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Synthesis of Diazacalix[8]arene and Triazacalix[12]arene Methyl Ethers via Intramolecular Aryl Amination

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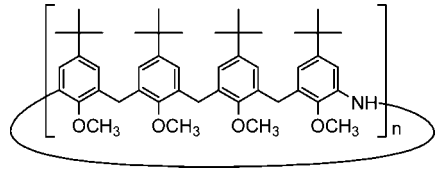
ABSTRACT



Azacalixarenes derived from *p-tert*-butylphenol are generated by an intramolecular aryl amination strategy as the ring-closing step. The reaction produces the first examples of larger *p-tert*-butylcalixarenes with regioselective substitution of bridging methylenes with nitrogen atoms.

Macrocyclic oligomers of *p*-alkylphenols and formaldehyde, the original members of the calix[*n*]arene family,[1] have received widespread interest as molecular hosts. The one-pot syntheses of *p-tert*-butylcalix[4], [6], and [8]arenes have made these major calixarenes the most thoroughly studied analogs. The small cavity size of *p-tert*-butylcalix[4]arene imparts the greatest amount of conformational rigidity, leading to the well-defined cone, partial cone, 1,2-alternate, and 1,3-alternate conformations. *p-tert*-Butylcalix[8]arene, on the other hand, is much more fluid in solution as a result of a larger annulus and is believed to exist in either a pleated loop[2] or pinched double cone conformation.[3] Furthermore, rich functionalization strategies are available for *p-tert*-butylcalix[*n*]arenes along their upper rim *p*-alkyl and lower rim phenolic groups to fine-tune their conformational and binding properties.

Recently focus has shifted to explore functionalization of the bridging methylene groups to develop heteroatom-bridged derivatives of calix[*n*]arenes.[4] Replacement of the bridging methylene groups with heteroatoms can alter the conformational properties of the macrocycle through changes in bond lengths and angles associated with the heteroatom in addition to participation of the heteroatom in hydrogen bonding along the lower rim. Furthermore, the heteroatom provides additional binding sites to the macrocycle and, in the case of nitrogen and sulfur, new avenues to further functionalize the bridge position. Heteroatom-bridged derivatives of the parent *p-tert*-butylcalix[4]arene **1** (Figure 1) include mono-, di-, tri-, and tetrathiacalix[4]arene **2**,[5] tetrasilacalix[4]arene **3**,[6] and tetraazacalixarene **4**,[7] as well as the expanded homooxa- and

(1) For reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes An Introduction*, 2nd ed.; Stoddart, J. R., Ed.; Royal Society of Chemistry: Cambridge, UK, 2008. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001.

(2) (a) Gutsche, C. D.; Gutsche, A. E.; Karaulov, A. I. *J. Inclusion Phenom.* **1985**, *3*, 447–451. (b) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052–6059.

(3) (a) Gutsche, C. D.; Bauer, L. J. *Tetrahedron Lett.* **1981**, *22*, 4763–4766. (b) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161–170. (c) A related chair-like structure has also been reported; see: Czugler, M.; Tisza, S.; Speir, G. *J. Incl. Phenom. Recognit. Chem.* **1991**, *11*, 323–331.

(4) For reviews, see: (a) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303–2310. (b) Wang, M.-X. *Chem. Commun.* **2008**, 4541–4551. (c) Maes, W.; Dehaen, W. *Chem. Soc. Rev.* **2008**, *37*, 2393–2402. (d) Tsue, H. *Top. Heterocycl. Chem.* **2008**, *17*, 73–96.

(5) (a) Sone, T.; Ohba, Y.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **1997**, *53*, 10689–10698. (b) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971–3972. (c) Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437–1443. (d) Lhoták, P. *Eur. J. Org. Chem.* **2004**, 1675–1692.

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homoazacalixarenes.[8] Larger derivatives include octathiacalix[8]arene,[9] hexaazacalix[6]arene,[10] heptaazacalix[7]arene,[11] and octaazacalix[8]arene.[12] Finally, a broad range of heterocalixarenes incorporating alternatives to phenol building blocks (benzene or heteroaromatic rings) linked by methylene and/or heteroatom bridges have been described.[4,13] In this paper we report on the preparation of diazacalix[8]arene and triazacalix[12]arene methyl ethers as examples of *p-tert*-butylazacalixarenes with regioselective substitution of bridging methylenes with free amino groups.

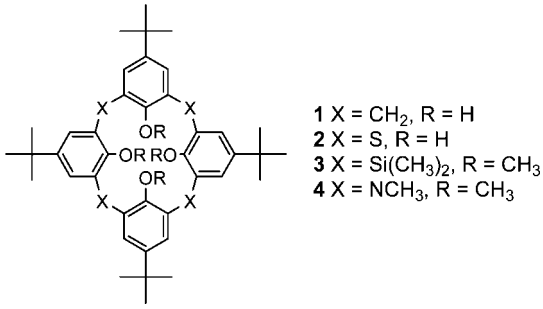
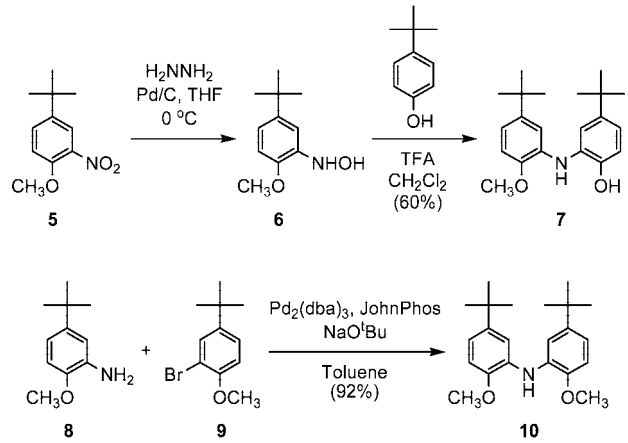


Figure 1. Heteroatom-bridged *p-tert*-butylcalix[4]arenes.

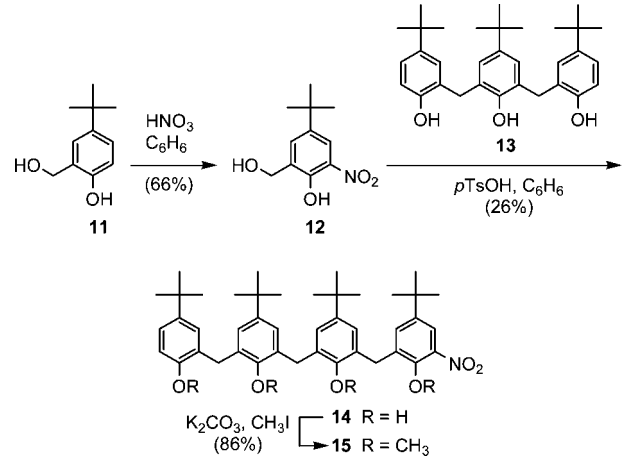
To investigate the effect of nitrogen bridge substitution on the conformational properties of *p-tert*-butylcalixarenes, our focus turned toward the synthesis of monoazacalix[4]arene. To prepare azacalixarenes with only partial substitution of bridging methylene groups with nitrogen atoms, a stepwise approach was required as opposed to one-pot syntheses available for symmetrical macrocycles. We envisioned preparing monoazacalix[4]arene through an open chain linear tetramer employing formation of an *N*-aryl bond as the ring-closing step. Two intermolecular strategies were examined to prepare diaryl amines derived from *p-tert*-butylphenol to test the scope of the ring-closing step (Scheme 1). We have previously reported on the synthesis and acid-catalyzed condensation of *N*-arylhydroxylamine **6** with *p-tert*-butylphenol to furnish diarylamine **7** in a combined two-step 60% yield from 4-*tert*-butyl-2-nitroanisole **5**.[14] Alternatively, Buchwald−Hartwig aryl amination[15] of aniline **8** with aryl bromide **9** employing $Pd_2(dba)_3$ as the catalyst in the presence of JohnPhos[16] and *t*-BuONa provided diaryl amine **10** in 92% yield. With two viable routes available to assemble model diarylamines the stage was set to examine intramolecular variants of these reactions to prepare azacalixarene macrocycles.

Scheme 1. Synthetic Routes toward Diarylamines Derived from *p-tert*-Butylphenol



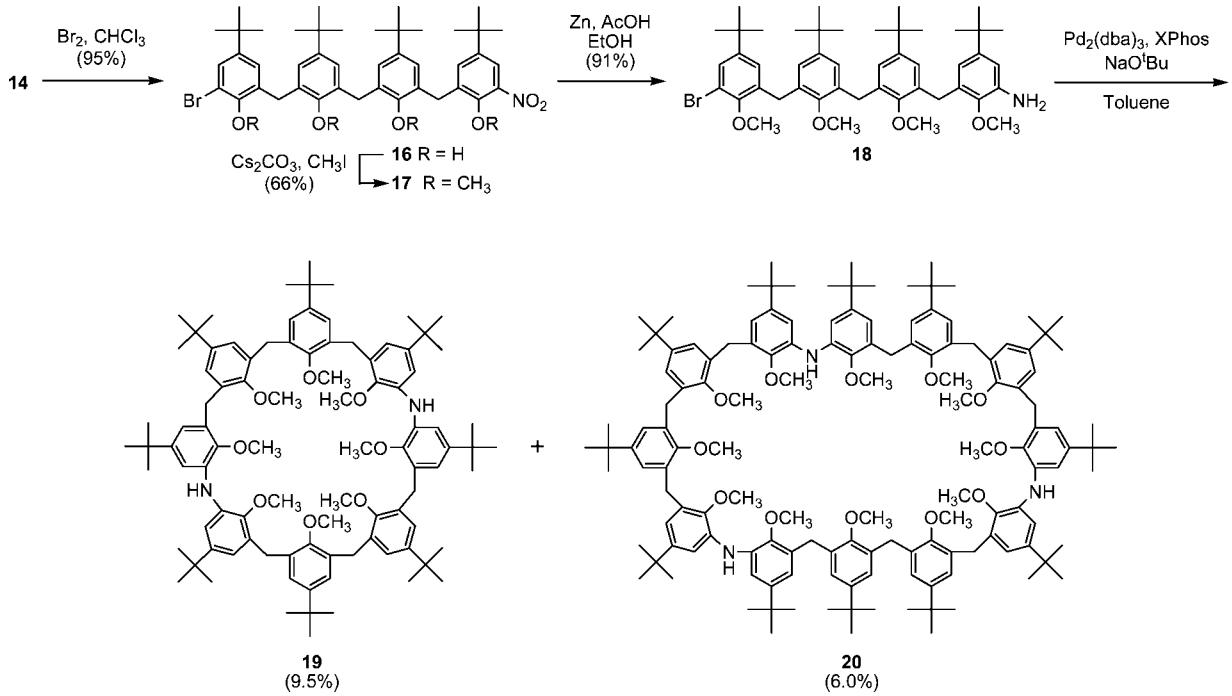
Initial efforts to prepare monoazacalix[4]arene focused on an intramolecular acid-catalyzed hydroxylamine condensation on a linear tetramer (Scheme 2). This approach parallels the syntheses of parent calixarenes employing intramolecular acid-catalyzed condensations of monohydroxymethylated linear tetramers originally described by Hayes and Hunter.[17] Nitration of 4-*tert*-butyl-2-(hydroxymethyl)phenol **11**[18] with cold HNO_3 in benzene readily afforded nitrophenol **12** in 66% yield. Subsequent acid-catalyzed condensation with a 5-fold excess of trimer **13**[19] in refluxing benzene produced nitrated tetramer **14** in 26% yield. Prior to reduction of the nitro group to the corresponding hydroxylamine, the acidic

Scheme 2. Synthesis of Nitro-tetramer **14**



(6) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 661–662.
(7) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165–2168.
(8) Masci, B. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; Chapter 12, p 235.
(9) Kondo, Y.; Endo, K.; Iki, N.; Miyano, S.; Hamada, F. *J. Inclusion Phenom.* **2005**, *52*, 45–49.
(10) Tsue, H.; Ishibashi, K.; Tokita, S.; Takahashi, H.; Matsui, K.; Tamura, R. *Chem. Eur. J.* **2008**, *14*, 6125–6134.
(11) Tsue, H.; Matsui, K.; Ishibashi, K.; Takahashi, H.; Tokita, S.; Ono, K.; Tamura, R. *J. Org. Chem.* **2008**, *73*, 7748–7755.
(12) Ishibashi, K.; Tsue, H.; Tokita, S.; Matsui, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2006**, *8*, 5991–5994.
(13) Vysotsky, M.; Saadioui, M.; Böhmer, V. *Calixarenes 2001*; Asfari, Z.; Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001; Chapter 13, p 250.
(14) Spence, J. D.; Raymond, A. E.; Norton, D. E. *Tetrahedron Lett.* **2003**, *44*, 849–851.

Scheme 3. Intramolecular Aryl Amination Route towards *p-tert*-Butylazacalixarenes



phenol groups were converted to their methyl ethers by treatment with CH_3I and K_2CO_3 to afford **15** in 86% yield. However, treatment of **15** with H_2NNH_2 and Pd/C in THF at low temperatures, conditions developed in our model studies, was unsuccessful in reducing the nitro group to the corresponding hydroxylamine and afforded the fully reduced amino product. Due to the difficulty in obtaining the labile hydroxylamine tetramer, we turned our attention toward palladium-catalyzed aryl amination chemistry to close the macrocycle.

To examine an intramolecular Buchwald−Hartwig aryl amination strategy, an open chain linear tetramer containing the requisite amino- and bromo-substituents at opposing ends was prepared (Scheme 3). With a rapid synthesis of nitrated tetramer **14** in hand, the remaining free *ortho*-phenolic position was brominated with Br_2 in $CHCl_3$ to afford **16** in 95% yield. To avoid competing O-arylation of the free phenols, exhaustive methylation was accomplished with CH_3I and Cs_2CO_3 to afford a 66% yield of **17**. Finally, selective reduction of the nitro group in **17** with Zn in AcOH/ethanol provided amino-bromo-derivative **18** in 91% yield. Initial attempts at intramolecular cyclization employing $Pd_2(dba)_3$ and *t*-BuONa in combination with phosphine ligands BINAP, $P(tBu)_3$, $P(Cy)_3$, JohnPhos, and *tert*-butyl JohnPhos in refluxing toluene were unsuccessful. In each case significant polymerization was observed with trace amounts of the corresponding debrominated amine obtained as the only isolable product. Upon changing the phosphine ligand to the bulkier XPhos,[20] two new products were observed whose ^1H NMR spectra were greatly simplified compared to their open chain tetramer counterparts. Upon purification NMR and mass spectroscopy confirmed the formation of diazacalix[8]arene octamethyl ether **19** and triazacalix[12]arene dodecamethyl ether **20** in 9.5% and 6.0% yield, respectively. Despite high dilution techniques monoazacalix[4]arene was not observed in the product mixture; however, ESI MS data indicated trace amounts of the higher homologue tetraazacalix[16]arene were produced.

The formation of azacalixarene macrocycles was confirmed by the relative simplicity of their ^1H NMR specta in $CDCl_3$ (see Supporting Information). Diazacalix[8]arene **19** displayed two equally integrating *tert*-butyl singlets at 1.2 and 1.1 ppm along with two equally integrating methoxy singlets at 3.45 and 3.41 ppm. Also observed were two singlets at 4.05 and 4.02 ppm that integrated in a 2:1 ratio for the bridging methylene groups along with four equally integrating doublets in the aromatic region. Finally, a broad NH singlet was observed at 6.24 ppm that is characteristic of intramolecular bifurcated NH···OCH_3 hydrogen bonding.[12] The symmetry of diazacalix[8]arene **19** in solution was further confirmed by ^{13}C NMR spectroscopy, which displayed 12 aromatic resonances, two methoxy resonances, and

(15) For reviews, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.

(16) 2-(Di-*tert*-butylphosphino)biphenyl. Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.

(17) (a) Hayes, B. T.; Hunter, R. F. *Chem. Ind.* **1956**, 193–194. (b) Hayes, B. T.; Hunter, R. F. *J. Appl. Chem.* **1958**, *8*, 743–748.

(18) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* **1980**, 124–125.

(19) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536–1539.

(20) 2-Dicyclohexylphosphino-2′,4′,6′-tri-isopropylbiphenyl. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

four *tert*-butyl resonances confirming the presence of two distinct aromatic rings. In addition, two resonances were observed at 30 ppm for the two unique methylene bridge carbons. Triazacalix[12]arene **20** displayed a similar ^{1}H NMR spectrum with downfield shifts for the methoxy resonances (3.60 and 3.58 ppm) and the NH singlet (6.38 ppm) compared to diazacalix[8]arene **19**. Ultimate verification of the macrocycle size was obtained by mass spectrometry data. Diazacalix[8]arene **19** gave a monocharged $[M + Na]^+$ molecular ion peak at *m*/*z* 1433.9407 (Δ 0.3 ppm) along with a double-charged $[M + 2Na]^{2+}$ ion at *m*/*z* 728.4656 (Δ 0.1 ppm) by high resolution ESI MS. In comparison, triazacalix[12]arene **20** displayed an M^+ peak at *m*/*z* 2116 by MALDI, and ESI gave an $[M + 2Na]^{2+}$ peak at *m*/*z* 1081.7008 (Δ 3.4 ppm).

Dynamic ^{1}H NMR studies of diazacalix[8]arene **19** over the temperature range 213−333 K displayed only slight broadening of the bridging methylene singlets at low temperature, indicating that the macrocycle remains conformationally mobile as observed for the parent *p*-*tert*-butylcalix[8]arene methyl ether.[21] To date, efforts to obtain suitable crystals to examine solid-state conformation have been unsuccessful. Attempts to exhaustively demethylate **19** by treatment with BBr_3 to examine conformational properties of the free phenol led to incomplete demethylation at low temperatures with competing de-*tert*-butylation upon warming to room temperature as observed in our model studies.[14]

In conclusion, we have developed an intramolecular Buchwald−Hartwig aryl amination strategy to prepare *p*-*tert*-butylazacalixarene macrocycles with selective substitution of bridging methylenes with free amino groups. Cyclization of amino-bromo open-chain tetramer **18** affords diazacalix[8]arene **19** and triazacalix[12]arene **20** methyl ethers in a combined 15.5% yield. Although larger macrocycles are observed by mass spectroscopy, no evidence of the monomeric azacalix[4]arene was noted. Studies to examine the effect of selective NH bridge substitution on the conformational properties of azacalixarenes are currently ongoing along with continued efforts to prepare monoazacalix[4], [5] and [6]arenes through intramolecular aryl amination strategies.

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Supporting Information Available: Full experimental procedures and spectroscopic data for compounds **12**, **14**, and **16**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6059–6063.