Preparation and Conformation of Monohalotetrahydroxycalix[5]arenes

Joel M. Van Gelder, Oleg Aleksiuk, and Silvio E. Biali*

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

Received June 17, 1996[⊗]

The *intra*annular introduction of a halogen into a calixarene skeleton is described. Monoaminotetrahydroxy-*p*-*tert*-butylcalix[5]arene (**2b**) was diazotized by treatment with isoamyl nitrite/HCl/EtOH. Thermal dediazoniation of the salt in chloroform yielded monochlorotetrahydroxy-*p*-*tert*-butylcalix[5]arene (**5a**) and the xanthenocalix[5]arene **6**. These products result from the capture of an intermediate phenyl cation derivative by chloride ion or intramolecularly, by a neighboring phenol ring. The product ratio **6**:**5a** was not affected by the addition of excess external chloride, suggesting that the reacting intermediate exists as an ion pair. The dediazoniation reaction in the presence of bromide and iodide ions afforded the corresponding halocalixarenes **5b** and **5c**, while in the presence of a fluoride ion the calixindazole **8** was obtained. X-ray diffraction indicates that **5b** exists in a distorted cone conformation (cone-in) in which the *extra*annular edge of the halophenyl ring is tilted toward the cavity center. The halocalixarenes undergo a cone-to-cone inversion process with a barrier in the 11.3−12.5 kcal mol^{-1} range in $CDCl_3$. The barrier height is a function of the size of the halo substituent. Xanthenocalix[5]arene **6** crystallizes with three ethanol solvent molecules and exists in a cone-like conformation.

Introduction

The synthetic availability of the macrocycles commonly known as calixarenes (**1**) makes these systems attractive molecular platforms for constructing hosts with tailor-made binding groups.[1] During the last years several groups have reported the partial or total replacement of the phenolic OH groups of the calixarenes by hydrogens,[2] thiol groups,[3] or amino groups[4] and the influence of this replacement on the conformation and rigidity of the systems.[2−4] We have described the synthesis of the monoaminopolyhydroxy-*p*-*tert*-butylcalixarenes **2a** and **2b** via reaction of the monospirodienone derivative of the corresponding calixarenes (**3a** and **3b**, respectively) with an amino nucleophile.[4b,d] In the case of **3b**, this was accomplished by its reaction with (2,4-dinitrophenyl)-hydrazine (DNP), followed by reductive cleavage of the resulting azo derivative.[4d,5] The relatively high efficiency of the transformation **3b** → **2b** allowed us to obtain sufficient amounts of the aminocalixarene to conduct a study of its reactions. In this article we describe the preparation, characterization, and thermal dediazoniation of the diazonium salts **4**[6] (potential key intermediates for the preparation of a vast array of *intra*annular substituted calixarenes) and the synthesis, conformation, and rotational barrier of calix[5]arenes in which an *intra*annular OH group has been replaced by a halogen.

Results and Discussion

Preparation of the Diazonium Salts. The diazonium salts **4a**−**c** were prepared by treatment of an ethanolic suspension of **2b**[4d] with isoamyl nitrite and concd HCl, HBr, or H_2SO_4, respectively.[7] The yellow diazonium salts precipitated from the solution. The salt **4a** was characterized by IR (ν_{NN}: 2236 cm^{-1} (strong)) and by NMR spectroscopy. The ^{1}H NMR of **4a** (400 MHz, $CDCl_3$, rt) displays in the aromatic region four doublets (each integrating for two protons) at δ 6.82−7.17 ppm and a singlet integrating for two protons at 7.50 ppm (Figure 1). The NMR pattern and, in particular, the low-field singlet are in agreement with a structure of C_s symmetry in which two symmetry-related aromatic protons are located in a ring substituted by the strongly electron withdrawing diazonium group.

Thermal Dediazoniation of 4a and 4b. The thermal dediazoniation of **4a** was conducted by heating a solution of the salt to 60 °C in a nonnucleophilic solvent ($CHCl_3$) for 40 min.[8] The two reaction products (obtained

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) For reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (d) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1.

(2) (a) Goren, Z.; Biali, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1484. (b) Grynszpan, F.; Goren, Z.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 532. (c) Grynszpan, F.; Biali, S. E. *Tetrahedron Lett.* **1991**, *32*, 5155. (d) McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, *41*, 5655. (e) de Vains, J.-B. R.; Pellet-Rostaing, S.; Lamartine, R. *Tetrahedron Lett.* **1994**, *44*, 8147. (f) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13337. (g) Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550. For additional synthesis of dehydroxylated calixarenes, see: Fukazawa, Y.; Demaya, K.; Usui, S. *Tetrahedron Lett.* **1992**, *33*, 5803. Usui, S.; Deyama, K.; Kinoshita, R.; Odagaki, Y.; Fukazawa, Y. *Tetrahedron Lett.* **1993**, *34*, 8127; Rajca, A.; Padmakumar, R.; Smithisler, D. J.; Desai, S. R.; Ross, C. R., II; Stezowski, J. J. *J. Org. Chem.* **1994**, *59*, 7701.

(3) (a) Gibbs, C. G.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 5338. (b) Ting, Y.; Verboom, W.; Groenen, L. C.; van Loon, J. D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1435. (c) Delaigue, X.; Harrowfield, J. McB.; Hosseini, M. W.; de Cian, A.; Fischer, J.; Kyritsakas, N. *J. Chem. Soc., Chem. Commun.* **1994**, 1579. (d) Delaigue, X.; Hosseini, M. W.; Kyritsakas, N.; de Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1995**, 609. (e) Gibbs, C. G.; Sujeeth, P. K.; Rogers, J. S.; Stanley, G. G.; Krawiec, M.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 8394.

(4) (a) Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett*, **1992**, *33*, 1217. (b) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 1994. (c) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.*, **1994**, *59*, 2070. (d) Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645.

(5) For a review on spirodienone calixarene derivatives, see: Aleksiuk, O.; Grynszpan, F.; Litwak, M. A.; Biali, S. E. *New J. Chem.* **1996**, *20*, 473.

(6) For reviews on diazonium derivatives, see: *The Chemistry of Diazonium and Diazo Groups;* Patai, S., Ed.; Wiley: Chichester, 1978.

(7) For a recent review on the chemistry of calix[5]arenes, see: Asfari, Z.; Vicens, J. *Acros Org. Acta* **1995**, *1*, 18.

S0022-3263(96)01142-5 CCC: $12.00

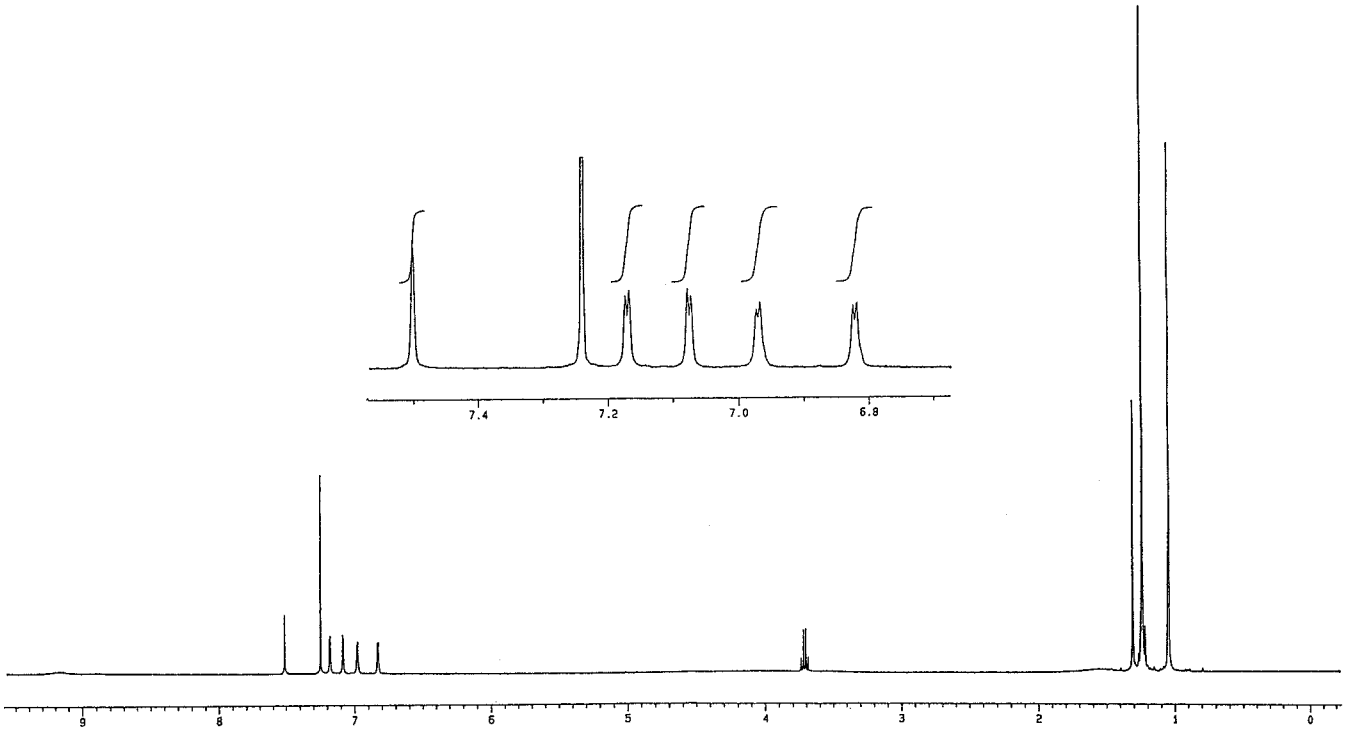
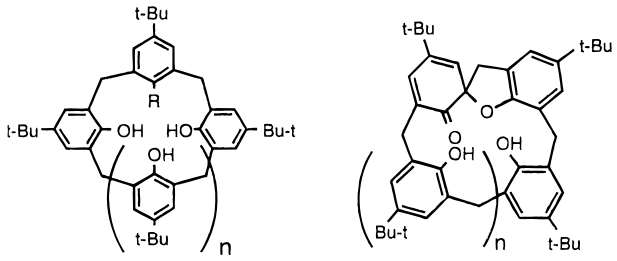
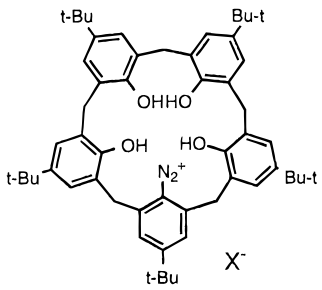


Figure 1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, rt) of the diazonium derivative **4a**.

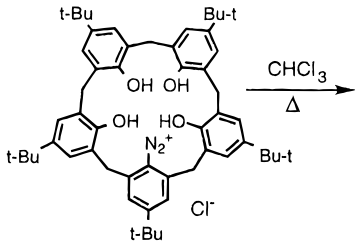


1a R=OH, n=1
1b R=OH, n=2
2a R=NH_2, n=1
2b R=NH_2, n=2

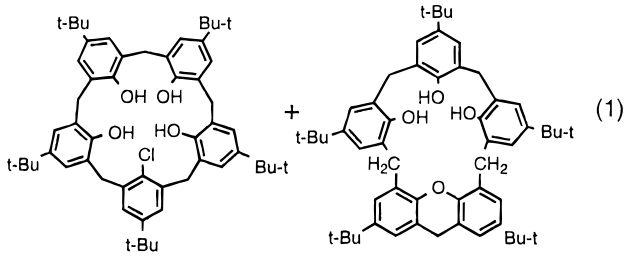
3a n = 1
3b n = 2
3c n = 3



4a X= Cl
4b X= Br
4c X= HSO_3
4d X= I
4e X= F



4a



5a **6**

(1)

in a 4:6 ratio according to ^{1}H NMR spectroscopy) were the chlorocalixarene **5a** and the xanthenocalix[5]arene **6** (eq 1).

Both **5a** and **6** display in the NMR spectrum (400 MHz, $CDCl_3$, rt) three singlets (in a 2:2:1 ratio) in the methylene region, in agreement with conformationally flexible structures on the NMR time scale. The hydroxyl groups of both products (**5a**, δ 6.44 (2H) and 7.76 (2H) ppm; **6**, 7.33 (2H) and 8.28 (1H) ppm) resonate at a higher field than those of **1** (δ 8.7 ppm)[9] as expected since no circular hydrogen bond is possible in both **5a** and **6**. *m*-Alkoxy substituted xanthenocalixarenes have been previously prepared by acid-catalyzed ring expansion of alcoholic solutions of large ring monospirodienone calixarene derivatives.[4d] The formation of **5a** and **6** can be rationalized by assuming that the thermal decomposition of the diazonium salt occurs by an ionic (S_N1) mechanism

(8) (a) For a review on dediazoniations, see: Zollinger, H. In *The Chemistry of Functional Groups, Supplement C*, Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 15. (b) For a review on aliphatic diazonium ions, see: Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 251.

(9) For a recent work on the conformation and inversion barriers of derivatives of *p-tert*-butylcalix[5]arene, see: Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

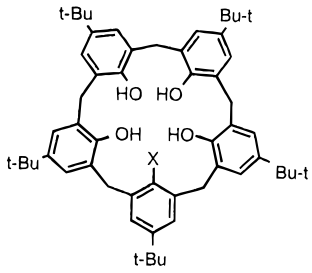
involving a phenyl cation-type intermediate. This can be captured by an external nucleophile (Cl^-) or intramolecularly, by the hydroxyl group of a neighboring phenol group, yielding **5a** and **6**, respectively.

Intramolecular vs Intermolecular Capture. The ratio between the two products (**6** and **5a**) obtained in the thermal dediazoniation of **4a** should reflect the rates of the intramolecular vs intermolecular capture of the phenyl cation by a proximal phenol ring or a chloride ion, respectively. If free ions are involved, the rate of the reaction leading to the chlorocalixarene should be of a second order (first order each in the intermediate and chloride ions), while the rate of formation of the xanthenocalixarene should be of a first order. The **5a**:**6** product ratio could then be modified by changing the rate of chlorocalixarene formation either by addition of an excess of external chloride ion or by changing the concentration of the diazonium salt. If, on the other hand, the intermediate is a phenyl cation/chloride ion pair, the product ratio should not be affected by such concentration changes since both reactions should be of a first order. In order to distinguish between both possibilities, large amounts of benzyltrimethylammonium chloride were added to a sample of **4a** in chloroform and the solution was refluxed. Integration of the *tert*-butyl signals gave a 6:4 ratio of **6**:**5a**, i.e., the same ratio found in the absence of excess Cl^-. Similarly, the thermal dediazoniation of a diluted solution of **4a** did not affect the **6**:**5a** ratio. This suggests that the reacting species in chloroform is not a free phenyl cation, but an ion pair.[8b]

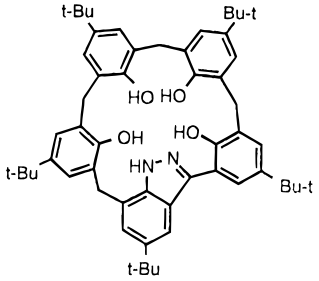
The **6**:**5a** product ratio is affected by the solvent, being ca. 1:1 in toluene while in acetonitrile only xanthene **6** was obtained. This may be the result of the different solvation of the Cl^- in the different solvents: the larger the solvation, the lower its reactivity, increasing the fraction of the xantheno product.

Preparation of Halocalixarenes 5b and 5c. For the preparation of the bromocalixarene **5b**, the diazonium salt **4b** was initially thermally dediazoniated in a chloroform solution. However, in addition to the xanthenocalixarene **6** and bromocalixarene **5b**, small amounts of **5a** were also formed, probably by chlorine atom abstraction from the solvent by the phenyl cation.[10] In order to avoid the formation of **5a**, calixarene **4b** was dediazoniated in toluene, which resulted in a ca. 1:1 mixture of **6** and **5b**.

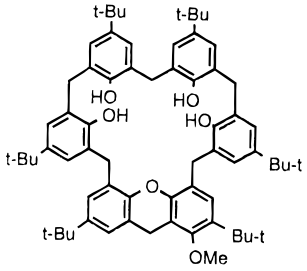
Attempts to prepare the diazonium salts **4d** and **4e** in one step via treatment of **2b** with isoamyl nitrite/HI or isoamyl nitrite/BF_3 were unsuccessful, and we attempted the anion exchange of the salt **4a** with an excess of a tetraalkylammonium iodide or fluoride. Attempts to prepare the iodocalixarene by the thermal dediazoniation of **4a** or **4c** in toluene (the solvent which gave the higher yield of the halocalixarenes **5a** and **5b**) in the presence of a tetraalkylammonium iodide salt resulted in the formation of the known[4d] monodehydroxylated calix[5]arene **7**. However, the thermal dediazoniation in chloroform yielded a mixture of **6**, **5a** (resulting either from the capture of the phenyl cation by the Cl^- or from reaction with the solvent), and the iodocalixarene **5c**. Unfortunately, we were unsuccessful in separating the halocalixarenes **5a** and **5c** by chromatography or fractional crystallization, and the sample examined by NMR consisted of 84% **5c** and 16% **5a**.



5a X= Cl
5b X= Br
5c X= I
5d X= F
7 X= H



8



9

Addition of excess tetrabutylammonium fluoride to a $CHCl_3$ solution of **4a** gave initially a red solution and resulted in a 1:1 mixture of a new product and the xanthenocalixarene **6**. The new product displayed in the ^1H NMR spectrum at low temperature only four pairs of doublets (integrating for eight protons) and five *t*-Bu signals, indicating that one methylene group of the precursor has reacted and that the five rings are symmetry nonequivalent. On the basis of the NMR and mass spectral data (CI MS: *m*/*z* 821.1 (MH^+)), we assign to this product the calixindazole structure **8.** Cyclization of *o*-alkyl substituted aromatic diazonium ions have been reported to afford 1*H*-benzpyrazoles (indazoles) if the alkyl group can behave as a carbon acid.[11] A possible rationalization for the formation of **8** is that the "naked" fluoride anion in chloroform behaves as a strong base partially deprotonating a methylene group *ortho* to the diazonium group.[12] These methylene protons are rendered acidic by the strongly electron withdrawing diazonium group.

Solution Conformation of the Halogenocalixarenes. Replacement of a hydroxyl by a halogen atom can affect both the preferred conformation and the inversion barrier of the calix[5]arene skeleton.[9] The low-temperature NMR spectra of **5a**−**c** in $CDCl_3$ are in agreement with the presence of a single conformer. The NMR signals were assigned by 2D NMR NOESY spectroscopy on the basis of the observed aromatic/*t*-Bu and aromatic/CH_2 cross peaks. In all cases NOE cross peaks were observed between the halophenyl singlet (δ 6.83 for **5a**) and a phenolic doublet (δ 7.18 for **5a**), as well as between one pair of signals corresponding to phenolic protons at different rings (δ 7.14 and 7.24 for **5a**). This suggests that **5a**−**c** exist in cone conformations in which pairs of *meta*-aromatic protons of different rings are in steric

(10) For other examples of formation of chlorobenzenes by abstraction of a chlorine atom from the solvent, see: Oae, S.; Shinhama, K.; Kim, Y. H. *Bull. Chem. Soc. Jpn.* **1980**, 2023.

(11) Wulfman, D. S. In ref 6; Chapter 8. See p 278 and references therein.

(12) Fluoride ion in an aprotic solvent may behave as a strong base. See, for example: Hoz, S.; Albeck, M.; Rappoport, Z. *Synthesis* **1975**, 162. Bartsch, R. A. *J. Org. Chem.* **1970**, *35*, 1023.

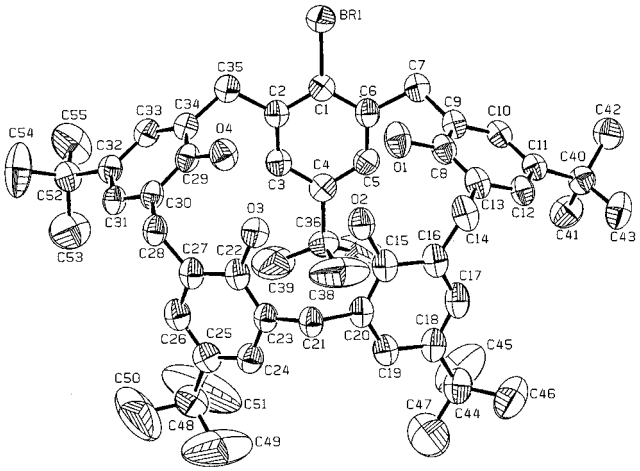


Figure 2. Numbering scheme of the crystal structure of **5b**.

Figure 3. Ball and stick side view of the crystal conformation of **5b**·EtOH. The cone conformation is distorted with the *extra*annular part of the halophenyl ring tilted toward the cavity. Hydrogen atoms were omitted for clarity.

proximity. In addition, the large chemical shift differences between pairs of protons on the same methylene group (identified by COSY spectroscopy) indicate that all rings are mutually syn, i.e., the conformation is cone. Interestingly, the *t*-Bu and the aromatic signals of the halophenyl ring are shifted upfield with the increase in bulk of the halogen (δ 0.78 and 6.88 for **5a**, δ 0.68 and 6.78 for **5b**, δ 0.49 and 6.58 for **5c**). It seems highly unlikely that these shifts (in particular those of the remote *t*-Bu group) are due to the inductive effect of the halogen. We therefore interpret them as indicating that the increase in bulk of the halogen along the series I > Br > Cl distorts the cone conformation toward a cone-in[9] conformation in which the *tert*-butyl group is oriented inward. The larger the halo group, the larger the distortion, which moves the aromatic protons and, in particular, the *p-tert*-butyl group of the halophenyl ring into the shielding region of the neighboring phenyl rings.

Crystal Structure of the Bromocalixarene 5b. A single crystal of **5b** suitable for X-ray crystallography was grown from EtOH.[13] The numbering scheme and a ball and stick side view of the crystal structure are shown in Figures 2 and 3, respectively. As shown in Figure 3, the bromocalixarene exists in a cone-in[9] conformation in which the halophenyl ring is tilted in an opposite direction to the other rings, supporting the conformational deduction from the NMR data. The ethanol molecule is hydrogen bonded to phenolic oxygen O(4) as judged by the short oxygen/oxygen interatomic distance (2.657(4) Å). The phenolic oxygen pairs O(4)/O(5) and O(3)/O(4) are within hydrogen bond distances (2.657(4) and 2.746-(4) Å, respectively).

(13) 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, U.K.

Table 1. Selected Chemical Shifts and Rotational Barriers of Monosubstituted *p-tert*-Butylcalix[5]arene Derivatives in $CDCl_3$

	δ			
compd	*t*-Bu[a]	Ar H[a]	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
7	1.24	7.02	234[b]	10.7[b]
5a	0.78	6.88	251	11.3
5b	0.68	6.78	259	11.7
5c	0.49	6.58	275	12.5
8			266	12.0

[a] Chemical shifts of the *t*-Bu and aromatic protons of the substituted ring. [b] In $CDCl_2F$ (ref 4d).

The relative hydrogen-bonding ability of the organic halides has been the subject of numerous studies. In a review, Dumas et al. concluded that the sequence of hydrogen-bond-accepting abilities is Cl > Br > I for both intramolecular and intermolecular hydrogen bonds.[14] According to the X-ray structure, the halogen is not hydrogen bonded and it is therefore highly likely that no halogen···HO hydrogen bonds exist for also **5c**.

Rotational Barriers. The rotational barriers of **5a**−**c** and **6** were determined by variable temperature NMR spectroscopy (Table 1). On the basis of the chemical shift difference between the axial and equatorial methylene protons within a given methylene group under slow exchange on the NMR time scale and their coalescence temperatures, barriers of $\Delta G_c^{\ddagger} = 11.3$, 11.7, and 12.5 kcal mol^{-1} were calculated for the ring inversion barrier of **5a**, **5b**, and **5c**, respectively (Table 1).[15] Although the barrier increases with the increase in bulk of the halogen, all these barriers are lower than the one reported for the parent *p-tert*-butylcalix[5]arene in $CDCl_3$ ($\Delta G_c^{\ddagger}$ =13.2 kcal mol^{-1}),[16] indicating that in these systems the loss of the circular hydrogen bonding array is not compensated by an increase in bulk of the *intra*annular group.[9] The rotational barriers of the calixarenes **6** and **8** are 11.4 and 12.0 kcal mol^{-1}, respectively.

Crystal Structure of Xanthenocalix[5]arene 6. A single crystal of the xanthenocalix[5]arene **6** was grown from ethanol and submitted to X-ray crystallography.[13] The molecule crystallized with three ethanol molecules and exists in a cone-like conformation of crystallographic C_s symmetry in which the three phenolic groups are pointing in the same direction (Figures 4 and 5). In this conformation the four oxygens are oriented toward the same face of a macrocyclic plane which can be defined by the four methylene groups which are not part of the xanthene moiety. One ethanol molecule is bisected by the crystallographic mirror plane while the other two are necessarily related by that plane. The *t*-Bu groups attached to C(4), C(4′), and C(18) were refined in two equally populated orientations.

We also examined the packing arrangement in the crystal, since we found for the xanthenocalix[6]arene **9** that the molecules are intermolecularly hydrogen bonded and display self-fitting.[4d] However, neither of these phenomena were observed (Figure 6). Instead, the phenolic oxygens are engaged in intermolecular hydrogen bonds with EtOH molecules as well as in intramolecular hydrogen bonds. The phenolic oxygens O(2) and O(2′) are within hydrogen-bonding distances to O(3) (2.668(4)

(14) Dumas, J.-M.; Gomerl, M.; Guerin, M. In *Supplement D: The chemistry of halides, pseudohalides and azides;* Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 21, pp 989−991.

(15) The barriers were calculated from the exchange rates at the coalescence temperatures calculated according to the following: Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

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

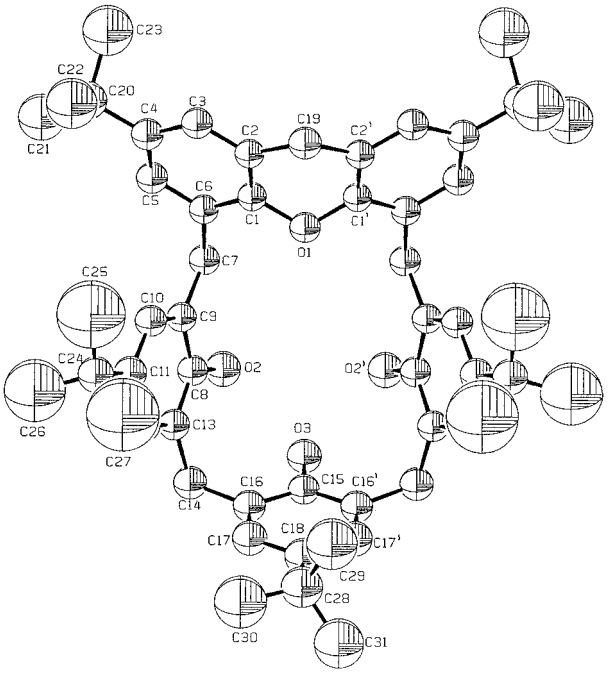


Figure 4. Numbering scheme of the crystal structure of **6**. Ethanol molecules were omitted for clarity. The molecule exists in a conformation of C_s symmetry. Mirror related atoms are denoted by the same number (e.g., C(1) and C(1′)). Only one of the two orientations of the *t*-Bu groups attached to C(4), C(4′), and C(18) are shown. The thermal ellipsoids of the *t*-Bu groups attached to C(11) and C(11′) are large due to unresolved rotational disorder.

Å) and to the oxygen of an EtOH molecule (O(2)−O(4) and O(2′)−O(4′): 2.672(3) Å). The ethanolic oxygens O(4) and O(4′) are hydrogen bonded to the third EtOH molecule (O(4)−O(5): 2.76 Å). Interestingly, the EtOH molecule bisected by the mirror plane is located within the cavity of a xanthenocalixarene molecule.

Experimental Section

Crystallography. The X-ray diffraction data were measured with an ENRAF-NONIUS CAD-4 computer-controlled diffractometer; Cu Kα (λ = 1.541 78 Å) radiation with a graphite crystal monochromator in the incident beam was used. All crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software.

Crystallographic Data. 5b: $C_{55}H_{69}O_4Br$·EtOH; space group $P2_1/n$; a = 16.827(4) Å, b = 20.795(8) Å, c = 15.854(3) Å, β = 107.54(2)°; V = 5290(2) Å^3, z = 4, ρ_{calc} = 1.15 g cm^{-3}, μ(Cu K$_\alpha$) = 13.83 cm^{-1}; number of unique reflections = 7888, number of reflections with $I \geq 3\sigma_I$ = 6216, R = 0.059, R_w = 0.082. **6**: $C_{55}H_{68}O_4$·3EtOH; space group *Pnma*, a = 18.871(3) Å, b = 23.796(4) Å, c = 12.782(3) Å, V = 9740(1) Å^3, z = 4, ρ_{calc} = 1.08 g cm^{-3}, μ(Cu Kα) = 5.05 cm^{-1}; number of unique reflections = 5418; number of reflections with $I \geq 3\sigma_I$ = 3135, R = 0.089, R_w = 0.122.

5,11,17,23,29-Penta-*tert*-butyl-31-amino-32,33,34,35-tetrahydroxycalix[5]arene for the Diazotation Experiment. The reductive cleavage of the DNP derivative of **3b** (1 g) was carried out with HI as described in ref 4d. After the reaction was complete, the HI was carefully neutralized with saturated $NaHCO_3$ until pH 5, and then a saturated solution of $Na_2S_2O_3$ was added until the iodine was reduced. CH_2Cl_2 was added, and the organic phase was dried and evaporated, yielding 0.8 g of the crude amino derivative, suitable for the diazotization experiment. This avoids the formation of large amounts of sulfur, which are formed in our original workup.

Diazotation of 5,11,17,23,29-Penta-*tert*-butyl-31-amino-32,33,34,35-tetrahydroxycalix[5]arene. To a suspension of 21 mg of **2b**[4d] in 2 mL of EtOH was added, with stirring, 0.1 mL of concd HCl (36%). The compound dissolved completely. The resulting solution was cooled to 0 °C, and 30 mg of isoamyl nitrite (Aldrich) was added. A yellow precipitate formed. After 30 min the precipitate was filtered behind a safety shield (CAUTION: diazonium salts are known to explode in the solid state),[5,17] washed with cold methanol, and dried in the filter, yielding 16 mg (71%) of the diazonium salt **4a**: ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 1.04 (s, 18H, *t*-Bu), 1.23 (s, 18H, *t*-Bu), 1.30 (s, 9H, *t*-Bu), 4.0 (br, 10H, CH_2), 6.82 (d, J = 2.0 Hz, 2H, Ar H), 6.97 (d, J = 2.0 Hz, 2H, Ar H), 7.08 (d, J = 2.0 Hz, 2H, Ar H), 7.17 (d, J = 2.0 Hz, 2H, Ar H), 7.50 (s, 2H, Ar H), 9.15 (br, OH); IR ν 2236 cm^{-1} (strong, NN stretching).

Thermal Dediazoniation of 4a. The diazonium salt **4a** (1 g) was dissolved in 50 mL of $CHCl_3$ and heated to 60 °C for 40 min. After evaporation of the solvent, the residue was triturated with hot EtOH and the insoluble xanthene **6** was filtered. The filtrate was kept at −10 °C for 3 days, which gave an additional amount of **6**, resulting in a total of 400 mg (43%), mp 270 °C dec. After evaporation of the filtrate, the residue was chromatographed, yielding 210 mg (22%) of **5a**, mp 281−283 °C dec.

Spectroscopic data for 5,11,17,23,29-penta-*tert*-butyl-31-chloro-32,33,34,35-tetrahydroxycalix[5]arene (5a): ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 0.78 (s, 9H, *t*-Bu), 1.22 (s, 18H, *t*-Bu), 1.31 (s, 18H, *t*-Bu), 3.73 (s, 2H, CH_2), 3.78 (s, 4H, CH_2), 4.08 (s, 4H, CH_2), 6.44 (s, 2H, OH), 6.88 (s, 2H, Ar H), 7.14 (d, J = 2.5 Hz, 2H, Ar H), 7.17 (d, J = 2.9 Hz, 2H, Ar H), 7.18 (d, J = 2.7 Hz, 2H, Ar H), 7.24 (d overlapping with residual $CHCl_3$, 2H, Ar H), 7.76 (s, 2H, OH); ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 30.61, 31.27, 31.40, 31.58, 33.86, 33.93, 33.96, 34.88, 125.53, 125.79, 125.98, 126.04, 126.39, 126.60, 126.65, 126.80, 129.40, 136.79, 143.36, 143.82, 147.56, 149.00, 149.25. CI MS 829.5 m/z (MH$^+$). Anal. Calcd for $C_{55}H_{69}O_4Cl$: C, 79.63; H, 8.38; Cl, 4.27. Found: C, 79.77; H, 8.61; Cl, 4.16.

Spectroscopic data for 6: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 1.15 (s, 9H, *t*-Bu), 1.267 (s, 18H, *t*-Bu), 1.270 (s, 18H, *t*-Bu), 3.82 (br s, 4H, CH_2), 4.03 (s, 6H, CH_2), 6.97 (s, 2H, Ar H), 7.01 (d, J = 2.2 Hz, 2H, Ar H), 7.09 (d, J = 1.8 Hz, 4H, Ar H), 7.13 (d, J = 2.3 Hz, 2H, Ar H), 7.33 (s, 2H, OH), 8.28 (s, OH). ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 29.78, 30.34, 31.32, 31.49, 31.55, 31.58, 31.64, 32.38, 33.95, 34.03, 34.18, 121.30, 123.59, 125.34, 125.41, 125.99, 126.17, 126.30, 127.36, 127.65, 142.92, 144.56, 145.47, 145.99, 148.00, 149.40. CI MS *m/z* 793.5 (MH$^+$). Anal. Calcd for $C_{55}H_{68}O_4$: C, 83.29; H, 8.64. Found: C, 83.01; H, 8.66.

Dediazoniation of 5a in the Presence of Excess Chloride Ion. Aminocalixarene **2b** (20 mg, 0.025 mmol) was diazotized (isoamyl nitrite/HCl), and the resulting salt was filtered and immediately dissolved in 8 mL of chloroform. Benzyltriethylammonium chloride (1.5 g; (6.58 mmol) was added, and the solution was refluxed for 40 min, and the organic phase was washed several times with water, dried ($MgSO_4$), filtered, and evaporated. Examination of the crude product by ^{1}H NMR indicated that it consists of a 4:6 mixture of **5a** and **6**. The thermal dediazoniation in the presence of 55 mg (0.3 mmol) of Et_4N^+ Cl^- resulted in an identical product ratio.

5,11,17,23,29-Penta-*tert*-butyl-31-bromo-32,33,34,35-tetrahydroxycalix[5]arene (5b). To a suspension of 100 mg of **2b** in 10 mL of EtOH was added, with stirring, 1 mL of concd HBr (48%). The compound dissolved completely. The resulting solution was cooled to 0 °C, and 1 mL of isoamyl nitrite was added. The yellow precipitate formed was filtered after 30 min behind a safety shield and was immediately dissolved in 15 mL of toluene. The solution was refluxed for 40 min, the solvent was evaporated, the residue was triturated with hot EtOH, and the undissolved material was filtered. The product was further purified by preparative TLC chromatography and recrystallization from EtOH yielding 20 mg of **5b** (18%): mp 261−263 °C; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 0.68 (s, 9H, *t*-Bu), 1.22 (s, 18H, *t*-Bu), 1.32 (s, 18H, *t*-Bu), 3.73

(17) The shock sensitivity of diazonium salts can be reduced by complexation with crown ethers (Sheppard, W. A.; Gokel, G. W.; Webster, O. W.; Betterton, K.; Timberlake, J. W. *J. Org. Chem*. **1979**, *44*, 1717.) It is not known at present whether the neighboring OH groups exert a similar effect.

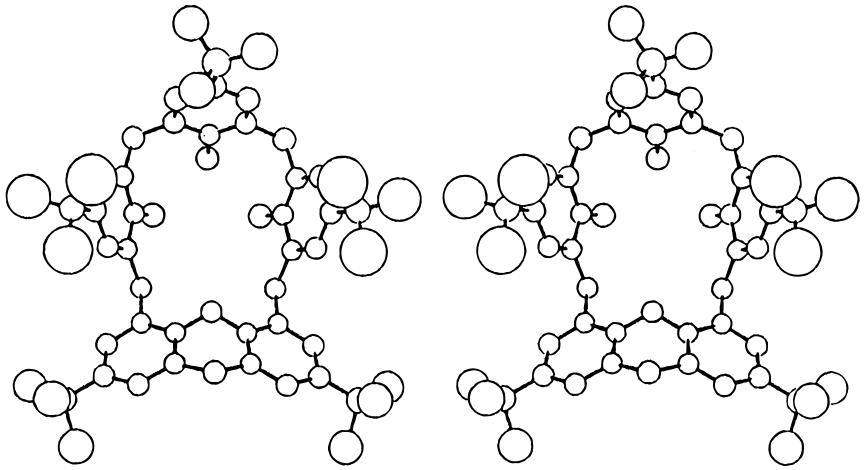


Figure 5. Stereoview of the crystal conformation of **6**. Ethanol molecules were omitted for clarity.

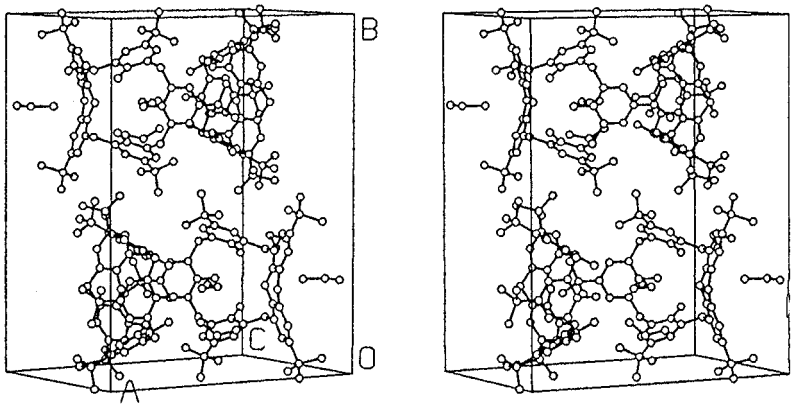


Figure 6. Packing arrangement of **6**·3 EtOH. One of the solvent molecules is partially included in the calix cavity.

(s, 2H, CH_2), 3.77 (s, 4H, CH_2), 4.13 (s, 4H, CH_2), 6.33 (s, 2H, OH), 6.78 (s, 2H, Ar H), 7.14 (d, 2H, Ar H), 7.17 (d, 4H, Ar H), 7.25 (d, J = 2.3 Hz, 2H, Ar H), 7.74 (s, 2H, OH); ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 30.46, 31.23, 31.40, 31.60, 33.86, 33.98, 38.27, 123.02, 125.53, 125.82, 125.88, 125.96, 126.18, 126.69, 126.94, 138.73, 143.38, 143.80, 147.54, 149.14, 149.84; CI MS *m/z* 872.4 (MH^+). Anal. Calcd for $C_{55}H_{69}O_4Br$·EtOH: C, 74.42; H, 8.16. Found: C, 74.12; H, 8.12.

5,11,17,23,29-Penta-*tert*-butyl-31-iodo-32,33,34,35-tetrahydroxycalix[5]arene (5c). 2b (120 mg) dissolved in 10 mL of EtOH was diazotized (isoamyl nitrite/HCl). After filtration, the diazonium salt was immediately dissolved in 15 mL of $CHCl_3$, and a solution of 500 mg of $Bu_4N^+ I^-$ in 15 mL of $CHCl_3$ was added. This solution was stirred for 10 min at rt and then refluxed for 40 min. The organic layer was washed several times with water, dried ($MgSO_4$), filtered, and evaporated. The residue was triturated with hot EtOH, and the undissolved material was filtered. The product was further purified by preparative TLC chromatography yielding 22 mg of a 84:16 mixture of **5c** and **5a.** The NMR spectra were determined on this sample: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 0.49 (s, 9H, *t*-Bu), 1.22 (s, 18H, *t*-Bu), 1.32 (s, 18H, *t*-Bu), 3.73 (s, 2H, CH_2), 3.77 (s, 4H, CH_2), 4.08 (s, 4H, CH_2), 6.09 (s, 2H, OH), 6.58 (s, 2H, Ar H), 7.11 (d, J = 2.3 Hz, 2H, Ar H), 7.15 (d, J = 2.4 Hz, 6H, Ar H), 7.27 (d, J = 2.3 Hz, 2H, Ar H), 7.71 (s, 2H, OH); ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 25.60, 30.19, 31.15, 31.39, 31.60, 33.61, 33.85, 34.00, 104.77, 125.09, 125.52, 125.88, 126.37, 126.48, 126.51, 126.69, 127.26, 142.41, 143.49, 143.75, 147.49, 149.26, 150.77; CI MS *m/z* 921.2 (**5c**H^+), 829.3 (**5a**H^+).

Preparation of the Calixindazole 8. 2b (40 mg) dissolved in 4 mL of EtOH was diazotized (0.4 mL of isoamyl nitrite/0.4 mL of concd HCl) as described above, and the diazonium salt was dissolved in 7 mL of chloroform. A solution of 200 mg of tetrabutylammonium fluoride trihydrate in 15 mL of chloroform was added. The color of the solution changed from yellow to red. This solution was stirred for 10 min at rt and then refluxed for 40 min. The red color of the solution disappeared during the reflux period. The organic layer was washed several times with water, dried ($MgSO_4$), filtered, and evaporated. The product was purified by chromatography (eluent: chloroform) yielding 8 mg of **8** (20%): mp 205 °C dec; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 1.13 (s, 9H, *t*-Bu), 1.14 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu), 1.28 (s, 9H, *t*-Bu), 1.35 (s, 9 H, *t*-Bu), 3.77 (s, 4H, CH_2), 3.97 (s, 2H, CH_2), 4.16 (s, 2H, CH_2), 5.91 (s, 2H, OH), 6.99 (d, J = 2.3 Hz, 1H, Ar H), 7.03 (d, J = 2.3 Hz, 1H, Ar H), 7.10 (d, J = 2.3 Hz, 1H, Ar H), 7.13 (d, J = 2.3 Hz, 1H, Ar H), 7.19 (s, 2H, Ar H), 7.31 (d, J = 2.1 Hz, 1H, Ar H), 7.39 (s, 1H, Ar H), 7.69 (s, 1H, Ar H), 7.85 (d, J = 2.1 Hz, 1H, Ar H), 9.68 (s, 1H, OH), 11.19 (s, 1H, OH), 13.36 (s, 1H, NH); ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 31.34, 31.43, 31.48, 31.55, 33.77, 33.84, 33.93, 34.21, 34.76, 114.37, 117.28, 121.15, 121.24, 124.98, 125.22, 125.61, 126.16, 126.28, 126.87, 127.22, 127.41, 128.40, 140.16, 142.45, 143.10, 143.47, 143.76, 145.67, 147.06, 147.74, 149.03, 149.25; CI MS *m/z* 821.1 (MH^+).

Acknowledgment. We thank Dr. Shmuel Cohen for the crystal structure determinations. This research was supported by a grant from the Germany-Israel Foundation (GIF) for Scientific Research and Development.

JO9611428