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Studies on Complexation of Alkaline Earth Metal Cations with Acyclic Polyether Dicarboxylic Acids

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Acyclic polyether dicarboxylic acids having butyl and tetradecyl side alkyl chains at the α-position of the carboxylic acid sidearm unit were prepared by the reaction of bisphenol and 2-bromoalkanoic acid in the presence of sodium hydride with quantitative yields. Complexation studies and solvent extraction on complexes of these ethers with alkaline earth metal ions indicate that 1,2-bis((2-2′-carboxybutyloxy)-phenoxy)ethane (**2**) shows an excellent selectivity for the calcium ion.

Introduction

A number of macrocyclic polyethers have been synthesized and employed for the separation of alkali, alkaline earth, and transition metal ions as a result of their complexation abilities (Cram and Trueblood, 1985; Dietrich et al., 1993; Inoue and Gokel, 1990). Complexation of a metal ion with polyethers that bear side alkyl chains has been studied (Vögtle and Weber, 1979). Several of these studies have focused on the determination of the selectivity and efficiency of podand-mediated extraction of metal ions from an aqueous phase into an organic medium or transport of metal ions through the organic media into an aqueous phase (Strzelbicki and Bartsch, 1981). The Complexation ability was markedly enhanced by the introduction of proton-ionizable groups such as carboxylic, phosphonic, and sulfonic acids onto the crown ether backbone (Bartsch et al., 1982, 1992). Metal ion extraction by such chelating agents bearing proton-ionizable groups does not involve concomitant transfer of one or more aqueous phase anions into the organic medium. This factor was found to be of immense importance to potential applications in which hard anions such as chloride, nitrate, and sulfate would be involved.

With this in mind, to provide greater insight into the factors that control the selectivity and efficiency of alkaline earth cation extraction by a lipophilic acyclic polyether dicarboxylic acid, synthetic ligands (**1**−**9**) have been prepared. On the basis of two-phase solvent extractions and potentiometric titrations, we report the results of calcium selective complexation.

Experimental Section

Syntheses. Melting points were measured with a Mel-Temp feature of a Fisher-Johns melting point apparatus without any correction. IR spectra were obtained with a Perkin-Elmer 1600 Series FT-IR using potassium bromide pellets and on a deposited KBr window in the case of solid product and oil. ^{1}H NMR spectra were recorded with a 400 MHz (Bruker ARX-400) spectrometer, and the chemical shifts (d) were reported downfield from the internal standard, tetramethylsilane. Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Tetrahydrofuran was freshly distilled from sodium metal ribbon or chunks. Dichloromethane was freshly distilled from lithium aluminum hydride. A series of bisphenols as starting materials were prepared by the method reported by Heo (1983).

General preparation methods for acyclic polyether dicarboxylic acids were as follows. After removal of the protecting mineral oil from NaH (50% dispersion in mineral oil, 6.00 g, 0.34 mol) by washing with pentane under nitrogen, a solution of bisphenol (10.0 g, 34.4 mmol) in 150 mL of dry tetrahydrofuran (THF) was added. The mixture was stirred for 2 h at room temperature. 2-Bromoalkanoic acid (86.2 mmol) in 20 mL of dry THF was added dropwise at room temperature during a period of 2 h. Upon the complete addition, the reaction mixture was stirred for an additional 10 h at room temperature. After careful addition of water to the reaction mixture in an ice bath to destroy the unreacted excess NaH, which gave a homogeneous solution, THF was removed in vacuo leaving an aqueous mixture. Into this basic solution was poured 100 mL of ethyl acetate to extract the unreacted bisphenol and organic impurities. The aqueous layer was washed with ethyl acetate (2 × 50 mL). Upon the acidification with concentrated HCl to pH 1, crude product was extracted with methylene chloride (3 × 50 mL) and dried over $MgSO_4$. Removal of methylene chloride in vacuo provided a colorless oil, which was recrystallized from 100 mL of diethyl ether to give white crystals in 90% yield.

Potentiometric Titration. The potentiometer was an ORION model 701A digital ion meter, which could be read

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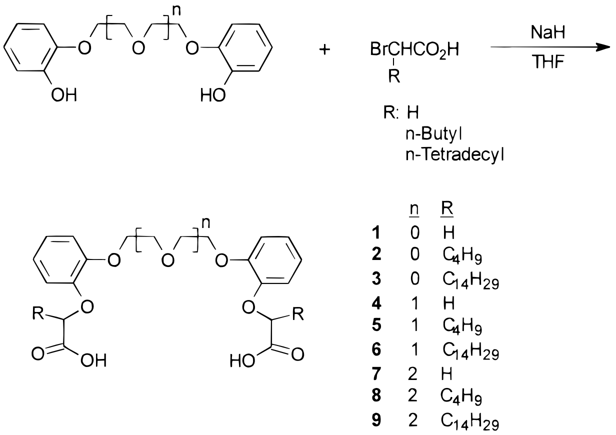
Scheme 1. Synthetic Route for Preparation Acyclic Polyether Dicarboxylic Acids (1−9)



to 0.001 pH unit. The glass combination electrode was an ORION Ross Electrode model 81-02. The filling solution was made of 3 M TMACl in 90 vol % methanol (90 mL MeOH/100 mL solution). The measurement was undertaken at (25 ± 0.1) °C under a nitrogen atmosphere. The pH meter was standardized against oxalate buffer solutions before titration. Oxalate buffer solution (pH 3.73) were made by ammonium oxalate monohydrate and oxalic acid in 90 vol % methanol. Succinate buffer solutions (pH 6.73) were made from succinic acid and sodium succinate salt in 90 vol % methanol. Tetramethylammonium chloride (0.1 M) was used to adjust the ionic strength. A glass combination electrode, a microburet with 5.0 mL capacity, and 50 mL of 1 mM ligand in 90 vol % methanol were introduced into a thermostated titration vessel equipped with a magnetic stirring bar. The concentration of titrant, tetramethylammonium hydroxide, was 20.3 mM. Titrations were conducted in triplicate. Protonation and stability constants were calculated by the program BEST (Martell, 1992).

Extraction Procedures. Solvent extraction was followed from the procedures reported by Bartsch et al. (1992). Advantages of this method that it is known to speed the experiment and it uses a small amount of organic ligand. For competitive extractions of alkaline earth metal chloride solution, a microextraction technique was used. An aqueous solution of alkaline earth metal chloride (2.00 mL, 0.125 M with 0.2 M cesium hydroxide for pH adjustment) and 2.00 mL of 0.01 M organic ligand in chloroform in a 10 mL centrifuge tube were mixed by vortex mixer for 5 min. After centrifuging, the equilibrium pH of the upper aqueous layer was measured. Then a 1.00 mL sample of the chloroform layer was taken and stripped with 1.00 mL of 0.1 M HCl solution. The concentration of metal ion in the aqueous phase was determined by an atomic absorption spectrometer.

Results and Discussion

Syntheses. The synthetic route for the preparation of acyclic polyether dicarboxylic acids is shown in Scheme 1. Bisphenol was used as a starting material, which can be prepared from the reaction of catechol with bis(2-chloroethyl) ether in NaOH solution. Reaction of bisphenol with 2.5 equiv of 2-bromoalkanoic acid in the presence of 5 mol of sodium hydride as a base provided the desired products in over 90% yield. Attempted reactions with potassium hydride instead of sodium hydride were found to be less effective. Recrystallization from diethyl ether gave a white solid. Their melting points, ^{1}H NMR spectra, and IR spectra are listed in Table 1.

Potentiometric Titration. Protonation constants and stability constants of synthesized organic ligands in this study were determined in 90 vol % methanol. Table 2 shows the first (log β_{H_2L}) and second protonation constant (log β_{H_2L}), respectively, for each ligand. Upon the elongation of the ethylene glycol unit connected between the two benzene rings, both protonation constants gradually increased. Stability constants for the complexation of alkaline earth metal ions were measured and are listed in Table 3. For most metal ions, the order of stability constant is $Ca^{2+} > Sr^{2+} \doteqdot Ba^{2+} \gg Mg^{2+}$. As the number of ethylene glycoloxy units decreases, the stability constants toward the calcium ion gradually decrease. It was reported that when a ligating agent complexes with a specific metal ion, major factors that influence the stability constant are radius of metal ion, oxidation state of metal ion, species of donor atoms, solvation effect, anion effect, and dipolar interaction between the organic ligand and metal ion (Vögtle and Weber, 1985). So, the calcium selectivity indicates that when the pseudo-cyclic conformation of the organic ligand is carried out, the length of the monoethylene glycol unit is sufficient to fit with the calcium ion to give a maximized ion−dipolar interaction and electrostatic interaction. The stability constants based on both efficiency and selectivity toward an alkaline earth cation are influenced by the introduction of a lipophilic group, C_4H_9. The lipophilic ligand shows better conformation when a metal ion is introduced. This is probably attributed to a micelle effect with which the cyclic formation takes place much more easily. From the distribution diagram, L^{2-} was observed to exist at over pH 6, indicating two hydrogens are completely dissociated. The distribution species of metal ion (M), complex (LM), and LMH_{-1} (MLOH), which combines with the OH anion, give information on 1:1 maximum complexation in the pH range 4−6. At pH over 10, basic conditions, most of the metal complexes were observed to exist as MLOH.

Two-Phase Extraction. To further prove the influence of the lipophilicity and the polyether length of the organic ligand on metal ion complexation, solvent extraction experiments with all ligands except **1**, **4**, and **7** (see Table 4) for alkaline earth metal ions were carried out. Solvent extraction using **1**, **4**, and **7**, which do not contain lipophilic side chains, could not be carried out with this experiment because of their low solubility in chloroform. A profile for stripped metal ion concentrations by HCl aqueous solution after extracted with the organic ligand **2** which performs the best complexation behavior among nine organic ligands in chloroform, is shown in Figure 1. The extracted metal ion concentration was observed to increase with pH increase. Calcium ion was selectively extracted at about 40−50% from the source phase. Table 4 shows the selectivity order of extracted metal ions as $Ca^{2+} > Sr^{2+} \doteqdot Ba^{2+} \gg Mg^{2+}$, indicating the same propensity of calcium ion selectivity over other alkaline earth metal ions as observed from potentiometric titration experiment. Hence the extraction ability of an organic ligand is strongly relate to that of the stability constant for complexation. The total loaded amount of metal ions is over 90% in all cases. Especially, ligand **2** shows the best extracting behavior to give 99.4 of loading percentage. In Table 4, the selectivity of calcium ion for **2**, **5**, and **8** in which butyl groups are branched was observed to be somewhat better than that for **3**, **6**, and **9** with tetradecyl group substituted. Walkowiak et al. (1992) have reported that when the pendent side

Table 1. Yields and Spectral Data for Acyclic Polyether Dicarboxylic Acids 1−9 Drawn in Scheme 1

compd	yield, %	T_m, °C	^{1}H NMR spectra (CDCl$_3$), ppm	IR spectra, cm^{-1}
1	91	165−168	4.33 (s, 4 H), 4.65 (s, 4 H), 6.71−7.10 (m, 8 H)	3450 (O−H), 1710 (C=O), 1107 (C−O)
2	92	127−130	0.86 (t, 6 H), 1.10−1.60 (m, 8 H), 2.80−2.11 (M, 4 H), 4.36 (s, 4 H), 4.57 (t, 2 H), 6.91 (s, 8 H)	3455 (O−H), 1711 (C=O)
3	95	108−110	0.77−1.00 (t, 6H), 1.10−2.00 (br s, 48H), 2.12−2.40 (m, 4 H), 4.36 (s, 4H), 4.57 (t, 2H), 6.87−7.07 (m, 8H)	3445 (O−H), 1713 (C=O)
4	92	140−141	3.92−3.98 (m, 4 H), 4.21−4.24 (m, 4 H), 4.62 (s, 4 H), 6.93−6.99 (m, 8 H)	3455 (O−H), 1713 (C=O)
5	90	158−162	0.90 (t, 6 H), 1.20−1.80 (m, 8 H), 1.80−2.10 (m. 4 H), 3.80−4.20 (m, 8 H), 4.55 (t, 2 H), 6.94 (s, 8 H)	3389 (O−H), 1703 (C=O)
6	93	92−93	0.77 (t, 6 H), 1.10−1.77 (m, 48 H), 2.10−2.40 (m, 4 H), 3.96 (m, 4 H), 4.15−4.23 (m, 4 H), 4.47 (t, 2 H), 6.87−7.07 (m, 8 H)	3450 (O−H), 1710 (C=O), 1110 (C−O)
7	90	69−71	3.75 (s, 4 H), 3.85 (s, 4 H), 4.14 (s, 4 H), 4.59 (s, 4 H), 6.88−6.95 (m, 8 H)	3427 (O−H), 1718 (C=O), 1107 (C−O)
8	91	97−99	0.93 (t, 6 H), 1.20−1.71 (m, 8 H), 1.77−1.88 (m, 4 H), 3.57−4.50 (m, 14 H), 6.85−7.12 (m, 8 H)	3430(O−H), 1715 (C=O), 1106 (C−O)
9	90	72−73	0.79 (t, 6 H), 1.11−1.90 (m, 48 H), 2.10−2.40 (m, 4 H), 3.96 (m, 4 H), 4.15−4.23 (m, 4 H), 4.30−4.41 (m, 4 H), 4.47 (t, 2 H), 6.87−7.07 (m, 8 H)	3429 (O−H), 1710 (C=O), 1107 (C−O)

Table 2. Protonation Constants for Acyclic Polyether Dicarboxylic Acids in 90 vol % Methanol at 25 °C and μ = 0.1 M

ligand	log β_{HL}[a]	log $\beta_{\mathrm{H_2L}}$[b]
1	4.51 ± 0.01	8.19 ± 0.02
2	4.92 ± 0.03	8.48 ± 0.02
4	4.63 ± 0.01	8.13 ± 0.02
5	5.63 ± 0.02	9.34 ± 0.01
7	5.68 ± 0.02	9.23 ± 0.04
8	5.98 ± 0.01	9.60 ± 0.04

[a] log β_{HL} is for the equilibrium $\mathrm{L^{2-} + H^+ \leftrightarrow HL^-}$. [b] log $\beta_{\mathrm{H_2L}}$ is for the equilibrium $\mathrm{HL^- + H^+ \leftrightarrow H_2L}$.

Table 3. Stability Constants for Acyclic Polyether Dicarboxylic Acids with Alkaline Earth Metal Cations in 90 vol % Methanol at 25 °C and μ = 0.1 M

	log K_{ML}[b]			
ligand	$\mathrm{Mg^{2+}}$	$\mathrm{Ca^{2+}}$	$\mathrm{Sr^{2+}}$	$\mathrm{Ba^{2+}}$
1	1.27 ± 0.10	6.63 ± 0.03	5.27 ± 0.01	4.95 ± 0.02
2	1.08 ± 0.12	7.86 ± 0.08	6.28 ± 0.05	5.35 ± 0.04
4	α[a]	6.07 ± 0.03	4.45 ± 0.02	5.52 ± 0.02
5	α	6.80 ± 0.05	4.35 ± 0.03	5.54 ± 0.03
7	α	6.04 ± 0.02	4.72 ± 0.01	5.94 ± 0.02
8	α	6.00 ± 0.04	5.19 ± 0.02	5.85 ± 0.04

[a] α: too small for calculation. [b] log K_{ML} is for the equilibrium $\mathrm{M^{2+} + L^{2-} \leftrightarrow ML}$.

alkyl chain is too long like the $\mathrm{C_{14}H_{29}}$ tail, the ligand reveals large lipophilicity to give a poor complexation ability due to entropic disfavor. Therefore, with this point, the lipophilicity with two butyl group in this study could be sufficiently enough for metal ion complexation in organic solution.

In conclusion, acyclic polyethers having a dicarboxylic end group able to carry out efficient transport of alkaline earth metal ion were successfully synthesized. Complexation studies and solvent extraction on complexes of these ethers with alkaline earth metal ions indicate that the ligand **2** show an excellent selectivity for the calcium ion. The high calcium ion selectivity and efficiency appear to arise from a unique combination of lipophilic group, number of polyether oxygens, and carboxylic end groups. To further investigate the influence of donor atom species and number of donor atoms on complexation, syntheses of acyclic polyethers containing nitrogen atom as a donor and complexation studies are in progress, and the results will be reported.

Table 4. Selectivity and Efficiency of Alkaline Earth Metal Cations from Aqueous Solution into Chloroform by Acyclic Polyether Dicarboxylic Acids

ligands	selectivity order and selectivity coefficients[a]	total loading %[b]
2	$\mathrm{Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}}$ 1.5 2.1 14.2	99.4
3	$\mathrm{Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}}$ 1.3 2.3 10.4	91.9
5	$\mathrm{Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}}$ 1.5 3.9 7.6	94.0
6	$\mathrm{Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}}$ 1.8 2.9 5.1	90.8
8	$\mathrm{Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}}$ 1.2 3.1 7.7	90.0
9	$\mathrm{Ca^{2+} > Ba^{2+} > Sr^{2+} > Mg^{2+}}$ 1.4 2.3 5.9	87.2

[a] Mole ratio of $\mathrm{Ca^{2+}}$/other alkaline earth metal cations. [b] (total metal ion concentration loaded)/(ligand concentration) × 100 (%).

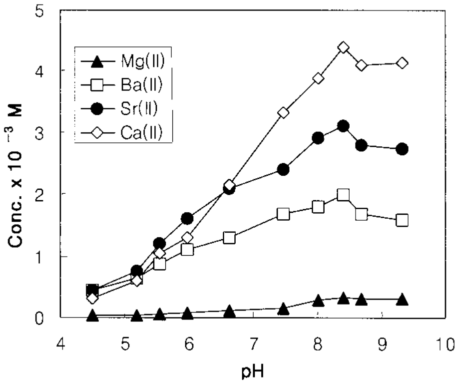


Figure 1. Profiles for molar concentrations of extracted metal ions using ligand **2**.

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