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Regio- and Stereoselective Alkylation of 5,5'-Bicalix[4]arene. Access to Double Calixarenes with Different Conformations of the Two Subunits†

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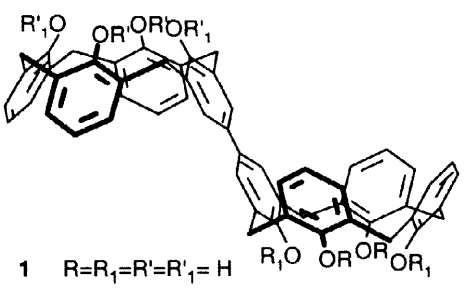
Abstract: Alkylation of 5,5'-bicalix[4]arene **1**, a double calix[4]arene with direct *para-para* linkage, with PrI or *p-tert*-butylbenzyl bromide in the presence of various bases has been investigated. Good control of the regio- and stereochemical outcome was obtained, leading to the isolation of tetra-*O*-alkylated bicalix[4]arene derivatives **3-5** with *syn*-distal disubstitution at the two subunits and octa-*O*-alkylated atropisomers in *double-cone* **2**, *cone/partial-cone* **6-8**, *double-1,3-alternate* **9**, and *1,3-alternate/partial-cone* **10-12** conformations.

Double or multiple calixarenes[1] have attracted the attention of several research groups as higher order supramolecular systems.[2] In the majority of these compounds two or more calixarene units are linked through the intermediacy of a proper spacer,[1-2] but very recently we have reported the first example of a bridgeless double calixarene, 5,5'-bicalix[4]arene **1**, in which the two units are linked "head-to-head" with a direct, biphenyl-like *para-para* linkage.[3] We have also shown that in properly functionalized derivatives of this dimer, for instance **2a**, the two halves may act cooperatively in the complexation of a suitable guest.[3]



1 $R=R_1=R'=R'_1=H$
2 $R=R_1=R'=R'_1=X$
3 $R_1=R'_1=X$; $R=R'=H$
4 $R_1=R'=X$; $R=R'_1=H$
5 $R=R'=X$; $R_1=R'_1=H$

a $X = CH_2CH_2OEt$
b $X = Pr$
c $X = p\text{-}CH_2C_6H_4Bu^t$

The peculiar structural features of **1** and its high stereochemical potential make it an interesting new building block in supramolecular chemistry. In any chemical manipulation of this compound it should be borne in mind that when the free rotation of the phenol rings through the annulus is prevented by alkylation of the hydroxyl with groups bulkier than ethyl a large number of atropisomers are possible.[1] For instance, its exhaustive propylation can give rise in principle to 36 isomeric forms, including 12 couples of inherently chiral enantiomers and 2 *meso*-forms. Therefore, the reaction would be without any practical use unless a satisfactory regio- and stereocontrol can be achieved.

Here we wish to report the results of our investigation in this direction which also led to the first examples, to the best of our knowledge, of double calixarenes having the two moieties blocked in different conformations.

† Dedicated to the memory of Professor Giacomino Randazzo

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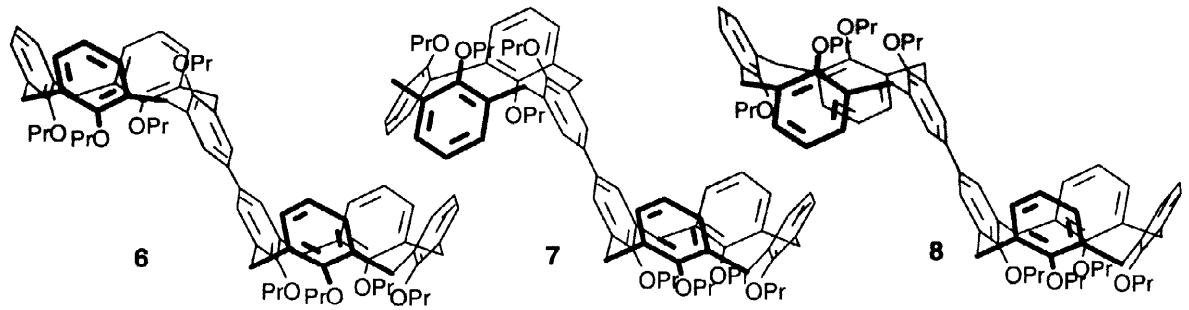
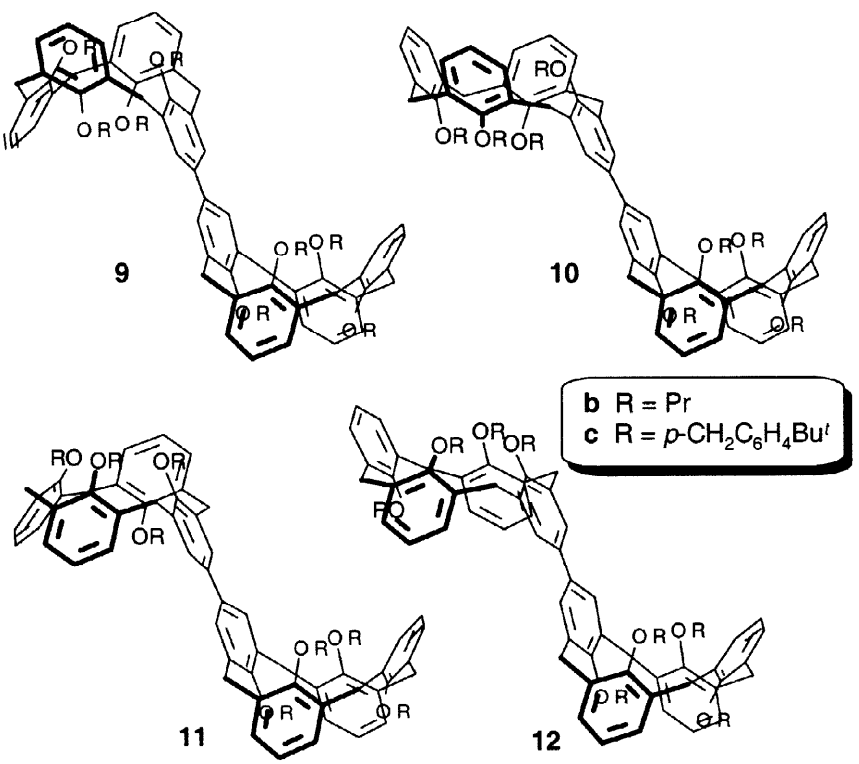
In approaching the problem we decided to investigate the alkylation of **1** under conditions known to be highly regio- and stereoselective for the corresponding monomer, calix[4]arene, so the reaction outcome could be anticipated, at least in the absence of unexpected cooperative or template effects.[1] Therefore, we subjected **1** to alkylation with *n*-PrI or *p-tert*-butylbenzyl bromide in the presence of K_2CO_3, which in calix[4]arene



chemistry is known to promote 1,3-*syn*-di-*O*-alkylation.[4] As expected, in both cases three compounds were isolated by column chromatography, arising from the combination of distal disubstitution in the two units of the molecule. Giving the rings involved in the junction numbers 1 and 1', these three products can be named 1,3,1',3'-, 1,3,2',4'-, and 2,4,2',4'-tetralkoxy-5,5'-bicalix[4]arene **3**, **4** and **5**, respectively.[5] As shown in Table 1 (entries 1 and 2) the three regioisomers are isolated in amounts close to the 1:2:1 statistical ratio, the 1,3,2',4'-isomer **4** being the most favored.

The use of NaH with excess alkylating agent is known to favour the *cone* conformation of calix[4]arenes[6] and indeed it has already been proved[3] that 5,5'-bicalix[4]arene in the presence of this base reacts with 2-(ethoxy)ethyl bromide to afford *double-cone* octaalkyl derivative **2a** in 55%. We have now observed that the use of PrI or *p-tert*-butylbenzyl bromide under similar conditions gives the *double-cone* octapropyl (**2b**) or octabenzyl (**2c**) derivatives in 21 and 60% yield, respectively (Table 1, entries 3 and 4). In addition, in the case of PrI atropisomers **6-8** were also isolated in 14, 9 and 7% yield.[5] These compounds have one subunit in the *cone* conformation and the other in the *partial-cone* conformation in which ring 1', 2' or 3' is inverted with respect to the other three, and hence they can be named *cone/1'-partial-cone* (**6**), *cone/2'-partial-cone* (**7**) and *cone/3'-partial-cone* (**8**). To the best of our knowledge, they represent the first examples of double calixarenes having the two moieties blocked in different conformations.



Alkylation in the presence of Cs_2CO_3 as base afforded preferentially *double-1,3-alternate*

Table 1. Alkylation Products of 5,5'-Bicalix[4]arene

Entry	Electrophile (equiv)	Base	Solvent (temp.)	Time (h)	Isolated Compd (yield %)
1	PrI (8)	K_2CO_3 (5)	DMF (60 °C)	48	**3b** (14), **4b** (26), **5b** (12)
2	*p*-Bu^t-BnBr (4)	K_2CO_3 (2.3)	MeCN (refl.)	7.5	**3c** (21), **4c** (37), **5c** (18)
3	PrI (32)	NaH (32)	DMF (60 °C)	6.5	**2b** (21), **6** (14), **7** (9), **8** (7)
4	*p*-Bu^t-BnBr (32)	NaH (32)	DMF (60 °C)	24	**2c** (60)
5	PrI (18)	Cs_2CO_3 (18)	THF/DMF, 10:1 (refl.)	16	**9b** (18), **10b** (7), **11b** (17), **12b** (18)
6	*p*-Bu^t-BnBr (18)	Cs_2CO_3 (18)	THF/DMF, 10:1 (refl.)	6	**9c** (53), **11c** (12), **12c** (18)

atropisomers **9b** and **9c** in 18 and 53% yield, respectively (Table 1, entries 5 and 6). In agreement with what had been observed for monomeric calix[4]arenes,[6] three additional stereoisomers were also isolated by chromatography and characterized as combinations of *1,3-alternate* and *partial-cone* subunits, namely *1,3-alternate/1'-partial-cone* (**10**), *1,3-alternate/2'-partial-cone* (**11**), and *1,3-alternate/3'-partial-cone* (**12**).[5]

The stereochemical assignments for tetra- and octaalkyl bicalix[4]arenes **2-10** followed from a careful analysis of ^{1}H and ^{13}C NMR patterns for $ArCH_2Ar$ groups according to well established rules for calix[4]arenes.[7] In particular, assignments of the *double-syn-distal* substitutions in **3-5** and the *double-cone* conformation of **2b-c** were secured by the presence of AX systems in their ^{1}H NMR spectra and ^{13}C NMR resonances at 30-32 ppm for $ArCH_2Ar$ groups (for instance, **2b**: 31.0 and 31.1 ppm, **2c**: 31.3 and 31.4 ppm). Analogously, the *double-1,3-alternate* structure in **9b** and **9c** was warranted by two ^{1}H NMR singlets and two ^{13}C NMR signals in the range 36-38 ppm (**9b**: 37.0 and 37.2 ppm, **9c**: 37.0 and 37.6 ppm).

In the case of compounds **6** and **8** the presence of three ^{13}C NMR signals (**6**: δ 30.6, 31.0 and 31.3; **8**: δ 30.7, 31.0, 31.2) for methylenes linked to aromatic rings in *syn* orientation and a single one for a methylene bound to aromatic rings in *anti* disposition (**6**: δ 36.2; **8**: δ 35.8) gave evidence of the presence of a *cone/partial-cone* geometry bisected by a symmetry plane. The two conformations compatible with these data, *cone/1'-partial-cone* and *cone/3'-partial-cone*, were respectively assigned to **6** and **8** on the basis of the long-range benzylic couplings observed in the 2D COSY NMR spectrum.[7b] For example, in the case of **6** a cross-peak between the tight AB system centred at 3.8 ppm (overlapped) for $ArCH_2Ar$ and the ArH singlet at 7.62 ppm of one of the junction rings indicated its *anti*-orientation with respect to the adjacent rings.

Similar arguments were used for the discrimination between *1,3-alternate/1'-partial-cone* (**10b**) and *1,3-alternate/3'-partial-cone* (**12b-c**), which all gave three ^{13}C NMR signals for methylenes between inverted aromatic rings and one for a methylene flanked by aromatic rings in *syn* orientation. Finally, the *cone/2'-partial-cone* and the *1,3-alternate/2'-partial-cone* strereostructures were tentatively assigned to compounds **7** and **11**, whose NMR data are also compatible with *cone/1',2'-alternate* and *1,3-alternate/1',2'-alternate* geometry, respectively, because on the basis of literature data their formation was considered more probable under the conditions used.[6]

In conclusion, we have demonstrated that a good control of regio- and stereochemical outcome can be obtained in the alkylation of 5,5'-bicalix[4]arene **1**. In fact, the combinations of *syn*-distal di-*O*-alkylation at the two calix[4]arene units can be easily obtained. In addition, the first examples of double calix[4]arenes having

the two units in different conformations can be obtained besides *double-cone* or *double-1,3-alternate* octaalkyl atropisomers. It is conceivable that the results described here for two typical electrophiles can be extended to a range of other alkylating agents, thus giving access to a number of new interesting three-dimensional architectures for applications in supramolecular chemistry.

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5. Satisfactory microanalytical and spectral data were obtained for compounds **2-12**. ^{1}H NMR spectra were taken at 250 MHz in $CDCl_3$ at rt (for brevity only the data of the methylene region of propyl derivatives are reported). **Compound 2b**: ^{1}H NMR δ 3.16 and 4.46 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 8 H), 3.17 and 4.46 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 8 H), 3.84 (t, *J* = 7.7 Hz, OCH_2, 8 H), 3.88 (t, *J* = 8.2 Hz, OCH_2, 8 H). **Compound 3b**: ^{1}H NMR δ 3.33 and 4.27 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 8 H), 3.38 and 4.32 (AX, *J* = 12.7 Hz, $ArCH_2Ar$, 8 H), 3.91 (t, *J* = 6.2 Hz, OCH_2, 4 H), 3.98 (t, *J* = 6.2 Hz, OCH_2, 4 H). **Compound 4b**: ^{1}H NMR δ 3.37 and 4.29 (AX, *J* = 13.2 Hz, $ArCH_2Ar$, 4 H), 3.40 and 4.31 (AX, *J* = 12.5 Hz, $ArCH_2Ar$, 4 H), 3.44 and 4.36 (AX, *J* = 13.1 Hz, $ArCH_2Ar$, 8 H), 3.90-4.03 (m, OCH_2, 8 H). **Compound 5b**: ^{1}H NMR δ 3.38 and 4.33 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 8 H), 3.44 and 4.36 (AX, *J* = 12.9 Hz, $ArCH_2Ar$, 8 H), 4.00 (t, *J* = 6.3 Hz, OCH_2, 8 H). **Compound 6**: ^{1}H NMR δ 3.07 and 4.10 (AX, *J* = 13.2 Hz, $ArCH_2Ar$, 4 H), 3.17 and 4.48 (AX, *J* = 13.2 Hz, $ArCH_2Ar$, 4 H), 3.22 and 4.52 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 4 H) 3.26-4.05 (m, OCH_2 and $ArCH_2Ar$, 20 H). **Compound 7**: ^{1}H NMR δ 3.04 and 4.08 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 2 H), 3.08 and 4.09 (AX, *J* = 14.0 Hz, $ArCH_2Ar$, 2 H), 3.13 and 4.44 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.15 and 4.47 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.66, 3.69 (s, $ArCH_2Ar$, 2 H each), 3.28-3.97 (m, OCH_2, 16 H). **Compound 8**: ^{1}H NMR δ 3.08 and 4.09 (AX, *J* = 13.2 Hz, $ArCH_2Ar$, 4 H), 3.16 and 4.47 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.24 and 4.50 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 4 H), 3.66 (s, $ArCH_2Ar$, 4 H), 3.54-3.96 (m, OCH_2, 16 H). **Compound 9b**: ^{1}H NMR δ 3.70, 3.77 (s, $ArCH_2Ar$, 8 H each), 3.40-3.52 (m, OCH_2, 16 H). **Compound 10b**: ^{1}H NMR δ 3.04 and 4.06 (AX, *J* = 13.7 Hz, $ArCH_2Ar$, 4 H), 3.17-3.86 (m, OCH_2, 16 H), 3.71, 3.74, 3.80 (s, $ArCH_2Ar$, 4 H each). **Compound 11b**: ^{1}H NMR δ 3.06 and 4.14 (AX, *J* = 13.5 Hz, $ArCH_2Ar$, 2 H), 3.13 and 4.10 (AX, *J* = 13.2 Hz, $ArCH_2Ar$, 2 H), 3.29-3.81 (m, $ArCH_2Ar$ and OCH_2, 28 H). **Compound 12b**: ^{1}H NMR δ 3.12 and 4.15 (AX, *J* = 13.0 Hz, $ArCH_2Ar$, 4 H), 3.20-3.84 (m, $ArCH_2Ar$ and OCH_2, 28 H).
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