

Synthesis and Ionophoric Properties of Calix[4]arene Having Two Convergent Carboxylic Acid Functions

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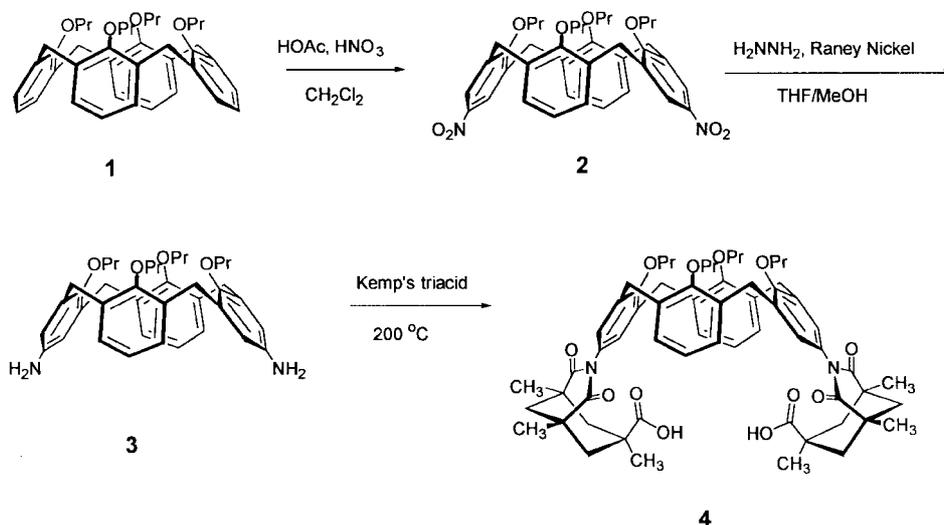
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Received April 9, 2001

Keywords : Ionophore, Calix[4]arene, Kemp's triacid, Transport.

The development of selective ionophores for the efficient binding and sensing of heavy metal ions offers exciting prospects in the field of supramolecular chemistry.¹⁻³ Heavy metal ions of Hg^{2+} , Pb^{2+} , and Cd^{2+} are particularly important species in applied chemical industries and biological systems, and various functional ionophores for these target ions have been developed continuously.⁴⁻⁶ Among those frequently employed carriers for the heavy metal ion separations are carboxylic acid derivatives. In these cases, the carboxylic acid functions generally act both as ligands and counter ions that beneficially do not necessitate concomitant transport of counter anions through membranes.⁷ Furthermore the binding strength of resulting ionophores can be controlled by the pH of the medium that makes the active transport of ionic guests possible. Recently, Rebek *et al.* developed a series of cleft type ionophores having two Kemp's triacid moieties and observed pronounced Ca^{2+} -selective carrier properties.⁸ Following this, closely related Kemp's triacid based dicarboxylic acid compounds having varying spacer groups have been prepared and found to have selective ionophoric properties toward toxic heavy metal ions of Hg^{2+} and Pb^{2+} .^{9,10} In this paper, we would like to report the synthesis of a new dicarboxylic acid derivative utilizing the molecular framework of calix[4]arene and its selective ionophoric properties toward heavy metal ions of Hg^{2+} and Pb^{2+} by the competitive transport experiments.

Bis(Kemp's triacid) derivative **4** was prepared by the condensation of diamino derivative of calix[4]arene **3** with Kemp's triacid (Scheme 1). Selective nitration of tetrapropyl ether **1** yields 1,3-dinitro derivative **2** along with undesired nitrated derivatives.¹² The crude 1,3-dinitro derivative **2** was separated from the reaction mixture by the column chromatography and subsequently purified by the crystallization from CH_2Cl_2 and MeOH (17%). Reduction of **2** with hydrazine/Raney Nickel afforded the diamino derivative **3** in good yield (89%).¹³ Finally condensation of **3** with Kemp's triacid without solvent¹⁴ yielded the desired dicarboxylic acid **4** (45%). In ^1H NMR spectra, all the prepared derivatives showed a characteristic AB splitting pattern for the bridging methylene protons of calix[4]arenes in cone conformation. The $\Delta\delta$ values between a pair of doublets for the bridging methylene protons are all within the range of 1.30-1.35 ppm, which suggests that the main structural characteristics of calix[4]arene framework of **1-4** are not so different. Interestingly, the dicarboxylic acid **4** showed a broad resonance at δ 6.83 for the protons of aromatic rings bearing Kemp's triacid moiety which is compared with sharp and well-resolved doublet and triplet for the protons of two unsubstituted distal aromatic rings. That is due to the presence of bulky imide group on the *para*-position of benzene rings and the broad peak is sharpened as the temperature increased. One more thing to note is that the dicarboxylic acid **4** is found to be rel-



Scheme 1



Scheme 2

atively non-polar and can easily be eluted with hexane/EtOAc mixture in column chromatography in spite of the presence of two polar carboxylic acid functions. That is due to the U-shaped relationship between the carboxylic acid functions of Kemp's triacid. With this relationship, the carboxylic acid functions of **4** are directed toward interior of the molecule and will take relatively buried conformation within the molecular framework of calix[4]arene.

A variety of dicarboxylic acids have been developed for the recognition of doubly charged metal ions.^{7,15,16} In the present study, we prepared as mentioned earlier a new dicarboxylic acid compound utilizing the characteristic structural properties of calix[4]arene framework in cone conformation. Based on this molecular framework, we postulated that the two Kemp's triacid moieties on the upper rim of calix[4]arene in distal position might provide two convergent carboxylic acid functions suitable for the recognition of doubly charged metal ions (Scheme 2). Ionophoric properties of dicarboxylic acid derivative **4** were investigated by the liquid membrane transport experiments through U-tube apparatus (Table 1). The transport was carried out under competitive condition and the source phase was a mixture of representative metal ions of alkali (Li^+ , Na^+ , K^+ , Rb^+), alkaline earth (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+}), transition metal (Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+}), and heavy metal ions (Hg^{2+} , Pb^{2+} , Cd^{2+}). The carrier **4** showed significantly selective transport behavior toward heavy metal ions of Hg^{2+} and Pb^{2+} ions over Cd^{2+} ions. Transport efficiency for the other surveyed metal ions are not so significant and generally less than 5%. Among the transition metal ions, a small selectivity of 4.3% toward Cu^{2+} ions was discernible and the selectivity order was $\text{Cu}^{2+} \gg \text{Zn}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+}$. Transport efficiency for the alkaline earth metal ions was also negligible except for a small selectivity toward Ba^{2+} ions. For alkali metal ions somewhat selectivity in transport efficiency around 5% toward Na^+ and K^+ was observed. This type of Hg^{2+} - and Pb^{2+} -selectivities

have been observed for some related dicarboxylic acid derivatives constructed using the Kemp's triacid as a basic structural motif.^{9,10}

FAB-MS measurement studies also revealed that the selective binding affinity of **4** toward the Hg^{2+} ions. FAB mass spectrum of **4** was measured in the presence of five equiv each of alkali, alkaline earth, transition metal, and heavy metal ions as acetate salt in *m*-NBA matrix.¹⁷ In its mass spectrum a prominent peak for the $[\text{4-H+Hg}]^+$ ion at $m/z = 1267.3$ was observed and the intensity of this peak is 1.2 times larger than the molecular ion peak of **4**. No other discernible peaks were observed for the rest of metal ions under the present measurement condition. This observation strongly suggests that the ionophore **4** has a high affinity toward Hg^{2+} ions among the surveyed metal ions.

In summary, a new ionophore having two convergent carboxylic acid functions has been prepared by utilizing structural motifs of Kemp's triacid and calix[4]arene in cone conformation and found to have selective ionophoric properties toward Hg^{2+} and Pb^{2+} ions in competitive transport experiments.

Experimental Section

General: Kemp's triacid and calix[4]arene were purchased (Aldrich) and used without further purification. Column chromatography was performed with silica gel 60 (230-400 mesh ASTM, Merck) and TLC was carried out with silica gel 60 F254. Melting points were measured by Gallenkamp melting point apparatus and are uncorrected. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were obtained on a Varian Gemini-2000 with TMS as an internal reference. ICP-AES measurements were done on a Jobin-Yvon JY-24 spectrometer. Mass spectral data were obtained with a Micromass Autospec mass spectrometer. Tetrapropyl ether **1**,¹¹ dinitro derivative **2**,¹² and diamino derivative **3**¹³ of calix[4]arene were prepared following the reported procedures.

Bis (Kemp's triacid) Derivative of Tetrapropoxy-calix[4]arene **4:** A well ground and mixed Kemp's triacid (465 mg, 1.8 mmol) and diamine **3** (310 mg, 0.5 mmol) were heated at 200 °C under N_2 atmosphere for 2 h. After the reaction, the residue was cooled and dispersed in CH_2Cl_2 . The solution was filtered and evaporated under reduced pressure. The product was purified by the column chromatography (silica gel, hexane/EtOAc) and followed by the recrystallization from CH_2Cl_2 /hexane mixture to yield light amber colored powder (240 mg, yield 45%). mp: 315-318 °C; R_f : 0.41

Table 1. Competitive Transport of Metal Ions by Carrier **4**^a

Carrier	Transport efficiency (%)														
	Hg^{2+}	Pb^{2+}	Cd^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Li^+	Na^+	K^+	Rb^+
4	40.3	22.6	0.61	^b	0.16	4.33	0.43	0.12	0.66	0.71	1.41	^b	5.26	2.36	0.60

^a Transport condition: source phase=mixture of 0.1 M each of alkali, alkaline earth, transition metal, and heavy metal ions in acetate salts in 5.0 mL of HOAc/NaOAc buffer (pH=6.0), membrane phase=5.0 mM of carrier in chloroform solution (15 mL), receiving phase=0.1 M HNO_3 (5.0 mL), at 25 ± 2 °C. ^b Less than 0.1%.

(hexane : EtOAc = 1 : 1); ^1H NMR (CDCl_3 , 300 MHz) δ 6.83 (br s, 4H), 6.25 (t, 2H, $J = 7.2$ Hz), 6.06 (d, 4H, $J = 7.5$ Hz), 4.38 (d, 4H, $J = 13.2$ Hz), 3.99 (t, 4H, $J = 8.1$ Hz), 3.61 (t, 4H, $J = 8.1$ Hz), 3.07 (d, 4H, $J = 13.5$ Hz), 2.88 (d, 4H, $J = 14.1$ Hz), 2.73 (d, 4H, $J = 13.5$ Hz), 2.01 (d, 2H, $J = 13.8$ Hz), 1.94-1.77 (m, 8H), 1.50 (d, 2H, $J = 13.8$ Hz), 1.39-1.21 (m, 18H), 1.07 (t, 6H, $J = 8.1$ Hz), 0.82 (t, 6H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 178.45, 177.89, 176.87, 171.44, 158.04, 155.20, 137.44, 132.85, 128.99, 128.28, 127.83, 123.22, 77.59, 77.17, 76.74, 76.46, 44.30, 44.23, 44.08, 42.52, 41.88, 41.73, 40.88, 40.17, 31.23, 31.05, 30.06, 26.18, 25.10, 23.54, 22.97, 10.93, 9.72; MS (FAB, m -NBA): m/z calcd for $\text{C}_{64}\text{H}_{78}\text{N}_2\text{O}_{12}$ 1066.6, found 1067.

Transport Experiment: Transport experiments were performed by using a U-tube (i.d. = 1.5 cm) through chloroform liquid membrane containing carrier ($[\mathbf{4}] = 5.0$ mM in 15 mL). The source phase was 5.0 mL of a mixture containing 0.1 M each of alkali (Li^+ , Na^+ , K^+ , Rb^+), alkaline earth (Mg^{2+} , Ca^{2+} , Sr^{2+} , Ba^{2+}), transition metal (Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+}), and heavy metal ions (Hg^{2+} , Pb^{2+} , Cd^{2+}) in acetate buffer (pH = 6). The receiving phase was 0.1 M HNO_3 solution (5.0 mL). The membrane phase was stirred magnetically at a constant speed of 200 rpm for 48 h at 25 ± 2 °C. After transport the receiving phase was carefully removed and the concentrations of transported metal ions were assayed by ICP-AES.

Acknowledgments. This work was supported by the fund from Chung-Ang University (Special Grant, 1999) and gratefully acknowledged. The authors thank professor B. H. Kim for generous providing samples of diamine **3**.

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