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Restricted Rotation of *tert*-Butyl Groups in Sterically Crowded Methylene-Functionalized Calix[4]arenes

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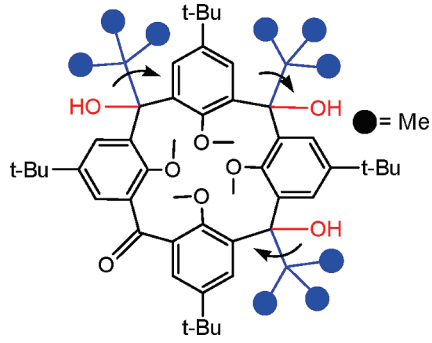
ABSTRACT



The crowded methylene-functionalized calix[4]arenes 4 and 5 display restricted rotation of the *tert*-butyl substituents at the bridges. At low temperatures, separate signals were observed for the methyls of these groups in the ^{1}H NMR spectra.

Calixarenes incorporating carbonyl groups at the bridges (ketocalixarenes) are useful starting materials for the preparation of methylene-functionalized calixarenes.[1−3] Reaction of the tetramethoxy ketocalixarene derivative **1a** with excess PhLi affords a mixture of the four possible configurational stereoisomers of **2**.[4] Notably, at rt significant broadening of signals of the phenyl groups was observed in the ^{1}H NMR spectrum, suggesting restricted rotation of the groups. Since in the tetrasubstituted bridges the rotation of 2-fold rotors (phenyl groups) is hindered, it was of interest to determine whether the rotation of 3-fold rotors (*t*-Bu groups) might be hindered as well.[5] The *tert*-butyl groups of the *p-tert*-butylcalix[*n*]arenes appear as a singlet in the ^{1}H NMR spectrum at all temperatures. Our goal was to test whether, when attached to a different point of the calix (namely, a tetrasubstituted carbon bridge), the tripodal rotation of a *t*-Bu will be sufficiently hindered that in the ^{1}H NMR spectrum different signals will be observed for its methyl moieties.

(1) For recent reviews on calixarenes see: (a) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19. (b) Gutsche, C. D. *Calixarenes: an Introduction*; Royal Society of Chemistry: Cambridge: 2008.

(2) (a) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Makromol. Chem.* **1990**, *191*, 81. (b) See also: Seri, N.; Simaan, S.; Botoshansky, M.; Kaftory, M.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7140.

(3) For selected examples of the preparation of methylene functionalized calixarenes, see: (a) Tabatabai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. (d) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667. (e) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (f) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741. (g) Kumar, S.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073. (h) Kogan, K.; Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 7327.

(4) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577.

(5) (a) For a recent report on the restricted rotation of *t*-Bu groups in hindered benzyl ethers, see: Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2006**, *71*, 4490. (b) For a review, see: Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Weinheim, 1985; p 255.

(6) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685.

(7) For simplicity, we refer to compounds **4** and **5** as the di-*tert*-butyl and tri-*tert*-butyl derivatives, respectively, disregarding the four *p-tert*-butyl groups present at the upper rim of the calix scaffold.

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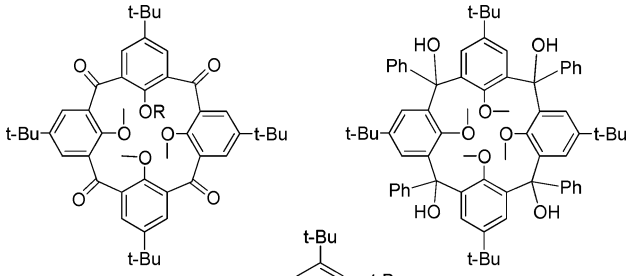
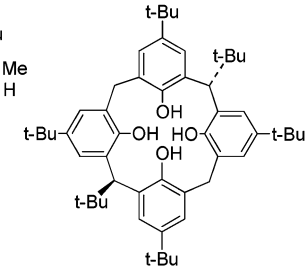
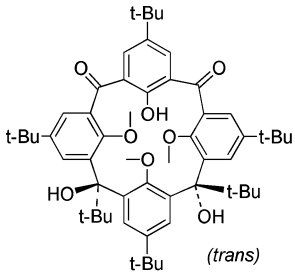


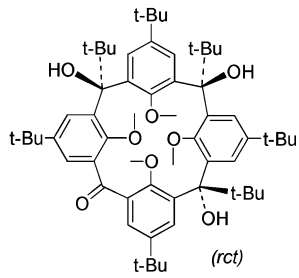


A single example is known of a calixarene possessing a pair of bridges substituted by *t*-Bu groups (**3**). Calixarene **3** adopts a cone conformation, but no restricted rotation of the *t*-Bu groups was observed.[6] However, we hypothesized that in a *t*-Bu analogue of **2,** the macrocycle will also adopt a 1,3-alternate conformation and that the presence of the geminal OH groups and the rigidity of the macrocycle will increase the rotational barrier of the *t*-Bu groups.

With the aim of synthesizing calixarenes substituted by both *t*-Bu and OH groups at the bridges, we conducted the reaction of **1a** with excess *t*-BuLi. In addition to the stereochemical interest of the potential product(s), the reaction with this bulky organometallic reagent is of synthetic interest as a means to test the steric limitations of the synthetic route (reaction of a ketocalixarene with a organometallic reagent). If the reaction proceeds with *t*-BuLi, it could be expected that derivatives possessing less crowded alkyl groups might be accessible by this route as well.

Reaction of **1a** in THF with excess of *t*-BuLi (8 equiv) afforded, judged by ^{1}H NMR, a complex mixture of addition products with the di-*tert*-butylated trimethoxy derivative **4** as the major product.[7]





Recrystallization of the crude product from chloroform/acetone afforded a mixture of **4** and the tri-*tert*-butylated derivative **5**. Both compounds are rare examples of calixarenes derivates functionalized at the bridges in two different fashions (i.e., carbonyl and alkylmethanol groups). Notably, in compound **4** two proximal (i.e., 1,2) bridges are *trans*-substituted by *t*-Bu groups and one phenolic OH group is present, indicating that one of the four methoxy groups of the starting material **1a** have been cleaved. The cleavage of a methyl ether group may be viewed as a S_N2 nucleophilic substitution (the nucleophile being a *t*-BuLi) on a methoxy group.[8] This reaction may be facilitated in **1a** by the electron-withdrawing effect of the carbonyl groups which render the ensuing substituted phenoxy group a better leaving group. The formation of calixarene **5** (probably the most crowded calix[4]arene known to date), which possess three *tert*-butyl groups at the bridges, was not accompanied by ether cleavage. In independent experiments, the isolated **4** and **5** were treated with 8 equiv of *t*-BuLi under the reaction conditions. As judged from the NMR spectrum of the crude product, both compounds essentially do not react further under these reaction conditions. The low reactivity of **5** under the reaction conditions may be due to the increase in steric strain that would result in a product possessing four bulky *t*-Bu groups at the bridges. In the case of **4**, its low reactivity under the reaction conditions is more difficult to rationalize.[9]

To test whether the demethylation step occurs before or after addition of the *t*-BuLi to the carbonyl groups, the reaction was repeated using trimethoxy ketocalixarene **1b**[10] as the starting material. Examination of the crude reaction product by NMR indicated a mixture of products, but no **4** could be detected. On this basis we conclude that the (deprotonated) **1b** is not an intermediate in the formation of **4** and that the demethylation step occurs after addition of one (or two) *t*-Bu groups to the ketocalixarene macrocycle.

The crystal structures of the *rccc* (i.e., all-*cis*) and *rcct* isomers of **2** have been determined by X-ray crystallography.[4,11] In both isomers the macrocycle adopts a 1,3-alternate arrangement, with a single (in the case of the *rccc* form) or a pair (for the *rcct* form) of methoxy groups oriented "in" and serving as acceptors of hydrogen bonds with neighboring OH groups while the rest of the methoxy groups are oriented "out". We have hypothesized that in the 1,3-alternate conformation of the macrocycle, intramolecular hydrogen bonding of a methoxy group with a neighboring OH group requires an "in" orientation of the methoxy. Only in the "in" conformation the lone pairs on the oxygen atom of the methoxy groups are oriented toward the exterior of the molecule, and are in steric proximity to a neighboring OH proton(s) on a bridge. Upon attempted recrystallization of a mixture of **4** and **5**, two types of crystals were obtained in a batch that were submitted to X-ray crystallography (Figure 1 and Figure S1 in Supporting Information). The structure of **4** could only be refined to a relatively high *R*

(8) In a related observation it has been reported that allyl ethers undergo cleavage in the presence of *t*-BuLi. (Bailey, W. F.; England, M. D.; Mealy, M. J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* **2000**, *2*, 489 For a review on ether cleavage see. Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833.

(9) Under the reaction conditions, the OH groups of **4** are deprotonated by the organolithium reagent, and the charge of the resulting phenolate is delocalized by the two ortho carbonyl groups. This delocalization decreases the electrophilicity of the carbonyl carbons, and may contribute to render them less susceptible to nucleophilic attack by the *t*-BuLi. In addition, agregation and intra- or intermolecular coordination of the lithium atoms with the oxygen atoms of the calix may also play a role in the decreased reactivity of **4**.

(10) Seri, N.; Biali, S. E. *J. Org. Chem.* **2005**, *70*, 5278.

(11) Kuno, L.; Biali, S. E. *J. Org. Chem.* **2009**, *74*, 48.

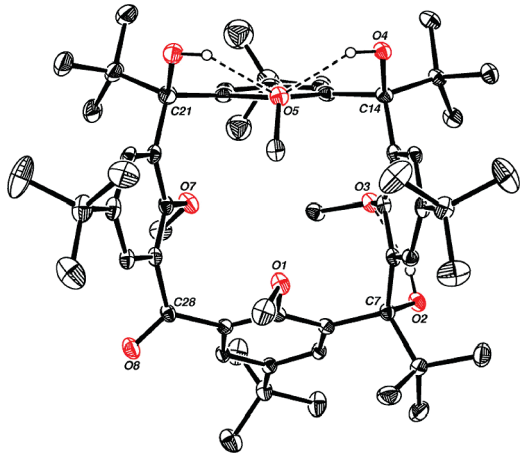


Figure 1. Crystal structure of tri-*tert*-butyl calix[4]arene derivative **5**.

factor, but the structural features obtained are most likely trustworthy. In **5**, the *tert*-butyl groups at the bridges possess a *rct* disposition. The calix macrocycle adopts a 1,3-alternate conformation. As observed in the crystal structures of the *rccc* the *rcct* isomers of **2**, the methoxy groups hydrogen bonded to the neighboring OH group(s) (O3−C and O5−C) are oriented "in", while the rest of the methoxy groups are oriented out. The methoxy group O5−C is hydrogen bonded in bifurcated fashion to the two neighboring OH groups.

A possible sequence of reactions leading to the formation of the *trans* and the *rct* isomers of **4** and **5**, respectively, is shown in Figure 2. The initially formed mono-*tert*-butyl

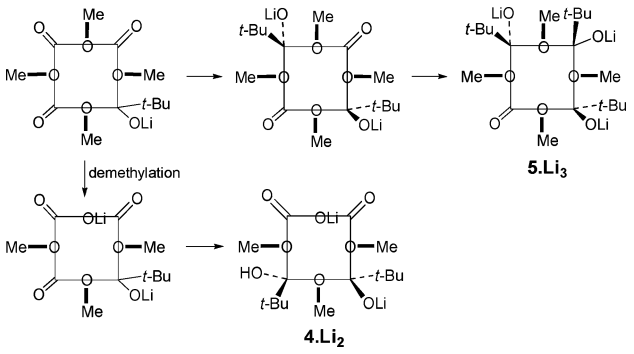


Figure 2. Schematic representation of a possible reaction sequence leading to **4** and **5**. The square represents a top view of the calix[4]arene skeleton. The corners and edges of the square represent the bridges (functionalized bridges or carbonyl carbons) and *para*-substituted aryl rings, respectively.

derivative undergoes demethylation preferentially at one of the rings distal to the substituted bridge. Reaction with *t*-BuLi occurrs preferentially at the single carbonyl not involved in delocalizing the negative charge, yielding the 1,2 derivative **4·Li$_2$**, which does not react further. From steric and electrostatic reasons, the addition occurs in *trans* fashion. Alternatively, the mono-*tert*-butyl derivative can further react with *t*-BuLi. For steric and electrostatic reasons, the reaction occurs in trans fashion at the carbonyl distal to the substituted bridge. Finally, reaction with *t*-BuLi leads to the *rct* product **5·Li$_3$** irrespectively of the direction of the attack.

Notably, the 500 MHz ^{1}H NMR spectrum of **4** and **5** at room temperature displayed sharp singlets for the *p*-*t*-Bu groups but broad signals for the *t*-Bu groups at the bridges, suggesting restricted rotation of the latter groups. Upon lowering of the temperature, separate signals were observed for each of the methyl groups (Figures 3 and 4) of the *t*-Bu

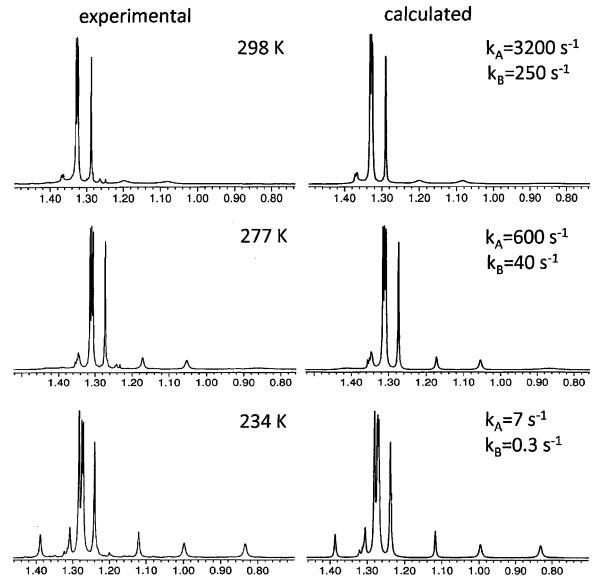


Figure 3. Experimental (left) and simulated (right) 500 MHz ^{1}H NMR spectrum (*t*-Bu region) of **4** at different temperatures.

groups. In **4**, five methyl groups were clearly observed (the sixth methyl signal is isochronous with one of the *p*-*t*-Bu singlets), whereas for **5** eight methyl signals were observed. Simulations of the dynamic NMR spectra at different temperatures (*t*-Bu region) were conducted with the gNMR program[12] assuming 3-fold exchange within the three methyl signals of a given *t*-Bu group. Sets of mutually exchanging methyl signals were identified in the spectra on the basis of their broadening. For example, the three signals resonating in the ^{1}H NMR spectrum of **4** at 234 K at δ 1.12, 1.31, and 1.38 ppm are sharper than the two signals as 0.84 and 1.00 ppm. The three sharper signals correspond to the same *t*-Bu group. Two and three different rates were needed to simulate the NMR spectra **4** and **5**, respectively, indicating that the rotational barriers of the symmetry nonequivalent *t*-Bu groups at the bridges are different.

From the rate constants obtained in the simulations at different temperatures, the rotational barriers could be determined ($\Delta G^{\ddagger}$ = 12.7, 14.1 and 13.7, 14.1, 14.5 kcal mol^{-1} for **4** and **5**, respectively). Interestingly, four of the rotational barriers are ca. 14 kcal mol, while the rotational barrier of one of the two

(12) *gNMR v4.1.0*; Cherwell Scientific Publishing: Oxford, U.K.

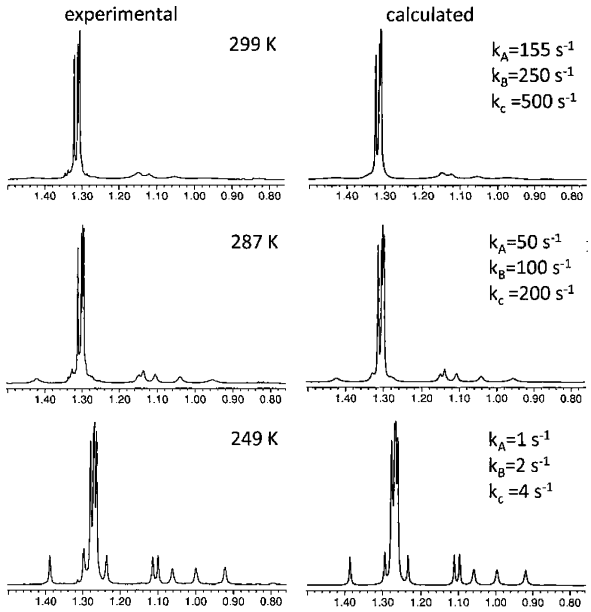
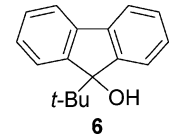


Figure 4. Experimental (left) and simulated (right) 500 MHz ^{1}H NMR spectrum of the *t*-Bu region of **5** at different temperatures.

t-Bu groups of **4** is lower (12.7 kcal mol^{-1}). This may indicate that the steric environment around this group is different than around the rest. We assign this unique *tert*-butyl signal to the *t*-Bu groups attached to C−O4H (see Figure S1 in Supporting Information), the only hydroxyl not involved in intramolecular hydrogen bonding. Although the *tert*-butyl rotational barriers are not record breaking,[13] they are substantial. For example, the barrier to rotation (through an eclipsed transition state) of tri-*tert*-butylmethanol (sharing with **4** and **5** the *t*-Bu-C(OH)R_2 structural subunit) is only 10 kcal mol^{-1},[14] the barrier of 9-*tert*-butylfluorenol (**6**) is 9.4 kcal mol^{-1},[15] and the rotational barriers of several hexaalkylethanes of general form *t*-BuC(Me)RR′ lie in the 8.4−11.0 kcal mol^{-1} range.[5b,16] The geometry of the 1,3-alternate conformation of the macrocycle, its relative rigidity and the presence of the geminal OH group, and its intramolecular hydrogen bonding (if present) probably all contribute to the rotational barrier.



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In summary, the sterically hindered methylene functionalized calixarenes **4** and **5** display restricted tripodal rotation of the *t*-Bu groups on the ^{1}H NMR time scale.

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Supporting Information Available: ^{1}H and ^{13}C spectra, parameters for the simulation of the temperature-dependent NMR spectra of **4** and **5**, and crystallographic information file of **5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For example, on the basis of the reported data by Brewer (Brewer, J. P. N.; Heaney, H.; Marples, B. A. *Chem. Commun.* **1967**, *27*), a barrier of ca. 20 kcal mol^{-1} has been estimated for the *t*-Bu rotation in a bicyclic system. See: Oki, M.; Yamamoto, G. *Chem. Lett.* **1972**, 45.

(14) Anderson, J. E.; Kirsch, P. A.; Lomas, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1065.

(15) Rieker, A.; Kessler, H. *Tetrahedron Lett.* **1969**, 1227.

(16) See: Anderson, J. E. In *The Chemistry of Alkanes and Cycloalkanes*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1992; Chapter 3.