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On the Occurrence of the 1,3,5-Trisubstitution Pattern in the *O*-Alkylation of *p-tert*-Butylcalix[6]arene

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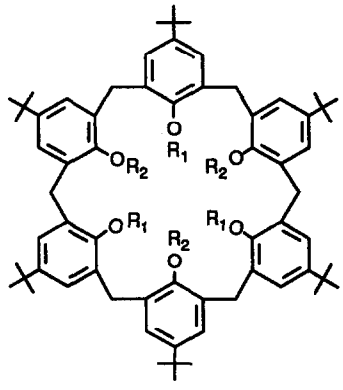
Abstract: 1,3,5-Trisubstitution at the phenolic hydroxyls of *p-tert*-butylcalix[6]arene (**1**), previously obtained in sizeable yield only with MeI (Casnati *et al. J. Chem. Soc., Chem. Commun.* **1991**, 1413), has been now achieved by direct *O*-alkylation with alkyl iodides (Et, *n*-Pr, *n*-Bu) and *p*-X-benzyl bromides, (X = *tert*-Bu, Me, Br, NO_2) in the presence of a weak base (K_2CO_3 or CsF). These results suggest that 1,3,5-trisubstitution can also be extended to other alkylating agents provided that an appropriate weak base is used. The 1,3,5-tris(*p*-X-benzyl) ethers **6-9**, whose structure have been established by ^{1}H-NMR spectral analysis and chemical correlation, in $CDCl_3$ solution adopt a conformation with only a 2-fold symmetry element bisecting two aromatic rings.

In the last few years attention has been paid at the selective functionalization of calix[6]arenes[1] because of its potential in the synthesis of new molecular receptors.[2-5] At the present time general procedures for the preparation of 1,4- and 1,2,4,5-derivatives of *p-tert*-butylcalix[6]arene (**1**) functionalized *via* regioselective alkylation at the phenolic hydroxyls are available in the literature and many compounds belonging to these two families have been reported.[3] On the contrary, formation of 1,3,5-tri-*O*-substituted compounds seems to be exceptional, since a single compound of this type, trimethyl ether **2**, has been obtained in sizeable yield.[2a-b,6]



	R_1	R_2		R_1	R_2
1	H	H	**8**	*p*-Br-Bn	H
2	Me	H	**9**	*p*-NO_2-Bn	H
3	Et	H	**10**	*p*-Bu^t-Bn	Me
4	*n*-Pr	H	**11**	$CH_2CO_2Bu^t$	Me
5	*n*-Bu	H	**12**	*p*-Me-Bn	Me
6	*p*-Bu^t-Bn	H	**13**	*p*-Br-Bn	Me
7	*p*-Me-Bn	H			

As recently we have observed that in the *O*-alkylation of *p-tert*-butylcalix[8]arene in the presence of a weak base methyl iodide behaves "anomalously" with respect to a variety of other electrophiles,[7] we were induced to suppose that the near unicity[8] of **2** as representative of the 1,3,5-derivatives of **1** could be due to a

similar anomaly. This prompted us to study in some details the *O*-alkylation of **1** in the presence of weak bases.

Reaction of **1** with homologues of MeI (EtI, *n*-PrI, *n*-BuI; 4 equiv) in refluxing acetone using K_2CO_3 (3 equiv) as base, followed by column chromatography of the reaction mixtures, afforded the 1,3,5-trialkoxy derivatives **3-5** in 15-25 % yield.[9] Assignment of the structures was based on ^{1}H-NMR spectral evidence. In fact, if conformational interconversion is fast in the NMR time scale, two singlets are to be expected for the *tert*-butyl groups on the substituted and, respectively, unsubstituted aromatic rings, while the bridging methylenes and the oxymethylenes should give rise to a singlet and a triplet in a 2:1 intensity ratio. All these features were observed in the ^{1}H-NMR spectra of compounds **3-5**. It is to be noted that all the signals in the spectra of these compounds become broader going from **3** to **5**, indicating that the dimension of the *n*-butyl group is close, but not enough, to that required for the conformational freezing in the NMR time scale.[3b]

The study of the alkylation of **1** has been successively expanded to other electrophiles. Using *p-tert*-butylbenzyl bromide in refluxing acetonitrile with CsF as base (K_2CO_3 gave inferior results), triether **6** was isolated in 35 % yield, whose ^{1}H-NMR spectrum was too complex to allow a straightforward assignment of the structure.[9] The presence of five signals for *tert*-butyl groups at 0.96, 1.11, 1.14, 1.37, 1.38 ppm in a 2:1:2:1:3 intensity ratio, together with 3 AB systems for the $ArCH_2Ar$ groups (Figure 1A), pointed to a structure with a 2-fold symmetry element bisecting two opposite aromatic nuclei. Since we had previously observed that *p-tert*-butylbenzyl groups are bulky enough to give rise to conformational isomers of partially functionalized *p-tert*-butyl-calix[6]arenes isolable at room temperature,[5] we supposed that **6** could be the 1,3,5-triether, blocked in one of the ten possible up-down conformations and less symmetrical than the cone or the 1,3,5-alternate.[10,11] The correctness of this conjecture was proved subjecting **6** to exhaustive methylation, that gave the mixed trimethoxy-tribenzyl ether **10**,[9] whose debenzylation yielded the known 1,3,5-trimethyl ether **2**.[12] It is noteworthy that **10** displays, in that differing from **6**, a highly symmetrical ^{1}H-NMR spectrum containing, *inter alia*, a single AB system (3.27 and 4.53 ppm, J = 15.2 Hz, 12 H) for the 6 equivalent $ArCH_2Ar$ groups and a single shielded singlet (2.12 ppm) for 3 methoxyl groups (Figure 2). This spectrum closely resembles that of trimethoxy-triester **11**, which was assigned a *flattened cone* conformation;[2a] therefore, we suggest that also **10** adopts a similar conformation.

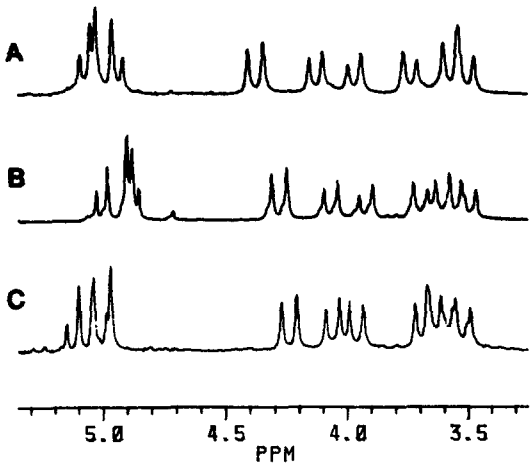


Fig. 1. Methylene region of the ^{1}H-NMR spectra of **6** (A), **8** (B), and **9** (C).

In the same experimental conditions used for **6**, *p*-methylbenzyl bromide, *p*-bromobenzyl bromide, and *p*-nitrobenzyl bromide also gave, in moderate yields (25-35 %) the corresponding 1,3,5-ethers **7-9**.[9] Their structures were assigned on the basis of the close similarity of the methylene and *tert*-butyl regions in their ^{1}H-

NMR spectra with those of **6** (Figure 1). Moreover, for compounds **7** and **8** confirmation was obtained *via* exhaustive methylation-debenzylation, which gave in both cases trimethyl ether **2**.[12] It is to be noted that the ^{1}H-NMR spectra of **12** and **13**,[9] very similar to those of **10** and **11** (Figure 2), indicate also for these mixed ethers a *flattened cone* conformation.

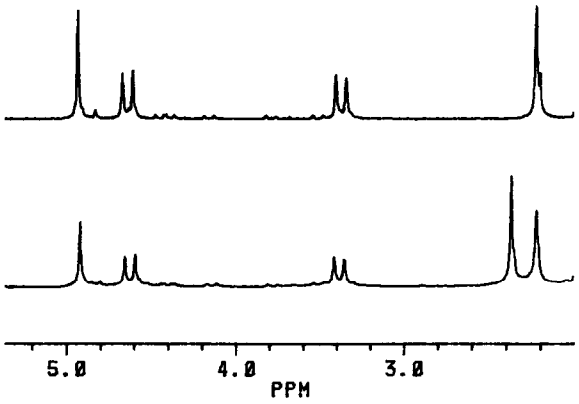


Fig. 2. Methylene region of the ^{1}H-NMR spectra of **10** (top) and **12** (bottom).

In summary, the results above demonstrate that the 1,3,5-trisubstitution takes place in the *O*-alkylation of *p-tert*-butylcalix[6]arene, in the presence of weak bases, not only with MeI but also with other electrophiles. Therefore, the above procedure seems to be a general methodology for the synthesis of 1,3,5-trisubstituted calix[6]arenes. Furthermore, the aforesaid data validate the opinion that alkylation of **1**, in the presence of weak base, proceeds through the formation of monoanions stabilized by two flanking hydrogen bonds and constitute an useful groundwork for the understanding calix[6]arene chemistry. The 1,3,5-triethers here described have structural characteristic preluding their use as intermediates in the construction of new calix[6]arene-based hosts with C_3 symmetry, exemplified by the "super-uranophile" of Shinkai.[13]

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5. Neri, P.; Rocco, C.; Consoli, G. M. L.; Piattelli, M. *J. Org. Chem.* **1993**, *58*, 6535.
6. The formation of **2** has been confirmed by Kanamathareddy and Gutsche (note 4 in ref 3c).

7. Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M., submitted.
8. In addition to **2**, a 1,3,5-tripyridinocalix[6]arene has been obtained in very low yield (ref 4b). A 1,3,5-tris(alkylphosphate) of **1** has been described (Markowskii, L. N.; Kal'chenko, V. I.; Parkhomenko, N. A. *Zh. Obshch. Khim.* **1990**, *60*, 2811; *Chem. Abstr.* **115**: 92382v), but this claim has been questioned in ref 2c.
9. Satisfactory microanalytical and spectral data were obtained for all new compounds. Compound **3**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 1.06, 1.22 [s, $C(CH_3)_3$, 27 H each], 1.29 (t, J = 6.9 Hz, OCH_2CH_3, 9 H), 3.80 (q, J = 6.9 Hz, OCH_2CH_3, 6 H), 3.87 (s, $ArCH_2Ar$, 12 H), 6.56 (brs, OH, 3 H), 6.93, 7.04 (s, ArH, 6 H each). Compound **4**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.62 (t, J = 7.3 Hz, $CH_3CH_2CH_2O$, 9 H), 1.09, 1.19 [s, $C(CH_3)_3$, 27 H each], 1.25 (m, $CH_3CH_2CH_2O$, 6 H), 3.58 (t, J = 6.9 Hz, $CH_3CH_2CH_2O$, 6 H), 3.89 (s, $ArCH_2Ar$, 12 H), 6.60 (brs, OH, 3 H), 6.96, 7.02 (s, ArH, 6 H each). Compound **5**: ^{1}H-NMR (250 MHz, $CDCl_3$, 335 K), δ 0.70 (q, J = 7.0 Hz, $CH_3CH_2CH_2CH_2O$, 9 H), 1.12, 1.24 [s, $C(CH_3)_3$, 27 H each], 1.16 (m, $CH_3CH_2CH_2CH_2O$, 6 H), 1.65 (m, $CH_3CH_2CH_2CH_2O$, 6 H), 3.74 (t, J = 7.0 Hz, $CH_3CH_2CH_2CH_2O$, 6 H), 3.91 (s, $ArCH_2Ar$, 12 H), 6.36 (brs, OH, 3 H), 6.98, 7.06 (s, ArH, 6 H each). Compound **6**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.96, 1.11, 1.14, 1.37, 1.38 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 9 H, 27 H, respectively], 3.50, 4.37 (AB, J = 15.0 Hz, $ArCH_2Ar$, 4 H), 3.57, 4.12 (AB, J = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.73, 3.96 (AB, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 4.93, 5.07 (AB, J = 10.2 Hz, OCH_2, 4 H), 5.02 (s, OCH_2, 2 H), 6.5-7.2 (ArH, 12 H), 7.46, 7.53 (AB, J = 8.4 Hz, *p*-*t*-Bu-BnH, 8 H), 7.49, 7.63 (AB, J = 8.0 Hz, *p*-*t*-Bu-BnH, 4 H). Compound **7**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.92, 1.07, 1.13, 1.33 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 9 H, respectively], 2.38 (s, *p*-CH_3-Bn, 9 H), 3.47, 4.31 (AB, J = 15.1 Hz, $ArCH_2Ar$, 4 H), 3.54, 3.90 (AB, J = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.69, 4.07 (AB, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 4.88, 5.02 (AB, J = 10.3 Hz, OCH_2, 4 H), 4.94 (s, OCH_2, 2 H), 6.5-7.2 (ArH, 12 H), 7.20, 7.44 (AB, J = 7.9 Hz, *p*-Me-BnH, 8 H), 7.20, 7.80 (AB, J = 7.9 Hz, *p*-Me-BnH, 4 H). Compound **8**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.95, 1.10, 1.18, 1.33 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 9 H, respectively], 3.49, 4.28 (AB, J = 15.5 Hz, $ArCH_2Ar$, 4 H), 3.60, 4.07 (AB, J = 14.3 Hz, $ArCH_2Ar$, 4 H), 3.69, 3.92 (AB, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 4.87, 5.00 (AB, J = 11.5 Hz, OCH_2, 4 H), 4.90 (s, OCH_2, 2 H), 6.6-7.2 (ArH, 12 H), 7.41, 7.53 (AB, J = 8.3 Hz, *p*-Br-BnH, 8 H), 7.44, 7.48 (AB, J = 8.4 Hz, *p*-Br-BnH, 4 H). Compound **9**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.94, 1.10, 1.19, 1.31 [s, $C(CH_3)_3$, 18 H, 9 H, 18 H, 9 H, respectively], 3.63, 3.96 (AB, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 3.69, 4.06 (AB, J = 14.2 Hz, $ArCH_2Ar$, 4 H), 3.52, 4.24 (AB, J = 15.3 Hz, $ArCH_2Ar$, 4 H), 4.97 (s, OCH_2, 2 H), 5.00, 5.13 (AB, J = 12.8 Hz, OCH_2, 4 H), 6.6-7.2 (ArH, 12 H), 7.66, 8.20 (AB, J = 8.4 Hz, *p*-NO_2-BnH, 4 H), 7.67, 8.24 (AB, J = 8.8 Hz, *p*-NO_2-BnH, 8 H). Compound **10**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.71, 1.24, 1.28 [s, $C(CH_3)_3$, 27 H each], 2.12 (s, OCH_3, 9 H), 3.27, 4.53 (AB, J = 15.2 Hz, $ArCH_2Ar$, 12 H), 4.83 (s, OCH_2, 6 H), 6.58, 7.17 (s, ArH, 6 H each), 7.31, 7.37 (AB, J = 8.3 Hz, *p*-*t*-Bu-BnH, 12 H). Compound **12**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.80, 1.37 [s, $C(CH_3)_3$, 27 H each], 2.21 (s, OCH_3, 9 H), 2.36 (s, *p*-CH_3-Bn, 9 H), 3.37, 4.61 (AB, J = 15.1 Hz, $ArCH_2Ar$, 12 H), 4.90 (s, OCH_2, 6 H), 6.66, 7.26 (s, ArH, 6 H each), 7.17, 7.41 (AB, J = 7.9 Hz, *p*-Me-BnH, 12 H). Compound **13**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ 0.81, 1.38 [s, $C(CH_3)_3$, 27 H each], 2.23 (s, OCH_3, 9 H), 3.38, 4.56 (AB, J = 14.8 Hz, $ArCH_2Ar$, 12 H), 4.90 (s, OCH_2, 6 H), 6.68, 7.25 (s, ArH, 6 H each), 7.41, 7.51 (AB, J = 8.4 Hz, *p*-Br-BnH, 12 H).
10. A comprehensive list of the possible up-down conformations for partially substituted calix[6]arenes appeared in supplementary material of ref 3a.
11. A conformational study of **6** has been undertaken and will be reported in due course.
12. The obtained compound was identical in all respect to an authentic sample prepared according to ref 2a.
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