Spirodienone Route for Aminodehydroxylation: Monoaminotrihydroxy-*p-tert*-butylcalix[4]arene

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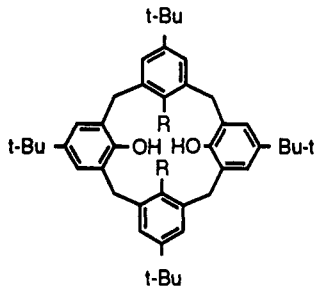
Summary: The replacement of one OH group of *p-tert*-butyl calixarene by an amino group is accomplished via a monospirodienone intermediate.

Calixarenes are readily available macrocyclic ligands composed of an alternate array of phenol and methylenic units.[1] One of the most difficult synthetic tasks in calixarene chemistry (or, for that matter, in organic chemistry in general) is the replacement of the phenolic oxygens by other heteroatoms.[2] Of special interest is the replacement of the OH by an amino group, since this basic binding site may alter drastically the properties of the systems. This substitution was attempted in the past unsuccessfully by us for *p-tert*-butylcalix[4]arene (1) using



1 R = OH
2 R = NH_2

Rossi and Bunnett's method[3] which involves derivatization of the OH groups to phosphate ester groups followed by treatment with KNH_2/NH_3.[4] Recently, Shinkai and coworkers prepared the diaminocalixarene **2** by that method by adding HMPA as cosolvent.[5] In this paper we report a novel approach for the oxygen substitution of a phenol and describe the preparation of monoaminotrihydroxy-*p-tert*-butylcalix[4]arene (**3**). The route benefits from the polyphenolic nature of the calixarenes and may be used for the mono or partial oxygen substitution in the systems. As substrate for the reaction we chose the monospirodienone derivative **4**[6,7] which can be prepared in one step by oxidation of **1**.[7a]

Our route was based on two premises: (i) The carbonyl group of a dienone may undergo condensation with an amine under proper reaction conditions. (ii) Rearomatization of the resulting Schiff base may be carried out leading to an aminocalixarene derivative. We chose hydrazine as the amino nucleophile since it may provide an entry to both hydrazocalixarenes and, after N–N cleavage, to aminocalixarenes. No azine product should be expected in the reaction between the spirodienone and hydrazine due to steric reasons.

Treatment of **4** with hydrazine dihydrochloride/MeOH/NaOH under reflux resulted in the partial regeneration of **1** accompanied by the formation of a main product (Scheme I). After chromatography the compound resulting from the condensation of **4** with hydrazine (**5**, mp 223–225 °C) was isolated in 20% yield. The ^{1}H NMR spectrum of **5** (400 MHz, $CDCl_3$ with a drop of D_2O, rt) displayed in the methylene region four doublets integrating for four protons in the δ 3.37–4.23 region and several multiplets in the δ 2.01–3.28 region integrating for eight protons, i.e., a total of *twelve* protons, instead of the expected eight protons appearing as four AB systems. The ^{13}C NMR spectrum of **5** (100 MHz, $CDCl_3$) displayed a signal at δ 158.85 ppm, assigned to a C=N moiety, and 15 C(sp^3) and 20 C(sp^2) signals in the δ 28.9–42.3 ppm and δ 121–152.2 regions, respectively.[8] The absence of signals in the δ 190–200 and 80–90 ppm region indicates that both the C=O and the spiro CO moieties are absent in the product. The presence of 15 aliphatic signals in the ^{13}C NMR and 12 protons in the methylene region of the ^{1}H NMR suggests that one of the double bonds of the diene was reduced. A single crystal of **5** was grown by evaporation of a MeCN solution and submitted to X-ray diffraction.[9] The numbering scheme is shown in Figure 1. The conformation somewhat resembles a 1,2-alternate conformation.[1] Two methylene groups attached to the cyclohexene ring (C(28) and C(21)) are in a trans relationship and are located in a pseudoaxial and a pseudoequatorial position of the reduced ring, respectively. Hydrogen bonding interactions involve the nitrogen attached to the ring as indicated by the short N(1)–O(3) distance (2.644(3) Å) and the hydroxyl groups on the two phenol rings in a mutual syn arrangement (O(1)–O(2): 2.898(3) Å). The double-bond reduction can be rationalized assuming that the substrate oxidizes the hydrazine to diimine which in turn reduces one of the double bonds of the diene.

Rearomatization of the ring was accomplished in one step by reflux of **5** with Pd/C in dry toluene (Scheme I).

(1) For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. In *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; p 93. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (d) Böhmer, V.; McKervey, M. A. *Chemie in unserer Zeit* **1991**, 195.

(2) Only a few examples are known in which phenolic oxygens of the calixarenes were replaced by another atom. For the replacement of oxygen by sulfur see: Gutsche, C. D. Reference 1a, p 107. Gutsche, C. D.; Rogers, J. S.; Stewart, D.; See, K.-A. *Pure Appl. Chem.* **1990**, *62*, 485. Ting, Y.; Verboom, W.; Groenen, L. C.; van Loon, J.-D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432.

(3) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 2314.

(4) Goren, Z.; Biali, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1484. Grynszpan, F.; Biali, S. E. *J. Phys. Org. Chem.* **1992**, *5*, 155.

(5) (a) Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 1217. (b) Araki, K.; Murakami, H.; Ohseto, F.; Shinkai, S. *Chem. Lett.* **1992**, 539.

(6) For a review on spirodienones see: Ward, R. S. *Chem. Br.* **1973**, *9*, 444. Barton, D. H. R. *Chem. Br.* **1967**, 330.

(7) (a) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11. (b) Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, *57*, 1943. (c) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393.

(8) ^{13}C NMR of **5**: (100 MHz, $CDCl_3$, rt) δ 29.00 (CMe_3), 31.06, 31.52 (CMe_3), 31.54 (CMe_3), 31.68 (CMe_3), 32.92, 33.97, 34.00, 34.17, 34.46, 35.08, 36.04, 37.52, 41.39, 42.20, 121.24, 124.43, 124.77, 125.10, 125.74, 126.41, 126.52, 126.87, 127.08, 127.67, 127.81, 129.92, 143.43, 143.60, 143.67, 145.04, 147.53, 150.32, 152.20, 158.85 (C=N).

(9) The authors have deposited atomic coordinates for the structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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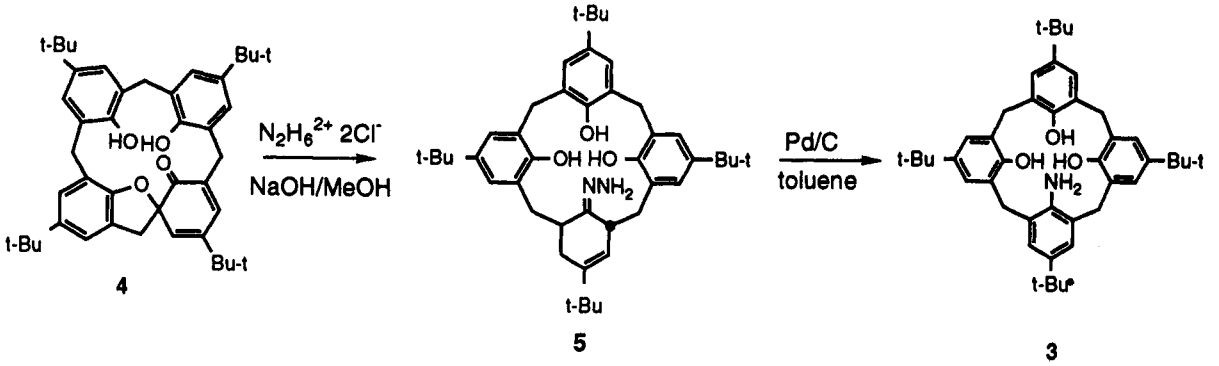
Scheme I



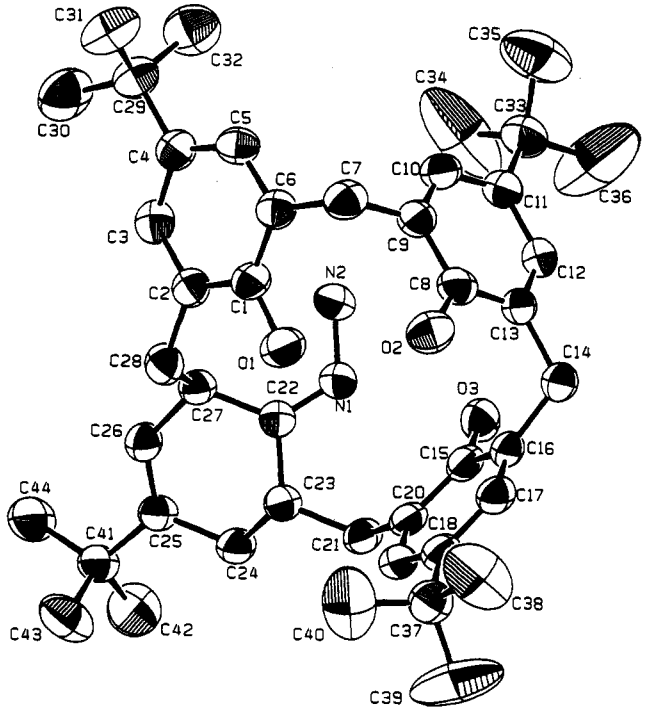


Figure 1. Molecular structure of **5**. The ethylenic C=C bond is located between C(25) and C(26).

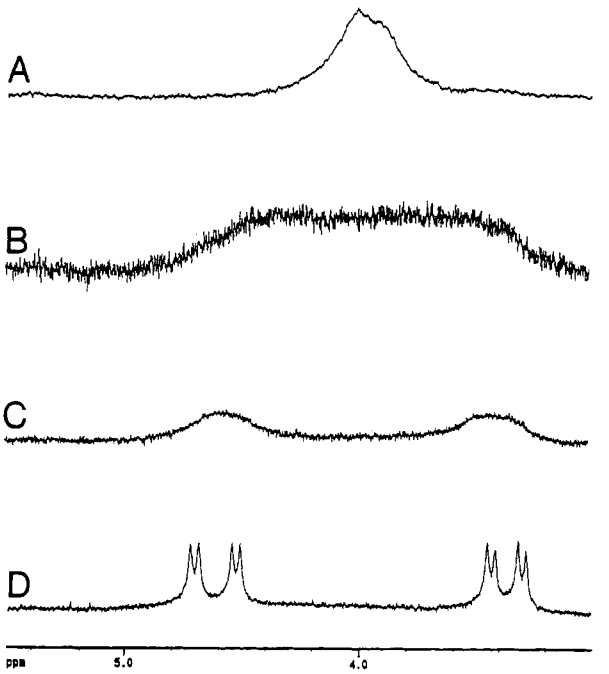


Figure 2. 400-MHz spectrum of the methylene region of $3H^+$ $TosO^-$ in $CD_3C_6D_5$ at different temperatures: A, at 380 K; B, at 365 K (coalescence temperature); C, at 350 K; D, at 325 K.

Under the reaction conditions the N–N bond was concomitantly cleaved resulting in the monoaminocalixarene **3** (mp 296–297 °C, 44% yield).[10] It seems likely that hydrogen atoms adsorbed in the catalyst as a result of the dehydrogenation are responsible for the cleavage.[11] To the best of our knowledge, this represents the first example in which a phenolic OH group was replaced by NH_2 by way of a spirodienone derivative. Interestingly, the conversion of **1** to **3** involves three steps, each involving either an oxidation or reduction.

The monoaminocalixarene displays in the ^1H NMR (400 MHz, $CDCl_3$, rt) three *tert*-butyl signals, two broad signals for the methylene protons and two singlets and AB system for the aromatic protons, and a broad signal (δ 9.28) for the OH protons. Upon lowering the temperature, the methylene signals decoalesced into two AB systems, in agreement with the presence of a frozen "cone" conformation of C_s symmetry while at high temperatures two singlets were obtained. From the coalescence data of the methylene protons a barrier of 14.8 kcal mol^{-1} was calculated for the inversion process.[12] This barrier has an intermediate value compared to the barriers measured for **1** and **2** in $CDCl_3$ (15.7 and 13.9 kcal mol^{-1})[5b,13] in agreement with Shinkai's observation that the substitution of a hydroxy by an amino group results in a reduction of the strength of the cyclic hydrogen bond.[5b] Changing the solvent to toluene-d_8 or pyridine-d_5 did not result in any significant change in the inversion barrier ($\Delta G_c^{\ddagger}$ = 14.8 and 14.7 kcal mol^{-1}, respectively). Unfortunately, crystals of **3** grown from $CHCl_3$ exist in a tetragonal space group which indicates that the molecules are disordered and are present in four different orientations.

The replacement of an OH by an amino group may confer basic properties on the calixarene. Adding to a $CDCl_3$ solution of **3** solid tosylic acid resulted in solubilization of

(10) Selected spectroscopic data for **3**: ^1H NMR (400 MHz, $CDCl_3$, rt) δ 1.18 (9 H, s, t-Bu), 1.19 (18 H, s, t-Bu), 1.21 (9 H, s, t-Bu), 3.48 (4 H, br, CH_2), 4.23 (4 H, br, CH_2), 6.98 (2 H, d J = 2.4 Hz, Ar-H), 7.04 (2 H, s, Ar-H), 7.05 (2 H, d J = 2.4 Hz, Ar-H), 9.28 (br, OH); ^{13}C NMR (100 MHz, $CDCl_3$, rt) δ 31.16, 31.38, 33.10, 33.92, 33.99, 34.15, 34.74, 125.61, 125.66, 125.67, 125.75, 127.64, 128.25, 128.32, 131.84, 135.21, 143.29, 143.72, 147.64, 147.92, 148.39; MS EI 647 (M) 632 (50%), CI 648 (MH^+); HRMS calcd for $C_{44}H_{57}NO_3$ 647.4338; found 647.4347.

(11) It has been reported that the reductive cleavage of hydrazines can be carried out by catalytic hydrogenation. See: Bozzini, S.; Stener, A. *Ann. Chim. (Rome)* **1968**, *58*, 169.

(12) The barrier was calculated from the exchange rates at the coalescence temperatures according to: Kurland, R. J.; Rubin, M. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426.

(13) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

an equimolar amount of the acid, as evidenced by the NMR integration ratio between the aminocalixarene and the tosylate protons. The chemical shifts of the tosylate aromatic protons are similar to the ones observed for a $CDCl_3$ solution of anilinium tosylate, although they are somewhat shifted downfield by 0.17 and 0.15 ppm. The *tert*-butyl and aromatic signals of the calixarene show moderate changes by the addition of the acid, but the methylene protons which appear at room temperature as broad signals for **3** appear as four pairs of sharp doublets. We ascribe the solubilization of the tosylic acid in $CDCl_3$, as well as the similar chemical shifts observed for the tosylic moiety in **3**·TsOH and in anilinium tosylate solutions, and the change in the methylene pattern to the formation of the salt $\mathbf{3H^+}\,TosO^-$. From the coalescence of the methylene signals in toluene-d_8 (Figure 2) the barrier for ring inversion was calculated as 16.4 kcal mol^{-1} indicating that protonation of the amino group increases the rigidity of the system by about 1.6 kcal mol^{-1}. While the NH_2 and hydroxy groups can serve as donors or acceptors of hydrogen bonds, the ammonium group can serve only as a donor. The increased rigidity of the salt may indicate that the loss of an OH···N hydrogen bond is more than compensated by the larger strength of the $ArNH_3^+\cdots OH$ hydrogen bond and probably by the formation of an endocalix complex between the calixarene and the tosylate.

In summary, we have shown that a monoaminocalix[4]arene can be prepared from a monospirodienone. The scope of the reaction and its extension to bis(spirodienone) systems and other nucleophiles are currently under investigation.

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Supplementary Material Available: Procedures and spectra (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.