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Synthesis of *p*-Phenylcalix[5]arene

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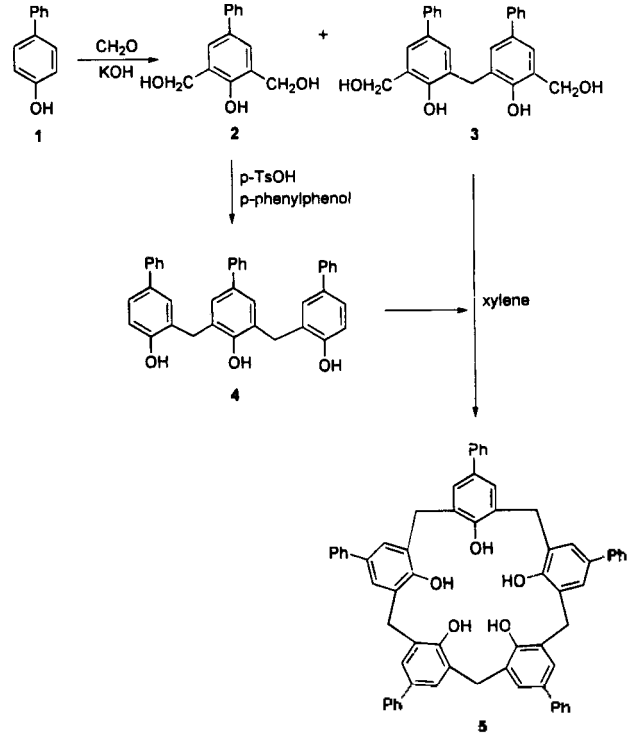
Calixarenes are macrocyclic compounds available in a variety of ring sizes and are of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.[1-3] From the standpoint of constructing an enzyme model the *p*-phenylcalix[n]arenes are specially attractive because not only do the phenyl groups increase the size of the calixarene cavity by considerable amount but they also provide potential sites at the 4' positions for the addition of functional groups. However, the chemistry of the deep-cavity calix[n]arenes has been slow to develop because of the lack of high-yield synthetic pathways. The direct base-induced condensation of *p*-phenylphenol with formaldehyde only afforded the *p*-phenylcalix[6]arene and p-phenylcalix[8]arene in low yields.[4] The *p*-phenyl-calix[4]arene was first synthesized by Gutsche and No using stepwise route in low overall yield[5,6] and an improved synthesis was reported by our laboratory[7] using the fragmentation condensation reaction between *p*-phenylphenol dimer and 2,2'-bishydroxymethylated *p*-phenylphenol dimer in the presence of $TiCl_4$. Recently, limited number of *p*-phenylcalix[4]arene derivatives were synthesized starting from the O-alkylation of the de-*tert*-butylated calix[4]arene followed by halogenation, metallation and then coupling with substituted benzene.[8-11]

On the other hand, the chemistry of calix[5]arenes is still unexplored even though they may possess a greater propensity to completely include small organic molecules than analogous calix[4]arenes due to their larger cavity size.[12-14] In 1982 Ninagawa and Matsuda[15] reported for the first time the one-step synthesis of *p-tert*-butylcalix[5]arene with *ca.* 6% yield. The yield was recently increased to 15% by Steward and Gutsche[16] to allow its chemistry to be investigated with relative ease. In 1992 Souley and coworkers[17] reported the synthesis of *p*-benzylcalix[5]arene from the reaction of *p*-benzylphenol and formaldehyde in 33% yield. However, *p*-phenylcalix[5]arene which has the deeper and larger hydrophobic cavity, was not reported and here we describe the first synthesis of *p*-phenylcalix[5]arene.

Results and Discussions

As shown in Scheme, *p*-phenylcalix[5]arene was synthesized by '3+2' fragmentation condensation reaction between *p*-phenylphenol trimer and bishydroxy-methylated *p*-phenylphenol dimer. When the mixture of *p*-phenylphenol and 35% formaldehyde was stirred for 4 days at 40 °C in the presence of potassium hydroxide, the mixture of monomer diol **2** and dimer diol **3** was resulted as white solid from which **2** and **3** could be separated in 35 and 55% yield respectively using the published procedure.[5,7,18] *p*-Phenylphenol trimer was prepared by the acid catalyzed condensation reaction between 2,6-bishydroxymethyl-4-phenylphenol **2** and *p*-phenylphenol. A solution of compound **2**, *p*-phenylphenol and *p*-toluenesulfonic acid in dioxane was refluxed to yield trimer **4** in 82% yield. Compound **4** can also be prepared in *ca.* 10% yield by the direct reaction of *p*-phenylphenol with paraformaldehyde.[20] A mixture of *p*-phenylphenol and paraformaldehyde in xylene was heated



Scheme

at 70 °C for 15 h in the presence of conc HCl. After partial removal of the unreacted *p*-phenylphenol by the fractional crystallization, the resulting residue was flash chromatographed to yield dimer and trimer of *p*-phenylphenol in 41% and 10% isolated yields. An equimolar mixture of *p*-phenylphenol trimer **4** and bishydroxymethyl dimer **3** in xylene was refluxed for 3.5 days under nitrogen atmosphere to afford *p*-phenylcalix[5]arene **5** in 20% yield. When the same reaction was carried out in the presence of conc HCl or $TiCl_4$ as catalyst, the resulting product mixture was much more complicated and the isolation of the desired product was not successful.

The structure of compound **5** was established by elemental analysis, mass spectrum and ^1H and ^{13}C NMR spectroscopy. In ^1H NMR spectrum of compound **5**, the resonance peak arising from the bridge methylene protons shows temperature dependent spectral patterns. At room temperature the pattern is a broad singlet at around 4.0 ppm, while at low temperature (−50 °C) it is AB quartet (J=14 Hz) at 4.30 and 3.24 ppm. This spectral pattern indicates the fast conformational interconversion at room temperature similarly to other calixarenes. Calix[5]arene can exist in four discrete conformational isomers.[21] ^{13}C NMR spectrum of **5**, showing 8 peaks from aromatic carbons and one peak at 31.84 ppm from the bridge methylene carbons, is also compatible with the proposed cyclic structure. The ring size of **5** was confirmed by the mass spectrum which showed molecular ion at m/e 910. We conclude that *p*-phenylcalix[5]arene, which has deeper and larger hydrophobic cavity, can be prepared in reasonable yield using the '3+2' fragmentation condensation reaction.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. 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) and Bruker AMX 500 instrument. Chemical shifts are recorded as δ values in parts per million relative to TMS (δ 0.0) as an internal standard. Elemental analyses were carried out at Organic Chemistry Research Center (OCRC). TLC analyses were carried out on silica gel plates (absorbent thickness 250 m). Flash chromatography was carried out with E. Merck silica gel (230-400 mesh ASTM). Elution rate were 2 in/min.

2,6-Bishydroxymethyl-4-phenylphenol 2 and 3-(3-Hydroxymethyl-5-phenyl-salicyl)-5-phenyl-2-hydroxybenzyl alcohol 3. were prepared in 35% and 55% yields respectively following the published procedure.[18]

2-[3-(5-Phenylsalicyl)-5-phenylsalicyl]-4-phenylphenol 4. To the heated solution of *p*-phenylphenol (4.40 g, 19.1 mmol) and *p*-toluenesulfonic acid (20 mg) in dioxane (35 mL), a solution of compound **2** (1.50 g, 6.51 mmol) in dioxane (35 mL) was added dropwise and then the reaction mixture was refluxed for 20h. After removal of solvent the resulting residue was purified by flash chromatography (eluent was 7:2 mixture of hexane and acetone) followed by a recrystallization from toluene and petroleum ether to yield the desired product (2.86 g, 82%) as a colorless powder: mp 193-194 °C; IR (KBr) 3210, 880 and 820 cm^{-1}; ^1H NMR (acetone d_6) δ 7.44-6.85 (m, 23H), 4.08 (s, 4H), 3.53 (s, 3H); ^{13}C NMR (acetone d_6): δ 154.84, 142.17, 141.95, 134.11, 133.97, 130.24, 129.60, 129.52, 128.63, 128.22, 127.28, 127.22, 126.81, 116.47 (Ar), 31.17 (CH_2); Anal. Calcd. for $C_{38}H_{30}O_3$: C, 85.37; H, 5.65. Found: C, 85.54; H, 5.68.

5,11,17,23,29-Pentaphenyl-31,32,33,34,35-pentahydroxycalix[5]arene 5. A mixture of dimer diol **3** (620 mg, 1.50 mmol) and trimer **4** (800 mg, 1.50 mmol) in xylene (100 mL) was refluxed for 3.5 days under N_2. After removal of solvent, the residue was purified by column chromatography (eluent was 6:1 mixture of hexane and acetone) to afford the calix[5]arene **5** (274 mg, 20%) as a colorless crystalline solid: mp 353-354 °C; IR (KBr) 3250 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C) δ 9.08 (s, 5H), 7.50-7.49 (m, 10H), 7.46 (s, 10H), 7.40-7.37 (m, 10H), 7.30-7.26 (m, 5H), 4.00 (br, 10H); ^1H NMR ($CDCl_3$, 50 °C) δ 9.06 (s, 5H), 7.52-7.27 (m, 35H), 4.01 (br, 10H); ^1H NMR ($CDCl_3$, 0 °C) δ 9.12 (s, 5H), 7.53-7.27 (m, 35H), 4.27 (br, 5H), 3.73 (br, 5H); ^1H NMR ($CDCl_3$, −50 °C) δ 9.25 (s, 5H), 7.56-7.23 (m, 35H), 4.30 (d, 5H, J=14.0 Hz), 3.74 (d, 5H, J=14.0 Hz); ^{13}C NMR ($CDCl_3$) δ 149.79, 140.79, 135.20, 128.70, 128.23, 127.05, 126.95, 126.87, 31.84; FAB MS 910 (M^+) (Calcd. M^+ 910); Anal. Calcd for $C_{65}H_{50}O_5$: C, 85.68; H, 5.54. Found: C, 85.49; H, 5.60.

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Improved Glass-Lined Stainless Steel Packed Microcolumns of 0.3 mm I.D.

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Scott and Kucera,[1,2] Tsuda and Novotny[3,4] and Ishii and coworkers[4-7] were the pioneers of microcolumn liquid chromatography. Techniques and designs relevant to microcolumn liquid chromatography have been continuously improved[8-21] since their work in late seventies. The necessary components of microcolumn liquid chromatography, that is, injectors with a very small sample loop, detectors with a very small flow cell, micro-flow pumps, and appropriate fittings are now commercially available.

Recently, most of the microcolumn separation tend to utilize commercial or home-made packed silica capillary columns.[22-37] On the other hand, we have tried to make use of packed glass-lined stainless steel microcolumns in our laboratory.[38-41] It seems that a mirror-like inner surface of the tubing is essential to secure good packing especially when the column diameter is smaller,[39] thus use of glass-lined stainless steel tubing is justified. The merit of glass-lined stainless steel tubing over silica capillaries is its solidity and convenience of handling. Very good care should be taken to prepare and use packed silica capillary columns because of their fragility.

So far, we have obtained numbers of theoretical plates of *ca.* 20,000 for columns of 0.5 mm I.D. (30 cm length),[41] and 10,000 for columns of 0.3 mm I.D.[40] In this study, we have improved the column packing procedure, and have achieved numbers of theoretical plates of 20,000 for columns of 0.3 mm I.D.

Experimental

A Shimadzu (Tokyo, Japan) 10AD pump, an Isco (Licoln, USA) CV4 capillary window detector, a Valco (Houston, USA) Cl4W.05 injector with a 50 nL injection loop, and a Younglin (Seoul, Korea) D520B computing integrator were combined to construct the appropriate micro-LC system.

Methanol was of HPLC grade and obtained from Fisher (Pittsburg, USA) and used without further purification. We chose *p*-nitroaniline, N,N-dimethyl-*o*-nitro-*p*-toluidine, and propylbenzene as the test solutes considering their polarity range and retention times. *p*-Nitroaniline and propylbenzene were purchased from Aldrich (Milwaukee, USA) as reagent grade and used without further purification. N,N-dimethy-*o*-nitro-*p*-toluidine was synthesized in our laboratory.[42]

The Adsorbosphere C18 (5 μ) stationary phase, glass-lined stainless steel tubing, and fitting elements were purchased from Alltech (Deerfield, USA).

We took special care in preparing microcolumns to minimize the extracolumn void volume. The column is directly connected to the injector without any connecting tubing or frit. We prepared a fritted silica tubing (5 cm, 50 μ I.D.) by putting a tiny amount of silica particles at the tip and sintering them on a propane flame,[40] and attached it to the column outlet. The detector optical window was prepared by burning a portion of the polymer coating of a 15 cm silica capillary (50 I.D.) and by introducing the capillary into the cell bolck until the optical window reached the appropriate position. The silica capillary of the column outlet and the silica capillary of the optical window were connected through a glass connector. The extracolumn void volume including the sampling loop of the injector and the inner volume of the transfer line between the column and the detector is estimated *ca.* 0.6 μL. The total mobile phase volume in the column (0.3 mm I.D., 30 cm length) is estimated 21.2 μL assuming the overall column porosity is 0.6.

The Alltech (Deerfield, USA) slurry packer was used to make microcolumns. The stationary phase was dried at 90 °C for 4 hours. The slurry was made by mixing 30 mg particles with 2 mL methanol, and was sonicated for 20 min. before packing. The slurry was transfered to the slurry reservoir (1.2 mL), and the pressure of the slurry packer was raised to 14,000 psi instantly. The pressure was maintained for 2 min., and decreased to 10,000 psi, and the final pressure was maintained for 10 min. The reservoir and the column were continuously vibrated while packing.

The chromatograms of the three test solutes were monitored at 254 nm. The eluent was 100% metanol. The flow rates were varied within 0.001-0.01 mL/min. The retention time and peak width at half height of each solute were measured to compute the number and height equivalents of