Azacalixarenes: New Macrocycles with Dimethyleneaza-Bridged Calix[4]arene Systems

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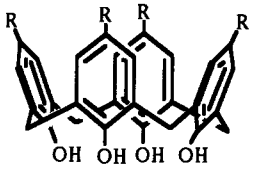
Received June 25, 1992 (Revised Manuscript Received February 12, 1993)

Introduction

Calixarenes[1] continue to attract attention from chemists because of their remarkable ability to act as selective ion carriers[1,2] and host molecules for inclusion of organic compounds.[1,3] These properties are most pronounced in calix[4]arene and its derivatives because these compounds adopt cone conformations.[4-6] The cyclic array of four hydroxyl groups at the lower rim of these molecules not only creates a preference for the cone conformation through strong intramolecular hydrogen bonding but also contributes to cation binding and transport functions.[1,7] However, the small size of the cavity and the mobile nature



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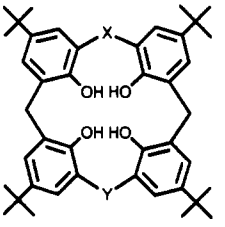

2; X= CH_2OCH_2, Y=CH_2
3; X= Y= CH_2OCH_2

of these compounds in solution leads to rapid inversion and other conformational changes at room temperature (other conformations include partial cone and 1,3- and 1,2-alternate).[4,8] The conformational instability of calix[4]arene derivatives provides a genuine cause for designing a wide variety of new calixarene analogues.

Efforts have also been made to synthesize calixarenes larger than calix[4]arenes. For this purpose, calix[*n*]arenes (*n* = 5-8)[9-11] and oxacalixarenes,[12,13] constructed by changing the methylene bridges ($-CH_2-$) in calixarene to dimethyleneoxa bridges ($-CH_2OCH_2-$), have been reported. The increased conformational mobility of the larger calixarenes however, makes the preferred conformation increasingly planar,[4a] and the increased planarity makes their architecture even less appropriate for inclusion.

Several approaches have been developed for the synthesis of conformationally rigid calix[4]arenes in solution, e.g., the introduction of suitable substituents on the phenolic oxygen atoms[14,15] and the connection of the two opposite para positions of calixarene units by an aliphatic chain (bridged calix[4]arenes).[16,17] The former approach has been widely applied, but it is accompanied by complete or partial disruption of the cyclic array of intramolecular hydrogen bonds. The latter approach leads to steric crowding in the open face of calixareenes.

The substitution of a methylene bridge of calix[4]arenes by a methyleneaza bridge ($-CH_2NHCH_2-$) provides novel homoazacalix[4]arenes. Participation of the nitrogen lone pairs in intramolecular hydrogen bonds leads to properties different from those of the corresponding homooxacalix[4]arenes. We describe here the synthesis and conformational behavior of these new types of macrocyclic compounds.

Results and Discussion

Synthesis. Azacalixarenes **6** and **7** were obtained by a slight modification of our previously communicated method[18] as outlined in Scheme I. Treatment of bis(hydroxymethyl)-*tert*-butylphenol tetramer (**4**) or dimer[12] (**5**) with benzylamine in refluxing xylene with continuous azeotropic removal of water afforded dihomoaza- and tetrahomodiazacalix[4]arenes **6** (22%) and **7** (20%), respectively. Predominant formation of macrocycles suggests that in nonpolar solvents like xylene the cyclization proceeds under the influence of the template effect of hydrogen bonding among the four hydroxyl groups and the nitrogen lone pairs.

VT ^{1}H NMR Study. The ^{1}H NMR spectrum of **6** is quite different from that of dihomooxacalix[4]arene **2**, which shows broad and featureless signals at room temperature.[4a] At 25 °C in $CDCl_3$, the aromatic protons

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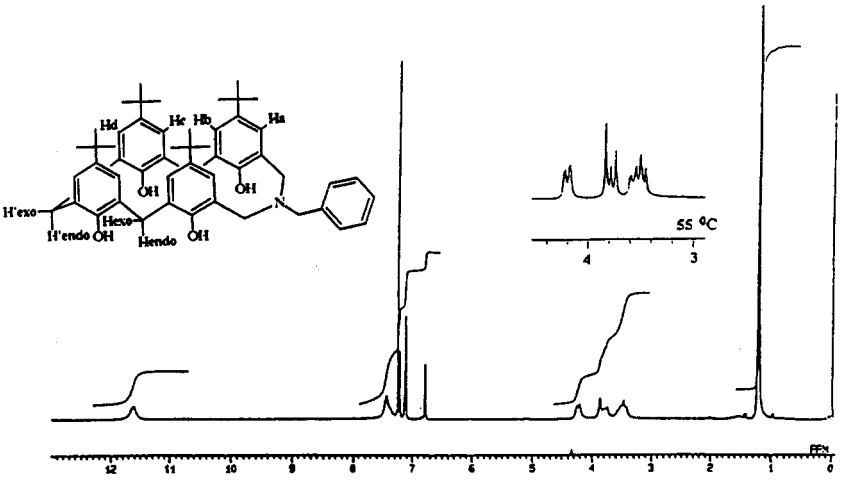
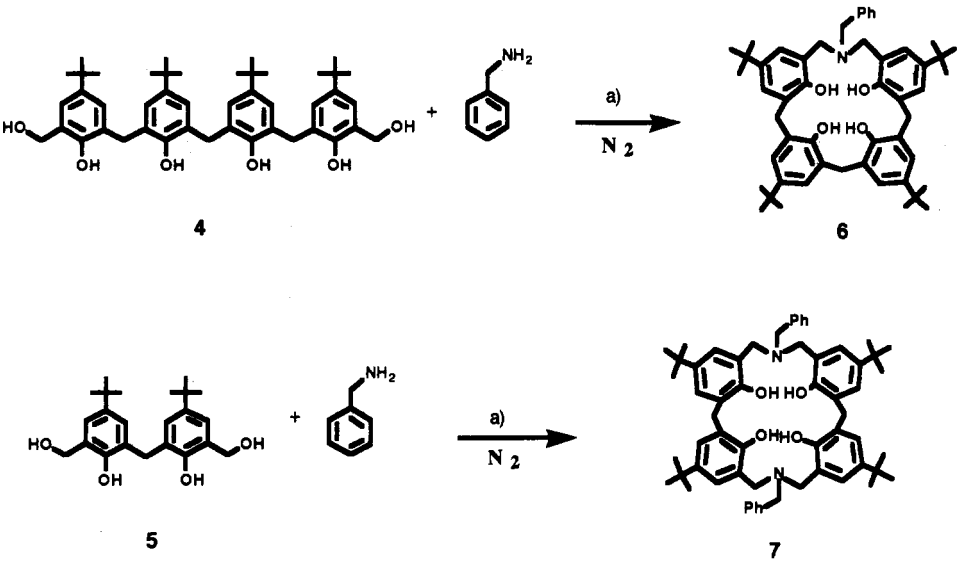


Figure 1. ^{1}H NMR spectrum of *p-tert*-butyldihomoazacalix[4]arene **6** at 24 °C (270 MHz, $CDCl_3$).

Scheme I. Synthesis of Azacalixarenes 6 and 7[a]



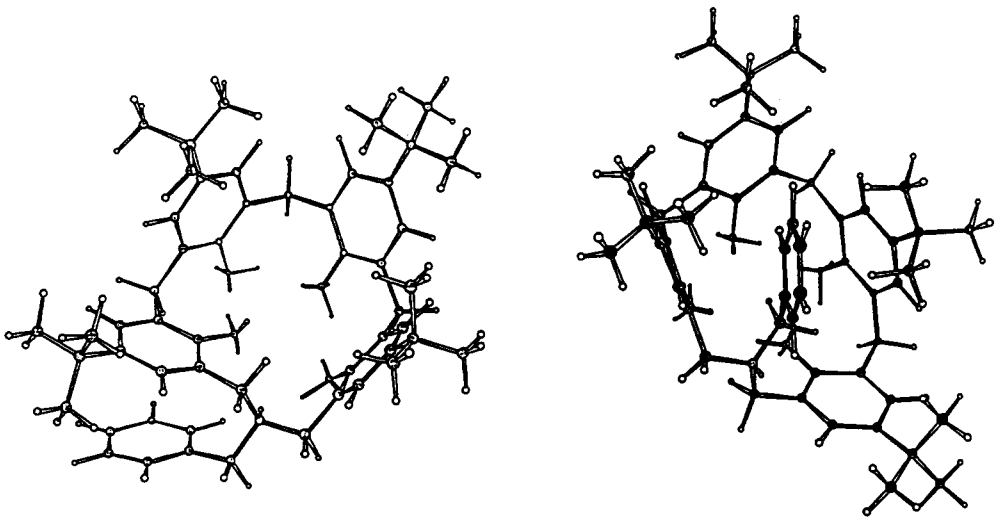
[a] Key: (a) 140 °C, 24 h, $-H_2O$.

of **6** display three sharp doublets [δ 6.80 (J = 2 Hz, H_a), 7.12 (J = 2 Hz, H_b), 7.22 (J = 2 Hz, $H_c + H_d$)] and a broad signal (δ 7.44) for the pendent benzylic group (Figure 1). The benzylic protons appear as two pairs of doublets that overlap with the singlet due to the NCH_2Ph group. The pair with the larger chemical shift difference is assigned to the methylene protons of $ArCH_2Ar$ [δ 3.45 (J = 13 Hz, Hexo, H'exo), 4.24 (J = 13 Hz, Hendo + H'endo)], and the other pair is ascribed to the dimethyleneaza protons [δ 3.50 (J = 13 Hz), 3.77 (J = 13 Hz)]. These assignments, which are based upon the proton integral ratio and NOE experiments, suggest that **6** adopts a cone conformation in solution.

A pair of doublets corresponding to the bridging methylene protons in **6** did not coalesce below 55 °C, the highest available temperature, in $CDCl_3$. The VT ^{1}H NMR spectra in solvents such as toluene, xylene, and DMSO show that the conformational inversion of the aryl ring is restricted over a wide range of temperatures; the characteristic pattern of doublets is retained in toluene-d_8 up to 90 °C. The doublets coalesce in xylene-d_{10} at 110 °C. The conformational inversion barrier ($\Delta G^{\ddagger}$)[19] is estimated to be 17.8 kcal/mol, 4.8 or 2.1 kcal/mol ($CDCl_3$) higher than that of dihomooxacalix[4]arene or calix[4]arene, respectively.[4a] In DMSO-d_6, the coalescence temperature (T_c) is lowered to 72 °C ($\Delta G^{\ddagger}$ = 15.9 kcal/mol). This decrease in T_c is attributed to the disruption of the intramolecular hydrogen bonds, which contribute to the conformational stability of **6**.

The optimized structures of **6** obtained from molecular mechanics calculations (MM2, Chem 3D plus) are shown in Figure 2. Both of the energy minimum structures, **6a** and **6b**, adopt a cone conformation. The reliability of the calculation results is questionable because they do not take the hydrogen bonds into account. Our expectation that **6a**, in which the lone pair of electrons is in the proximity of the cyclic array of hydroxyl groups, is likely to be favored is confirmed by analysis of the VT ^{1}H NMR spectra at lower temperature. The ^{1}H NMR shows that even when **6** is fixed in a cone conformation, a slow conformational change continues to occur in another part of the molecule; the azamethylene ($-CH_2NHCH_2-$) groups undergo inward and outward flexing movement, and in

(19) $\Delta G^{\ddagger}$ was calculated by the following equation $\Delta G^{\ddagger}$(kcal/mol) = $2.987T_c(10.319 - \log_{10} k_c + \log_{10} T_c)$ where $k_c = (\pi/\sqrt{2})[(\nu_A - \nu_B)^2 + 6J^2]^{1/2}$. Kurland, R. S.; Rubin, N. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426–2427.



6a 6b

Figure 2. Energy-minimized conformations of *p-tert*-butyldihomoazacalix[4]arene **6** obtained from molecular mechanics calculations (MM2 Chem 3D).

Table I. Coalescence Temperatures (T_c) and Free Energies of Activation ($\Delta G^{\ddagger}$) for Conformational Inversion of the Aryl Ring in Various Calixarenes

	T_c, °C	solvent	$\Delta G^{\ddagger}$, kcal/mol
calix[4]arene[a] 1	52	$CDCl_3$	15.7
dihomooxacalix[4]arene[a] 2	−2	$CDCl_3$	13.0
tetrahomodioxacalix[4]-arene[a] 3	−40	$CDCl_3$	11.9
dihomoazacalix[4]arene 6	>55	$CDCl_3$	
	>90	toluene-d_8	
	72	DMSO-d_6	15.9
	110	xylene-d_{10}	17.8
tetrahomodiazacalix[4]-arene 7	40	$CDCl_3$	14.4

[a] Reference 4a.

fact, the phenomenon seems to be involved in the interconversion of **6a** and **6b**. At 0 °C, the process is slowed down on the NMR time scale, and one pair of doublets corresponding to these protons changes to a broad singlet. Further lowering of the temperature to −80 °C results in complete freezing of this movement, and the pair of doublets at higher field reappears as two new sets of resonances in the same range as those observed in the higher temperature spectrum. The fact that two azamethylene and four hydroxyl signals (discussed latter) are in different chemical environments agrees with the NMR behavior of **6a**.

The phenolic hydroxyl groups of **6** appear at 11.6 ppm (the lowest value in the calixarenes) as a singlet at 25 °C. The tendency of the nitrogen long pair to form a favorable hydrogen bond with the nearest phenolic hydroxyl protons increases the exchange rate of the hydroxyl protons compared to those of simple calixarenes, and on the NMR time scale it is impossible to differentiate between the protons near to and far from the nitrogen. Lowering the temperature to −50 °C slows down the rate of exchange as well as the conformational process of the movement of nitrogen described above. The two hydroxyl groups that are in the proximity of the nitrogen lone pair are more affected by this change, and they appear at 12.8 ppm, whereas the remaining two appear at 9.8 ppm. When the sample is further cooled to −80 °C, conformationally frozen **6a**, in which all of the hydroxyl groups are nonequivalent, is a major conformer. The ^1H NMR spectrum at this temperature shows signals for hydroxyl groups at 13.8, 12.2, 9.8, and 9.0 ppm in an integral ratio of 1:1:1:1 in addition to the small signals for minor isomer **6b**.

The VT ^1H NMR study of **7** indicates that it is a more flexible molecule than **6**. The ^1H NMR at 25 °C shows three aromatic signals [δ 6.87 (d, J = 2 Hz), 7.30 (d, J = 2 Hz), 7.37 (broad s)] and a broad signal at 10.7 ppm for the OH protons. The benzylic protons again appear as two pairs of doublets, and this pattern is quite pronounced at −10 °C. From the results obtained from NOE experiments, the pair of doublets with the larger chemical shift difference is assigned to the methylene protons of $ArCH_2$-Ar [δ 3.45 (J = 14 Hz), 4.39 (J = 14 Hz)], and the pair appearing at relatively higher field is ascribed to the azamethylene protons [δ 3.49 (J = 11 Hz), 3.69, (J = 11 Hz)]. In $CDCl_3$, the coalescence temperature of the methylene protons of $ArCH_2Ar$ is 40 °C, which corresponds to a free energy barrier ($\Delta G^{\ddagger}$) of 14.4 kcal/mol. The lower $\Delta G^{\ddagger}$ value for aryl ring inversion of **7** compared with that of **6** is explained by the weakened hydrogen bonds and the increased ring size in **7**. The coalescence temperatures and inversion barriers for the various calixarenes are summarized in Table I.

IR Spectra. The infrared spectra of calix[4]arenes are characterized by their low stretching OH frequencies due to strong hydrogen bonds. The ν_{OH} values for azacalixarenes **6** and **7** and hexahomotriazacalix[3]arenes **8**[18]

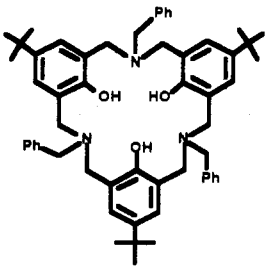


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Table II. Frequencies of the O–H Stretching Vibrations (KBr Disks) and the Chemical Shifts of the Phenol OH Protons ($CDCl_3$) in Various Calixarenes

	ν_{OH}[a] (cm^{-1})	δ_{OH}[b] (ppm)
calix[4]arenes[c] 1	3160	10.2
dihomooxacalix[4]arenes[c] 2	3300	9.0, 9.7
tetrahomodioxacalix[4]arenes[c] 3	3370	9.0
dihomoazacalix[4]arenes 6	2700	11.6
tetrahomodiazacalix[4]arenes 7	3000	10.7
hexahomotriazacalix[3]arenes 8	2800	11.2

[a] KBr disk. [b] $CDCl_3$. [c] Reference 4a.

appear as broad signals at much lower frequencies than those of the corresponding oxa analogues (2 and 3) and calix[4]arene (1) itself. This result also suggests that participation of the nitrogen lone pairs in the hydrogen bonds of the cyclic array of four hydroxyl groups further strengthens the hydrogen bond. The ν_{OH} values and the chemical shifts of the phenolic hydroxyl protons of various calixarenes are summarized in Table II.

Conclusion

Our new synthetic method provides a facile route to azacalix[4]arenes, novel calix[4]arene derivatives. The ^1H NMR studies prove that azacalixarenes 6 and 7 are highly rigid molecules that exist in cone conformations over a wide range of temperatures in various solvents. The result differs from the expectation that the conformational flexibility of the calixarenes would increase with increasing ring size. The rather unusual conformational rigidity of 6 and 7 can be ascribed to the strengthening of the hydrogen bonds caused by the participation of the properly positioned nitrogen lone pair in hydrogen bonds with the cyclic array of hydroxyl groups. Such interactions in intermolecular phenol–amine systems have already been investigated, and stable complexes have rarely been isolated and characterized.[20]

Azacalixarenes are much more soluble in organic solvents than calixarenes and oxacalixarenes. Taking advantage of this property, we are now studying the use of azacalixarenes for lanthanide ion binding and inclusion hosts for large neutral organic guests.

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Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at either 270 or 400 MHz in $CDCl_3$ unless otherwise indicated. The EI spectrum of 6 was obtained at an ionization energy of 70 eV. The FAB mass spectrum of 7 was recorded with *m*-nitrobenzyl alcohol as a matrix. Wako gel C 300 and Merck 60 PF_{254} were used for column chromatography and preparative TLC, respectively.

General Procedure for the Preparation of Azacalixarenes 6 and 7. A solution of bis(hydroxymethyl)-*p-tert*-butylphenol tetramer 4 or dimer 5 (6 mmol) and of freshly distilled benzylamine (6 mmol) in xylene (70 mL) was refluxed for 24 h under an atmosphere of N_2. Water formed during the course of the reaction was removed by a Dean-Stark trap. The mixture was allowed to cool, and the xylene was removed under reduced pressure. The resulting yellow solid was subjected to silica gel column chromatography. The column was first eluted with CH_2Cl_2 until the eluate did not contain any aromatic substance. This procedure eliminated most byproducts, such as calixarenes and oxacalixarenes. Then the column was eluted with 3% acetone in CH_2Cl_2 to afford the crude product. Further purifications are described for the specific compound.

***N*-Benzyl-7,13,19,25-tetra-*tert*-butyl-27,28,29,30-tetrahydroxy-2,3-dihomo-3-azacalix[4]arene (6).** The crude product was washed with acetone, and the resulting white solid was recrystallized from cyclohexane to give transparent needles in 22% yield: mp 253–255 °C; IR (KBr) ν_{OH} 2750 cm^{-1}; MS *m/z* M^+ 768. Anal. Calcd for $C_{52}H_{65}NO_4$: C, 81.31; H, 8.53; N, 1.82. Found: C, 81.18; H, 8.49; N, 1.72.

***N,N*-Dibenzyl-7,13,21,27-tetra-*tert*-butyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazacalix[4]arene (7).** The crude product was recrystallized twice from CH_3OH/CH_2Cl_2 to afford 7 as a white powder in 20% yield: mp 210–211 °C; IR (KBr) ν_{OH} 3000–2800 cm^{-1}; FABMS *m/z* $(M + H)^+$ 887. Anal. Calcd for $C_{60}H_{74}N_2O_4$: C, 81.22; H, 8.40; N, 3.15. Found: C, 80.95; H, 8.39; N, 3.21.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 04217103) from the Ministry of Education, Science and Culture of Japan. We are very grateful to the Ministry for the award of scholarship to I.U.K. for study at Kyushu University. We also thank Dr. Yuji Miyahara for helpful discussions and Miss Mie Tomono for 400-MHz ^1H NMR measurements.