# Notes

## Proton-diionizable Bis-calix[4]azacrown Ether through *Mannich* Reaction

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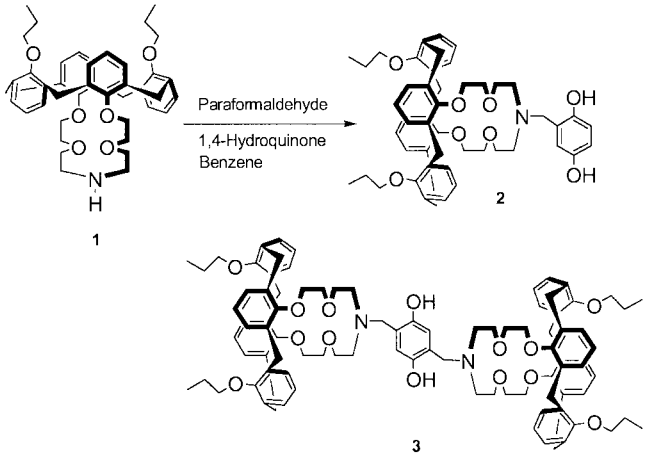
Over the past few decades, a considerable number of studies on *N*-pivot azacrown ethers have been made because they selectively entrap the specific metal cations not only through an electrostatic interaction between the hetero-atoms of the azacrown loop and the target metal ions but also through three-dimensional encapsulating assistance of the appended side arm on the nitrogen atom.[1] Especially, aza-crown ethers having phenolic side arm possess the distinct advantage over neutral azacrown ethers in that transport of metal ions from aqueous phase into an organic medium does not involve concomitant transfer of the counter-anions.[2] Such phenol-containing lariat ethers have shown selective cation extractability in basic condition.[3,4] For synthesis of such phenolic azacrown compounds, Bradshaw group has found one-step method based on *Mannich* reaction for which *N*-(methoxymethyl)azacrown and appropriate phenols were used.[5] Compared with the alkylation of azacrown ethers with 2-hydroxybenzyl halide, this *Mannich* reaction has at least two advantages: (i) the substituted phenols are readily available and (ii) due to the electrophilic character of the reaction it is not necessary to protect the functional groups of the substituted phenols, sensitive to nucleophilic attack by the azacrown ether nitrogen.[5] Lagow recently also reported one-pot synthesis using 1,10-diaza-18-crown-6 and *para*-substituted phenol in the presence of paraformaldehyde to give the *Mannich* reaction product.[6] Recently, we have been intrigued by the synthesis of ditopic receptor that is defined with *bis*-calixazacrown molecule capable of binding two guest ions in the azacrown cavity.[7-10] For this system we have also tried to synthesize the methoxymethylated compound on the nitrogen atom of the calixazacrown as a precursor of the *Mannich* product, but the reaction was not accomplished. Interestingly, we then finally found one-pot synthetic method for 2 and 3 as shown in Scheme 1. Our synthesis began with 25,27-*bis*-(1-propyloxy)calix[4]aza-crown-5 (**1**) which was prepared by following our previous report.[7] Under the nitrogen atmosphere, treatment of **1** with paraformaldehyde and 1,4-hydroquinone in benzene led to 1,3-alternate mono- **2** and disubstituted **3** with 2 : 8 ratio




**Scheme 1**. Synthetic route for compound **2** and **3**.

calculated by the NMR integration. We obtained **2** and **3** with 8% and 55%, respectively. The presence of only one singlet for methylene bridge of the calixarene unit in the $^{1}H$ NMR (about 3.80 ppm) and $^{13}C$ NMR (about 38 ppm) spectra clearly established that both **2** and **3** are in the 1,3-alternate conformation.[7] Consistent with the NMR results is the X-ray crystal structure of **3** as shown in Figure 1. Interestingly, the two oxygen atoms of the two OHs seemed to lie over the two calixazacrown loops to adopt the three dimensional encapsulation when metal ion approaches the azacrown cavity, for which one called it 'pre-organized' structure. Bradshaw group reported that in the case of *N*-

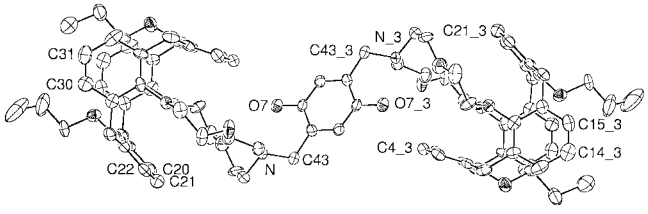



**Figure 1**. ORTEP diagram for **3**.

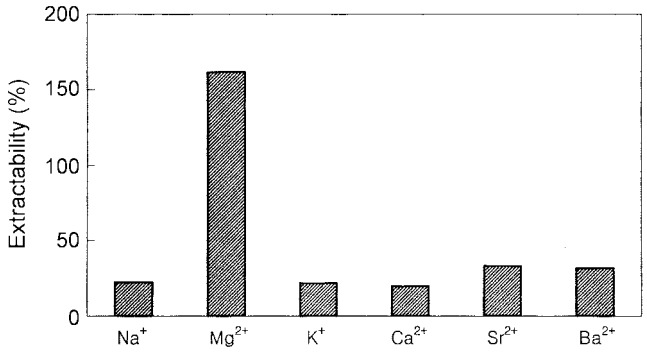



**Figure 2**. Extractability using **3** in basic condition toward metal cations.

CHQ-18-azacrown-6 there was a significant intramolecular hydrogen bond between OH and nitrogen atom, affecting the low extractability toward alkali, alkalineearth, and transition metal ions in two-phase extraction because the nitrogen atom of the azacrown unit has a partial positive character driven by the hydrogen bonding which raises a significant repulsion with the metal cation approached.[11] For **3**, however, the distance of H(O7)-N was observed to be 3.605 Å too long to be regarded as hydrogen bond, implying that the nitrogen atom can freely participate in the metal ion complexation.

Two-phase extractions were carried out using ligand **3** and the results are shown in Figure 2. The proton-ionizable calix-azacrown can extract certain cations by undergoing proton-dissociation on the pendant phenolic group of the ligand to yield an anion which in turn interacts intramolecularly with a metal ion complexed by the azacrown ether moiety.[12] In our extraction experiment, aqueous phase was adjusted to neutral and pH 12 using tetramethylammonium hydroxide. The nitrate salts of $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$, $Sr^{2+}$, and $Ba^{2+}$ were used to evaluate metal ion binding. Under neutral condition, no significant extractability and selectivity were observed.[13] In contrast, basic extraction (pH 12) gave remarkable extractability and selectivity for $Mg^{2+}$ ion when 5.0 mM of metal ion and 2.5 mM of **3** were used (Figure 2). More than 100 % extractability for $Mg^{2+}$ ion indicates that compound **3** forms 1 : 2 (ligand : metal ion) complex. It is certain that in basic condition the intermolecular or intramolecular hydrogen bond which can be estimated in solution state can be ruled out by deprotonation of the OH. This strongly indicates that the $Mg^{2+}$ ion is selectively encapsulated by the calixazacrown not only through the size agreement between the azacrown cavity and $Mg^{2+}$ ion but also through cation/$\pi$-interaction proposed by Kim[7-10] and Reinhoudt.[14] Most importantly, the additional coordinative phenoxy anion plays an significant role in the high extractability for $Mg^{2+}$ ion.

In conclusion, attachment of a mono- and diproton-ionizable group as a pendant unit onto the nitrogen of the calix[4]arene azacrown framework was successful through *Mannich* reaction. X-ray crystal structure and NMR spectra of **3** indicates that it is in the symmetrical 1,3-alternate conformation and has a pre-organized capsular cavity in which its two hydroxy groups of the hydroquinone lie over the azacrown cavity. Consequently, in two-phase extraction, we can conclude that **3** can selectively encapsulate the $Mg^{2+}$ ion at high pH condition due to the additional coordinative phenoxide anion in organic medium. The design, development, and elucidation of other types of the proton-ionizable calixarene receptors according to this concept are in progress.

## Experimental Section

**Synthesis**. Mono-substituted **2** and di-substituted **3**: to a solution of calix[4]arene azacrown ether (0.7 g, 1.05 mmol) and paraformaldehyde (0.042 g, 1.4 mmol) in dry benzene (25 mL) was added hydroquinone (0.058 g, 0.525 mmol) under nitrogen. The resulting mixture was then heated and held at reflux for 72 h. After removing benzene *in vacuo*, 50 mL of $CH_2Cl_2$ was added and dried over anhydrous $MgSO_4$. Removal of $CH_2Cl_2$ *in vacuo* gave a reddish solid. The crude product was isolated by column chromatography using methyl alcohol-ethyl acetate (1 : 10) as an eluent on silica gel. Recrystallization from a solution in ethyl acetate-dichloromethane gave **2** as colorless oil and **3** as a colorless crystalline in 8.0 and 55.3% yield, respectively. For **2**: oil, IR (KBr, neat, $cm^{-1}$) = 3390 (O-H). $^1$H NMR (600 MHz, $CDCl_3$, Bruker ARX-600 in Korea Basic Science Institute in Taejon, Korea): $\delta$ 7.08 (d, $J$ = 7.5 Hz, 4H, Ar-*H*), 7.02 (d, $J$ = 7.5 Hz, 4H, Ar-*H*), 6.88 (t, $J$ = 7.5 Hz, 2H, Ar-*H*), 6.79 (t, $J$ = 7.5 Hz, 2H, Ar-*H*), 6.72-6.50 (m, 3H, Ar-*H*), 3.81 (s, 8 H, Ar*CH*$_2$Ar), 3.69 (s, 2H, N*CH*$_2$Ar), 3.52 (t, $J$ = 4.8 Hz, 4H, PhO*CH*$_2$), 3.36 (t, $J$ = 7.5 Hz, 4H, O*CH*$_2$CH$_2$CH$_3$), 3.29 (t, $J$ = 4.8 Hz, 4H, O*CH*$_2$), 3.26 (t, $J$ = 4.8 Hz, 4H, O*CH*$_2$), 2.64 (t, $J$ = 4.6 Hz, 4H, *CH*$_2$N*CH*$_2$), 1.16 (m, $J$ = 7.5 Hz, 4H, OCH$_2$*CH*$_2$CH$_3$), 0.68 (t, $J$ = 7.5 Hz, 6H, OCH$_2$CH$_2$*CH*$_3$). For **3**, Mp 245-247 °C, IR (KBr, $cm^{-1}$) = 3391 (O-H). $^1$H NMR ($CDCl_3$): $\delta$ 7.09 (d, $J$ = 7.5 Hz, 8H, Ar-*H*), 7.02 (d, $J$ = 7.5 Hz, 8H, Ar-*H*), 6.89 (t, $J$ = 7.5 Hz, 4H, Ar-*H*), 6.79 (t, $J$ = 7.5 Hz, 4H, Ar-*H*), 6.51 (s, 2H, Ar-*H*), 3.81 (s, 16H, Ar*CH*$_2$Ar), 3.71 (s, 4H, N*CH*$_2$Ar), 3.53 (t, $J$ = 4.8 Hz, 8H, PhO*CH*$_2$), 3.36 (t, $J$ = 7.5 Hz, 8H, O*CH*$_2$CH$_2$CH$_3$), 3.29 (t, $J$ = 4.8 Hz, 8H, O*CH*$_2$), 3.26 (t, $J$ = 4.8 Hz, 8H, O*CH*$_2$), 2.67 (t, $J$ = 4.6 Hz, 8H, *CH*$_2$N*CH*$_2$), 1.16 (m, $J$ = 7.5 Hz, 8H, OCH$_2$*CH*$_2$CH$_3$), 0.68 (t, $J$ = 7.5 Hz, 12H, OCH$_2$CH$_2$*CH*$_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 157.17, 156.97, 150.21, 134.06, 133.66, 129.72, 129.60, 122.41, 122.26, 122.14, 116.06, 71.89, 70.72, 69.79, 69.63, 59.27, 53.10, 38.26, 22.24, 9.96. Anal. Calcd for $C_{92}H_{108}N_2O_{14}$: C, 75.32; H, 7.37. Found: C, 75.38; H, 7.33.

**X-ray cystallography**. Colorless crystals of $C_{92}H_{108}N_2O_{14}$ were obtained by the slow evaporation of solvent from a solution of **3** in methanol, and a crystal of approximately $0.462 \times 0.363 \times 0.066$ mm was mounted and aligned on an Enraf-Nonius Cad-4 diffractometer.

Crystal Data: colorless plate, $a$ 24.563(4), $b$ 10.325(2), $c$ 16.715(5) Å, $\alpha$ 90.0, $\beta$ 94.74, $\gamma$ 90.0°, $V$ 4224.9(17) Å$^3$, 290 K, space group $P2_1/c$, $Z$ 2, $\mu$ 0.077 $mm^{-1}$, number of reflection measured 3970, number of independent reflection

measured 3856, $R_{int}$ 0.1426, and final value for R 0.1194.

**Two-phase extraction**. Aqueous phase: 5.0 mM of metal ions in 3 mL $(CH_3)_4NOH$ solution (pH 12). Organic Phase: 2.5 mM of **3** in 3 mL of $CHCl_3$. They were mixed and equilibrated by shaking for 30 min at 25 °C. Concentrations of metal ion remained in aqueous phase were determined by ICP-ASE (Perkin-Elmer, Optima 3300DV).

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