

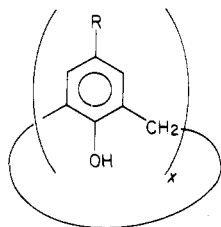
A Calix[4]arene Type Molecule and Its Hydrate

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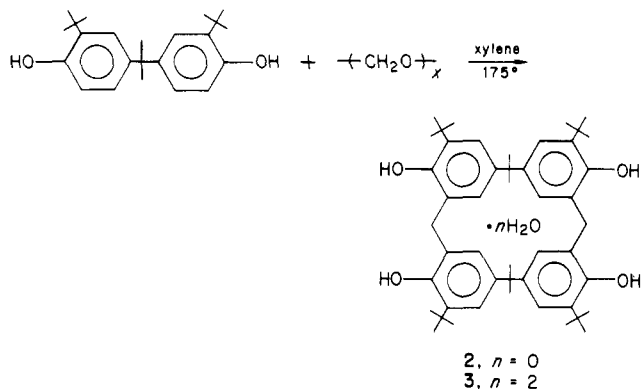
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Within the last five years there has been tremendous interest¹ in a class of compounds commonly referred to as calix[*n*]arenes, 1. These compounds exist in a cuplike

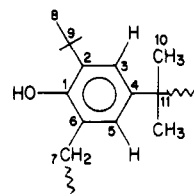
1, $x = 4-8$

structure due to intramolecular hydrogen bonding between the inward-turned hydroxyl groups. The cavity thus created is sometimes capable of complexing one or more solvent molecules which can be removed with more or less difficulty. This report concerns the synthesis and characteristics of 5,11,17,23-tetrakis(1,1-dimethylethyl)-2,2,14,14-tetramethylpentacyclo[19.3.1.1.3^{7,1}.9,13^{15,19}]octacosane-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane-6,10,18,22-tetrol, 2, a calix[4]arene type structure whose hydroxyl groups are on the outside periphery of the macrocycle.

The reaction of 2,2'-di-*tert*-butyl-4,4'-isopropylidenebis(phenol)² with paraformaldehyde in xylene at 170 °C affords a mixture of various oligomeric species. However,



when the crude product is dissolved in acetonitrile, a white solid, mp 325-330 °C, remains. While the molecular weight (704) by field desorption/mass spectrometry (FD/MS) and by high-resolution mass spectrometry (704.4787) were consistent with 2, the ¹H NMR spectrum revealed an additional unaccounted for absorption (see Experimental Section) at 1.58 ppm which disappeared upon addition of D₂O. In addition, the elemental analysis was too low in carbon, even after extensive purification by column chromatography. However, these observations are consistent with 3, the dihydrate of 2. The source of water was from the condensation reaction itself. When 3 was heated at 110 °C (2 mm) for 3 h, the resulting material gave an elemental analysis and ¹H NMR spectrum consistent with 2.

Table I. ¹³C NMR Spectral Data for 3^a

no.	δ , CDCl ₃ ^b (J, Hz)	δ , C ₆ D ₆ ^c
1	149.93 (t, ³ J ~ 4)	150.44
2	143.04 (s)	143.43
3 ^d	127.72 (dd, ¹ J = 155, ³ J ~ 7)	128.37
4	135.07 (s)	135.69
5 ^d	122.44 (dd, ¹ J = 153, ³ J ~ 7)	122.60
6	125.36 (t, ² J ~ 5)	126.11
7 ^e	31.15	30.97
8	30.12 (q, ¹ J = 125.6)	30.18
9	34.71 (q, ² J ~ 5.5)	34.97
10	31.15 (q, ¹ J = 125)	31.32
11	42.39 (q, ² J ~ 5.5)	42.65

^a 2 and 3 exhibited ¹³C chemical shifts within ± 0.04 ppm of one another. ^b Both the totally proton decoupled and coupled spectra were obtained. ^c Only the totally proton decoupled spectrum was obtained in order to distinguish carbons 7 and 10. ^d These assignments may be reversed. ^e Due to overlap of absorptions in the coupled spectrum, the *J* value could not be determined. This assignment was based upon the decoupled spectrum and the C₆D₆ results.

Both the totally proton coupled and decoupled ¹³C NMR spectra of 2 and 3 were identical within ± 0.04 ppm (see Table I) of one another and the chemical shifts, coupling constants, and coupling patterns were as expected. The only anomaly was that the CH₂ bridge and the *gem*-dimethyl carbons possessed identical shifts in CDCl₃ solution, although these two carbon resonances could be resolved in C₆D₆ solution.

The infrared spectra (Nujol) of 2 and 3 differed only in the hydroxyl region. While there were three distinct hydroxyl absorptions in each (see Experimental Section), the absorptions in 3 were at lower frequency and were considerably broader than those in 2, suggestive of more intense hydrogen bonding.

The FD/MS of 2 and 3 were also identical, showing an M⁺ at 704. Scans up to 2100 revealed no higher cyclic oligomers, e.g., octamer. The molecular weight of 3 was determined by vapor-phase osmometry (VPO) and was shown to be 747, very close to the 740 expected for the dihydrate. These data certainly exclude the possibility of 3 being a higher molecular weight cyclic oligomer.

When 3 is heated (10°/min up to 350 °C) in a thermogravimetric analyzer (under nitrogen), about 5% by weight of the material is lost by ca. 110 °C after which no weight loss occurs until ca. 300 °C. The derivative thermogravimetric analysis shows that there are two stages resulting in equal weight loss, one near 65 °C and one near 100 °C. This suggests that 3 is being dehydrated in two steps, since the two water molecules make up about 4.9% of the weight of 3.

2 does not complex with chloroform, acetonitrile, or methanol but does rehydrate when it is dissolved in wet tetrahydrofuran. At this time, it is not clear whether the water is held in a molecular cavity generated by the hydrogen bonding of adjacent hydroxyl groups in 3, is bound to the hydroxyl groups external to the molecule, or is some combination of the two.

Experimental Section

Elemental analyses and VPO molecular weights were performed at Huffman Labs, Wheatridge, CO. Melting points were obtained

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(2) Young, D. W.; Serniuk, G. E.; Cottle, D. L. U. S. Patent 2 745 726, 1956.

on a Mel-Temp apparatus and are uncorrected. The ^1H (200.13 MHz) and ^{13}C (50.28 MHz) NMR spectra were obtained on a Bruker WH-200 instrument and the chemical shifts are reported in ppm downfield from internal tetramethylsilane. A Perkin-Elmer Model 467 spectrometer was used for infrared spectra. The field desorption/mass spectra were acquired on a Finnigan MAT 311A instrument. The TGA data were obtained on a Perkin-Elmer Model TGS-2 instrument.

Preparation of 3. 2,2'-Di-*tert*-butyl-4,4'-isopropylidenebis(phenol)² (100 g, 0.29 mol), paraformaldehyde (10.6 g, 0.35 mol), and xylene (1 L) are charged into a 1780-mL stainless steel autoclave and heated at 175 °C for 12 h. The reaction is cooled and filtered, and the solvent is removed under vacuum. The resulting yellow friable glass is stirred in a minimum amount of acetonitrile for 1-1.5 h, after which time a white powder remains. Filtration affords **3**, mp 325-330 °C. Second and third crops can be obtained by concentrating the acetonitrile. Total yield is 20 g (20%) of **3**.

An analytical sample of **3** is obtained by column chromatography 2 g of **3** on 150 g of 0.063-0.2-mm silica gel (ICN Pharmaceuticals, Inc.) using as eluent 1:3 hexane:chloroform in a 4 × 30 cm column: IR (Nujol) 3460, 3570, 3615 cm^{-1} (hydroxyl),

1180-1220 cm^{-1} (Ar-O); FD/MS, m/e 704 (M^+); high-resolution mass spectrum, 704.4787 (calcd 704.4804); ^1H NMR (CDCl_3) δ 1.42 [s, 36 H, $\text{C}(\text{CH}_3)_3$], 1.56 [s, 12 H, $\text{C}(\text{CH}_3)_2$], 1.58 (s, 2 H_2O),³ 3.68 (s, 4 H, CH_2), 5.24 (s, 4 H, OH),³ 6.40 (d, 4 H, $J = 2.4$ Hz, Ar H), 7.24 (d, 4 H, $J = 2.4$ Hz, Ar H); VPO molecular weight (THF solvent at 45 °C), 747 (calcd 740). Anal. Calcd for $\text{C}_{48}\text{H}_{64}\text{O}_4 \cdot 2\text{H}_2\text{O}$: C, 77.84; H, 9.19. Found: C, 78.05; H, 9.13.

Preparation of 2. **3** is heated at 110 °C (2 mm) for 3 h in a vacuum oven: IR (Nujol) 3510, 3550, 3625 cm^{-1} (hydroxyl); ^1H NMR (CDCl_3) δ 1.42 [s, 36 H, $\text{C}(\text{CH}_3)_3$], 1.56 [s, 12 H, $\text{C}(\text{CH}_3)_2$], 3.68 (s, 4 H, CH_2), 5.24 (s, 4 H, OH), 6.40 (d, 4 H, $J = 2.4$ Hz, Ar H), 7.24 (d, 4 H, $J = 2.4$ Hz, Ar H); FD/MS, m/e 704 (M^+). Anal. Calcd for $\text{C}_{48}\text{H}_{64}\text{O}_4$: C, 81.81; H, 9.09. Found: C, 81.25; H, 9.11.

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(3) These absorptions disappeared upon addition of D_2O .

Communications

New Syntheses of Carbocycles from Carbohydrates. Cyclization of Radicals Derived from Unsaturated Halo Sugars

Summary: The cyclization of radicals derived from unsaturated aldoses promises to constitute an efficient and general preparation of hydroxylated cyclopentane and cyclohexane derivatives. The first example of this powerful new strategy for the preparation of polyhydroxylated carbocycles from aldoses is described. The effect of olefin geometry and hydroxyl group derivatization on product geometry is reported.

Sir: In the past decade, the potential use of carbohydrates as readily available polyhydroxylated structural units (chiral synthons) has been vigorously developed in several research groups.¹ The preparation of acyclic and heterocyclic products from aldoses has received great attention. In contrast, technology for the preparation of carbocycles from carbohydrates by the cyclization of acyclic aldose derivatives is in need of further development.² We report here the successful cyclization of an aldose derivative by a process that maintains all of the stereogenic carbon nuclei present in the original aldose. This powerful new strategy should find wide application in the preparation of biologically active polyhydroxylated carbocyclic natural products.

The formation of carbocycles by cyclization of unsatu-

rated radicals is a well-known process that is undergoing rapid development.³ Because the conditions required for such carbon-carbon bond formations are mild and asymmetric carbon nuclei can be retained immediately next to the sites of bond formation,⁴ it appeared that this general strategy would be an especially effective technique for the cyclization of carbohydrate derivatives. Problems associated with carbanionic methods (regiospecific anion generation and stabilization, β -elimination) are avoided by using radical or cationic processes. On this basis it was hypothesized that polyhydroxylated carbocycles might be readily prepared from unsaturated halo sugars (Chart I).

To test this concept the hydroxy lactone **1**⁵ was converted by the action of *N*-bromosuccinimide and triphenylphosphine⁶ into the corresponding bromide **2** ($[\alpha]^{25}_{\text{D}} -39.5^\circ$, c 1.02)⁷ and reduced to afford lactol **3** ($[\alpha]^{25}_{\text{D}} -37.5^\circ$, c 1.02)⁷ in 82% overall yield. Treatment of this lactol with (carbethoxymethylidene)triphenylphosphorane afforded the olefinic halides (*Z*)-**4a** ($J_{2,3} = 12$ Hz; ($[\alpha]^{25}_{\text{D}} +87.4^\circ$, c 1.26)⁷) and (*E*)-**4a** ($J_{2,3} = 16$ Hz; ($[\alpha]^{25}_{\text{D}} +29.1^\circ$, c 1.34)⁷) in

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(2) It must be emphatically acknowledged that a number of creative approaches to the preparation of carbocycles from carbohydrates have been recorded. For recent examples, see: (a) Fleet, G. W. J.; Shing, T. K. M.; Warr, S. M. *J. Chem. Soc., Perkin. Trans. 1* 1984, 904. (b) Ferrier, R. J.; Prasit, P.; Tyler, P. C. *Ibid.* 1983, 1641. (c) Bernet, B.; Vasella, A. *Helv. Chim. Acta* 1979, 62, 1990, 2400, 2411. (d) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* 1978, 50, 1363. (e) Dugger, R. C.; McDonald, C. E. "Abstracts of Papers", 186th National Meeting of the American Chemical Society; American Chemical Society: Washington, D.C., Sept 1983; ORGN Abst. No. 129. (f) Grosheintz, J. M.; Fischer, H. O. L. *J. Am. Chem. Soc.* 1948, 70, 1479. (g) Lichtenthaler, F. W. *Angew. Chem., Int. Ed. Engl.* 1964, 3, 211. (h) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* 1979, 1455.

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(6) Hanesian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohydr. Res.* 1972, 24, 45.

(7) Elemental analysis (combustion or mass spectrometric), magnetic resonance spectra (^1H and ^{13}C), and infrared spectra were consistent with the indicated structure for this molecule. Optical rotations were measured in ethanol free chloroform. Concentration (c) is given as g/100 mL.