Preparation and Metal Extraction Behavior of Macrocyclic Complexing Agent Bearing Trifluoromethanesulfonamide Deprotonating Groups

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A diaza-18-crown-6 derivative bearing two trifluoromethanesulfonamide groups on *N,N′*-sites (**1**(H_2L)) extracted divalent metal ions (M^{2+}: Hg, Cu, Pb, Ca, Sr, Ba) into dichloromethane according to the reaction, $M^{2+}(aq)+H_2L(org)\rightleftarrows ML(org)+2H^+(aq)$, $K_{ex}=[ML][H^+]^2/[H_2L][M^{2+}]$. The magnitude of K_{ex} values followed the order Hg>Pb>Cu>>Sr>Ca>Ba. This paralleled the selectivity obtained with the corresponding phenolic reagent, but the affinity to "soft" metal ions was enhanced for **1**, reflecting the N,N,N^-,N^--coordinating nature of **1**. Moreover, **1** formed a 1:2 complex with Cu(II) by the reaction, $M^{2+}(aq)+2H_2L(org)\rightleftharpoons M(HL)_2(org)+2H^+(aq)$. This suggests that the 1:1 complex of Cu(II) was sterically hindered due to the coordination by the bulky sulfonamido groups.

When designing a selective extractant for a certain metal ion, it is important to consider a spatial arrangement of coordinating groups. Macrocyclic compounds have been utilized as the "template" for coordinating groups to be arranged spatially.[1,2] We have taken advantage of diazacrown ethers as the skeleton; *N,N′*-bis(2-hydroxy-5-nitrobenzyl)cryptand-22 (**2**) was found to be a sensitive and selective reagent for calcium ion and was successfully applied to its determination in blood serum.[3,4] **2** was also found to be a selective extractant for some other heavy meal ions: **2** formed more stable complexes with divalent copper and lead than with calcium.[5] Since the phenolic oxygen is a "hard" coordinating atom, the selectivity by **2** toward "soft" lead ion seemed at least partially due to the two nitrogens of the template (i.e., cryptand-22) rather than the phenolic oxygens.

On the other hand, proton-dissociable sulfonamide groups ($R'SO_2NHR$) have been the subject of our continued study for the development of metal extractants since the anionic sulfonamido coordinating groups ($R'SO_2N^-R$) has a soft coordinating atom, N^-.[6] In addition, the anionic nitrogen bears a bulky sulfonyl group, which can cause steric hindrance when the sulfonamido group binds to small metal ions. This steric factor has been suggested to be responsible at least partially for the poor coordination ability by a sulfonamido anion toward iron(III), aluminum(III) and alkaline-earth metal ions.[7]

Among sulfonamide groups trifluoromethanesulfonamide (CF_3SO_2NHR) is the most readily proton-dissociable and is expected to afford a sulfonamido anion ($CF_3SO_2N^-R$) in nearly neutral pH region. In the present study, trifluoromethanesulfonamide coordinating groups were combined with diaza-18-crown-6 skeleton to give **1**(H_2L) to explore new metal selectivity in the extractive separation of metal ions. The extraction behavior of divalent metal ions was studied and discussed in comparison with the phenol-type extractant **2** (Chart 1).

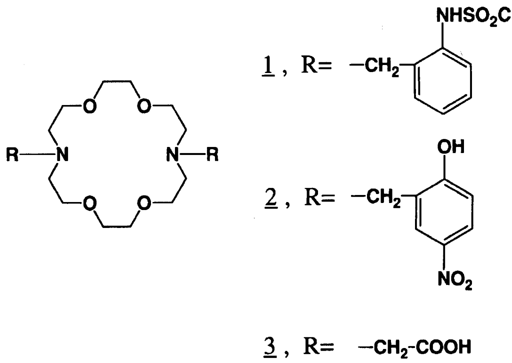

Chart 1.

Experimental

Synthesis of *N,N′*-Bis(2-trifluoromethanesulfonamidobenzyl)diaza-18-crown-6. Trifluoromethanesulfonic anhydride (5.0 g, 18 mmol) in dichloromethane (10 ml) was added dropwise[8] under stirring to *N,N′*-bis(2-aminobenzyl)diaza-18-crown-6[9] (3.75 g, 8 mmol) in dichloromethane (5 ml) during 30 min at −52 °C, and the mixture was stirred for 10 min. The reaction was carried out under dry nitrogen. Triethylamine (1 ml) was added to the mixture, which was kept stirred for 3 h. The mixture was then diluted with dichloromethane and washed with aqueous ammonium chloride (pH 5). The organic layer was dried with magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from chloroform to give a white solid (yield: 83%); mp=215.2—216.2°C; IR (KBr) 3140, 1295, 1145 cm^{-1}; ^1HNMR (DMSO) $\delta=3.35$ (4H, s, $-N-\underline{CH_2}-CH_2-O-$), 3.60 (4H, s, $N-CH_2-\underline{CH_2}-O-$), 3.81 (4H, s, $-\underline{O-CH_2}-$), 4.37 (2H, s, $Ar-CH_2-N-$), 6.81—8.43 (4H, m, Ar-H); ^{13}CNMR (DMSO) $\delta=53.08$, 64.66, 69.99, 117.14, 119.93 (q, $J=80$ Hz), 120.84, 129.83, 130.42, 130.60. Elemental analysis. Found: C, 45.72; H, 5.23; N, 7.55%. Calcd for $C_{28}H_{38}N_4O_8S_2F_6$: C, 45.71; H, 5.22; N, 7.55%.

Acid Dissociation Constant. The compound **1** was dissolved in a 0.10 M (1 M=1 mol dm^{-3}) aqueous lithium chloride solution which contained lithium hydroxide in 2.2 molar excess of **1**. The solution was then titrated with 0.01 M standard hydrochloric acid. The pH values measured were calibrated against standard acid-base titration to obtain $-\log[H^+]$ values.

Extraction Study. Ten milliliters of a dichloromethane solution of **1** and 10 ml of an aqueous solution containing a 100-fold molar excess of divalent metal ion were placed in a stopped glass tube (50 ml). The pH of the aqueous solution was adjusted to a desired value between 1 and 3 with 0.2 M nitric acid–lithium nitrate, between 3 and 5 with 1×10^{-2} M acetic acid–lithium acetate, between 6 and 8 with 1×10^{-2} M HEPES buffer, between 8 and 10 with 1×10^{-2} M lithium hydroxide–boric acid, and above 11 with lithium hydroxide.

The tube was shaken for 20 min at 25°C. After centrifugation at 3000 rpm for 10 min, the pH of the aqueous solution was measured. The organic solution was subjected to UV-absorption spectroscopy. The absorption maximum (λ_{max}) of free **1**(H_2L) in dichloromethane was at 289 nm (ε, 3.2×10^3), whereas those of the metal complex (1 : 1 complex) were at 258 (ε, 6.3×10^3), 276 (ε, 4.7×10^3), 281 (ε, 6.3×10^3), 280 (ε, 7.8×10^3), 284 (ε, 8.1×10^3), and 262 (ε, 1.8×10^4) nm for Hg, Sr, Ca, Ba, Cu, and Pb, respectively. The absorbance at λ_{max} was used for the spectrophotometric determination of metal concentration in the organic phase.

The composition of the extracted species was determined by mole ratio method; the absorbance was measured at λ_{max} of the complexes at pH 2.5, 9.0, 10, 12.5, 5, and 3.5 for Hg, Sr, Ca, Ba, Cu, and Pb, respectively. Concentration of divalent metal ion was 1×10^{-4} M except for Pb, for which it was 5×10^{-5} M since Pb-**1** complex had a large value of ε in comparison with other metal complexes.

In the case of copper(II), relatively high concentration of **1** was used to study the formation of 1 : 2 complex. The extraction was followed by atomic absorption spectrophotometry.

Results and Discussion

Two proton dissociation processes were identified for **1**(H_2L), which corresponded to the deprotonation from H_4L^{2+} and H_3L^+ species. The maximum concentration of **1** manageable in aqueous solution was only 1×10^{-4} M because of the solubility limitation, and this hampered the study for the succeeding weak deprotonation processes from H_2L and HL^-. The dissociation constants (pK_a values) obtained were 5.4 and 8.15 at 25°C. These values are in parallel with those for the corresponding phenolic reagent **2** (pK_a: 4.03 and 6.56 in 9 : 1 water–dioxane).[4] Since the pK_a values for the protonated tertiary amine nitrogens in the azacrown ether are expected to fall around 10 or above,[2,4] the values obtained for **1** in the present study should be ascribed to the dissociation of the two sulfonamide protons. Unfortunately, **1** like other trifluoromethanesulfonamides[5] did not produce unique UV-vis spectral change on deprotonation, and therefore a direct evidence for the deprotonation of sulfonamide groups in **1** was not obtained.

The extraction equilibrium for the 1 : 1 complex of divalent metal ions with **1** may be represented by the following equation:

$$(H_2L)_{org} + M^{2+} \rightleftharpoons (ML)_{org} + 2H^+, \tag{1}$$

where the subscript "org" indicates the organic phase. Then, the extraction constant (K_{ex}) can be defined as

$$K_{ex} = \frac{[ML]_{org}[H^+]^2}{[M^{2+}][H_2L]_{org}}. \tag{2}$$

The partition of **1** between dichloromethane and water strongly favored the organic phase, and the extractant species were never found in aqueous phase to a measurable extent throughout the present extraction study. The absorption spectrum of dichloromethane solution of **1** did not change in the pH region studied when the aqueous solution contained only an alkali metal ion (lithium) and buffer species. These observations indicate that **1** does not have measurable affinity to alkali metal ions. On the other hand, the spectrum changed when the aqueous solution contained divalent metal ions and the pH was raised. This is accounted for by the formation of complex species like ML in organic solution.

By measuring the absorption spectra of organic phase, the concentration ratio (Q) of free ligand H_2L to the complex ML was readily obtained. Using the quantity Q, Eq. 2 is rewritten as

$$\log Q = \log\{[ML]_{org}/[H_2L]_{org}\} = 2\text{pH} + \log[M^{2+}] + \log K_{ex}. \tag{3}$$

Figure 1 shows the dependence of log Q on pH. As expected, a linear relationship with a slope of 2 was obtained for each metal ion. This indicates that divalent metals are extracted with **1** by forming the complex of 1 : 1 stoichiometry in good accordance with the behavior of other proton-dissociable macrocyclic ligands of similar structure.[1] However, it was unexpectedly found for copper extraction that the linear relationship of Eq. 3 was not obeyed when the extractant concentration was increased to 3×10^{-5} M. This seemed to indicate the extraction of 1 : 2 complex.

Assuming the intervention of singly-deprotonated **1** species in the complexation, the extraction of copper(II) may be described by Eqs. 4 and 5.

$$2(H_2L)_{org} + M^{2+} \rightleftharpoons (M(HL)_2)_{org} + 2H^+, \tag{4}$$

$$K_{ex} = \frac{[M(HL)_2]_{org}[H^+]^2}{[M^{2+}][H_2L]^2_{org}}. \tag{5}$$

The latter equation is rewritten to Eq. 6.

$$\log\{[M(HL)_2]_{org}/[H_2L]^2_{org}\} = 2\text{pH} + \log[M^{2+}] + \log K_{ex}. \tag{6}$$

Figure 2 gives the plots of log $\{[M(HL)_2]_{org}/[H_2L]^2_{org}\}$ against pH at the extractant concentration of 1×10^{-4} M. The concentration of complex species was determined by molecular absorption spectrophotometry. A linear relationship of Eq. 6 held and this is a partial support for the reaction (4).

A more explicit proof for the 1 : 2 complex formation

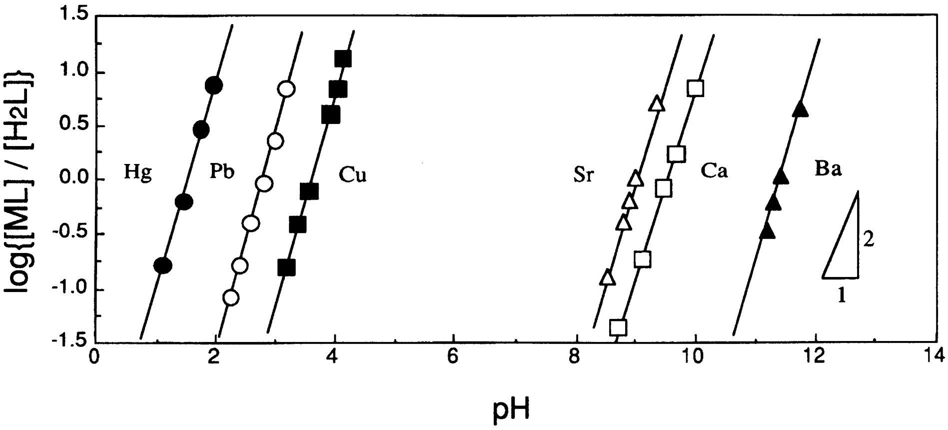

Fig. 1. pH dependence of divalent metal extraction. Initial metal concentration in aqueous phase, 1×10^{-3} M; initial concentration of **1**, 1×10^{-5} M.

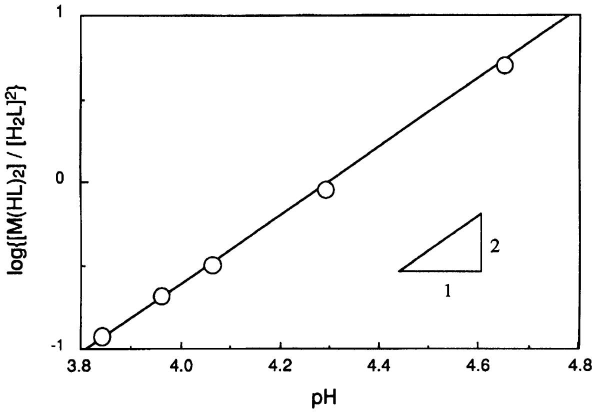

Fig. 2. pH dependence of copper(II) extraction. Initial copper concentration in aqueous phase, 1×10^{-3} M; initial concentration of **1**, 1×10^{-4} M.

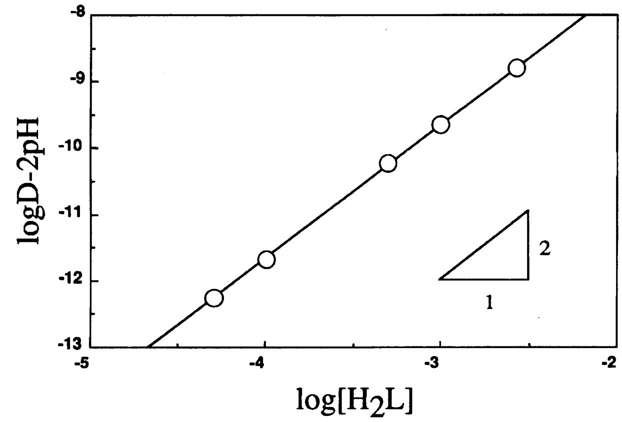

Fig. 3. Dependence of copper(II) extraction on extractant concentration. Initial copper concentration in aqueous phase, 1×10^{-5} M; pH 4.3.

came from Eq. 7 through Eq. 10.

$$n(\mathrm{H_2L})_{\mathrm{org}} + \mathrm{M}^{2+} \rightleftharpoons (\mathrm{M}(\mathrm{H}_{2n-2}\mathrm{L}_n))_{\mathrm{org}} + 2\mathrm{H}^+, \quad (7)$$

$$K_{\mathrm{ex}} = \frac{[\mathrm{M}(\mathrm{H}_{2n-2}\mathrm{L}_n)]_{\mathrm{org}}[\mathrm{H}^+]^2}{[\mathrm{M}^{2+}][\mathrm{H_2L}]^n_{\mathrm{org}}}, \quad (8)$$

$$D = [\mathrm{M}(\mathrm{H}_{2n-2}\mathrm{L}_n)]_{\mathrm{org}}/[\mathrm{M}^{2+}] \quad (n = 1, 2), \quad (9)$$

$$\log D - 2\mathrm{pH} = n \log[\mathrm{H_2L}]_{\mathrm{org}} + \log K_{\mathrm{ex}} \quad (n = 1, 2). \quad (10)$$

The distribution raito (D) of copper between the two phases was obtained by atomic absorption spectrophotometry while changing the concentration of the extractant in organic phase. The results are summarized in Fig. 3. The plots of log $D-2$pH against log $[\mathrm{H_2L}]_{\mathrm{org}}$ gave a slope of 2, which verified that the extraction took place according to Eq. 11.

$$\mathrm{Cu}^{2+} + 2\mathrm{H_2L} \rightleftharpoons \mathrm{Cu(HL)_2} + 2\mathrm{H}^+. \quad (11)$$

Binding ratio between metal ion and **1** was also estimated by mole ratio study (Fig. 4). The plots showed an inflection at the mole ratio (ligand to metal) of 2 for copper, whereas the inflections are at the ratio of 1 for all other metal ions. This shows that copper formed 1 : 2 complex, while other metals formed 1 : 1 complex.

An ambiguity exists in the structure of complex Cu(HL)$_2$. The complex is even to be described as CuL(H$_2$L) like the case in the extraction of alkali metal ions by 4′-picrylaminobenzocrown ethers.[10] However, we prefer the formulation Cu(HL)$_2$ because of the following reasons. In the metal extraction by **2**, no complex of the type ML(H$_2$L) was observed but the type ML. A very stable ML-type complex is also formed with "crown complexanes" (e.g., **3**)[11,12] which bear molecular skeletons substantially similar to **1** and **2**. The crystal structure of such complexes was elucidated for copper 2,2-cryptand-*N*,*N*′-diacetate complex (a copper complex from **3**).[13] The complex is featured by a very elongated octahedral coordination with two nitrogens and two carboxylate oxygens on the square plane and the two ethereal oxygens along the axis;[13] the copper is completely encapsulated into the spherical cavity provided by the crown complexane. Therefore, the complex formulation CuL(H$_2$L) for **1** is not at all in harmony with these facts; if CuL assumes an encapsulated struc-

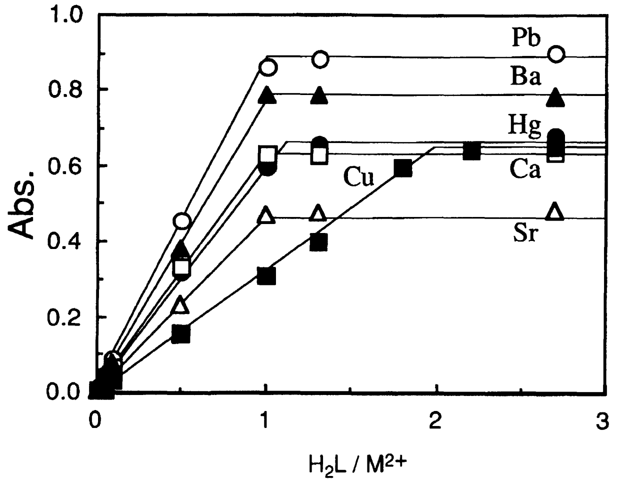

Fig. 4. Mole ratio plots for extraction of divalent metal ion with **1**. The optical absorbance of dichloromethane phase was monitored at the absorption maximum for the metal-**1** complex at 25°C (Hg(II), 258 nm; Sr(II), 276; Ca(II), 281; Ba(II), 280; Cu(II), 284; Pb(II), 264). Initial concentration of metal: 5×10^{-5} M (Pb(II)), 1×10^{-4} M (other metals). pH of aqueous phase: 2.5 (Hg), 9.0 (Sr), 10 (Ca), 12.5 (Ba), 5 (Cu), 3.5 (Pb).

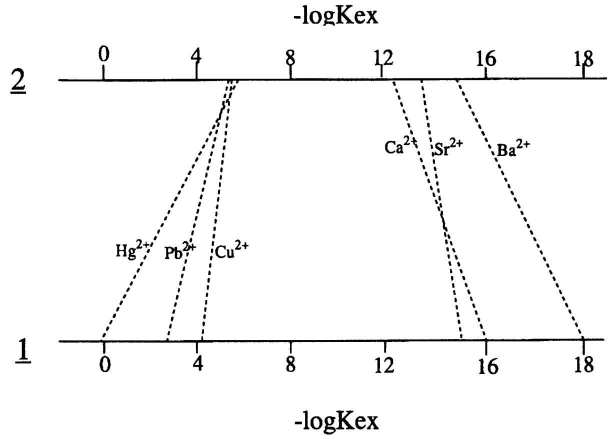

Fig. 5. Extractability with phenol-type **2** and sulfonamide-type **1** extractants.

ture, such a coordinatively saturated complex should not show such a strong affinity to H_2L to form the adduct $CuL(H_2L)$. The complex $Cu(HL)_2$ with **1** presumably involves square planar coordination where each HL unit offers an anionic sulfonamido nitrogen and a neutral tertiary amine nitrogen to fill a half of the four coordination sites on the square planar copper in the $Cu(HL)_2$ complex. The bulkiness of trifluoromethanesulfonyl group on the nitrogen likely prevents copper ion from accepting axial ligands.

Extraction constants were calculated from the intercept of line in Fig. 1, and summarized in Table 1. From Table 1, the difference in pK_{ex} between soft metals (Hg^{2+}, Pb^{2+}, Cu^{2+}) and alkaline earth metals was more than 10; soft metals are much more extractable than alkaline earth metals. If one compares **1** with the phenol-type extractant **2**,[9] soft metals are more easily extracted by **1**. For copper, however, **1** has a similar extraction ability to **2** as seen from Fig. 5. In addition, 1 : 2 complex formation was found to be dominant when the concentration of copper is comparable to that of the extractant. For copper, therefore, the extraction cannot be explained simply by metal softness.

Table 1. Extraction Equilibriun Constant of Divalent Metal Ions

M (II)	$-\log K_{ex}$ (1 : 1)	$-\log K_{ex}$ (1 : 2)
Hg	0.0	—
Pb	2.5	—
Cu	4.2	3.6
Sr	15	—
Ca	16	—
Ba	18	—

Because the ionic diameter of copper is much smaller than the internal cavity diameter of the crown, the macrocyclic encapsulation can not give particular advantage on copper complexation. Therefore, the stabilizing effect on copper complexation by **1** should come from the coordination by the anionic side arms on the aza-crown skeleton as is the case in the crown complexane. In the phenol type extractants, phenolic oxygens do not have any additional substituent on the coordinating oxygen atoms. In the sulfonamide-type, in contrast, trifluoromethanesulfonyl group attached to the coordinating nitrogen is bulky, so that a simultaneous coordination to copper by two amido-nitrogens and two tertiary amine-nitrogens within a single crown ether molecule can cause a severe steric hindrance in its molecular skeleton. This is readily envisaged by inspecting a CPK space-filling model. As a result, 1 : 2 complex turns out to be relatively easy to form.

Although the steric hindrance of sulfonamide ligand on coordination has been suggested earlier,[7] the present result seems to support the idea in more conclusive manner. Thus trifluoromethanesulfonamido group seems to offer a unique possibility in designing metal complexation reagents in future.

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