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Synthesis of azacalix[4]arene betaine

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Abstract

Azacalix[4]arene betaine, which possesses intramolecular positive and negative charges, was synthesized. *N,N'*-Dimethylazacalix[4]arene was prepared by a simple procedure and subsequent *N*-quaternarization afforded the *N,N,N',N'*-tetramethyl diammonium compound. It was converted into the betaine structure in methanol at pH 9.

Keywords: betaines; zwitterions; cyclophanes; calixarenes; macrocycles.

Our continuing studies on azacalix[*n*]arenes revealed a new approach to the construction of host molecules. A wide variety of applications for guest bindings are expected due to the bifunctional structures containing nitrogen and oxygen donor atoms. In previous reports, the synthesis and properties of the azacalix[*n*]arenes, which have benzyl side arms, were described.[1] In order to construct new host molecules employing the structural features of the azacalixarenes, we designed compound **1**, which possesses positive and negative charges in its molecule. Only a few reports concerned with related compounds are known.[2]

Although the conventional azacalixarene derivatives could be easily obtained by the direct coupling reaction between bis(hydroxymethyl)phenol derivatives and benzylamines, the NMR spectra become complex because the methylene and aromatic signals overlap with those of the side arms. In addition, several attempts to synthesize the azacalixarene betaine starting from *N*-benzyl derivatives gave poor results. The bulky benzyl side arms prevent smooth *N*-quaternarization. In order to simplify the spectra and reduce the steric hindrance caused by the *N*-quaternarization, we developed the synthetic method of *N*-methylazacalixarene derivative.

Heating an excess of aqueous methylamine (>10 equiv.) with diphenol **5** in ethanol at 50–55°C for 24 h yielded a yellow resinous product. This is the precursor of the cyclic product.

The precursor was heated in refluxing toluene for 48 h. Concentration of the reaction mixture gave a colorless powder, which was recrystallized from cyclohexane. The desired *N,N'*-dimethyltetrahomodiazacalix[4]arene **2** was obtained in 44% yield. When using aq. $MeNH_2$ in a

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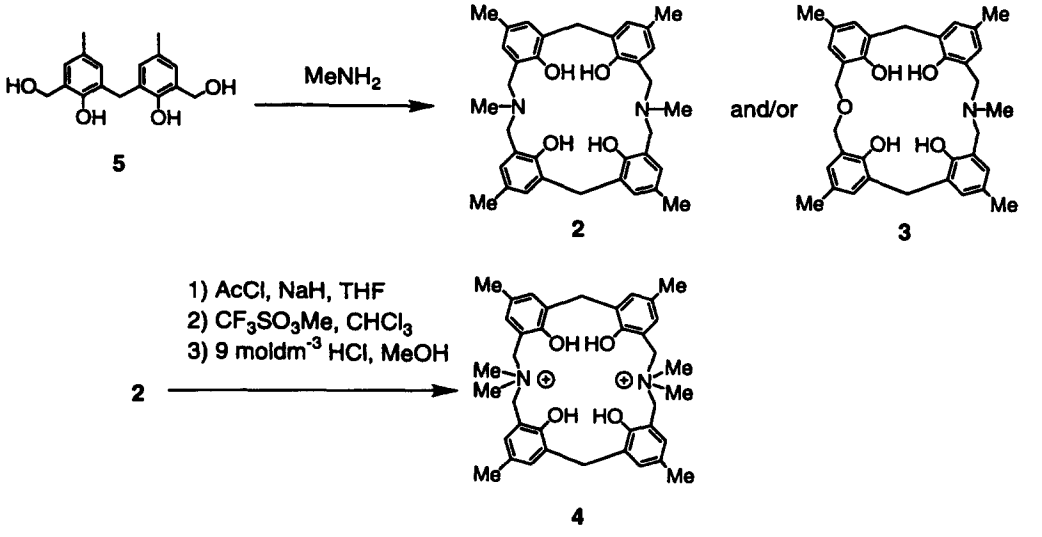
stoichiometric amount or less than 5 molar excess, azaoxacalix[4]arene **3** was obtained in 23% yield (Scheme 1). This is also an interesting cyclic product since it has OH, -O-, and -N donor moieties in its structure. Since direct methylation of **2** did not afford **4**, the phenolic OH groups were protected with an acetyl group. Quaternarization of the nitrogen of the tetraacetyl compound was performed by using CF_3SO_3Me, a strong methylating reagent. The reaction was completed in 3 h at room temperature in $CHCl_3$. Other common methylating reagents, i.e. MeI or Me_2SO_4, gave poor results. Deprotection of the tetraacetyl ammonium compound was achieved by heating the compound with 9 mol/dm^3 HCl in methanol. The compound **4** was precipitated from the solution in the pure form. The overall yield starting from **2** was 41%.



Scheme 1.

In contrast to the *N*-benzylazacalixarene series, intramolecular hydrogen bonds were not very strong in compounds **1**–**4**.[1] In the ^{1}H NMR spectra, the OH signals of **2** ($CDCl_3$) and **4** (DMSO-d_6) appeared at 9.8 and 9.7 ppm, respectively.[3] The OH signal of **1** ($CDCl_3$ and/or DMSO-d_6) was not observed because of the complete broadening of the signal due to the proton exchange. In the IR spectra of **1** and **4**, ν_{OH} signals appeared as very broad bands centered at 3420 and 3365 cm^{-1}, respectively. These are in sharp contrast to the calix[4]arene (3164 cm^{-1}) or dihomooxacalix[4]arene (3300 cm^{-1}) in which the ν_{OH} signal appear as relatively sharp bands.[3] The pH-metric titration was carried out in order to estimate the pKa values of each phenolic OH group. Since the compound **4** was insoluble in water, the measurement was performed in methanol. As a result, pK_1=4.50, pK_2=6.17, pK_3=11.88, and pK_4=12.01 were obtained. Under the same conditions, the pKa values of the reference compound, 2,2′-methylenebis(*p*-methyl)phenol were estimated to be pK_1=10.48 and pK_2=11.68. Because of the charge repulsion, pK_1 and pK_2 of **4** are significantly shifted to the acidic region, but pK_3 and pK_4 are in the basic region. The distribution of each species is calculated and shown in Fig. 1. The desired betaine species predominates over a wide range of pH (8–10). Therefore, the betaine was easily isolated as stable crystals by treatment of the methanol solution of **4** with $NaHCO_3$. Betaine **1** was obtained as a precipitate, which was fully characterized by NMR, MS, and elemental analysis.[4] Unfortunately, a single crystal suitable for X-ray crystallographic analysis was not obtained in spite of several attempts. In the ^{1}H NMR spectra in $CDCl_3$, the methylene signals appeared as four broad singlets at room temperature, which coalesced at 50°C (in DMSO-d_6, the signals became two broad singlets corresponding to -CH_2-N-CH_2- and Ar-CH_2-Ar above 70°C). At low temperatures, the signal became two pairs of doublets below 10°C. Aromatic signals appeared as

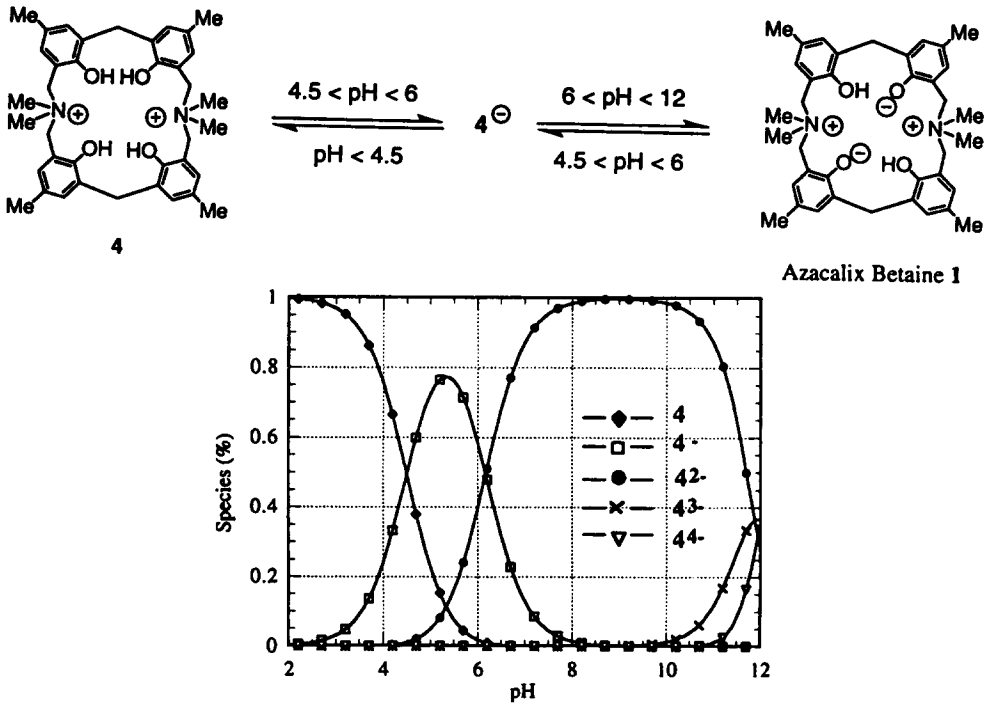


Figure 1.

two singlets which were not changed over a wide range of temperatures (50–70°C). According to this spectral pattern, the predominant conformation of the betaine **1** at low temperature is anticipated to be a cone or alternate conformer in which the two aromatic rings connected to -CH_2-N-CH_2- are inverted. The studies of the inclusion properties for amino acids, cations or anions are now underway.

Acknowledgements

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4. *N,N'*-Dimethyl-*p*-methyl-tetrahomoazacalix[4]arene **2**. Mp (from cyclohexane) 224°C; ^{1}H NMR (400.1 MHz, 25°C, $CDCl_3$, TMS) δ 9.78 (4H, br s, OH), 7.05 (4H, s, Ar-H), 6.69 (4H, s, Ar-H), 4.0 (8H, br s, -CH_2-N), 3.4 (4H, br s, Ar-CH_2-Ar), 2.23 (12H, s, Ar-CH_3), 1.98 (6H, s, N-CH_3,); IR ν_{max} (KBr, cm^{-1}), 3185 (OH); *m/z* (FAB) 567 ($M+H^+$).

Anal. calcd for $C_{36}H_{42}N_2O_4$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.36; H, 7.42; N, 4.73. *N*-Methyl-*p*-methyl-tetrahomoazaoxacalix[4]arene **3**. Mp (from toluene) 249–250°C; ^{1}H NMR (400.1 MHz, 25°C, $CDCl_3$, TMS) δ 8.94 (4H, br s, OH), 7.10 (2H, d, *J*=2 Hz, Ar-H), 7.06 (2H, d, *J*=2 Hz, Ar-H), 6.77 (2H, d, *J*=1.5 Hz, Ar-H), 6.70 (2H, d, *J*=1.5 Hz, Ar-H), 4.56 (4H, s, -O-CH_2-), 3.87 (4H, s, -CH_2-N), 4.02 (2H, d, *J*=12 Hz, Ar-CH_2-Ar), 3.32 (2H, d, *J*=12 Hz, Ar-CH_2-Ar), 2.24 (6H, s, Ar-Me), 2.22 (6H, s, Ar-Me), 2.05 (3H, s, N-CH_3); IR ν_{max} (KBr, cm^{-1}), 3298 (OH); *m/z* (FAB) 554 ($M+H^+$). Anal. calcd for $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N, 2.53. Found: C, 75.93; H, 7.09; N, 2.37. *N,N,N',N'*-Tetramethyl-*p*-methyl-tetrahomoazacalix[4]arene dihydrochloride **4**. Mp (from MeOH/H_2O) 190°C (dec.); ^{1}H NMR (400 MHz, 25°C, CD_3OD, TMS) δ 7.29 (4H, s, Ar-H), 7.16 (4H, s, Ar-H), 4.52 (8H, br s, N-CH_2-), 3.92 (4H, br s, Ar-CH_2-Ar), 2.76 (12H, s, N-Me), 2.30 (12H, s, Ar-Me); IR ν_{max} (KBr, cm^{-1}) 3365 (OH); *m/z* (FAB) 595 ($M-H^+$). Anal. calcd for $C_{38}H_{48}N_2O_4Cl_2 \cdot 2H_2O$: C, 64.86; H, 7.45; N, 3.98. Found: C, 64.63; H, 7.38; N, 3.94. Betaine **1**. Mp (from $CHCl_3$) 179–180°C; ^{1}H NMR (400.1 MHz, 25°C, $CDCl_3$, TMS) δ 7.10 (4H, s, *J*=2Hz, Ar-H), 6.70 (4H, s, Ar-H), 5.35 (4H, br s, N-CH_2-), 4.48 (2H, br s, Ar-CH_2-Ar), 3.68 (4H, br s, N-CH_2-), 3.37 (2H, br s, Ar-CH_2-Ar), 2.76, 2.54, 2.40 (12H, br s, N-Me), 2.19 (12H, s, Ar-Me); ν_{max} (KBr, cm^{-1}) 3421 (OH); *m/z* (FAB) 595 ($M+H^+$). Anal. calcd for $C_{38}H_{46}N_2O_4 \cdot CHCl_3 \cdot 1/2H_2O$: C, 64.77; H, 6.69; N, 3.87. Found: C, 65.07; H, 6.59; N, 3.91.