ORGANIC
LETTERS

2005
Vol. 7, No. 9
1817−1820

Preferential Axial Protonation in a Zwitterionic Calix[4]arene

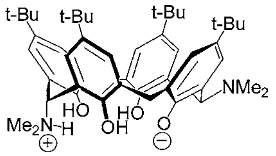
Samah Simaan and Silvio E. Biali*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

silvio@vms.huji.ac.il

Received February 28, 2005

ABSTRACT



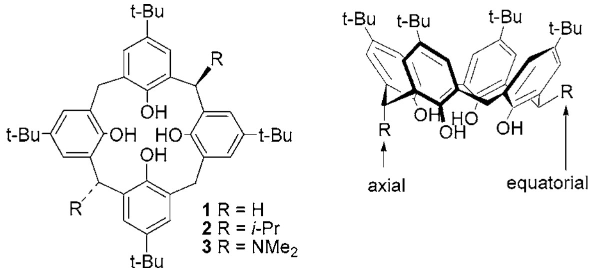
Calixarene 3, substituted at two methylene bridges by dimethylamino groups, exists in the crystal and in polar solvents as a zwitterion, with the axial dimethylamino group protonated.

The differential reactivity of axial and equatorial groups on six-membered rings is one of the cornerstones of conformational analysis.[1] *p-tert*-Butylcalix[4]arene (**1**) adopts a cone conformation in which the two symmetry-nonequivalent protons (or more generally, positions) on the methylene bridges are designated as axial and equatorial.[2] The phenolic OH groups play a crucial role in the stabilization of the *cone* form. In that conformation, the groups are arranged in spatial proximity, enabling a cyclic array of hydrogen bonds in which each OH serves both as a donor and as an acceptor. The hydrogen-bonding stabilization of the phenolate ensuing upon deprotonation renders **1** more acidic than a simple phenol.[2,3]

By analogy with the cyclohexyl derivatives, it could be expected that a pair of otherwise identical substituents should differ in their properties (and reactivities) based on their equatorial or axial disposition on the calix scaffold.[4,5]

Examination of molecular models suggests that in the cone conformation an axial substituent should be located in the immediate vicinity of the intraannular OH groups. Systems possessing a pair of opposite bridges substituted in a *trans* fashion by identical substituents (cf. Scheme 1) are good substrates to examine the issue of the different properties of axial and equatorial groups, since necessarily in the cone conformation one of the substituents must be located in an axial position

Scheme 1



Preparation of the calixarene derivative **3** substituted at two opposite bridges in a trans fashion by dimethylamino

---

(1) For a review, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(2) For reviews on calixarenes, see: (a) Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 1. (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (c) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001. (d) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(3) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3480.

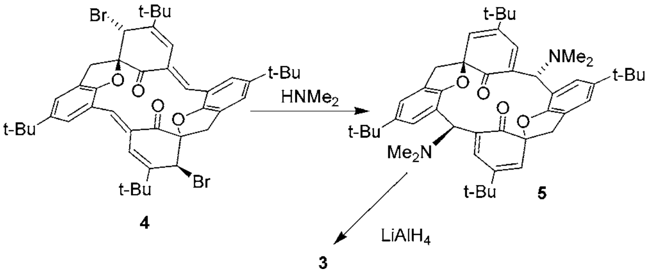
(4) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938.

(5) For a review on the stereochemistry of methylene-functionalized calixarenes, see: Simaan, S.; Biali, S. E. *J. Phys. Org. Chem.* **2004**, *17*, 752.

10.1021/ol0504392 CCC: $30.25

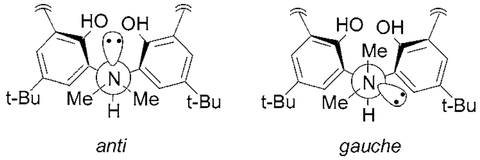
groups was conducted using the spirodiene route described previously.[6−8] Reaction of the *meso* bis(spirodiene) calixarene **4**[8] with dimethylamine in EtOH proceeded readily affording a bis(spirodienone) calixarene derivative trans-substituted at two bridges with dimethylamino groups (**5**).[9] Reaction of **5** with $LiAlH_4$ resulted in reductive cleavage of the spiro bonds and aromatization, affording the target derivative **3** (Scheme 2).

Scheme 2



In principle, two different staggered conformations (*anti* and *gauche*) are possible for the dimethylamino groups of **3** (Scheme 3). According to the NMR data, in the preferred conformation of **2** the isopropyl groups adopt the *anti* arrangement.[10] Calculations performed on a calixarene with one bridge substituted by an isopropyl group had indicated that such arrangement of the group is the lowest in energy.[3]

Scheme 3



anti *gauche*

Since a dimethylamino group is sterically similar to an isopropyl group,[11] and disregarding electronic repulsion between the lone pairs on the oxygen and nitrogen atoms, it may be expected that the conformational behavior of **3** should be similar to that of **2** and that in the cone conformation the *anti* arrangement of the dimethylamino groups should be sterically favored over the *gauche*. In the former arrangement, both dimethylamino groups direct their lone pairs toward the cavity of the calix.

A single crystal of **3** was grown from acetonitrile and submitted to X-ray diffraction. Data for the X-ray diffraction were collected at 123(2) K.[12] Calixarene **3** crystallized with two MeCN molecules, with one molecule located inside the calix cavity. One *t*-Bu group (C42−C44) was disordered between two nonequivalent orientations (with populations 0.8:0.2). Calixarene **3** adopts a cone conformation and exists as a zwitterion with the axial dimethylamino group protonated and one of the hydroxyl groups opposite to the axial substituent deprotonated (Figure 1).[13] Compound **3** possesses a rather unusual hydrogen bond pattern for a tetrahydroxycalix[4]arene. The protonated NMe_2 group (that adopts an *anti* arrangement) is involved in the array of hydrogen bonds via a bifurcated hydrogen bond, while the deprotonated phenol ring serves as an acceptor of two hydrogen bonds.[14]

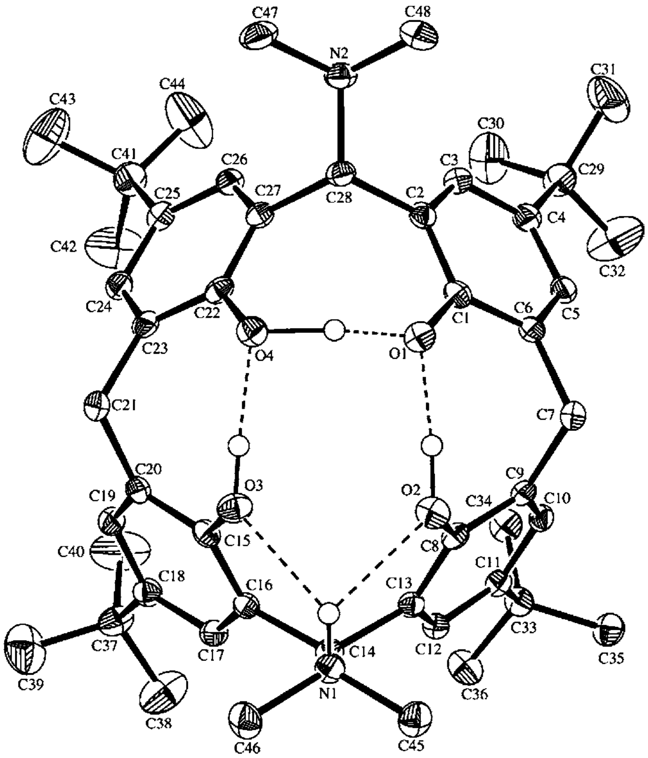


Figure 1. Top view of the X-ray structure of **3**. MeCN molecules that cocrystallized were omitted for clarity. Only one orientation of the *t*-Bu group (C42−C44) is shown.

According to the crystal structure, **3** exists in the crystal as the zwitterionic structure **3b** (Scheme 4) but in solution the species is expected to be in rapid equilibrium with a structure with a protonated equatorial dimethylamino group (**3c**) as well as with the neutral **3a**. In principle, the favored

---

(6) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 95.

(7) For a review on the stereochemistry of methylene-functionalized calixarenes, see: Simaan, S.; Biali, S. E. *J. Phys. Org. Chem.* **2004**, *17*, 752.

(8) (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.

(9) For a review on spirodienone calixarene derivatives, see: Biali, S. E. *Synlett* **2003,** 1.

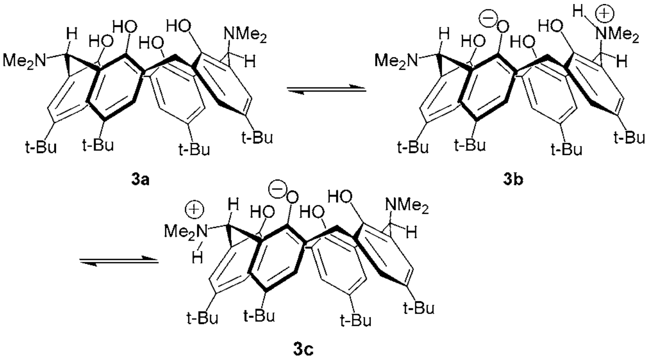
(10) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634.

(11) See for example: Chance, J. M.; Kahr, B.; Buda, A. B.; Toscano, J. P.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 3226.

(12) Selected crystal data: $a = 18.578(3)$ Å, $b = 13.143(2)$ Å, $c = 21.494(3)$ Å, $\beta = 111.874(3)°$, $Z = 4$. Final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0554$, w$R_2 = 0.1413$. All the hydrogens attached to the O and N atoms were found in the Fourier difference map and were refined isotropically,

(13) A "free" form of the *N*-benzyltetrahomodiazacalixarene derivative exists in the crystal in its neutral form, but its uranyl complex can be viewed as resulting from binding the metal to a zwitterionic form of the macrocycle. See: Thuery, P.; Nierlich, M.; Vicens, J.; Masci, B.; Takemura, H. *Eur. J. Inorg. Chem.* **2001**, 637. For a complex of **1** existing as a zwitterion, see: Khasnis, D. V.; Lattman, M.; Gutsche, C. D. *J. Am. Chem. Soc.* **1990**, *112*, 9423.

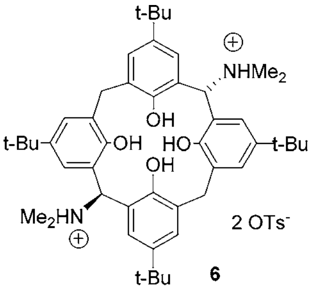
Scheme 4



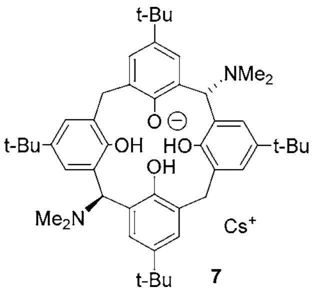
species in solution may differ from that observed in the crystal. To determine the major species in solution we resorted to ^{1}H NMR spectroscopy. As models for the expected chemical shifts for neutral and protonated NMe_2 groups we initially examined the spectrum of the Cs^+ salt **7** (where both the dimethylamino groups are nonprotonated) and **6** with two protonated amino groups.

The salt **7** was prepared by treatment of **3** with Cs_2CO_3 in refluxing acetonitrile.[15] ^{1}H NMR analysis of the product indicated that it consists of a mixture of unreacted **3** and an additional species ascribed to the Cs^+ salt **7**.[16] Treatment of **3** with excess tosylic acid in an NMR tube generated a species ascribed to the diprotonated salt **6.** The dimethylamino groups in either **6** and **7** displayed a rather similar chemical shift in the ^{1}H NMR in $CDCl_3$, as expected for systems with both NMe_2 groups existing in a free and protonated form, respectively, but the NMe_2 groups of **6** were ca. 0.65 ppm shifted downfield as compared to those of **7** as a result of the protonation.[17] Notably, both methine protons of **6** appeared as doublets ($J = 10.0$ and 8.9 Hz), indicating a structure with both NMe_2 groups protonated and *anti* oriented. The spectra suggest that the chemical shifts of the NMe_2 groups are mainly sensitive to the protonation state of the groups and are not strongly influenced by their axial or equatorial arrangement.

In calix[4]arene derivatives, axial methines and methylene protons resonate at a lower field than the corresponding equatorial ones.[18] On these grounds, it should be expected that protonation of the axial NMe_2 should result in a deshielding of the equatorial methine, therefore reducing the



6



7

intrinsic chemical shift difference between axial and equatorial methine protons. Thus, qualitatively a ^{1}H NMR displaying a "small" $\Delta\delta$ between the axial and equatorial methines but a "large" $\Delta\delta$ between the two dimethylamino groups could be taken as indicating the presence of zwitterionic species in which the axial dimethylamino group is preferentially protonated.

The ^{1}H NMR spectrum of calixarene **3** is strongly solvent-dependent. Calixarene **3** displays in the NMR spectrum (400 MHz, $CDCl_3$, rt) pairs of signals for the methine, methylene, and dimethylamino groups in agreement with a frozen cone conformation (on the NMR time scale) of C_s symmetry possessing axial and equatorial substituents at the bridges. The presence of a cone conformation in $CDCl_3$ and C_6D_6 was corroborated by NOESY spectra in those solvents. The chemical shifts of the equatorial methylene protons were only moderately sensitive to the solvent (e.g., δ 3.30 (THF-d_8), 3.61 ($C_6D_5NO_2$) Table 1), while the protons of the methine groups and dimethylamino groups showed a marked sensitivity. As shown in Table 1, the spectrum in THF is consistent with the presence of a zwitterionic species with the axial dimethylamino group protonated, while in the nonpolar C_6D_6 the spectrum is consistent with a neutral species.[19] Since the chemical shifts of **3** observed in the polar and nonpolar solvents could be the result of differential associations in solutions, we examined the diffusion coef-

Table 1. ^{1}H NMR Chemical Shifts of the Methine, Methylene, and *N*-Methyl Groups of **3** in Different Solvents at Room Temperature

solvent	CH	CH_2	NMe_2
$CDCl_3$	4.78/4.48	4.27/3.37	2.74/2.29
$CDCl_3$ (**6**)[a]	5.12/4.16	4.68/3.23	2.31/2.29
$CDCl_3$ (**7**)[b]	6.30/4.91	4.27/3.32	2.96/2.95
$C_2D_2Cl_4$	4.83/4.70	4.25/3.35	2.95/2.25
acetone-d_6	5.26/4.88	4.20/3.36	3.11/2.23
C_6D_6	5.05/4.07	4.53/3.33	2.31/2.10
THF-d_8	4.87/4.83	4.22/3.30	2.88/2.23
	5.31/4.81[c]	4.14/3.35[c]	2.99/2.29[c]
pyridine-d_5	5.55/5.24	4.65/3.58	2.96/2.45
CD_3CN	5.03/4.76	4.12/3.33	2.96/2.19
$C_6D_5NO_2$	5.30/5.26	4.54/3.61	3.10/2.44
DMF-d_7	5.46/4.94	4.19/3.43	3.10/2.25
CF_3COOD[d]	5.81/4.71	3.94/3.23	2.82−2.72

[a] Monodeprotonated form **7** (Cs^+ salt). [b] Diprotonated form **6**. [c] At 170 K in dry THF-d_8. [d] Both NMe_2 groups are deuteronated.

---

[14] The proton located between O4 and O1 is nearly equidistant to the two oxygens. For clarity in Figure 1 the proton is shown covalently bonded to the nearest oxygen (O4) and hydrogen bonded to O1 although the structure could be also described with the negative charge equally distributed in O1 and O4 and with the hydrogen symmetrically located between the two oxygens.

[15] These are the reaction conditions that yield the monoanion of **1** (as its Cs^+ salt). See: Harrowfield J. M.; Odgen, M. I.; Richmond, W. R.; White, A. H. *J. Chem. Soc., Chem. Commun*. **1991**, 1159.

[16] The presence of a mixture of **3** and a higher deprotonated species (e.g., a dideprotonated form) is unlikely since both forms should readily react in an acid/base reaction.

[17] A smaller shift was observed in the ^{1}H NMR spectrum of the methylene groups of Et_3N and Et_3NH^+ $OTos^-$ (0.4 ppm in $CDCl_3$).

[18] See, for example: (a) Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335. (b) Zetta, L.; Wolff, A.; Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911.

ficients of **3** in both C_6D_6 and DMF-d_7 at 298 K using the pulse gradient spin−echo (PGSE) NMR technique.[20] For comparison purposes, the diisopropyl derivative **2** (where no self-association is expected) was examined as well. The diffusion coefficients of **3** (0.50 and 0.78 10^{-5} cm^2 s^{-1} in DMF-d_7 and C_6D_6, respectively) were very similar to those found for the model **2** in the two solvents (0.49 and 0.77 10^{-5} cm^2 s^{-1}),[21] indicating that the differences in chemical shifts observed in the polar and nonpolar solvent are not due to different self-associations.

Although in the spectrum of **6** the methine signals appear as doublets (indicating the protonation of both amino groups) the corresponding signals of **3** appeared as singlets in all the solvents examined.[22] The lack of coupling (probably due to fast exchange of the NH proton with traces of water in the solvent) is rather unfortunate since such interaction could be used as an unequivocal indication of the existence of a HCNH unit and, therefore, of the presence of a zwitterionic species in **3**. To detect this "missing" coupling interaction, and to minimize the proton exchange, the ^{1}H NMR spectrum of **3** was determined in dry THF-d_8 (freshly distilled from a Na/K alloy) in a sealed tube at 170 K. The methine region displayed two signals (at 5.31 and 4.81 ppm) with the lower field signal split into a doublet. We assign the signal at 5.31 ppm to the equatorial methine, which as a result of the deshielding effects ensuing from protonation of the axial NMe_2 group and solvation effect, at the low-temperature resonates at a lower field than the axial one.[23] The coupling interaction observed indicates conclusively that **3** exists as a zwitterion in THF and most likely also in other polar solvents.

To assess the influence of the protonation of the NMe_2 groups on the rigidity of the calix macrocycle, the temperature-dependent NMR spectra of **3** and **6** (400 MHz, $C_2D_2Cl_4$) were determined. From the $\Delta\nu$ value (288.3 Hz), the coupling constant (J = 12.9 Hz), and the coalescence temperature (342 K) of the methylene protons, the barrier of the cone-to-cone inversion of **3** was determined as 15.7 kcal mol^{-1}.[24] Notably, the axial and equatorial $NHMe_2^+$ groups of **6** ($\Delta\nu = 288.3$ Hz) coalesced at 405 K, providing a barrier of 20.2 kcal mol^{-1}. Formation of the ditosylate salt of **3** significantly increases the rigidity of the cone conformation.

The solution NMR data suggest that the two zwitterionic forms **3b** and **3c** differ in their stability. The axial group is probably preferentially protonated due to a combination of two effects. In the neutral form repulsion between the lone pairs of the amino and phenolic oxygens is expected to be larger for the axial group. In addition, only the protonated form of the axial group can be stabilized by hydrogen bonding with the phenolic oxygens in the cone conformation. These two effects, which work in synergetic fashion, render **3b** the preferred zwitterionic form.

Acknowledgment. We thank Dr. Shmuel Cohen for the crystal structure determination and Dr. Roy Hoffman for helpful suggestions and assistance with the NMR experiments. Acknowledgment is made to the donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, for support of this research.

Supporting Information Available: Crystallographic data for **3** and experimental procedures for the preparation of **5** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0504392

---

[19] The spectrum in CF_3COOD displayed a signal pattern (a "large" $\Delta\delta$ between the axial and equatorial methines and a "small" $\Delta\delta$ between the two dimethylamino groups) which is similar to the one observed in **6**. This is ascribed to a species in which both amino groups are deuteronated.

[20] Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *42*, 288. For a recent review on diffusion NMR spectroscopy of supramolecular systems see: Cohen, Y.; Avram, L.; Frisch, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520.

[21] The diffusion coefficient of **1** in $CDCl_3$ at 298 K is 0.78 10^{-5} cm^2 s^{-1} (Mayzel, O.; Aleksiuk, O.; Grynszpan, F.; Biali, S. E.; Cohen, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1183).

[22] In different samples, the methine signals appeared sometimes as sharp and sometimes significantly broad. Although experiments aimed to observe broadening of the methine signals by addition of small amounts of water to samples displaying sharp signals failed, we tentatively ascribe this phenomenon to the presence of different amounts of water and/or acidic impurities in the deuterated solvents.

[23] An alternative explanation to the observed pattern is that the axial methine proton resonates at a lower field than the equatorial one (as usually observed) and the protonation occurs preferentially at the equatorial NMe_2 group. However, on the basis of the small $\Delta\delta$ value between the methine protons, this explanation seems highly unlikely.

[24] Exchange rates at the coalescence temperatures (k_c) were estimated using the equation $k_c = 2.22\ (\Delta\nu^2 + 6J^2)^{1/2}$. See: Juaristi E. *Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; p 253.