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Double-two-point and Four-point Intramolecular Bridging of *p-tert*-Butylcalix[8]arene

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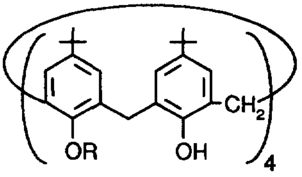
Abstract: Calix[8]arenes bis-bridged at the lower rim with *ortho-* or *meta-*xylene unit (**3a-b** and **4a-b**) have been obtained in high yields by reaction of 1,3,5,7-tetra-*O*-substituted calix[8]arenes with 1,2- or 1,3-bis(bromomethyl)benzene. The use of 1,2,4,5-tetrakis(bromomethyl)benzene afforded the four-point intrabridged calix[8]arenes **5a-b** in yields up to 41%. VT NMR studies indicated that the flipping motion of aromatic rings in these compounds is inhibited by the intramolecular bridging. Molecular modeling suggested an unprecedented *pseudo* pleated loop conformation for compounds **5a-b**.

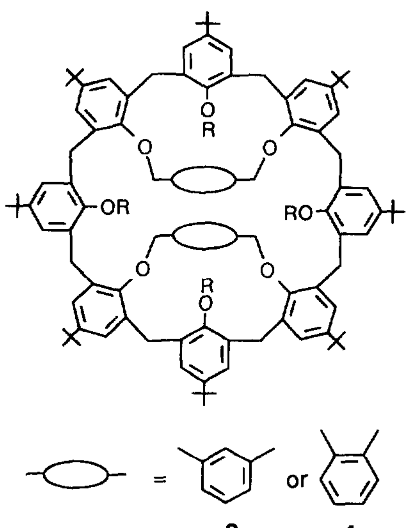
In recent years, interest in preorganization of the conformationally mobile calixarene macrocycles in order to enhance their complexing capabilities has risen rapidly.[1] To meet this goal, the intramolecular bridging is deemed to be the most promising approach for the larger oligomers of this class, hexamers[2] and octamers.[3] As regards calix[8]arenes in particular, only very recently a few examples of intramolecular bridging have been reported, including 1,5-bridging with a *p*-xylene unit,[4a] 1,3-5,7- or 1,5-3,7-double-bridging with polyether chains,[4b] and 1,3,5,7-four-point capping with a calix[4]arene.[4c] In this paper we wish to report on the synthesis, in many instances with very high yields, of double-two-point and four-point intrabridged calix[8]arenes.



1 R = H
2a R = p-$CH_2C_6H_4Bu^t$
2b R = $CH_2CO_2Bu^t$

The previous observation that a *p*-xylene unit is able to bridge the calix[8]arene framework between the positions 1 and 5 of the lower rim[4a] prompted us to explore the bridging capabilities of the isomeric *ortho-* and *meta-*xylene units. After unsuccessful attempts with the parent *p-tert*-butylcalix[8]arene (**1**) we resorted to the use of its 1,3,5,7-tetra-*O*-substituted derivatives,[5] already employed with good results as substrates in intrabridging reactions.[4a-b] The reaction of 2.4 equiv of 1,3-bis(bromomethyl)benzene with 1,3,5,7-tetrakis(*p-tert*-butylbenzyl)calix[8]arene **2a**[5] in refluxing THF with Cs_2CO_3 (8 equiv) as base afforded in surprisingly high yield (92%) the 1,3-5,7-doubly-bridged derivative **3a.**[6] Similarly, 1,3,5,7-tetraester **2b**[5] afforded in 98% yield the corresponding doubly-bridged calix[8]arene **3b.**[6]

The structure of the bis(*m*-xylene)-bridged **3a** and **3b** was deduced from FAB(+) MS spectra, which gave in both cases the expected molecular ion peak, and from analysis of ^1H and ^{13}C NMR spectra.[6] The 1,3-intrabridging was assigned from the pattern of the *tert*-butyl signals in the ^1H NMR spectrum, consisting of three singlets in a 1:1:2 ratio for the *t*-Bu groups attached to the calix[8]arene framework (**3a**: δ 0.96, 0.97 and 1.39; **3b**: δ 0.90, 0.92 and 1.37) and two distinct resonances for the *t*-Bu groups of the benzyl (**3a**: δ 1.32 and 1.41) or ester moiety (**3b**: δ 1.43 and 1.60). In both cases the $ArCH_2Ar$ groups originate two well spaced AX systems and the OCH_2 groups two separate singlets.

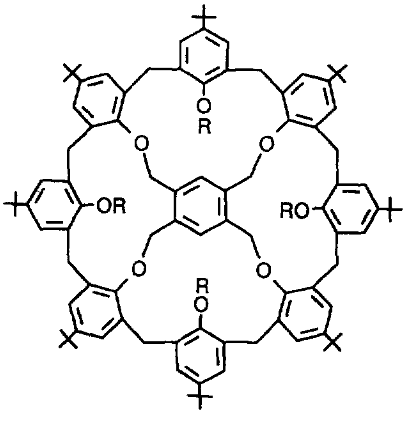


3 **4**

a R = *p*-$CH_2C_6H_4Bu^t$
b R = $CH_2CO_2Bu^t$

The high yields obtained in the 1,3-intrabridging with a *meta*-xylene unit indicate that the aromatic rings at positions 1 and 3 are on the average very close to each other, thus suggesting the possible formation of shorter bridges with *ortho*-xylene units. In fact, reaction of **2a** and **2b** with 1,2-bis(bromomethyl)benzene afforded, respectively, **4a** and **4b** both in 98% yield,[6] indicating that the *ortho* spacer is as well suited as the *meta* one. These two doubly-bridged calix[8]arene derivatives have NMR spectral features in the 0.5-5.2 ppm region very similar to those of compounds **3a** and **3b**, evidencing the same 1,3-5,7-doubly-bridging.[6]

These results prompted us to attempt the four point intramolecular bridging with a durene unit, which on computer models[7] appeared to fit well within the cavity of calix[8]arene ring in the pleated loop conformation. Reaction of **2a** with 1.2 equiv of 1,2,4,5-tetrakis(bromomethyl)benzene in the same conditions adopted above afforded the desired 1,3,5,7-bridged derivative **5a** in 41% yield.[6] Similarly, **2b** gave the corresponding four-point-bridged compound **5b**, although in lower yield (15%).[6] The presence of two orthogonal symmetry planes in structures **5** originates a pattern of *tert*-butyl signals in their ^1H NMR spectra very similar to that observed for compounds **3a-b** and **4a-b**, comprising three 1:1:2 resonances for the groups attached to the calix[8]arene framework and two 1:1 signals for the *t*-Bu groups of the substituents. Similarly, the $ArCH_2Ar$ groups give rise to two AX systems.[6]



5a R = *p*-$CH_2C_6H_4Bu^t$
5b R = $CH_2CO_2Bu^t$

The conformational mobility of the calix[8]arene macrocycle in compounds **3-5** is strongly reduced in comparison with the parent compounds, as indicated by the presence of two AX systems for the $ArCH_2Ar$ groups. The extent of the reduction was investigated for compounds **3a**, **4a**, and **5a** by Dynamic NMR in $CDCl_3$ or $C_6D_5NO_2$, which evidenced the absence of conformational interconversion in the 230-390 K range. This result indicates that the flipping motion of the aromatic rings belonging to the calixarene annulus is effectively inhibited by both the bis-two-point and the single-four-point bridging.

The conformation adopted by the doubly-bridged derivatives **3** can be deduced from the chemical shift separation of the AX-systems for the $ArCH_2Ar$ groups ($\Delta\delta$ = 0.63-0.98) and the chemical shift values of the pertinent carbon signals (29.6-31.5 ppm), which agree with a *syn* orientation of the eight calix[8]arene aromatic rings comparable to that proposed for a 1,3-5,7-calix[8]-bis-crown-5 derivative[4b] (remarkable is the shielding effect of the 1,3-bridging *m*-xylene ring on the OCH_2 groups of the pendant moiety at position 2 in comparison with that at position 4, with a $\Delta\delta$ = 0.90 for **3a** and 1.10 for **3b**). Similar considerations allowed to assign the *syn* conformation to the *o*-xylene bridged derivatives **4a** and **4b**. However, the smaller chemical shift separation ($\Delta\delta$ = 0.28-0.33) for one AB system due to the $ArCH_2Ar$ group indicates a very flattened orientation of two phenolic rings, probably owing to the stretching effect of the shorter bridge. An insight into the conformation of 1,3,5,7-bridged derivatives **5** can be obtained by computer molecular modeling,[7] which indicates that the four phenolic rings connected with the durene bridge lay on an average plane containing the bridge itself, in a sort of distorted pleated loop conformation. The substituents at the 2,4,6,8 positions can be located, in principle, either above or below this average plane originating five different arrangements. Only two out of these five are compatible with the symmetry deduced from NMR spectra, namely those with *syn* or alternate orientation of the four groups. Since discrimination between them was impossible on the basis of NMR data, a computational study using MacroModel V4.5 program[7] was undertaken and the lowest energy structures for both arrangements were found by Monte Carlo conformational searches. The energy evaluation for these structures using either MM2 or MM3 force-field and a GB/SA model solvent for $CHCl_3$ favoured the *syn* orientation by 3-4 Kcal/mol and we suggest it as the most probable conformation for both **5a** and **5b**.

The four-point bridged derivatives **5a-b** represent the first example of calix[8]arenes with a "fixed" *pseudo* pleated loop conformation, whose unprecedented architecture is reminescent of Collman's picket fence porphyrins.[8] Changing the nature of the pendant groups and/or the bridge could give compounds for applications in host-guest chemistry which remain for future studies.

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REFERENCES AND NOTES

1. For a comprehensive review on calixarenes up to 1994 see: Böhmer, V. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713 and references cited therein.

2. Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032. Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai S. *Chem. Lett.* **1994**, 1251. Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, *35*, 6555.

3. Neri, P.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Piattelli, M. *New J. Chem.* **1996**, in press.

4. (a) Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917. (b) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, *36*, 5429. (c) Arduini, A.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1995**, 879.

5. Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880.

6. Satisfactory microanalytical and spectral data were obtained for all new compounds. Molecular weights were deduced by FAB(+) MS using 3-nitrobenzyl alcohol as matrix. ^{1}H-NMR spectra were taken at 250 MHz in $CDCl_3$ at rt unless otherwise stated. Assignments were aided by COSY and HETCOR 2D NMR experiments. The abbreviations Xy and Du are used for xylene and durene moieties, respectively. **Compound 3a:** mp 285-287 °C. ^{1}H-NMR δ 0.96, 0.97, 1.32, 1.41, [s, $C(CH_3)_3$, 18H each], 1.39 [s, $C(CH_3)_3$, 36H], 3.41 and 4.39 (AX, J = 11.0 Hz, $ArCH_2Ar$, 8H), 3.49 and 4.40 (AX, J = 16.6 Hz, OCH_2Xy, 8H), 3.92 and 4.59 (AB, J = 16.9 Hz, $ArCH_2Ar$, 8H), 4.19, 5.09 (s, $ArCH_2O$, 4H each), 6.72, 6.78 (s, ArH, 4H each), 6.96 and 6.98 (AB, J = 4.1 Hz, ArH, 8H), 7.18 and 7.30 (AB, J = 8.2 Hz, *p-t*-Bu-BnH, 8H), 7.26 (bs, XyH, 6H), 7.32 (bs, XyH, 2H), 7.52 and 7.59 (AB, J = 8.4 Hz, *p-t*-Bu-BnH, 8H). **Compound 3b:** mp 340 °C dec. ^{1}H-NMR (320 K) δ 0.90, 0.92, 1.43, 1.60 [s, $C(CH_3)_3$, 18 H each], 1.37 [s, $C(CH_3)_3$, 36 H], 3.21 and 4.19 (AX, J =10.7 Hz, $ArCH_2Ar$, 8H), 3.49 and 4.23 (AX, J = 16.3 Hz, OCH_2Xy, 8H), 3.87 and 4.50 (AB, J = 16.9 Hz, $ArCH_2Ar$, 8H), 3.49, 4.59 (s, OCH_2CO_2, 4H each), 5.11 (bs, XyH, 2H), 6.67, 6.73 (s, ArH, 4H each), 7.0 (bs, XyH, 6H), 7.20 and 7.22 (AB, J = 2.3 Hz, ArH, 8H). **Compound 4a:** mp 284-286 °C. ^{1}H-NMR δ 0.69, 1.02, 1.30, 1.39 [s, $C(CH_3)_3$, 18H each], 1.36 [s, $C(CH_3)_3$, 36 H], 3.40 and 4.72 (AX, J = 15.0 Hz, $ArCH_2Ar$, 8H), 3.74 and 3.84 (AB, J = 12.1 Hz, OCH_2Xy, 8H), 4.05 and 4.38 (AB, J = 17.7 Hz, $ArCH_2Ar$, 8H), 4.78, 4.81 (s, $ArCH_2O$, 4H each), 6.42, 7.01 (s, ArH, 4H each), 6.99 and 7.23 (AB, J = 8.2 Hz, *p-t*-Bu-BnH, 8H), 7.12 and 7.35 (AB, J = 2.0 Hz, ArH, 8H), 7.49 (bs, *p-t*-Bu-BnH, 8H), 7.65 (m, XyH, 8H). **Compound 4b**: mp 270-272 °C. ^{1}H-NMR δ 0.61, 0.97, 1.39, 1.58 [s, $C(CH_3)_3$, 18H each], 1.34 [s, $C(CH_3)_3$, 36H], 3.54 and 4.68 (AX, J = 15.3 Hz, $ArCH_2Ar$, 8H), 3.60 and 3.74 (AB, J = 12.0 Hz, OCH_2Xy, 8H), 3.99 and 4.27 (AB, J = 16.6 Hz, $ArCH_2Ar$, 8H), 4.30, 4.31 (s, OCH_2CO_2, 4H each), 6.34, 6.93 (s, ArH, 4H each), 7.08 and 7.35 (AB, J = 2.2 Hz, ArH, 8H), 7.54 (m, XyH, 8H). **Compound 5a:** mp 320 °C dec. ^{1}H-NMR δ 0.95, 0.96, 1.06, 1.19, [s, $C(CH_3)_3$, 18 H each], 1.41 [s, $C(CH_3)_3$, 36 H], 3.04 and 4.47 (AX, J = 15.1 Hz, $ArCH_2Ar$, 8H), 3.22 and 4.53 (AX, J = 14.9 Hz, $ArCH_2Ar$, 8H), 3.95 and 4.15 (AB, J = 12.1 Hz, OCH_2Du, 8H), 4.50, 4.83 (s, $ArCH_2O$, 4H each), 6.50, 6.73 (s, ArH, 4H each), 6.96 (bs, *p-t*-Bu-BnH, 8H), 6.97 and 7.09 (AB, J = 8.2 Hz, *p-t*-Bu-BnH, 8H), 7.21 and 7.23 (AB, J = 3.2 Hz, ArH, 8H), 7.70 (s, DuH, 2H). **Compound 5b:** mp 355 °C dec. ^{1}H-NMR δ 0.93, 1.01, 1.28, 1.31 [s, $C(CH_3)_3$, 18 H each], 1.44 [s, $C(CH_3)_3$, 36 H], 3.45 and 4.55 (AX, J = 15.3 Hz, $ArCH_2Ar$, 8H), 3.45 and 4.70 (AX, J = 15.3 Hz, $ArCH_2Ar$, 8H), 3.93 and 4.03 (AB, J = 12.4 Hz, OCH_2Du, 8H), 4.25, 4.31 (s, OCH_2CO_2, 4H each), 6.46, 6.84 (s, ArH, 4H each), 7.28 and 7.35 (AB, J = 2.3 Hz, ArH, 8H), 7.31 (bs, DuH, 2H).

7. The program used was *MacroModel V4.5*: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.

8. Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427.

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