

Synthesis and Hg(II)-selective Ionophoric Properties of Kemp's Triacid-based Amidine Derivative

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The development of selective ionophores for the detection and separation of heavy metal ions has received much current attention in recent years.¹ Particularly interesting is the treatments of the mercurials in the environment and in the industrial waste streams, because many mercurial compounds are highly toxic and their effects are long lasting.² Among many approaches toward the design of mercury selective ionophores, thia-crown ethers,³ thioamides,⁴ and some carboxylic acid derivatives⁵ are representative examples. More recently, a series of Kemp's acid imides, amides, and esters has been prepared⁶ by utilizing the unique structural characteristics of the Kemp's triacid moiety,⁷ and some simple derivatives exhibited remarkable Hg(II) selective carrier properties.⁸ However, as Rebek *et al.* have pointed out, some of Kemp's imide acid derivatives are quite unstable to aqueous acids and bases.⁹ This hydrolytic instability might be a crucial drawback of thus designed derivatives in the extreme pH conditions which are often required for the applications as transport carriers for ionic guests. In this paper, we would like to report the synthesis and Hg(II)-selective ionophoric properties of the amidine derivative **3**, which is designed to enhance the hydrolytic stability and the preorganization of the ionophore, by means of the competitive transport experiments.

The amidine derivative was prepared by the condensation of vicinal diaminocatechol derivative with Kemp's triacid. The 4,5-dinitro catechol was reacted with 1-bromooctane (Cs₂CO₃, DMF, 100 °C) to afford dinitro-dioctyl ether derivative **1** (60%).¹⁰ Reduction of **1** with Pd/C and NH₂NH₂ · H₂O yields the diamino derivative **2** (84%).¹⁰ which was subsequently condensed with Kemp's triacid without solvent at

180 °C to afford the desired amidine derivative **3** (67%).¹¹ The octyl ether moiety was chosen to improve the lipophilicity and solubility in common organic solvents of the resulting amidine derivative. The amidine derivative prepared, in principle, is composed of two stereoisomers. However, we used the racemate as it is without cumbersome attempts to separate the isomers, because the purpose of the present study is to develop ionophores for the guests of spherical shaped metal ions.

The ionophoric behaviors of the amidine carrier **3** for the various metal ions were investigated by the competitive transport experiments through chloroform liquid membrane using a U-tube apparatus. The source phase was a mixture of metal acetates in acetate buffer (HOAc/NaOAc, pH = 6.0) and the receiving phase was acidic solution of 0.1 M HNO₃. The receiving phase was sampled after one day of experiment and the concentration of the transported metal ions was determined by means of ion chromatography (IC) or inductively coupled plasma-atomic emission spectrometry (ICP-AES).

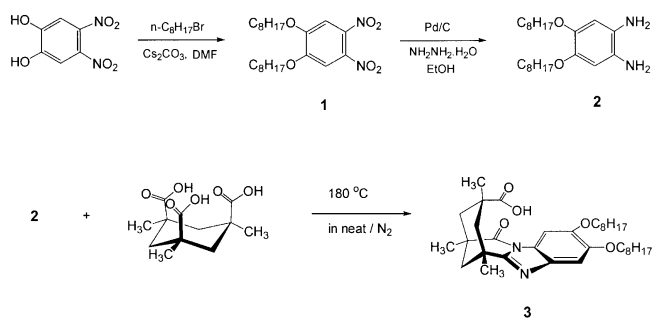


Table 1. Competitive Transport of Heavy Metal Ions with Alkali Metal Cations^a

Carrier	Metal ions transported ($\times 10^{-9}$ mol/h)								Selectivity	
	Hg ²⁺	Pb ²⁺	Cd ²⁺	Li ⁺	Na ⁺	K ⁺	Rb ⁺	Cs ⁺	Hg ²⁺ /Pb ²⁺	Hg ²⁺ /Cs ⁺
3	133.5	3.5	0	0.12	2.41	0.28	0	2.3	38.2	58.0

^aTransport condition. Source phase: 5.0 mmol of each metal acetates in 10 mL of NaOAc/HOAc buffer (pH 6). Membrane phase: 5.0 mmol of carrier **3** in 15 mL of CHCl₃. Receiving phase: 10 mL of 0.1 M HNO₃. At 25 ± 1 °C.

Table 2. Competitive Transport of Heavy Metal Ions with Alkaline Earth Metal Cations^a

Carrier	Metal ions transported ($\times 10^{-9}$ mol/h)							Selectivity	
	Hg ²⁺	Pb ²⁺	Cd ²⁺	Mg ²⁺	Ca ²⁺	Sr ²⁺	Ba ²⁺	Hg ²⁺ /Pb ²⁺	Hg ²⁺ /Ca ²⁺
3	90.1	4.2	0	0.40	0.68	0	0	21.5	133

^aTransport condition: Same as in Table 1.

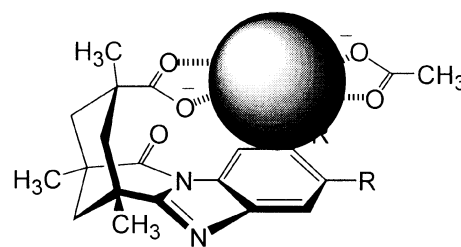
The preliminary transport results showed that the carrier **3** exhibited a pronouncedly high transport efficiency toward Hg(II) ions among the surveyed metal cations. So, the systematic investigations under the competitive transport conditions in the presence of other metal ions were performed. The carrier exhibited highly selective transport behavior toward Hg(II) with almost insignificant transport of alkali metal ions (Table 1). The transport of alkali metal cations by carrier **3** was not efficient, and the transport rate is around 10^{-9} mol/h range. An almost indiscernible selectivity toward Cs⁺ ion over other alkali metal ions is observed. As can be seen from the Table, the selectivity decreases in the sequence of Hg(II) \gg Pb(II) $>$ alkali metal ions \approx Cd(II).

In the competitive transport experiments of heavy metal ions with alkaline earth metal ions, as can be seen from the Table 2, the transport of alkaline earth metal ions is found to be negligible and the high affinity of carrier **3** toward Hg(II) still retained in the presence of doubly charged alkaline earth metal ions. The transport efficiency for alkaline earth metal ions is comparable to the alkali metal ions and the carrier **3** exhibited a little selectivity toward Mg(II) and Ca(II) ions.

Finally, competitive transport of heavy metal ions in the presence of some representative transition metal ions was also investigated. The carrier **3** exhibited again a remarkably selective transport efficiency toward Hg(II) among the surveyed transition metal and other heavy metal ions of Pb(II) and Cd(II). The selectivity ratio of Hg(II)/Cu(II), for the Cu(II) ion that is most interfering transition metal ions, was over 150, which is quite large for this type of ionophore having simple structural properties.

Interesting thing is the fact that amidine carrier **3** does not transport other heavy metal ions of Pb(II) and Cd(II) so efficiently under the present condition. In fact, Cd(II) is not transported any significant amount at all: the selectivity ratio of Hg(II)/Cd(II) is well over 1000. The only major interference is found to be Pb(II) among the surveyed metal ions. However, the selectivity ratio in the range of 21-38 were observed for all the transport experiments.

To elucidate partly the transport mechanism of the present system, the contents of the receiving phase after the transport experiments were analyzed. The analysis of the receiving phase with IC technique revealed that a significant amount of acetate ion is transported and the ratio of the [acetate]/[Hg(II)] is found to be 0.95, which means that the major species for the Hg(II) transport is in the form of **3** · Hg(OAc) as depicted in the Scheme 1. This observation is well consistent with the results obtained by the similar structured Kemp's triacid based imide-acid derivatives.⁸ Furthermore, Czarnik *et al.* have discussed the possibility of additional interaction of the guest metal ion with the aromatic ring to rationalize the enhanced affinity of Hg(II) for the anthracene-based chemosensor.¹²



Scheme 1

matic ring to rationalize the enhanced affinity of Hg(II) for the anthracene-based chemosensor.¹²

This type of selective transport behavior toward Hg(II) of the simple Kemp's imide acid has already been reported by Hirose *et al.*⁸ However, the present ionophore has improved stability toward varying pH conditions which will allow more versatility in its application as a carrier molecule in the active transport systems. All the results obtained strongly suggests the possible application of this amidine derivative for the selective removal of the toxic heavy metal ions of Hg(II) for the waste treatments by the liquid membrane or other related systems.

Experimental Section

General. Most of reagents including Kemp's triacid (Aldrich), 1-bromooctane (Aldrich), and 4,5-dinitrocathecol (Janssen) were purchased and used without further purification. Dichloromethane, CHCl₃, and DMF were used after standard 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 Gallen-Kamp 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. IR spectra were recorded with a Bio-Rad SPC 3000 FT-IR spectrophotometer. IC and ICP-AES measurements were done on a Sykam Gmb IIS-135 and Jobin-Yvon JY-24 spectrometer, respectively. Mass spectral data were obtained with a Micromass Autospec mass spectrometer.

Synthesis of ligand.

1,2-Bis(octyloxy)-4,5-dinitrobenzene (I): To a mixture of 4,5-dinitrocathecol (302 mg, 1.5 mmol) and Cs₂CO₃ (984 mg, 3.0 mmol) in DMF (5 mL) was added 1-bromooctane (0.78 mL, 4.5 mmol) and the resulting mixture was stirred at 100 °C for 3h under N₂ atmosphere. After evaporation of the volatile reaction mixture, the product was purified by column chromatography (SiO₂, hexane/EtOAc = 40/1) to yield the product **I** as a yellowish solid (382 mg, 60%). mp 71-74

Table 3. Competitive Transport of Heavy Metal Ions with Transition Metal Cations^a

Carrier	Metal ions transported ($\times 10^{-9}$ mol/h)							Selectivity	
	Hg ²⁺	Pb ²⁺	Cd ²⁺	Zn ²⁺	Co ²⁺	Ni ²⁺	Cu ²⁺	Hg ²⁺ /Pb ²⁺	Hg ²⁺ /Cu ²⁺
3	89.0	3.7	0	0	0	0	0.56	24.1	159

^aTransport condition: Same as in Table 1.

°C: ^1H NMR (300 MHz, CDCl_3) δ 7.29 (s, 2H), 4.10 (t, $J = 6.6$ Hz, 4H), 1.85 (q, $J = 7.2$ Hz, 4H), 1.29-1.55 (m, 20H), 0.89 (t, $J = 6.6$ Hz, 6H); IR (KBr) 2826, 2857, 1533, 1336, 1226 cm^{-1} ; FABMS calcd for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_6$ m/z 424.3 [M] $^+$ found 424.3.

1,2-Bis(octyloxy)-4,5-diaminobenzene (2): To a solution of dinitrobenzene **1** (580 mg, 1.37 mmol) in EtOH (40 mL), 10% Pd/C (40 mg) and hydrazine monohydrate (2.5 mL, 15 mmol) were added. After 5h of refluxing, the hot solution was filtered through Celite. After cooling, the white precipitate was filtered off and rinsed with cold MeOH to yield diamine **2** (430 mg, 86%). The diamine is quite unstable to storage and the following step was carried out immediately. ^1H NMR (300 MHz, CDCl_3) δ 6.38 (s, 2H), 3.89 (t, $J = 6.6$ Hz, 4H), 1.74 (q, $J = 7.8$ Hz, 4H), 1.28-1.42 (m, 20 H), 0.88 (t, $J = 6.9$ Hz, 6H); IR (KBr) 3396, 3315, 2921, 2853, 1528, 1468, 1434, 1242, 1214, 1145 cm^{-1} .

Amidine-Kemp's acid (3): A mixture of Kemp's triacid (258 mg, 1 mmol) and diamine **2** (364 mg, 1 mmol) was grounded and heated without solvent at 180 °C for 4h under the N_2 atmosphere. After cooling, the crude reaction mixture was dissolved in CHCl_3 (50 mL) and filtered, and the filtrate was evaporated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc = 1/1) and subsequent crystallization from hexane yielded amidine derivative **3** as yellow powder (382 mg, 67%), mp 167-168 °C; ^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, $J = 6.3$ Hz, 6H), 1.29-1.50 (m, 32H), 1.80 (q, $J = 6.9$ Hz, 4H), 2.18 (d, $J = 13.8$ Hz, 1H), 2.58 (dd, $J = 13.8$ Hz, 2H), 3.98 (m, 4H), 7.05 (s, 1H), 7.58 (s, 1H); IR (KBr) 3396, 3315, 2921, 2853, 1528, 1468, 1434, 1242, 1214, 1145 cm^{-1} ; FABMS calcd for $\text{C}_{34}\text{H}_{53}\text{N}_2\text{O}_5$ m/z 569.4 [M+H] $^+$ found 569.5.

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 acetate buffer (10 mL, made from NaOAc and HOAc buffer at pH 6.0). The receiving phase was aqueous 0.1 M HNO_3 (10 mL). Membrane phase was chloroform solution (15 mL) containing 5.0 mmol of

amidine carrier **3** and magnetically stirred at constant speed of 200 rpm (displayed by a tachometer). After one day of transport, the amount of the transported metal ions was analyzed by IC for alkali metal ions or ICP-AES for alkaline earth, transition metal, and heavy metal ions.

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