New Azobenzene Crown *p-tert*-Butylcalix[4]arenes as Switchable Receptors for Na+ and K+ ions: Synthesis and Isomerization Studies

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Two new azobenzene crown ether calix[4]arenes, **10** and **11**, were synthesized by two pathways. In the first pathway, two ethoxy nitrobenzene groups were attached to *t*-butylcalix[4]arenes in a 1,3 position. Subsequent reduction of the nitrobenzene groups by metallic zinc in an alkaline solution afforded **10** and **11** in 8% and 12%, respectively. In the second pathway, an azobenzene containing two glycolic units was prepared prior connecting to *t*-butylcalix[4]arenes. The yields from the second approach (5%, 8% for **10** and **11**, respectively) were lower than those from the former approach. Single crystals of **10** suitable for X-ray crystallography was obtained by recrystallization in methanol. Both the X-ray structure and the ^{1}H-NMR spectrum of **10** indicated that the stereoisomer of the azobenzene moiety was *trans* and the calixarene platform was in *cone* conformation. ^{1}H NMR spectroscopy suggested that **10** underwent an observable *cis-trans* isomerization in CDCl$_3$ under room light and upon UV irradiation with *cis:trans* ratios of 33:67 and 36:64, respectively. Compound **6** which was the precursor of **11** showed fluxional behavior and was found to have mixed conformations of cone and partial cone with a ratio of 47:53 at -30 °C. ^{1}H NMR spectrum of **11** suggested that **11** was initially isolated as *cis* azobenzene with calix[4]arene in cone conformation and underwent conformational interconversion through calix[4]arene annulas in a similar fashion to **6** upon exposing to light. The complexation studies of **10** with picrate salts of Na+ and K+ using ^{1}H NMR spectroscopy suggested that Na+ preferred to bind the *cis* form of **10** while K+ preferred to bind the *trans* form. The stereoisomer of the azobenzene unit in **11** changed partially from *cis* to *trans* upon complexing with K+.

Introduction

Large and complex molecular systems can be constructed utilizing various synthetic techniques. Attaching functional moieties into specific molecular frameworks can result in interesting molecular or supramolecular devices.[1] Azobenzenes make up an interesting class of compounds that exhibit photoresponsive properties. They have been incorporated into a number of supramolecular frameworks to produce ionophores for transports and photo-switchable receptors.[2] Calix[n]arenes have been of particular interest as molecular platforms for synthesizing selective ionophores in inclusion complexation.[3] Yamada et al. have shown that an azobenzene-capped calix[4]arene possessed a higher binding ability to metal ions such as Na+, K+, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Al^{3+} in the *trans* form than in *cis* isomer.[4] Later, Vicens and colleagues have synthesized a series of *trans* and *cis* azobenzene crown calix[4]arenes.[5] From the crystal structure, an azobenzene calix[4]arene containing one glycolic unit existed in *cis* isomer.[6] Azobenzene crown calix[4]arenes that contained more than one glycolic unit exhibited allosteric properties. Changes have been observed in *cis/trans* ratio from 70/30 for the free ligand to 80/20, 80/20, 75/25 and 85/15 for K+, Rb+, Cs+ and NH$_4^+$, respectively.[7]

We are interested in constructing a switchable molecular system which can selectively bind Na+ or K+ to mimic the biological Na+/K+ ion pump.[8] According to a report by Swa-

ger and coworkers, it was found that bithiophene calix[4]-arenes containing 6 ethereal oxygen donors can bind Na+ and K+ to different extents.[9] We therefore synthesized two azobenzene crown ether calix[4]arenes (**10** and **11**) in which the azo benzene unit was connected to the glycolic chains of the calix[4]crown and studied their isomerization and inclusion properties. It is anticipated that azobenzene crown ether calix[4]arenes will form complexes with both Na+ and K+, and the binding abilities can then be switchable by external stimuli.

Experimental Section

Materials. All materials and solvents were standard analytical grade, purchased from Fluka, J. T. Baker or Merck, and used without further purification. Commercial grade solvents such as acetone, dichloromethane and methanol were distilled and stored over 4 Å molecular sieves. Acetonitrile was dried according to the standard technique.[10] Chromatographic separations were performed on silica gel columns (kieselgel 60, 0.063-0.200 mm, Merck). Thin layer chromatography (TLC) were carried out using silica gel plates (kieselgel 60 F$_{254}$, 1 mm, Merck). *p-tert*-Butylcalix[4]arene, **1**,[11] and 26,28-dimethoxy-*p-tert*-butylcalix[4]arene, **2**,[12] were prepared according to methods described in the literature. Unless otherwise noted, all reactions were carried out under nitrogen.

Analytical Instruments. Elemental analyses were carried out on a Perkin Elmer CHON/S analyzer (PE2400 series II). Melting points were taken on an Electrothermal 9100 apparatus. UV-visible spectra were recorded on a Spectronic 3000 array spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker ACF 200 MHz or a Bruker AM 400 MHz nuclear magnetic resonance spectrometer. Variable temperature NMR experiments were carried out on a JEOL 500 MHz NMR spectrometer. UV-visible spectra were recorded on a Spectronic 3000 spectrophotometer. In all cases, samples were mixed in deuterated chloroform and chemical shifts were recorded using a residual chloroform signal as internal reference.

Synthesis.

Preparation of 2-(2′-bromoethoxy)nitrobenzene, 3. In a 500 mL two-necked flask equipped with a magnetic bar and a reflux condenser, *o*-nitrophenol (4.45 g, 32.0 mmol), 1,2-dibromoethane (60.11 g, 320.0 mmol) and K_2CO_3 (8.85 g, 64.0 mmol) were mixed in CH_3CN (150 mL). The mixture was refluxed for 24 hours and then allowed to cool to room temperature. The solid was separated by filtration and washed with CH_2Cl_2. The combined solution was then evaporated to dryness to obtain a yellow residue. Methanol was subsequently added to dissolve this residue, and the solution was chilled in an ice bath to precipitate white solid identified as ethoxy dinitrobenzene, **4**. The white precipitate was filtered and washed with cold methanol (0.55 g, 7%). The supernatant was evaporated to dryness. The residue was then dissolved in diethyl ether. Hexane was added and the mixture was cooled in an ice bath. The desired product, **3**, crystallized as a bright yellow solid (5.80 g, 74%). mp 164-165 ^{o}C.

^{1}H NMR (200 MHz, CDCl$_3$) δ_H 3.65 (2H, t, $J = 6.0$, -OCH$_2$C*H*$_2$Br), 4.40 (2H, t, $J = 6.0$, -OC*H*$_2$CH$_2$Br), 7.02-7.10 (2H, m, aromatic), 7.52 (1H, t, $J = 8.0$, aromatic), 7.81 (1H, d, $J = 8.0$, aromatic). Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.07; H, 3.21; N, 5.65.

Preparation of 25,27-di(2-ethoxy)nitrobenzene-*p-tert*-calix[4]arene, 5. In a 500 mL two-necked flask equipped with a magnetic bar and a reflux condenser, **1** (6.48 g, 10.0 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) were mixed in CH_3CN (230 mL) and refluxed for 3 hours. The compound **3** (4.92 g, 20.0 mmol) was then added dropwise to the reaction mixture, and the mixture was further refluxed for 4 days. The mixture was then allowed to cool to room temperature. The solid was separated by filtration. The solution was evaporated to dryness. The residue was subsequently dissolved in water and extracted with 3 portions of CH_2Cl_2 (50 mL). Drying and removal of the solvent afforded a yellow solid. The solid was redissolved in CH_2Cl_2 to get a clear yellow solution in which a small quantity of acetone was then added. Upon slow evaporation of the solvent, sugar-like crystals of **5** were obtained (6.51 g, 66%). mp 205-207 ^{o}C.

^{1}H NMR (200 MHz, CDCl$_3$) δ_H 0.94 and 1.28 (18H each, s, *t*-Bu protons), 3.28 (4H, d, $J = 13.0$, ArC*H*$_2$Ar), 4.26-4.33 (4H, m, ArC*H*$_2$Ar and -OCH$_2$C*H*$_2$O-), 4.45-4.47 (4H, m, -OC*H*$_2$CH$_2$O-), 5.19 (2H, s, *H*OAr), 6.75 (4H, s, HOAr*H*),

6.95 (2H, t, $J = 8.0$, nitrobenzene), 7.03 (4H, s, ROAr*H*), 7.24 (2H, d, $J = 8.0$, nitrobenzene), 7.46 (2H, t, $J = 7.0$, nitrobenzene), 7.7 (2H, d, $J = 8.0$, nitrobenzene). Anal. Calcd for $C_{60}H_{70}N_2O_{10}$: C, 73.60; H, 7.21; N, 2.86. Found: C, 73.62; H, 7.27; N, 2.73.

Preparation of 25,27-[di(2-ethoxy)nitrobenzene]-26,28-dimethoxy-*p-tert*-butylcalix[4]arene, 6. Compound **6** was synthesized from the reaction between **2** (1.37 g, 2.03 mmol) and **3** (1.0 g, 4.06 mmol) in the presence of K_2CO_3 (1.12 g, 8.11 mmol) as well as KOH (3 pellets) in a similar fashion to the preparation of **5**. The desired product can be separated by column chromatography using 10% ethyl acetate/hexane as eluent. Upon addition of methanol into the solution of **6** orange needles precipitated (0.41 g, 20%). mp 189-191 ^{o}C.

^{1}H NMR (200 MHz, CDCl$_3$) δ_H 0.84 and 1.05 (9H each, br s, CH$_3$OAr*t-Bu*), 1.28 (18H each, br s, ROAr*t-Bu*), 3.00-3.40 (4H, br, ArC*H*$_2$Ar), 3.47 (6H, s, OC*H*$_3$), 3.60-4.60 (12H, br, ArC*H*$_2$Ar and OC*H*$_2$C*H*$_2$O-), 6.40-6.69 (4H, br, CH$_3$OAr*H*), 6.92-7.30 (8H, br, nitrobenzene and ROAr*H*), 7.51 (2H, t, $J = 7.0$, nitrobenzene), 7.81 (2H, d, $J = 8.0$, nitrobenzene). Anal. Calcd for $C_{62}H_{74}N_2O_{10}$: C, 73.93; H, 7.40; N, 2.78. Found: C, 73.92; H, 7.46; N, 2.76.

Preparation of 2-(2′-hydroxyethoxy)nitrobenzene, 7. In a similar fashion to the synthesis of **3**, the reaction between *o*-nitrophenol (2.78 g, 20.0 mmol) and 2-bromoethanol (7.50 g, 60.0 mmol) in the presence of K_2CO_3 (2.90 g, 21.0 mmol) gave **7** as a yellow liquid. (2.3 g, 63%).

^{1}H NMR (200 MHz, CDCl$_3$) δ_H 3.83 (2H, t, $J = 4.5$, -OCH$_2$C*H*$_2$OH), 4.10 (2H, t, $J = 4.5$, -OC*H*$_2$CH$_2$OH), 4.41 (1H, s, -O*H*), 6.91 (1H, t, $J = 7.0$, aromatic), 7.01 (1H, d, $J = 8.0$, aromatic), 7.40 (1H, t, $J = 7.0$, aromatic), 7.68 (1H, d, $J = 8.0$, aromatic). MS (m/z): 183 (87), 139 (M$^+$, 100), 122 (67).

Preparation of 2,2-di(2′-hydroxyethoxy)azobenzene, 8. A mixture of **7** (2.01 g, 10.92 mmol) in methanol (10 mL), sodium hydroxide (4.37g ,109.3 mmol) in H_2O (6 mL) was stirred in a 50 mL round bottom flask, and zinc (2.86 g, 43.74 mmol) was then added. The mixture was refluxed under nitrogen atmosphere for 48 hours and allowed to cool to room temperature. The solid was removed by filtration and washed with CH_2Cl_2. The combined filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2 and it was then extracted with saturated ammonium chloride. The combined organic layer was separated and dried over Na_2SO_4. After removal of Na_2SO_4, the filtrate was evaporated to give a viscous orange residue. The residue was redissolved in minimum CH_2Cl_2 and chromatographed on a silica gel column with 15% ethyl acetate/dichloromethane as eluent. The product crystallized as an orange solid upon addition of methanol and slow evaporation of the solvent (0.51 g, 30%).

^{1}H NMR (200 MHz, CDCl$_3$) δ_H 3.28 (4H, br t, -OCH$_2$-C*H*$_2$OH), 4.25 (4H, br t, -OC*H*$_2$CH$_2$OH), 5.04 (2H, br, -O*H*), 7.12-7.65 (4H, m, aromatic), 7.38 (2 H, t, $J = 8.0$, aromatic), 7.70 (2H, d, $J = 8.0$, aromatic). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.56; H, 6.19; N, 9.29.

Preparation of 2,2-di(2′-mesylethoxy)azobenzene, **9**. Into a 100 mL two-necked flask equipped with a magnetic bar, methane sulfonylchloride (0.67 g, 5.83 mmol) and triethylamine (1.07 g, 10.60 mmol) were dissolved in 20 mL of dichloromethane and stirred for 30 min at 0-5 °C. Compound **8** (1.21 g, 2.65 mmol) in 5 mL of CH_2Cl_2 was then added slowly into the mixture and it was stirred for 1 hr. After warming to room temperature, the mixture was extracted with 2 portions of 1 M HCl (20 mL) and water. The organic phase was separated and dried over Na_2SO_4. Removal of Na_2SO_4 yielded an orange solution which was evaporated to give an orange-brown residue. The residue was chromatographed on a silica gel column with 30% ethyl acetate/hexane as eluant. The product was crystallized as orange crystals by adding dichloromethane and ethyl acetate (0.40 g, 33%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 3.04 (6H, s, $-SO_2CH_3$), 4.44 (4H, t, $J = 4.0$, $-OCH_2CH_2OMs$), 4.69 (4H, t, $J = 4.0$, $-OCH_2CH_2OMs$), 7.05-7.09 (4H, m, aromatic), 7.50 (2H, t, $J = 8.0$, aromatic), 7.60 (2H, d, $J = 8.0$, aromatic). Anal. Calcd for $C_{18}H_{22}N_2O_8S_2$: C, 47.15; H, 4.84; N, 6.11. Found: C, 47.11; H, 4.85; N, 6.12.

Preparation of 25,27-di(2-ethoxy)azobenzene *p-tert*-butylcalix[4]arene, 10.

Method A: In a 50 mL round bottom flask, a mixture of **5** (0.70 g, 0.71 mmol) in isopropanol (8.0 mL), NaOH (0.28 g, 7.0 mmol) in H_2O (4 mL) and Zn (0.2 g, 3.06 mmol) was stirred and refluxed under nitrogen for 48 hours. It was then allowed to cool to room temperature. The workup procedures were carried out in the same manner as the synthesis of **8**. The product was purified by column chromatography with 15% ethyl acetate/hexane as eluant. Compound **10** was crystallized from hot methanol to obtain orange crystals (0.05 g, 8%).

Method B: In a 250 mL two-necked flask, compound **1** (1.02 g, 1.54 mmol) and Na_2CO_3 (0.16 g, 1.55 mmol) were dissolved in CH_3CN (100 mL). The mixture was stirred for 24 hours at 40 °C. Compound **9** (0.84 g, 1.84 mmol) in CH_3CN (20 mL) was then slowly added. The reaction mixture was further refluxed for 1 day. After cooling to room temperature, the solid was separated by filtration and washed with CH_2Cl_2. The combined solution was evaporated to dryness. The residue was neutralized with 1 M HCl (50 mL) and extracted with dichloromethane (2×50 mL). The organic layer was separated and dried over Na_2SO_4. After filtration, the solvent was removed by a rotary evaporator to give an orange oily residue which was further purified by column chromatography (SiO_2) with 10% ethyl acetate/hexane as eluant. The product was crystallized from hot methanol to give orange crystals (0.07 g, 5%). mp 195-197 °C (decomp.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.03 and 1.20 (18H each, s, *t*-Bu protons), 3.20 and 4.15 (4H each, d, J_{AB} 13.0, ArCH_2Ar), 4.38 and 4.84 (4H each, br t, OCH_2CH_2O-), 6.86 (4H, s, ROArH), 6.92 (4H, s, HOArH), 7.08 (2 H, t, $J = 6.0$, azobenzene), 7.16 (2H, d, $J = 8.0$, azobenzene), 7.34 (2H, t, $J = 6.0$, azobenzene), 7.61 (2H, s, HOAr), 7.70 (2H, d, $J = 8.0$, azobenzene). Anal. Calcd for $C_{60}H_{70}N_2O_6C_4H_8O_2$: C,

76.62; H, 7.84; N, 2.79. Found: C, 77.21; H, 7.51; N, 2.72. UV/vis [λ (nm), ε (dm³ · mol⁻¹ · cm⁻¹)]: 344, 19233; 446, 3167.

Preparation of 25,27-[di(2-ethoxy)azobenzene]-26,28-dimethoxy-*p-tert*-butylcalix[4]arene, 11.

Method A: A mixture of **6** (0.51 g, 0.50 mmol) in isopropanol (10 mL), NaOH (0.2 g, 5.0 mmol) in H_2O (2 mL) and Zn (0.13 g, 2.0 mmol) was placed in a 50 mL round bottom flask. The mixture was refluxed for under nitrogen for 2 days. The isolation and purification procedures were carried out in the same manner as compound **8**. Compound **11** was obtained as orange crystals in methanol and ethyl acetate (0.06 g, 12%).

Method B: In a 250 mL two-necked flask, compound **2** (0.82 g, 1.18 mmol) and Na_2CO_3 (0.25 g, 2.36 mmol) were dissolved in CH_3CN (120 mL). The mixture was stirred for 24 hours at 40 °C. Compound **9** (0.65 g, 1.42 mmol) in CH_3CN (20 mL) was then slowly added. The reaction mixture was further refluxed for 2 days. The separation and purification procedures were carried out in the same manner as compound **10**. The product was crystallized as orange crystals in methanol and ethyl acetate (0.09 g, 8%). mp 228-230 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.82 and 1.28 (18H each, s, *t*-Bu protons), 3.10 and 4.23 (4H each, d, J_{AB} 12.0, ArCH_2Ar), 3.44 (6H, s, $-OCH_3$), 4.34 and 4.63 (8H, m, $-OCH_2CH_2O$-), 6.42 (4H, s, CH_3OArH), 6.94 (2H, m, azobenzene), 7.01 (4H, s, ROArH), 7.08 (4H, m, azobenzene), 7.41 (2H, m, azobenzene). Anal. Calcd for $C_{62}H_{74}N_2O_6$: C, 78.95; H, 7.91; N, 2.97. Found: C, 79.06; H, 7.91; N, 2.97. UV/vis [λ (nm), ε (dm³mol⁻¹cm⁻¹)]: 334, 19385; 440, 7714.

Isomerization studies. Isomerization studies of **10** and **11** have been carried out in NMR tubes. Typically, an NMR tube containing **10** or **11** (3.28 mmol) in $CDCl_3$ (0.7 mL) was placed in a photo-reactor (quartz) and irradiated with a 180 W mercury low-pressure lamp for at least 4 hours. Isomerization was followed by ^{1}H NMR spectroscopy using a Bruker AM400 MHz NMR spectrometer (every 30 minute). Isomerization of **10** or **11** was also studied under room light. All compounds were left standing for at least 4 days. NMR spectra were recorded every 2 hours. All experiments were performed at 25 °C, and each set of experiments was repeated at least twice.

Isomerization and complexation studies with Na⁺ and K⁺ ions. Typically, an NMR tube containing **10** or **11** (3.28 mmol) in $CDCl_3$ (0.7 mL) was placed in a phto-reactor (quartz) and irradiated with a 180 W mercury low-pressure lamp for at least 4 hours. Sodium or potassium picrate (9.84 mmol) was then added as solid into the tube. NMR spectra (400 MHz) of the mixture were recorded after 2 days. All experiments were repeated at least twice.

X-ray crystallography. Diffraction data of **10** · $C_4H_8O_2$ were collected at 298 K on a crystal of dimension 0.6 mm × 0.3 mm × 0.3 mm with a Bruker SMART CCD area detector diffractometer using ω rotation scans (scan width of 0.3°) and graphite-monochromated MoKα radiation ($\lambda = 0.71073$) at a detector distance of 4.5 cm. A hemisphere of the reciprocal

Table 1. X-ray crystallographic data for $10 \cdot C_4H_8O_2$

| formula	$C_{64}H_{78}N_2O_8$
fw	1003.28
T, K	293 (2)
λ, Å	0.71073
crystal system	monoclinic
space group	*Cc*
a (Å)	15.1260 (3)
b (Å)	31.1347 (3)
c (Å)	12.6692 (3)
β (°)	98.4970 (10)
V (Å^3)	5900.99 (19)
Z	4
ρ (calcd) (Mg/m^3)	1.129
abs coeff (μ, mm^{-1})	0.073
Final R indices [I > 2σ(I)]	R1 = 0.0731
	wR2 = 0.1663
R indices (all data)	R1 = 0.1178
	wR2 = 0.1982

space was covered by combination of three sets of exposures. Each set had a different ϕ angle (0°, 88°, 180°) and each exposure lasted 30 seconds. The collected data were reduced using the program SAINT.[13] Empirical absorption correction was done by the program SADABS[14] with T_{min} and T_{max} of 0.6302 and 1.0000, respectively. A total of 21,214 reflections were measured within $2\theta_{max}$ of 61.05°. The structure was solved by direct methods and refined with anisotropic thermal parameters for all non-hydrogen atoms by full matrix least square using SHELX-97 package.[15] All hydrogen atoms were found in different Fourier maps and were included in the refinement. Due to vibrational disorder of the solvent of crystallization, refinement converged with rather high *R* and w*R* values (0.731 and 0.1663, repectively). Detailed crystallographic data are described in Table 1.

Results and Discussion

Synthesis and characterization. The synthesis of compounds **10** and **11** was conducted in two different pathways. In pathway A, two ethoxy nitrobenzene groups were attached to the calix[4]arene framework by a nucleophilic substitution reaction between *o*-nitrophenol and 1,2-dibromoethane. A reductive coupling of nitrobenzene groups was then carried out to afford the azobenzene crown ether calix[4]arenes. Alternatively, in pathway B the ethoxy nitrobenzene moieties were subjected to reductive coupling prior attaching them to the calix[4]arene units. The synthesis of compounds **10** and **11** can be summarized in Scheme 1.

Alkylation of *o*-nitrophenol with 10.0 equiv. of 1,2-dibromoethane in the presence of excess K_2CO_3 in acetonitrile gave yellow needle-shaped crystals of **3** as a major product (74%) and **4** as a minor product (7%). The reaction needed excess 1,2-dibromoethane in order to produce the mono-substituted product. If the equimolar amount of 1,2-dibromoethane was used, the major product would be the disub-
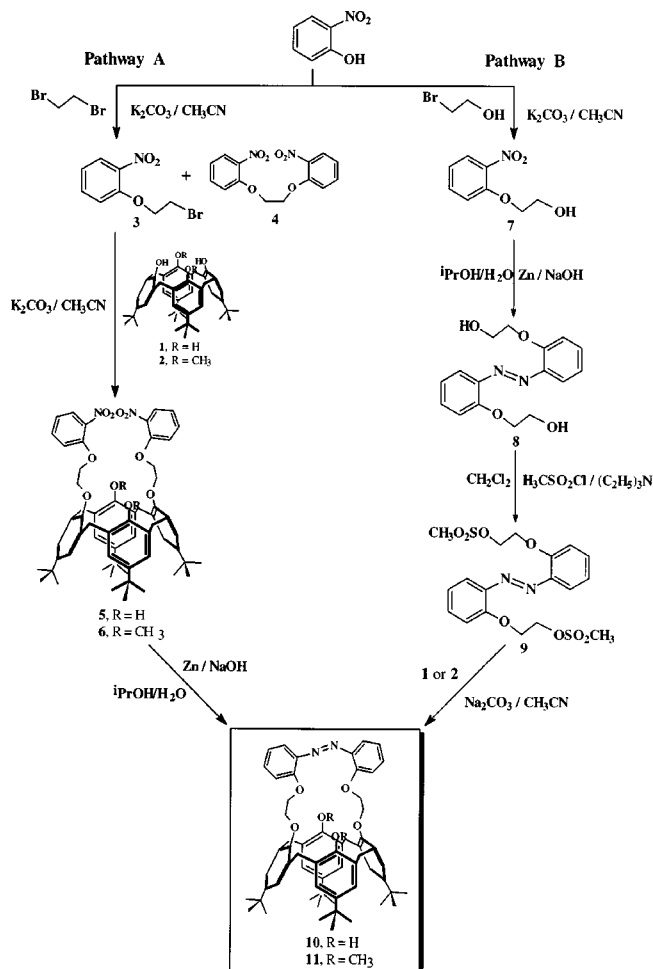
Scheme 1. Synthetic procedures of **10** and **11**.

stituted compound, **4**.

A nitrobenzene derivative of calix[4]arene, 25,27-di(2-ethoxy)nitrobenzene-*p*-*tert*-butylcalix[4]arene, **5**, was prepared by alkylation of *p*-*tert*-butylcalix[4]arene, **1** with 2.0 equiv.of compound **3** in acetonitrile in the presence of 1.05 equiv. K_2CO_3. Compound **5** was crystallized in dichloromethane and acetone to give sugar-like crystals in 66%. The same reaction also produced needle-like crystals which were characterized as the trisubstituted product, **12**. The ^{1}H NMR spectrum of **5** showed the signals of nitroaromatic protons at 6.95-7.74 ppm. The product has intra-molecular hydrogen bonds indicated by a singlet peak of OH proton at 6.85 ppm. The spectrum also consists of two doublet signals due to the methylene bridge protons at 3.50 ppm and 4.25 ppm and two

12　　　　　　　　　**13**
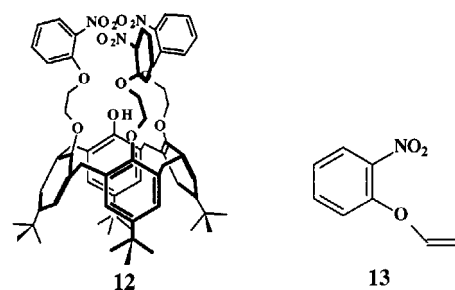
signals due to *tert*-butyl groups at 1.28 ppm and 0.94 ppm indicating that the calix[4]arene unit is in cone conformation.

In early attempts, we tried to prepare compound **6** from alkylation reaction of the dimethylated compound, **2**, with **3** in various conditions. A preparation using potassium *tert*-butoxide as base in THF gave the elimination product of **3**, compound **13**, instead. Another method, using NaH as base gave **13** in 24% along with compound **6** in only 8%. Nevertheless, higher yield of **6** can be obtained from alkylating compound **2** with 2.0 equiv. of compound **3** in acetonitrile in the presence of 4.0 equiv. of K_2CO_3 and KOH. The desired product was separated on a silica gel column with 10% ethyl acetate/hexane as eluent to afford compound **6** in 20%. The yield was quite low due to the steric congestion of the methyl group which may decelerate the rate of the substitution reaction and the elimination product, **13**, was an inevitable side reaction under basic condition. The ¹H NMR spectrum of **11** showed broad signals due to the absence of intramolecular hydrogen bonding causing in various conformations of the calix[4]arene framework to exist in the solution, *vide infra*.

Reductive coupling was carried out with a modified procedure from the literature.[16] Typically, the mixture of dinitrobenzene calix[4]arene, **5**, in isopropanol in the presence of aqueous sodium hydroxide and zinc was stirred and refluxed under nitrogen atmosphere for 48 hours. The product was obtained as orange crystals in 8% yield after an extensive purification by chromatography and recrystallization. The ¹H NMR spectrum of **10** shown in Figure 3a contains two doublets of the methylene bridged protons at 3.20 and 4.15 ppm and two singlets of *tert*-butyl protons at 1.03 and 1.20 ppm suggesting the cone conformation of the calix[4]arene framework was retained.

A similar coupling reaction of compound **6** gave compound **11** which was purified by crystallization in methanol and ethyl acetate/hexane to give orange crystals of **11** (12%). The signal of aromatic protons of compound **11** (Figure 3c) appeared as a pair of sharp singlet peaks at 7.01 ppm and 6.42 ppm unlike the broad peaks of compound **6**. The spectrum also showed two pairs of doublets due to the methylene bridge protons. The results implied that compound **11** became more rigid and the calix[4]arene framework resumed the cone conformation.

Compound **7** was prepared from a nucleophilic substitution reaction between *o*-nitrophenol with 3.0 equiv. of 2-bromoethanol in the presence of 1.05 equiv. of K_2CO_3 in acetonitrile. After separation and purification, a yellow liquid of **7** was obtained in 63%. A reductive coupling of compound **7** with metallic zinc in *i*-PrOH in the presence of sodium hydroxide solution and purification of the crude by silica gel column chromatography with 15% ethyl acetate/dichloromethane as eluent gave **8** as an orange viscous liquid which was then crystallized as an orange solid upon addition of methanol (30%).

Compound **8** was converted into a methane sulfonate ester, **9**, to facilitate the nucleophilic substitution reaction. The mesylation of **8** with 2.2 equiv. methane sulfonylchloride and excess triethylamine in dichloromethane gave **9** in 33% after purification. The nucleophilic substitution of **9** with **1** or **2** in the presence of Na_2CO_3 in acetonitrile gave azobenzene calix[4]arenes **10** (5%) and **11** (8%), respectively. The low yield of nucleophilic substitution reactions may stem from the competing polymeric formation during the reactions. It should be noted that the overall yields of the products in pathway A are higher than those in pathway B.

The crystal structure of 10. We were able to obtain crystals of both **10** and **11**. However, only crystals of **10** are suitable for single crystal X-ray analysis. The X-ray structure of **10** illustrated in Figure 1 shows that a molecule of ethyl acetate has included into the calix[4]arene unit of **10** pointing the -CH_2CH_3 moiety into the upper rim cavity. The aromatic C_{sp2}-C_{sp2} distances in the molecule vary from 1.333 (15) to 1.449 (10) Å with an everage value of 1.396 Å while the C_{sp3}-C_{sp3} distances vary form 1.462 (9) to 1.560 (8) Å with a mean value of 1.525 Å. The aromatic C_{sp2} bond angles are in the range of 116.3 (3)°-123.7 (3)°, and C_{sp3} bond angles of 103.9 (7)°-112.6 (4)° which are in line with trigonal planar and tetrahedral geometry. Bond angles involving bridging methylenes vary from 110.6 (3)° to 111.9 (3)° which are slightly larger than the tetrahedral angle. The C-O distances vary from 1.377 (4) to 1.443 (4) Å with a mean value of 1.412 Å. The distances of N(1)-C(54) and N(2)-C(48) are 1.515 (7) and 1.431 (8) Å, respectively. The azobenzene unit is in *trans* isomer with a N=N distance of 1.179 (6) Å. The relative torsion angle of C(48)-N(2)-N(1)-C(54) is 178.35° indicating that the azobenzene unit is almost flat. The distances between ethereal O atoms are O(1)-O(6)=4.618 and O(3)-O(5)=5.813, and the distances between ethereal and phenoxy oxygen atoms are O(2)-O(6)=3.338 and O(4)-O(5)
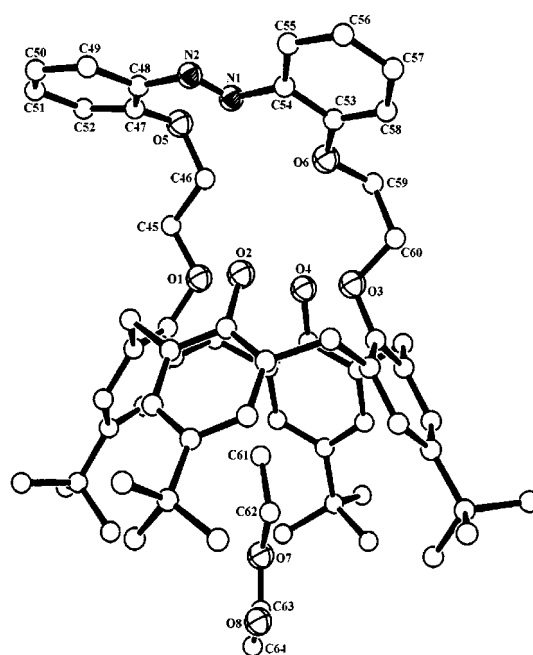

Figure 1. The crystal structure of **10**·$C_4H_8O_2$. Hydrogen atoms were omitted for clarity.

=5.073 Å. The ethereal and hydroxy oxygen atoms are, therefore, preorganized for binding alkali cations.

Solution behavior of compound 6. Due to the lack of intramolecular hydrogen bonding compound **6** possessed conformational interconversion through the calixarene annulas. The ^{1}H NMR spectrum of **6** in CDCl$_3$ at room temperature (Figure 2a) shows complicated broad signals which indicate mixed conformations of the calix[4]arene framework. Upon decreasing temperature, the broad signals became sharper. However, signals due to protons on nitrobenzene rings do not change significantly when compared to other signals. This implies that the movement of the calix[4]arene unit occurred on the aryl rings containing methoxy groups. The 500 MHz ^{1}H NMR spectrum of **6** at -30 °C (Figure 2b) reveals that in solution (CDCl$_3$) **6** existed as a mixture of two conformers: partial cone and cone conformations. The mixed conformations of cone and partial cone were also found in tetramethoxycalix[4]arenes bridged by a polyether chain at the upper rim.[17] The cone conformation possesses two planes of symmetry. The *t*-butyl protons appear as two singlets at 0.78 and 1.29 ppm, and the methoxy protons appear as a singlet at 3.81 ppm. On the other hand, the partial cone conformation has only one plane of symmetry. The *t*-butyl protons appear as three singlets at 1.04, 1.18 and 1.28 ppm (ratio 2 : 1 : 1). The methoxy protons appear as two singlets at 3.01 and 3.18 ppm (ratio 1 : 1). The spectrum also consists of 5 peaks due to the aromatic protons of the calix[4]arene unit at 7.09, 7.04, 6.91, 6.58 and 6.43 ppm. There should be at least 5 pairs of signals due to methylene bridge protons in the spectrum; however, some signals are superimposed on the glycolic proton signals which appear as 4 sets of multiplets between 4.0-4.5 ppm. The ratio of cone:partial cone can be calculated from the integration ratio of either *t*-butyl protons or methoxy protons of each conformation to be 43:57.

Isomerization studies of compounds 10 and 11. Nakamura and colleagues have demonstrated use of UV spectrophotometry to study photoisomerization of azobenzocrown ethers.[18] Unfortunately, both *trans* and *cis* + *trans* forms of **10** and **11** gave almost the same UV spectra. This may stem from the fact that after isomerization the *cis*:*trans* ratio of **10** became 36 : 64 in which the amount of the *cis* form was not enough to influence the alteration of absorption bands in the UV spectra. NMR spectroscopy was then used in the investigation of isomerization.
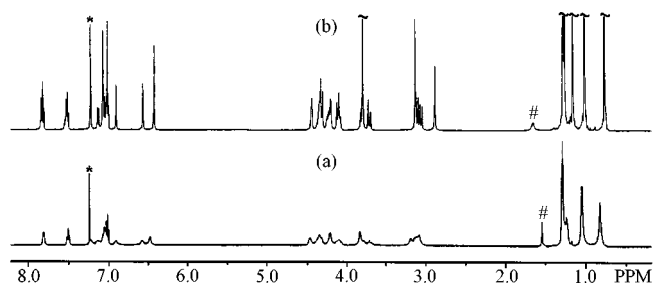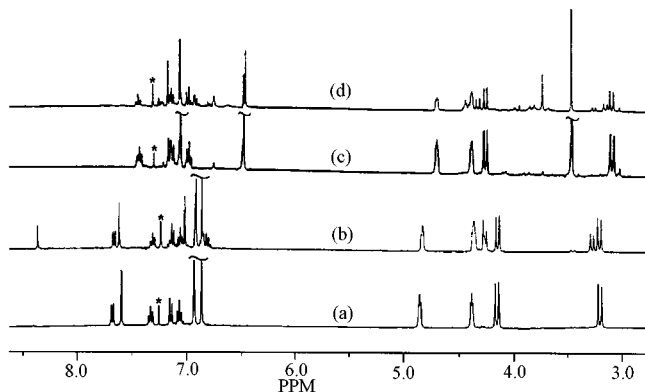
Partial ^{1}H NMR spectra of **10** before and after irradiation depicted in Figures 3a and 3b show discrete features. The signals belonging to the *cis* isomer, *t*-Bu (1.21 and 1.19 ppm), ArC*H*$_2$Ar (3.31 and 4.35), ROAr*H* (6.97), HOAr*H* (7.06) and ArO*H* (8.41),[19] of **10** distinctively appear in the spectrum after irradiation. Compound **10** reached the photostationary state after 24 hours, and the ratio of *cis* and *trans* was then able to be estimated from the integral area of the signals to be 36 : 64. Interestingly, we found that upon standing under room light for several days, compounds **10** in CDCl$_3$ also underwent isomerization to give the *cis*:*trans* ratio of 33 : 67. This result correlates with the observation of Vicens *et al.* in which azobenzene calixcrowns containing one glycolic unit were stable as *cis* isomers.[5] However, thus far, we cannot isolate the *cis* isomer of **10**. The *trans* form is, therefore, still thermodynamically more stable.

Interestingly, when CH$_3$CN (10 μL) was added into the CDCl$_3$ solution of **10** after isomerization, the signals due to *tert*-butyl, aromatic, ethereal and hydroxy protons shifted dramatically. The signal due to methyl protons of included CH$_3$CN appeared at 2.05 and 2.10 ppm for *cis* and *trans* isomers of compound **10**. The results suggest that both *cis* and *trans* forms of **10** can include CH$_3$CN into the cavity of calix[4]arene.

^{1}H NMR spectrum of **11** also changed remarkably after irradiation and upon standing under room light for several hours. However, we cannot conclusively say that the *cis*-*trans* isomerization has occurred since we do not have a crystal structure of **11** to substantiate the isomer of the azobenzene moiety before irradiation. It is found that the aromatic protons in *cis*-azobenzene are more shielded than those in *trans*-azobenzene.[20,21] ^{1}H NMR spectra of **8**, **9**, **10** and compounds containing *trans*-azobenzene groups[20,21] consist of doublet signals at ~7.6-7.9 ppm while those of **11**, before and after irradiation, do not have signals in this region. In addition, the ^{1}H NMR spectrum of **11** in Figure 3d shows complicated signals of aromatic, methylene bridge and *tert*-butyl protons which could result from various conformations of the calix[4]arene unit. The bithiophene analogue of compound **11** was also found to have a complicated


Figure 2. ^{1}H NMR (500 MHz, CDCl$_3$) spectra of compound **6** at (a) 25 °C and (b) -30 °C. * and # denote signals of the solvent and trace of water, respectively.

Figure 3. Partial ^{1}H NMR (400 MHz, CDCl$_3$) spectra of **10** (a) before, (b) after UV irradiation and **11**, (c) before, (d) after irradiation. * denotes signals of the solvent.

NMR spectrum due to fluxional behavior.[9] We suspect that **11** stays in the *cis* form and just undergoes the conformational change of the calix[4]arene framework in the same manner as its precursor, **6**, rather than the *cis-trans* isomerization.

Effects of Complexation of Na⁺ and K⁺ ions. The picrate salts of Na⁺ and K⁺ ions were employed in complexation studies. Normally, the picrate salts were not soluble in CDCl₃ and were added as solid into NMR tubes containing solutions of **10** and **11**. The inclusion of cations into ligands can be notified by the appearing of a singlet signal of aromatic protons of the picrate anion around 8.6-8.9 ppm which is well separated from the signals of the ligands. The metal salts were added into the ligands before and after UV irradiation.[22] ¹H NMR spectra of complexes of **10** after addition of sodium and potassium picrates possessed two doublet signals at 3.26 and 4.20 ppm (J~13 Hz) indicating that **10** maintained the cone conformation of calix[4]arene after complexation with the metal ions.

¹H NMR spectra (400 MHz, CDCl₃) of **10** in Figure 4 shows significant changes from the spectrum of the free ligand (Figures 2a and 2b). The spectrum in Figure 4a shows a singlet signal of picrate protons at 8.64 ppm. The broad peak of the glycolic protons of *trans* isomer at 4.44 ppm separates from those of *cis* isomer at 4.40 ppm and the multiplet signals appear around 6.82-6.93 ppm. Furthermore, doublet peaks of methylene bridge protons of the *trans* form at 3.26 ppm and the *cis* form at 3.32 ppm slightly shift from those of the free ligand. It was found from the integration that the amount of *cis* isomer increased from 36% to the range of 42-47%.

Addition of potassium picrate into **10** results in an appearance of a singlet signal of picrate protons at 8.92 ppm. The intensity of the signals corresponding to the *cis* isomer decreases dramatically. The integration showed that the percentage of *cis* isomer decreased from 36% to the range of 10-16%, and the amount of *trans* isomer increased to the range of 84-90%. However, upon standing under the room light, the amount of the *cis* form gradually increased to 25% after standing for 19 days, and reached 42% in 30 days. We do not have a definite explanation for the increasing of *cis* isomer. However, it is possible that K⁺ firstly formed a com-
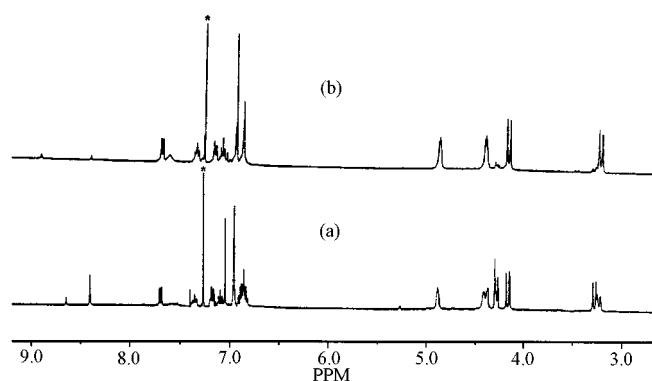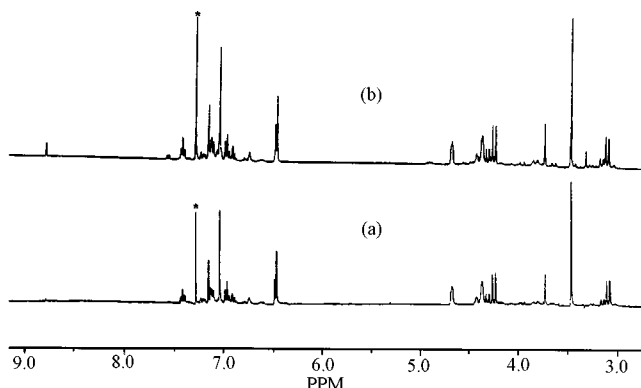
Figure 5. Partial ¹H NMR (400 MHz, CDCl₃) of **11** in the presence of (a) Na⁺ (b) K⁺. * denotes signals of the solvent.

plex with the *trans* form of **10** and increased the percentage of the *trans* form. Later, the thermal *trans* to *cis* isomerization took place and increased the amount of the *cis* form. The result also implies that the stability of the *trans*-**10**·K complex is not very strong.

¹H NMR spectra of ligand **11** in the presence of Na⁺ and K⁺ picrates are shown in Figure 5. The singlet signals of picrate aromatic protons are observed at 8.78 ppm. Figure 5a shows that, upon addition of Na⁺, the spectrum of **11** does not change significantly from that of the free ligand and a signal due to picrate protons has very low intensity. This suggests that the presence of Na⁺ has no effect to isomerization of the azobenzene unit. On the other hand, the presence of K⁺ caused significant changes in the ¹H NMR spectrum (Figure 5b). A doublet at 7.55 ppm and a singlet peak at 3.33 ppm are observed in the spectrum upon addition of potassium picrate into the solution of **11** for only 2 days. The doublet around 7.55 ppm was generally found in various *trans* azobenzenes[20,21] and the singlet at 3.33 ppm was in the region of methoxy protons. The result implies that *cis* to *trans* isomerzation of **11** occurs partially in the presence of K⁺, and this is also in line with the results obtained from compound **10**.

Conclusion

Two new azobenzene calix[4]crowns (**10** and **11**) have been synthesized by two different pathways. Compound **10** was isolated as *trans* isomer and was found to undergo *trans* to *cis* isomerization under room light and UV irradiation. Compound **6**, the precursor of compound **11**, underwent conformational interconversion due to the absence of intramolecular hydrogen bonding and was found to exist in mixed conformations of cone and partial cone (47 : 53) at -30 °C. Compound **11** was believed to exist in the *cis* form and undergo conformational interconversion rather than *cis-trans* isomerization upon exposing to UV or room light. The complexation studies showed that for **10**, the percentage of *cis* isomer increased in the presence of Na⁺ while the amount of *trans* isomer increased in the presence of K⁺. It also implies that the *cis* form is suitable for binding Na⁺ while the

Figure 4. Partial ¹H NMR (400 MHz, CDCl₃) of **10** in the presence of (a) Na⁺ (b) K⁺. * denotes signals of the solvent.

trans form is appropriate for K^{+}. In case of compound **11**, it was found that *cis* to *trans* isomerization occurred somewhat in the presence of K^{+}. Compared to the azobenzene crown ether synthesized by Shinkai and coworkers which showed the extractability of K^{+} over Na^{+} in both *cis* and *trans* forms,[23] our compounds **10** and **11** which consisted of 6 oxygen donor atoms from the ethoxy azobenzene unit attaching to the calix[4]arene frameworks showed selectivity of the *cis* and *trans* forms towards Na^{+} and K^{+}, respectively. Compounds **10** and **11** can thus possibly be used as switchable receptors or sensors for Na^{+} and K^{+} ions.

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