Inherently Chiral Calix[4]arene

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Received August 16, 1995

Three inherently chiral calix[4]arenes **3-5** were synthesized as racemate starting from the ethylation at 1.3-distal hydroxy groups of calix[4]arene **2** which has two phenyl groups at upper rim in AABB fashion, and then two remaining hydroxy groups were acetylated by treatment with acetyl chloride in the presence of NaH to produce calix[4]arene **4**. Treatment of **4** with $AlCl_3$ under Fries rearrangement conditions, only one acetyl group was rearranged to the para-position to afford calix[4]arene **5** with AABC substitution pattern at the upper rim of calix. The structure of chiral calix[4]arenes were confirmed based on NMR and mass spectra.

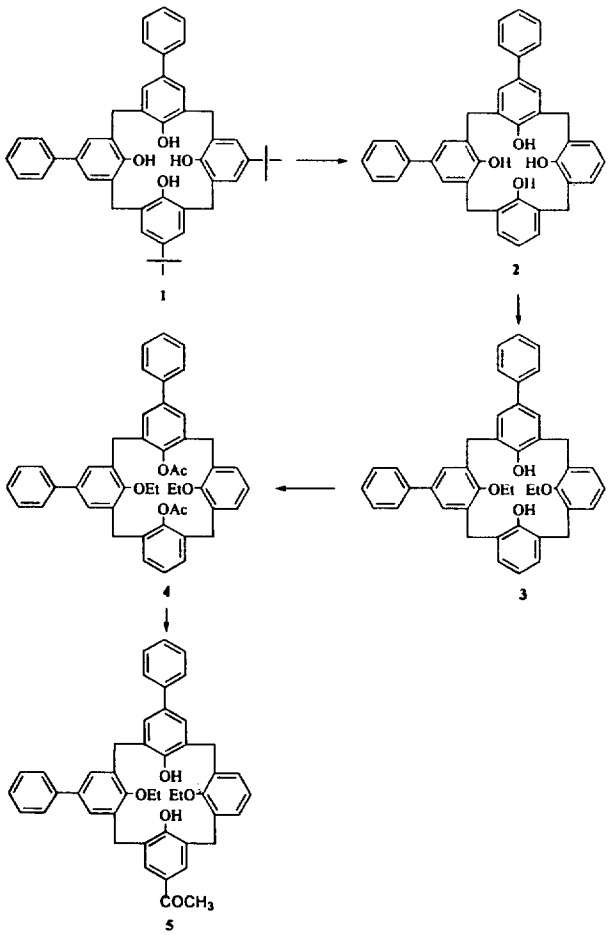
Introduction

Calixarenes, a class of synthetic macrocycles having phenolic residues in a cyclic array linked by methylene groups at the position "ortho" to the hydroxy groups, have cavities of sufficient size to form host-guest complexes, thus, are particularly attractive compounds for attempting to construct systems that mimic the catalytic activity of the enzyme and have received a great deal of attention in recent years.[1~3]

Chiral recognition is the most sophisticated function of enzyme which remains difficult to realize with artificial enzyme mimics. Calix[4]arenes with a chiral cavity are of particular interest for the chiral recognition and several approaches have been reported for the synthesis of chiral calix[4] arenes. The most simple method to synthesize chiral calix[4] arenes is the introduction of chiral substituent at the lower[4,5] or upper[6,7] rim of calixarene skeleton. More interest has been focused on the possibility of synthesizing "inherently" chiral calix[4]arenes, which are built up of nonchiral subunits and consequently owe their chirality to the fact that the calixarene molecule is not planar. The attempts for asymmetric molecules of this type involved the synthesis of calix[4]arenes with three (in AABC pattern) or four different p-substituted phenol units[8,9] or the introduction of *m*-substituted phenol units.[10~14] The same asymmetric pattern can be achieved by O-alkylation or O-acylation at the lower[15~18] rim of calixarene. The synthesis of asymmetric calix[4]arenes having three or four different phenolic units was reported by Boehmer using the '2+2' or '3+1' coupling procedure.[8,9] Although in principle versatile, the fragment condensation procedure is plagued by serious synthetic problems (several steps for the preparation of coupling components with lower yield).

As shown on the following scheme, this paper deals with the facile synthesis of the chiral calix[4]arene, having three different substituents in AABC pattern at the upper rim, starting from the calix[4]arene with AABB substitution pattern which was obtained in resonable yield by the fragment condensation reaction. The coupling components AA and BB were synthesized in the one-step reaction with excellent yield respectively.

Recently several authors reported that O-alkylation or O-acylation of calix[4]arenes can be easily achieved at the 1,3-positions under carefully controlled conditions leading in high yields to the corresponding disubstituted derivatives.[19~23] If such a derivatization is carried out with a calix[4]arene consisting of two different phenolic units (in AABB pattern) the resulting calix[4]arene is chiral (however obtained in racemate).



Scheme 1.

Calix[4]arene **1** with AABB substitution pattern at the upper rim of calixarene skeleton was first synthesized by No and Gutsche[24] using the five-step procedures and then followed by Boehmer and cowokers[25] using the fragmentation condensation of dimer (AA) with a bisbromomethylated

dimer (BB) without detailed procedures for the preparation of coupling component (AA and BB). We also reported the synthesis of **1** using the '2+2' fragmentation condensation procedure between dimer of *p*-*t*-butylphenol (AA) and bisbromomethyl dimer of *p*-phenylphenol (BB).[26] In the present study the preparation of compound **1** was performed by following the published procedures[26] except the use of 2,6'-bishydroxymethyl *p*-phenylphenol dimer (BB) instead of bisbromomethyl dimer, which means the reduction of the synthetic steps from three to two (elimination of bromination).

Compound **1** was treated with $AlCl_3$ in benzene to produce the de-*t*-butylated calix[4]arene **2** in 69% yield, which was refluxed with ethyl iodide in acetone in the presence of potassium carbonate to yield the corresponding 1,3-O-ethylated derivative **3** after flash chromatographic separation.[27] The calix[4]arene **3** is composed of four different phenolic units so it is a chiral compound. ^1H NMR spectrum of **3** shows seven sets of doublet from bridge methylene protons, two sets of quartet from O-CH_2 protons, two sets of triplet from methyl protons of ethyl groups. ^{13}C NMR spectrum is also very complex, shows 26 peaks from aromatic carbons, three peaks from bridge methylene carbons at around 32 ppm where one peak is almost twice intensive than the other two peaks. Both of the ^1H and ^{13}C NMR spectra support the cone conformation and chirality of **3**. A similar result was reported by the Boehmer.[25]

Compound **3** was treated with acetyl chloride in THF in the presence of NaH to yield diacetylated compound **4** as a 1 : 1 : 2 mixture of conformers based on ^1H NMR spectrum and HPLC analysis. The isolation of pure conformer was tried by flash chromatography, however only one conformer **4a** (the highest Rf value) was isolated and the other two conformers, **4b** and **4c**, were obtained as a mixture. ^1H NMR spectrum of **4a** shows seven sets of doublet from bridge methylene protons, two sets of quartet and triplet from the methylene and methyl protons of two ethyl groups and two singlets from methyl protons adjacent to carbonyl groups. ^{13}C NMR spectrum has two peaks from carbonyl carbons, 31 peaks from aromatic carbons, two peaks each from methylene and methyl carbons of ethyl groups, and two peaks from methyl carbons adjacent to carbonyl groups. The bridge methylene carbons show four peaks at around 31 ppm. All the spectral patterns are commensurate with the cone conformation. The NMR and IR spectra of the mixture of **4b** and **4c** are also commensurate with the proposed structure of compound **4**, in which both of two hydroxy groups are acetylated. The resonance peak from methyl protons adjacent to carbonyl groups are upfield shifted from 2.56 and 2.53 ppm of cone conformer **4a** to 1.75, 1.70, 1.63 and 1.62 ppm of mixture of **4b** and **4c**. In ^{13}C NMR spectrum the mixture shows a total of eight peaks, four at around 38 ppm and the remaining four at around 31 ppm, from the carbons of bridge methylene groups. Based on these spectral pattern cone and 1,3-alternate conformations are clearly ruled out. Eleven conformational isomers (one cone, four partial cone, four 1,2-alternate, and two 1,3-alternate) are expected for **4**. According to CPK molecular model study, in partial cone conformers, in which either benzene ring containing acetate group is inverted, acetyl groups are located proximate to the benzene moiety of the opposite (1,3-distal each other) position. The proximate benzene moiety, then, must be postulated to exert a diamagnetic anisotropic shielding effect that shifts the resonance of methyl protons adjacent to carbonyl group upfield. However we were not able to assign the correct conformation of **4b** and **4c** and the product mixture was used for the next step without separation. Compound **4** was stirred with $AlCl_3$ in nitrobenzene under the Fries rearrangement conditions similar to those described by us[28] to afford the rearranged product **5**. The Rearrangement was confirmed by spectral comparison between starting material **4** and product **5**. In Infrared spectrum, the OH stretching band appeared and the position of carbonyl stretching band was shifted from 1750 cm^{-1} of ester to 1670 cm^{-1} of aromatic ketone. The mass spectrum of **5** has the molecular ion peak at m/e 674. ^1H NMR spectrum has only one singlet arising from the acetyl protons and ^{13}C NMR spectrum also has only one peak from carbonyl carbon. There is no indication of presence of AB quartet resonance peak with ortho coupling of para disubstituted benzene protons. In the comparison of the FT-IR spectrum of **5** with that of **4**, the general appearance of two spectra at 900-700 cm^{-1} region are almost identical and there is no absorption band at around 810 cm^{-1}. According to these data, the acetyl group on unsubstituted phenol was rearranged to the para position and the other acetyl group was simply cleaved. The remaining ^1H and ^{13}C NMR spectral patterns are commensurate with the cone conformation and chiral nature of **5**. In ^1H NMR spectrum, there are two singlets from hydroxy protons, eight sets of doublet from bridge methylene protons, and two sets of quartets and triplets from the methylene and methyl protons of ethyl groups. ^{13}C NMR spectrum shows 28 peaks from aromatic carbons and two peaks each from methylene and methyl carbons of the ethyl groups. The bridge methylene carbons show four peaks at around 32 ppm.

In this investigation three inherently chiral calix[4]arene were synthesized as a racemate starting from the calix[4]arene with two different substituents in AABB patterns. The chiral resolution of pure enantiomer was not tried. Chiral calix[4]arene **5** which has three different possible reaction sites at upper rim provides an easy access to a new type of chiral host molecule in which the remaining two free hydroxy groups offer additional advantage.

Experimental

Melting points of all compounds were taken in sealed and evacuated capillary tubes on an Syblon thermolyne apparatus with polarizing microscope and were not corrected. IR spectra were determined on a Nicolet Impact 400 FT-IR spectrometer as KBr pellet. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300 (300 and 75 MHz) (OCRC) and Bruker AMX 500 instrument (Seoul National University). Chemical shifts are recorded as δ values in parts per million relative to TMS (δ 0.0) as an internal standard. Mass spectra were recorded on Hewlett-Packard 5890-JMS AX505WA GC-Mass Spectrometer. $HPLC_1$analysis was carried with Shimadzu LC-10 series instrument (Shim-pack CLS-ODS C18 Reverse Phase Column, Eluent acetone/water 7 : 3 mixture, Detection UV 214 nm). TLC analyses were carried out on silica gel plates (absorbent thickness 250 μm). Flash chromatography was carried out with E. Merck silica gel (230-400 mesh ASTM). Elution rate were 2 in/min.

5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene 1. was prepared in 24% yield from the coupling of 3-(3-hydroxymethyl-5-phenylsalycyl)-5-phenyl-2-hydroxybenzyl alcohol and 2-(5-*tert*-butylsalicyl)-4-*tert*-butylphenol using the published procedure.[26] mp 332-333 ℃ (lit[26] 332-333 ℃).

5,11-Diphenyl-25,26,27,28-tetrahydroxycalix[4]arene 2. was prepared in 69% yield by the published procedure.[24] mp 275-276 ℃ (lit[24] 276-277 ℃).

5,11-Diphenyl-25,27-diethoxy-26,28-dihydroxycalix[4]arene 3. Ethyl iodide (0.8 mL) was added to the heated solution of compound **2** (65.0 mg, 1.14 mmole) and K_2CO_3 (55.0 mg) in 25 mL of acetone and then the reaction mixture was refluxed for 20 hrs. After removal of solvent the resulting residue was dissolved in chloroform (20 mL) which was washed with 2 N HCl, water and brine. The residue, obtained by evaporation of solvent and trituration with methanol, was purified by flash chromatography (eluent was 3 : 1 mixture of petroleum ether and chloroform) to yield 430 mg (60%) of compound **3** as colorless crystalline solid: mp 228-230 ℃; IR (KBr) 3330 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 8.48 (s, 1, OH), 8.33 (s, 1, OH), 7.53-6.62 (m, 20, ArH), 4.41 (d, 2, CH_2, J=13.2 Hz), 4.40 (d, 1, CH_2, J=12.9 Hz), 4.35 (d, 1, CH_2, J=12.9 Hz), 4.17 (q, 2, OCH_2, J=7.2 Hz), 4.15 (q, 2, OCH_2, J=7.2 Hz), 3.52 (d, 1, CH_2, J=13.2 Hz), 3.46 (d, 1, CH_2, J=13.2 Hz), 3.45 (d, 1, CH_2, J=13.2 Hz), 3.41 (d, 1, CH_2, J=13.2 Hz), 1.71 (t, 3, CH_3, J=7.2 Hz), 1.70 (t, 3, CH_3, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 153.65, 153.52, 152.56, 152.23, 142.02, 141.17, 138.29, 134.62, 134.28, 134.21, 134.09, 132.92, 129.44, 129.31, 129.03, 128.93, 128.87, 128.37, 128.14, 128.81, 127.74, 127.39, 127.28, 126.69, 125.77, 119.79 (Ar), 72.55, 72.46 (OCH_2), 32.21. 31.81, 31.72 ($ArCH_2Ar$), 15.33 (CH_3).

5,11-Diphenyl-25,27-diethoxy-26,28-diacetyloxycalix[4]arene 4. To the heated suspension of compound **3** (920 mg, 1.46 mmole) and NaH (228 mg, 9.51 mmole, 60% oil dispersion) in THF (50 mL) a solution of acetyl chloride (1.0 mL, 14.1 mmole) in 20 mL of THF was added dropwise. After the reaction mixture was refluxed for 1.5 hr, water (50 mL) was added and then organic material was extracted with chloroform. The organic layer was separated, washed with water, dried, and then evaporated solvent to afford slightly waxy residue, which was triturated with methanol to yield 948 mg (91%) of colorless crystalline solid as a mixture of three conformers of the desired product. The small amount of analytical sample of cone conformer **4a** was obtained by flash chromatography (eluent was 1 : 5 mixture of acetone and hexane): mp 249-250 ℃; IR (KBr) 1750 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.55-6.29 (m, 20, ArH), 4.18 (q, 2, OCH_2, J=7 Hz), 4.15 (d, 1, $ArCH_2Ar$, J=13.5 Hz), 4.14 (q, 2, OCH_2, J=7 Hz), 4.11 (d, 1, $ArCH_2Ar$, J=13.5 Hz), 4.10 (d, 1, $ArCH_2Ar$, J=13.6 Hz), 4.07 (d, 1, $ArCH_2Ar$, J=13.5 Hz), 3.34 (d, 1, $ArCH_2Ar$, J=13.6 Hz), 3.29 (d, 2, $ArCH_2Ar$, J=13.5 Hz), 3.23 (d, 1, $ArCH_2Ar$, J=13.5 Hz), 2.56 (s, 3, $COCH_3$), 2.53 (s, 3, $COCH_3$), 1.52 (t, 3, CH_3, J=7 Hz), 1.50 (t, 3, CH_3, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.11, 170.03 (C=O), 156.11, 155.80, 145.75, 145.49, 141.01, 140.81, 137.85, 136.18, 135.96, 135.87, 135.75, 135.68, 133.35, 133.05, 133.02, 132.75, 129.27, 129.19, 128.69, 128.28, 127.88, 127.71, 127.66, 127.60, 127.03, 126.93, 126.84, 126.71, 126.60, 124.90, 123.00 (Ar), 70.14, 70.04 (OCH_2), 31.46, 31.30, 31.26, 31.09 ($ArCH_2Ar$), 21.44, 21.39 ($CO\underline{C}H_3$), 15.80, 15.77 (CH_3); mass spectrum (EI) m/e 716 (calc. M^+ 716).

From the flash chromatographic separation the mixture of two conformers, **4b** and **4c**, was obtained: mp 170 ℃; IR (KBr) 1751 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.67-6.61 (m, 20, ArH), 4.03-3.22 (m, 12, $ArCH_2Ar$ & OCH_2), 1.75, 1.70, 1.63, 1.62 (s, 6, $COCH_3$), 1.43, (t, 3, CH_3, J=7 Hz), 1.40 (t, 3, CH_3, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.95, 171.73, 168.83, 168.74 (C=O), 155.23, 154.99, 154.96, 148.89, 148.31, 148.12, 147.67, 140.93, 140.77, 140.53, 140.46, 138.65, 138.15, 135.86, 135.63, 135.58, 135.35, 135.05, 134.27, 134.10, 134.06, 133.89, 133.76, 133.53, 133.44, 133.19, 132.71, 132.44, 132.33, 132.10, 130.54, 130.46, 129.63, 129.51, 129.45, 129.40, 128.77, 128.71, 128.60, 128.57, 128.36, 128.33, 128.00, 127.90, 127.37, 127.26, 127.22, 127.16, 127.10, 126.98, 126.72, 126.38, 126.35, 125.65, 126.07, 122.36, 122.28 (Ar), 70.09, 70.05, 69.98, 69.95 (OCH_2), 37.92, 37.90, 37.73, 37.59 ($ArCH_2Ar$), 31.06, 30.87, 30.82, 30.69 ($ArCH_2Ar$), 21.86, 21.67, 21.31, 21.29 ($CO\underline{C}H_3$), 15.91, 15.78 (CH_3).

5,11-Diphenyl-17-acetyl-25,27-dihydroxy-26,28-diethoxycalix[4]arene 5. The mixture of compound **4** (400 mg, 0.56 mmole) and aluminum chloride (447 mg, 3.35 mmole) in nitrobenzene (45 mL) was stirred for 20 hr at room temperature. After water was added solvent was removed by steam distillation, the residue was collected by filtration and dissolved in chloroform, which was washed with water and dried. The resulting slightly oily residue obtained by evaporation of solvent, was triturated with hexane to afforded the colorless solid which was purified by flash chromatography (eluent was 2 : 5 mixture of acetone and hexane) to yield 260 mg (69%) of compound **5** as colorless crystalline solid: mp 312-313 ℃; IR (KBr) 3270 (OH) 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.02 (s, 1, OH), 8.29 (s, 1, OH), 7.77-6.77 (m, 19, ArH), 4.41 (d, 1, CH_2, J=13.6 Hz), 4.39 (d, 1, CH_2, J=13.0 Hz), 4.38 (d, 1, CH_2, J=13.6 Hz), 4,34 (d, 1, CH_2, J=13.0 Hz), 4.18 (q, 2, OCH_2, J=6.9 Hz), 4.15 (q, 2, OCH_2, J=6.9 Hz), 3.53 (d, 1, CH_2, J=13.2 Hz), 3.52 (d, 1, CH_2, J=13.2 Hz), 3.48 (d, 1, CH_2, J=13.0 Hz), 3.47 (d, 1, CH_2, J=13.0 Hz), 2.46 (s, 3, $COCH_3$), 1.71 (t, 3, CH_3, J=6.9 Hz), 1.69 (t, 3, CH_3, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 197.67 (C=O), 158.92, 153.44, 138.55, 134.31, 134.13, 133.58, 133.28, 130.13, 130.02, 129.82, 129.45, 129.04, 128.94, 128.74, 128.67, 128.63, 128.51, 128.40, 128.24, 127.83, 127.74, 127.55, 127.45, 127.36, 127.25, 127.17, 126.75, 125.94 (Ar), 72.69, 72.60 (OCH_2), 32.11, 31.87, 31.80, 31.72 ($ArCH_2Ar$), 26.40 ($CO\underline{C}H_3$), 15.34, 15.30 (CH_3); mass spectrum (EI) m/e 674 (calc. M^+ 674).

Acknowledgment. The present study was supported financially from the Basic Science Research Institute Program, Ministry of Education, 1994, Project No. BSRI-94-3406 and the Organic Chemistry Research Center (OCRC). We also want to thank professor H. Jeong at Sookmyung Women's University for the HPLC analysis and to the OCRC for the use of a Varian Gemini 300 NMR spectrometer.

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