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Tetraaddition of PhLi to a Ketocalixarene Derivative

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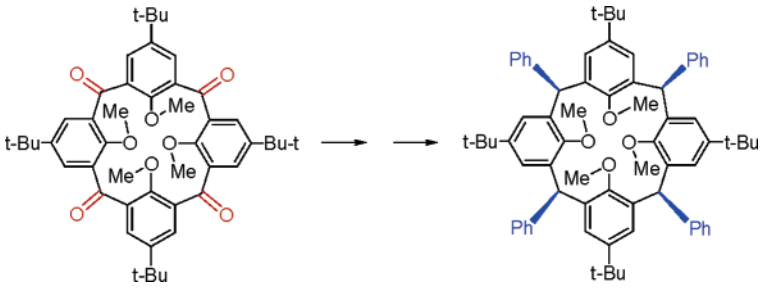
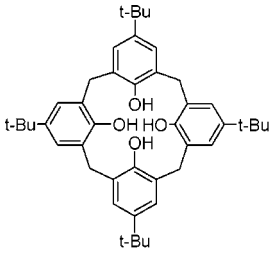
ABSTRACT

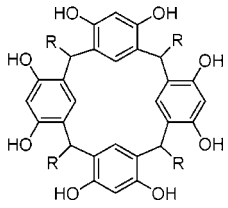


Reaction of a ketocalixarene with 2.2 equiv or an excess of PhLi affords diaddition and tetraaddition products, respectively. Ionic hydrogenation of the tetraalcohol 8a yields a calix[4]arene monosubstituted by phenyl groups at all four methylene bridges.

Calixarenes (e.g., **1**) are synthetic macrocycles that are currently intensively studied as ligands and hosts.[1] The best synthetic procedure for the preparation of the systems involves condensation of a *p*-alkyl phenol (usually *p-tert*-butylphenol) with formaldehyde and base.[2] Consequently, the calixarenes are usually obtained with nonfunctionalized methylene bridges. This is in contrast to the resorcinarenes (**2**), which are usually prepared via acid-catalyzed condensation of resorcinol and an aldehyde different from formaldehyde.[3] As a result, resorcinarenes are generally obtained with the four bridges substituted by an alkyl or aryl group.



1



2

Several synthetic methods have been reported for the preparation of calixarenes possessing one or two substituted functionalized methylene bridges.[4−7] Only few systems (i.e., **3** and **4**) have been reported so far in which all the methylene bridges in the calix[4]arene scaffold are substituted.[8,9] The

(1) For reviews on calixarenes, see: (a) *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (c) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1. (d) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 2, p 103. (e) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (f) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001. (g) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(2) (a) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234. (b) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1989**, *68*, 238. (c) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1989**, *68*, 243.

(3) For a review on resorcinarenes, see: Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.

(4) Fragment condensation method: (a) Tabatai, 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) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311. (d) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938. (e) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (f) Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071. For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods, see: Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019.

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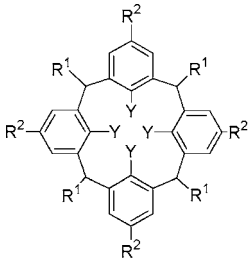
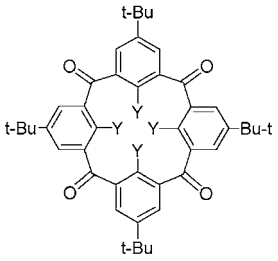
tetrabromo derivatives **3a** and **3b** have been prepared by radical bromination of tetramethoxy calixarene derivatives,[9] and **4** has been prepared by Görmar via $LiAlH_4$ reduction of ketocalixarene **5**.[8] However, so far, no calixarene derivative has been synthesized with all the bridges monosubstituted by alkyl or aryl groups.



3a Y = OMe, R^1 = Br, R^2=H
3b Y = OMe, R^1 = Br, R^2=t-Bu
4 Y = OH, R^1 = OH, R^2=t-Bu



5 Y = OH
6 Y = OMe

In principle, ketocalixarene **5** could serve as a starting material for the preparation of calixarene derivatives that are functionalized at all the methylene groups. This was recognized by Gutsche who stated in his 1998 book, "ketocalixarenes...now offer the potential of allowing the incorporation of this structural feature [the incorporation of substituents at the sites of the bridging methylene groups] in the phenol-derived calixarenes, but to date there have been no reports exploring this possibility".[10] Here we report the preparation of calixarene derivatives with four methylene groups substituted by phenyl groups. Our synthetic strategy was based on the reaction of the carbonyl groups of a derivative of **5** with an organometallic reagent. We chose to protect the OH groups with methyl groups to avoid their acid−base reaction with the organometallic reagent. The tetramethoxy derivative **6** readily available by methylation of **5** adopts the 1,3-alternate conformation.[11]

Disregarding conformational isomers, four different stereoisomers are possible for the tetraaddition product. A schematic representation of these isomers is shown in Figure 1.[12,13] For the second step of the transformation (reduction of the OH groups), we chose ionic hydrogenation, hoping

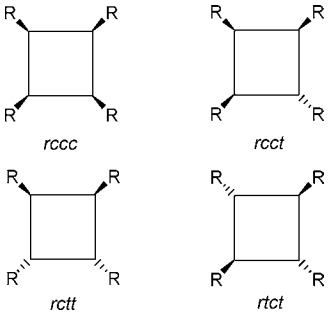
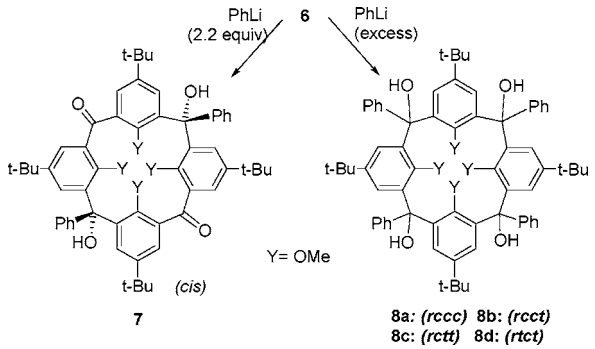


Figure 1. Schematic representation of the four possible isomers of a calix[4]arene possessing four identically functionalized methylene bridges. The label "R" represents alkyl or aryl substituents.

that, even if the addition of the organometallic reagents yields a stereoisomeric mixture, epimerization of the substituted methylene bridges under the ionic hydrogenation conditions[14] will yield a single stereoisomer.

Reaction of **6** with 2.2 equiv of PhLi (eq 1) in THF at 0 °C afforded the diaddition product **7** in 42% yield (Scheme 1).[15] The compound displayed in the ^{1}H NMR spectrum a

Scheme 1



broad signal for the phenyl groups at the bridges and two methoxy signals at δ 2.81 and 3.09 but a single signal for the two functionalized bridges in the ^{13}C NMR. The observed NMR pattern indicates two types of aryl rings but a single kind of functionalized bridge and is consistent with a frozen 1,3-alternated arrangement of the rings (on the NMR time scale) and a *cis* disposition of the phenyl substituents at the bridges.[16] Pairs of methoxy groups on geminal rings are diastereotopic in the 1,3-alternate conformation but enantiotopic in the cone form. In principle, a fast (on the NMR time scale) 1,3-alternate/cone interconversion (Scheme 2) should render isochronous all the methoxy groups.

(5) Spirodienone route: (a) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (b) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (c) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634. (d) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685. For a review on spirodienone calixarene derivatives, see: Biali, S. E. *Synlett* **2003**, 1.

(6) Homologous anionic ortho-Fries rearrangement: Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667.

(7) Alkylation of monolithiated tetramethoxy *p-tert*-butylcalix[4]arene: Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741.

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

(9) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. Kumar, S.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073.

(10) Ref 1e, page 130.

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

(12) The four isomers are analogous to the four forms of a resorcinarene of general formula **2** (R = alkyl or aryl). It should be stressed that these forms are configurational isomers and not conformers because their mutual interconversion requires cleavage of bonds.

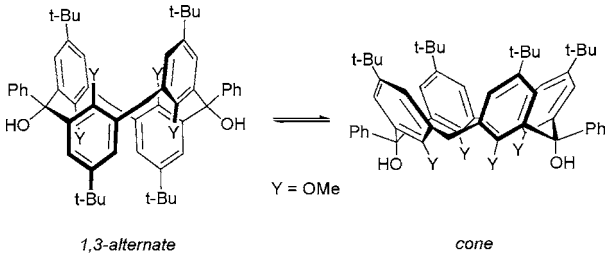
(13) The nomenclature is identical to the one used by Böhmer for the designation of the stereoisomers of resorcinarenes. One substituent on a bridge is taken as the reference (*r*). The arrangement of the other substituents is designated as *cis* (*c*) or *trans* (*t*) relative to the reference substituent. See ref 1g, page 1382.

(14) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.

(15) If the reaction is conducted using commercially available PhLi, the use of fresh reagent is recommended.

(16) Preliminary X-ray data corroborate this structural assignment.

Scheme 2



Heating a sample of **7** in $CDCl_2CDCl_2$ to 418 K did not result in any apparent broadening of the methoxy signals. On the basis of the chemical shift difference between the two methoxy signals (102.3 Hz at 400 MHz), a lower limit of $\Delta G^{\ddagger} = 20.2$ kcal mol^{-1} can be estimated for the ring inversion process (rotation through the annulus of the aryl rings of the macrocycle).[17]

Reaction of **6** with excess PhLi at room temperature afforded a mixture of tetraaddition derivatives (Scheme 1). NMR analysis of the crude reaction product indicated that all four possible isomers were formed and that the **8a**/**8b**/**8c**/**8d** ratio in the crude product is ca. 3:4:1:1 (Figure 2).[18]

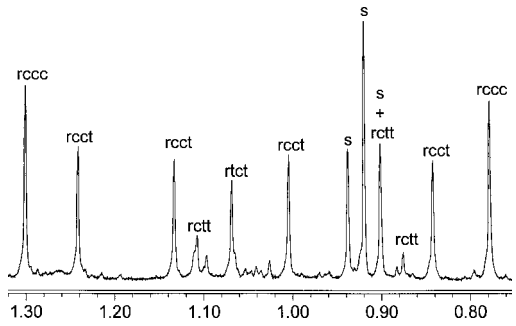


Figure 2. 400 MHz, ^{1}H NMR spectrum (*tert*-butyl region, $CDCl_3$, rt) of the crude product obtained by reacting **6** with an excess of PhLi. The triplet at ca. 0.92 ppm is due to residual dibutyl ether.

Upon recrystallization from $CHCl_3$/acetone, **8a** precipitated in pure form.[19,20] This product displayed in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) two singlets each for the *tert*-butyl, methoxy, and aromatic protons (δ 7.97 and 6.60 ppm) of the macrocyclic rings (Figure 3). The absence of mutual coupling between the two signals indicates that the protons are located on different rings, and their large chemical shift

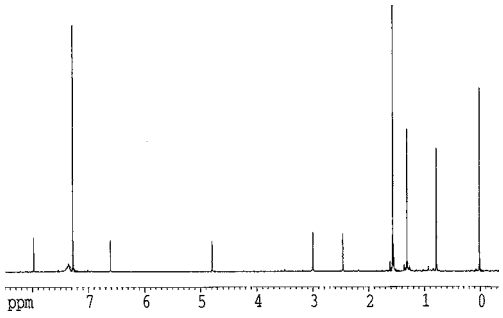


Figure 3. 400 MHz ($CDCl_3$, rt) ^{1}H NMR spectrum of **8a**.

difference suggests that they are differently influenced by the shielding/deshielding effects of the phenyl rings on the bridges. The observed NMR pattern again indicates two types of macrocyclic aryl rings but a single kind of functionalized bridge and is consistent with a *rccc* derivative **8a** adopting a frozen (on the NMR time scale) 1,3-alternate conformation of the macrocycle. X-ray crystallography of a single crystal confirmed these configurational and conformational assignments (Figure 4).[21] Notably, a pair of methoxy groups on

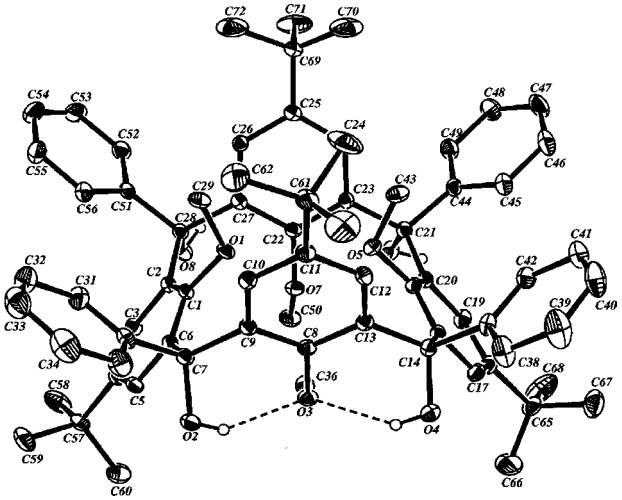


Figure 4. X-ray structure of **8a**. Chloroform and ether molecules are omitted for clarity.

opposite rings (those pointing "down" in Figure 4) adopt an "in−out" arrangement, with the "in" methoxy group hydrogen bonded to two hydroxyl groups.

At room temperature, the aromatic protons on the phenyl rings on the bridges appear as a broad signal. This signal decoalesces upon lowering the temperature of a THF-d_8 solution, and at 275 K, four signals are observed (in a 1:1:2:1 ratio). This suggests that the rotation of the phenyl rings

(17) A lower limit for the exchange rate at 418 K was estimated using the Gutowsky−Holm equation: Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

(18) Two, four, three, and one *t*-Bu signals are expected for **8a**, **8b**, **8c**, and **8d**, respectively, assuming a 1,3-alternate conformation of the macrocycle in all forms.

(19) The second crop of crystals afforded a sample of the *rctc* isomer in 81% purity.

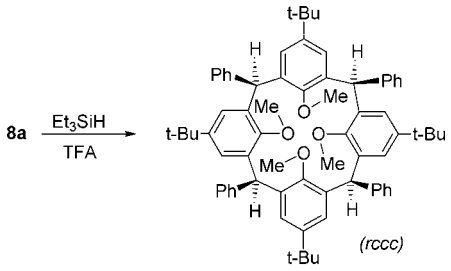
(20) Recrystallization of the crude product from $CHCl_3$/acetonitrile affords mainly the *rctt* form.

(21) Selected crystal data: $P2(1)n$, $a = 23.5483(3)$ Å, $b = 11.9852(7)$ Å, $c = 26.1138(15)$ Å, $\beta = 108.463(1)°$, $Z = 4$, $T = 173$ K. Final R indices [$I > 2\sigma(I)$] $R_1 = 0.0678$, $wR_2 = 0.1804$.

around the Ph−C bonds is slow on the NMR time scale and that the two edges of the phenyl rings are symmetry nonequivalent.

Reduction of the hydroxyl group at the bridges of **8a** was conducted with Et_3SiH/CF_3COOH (Scheme 3).[14] The ^1H NMR spectrum of the product displayed single singlets for the *tert*-butyl groups, methoxy, and methine protons, consistent only (precluding accidental isochrony) with *rccc* or *rctt* configurations of the bridges (Figure 5). However, the chemical shift of the methine proton (δ 6.30 ppm) is similar to the chemical shift observed for the axial proton of a calixarene carrying two tolyl groups at the bridges (*trans* isomer, δ 5.94 and 5.23 ppm for the axial and equatorial methine protons).[4d] On these grounds, we ascribe to **9** a *rccc* stereochemistry, with the macrocycle adopting a cone conformation and the phenyls on the bridges located equatorially.[22] The ionic hydrogenation reaction was also conducted on the crude product mixture of configurational isomers of **8**. Judging from the NMR of the crude product, the main product of the reaction is also **9** (*rccc* isomer), but the reaction is not as clean as when starting from pure **8a**.

Scheme 3



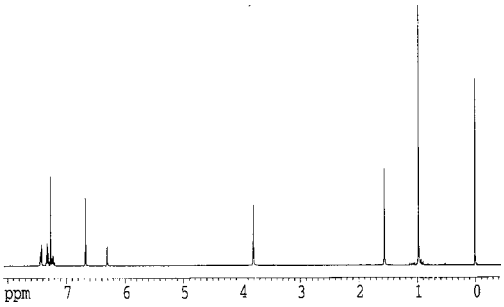


Figure 5. 400 MHz ($CDCl_3$, rt) ^1H NMR spectrum of the tetrafunctionalized calixarene **9**.

To conclude, a ketocalixarene derivative can be used as starting material for the preparation of calixarenes monosubstituted by an aryl group at all four bridges.

Acknowledgment. We thank Dr. Shmuel Cohen (The Hebrew University of Jerusalem) for the crystal structure determination. This research was supported by the Israel Science Foundation (grant no. 934/04).

Supporting Information Available: Experimental procedures for the preparation of **7**−**9** and crystallographic data for **8a** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Because the methine protons of **9** are located at axial positions, the phenyl groups at the bridges must be located at equatorial ones.