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Synthesis, Structure, and Complexing Property of *p-tert*-Butylcalix[4]arene 1,3-Digallate

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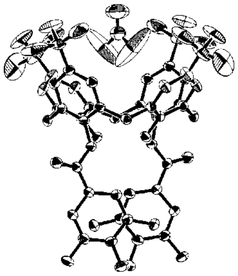
ABSTRACT



***p-tert*-Butylcalix[4]arene 1,3-digallate, which contains a nonbonded close contact between galloyl groups, was synthesized and its structure was determined by dynamic ^{1}H NMR and X-ray crystallography. The electronic spectra showed that a new absorption band of the complexes appeared at a longer wavelength region upon adding Ag^+ ion. This spectral shift was explained in terms of the interaction between the facing galloyl groups of the lower rim of the calixarene framework.**

Considerable attention has been paid to the synthesis and properties of functionalized calixarenes because of their potential utility as molecular receptors and ionophores.[1] The design of calixarenes containing the desired properties requires the control of their conformation, which possibly is achieved by the use of intramolecular hydrogen-bonding interactions between substituents on the calixarene skeleton.[2]

Gallic acid is a component of plant tannin[3] and exhibits a variety of chemical and biological properties that include pharmacological activity[4] and also binding to protains[5] and metal ions.[6] Three hydroxyl groups of gallic acid play an important role in these propaties.[4,5] On the basis of these backgrounds, we thought that the introduction of gallic acids into the lower rim of *p-tert*-butylcalix[4]arene may serve to stabilize the conformation of the calixarene through hydrogen bonding and act as a binding site toward guest molecules or ions. We now report the synthesis of *p-tert*-butylcalix[4]arene 1,3-digallate and its binding property toward metal ions in connection with the conformation.

Calixarene **2** was prepared by the reaction of *p-tert*-butylcalix[4]arene **1** (1.54 mmol) with *O*-acetylgalloyl chloride (12.4 mmol) in CH_2Cl_2 in the presence of triethylamine (12.4 mmol).[7] Calixarene **2** was obtained as prisms in 87% yield. Deacetylation of **2** with $NH_2NH_2{\cdot}H_2O$ or

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[1] (a) Gutsche, C. D. *Calixarenes, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Böhmer, V., Ed.; Kluwer Academic Publishers: Dordrecht, 1991.

[2] (a) Nomura, E.; Takagaki, M.; Nakaoka, C.; Uchida, M. Taniguchi, H. *J. Org. Chem.* **1999**, *64*, 3151. (b) Rudkevich, D.; Hilmersson, M. G.; Rebek, J. J. *J. Am. Chem. Soc.* **1997**, *119*, 9911. (c) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; v. Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476.

[3] *Plant Polyphenols*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992.

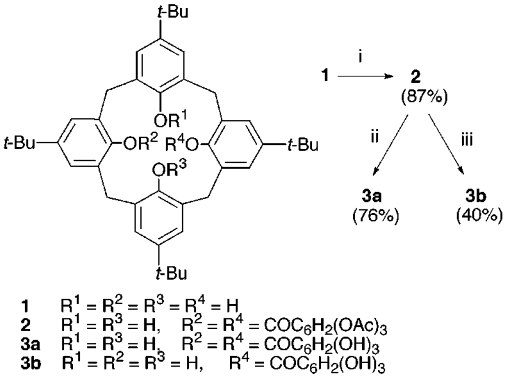
[4] *Economic and Medicinal Plant Research*, Vol. 5; Wagnner, H., Farnsworth, N. R., Eds.; Academic Press: New York, 1991.

[5] Okuda, T. Mori, K.; Hatano, T. *Chem. Pharm. Bull.* **1985**, *33*, 1424.

[6] Okuda, T.; Mori, K.; Shiota, M.; Ida, K. *Yakugaku Zasshi* **1982**, *102*, 735.

10.1021/ol9913993 CCC: $19.00

Scheme 1[a]



[a] Reagents and conditions: (i) $ClCOC_6H_2(OAc)_3$, Et_3N, CH_2Cl_2, rt, 5 h; (ii) $H_2NNH_2{\cdot}H_2O$, CH_3CN, rt, 30 min; (iii) aqueous NH_3, CH_3CN, rt, 2 h.

aqueous NH_3 in MeCN at room temperature gave **3a** and **3b** in 76 and 40% yields, respectively (Scheme 1). The structures of all the compounds were established by NMR and elemental analyses.

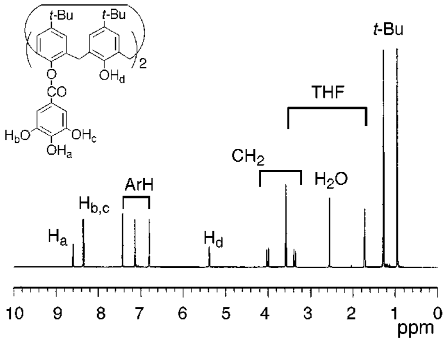


Figure 1. ^{1}H NMR spectrum (400 MHz) of **3a** in THF-d_8 at 20 °C.

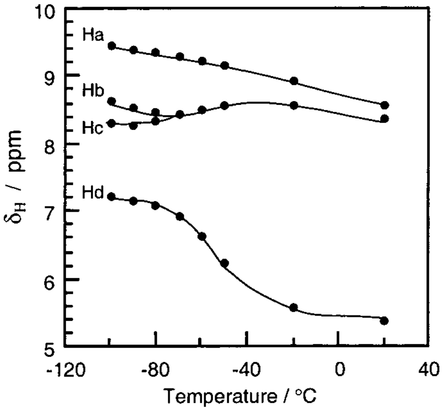


Figure 2. Temperature dependence of chemical shifts for the OH protons of **3a** (400 MHz, THF-d_8).

The ^{1}H NMR spectrum of **3a** in THF-d_8 at 20 °C was simple, as shown in Figure 1. A pair of singlet signals arising from the *tert*-butyl protons and a pair of doublet signals from the $ArCH_2Ar$ methylene protons strongly suggest that **3a** has a C_2 symmetry and a cone conformation.[8] The H_b and H_c proton signals gave the same resonance at 8.36 ppm. This indicates that the galloyl groups in **3a** undergoes rapid rotation on a NMR time scale at 20 °C. The chemical shifts of the OH proton signals of the galloyl groups and the calixarene skeleton varied with loss of temperature (Figure 2). The signal arising from the H_b and H_c protons at 8.36 ppm at 20 °C shifted downfield upon cooling to −40 °C and then upfield until reaching −70 °C. This signal separated into two signals which appeared at 8.64 (H_b) and 8.32 (H_c) ppm at −100 °C. The aromatic proton signals of the galloyl groups were also observed as two separated signals at 8.24 and 7.13 ppm at −100 °C. The separated upfield signal of the H_c proton suggests that the OH_c group is situated at a position which is affected by the ring current effect associated with the facing galloyl group. The H_d proton also shifted downfield by 1.74 ppm upon cooling from 20 to −100 °C. This suggests that the OH_d group forms a hydrogen bond with the neighboring ether oxygen atom[8] (see later).

When **3a** was recrystallized from acetone, prism crystals which include acetone molecules inside the crystals were obtained, and on standing the crystals changed gradually from clear to opaque crystals upon losing acetone molecules. The crystal structure of **3a** was determined by a single-crystal X-ray analysis (Figure 3).[9] Calixarene **3a** was found to have a cone conformation with a C_2 symmetry and to form a 1:5 clathrate with acetone molecules. Four acetone molecules are captured in the channel of the crystal lattice, and one acetone molecule is held inside the molecular cavity of **3a** with the CH_3 group pointing into the cavity.[10] The acetone molecule within the cavity exists in a position where a $CH_3{-}\pi$ interaction between one of the CH_3 groups of acetone and the aromatic ring of the calixarene could be present.[11] In fact, the CH_3 carbon of acetone is situated at a distance of 3.54(4) Å above the center of the phenyl ring of **3a**. There are two intramolecular OH···O hydrogen bonds between the phenolic hydroxyl groups of the calixarene ring and the

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(7) For a similar selective esterification, see: See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, *56*, 7256.

(8) Mogck, O.; Böhmer, V.; Furguson, G.; Vogt, W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1711.

(9) Crystal data for $C_{58}H_{64}O_{12}{\cdot}5(C_3H_6O)$. **3a**: $M = 1243.54$, tetragonal, $a = b = 13.9382(3)$ Å, $c = 35.3234(8)$ Å, $V = 6862.4(3)$ Å^3, $T = -100$ °C, space group $P4_12_12$ (No. 92), $Z = 4$, μ(Cu Kα) = 6.89 cm^{-1}, $D_c = 1.204$ g cm^{-3}, 69324 reflections measured, 1216 unique ($R_{\text{int}} = 0.039$), residuals of $R = 0.069$ and $R_w = 0.102$ were obtained from the 2652 reflections with $I > 2.00\sigma(I)$ and 408 variable parameters used in the refinement.

(10) Calixarene−acetone clathrates, see: Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1979.

(11) For $CH_3{-}\pi$ interactions between the methyl groups of the host and the aromatic moiety of pyridine, see: Andreetti, D.; Ori, O.; Ugozzoli, F.; Alfieri, C.; Pochini, A.; Ungaro, R. *J. Inclusion Phenom.* **1988**, *6*, 523.

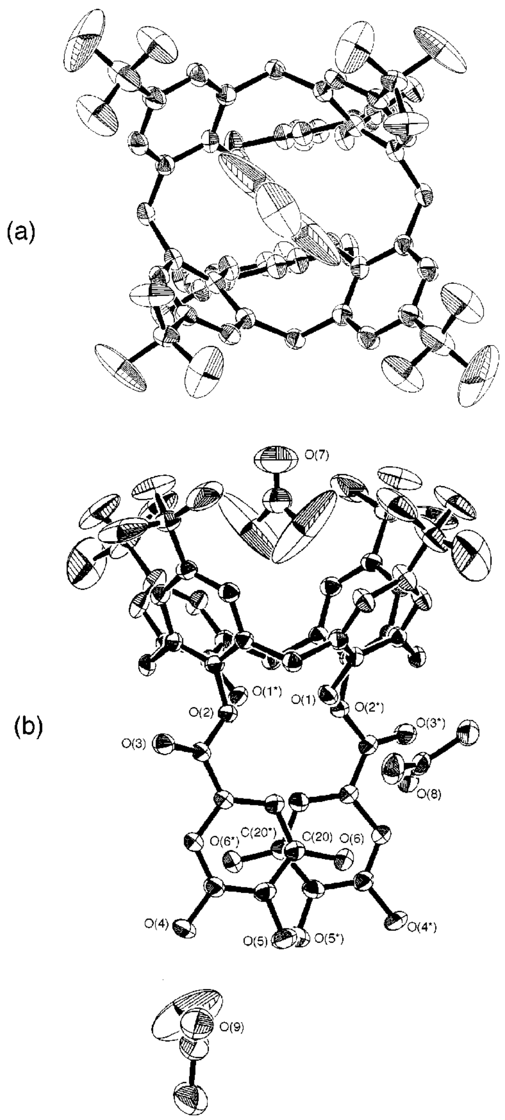

Figure 3. Top (a) and side (b) views of the X-ray crystallographic structure of **3a** (30% probability). Hydrogen atoms have been omitted for clarity. In the top view, acetone molecules in the channel of the crystal latice have been omitted for clarity. Close contacts (Å): C(20)···C(20*), 3.30(1); O(1)···O(2), 2.871(5); O(6)···O(8), 2.760(7); O(4)···O(9), 2.74(1); O(5)···O(5*), 3.224(8). For example, O(1*) and O(2*) are related to O(1) and O(2), respectively, by 2-fold symmetry.

proximal ether O atoms in which the O(1)···O(2) distance is 2.871(5) Å. These hydrogen bonds were found for many 1,3-substituted calix[4]arenes.[12] The four hydroxyl groups of the galloyl groups form intermolecular hydrogen bonds with four acetone molecules, and the distance of O(6)···O(8) is 2.760(7) Å and that of O(4)···O(9) is 2.74(1) Å. There is weak hydrogen bonding between the OH$_a$ groups of facing galloyl groups, and the distance of O(5)···O(5*) is 3.224(8) Å. The OH$_c$ group is placed in a position where significant nonbonded contacts are observed between the OH$_c$ group and the aromatic ring of the galloyl groups facing each other, which is consistent with the model predicted from the ^{1}H NMR spectral data. The hydroxyl oxygen O(6) is situated in a position which is 3.247(7) Å above the least-squares plane of the facing phenyl ring of the galloyl group. This interaction makes it possible to exert an OH−π interaction.[13] In the solid state, it can be assumed that hydrogen bonding between the OH group of the galloyl group and the acetone molecule is preferred.

The interaction with metal ions was evaluated by means of electronic spectra. Figure 4 shows the electronic spectra of **3a** in ethanol solutions in the presence of several metal nitrates. Upon adding Mg$^+$, Ca$^+$, and Al^{3+} ions, the absorbances at around 280 nm decreased with slight bathochromic shifts and new absorption bands appeared at around 340, 330, and 315 nm, respectively. Furthermore, upon adding Ag$^+$ ion, the absorbance changed markedly and a new strong band was observed at around 420 nm. On the other hand, when the monoester **3b** was used, such a spectral change was not observed upon adding Ag$^+$ ion. These spectral changes for **3a** are thought to arise from the structure of the calixarene in which the facing galloyl groups are located in a position of nonbonded close contact.

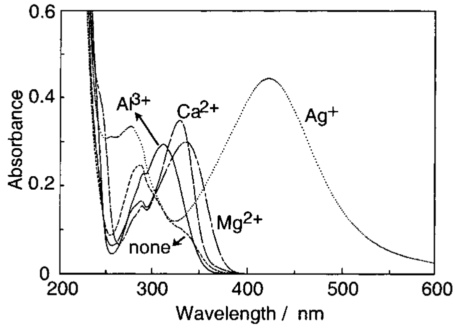

Figure 4. Electronic spectra of **3a** in EtOH in the presence of metal nitrates. [**3a**] = 1.0×10^{-5} mol dm^{-3}, [M(NO$_3$)n] = 1.0×10^{-3} mol dm^{-3}.

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Supporting Information Available: Experimental details for compounds prepared and crystallographic data and structure refinement details for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org

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[12] (a) Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; Mckervey, M. A.; Madigan, E.; Moran, M. B.; Phillips, J.; Williams, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1521. (b) Collins, E. M.; Mckervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137.

[13] For OH−π interaction between H$_2$O and aromatic π electrons, see: Atwood, J. L.; Hamada, F.; Robinson, K. D.; Orr, G. W.; Vincent, R. L. *Nature* **1991**, *349*, 683.