

Complexation and Conformational Flexibility of Calix[4]arene Dibenzo-crown Ethers

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1,3-Dipropylcalix[4]arene dibenzocrown ethers were synthesized in the fixed 1,3-alternate conformation by the reaction of 1,3-dipropylcalix[4]arenes with a dibenzo dimesylates. Complexation toward alkali metal ions using ISEs showed a high cesium selectivity. Conformational flexibility of the corresponding 1,3-alternate calixcrown ether (**4**) with respect to the NMR time scale is found to depend on the temperature and polarity of the NMR solvent.

Introduction

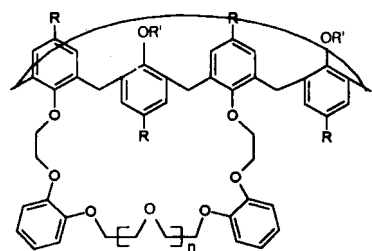
Calix[4]arene molecules, cyclic tetramers of phenols, are a useful three dimensional molecular building blocks for the synthesis of molecules with specific properties.¹ 1,3-Distal capping of calix[4]arene at the lower rim has been achieved with polyether linkages to produce calixcrown ether,² calix-doubly-crown,³ and double-calix-crown compounds.⁴ Recently, it was reported that the 1,3-alternate conformation of 1,3-dialkoxycalix[4]arene-crown-6 showed a high cesium selectivity.⁵ In addition, it has been reported that introducing aryl substituents, such as phenyl or naphthyl, into the polyether ring greatly enhances the carrier lipophilicity which favors the stability of supported liquid membranes and their cesium selectivity over other alkali metal ions.⁶ Recently, we reported that calix[4]arene dibenzocrown ethers (**1** and **2**) were successfully synthesized and the corresponding cavity size of crown ether linkage in compound **2** was found to be too large to complex selectively with cesium ion.⁷ Now we report the preparation of a series of calixcrown ethers in which propyl is substituted on phenoxy group and two lipophilic benzo groups connected with

diethylene glycol. Measurement of their potentiometric selectivity in ion-selective electrodes (ISEs), and their conformational flexibility by ¹H NMR spectroscopy are now reported.

Experimental

Chemical Analysis. Melting points were taken by the use of a Mel-Temp of Fisher-Johns melting point apparatus without any correction. IR spectra were obtained with a Perkin-Elmer 1600 Series FT-IR on potassium bromide pellet and on deposited KBr window in the case of solid product and oil, respectively, are recorded in reciprocal centimeters. ¹H and ¹³C NMR spectra were recorded with a 400 MHz (Bruker ARX-400) and an 100 MHz spectrometer, respectively, the chemical shifts (δ) reported downfield from the internal standard, tetramethylsilane. Elemental analysis was performed by Vario EL of Elemental Analyzer in Korea Basic Science Institute in Seoul, Korea. FAB⁺ mass spectra were obtained from JEOL-JMS-HX 110A/110A High Resolution Tandem Mass Spectrometry in Korea Basic Science Institute in Taejeon, Korea.

Chemicals. Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Dry solvents were prepared as follows: dichloromethane was freshly distilled from lithium aluminum hydride. Acetonitrile was pre-dried from molecular sieves (3 Å and distilled over diphosphorous pentoxide. 1,5-Bis[2-(2'-methanesulfonyloxyethoxy)phenoxy]-3-oxapentane (**7**) and precursors were prepared by adaptation of reported procedures.⁷⁻¹⁰ Poly(vinyl chloride) (PVC) with an average polymerization degree of 1,100 was purchased from Waco Pure Chemical Industries. o-Nitrophenyloctyl ether (NPOE) and potassium tetrakis(*p*-chlorophenyl)borate (KTPCIPB) were obtained from Dojindo Lab. Deionized water was prepared by passing distilled water through an Organo G-10 cartridge.



	n	R	R'
1	1	H	allyl
2	2	H	allyl
3	1	H	propyl
4	1	<i>t</i> -butyl	propyl

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ments. PVC (50 mg), NPOE (100 mg), the calixarene crown ether (5.0 mg), and KTpCIPB (1.0 mg) were dissolved in 1.5 mL of THF. The aliquot of THF solution was poured onto a porous poly(tetrafluoroethylene) (PTFE) membrane attached to a PVC tube, and the solvent was allowed to evaporate for 10-20 min. Addition of the THF solution and evaporation were repeated ten times. The resulting PVC tube with the coated PTFE membrane was fixed on a DKK No. 7900 (Denki Kagaku Keiki, Musashino, Tokyo, Japan) electrode body. Potentiometric measurements with a membrane electrode were carried out at 24-25 °C with a voltage meter (Fisher Scientific Accumet 50 pH meter), a double-junction Ag-AgCl reference electrode (DKK No 4083), and a magnetic stirrer to agitate the sample solution. Selectivity coefficients ($K_{Cs,M}^{Pot}$) were determined by the fixed interference method.¹¹

Synthesis. **25,27-Bis(1-propyloxy)calix[4]arene dibenzocrown-7,1,3-alternate (3).** 25,27-dipropyloxy-calix[4]arene **5** (1.00 g, 2.0 mmole) was dissolved in 50 mL of acetonitrile and added an excess of Cs_2CO_3 (1.62 g, 5.0 mmole) and 1,5-bis[2-(2-mesyloxyethoxy)phenoxy]-3-oxapentane (**7**) (1.12 g, 2.1 mmole) under nitrogen atmosphere. The reaction mixture was refluxed for 24 h. The acetonitrile was removed *in vacuo* and the residue was extracted with 100 mL of methylene chloride and 50 mL of 10% aqueous HCl solution. The organic layer was separated and washed twice with water. The organic layer was separated and dried over anhydrous magnesium sulfate, and then concentrated *in vacuo* to give a brownish oil. With TLC analysis, the crude product shows an only one spot (R_f = 0.4, ethyl acetate : hexane = 1 : 4 as enveloping solvents). Filtration column chromatography with ethyl acetate : hexane = 1 : 6 as eluents provided the pure product: 90% yield; mp 178-181 °C; IR (KBr pellet, cm^{-1}): 3068 (Ar-H), 1501, 1451, 1254, 1196; 1H NMR ($CDCl_3$) δ 7.02-6.87 (m, 16H), 6.78-6.70 (m, 4H), 4.22 (t, $J=5.1$ Hz, 4H), 4.08 (t, $J=5.1$ Hz, 4H), 3.89 (t, $J=5.1$ Hz, 4H), 3.76 (t, $J=5.1$ Hz, 4H), 3.70 (s, 8H, $ArCH_2Ar$), 3.41 (t, $J=7.4$ Hz, 4H, $OCH_2CH_2CH_3$), 1.47-1.38 (m, $J=7.4$ Hz, 4H, $OCH_2CH_2CH_3$), 0.77 (t, $J=7.4$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): ppm 157.4, 156.8, 150.7, 149.8, 134.4, 134.3, 130.6, 130.5, 123.1, 122.8, 122.6, 122.3, 118.3, 116.1, 73.4, 71.1, 70.6, 69.8, 38.1, 23.7, 10.8; FAB MS m/z (M^+) calcd 850.31, found 850.30. Anal. Calcd for $C_{54}H_{58}O_9$: C, 76.20; H, 6.82. Found: C, 76.18; H, 6.87.

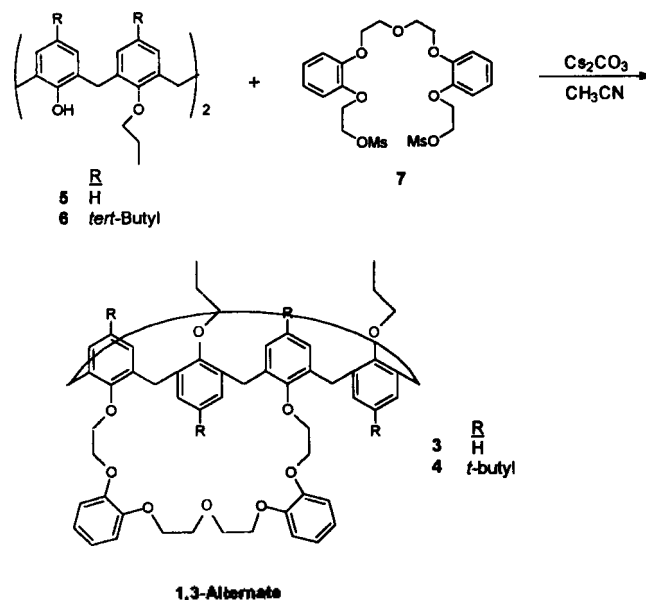
25,27-Bis(1-propyloxy)-*p*-tert-butylcalix[4]arene dibenzocrown-7,1,3-alternate (4) was prepared by the method described above. Crystallization from the oil residue with 5/1 diethyl ether-hexanes gave a desired product in an 82% yield. mp 278-280 °C; IR (KBr pellet, cm^{-1}): 3068 (Ar-H), 1501, 1366, 1258, 1208; 1H NMR ($CDCl_3$): δ 7.00-6.81 (m, 16H), 4.07 (t, 4H, $OPhO-CH_2CH_2-OPHO-$), 3.94 (t, 4H, $OPhO-CH_2CH_2OCH_2CH_2-OPHO-$), 3.87 (AB quartet, $J=16$ Hz, $\Delta v=12$ Hz, 8H, $ArCH_2Ar$), 3.52 (t, $J=6.0$ Hz, 4H, $OCH_2CH_2CH_3$), 3.36-3.13 (two triplet, $J=8.0$ Hz, 8H, OCH_2CH_2O), 1.28 (s, 18H, *t*-butyl), 1.12 (s, 18H, *t*-butyl), 0.94 (m, $J=6.0$ Hz, 4H, $OCH_2CH_2CH_3$), 0.62 (t, $J=6.0$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$): ppm 155.5, 154.7, 150.9, 149.8, 145.3, 144.4, 134.1, 133.9, 126.69, 126.66, 123.3, 121.7, 120.3, 114.1, 72.5, 70.8, 70.6, 69.4, 68.8, 40.0, 34.6, 34.5, 32.2, 32.0, 22.6, 10.5; FAB MS m/z (M^+): calcd 1075.47, found 1075.45. Anal. Calcd for $C_{76}H_{80}O_9$: C,

78.18; H, 8.44. Found: C, 78.25; H, 8.31.

Results and Discussion

Synthesis. To study influences of ring size and steric congestion of the organic carrier when the calix[4]arene dibenzocrown ether complexes with a specific metal, a series of diametrically *O*-alkylated calix[4]arene **5** and **6** as precursors were prepared in the cone form. Synthetic route of the calix[4]arene dibenzocrown ethers are depicted in Scheme 1. We have reported that the use of only one equivalent of K_2CO_3 as a base for dialkylation of calix[4]arene gives a desired product in more than 90% yield.⁷ Dipropylation of *p*-tert-butylcalix[4]arene using the same method was also successfully conducted to give compound **6** with an 88% yield. Compound **5** and **6** showed AB quartet splitting pattern ($J=12.8$ Hz, $\Delta v=199$ Hz, chemical shift difference value) in 1H NMR spectrum, indicating a characteristic cone conformation. Cyclization of the corresponding calix[4]arene with a dibenzo dimesylate (**7**) in the presence of Cs_2CO_3 provided the desired product in the fixed 1,3-alternate conformation in 90% yield. No other conformational isomers were observed. The compounds were fully characterized by 1H NMR and ^{13}C NMR spectroscopy, FAB positive mass spectrometry, and elemental analysis.

Complexation. Compounds **1**, **3**, and **4** were incorporated into solvent polymeric membranes in which poly(vinyl chloride) was the polymer and *o*-nitrophenyl octyl ether was the membrane solvent. For the ISEs prepared from these membranes, potentiometric selectivities for Cs^+ relative to Na^+ , K^+ , and Rb^+ were determined by the fixed interference method.¹¹ The potentiometric response showed excellent selectivities for cesium ion over other alkali metal cations as shown in Table 1. Elongation of the crown ether linkage to a triethylene glycol unit decreased the Cs/Na and Cs/K selectivities in bulk liquid membrane system, but the Cs/Rb selectivity increased slightly.⁷ So, the connecting group bet-



Scheme 1. Synthetic route for the preparation of calix[4]arene dibenzocrown ethers **3** and **4**.

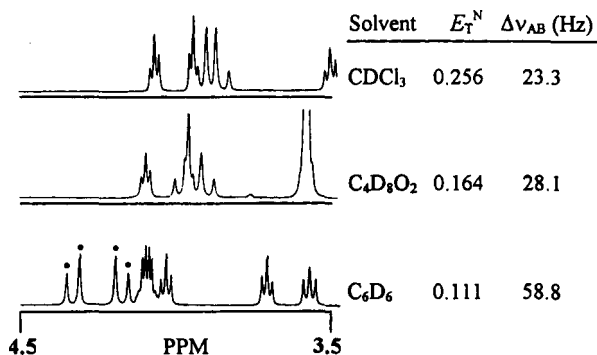
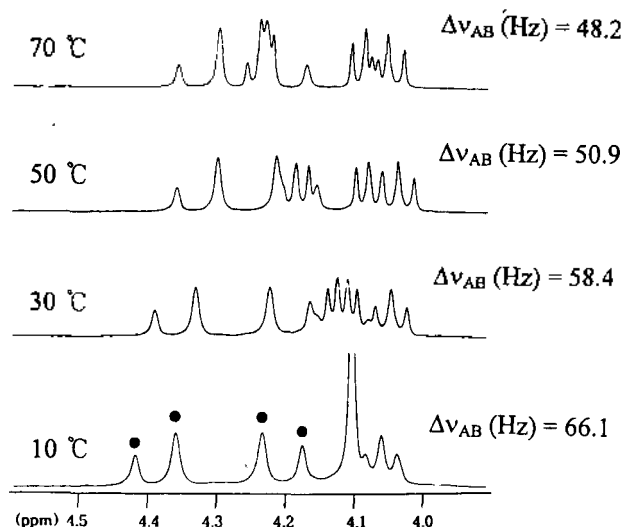
Table 1. Potentiometric selectivities of solvent polymeric membrane electrodes containing calixcrown ethers **1**, **3**, and **4**

Compd.	$\log K_{Cs,Na}^{Pot}$	$\log K_{Cs,K}^{Pot}$	$\log K_{Cs,Rb}^{Pot}$
1	-4.30	-1.69	-0.81
3	-4.49	-1.70	-0.80
4	-2.19	-0.70	-0.43

ween two benzo groups was fixed to be a diethylene glycol unit and alkyl group attached on lower rim was changed to propyl. The cesium ion selectivity of compound **3** increases compared to that of **1**. The presence of *p*-*tert*-butyl groups such as **4** gave much worse selectivity, clearly indicating that when it exists in the 1,3-alternate conformation, two bulky *tert*-butyl groups positioned inside of the crown ether linkage strongly inhibit the metal ion complexation.

NMR behavior. It has been known that when calix[4] arene crown ether takes an 1,3-alternate conformation, singlet peak (8 hydrogens of methylene bridge) around 3.8 ppm is shown in 1H NMR.⁵ Compounds **3** are locked in the 1,3-alternate conformation as inferred from their 1H NMR spectra (400 MHz, $CDCl_3$) which show a singlet at 3.71 ppm for the bridging methylene hydrogens of the calix[4] arene moiety. However, compound **4** appears to be less flexible than **3** in that it exhibits an AB splitting pattern which shows that H_{exo} and H_{endo} are not equivalent on the NMR time scale. It was presumed that the difference in chemical shifts for the two hydrogens in the methylene group by geminal coupling, $\Delta\nu_{AB}$, might be used as a qualitative measure of the relative rates of conformational flexibility of compound **4**.¹² To probe the solvent effects on the conformational mobility of **4**, 1H NMR spectra were taken in three different deuterated solvents and are depicted in Figure 1. The $\Delta\nu_{AB}$ values are noted to decrease as the solvent polarity (E_T^N)¹³ increases in going from benzene to 1,4-dioxane and to chloroform. This propensity matches well with the solvent polarity parameter E_T^N , indicating that in a more polar solvent the compound is more flexible.

The NMR results described above were obtained at room temperature. To further probe the conformational mobility of 1,3-alternate calix[4]arene crown ether, the influence of temperature upon the $\Delta\nu_{AB}$ values of **4** in benzene- d_6 was recorded in Figure 2. It was known that when two protons attached on the calix[4]arene skeleton are magnetically none-

**Figure 1.** 1H NMR spectra of compound **4** in solvents of differing polarity (E_T^N) and the corresponding chemical difference values.**Figure 2.** Influence of temperature upon the chemical shift difference values for the methylene group hydrogens in *p*-*tert*-butylcalixcrown **4** in C_6D_6 .

quivalent, H_{exo} and H_{endo} being assigned to the higher and lower magnetic field, respectively, with increasing temperature the peaks of the AB pattern are gradually broadened without change of $\Delta\nu_{AB}$ values and finally coalesce into single peak.¹⁴ However, in our system, the $\Delta\nu_{AB}$ values are found to decrease as the temperature is raised from 263 K to 343 K in 20 degree increments. This results for the 1,3-alternate calix[4]arene dibenzocrown ether are based on facts that the flexibility of organic molecules are enhanced at higher temperature in the solvent medium. The AB splitting pattern did not coalesce even at the boiling temperature of benzene- d_6 . NMR measurements in a higher temperature boiling solvent such as DMSO- d_6 were unsuccessful due to a low solubility.

Therefore we conclude that although the ring size of ether linkage is the most important factor, steric disfavoring by the presence of a bulky substituent, such as a *p*-*tert*-butyl group, also plays an important role in determining the selectivity and efficiency of metal ion complexation. In addition, we found that 1,3-alternate calix[4]arene crown ether (**4**) shows AB splitting pattern in 1H NMR spectrometer, indicating that it has somewhat conformational rigidity. Conformational flexibility of 1,3-alternate conformer in solution is found to be dependent on the solvent polarity and on the temperature at which the spectrum is measured.

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Stoichiometric Solvation Effects. Part 4. Product-Rate Correlations for Solvolyses of *p*-Methoxyphenyl Chloroformate in Alcohol-Water Mixtures

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Solvolyses of *p*-methoxyphenyl chloroformate in water, D₂O, CH₃OD, 50% D₂O-CH₃OD, and in aqueous binary mixtures of acetone, ethanol and methanol are investigated at 25.0 °C. Product selectivities are reported at 25 °C for a wide range of ethanol-water and methanol-water solvent compositions. The Grunwald-Winstein plots of first-order rate constants for *p*-methoxyphenyl chloroformate with Y_{Cl} (based on 1-adamantyl chloride) show marked dispersions into three separate curves for the three aqueous mixtures with a small *m* value and a rate maximum for aqueous alcohol solvents. Third-order rate constants, k_{wv} , k_{av} , k_{va} and k_{aa} were calculated from the observed k_{wv} and k_{aa} values together with k_{av} and k_{va} calculated from the intercept and slope of the plot of $1/S$ vs. [alcohol]/[water]. The calculated rate constants, k_{calc} and mol % of ester agree satisfactorily with those of the observed rate constants, k_{obs} , and mol % of ester, supporting the stoichiometric solvation effect analysis. The kinetic solvent isotope effects determined in water and methanol are consistent with the proposed mechanism of the general base catalyzed carbonyl addition-elimination.

Introduction

The mechanism of acyl-transfer reactions has been investigated intensively for many years both experimentally¹ and theoretically.² The mechanism of most of these reactions is, however, still not well established. The solvolysis of acyl halides, RCOX, is believed to proceed either through a direct displacement mechanism (S_N2) or through an associative addition-elimination mechanism involving a tetrahedral intermediate.³ Many acyl-transfer reactions in protic solvents involving esters,⁴ amide derivatives⁵ and acid chlorides⁶ are third order overall, and it is thought that one molecule of solvent acts as a nucleophile and a second molecule acts as a general base.⁷ In the third order process, methanol probably acts as both nucleophile and general base, because large rate enhancements are observed when chloride ion (a base in acetonitrile) is added while only minor rate enhancements are observed when phenol is added.⁶

The other process may be pseudo second order, and may

involve methanol as nucleophile with acetonitrile, present in large excess, acting as general base.^{6a} Similar results have been obtained for aminolyses involving primary and secondary amines.⁸ Depending on reaction conditions, as substrates, and solvent compositions, nucleophilic reactions of acyl halides were reported as an addition-elimination, S_N1 or S_N2 reaction mechanism.^{9,10} Based on the product-rate study, benzoyl chloride (I) solvolyses by an S_N2 mechanism in high polarity solvents, whereas it favors general-base catalyzed or possible addition-elimination pathway (S_N1) in less polar media.^{11,12}

Nucleophilic substitution reactions of furoyl chloride (II) and thenoyl chloride (III) were reported to proceed via different reaction mechanisms, the former by an addition-elimination and the latter by an S_N2 mechanism based on the product-rate study.¹³ Though the only difference between two substrates is sulfur atom in thenoyl chloride which is replaced by an oxygen atom in furoyl, two substrates show a remarkable change in reaction mechanism.⁸