

Synthesis and Selective Transport Properties of Cleft-Type Ionophores Having Two Convergent Hydroxamic Acid Functions

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A series of cleft-type ionophores having two convergent hydroxamic acid functions are prepared and their selective ionophoric properties toward heavy metal and transition metal ions have been investigated. Hydroxamic acids **3** exhibited a prominent selectivity toward heavy metal ions of Hg^{2+} and Pb^{2+} , and transition metal ions of Cu^{2+} over other transition metal and alkaline earth metal ions from slightly acidic source phase (pH 6) to an acidic receiving phase (pH 1). Selective ionophoric properties toward Pb^{2+} and Cu^{2+} ions over other surveyed metal ions are also confirmed by the FAB-MS measurements.

Keywords : Hydroxamic acid, Kemp's triacid, Transport, Heavy metal ions.

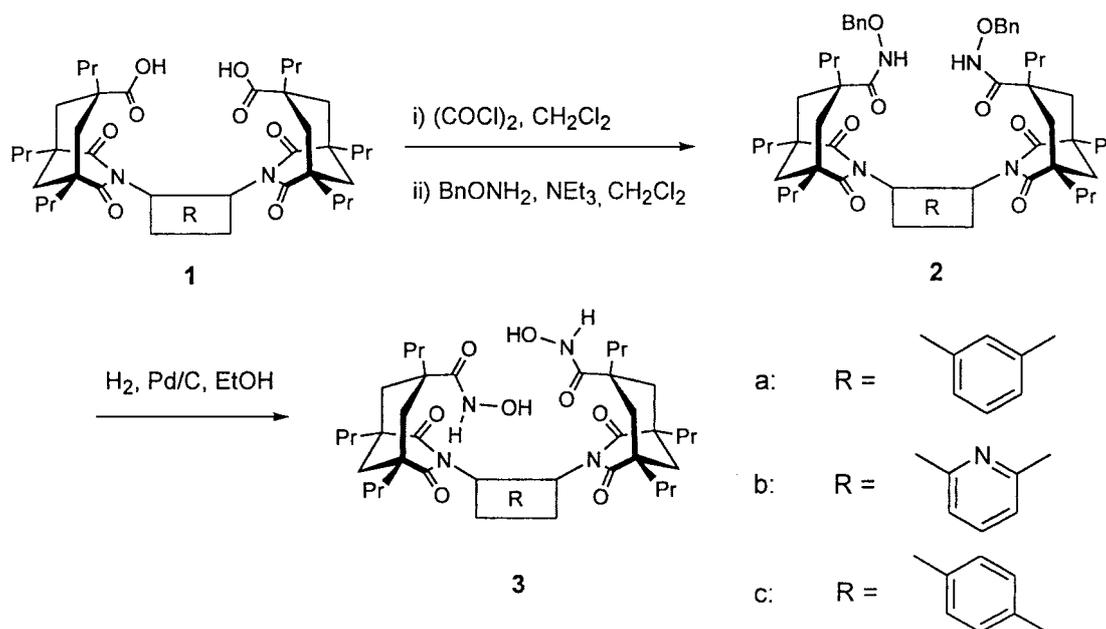
Introduction

The appropriate treatments of toxic materials in industrial wastes are crucial for the protection of our environment. Especially, the developments of efficient techniques for the removal of heavy metal ions and some of transition metal ions are utmost important because their toxic impacts are serious and long lasting.¹ Hydroxamic acids are one of the most important functional groups that have been employed for the design of novel ionophores. It is well known that the hydroxamic acid functions are ingeniously utilized in natural siderophores and related compounds for the sequestering of iron species.² The design and selective ionophoric properties of hydroxamic acid derivatives toward some transition metal and other important metal ions have been studied for several interesting structural systems derived from crown ethers,^{3,4}

podands,^{5,6} and calixarenes.^{7,8} The basic skeleton of Rebek's Ca^{2+} ion selective ionophores⁹ is well suited for the application as an efficient ionophore for the recognition of doubly charged metal ions. The selective transport of Hg^{2+} and some doubly charged metal ions by a series of related compounds having Kemp's triacid moieties have also been reported.¹⁰⁻¹⁶ In this paper, we report the synthesis of new Kemp's triacid-based ionophores having two convergent hydroxamic acid functions and their selective and efficient transports of Pb^{2+} , Hg^{2+} , and Cu^{2+} ions through chloroform liquid membrane.

Results and Discussion

The desired ionophores having two convergent hydroxamic acid functions were prepared from the dicarboxylic acids as shown in Scheme 1. Basic molecular skeletons **1**



Scheme 1

having two convergent Kemp's triacid moieties were prepared by the condensation of appropriate diamines with two equivalents of Kemp's triacid without solvent at 200 °C (69-76%).¹⁴ Diamines employed are 1,3-phenylenediamine, 1,4-phenylenediamine, and 2,6-diaminopyridine for the purpose of optimization of the ionophoric behavior of the resulting compounds by varying the aromatic spacer group in the final structure. Bis(carboxylic acid) derivatives **1** were converted into their acyl chlorides (oxalyl chloride/CH₂Cl₂) which were subsequently reacted with O-benzylhydroxylamine (NEt₃/CH₂Cl₂) to yield corresponding O-benzyl hydroxamates **2** (75-89%). Hydrogenolysis of **2** (Pd/C, EtOH) afforded the desired hydroxamic acid derivatives **3** in good yield (88-91%). Initially, hydroxamic acid derivatives **3** derived from the methyl analogue of Kemp's triacid were prepared. However, they have limited solubilities toward common organic solvents, which preclude the examination of the ionophoric properties. To overcome this problem and to enhance the lipophilicity of the ionophores, we prepared more lipophilic derivatives by using propyl analogue of Kemp's triacid. Generally, the preparation of the propyl analogues require somewhat longer reaction time compared with the methyl analogue, possibly due to the increased steric congestion around the reacting site of spacer and Kemp's triacid moiety.

The ionophoric properties of the hydroxamic acid compounds **3** were investigated by the transport experiments through chloroform liquid membrane. The transport experiments were performed under competitive conditions with a solution containing representative heavy metal ions, transition metal ions, and alkaline earth metal ions at 25 °C using a U-tube (*i.d.* = 1.5 cm) apparatus. After 24 h of transport, the concentration of transported metal ions in receiving phase was determined by the inductively coupled plasma atomic emission spectrometry (ICP-AES).

As shown in Table 1, the 1,3-phenylenediamine based hydroxamic acid ionophore **3a** showed a significantly selective and efficient transport behavior toward Pb²⁺ and Hg²⁺ ions among the heavy metal ions. Transport of Cd²⁺ ions was inefficient and the selectivity pattern was Pb²⁺ > Hg²⁺ >> Cd²⁺. The transport efficiency toward Pb²⁺ over Cd²⁺ ions was larger than 11. Another observation to note is that the ionophore **3a** also showed a significant selectivity toward Cu²⁺ ions among the surveyed transition metal ions. For the rest of transition metal ions, inefficient transports are observed and the selectivity pattern can be summarized as follows: Cu²⁺ >> Co²⁺ > Zn²⁺ > Ni²⁺. It has been reported that some of the hydroxamic acid derivatives showed a high affinity

toward Cu²⁺ ions over other transition metal ions.^{5,17} As regards to the alkaline earth metal ions, compound **3a** showed almost negligible transport behavior in spite of being similar doubly charged nature with a slight selectivity toward Ca²⁺ ions. Transport of alkali metal ions by **3a** was found to be negligible.

To have an insight for the optimized structure for the selective recognition of targeted metal ions, we investigated the effects of the geometry provided by the three aromatic spacers of **3a-3c** on the transport behavior (Table 1). 2,6-Diaminopyridine based compound **3b** also showed similar transport behavior compared with **3a**. The selective ionophoric properties of **3b** toward Cu²⁺ ions among the transition metal ions are also significant and selectivity ratio of larger than 70 was observed over other transition metal ions. However, the efficiency toward Cd²⁺ and Co²⁺ ions is much reduced that results in large selectivity enhancements. We initially anticipated that the presence of extra binding site of basic nitrogen donor atom of pyridine moiety in **3b** would enhance the transport efficiency compared with **3a**, however, the effect is not so discernible. In the present case, the effect of pyridine nitrogen atom in the binding process seems to be dominated by much stronger effect of dihydroxamate functions. For 1,4-phenylenediamine isomer **3c**, the transport efficiency for the Hg²⁺ ions is slightly enhanced compared with **3a** but efficiencies for the Pb²⁺ and Cu²⁺ ions are significantly decreased. The transport selectivity of **3c** toward Hg²⁺ and Pb²⁺ over Cd²⁺ was ranged up to 137. Although there exist some differences in ionophoric properties of three prepared compounds, the observed selectivity of **3** toward Pb²⁺, Hg²⁺, and Cu²⁺ over other heavy metal and transition metal ions as well as alkaline earth metal ions is believed to be sufficient for the selective removal of these toxic metal ions from a variety of contaminated chemical systems.

The selective binding strengths of the hydroxamate ionophores were further confirmed by the FAB-MS measurements. The hydroxamic acid **3b** was treated with a mixture of three most efficiently transported metal ions of Pb²⁺, Hg²⁺, and Cu²⁺ ions in *m*-NBA matrix and mass spectrum was measured under competitive condition. In its mass spectrum, a prominent peak for [3b-H+Cu]⁺ ions at *m/z* = 813.0 (relative intensity = 79%) along with peaks for [3b+Cu+OAc]⁺ and [3b+Pb+OAc]⁺ at *m/z* = 873.4 (relative intensity = 89%) and 1018.9 (relative intensity = 71%), respectively, were observed. In this case, there were no peaks corresponding to the molecular ion species around *m/z* = 751.5 and

Table 1. Competitive transport of metal ions by hydroxamic acids **3**^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⁺
3a	57.4	87.3	7.6	7.4	— ^b	59.4	2.1	0.2	1.3	— ^b	— ^b
3b	71.8	89.9	0.9	0.2	— ^b	55.9	0.8	0.2	0.9	— ^b	0.3
3c	68.6	56.6	0.5	0.4	— ^b	27.3	0.5	0.2	0.6	— ^b	0.2

^aTransport conditions. Source phase: 5.0 mmol of metal acetates in 5.0 mL of NaOAc/HOAc buffer (pH 6). Membrane phase: 5.0 mmol of carrier in 15 mL of CHCl₃. Receiving phase: 5.0 mL of 0.1 M HNO₃. ^bLess than 0.1%.

peaks for the Hg^{2+} derived species. These observations suggest that the ionophore **3b** forms strong complexes with Pb^{2+} and Cu^{2+} ions and are in qualitative support with the transport behaviors of hydroxamate ionophore **3b**.

In conclusion, Kemp's triacid derivatives having two convergent hydroxamic acid functions showed efficient transport behavior toward Hg^{2+} , Pb^{2+} , and Cu^{2+} ions in competitive transport experiments. The selectivity for the three target metal ions are generally in the order of **3b** > **3c** > **3a**. The results obtained suggest that the hydroxamic acid derivatives **3** can be used as selective and efficient carriers for the removal of toxic metal ions of Pb^{2+} , Hg^{2+} , and Cu^{2+} ions in the industrial waste effluents.

Experimental Section

General. Most of the reagents including propyl analogue of Kemp's triacid and O-benzylhydroxylamine hydrochloride (Aldrich) were purchased and used without further purification. 2,6-Diaminopyridine, 1,3-phenylenediamine, and 1,4-phenylenediamine (Aldrich) were used after purification by passing through a short column (silica gel, THF). 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 Gallen-Kamp melting point apparatus and are uncorrected. ^1H NMR (300 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. Compound **1b** was prepared following the reported procedure.¹⁴

Preparation of 1a. A mixture of Kemp's propyl triacid (685 mg, 2 mmol) and 1,3-phenylenediamine (108 mg, 1 mmol) was ground and heated at 200 °C for 3h under N_2 atmosphere. After cooling, the crude product was dissolved in 50 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 **1a** as white powder (657 mg, 75.1%). mp 231-232 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.37 (m, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 6.84 (dd, $J = 8.0$ Hz, 2H), 2.89 (d, $J = 13.8$ Hz, 4H), 2.34 (d, $J = 13.2$ Hz, 2H), 2.12-1.94 (m, 4H), 1.70-1.56 (m, 2H), 1.48-1.14 (m, 24H), 0.98-0.82 (m, 18H); MS (FAB): m/z calcd for $\text{C}_{42}\text{H}_{60}\text{N}_2\text{O}_8\text{K}$ $[\text{M}+\text{K}]^+$ 759.4, found 759.3 (100%).

Preparation of 1c. Compound **1c** was prepared by the reaction of Kemp's triacid with 1,4-phenylenediamine (68.9%); mp 172-173 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.80 (t, $J = 7.8$ Hz, 1H), 6.90 (t, $J = 7.8$ Hz, 2H), 2.71 (d, $J = 13.5$ Hz, 4H), 2.29 (d, $J = 13.2$ Hz, 2H), 1.95 (m, 4H), 1.52-1.21 (m, 26H), 0.93-0.84 (m, 18H). MS (FAB): m/z calcd for $\text{C}_{42}\text{H}_{61}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}]^+$ 721.4, found 721.4 (100%), calcd for $\text{C}_{42}\text{H}_{60}\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 743.4, found 743.4 (82%).

Preparation of 2a. To a solution of compound **1a** (361 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 (200 mg, 1.25 mmol) and triethylamine (0.487 mL, 3.5 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 chromatography (silica gel, eluting with 4 : 1 hexane/EtOAc) to yield **2a** as white powder (85.7%). mp 139-140 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.31 (s, 2H), 7.46 (s, 1H), 7.32 (d, $J = 8.3$ Hz, 2H), 7.24 (m, 6H), 7.14-7.05 (m, 4H), 6.94 (t, $J = 8.1$ Hz, 1H), 4.60 (s, 4H), 2.70 (d, $J = 14.1$ Hz, 4H), 1.99 (d, $J = 13.2$ Hz, 2H), 1.82-1.72 (m, 4H), 1.52-1.43 (m, 4H), 1.39-1.20 (m, 14H), 1.11-0.92 (m, 8H), 0.85 (t, $J = 7.2$ Hz, 9H), 0.73 (t, $J = 7.2$ Hz, 9H); MS (FAB): m/z calcd for $\text{C}_{56}\text{H}_{75}\text{N}_4\text{O}_8$ $[\text{M}+\text{H}]^+$ 931.6, found 931.3 (68%).

Preparation of 2b. The product was purified by the column chromatography (silica gel, eluting with 3 : 1 hexane/EtOAc) to yield white powder (75.1%); mp 216-217 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 8.1$ Hz, 2H), 7.71 (s, 1H), 7.31 (t, $J = 8.1$ Hz, 1H), 7.22 (s, 10H), 4.75 (s, 4H), 2.68 (d, $J = 14.1$ Hz, 4H), 2.11 (d, $J = 13.2$ Hz, 2H), 2.01 (m, 4H), 1.56-1.51 (m, 4H), 1.42-1.14 (m, 22H), 0.96-0.86 (m, 18H); MS (FAB): m/z calcd for $\text{C}_{55}\text{H}_{74}\text{N}_5\text{O}_8$ $[\text{M}+\text{H}]^+$ 932.6, found 932.4 (100%).

Preparation of 2c. The product was purified by the column chromatography (silica gel, eluting with 3:1 hexane/EtOAc) to yield white powder (89.1%); mp 131-132 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 2H), 7.33-7.24 (m, 10H), 7.15-7.12 (m, 4H), 4.60 (s, 4H), 2.67 (d, $J = 14.1$ Hz, 4H), 1.95 (d, $J = 13.2$ Hz, 2H), 1.84-1.72 (m, 4H), 1.56-1.44 (m, 4H), 1.38-0.95 (m, 20H), 0.82-0.75 (m, 18H); MS (FAB): m/z calcd for $\text{C}_{56}\text{H}_{74}\text{N}_4\text{O}_8$ $[\text{M}]^+$ 930.5, found 930.5 (100%).

Preparation of 3a. Compound **2a** (350 mg, 0.38 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 **3a** (260 mg, 91%); mp 177.5 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.43 (s, 2H), 9.10 (s, 2H), 7.31 (d, $J = 8.3$ Hz, 2H), 7.18-7.12 (m, 1H), 7.05 (t, $J = 8.1$ Hz, 1H), 2.63 (d, $J = 13.2$ Hz, 4H), 2.01 (d, $J = 12.0$ Hz, 2H), 1.85-1.71 (m, 4H), 1.53-1.0 (m, 26H), 0.92-0.73 (m, 18H); MS (FAB): m/z calcd for $\text{C}_{42}\text{H}_{62}\text{N}_4\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 773.4, found 773.4 (28%).

Preparation of 3b. The desired compound **3b** was prepared from **2b** (91%); mp 177.5 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.98 (s, 1H), 7.67 (d, $J = 7.8$ Hz, 2H), 7.53 (t, $J = 8.1$ Hz, 1H), 2.72 (d, $J = 14.1$ Hz, 4H), 2.23 (d, $J = 13.2$ Hz, 2H), 2.02 (m, 4H), 1.59-1.25 (m, 26H), 0.96 (t, $J = 6.9$ Hz, 9H), 0.87 (t, $J = 6.9$ Hz, 9H); m/z calcd for $\text{C}_{41}\text{H}_{62}\text{N}_5\text{O}_8$ $[\text{M}+\text{H}]^+$ 752.5, found 752.5 (100%).

Preparation of 3c. The desired compound **3c** was obtained from **2c** (88.6%); mp 279 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 2H), 9.02 (s, 2H), 7.23 (m, 4H), 2.58 (d, $J = 13.8$ Hz, 4H), 2.00 (d, $J = 13.2$ Hz, 2H), 1.82-1.71 (m, 4H),

1.50-1.42 (m, 4H), 1.39-0.98 (m, 20H), 0.90-0.71 (m, 18H); MS (FAB): m/z calcd for $C_{42}H_{62}N_4O_8$ $[M]^+$ 750.5, found 750.4 (100%).

Transport Experiments. Transport experiments were performed through a U-type tube ($i.d.$ = 1.5 cm). The temperature of the entire apparatus was controlled at 25 ± 1 °C. The source phase was an aqueous mixture of metal acetates (each in 5.0 mmol) dissolved in 5 mL of acetate buffer at pH 6.0. The receiving phase was an aqueous 0.1 M HNO_3 solution. Membrane phase was chloroform solution (15 mL) containing 5.0 mmol of carrier and magnetically stirred at a constant speed of 200 rpm. Receiving phase was 0.1 M HNO_3 solution (5 mL). After one day of transport, the amount of transported metal ions was analyzed by ICP-AES.

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