Synthesis and Ionophoric Properties of Crown Ether Capped with a Convergent Hydroxamic Acid Function

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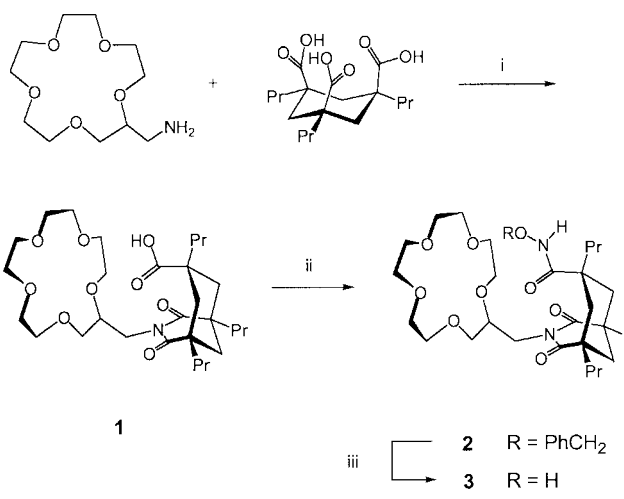
The structures and functions of classical crown ethers have been continually evolved to meet the specific requirements for the recognition of more demanding target systems.[1] One of the most frequently employed approaches is the introduction of extra binding sites into the basic framework of crown ethers as are well-exemplified systems of the lariat crown ethers.[2] Among these, lariat crown ethers having pH-responsive functions in their arm, such as carboxylic acid and hydroxamic acid derivatives, are particularly attractive for the ionophoric applications.[3] In particular, hydroxamic acid functions are employed frequently in many natural and synthetic ionophore systems and exhibited very unique binding behaviors toward some transition metal ions.[4-7] Meanwhile, in many of the designed supramolecular systems, obtaining a specific convergent orientation of particular ligating functions toward active site is highly desirable for selective and strong binding of targeted guests. For these purpose, U-shaped structural motif of Kemp's triacid is known to be very useful and resulted in the developments of many sophisticated supramolecular systems.[8-10] In this paper, we report the synthesis of a novel crown ether having a convergent hydroxamic acid function by utilizing the structural motif of Kemp's triacid and its selective ionophoric behavior toward some of heavy and transition metal ions in competitive transport experiments.



Scheme 1. *Reagents and conditions*: i, 200 °C; ii, oxalyl chloride in CH_2Cl_2, then $PhCH_2ONH_2$, Et_3N, CH_2Cl_2; iii, Pd/C, H_2 in EtOH.

The hydroxamic acid derivative **3** was prepared from the Kemp's triacid-capped 15-crown-5 ether **1** as shown in Scheme 1. Kemp's triacid-capped derivative **1** was prepared by the reaction of 2-aminomethyl-15-crown-5 ether[11] with Kemp's triacid following the reported procedure.[12] The acid derivative was converted into its acyl chloride by the treatment with oxalyl chloride, which was subsequently reacted with O-benzylhydroxylamine (CH_2Cl_2/NEt_3) to yield benzyl derivative **2** (60%). Deprotection of benzyl derivative by hydrogenation under Pd/C condition[13] afforded the desired hydroxamic acid derivative **3** in moderate yield (85%).[14] Due to the seemingly lower lipophilicity of the compound derived from methyl Kemp's triacid for an efficient carrier, propyl analogue of Kemp's triacid was employed for the construction of final ionophore structure. The enhancement in lipophilicity of the resulting propyl derivative **3** due to the replacement of three methyl groups of Kemp's triacid moiety with propyl groups is estimated to be 3.0 in Hansch's lipophilicity increment parameter (π_x),[15] which we believe is much favorable and effective in transport efficiency compared with the derivative prepared from the methyl analogue of Kemp's triacid.

The hydroxamic acid derivative **3** was believed to exhibit quite diverse ionophoric behavior compared with its carboxylic acid derivative **1**. The examination of CPK molecular model of **3** suggests that both the carboxylic acid and hydroxamic acid functions could have relatively convergent relationship with respect to the very plane of the crown ether moiety. In this situation, the complexed target metal ions can be efficiently stabilized both by the hydroxamate function and crown ether moiety. Furthermore, as is well known, the hydroxamate function in the prepared compound can act as a counter ion in addition to the ligating site for the guest metal ions, that is definitely favorable for the action as an efficient ionophore.[16,17]

The ionophoric properties of prepared compounds were investigated by the solvent extraction and transport experiments. To have a general idea about the ionophoric properties of **3**, a preliminary solvent extraction experiment of metal ions from aqueous phase (buffered at pH 6 with HOAc/NaOAc) into chloroform solution was performed. Extraction experiments were done under the competitive condition with a mixture containing alkali (Li^+, Na^+, K^+, Rb^+), alkaline earth (Mg^{2+}, Ca^{2+}, Ba^{2+}), transition (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}), and heavy metal ions (Pb^{2+}, Cd^{2+}). As shown in Table 1, the hydroxamic acid **3** showed a selective

Table 1. Extraction of metal ions into chloroform phase by 15-crown-5 ether ionophores[a]

Ionophore	Extraction efficiency (%)												
	Pb^{2+}	Cd^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Mg^{2+}	Ca^{2+}	Ba^{2+}	Li^+	Na^+	K^+	Rb^+
1	51.6	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]	1.7	–[b]	4.7	6.5	4.8	3.1
3	1.8	–[b]	–[b]	–[b]	20.6	–[b]	–[b]	1.6	–[b]	4.8	10.8	4.9	3.2

[a]Extraction condition. Aqueous phase: a mixture containing 5.0 mmol each of metal acetates in 5.0 mL of NaOAc/HOAc buffer (pH 6). Organic phase: 5.0 mmol of ionophore in 5.0 mL of $CHCl_3$. [b]Less than 1.0%.

Table 2. Transport of metal ions by 15-crown-5 ether ionophores[a]

Ionophore	Transport efficiency (%)												
	Pb^{2+}	Cd^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Mg^{2+}	Ca^{2+}	Ba^{2+}	Li^+	Na^+	K^+	Rb^+
1	12.6	–[b]	–[b]	–[b]	0.24	–[b]	0.52	0.35	–[b]	–[b]	2.1	0.23	–[b]
3	23.7	–[b]	0.18	–[b]	72.0	0.75	–[b]	–[b]	–[b]	–[b]	2.2	0.26	–[b]

[a]Transport condition. Source phase: a mixture containing 5.0 mmol each of metal acetates in 5.0 mL of NaOAc/HOAc buffer (pH 6). Membrane phase: 5.0 mmol of ionophore in 15 mL of $CHCl_3$. Receiving phase: 5.0 mL of 0.1 M HNO_3. [b]Less than 0.1%.

extraction behavior toward Cu^{2+} ions among the surveyed metal ions of alkaline earth, transition, and heavy metal ions. On the other hand, the carboxylic acid derivative **1** revealed quite efficient extraction behavior toward Pb^{2+} ions over other transition metal ions and alkaline earth metal ions. One thing to note is the relatively moderate extraction results of **1** and **3** toward alkali metal ions that might be originated from the intrinsic binding affinity of the 15-crown-5 ether moiety.

Based on this extraction result, we next performed transport experiments of metal ions by the ionophores **1** and **3** through chloroform liquid membrane at 25 °C using a standard U-tube apparatus (i.d. = 1.5 cm). After transport of a mixture of alkali, alkaline earth, transition, and heavy metal ions from pH 6 acetate buffer for 24 h, an aliquot of the receiving phase was removed and the metal ion concentrations were determined by the inductively coupled plasma-atomic emission spectrometry (ICP-AES) (Table 2). Control experiment without any carrier in the membrane phase showed almost negligible transport efficiency toward all the tested metal ions. First thing to note is that the ionophore **3** showed a highly selective transport behavior toward Cu^{2+} ions. Transport selectivity toward Cu^{2+} over other transition metal ions is larger than 100-fold. Compound **3** also showed a high selectivity for Cu^{2+} ions over alkali and alkaline earth metal ions of more than 138-fold and 167-fold in transport efficiency, respectively. This type of high transport selectivity toward Cu^{2+} ions has been reported for a podand type bis(hydroxamic acid) derivative by Bromberg *et al.*[18]

To obtain more information about the role of hydroxamic acid function[19,20] on the ionophoric properties of **3**, the transport behavior of closely related carboxylic acid derivative **1** was also investigated. Carboxylic acid **1** showed somewhat efficient transport behavior toward Pb^{2+} ions but very inefficient carrier properties toward most of the transition metal ions, alkaline earth metal ions, and alkali metal ions surveyed at the present experimental condition. Although a small selectivity toward alkaline earth metal ions of Mg^{2+} and Ca^{2+} ions are discernible, the transport efficiency is unsatisfactory for the application of **1** as a carrier for the separation of targeted metal ions.

In summary, the hydroxamic acid derivative **3** designed by conjugating the 15-crown-5 ether and Kemp's triacid motifs exhibited significantly selective and efficient transport behavior toward Cu^{2+} ions over other transition metal ions. This observation suggests possible applications of the present results for the selective removal and treatment of various toxic industrial waste effluents containing Cu^{2+} ions.

Experimental Section

General: ^1H NMR (300 MHz) spectra were obtained by a Varian Gemini 2000 Spectrometer. ICP-AES measurements were performed on a Jovin Yvon JY-24. FAB-MS measurements were performed on a Micromass Autospec mass spectrometer. Propyl analogue of Kemp's triacid, 2-aminomethyl-15-crown-5 ether, and O-benzylhydroxylamine were purchased from Aldrich Co. and used without further purification.

Preparation of carboxylic acid 1. A mixture of Kemp's propyl triacid (343 mg, 1 mmol) and 2-aminomethyl-15-crown-5 ether (250 mg, 1 mmol) was well mixed and heated at 200 °C for 3h under N_2 atmosphere. After cooling, the crude product was dissolved in 30 mL of $CHCl_3$ and filtered, and the filtrate was evaporated under reduced pressure. The product was purified by the column chromatography (silica gel, eluting with 3 : 1 hexane/EtOAc) to yield **1** as low melting solid (456 mg, 82%); ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.78-3.62 (m, 16H), 3.64 (q, J = 13.0 Hz, 2H), 2.64 (d, J = 13.8 Hz, 2H), 2.18 (d, J = 13.2 Hz, 2H), 1.99 (m, 2H), 1.45-1.24 (m, 12H), 0.94 (m, 6H), 0.88 (t, J = 7.2 Hz, 3H); FAB MS (*m*-NBA) $[M+1]^+$ 556.2 (100%), $[M+Na]^+$ 578.2 (71%), $[M+K]^+$ 594.2 (28%).

Preparation of benzyl ether 2. To a solution of compound **1** (228 mg, 0.5 mmol) in CH_2Cl_2 (5 mL), oxalyl chloride (0.18 mL, 2 mmol) and a drop of DMF were added in sequence. The reaction mixture was stirred for 2h at rt. After complete evaporation of oxalyl chloride and CH_2Cl_2 under reduced pressure, the remaining solid was dissolved in

CH_2Cl_2. To the solution of O-benzylhydroxylamine hydrochloride (100 mg, 0.63 mmol) and triethylamine (0.25 mL, 1.8 mmol) in CH_2Cl_2 the acid chloride (in CH_2Cl_2) was added and heated at 40 °C under N_2 atmosphere. After overnight stirring, the solution was filtered, and washed with 0.1 M HCl. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by the column chromatograph (silica gel, eluting with 3 : 1 hexane/EtOAc) to yield **2** as low melting solid (396 mg, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.11(s, 1H), 4.78 (s, 2H), 3.84 (m, 1H), 3.76-3.60 (m, 20H), 3.46 (d, J = 4.5 Hz, 2H), 2.35 (d, J = 13.8 Hz, 2H), 2.14 (d, J = 13.2 Hz, 2H), 1.96 (m, 2H), 1.33-1.10 (m, 12H), 0.92 (t, J = 6.8 Hz, 6H), 0.77 (t, J = 7.2 Hz, 3H); FAB-MS (*m*-NBA) $[M+1]^+$ 661.5 (100%), $[M+Na]^+$ 683.5 (5%).

Preparation of hydroxamic acid 3. Compound **2** (260 mg, 0.4 mmol) was dissolved in EtOH (25 mL) and treated with 5% Pd/C (30 mg) under 1 atm of H_2 for 2h at rt. The reaction mixture was filtered and evaporated to give the desired compound **3** (194 mg, 84.5%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.81-3.47 (m, 21H), 2.62 (d, J = 14.1 Hz, 2H), 2.08-1.91 (m, 4H), 1.36-1.13 (m, 12H), 0.92 (t, J = 4.2 Hz, 6H), 0.87 (t, J = 7.2 Hz, 3H); FAB-MS (*m*-NBA) $[M+1]^+$ 571.4 (100%), $[M+Na]^+$ 593.4 (90%).

Extraction and transport experiments. The stock solution was a mixture of alkali, alkaline earth, transition, and heavy metal ions in acetate salts (8.0 mM) in HOAc/NaOAc buffer at pH 6. The aqueous metal solution (5.0 mL) was extracted with $CHCl_3$ solution ([ionophore] = 4.0 mM, 5.0 mL) at 25 °C. After the extraction the system was centrifuged to ensure the complete separation. The separated organic phase was back extracted with 1 M HNO_3 and the extracted metal ions were analyzed by ICP-AES. Extraction efficiency was calculated by dividing the moles of metal ion extracted with the moles of ionophore. Transport experiments were performed as reported earlier.[14] Extraction and transport experiments for mercury ions were not performed due to its relatively significant solubility in the organic phase under the present experimental condition.

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