-Butylcalix[7]arene†

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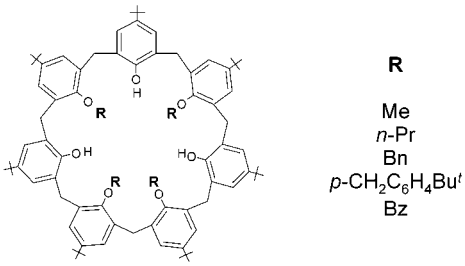
ABSTRACT



The first examples of selectively functionalized calix[7]arenes have been obtained by weak-base promoted *O*-alkylation or *O*-benzoylation of *p-tert*-butylcalix[7]arene. Mono-, 1,3- and 1,4-disubstituted calix[7]arenes have been obtained in workable yields, while the 1,2,4,6-tetrasubstitution was achieved with surprisingly high selectivity (50–88% yield) by using K_2CO_3 as base. A rationale for this finding is proposed.

In the past two decades, considerable attention has been devoted to the chemical modification of the "major" even-membered calix[*n*]arenes ($n = 4, 6, 8$),[1,2] usually obtainable in good to excellent yields with typical one-pot procedures.[3] In contrast, the chemistry of the "minor" odd homologues ($n = 5, 7$) has lagged behind because of their less efficient preparation. Recently, as a consequence of improvements in their synthesis, significant progress has also been made for calix[5]arenes,[4] whereas calix[7]arenes still remain largely unstudied.[5,6]

The recent publication of improved procedures[7] for the synthesis of *p-tert*-butylcalix[7]arene **1**,[8] now obtainable in 16−25% yield, has induced us to investigate the chemistry of this macrocycle and we wish to report here the first examples of selectively functionalized calix[7]arenes.

As groundwork to define the regioselectivity under diverse conditions, we first studied the methylation of phenolic hydroxyls (lower rim) of **1**, which could afford useful substrates for subsequent manipulations.[9] Therefore, we

† Dedicated to the memory of Professor Guido Sodano (Università di Salerno).

(1) For general reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (c) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001.

(2) For an update on the chemical modification of "major" calixarenes, see, in particular, the following chapters in ref 1c: (a) Calix[4]arenes. Thondorf, I.; Shivanyuk, A.; Böhmer, V. Chapter 2, pp 26−53. (b) Calix-[6]arenes: Lüning, U.; Löffler, F.; Eggert, J. Chapter 4, pp 71−88. (c) Calix-[8]arenes: Neri, P.; Consoli, G. M. L.; Cunsolo F.; Geraci, C.; Piattelli, M. Chapter 5, pp 89−109.

(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234. Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238. Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243. See also ref 1c: Gutsche, C. D. Chapter 1, pp 1−25.

(4) See ref 1c: Notti, A.; Parisi, M. F.; Pappalardo, S. Chapter 3, pp 54−70.

(5) Only a few examples of complete functionalization of calix[7]arenes at the upper-rim have been reported: Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689. Yao, B.; Bassus, J.; Lamartine, R. *An. Quim. Int. Ed.* **1998**, *94*, 65. Bouoit, S.; Bassus, J.; Lamartine, R. *An. Quim. Int. Ed* **1998**, *94*, 342.

(6) The conformational preferences of the calix[7]arene skeleton have been investigated by MM3 calculations (Harada, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2231) and by X-ray crystallography (Perrin, M.; Lecocq, S. *C. R. Acad. Sci. Paris* **1990**, *310*, 515. Andreetti, G. D.; Ugozzoli, F.; Nakamoto, Y.; Ishida, S.-I. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *10*, 241. Atwood, J. L.; Hardie, M. J.; Raston, C. L.; Sandoval, C. A. *Org. Lett.* **1999**, *1*, 1523).

(7) (a) Vocanson, F.; Lamartine, R.; Lanteri, P.; Longeray, R.; Gauvrit, J. Y. *New J. Chem.* **1995**, *19*, 825. (b) Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, 4136.

(8) Nakamoto, Y.; Ishida, S.-I. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 705.

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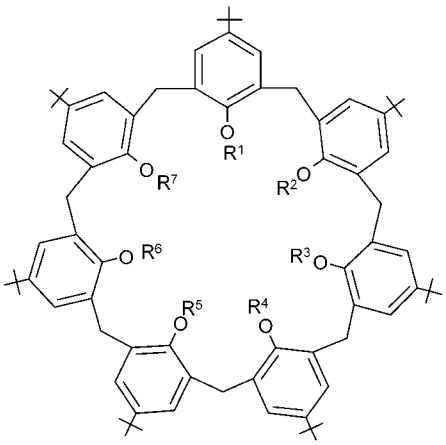
subjected *p-tert*-butylcalix[7]arene, prepared according to the acid-catalyzed, one-pot procedure described by Stewart and



1 R^{1-7} = H
2 R^{1-7} = Me
3 R^{1} = Me, R^{2-7} = H
4 $R^{1,3}$ = Me, $R^{2,4-7}$ = H
5 $R^{1,4}$ = Me, $R^{2,3,5-7}$ = H
6a $R^{1,2,4,6}$ = Me, $R^{3,5,7}$ = H
6b $R^{1,2,4,6}$ = *p*-$CH_2C_6H_4Bu^t$, $R^{3,5,7}$ = H
6c $R^{1,2,4,6}$ = $CH_2C_6H_5$, $R^{3,5,7}$ = H
6d $R^{1,2,4,6}$ = *n*-Pr, $R^{3,5,7}$ = H
6e $R^{1,2,4,6}$ = COC_6H_5, $R^{3,5,7}$ = H

Gutsche,[7b,10] to alkylation with MeI in the presence of a base under the conditions reported in Table 1.

As expected, exhaustive methylation of **1** occurred smoothly, using a large excess of MeI (70 equiv) and Cs_2CO_3 as base in acetone at reflux, to afford heptamethoxycalix[7]arene **2** in 90% yield (Table 1, entry 1). On the other hand, monomethoxycalix[7]arene **3** was obtained in lower yield (25%) in addition to unreacted **1** (Table 1, entry 2) in the presence of CsF. The use of $KHCO_3$ (3.3 equiv) afforded **3** in a better yield (42%) (Table 1, entry 3).

Limited amounts of K_2CO_3 (2−3 equiv) led to the isolation of 1,3- and 1,4-dimethoxycalix[7]arenes, **4** and **5**, in 14 and 32% yield, respectively (Table 1, entry 4).

More interesting was the methylation in the presence of 4−6 equiv of K_2CO_3, which afforded 1,2,4,6-tetramethoxycalix[7]arene **6a** in 88% yield with a surprisingly high selectivity (Table 1, entry 5).

This result induced us to extend these conditions to other alkylating or acylating agents, such as *p-tert*-butylbenzyl bromide, benzyl bromide, *n*-propyl iodide, and benzoyl chloride. As shown in Table 1 (entries 6−9), in all of these instances good to high yields of 1,2,4,6-tetra-*O*-substituted calix[7]arenes **6b**−**e** were obtained, suggesting a wide applicability for this procedure.[11]

Structure assignment for *O*-substituted calix[7]arenes **2**−**6** relied essentially on spectral analysis.[12] Molecular masses

Table 1. Alkylation Products of *p-tert*-Butylcalix[7]arene (**1**) in Acetone

entry	electrophile (equiv)	base (equiv)	temp	isolated compd (yield %)
1	MeI (70)	Cs_2CO_3 (35)	reflux	**2** (90)
2	MeI (30)	CsF (1.0)	reflux	**1** (50) **3** (25)
3	MeI (60)	$KHCO_3$ (3.3)	reflux	**3** (42)
4	MeI (60)	K_2CO_3 (2.1)	reflux	**3** (8) **4** (14) **5** (32) **6a** (24)
5	MeI (60)	K_2CO_3 (4.0)	reflux	**6a** (88)
6	*p*-$Bu^tC_6H_4CH_2Br$ (20)	K_2CO_3 (4.0)	reflux	**6b** (72)
7	$C_6H_5CH_2Br$ (20)	K_2CO_3 (4.0)	reflux	**6c** (65)
8	*n*-PrI (20)	K_2CO_3 (4.0)	reflux	**6d** (50)
9	C_6H_5COCl (20)	K_2CO_3 (4.0)	rt	**6e** (70)

(9) For similar reasons, *O*-methylation has been thoroughly investigated for *p-tert*-butylcalix[*n*]arenes (n = 4, 5, 6, 8), leading to a very large number of all possible *O*-methylation products. See: Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *J. Org. Chem.* **1998**, *63*, 6852 and references therein.

(10) We thank Prof. Gutsche for useful details concerning this procedure.

(11) **Typical procedure for the preparation of 1,2,4,6-tetra-*O*-substituted calix[7]arenes 6a**−**e.** A suspension of *p-tert*-butylcalix[7]arene (**1**) (400 mg, 0.352 mmol), alkylating agent (7−25 mmol, see Table 1), and K_2CO_3 (194 mg, 1.41 mmol) in acetone (25 mL) was stirred overnight under reflux or at room temperature (see Table 1). The mixture was dried under vacuum and partitioned between CH_2Cl_2 (20 × 3 mL) and 0.1 M HCl (20 mL). The total organic phase was washed (× 3) with H_2O (20 mL) and dried. The solid was washed with MeOH to afford a crude product which contained the 1,2,4,6-tetra-*O*-substituted calix[7]arene as the major compound (TLC) isolable in analytically pure form by appropriate column chromatography.

(12) Satisfactory microanalytical and spectral data were obtained for all new compounds. ^{1}H and ^{13}C NMR spectra were acquired at 400 and 100 MHz, respectively, in $CDCl_3$ or C_6D_6. FAB(+) MS measurements were performed using 3-nitrobenzyl alcohol as matrix. Compound **2**: mp 145 °C; FAB(+) MS *m*/*z* 1233 (MH^+); ^{1}H NMR ($CDCl_3$, 298 K) δ 1.10 [s, $C(CH_3)_3$, 63 H], 3.22 (s, OCH_3, 21 H), 3.97 (s, $ArCH_2Ar$, 14 H), 6.96 (s, ArH, 14 H). Compound **3**: mp 218 °C; FAB(+) MS *m*/*z* 1149 (MH^+); ^{1}H NMR ($CDCl_3$, 323 K) δ 1.23, 1.25, 1.29, 1.31 [s, $C(CH_3)_3$, 18 H, 18 H, 18 H, 9 H], 3.70 (s, OCH_3, 3 H), 3.81, 3.89, 3.97 (bs, $ArCH_2Ar$, 2 H, 8 H, 4 H), 7.05, 7.13, 7.18, 7.24 (bs, ArH, 2 H, 4 H, 6 H, 2 H), 8.90, 9.33, 9.63 (bs, OH, 2 H, 2 H, 2 H). Compound **4**: mp 210 °C; FAB(+) MS *m*/*z* 1163 (MH^+); ^{1}H NMR ($CDCl_3$, 323 K) δ 1.20, 1.25, 1.27, 1.28 [s, $C(CH_3)_3$, 18 H, 18 H, 9 H, 18 H], 3.80 (s, OCH_3, 6 H), 3.86, 3.90, 4.01 (s, $ArCH_2Ar$, 6 H, 6 H, 2 H), 6.99, 7.05, 7.13, 7.14, 7.20 (bs, ArH, 2 H, 2 H, 2 H, 6 H, 2 H), 7.90, 8.75, 9.59 (bs, OH, 1 H, 2 H, 2 H). Compound **5**: mp 203 °C; FAB(+) MS *m*/*z* 1163 (MH^+); ^{1}H NMR ($CDCl_3$, 323 K) δ 1.20, 1.24, 1.26, 1.29 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 18 H], 3.68 (s, OCH_3, 6 H), 3.81, 3.87, 4.18 (s, $ArCH_2Ar$, 4 H, 8 H, 2 H), 7.01, 7.12, 7.14, 7.17 (bs, ArH, 2 H, 4 H, 4H, 4 H), 8.90, 9.44, 9.87 (bs, OH, 2H, 2 H, 1 H). Compound **6a**: mp 246 °C; FAB(+) MS *m*/*z* 1191 (MH^+); ^{1}H NMR ($CDCl_3$, 298 K) δ 1.12, 1.13, 1.22, 1.23 [s, $C(CH_3)_3$, 18 H, 18 H, 18 H, 9 H], 3.55, 3.65 (s, OCH_3, 6 H, 6 H), 3.89, 3.93, 4.04 (s, $ArCH_2Ar$, 8 H, 4 H, 2 H), 6.96−7.04 (overlapped, ArH, 14 H), 7.44 (s, OH, 1 H), 7.55 (s, OH, 2 H). Compound **6b**: mp 140 °C; FAB(+) MS *m*/*z* 1761 (MK^+); ^{1}H NMR ($CDCl_3$, 298 K) δ 0.92, 1.21, 1.23, 1.28, 1.30 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 18 H, 36 H], 3.78, 3.90, 3.93, 4.07 (s, $ArCH_2Ar$, 4 H, 4 H, 4 H, 2 H), 4.83, 4.87 (s, OCH_2Ar, 2 H, 2 H), 6.78, 6.88, 6.94, 6.97, 7.02, 7.06, 7.11 (bs, ArH, 2 H, 2 H, 2 H, 2 H, 2 H, 2 H), 6.84 (bs, OH, 3 H), 7.28−7.34 (overlapped, ArH, 16 H). Compound **6c**: mp 141 °C; FAB(+) MS *m*/*z* 1537 (MK^+); ^{1}H NMR ($CDCl_3$, 298 K) δ 0.93, 1.11, 1.17, 1.26 [s, $C(CH_3)_3$, 18 H, 18 H, 18 H, 9 H], 3.80, 3.84, 3.91, 4.09 (s, $ArCH_2Ar$, 4 H, 4 H, 4 H, 2 H), 4.68, 4.94 (s, OCH_2Ar, 2 H, 2 H), 6.61 (bs, OH, 3 H), 6.86, 6.95, 7.06, 7.07, 7.14, 7.18 (bs, ArH, 2 H, 4 H, 2 H, 2 H, 4 H, 2 H), 7.21−7.31 (overlapped, ArH, 10 H), 7.43, 7.45 (bs, ArH, 6 H, 2 H). Compound **6d**: mp 146 °C;

were determined by FAB(+) mass spectrometry, while assignment of the substitution pattern, based on a careful analysis of ^{1}H and ^{13}C NMR data, deserves some comment. In fact, 16 partially substituted calix[7]arene derivatives are possible.[13] Among them, only two possess an asymmetric substitution pattern, namely, the 1,2,4-tri- and 1,2,3,5-tetrasubstituted ones. All the remaining derivatives possess a symmetry plane bisecting one aromatic ring and one $ArCH_2Ar$ group (Ar—CH_2 symmetry). Therefore, under the assumption of conformational mobility,[14] asymmetric NMR spectra are expected for the formers, while all the others would give rise to a similar symmetrical spectrum showing four *t*-Bu and four $ArCH_2Ar$ resonances in a 2:2:2:1 ratio. Consequently, assignment of substitution pattern cannot simply rely on symmetry considerations. To this end we used the chemical shifts of OH groups, which allowed their easy distinction as "isolated", "singly-H-bonded", or "doubly-H-bonded", according to the number of flanking H-bonds with proximal hydroxyls.[15]

As an example we mention here the case of 1,2,4,6-tetrabenzyl derivative **6c**,[12] which showed the expected ^{1}H NMR resonances for *t*-Bu and $ArCH_2Ar$ groups at δ 0.93, 1.11, 1.17, 1.26 (2:2:2:1), and 3.80, 3.84, 3.91, 4.09 (2:2:2:1), respectively, in addition to those of benzylic oxymethylenes at δ 4.68 and 4.94 (1:1) (Figure 1). Obviously, these

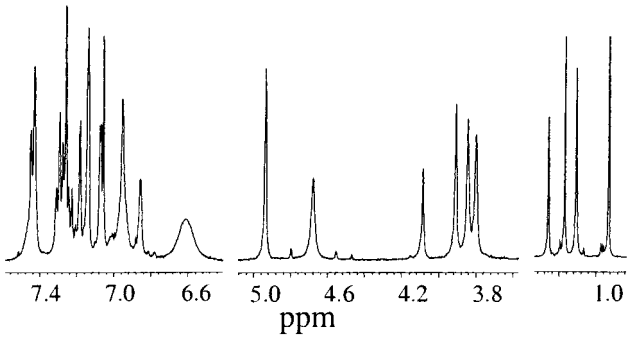


Figure 1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of 1,2,4,6-tetrakis(benzyloxy)calix[7]arene **6c**.

data are indicative of an Ar—CH_2 symmetry and are compatible with three tetrasubstitution patterns, namely, 1,2,4,6, 1,2,3,4, and 1,2,4,5. The first of them was assigned to **6c** on the basis of the OH resonance at δ 6.61 (D_2O exchangeable) indicative of three "isolated" hydroxyls. The two others patterns would give rise to at least one "singly-H-bonded" OH at a significant lower field. A similar reasoning was used for the other tetrasubstituted derivatives

FAB(+) MS *m/z* 1303 (MK^+); ^{1}H NMR ($CDCl_3$, 298 K) δ 0.69, 0.71 (t, J = 7.5 Hz, $CH_2CH_2CH_3$, 3 H, 3 H), 1.05, 1.13, 1.22, 1.23 [s, $C(CH_3)_3$, 18 H, 18 H, 18 H, 9 H], 1.60, 1.69 (m, $CH_2CH_2CH_3$, 4 H, 4 H), 3.63, 3.72 (t, J = 7.0 Hz, OCH_2, 4 H, 4 H), 3.87, 3.88, 4.02 (s, $ArCH_2Ar$, 8 H, 4 H, 2 H), 6.88−7.16 (overlapped, ArH, 14 H), 7.53 (bs, OH, 3 H). Compound **6e**: mp 190 °C; FAB(+) MS *m/z* 1551 (MH^+); ^{1}H NMR (C_6D_6, 348 K) δ 0.96, 1.08, 1.17, 1.24, [s, $C(CH_3)_3$, 18 H, 18 H, 9 H, 18 H], 3.74, 3.94, 4.15 (bs, $ArCH_2Ar$, 4 H, 4 H, 6 H), 6.96−7.22 (overlapped, ArH, 26 H), 7.35 (bs, OH, 3 H), 7.95 (bd, ArH, 4 H), 8.12 (bd, ArH, 4 H).

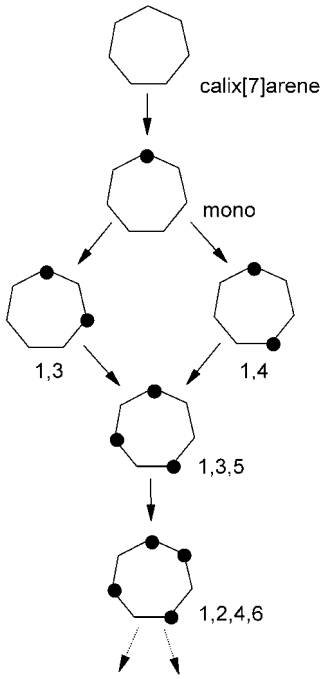


Figure 2. Plausible pathways for weak-base promoted alkylation of *p-tert*-butylcalix[7]arene (**1**) leading to 1,2,4,6-tetra-*O*-substituted derivatives.

6a,**b** and **6d**,**e**, which showed only isolated OH signals in the 6.84−7.55 ppm range.[12] In accordance, 1,3- and 1,4-dimethoxycalix[7]arene showed the expected type of OH signals [**4**, δ 7.90 (isolated, 1 H), 8.75 (singly-H-bonded, 2 H), 9.59 (doubly-H-bonded, 2 H); **5**, δ 8.90, 9.44 (singly-H-bonded, 2 H, 2 H), 9.87 (doubly-H-bonded, 1 H)].[12]

The observed regioselectivity is easily explainable in terms of preferential formation of doubly-H-bonded monoanions previously used for the *syn*-distal alkylation of calix[4]-arenes[16] and for the "alternate alkylation" of calix[8]arenes.[17] Here it is worth mentioning that the selectivity observed is probably the highest among the weak-base promoted alkylation of calix[5]-,[4] -[6]-,[18] and -[8]arenes.[17] It is comparable

(13) For a representation of these 16 derivatives, see ref 2c.

(14) It is worth recalling here that the "*tert*-butyl through the annulus" inversion is operative for *p-tert*-butylcalix[7]arenes. Therefore, all the **2**−**6** derivatives have a conformational mobility faster or close to the NMR time scale, giving rise to sharp or slightly broadened resonances.

(15) This argument has already been used for structure assignment of partially substituted calix[5]- and -[8]arenes, see: Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019. Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880. Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

(16) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. (b) Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137.

(17) Neri, P.; Geraci C.; Piattelli, M. *J. Org. Chem.* **1995**, *60*, 4126 and references therein.

(18) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380. Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Piattelli, M. *Tetrahedron Lett.* **1994**, *35*, 2795.

to the well-known selectivity of calix[4]arenes, which afford high yields of 1,3-disubstituted derivatives.[2a,16,19] This can be rationalized by considering that under the above assumptions only two pathways should be possible, leading to 1,3- and 1,4-disubstituted derivatives (Figure 2). These, in turn, would imply the convergent formation of a 1,2,4,6-tetrasubstituted derivative, through the intermediate 1,3,5-trisubstituted compound.

The first examples of partially substituted calix[7]arenes here described can be considered valuable intermediates for the synthesis of new calix[7]arene-based hosts. In addition, the reported results represent useful information toward a more complete understanding of the chemical behavior of the calixarene family.

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(19) For an additional recent example, see: Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3103.