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Solvent Extraction of Copper(II) with Lipoic Acid in Benzene. Evidence for the Preferential Coordination of Carboxylate

Hiromichi Yamada,* Toshiyuki Okuda, Yukio Fujii,
Masateru Mizuta, and Motoharu Tanaka†
Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11
†Laboratory of Analytical Chemistry, Faculty of Science, Nagoya University, Chikusa-ku, Nagoya 464

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The extraction of copper(II) was carried out with lipoic acid in benzene at 25 °C and at a constant ionic strength in the aqueous phase: 0.1 mol dm^{-3} ($NaNO_3$). The partition constant, $K_{D,HA}$ of lipoic acid between benzene and water, and the dimerization constant, $K_{2,HA}$ of lipoic acid in benzene were determined: log $K_{D,HA}$=1.17 and log $K_{2,HA}$=2.51. The dimeric copper(II) lipoate is responsible for the extraction:

$$2Cu^{2+} + 3(HA)_{2,o} \overset{K_{ex(22)}}{\rightleftharpoons} (Cu_2A_4(HA)_2)_o + 4H^+$$

with the extraction constant, log $K_{ex(22)}$=−11.00. It was proved that lipoate ion coordinates to copper(II) with the carboxylate group without a remarkable participation of the disulfide moiety in the coordination.

1,2-Dithiolane-3-pentanoic acid (lipoic acid) is widely distributed in nature in a protein-bound form, and it is an essential component of "multienzyme" units which catalyze the oxidative decarboxylation of α-keto acids. Lipoic acid has two different binding sites, that is, the carboxyl group and the disulfide linkage. The carboxylate group is known to coordinate dominantly to the biologically important metal ions, while the disulfide group is also anticipated to participate in coordination. These coordination tendencies of two groups in solution were summarized and discussed in relation to their biochemical significance by Sigel.[1,2]

Recently, some synthetic applications of lipoic acid derivatives to organic reactions utilizing their redox function were reported.[3]

It is well-known that the copper(II) carboxylates have a dimeric structure not only in the crystalline state but also in various nonsolvating solvents. It has been previously reported that only the dimeric copper(II) decanoate involving free decanoic acids, $Cu_2A_4(HA)_2$ is responsible for the extraction of copper(II) with decanoic acid in some nonsolvating solvents such as benzene and carbon tetrachloride.[4]

The present paper describes the results of the extraction of copper(II) with lipoic acid in benzene. Comparing the present results with those obtained in the extraction of copper(II) decanoate in benzene, it was found that the carboxylate group preferentially coordinates to copper(II) ions in the dimeric copper(II) lipoate, that is, the disulfide group does not participate in complex formation.

Experimental

Reagents. Lipoic Acid: Reagent grade DL-α-lipoic acid (purity: over 98%) was dissolved in benzene just before its use.

Benzene: Reagent grade benzene was washed successively with concentrated sulfuric acid, with dilute potassium hydroxide solution, with dilute perchloric acid solution, and then with distilled water. All other reagents were reagent grade and used without further purification.

Procedure. Partition was carried out in a bath thermostated at 25.0±0.2 °C. 15 cm^3 each of the aqueous and organic phases were contacted in a brown centrifuge tube. Ionic strength of the aqueous phase was adjusted to 0.1 mol dm^{-3} with sodium nitrate. Shaking for about 1 h was found sufficient for complete equilibration. After centrifugation, the aqueous phase was immediately separated from the organic phase. And then, hydrogen-ion concentration of the aqueous phase was measured with 1.00×10^{-2} mol dm^{-3} nitric acid solution (ionic strength 0.1 mol dm^{-3}) as a standard. The measured pH values were corrected for the apparent liquid junction potential. The concentration of copper in the aqueous phase was determined compleximetrically, with 4-(2-thiazolylazo)resorcinol (TAR) as an indicator.[5] In the partition of lipoic acid between water and benzene, the concentration of lipoic acid in the aqueous phase was determined by potentiometric titration. An absorption maximum at 330 nm of DL-lipoic acid was used for the determination of the lower concentration of lipoic acid in the aqueous phase.

Apparatus. For mechanical shaking in a thermostat, Taiyo Incubator M-100^{N} (Taiyokagaku-Kogyo Co., Tokyo) was used. The pH measurements and potentiometric titrations were carried out with a Horiba pH Analyzer F-80 (Horiba Seisakusho Ltd., Kyoto). Spectrophotometric determination was performed on a UVIDEC-430A Double Beam Spectrophotometer (Japan Spectroscopic Co. Ltd., Tokyo). KNAUER Vapor Pressure Osmometer (KNAUER Ltd., Berlin, West Germany) was used for the determination of dimerization constant of lipoic acid in benzene. A Swing Type Centrifuge Model CD-50SR (Tomy Seiko Co. Ltd., Tokyo) was used for centrifugation.

Results and Discussion

Distribution of Lipoic Acid. In studying the extraction of a metal ion with a carboxylic acid, it is indispensable to have information about the partition of the carboxylic acid between the aqueous and organic phases. Then in the present extraction system the following equilibria should be considered.

(a) The dissociation of lipoic acid HA in the aqueous phase:

$$\mathrm{HA + H_2O \rightleftharpoons H_3O^+ + A^-}$$

with the dissociation constant,

$$K_a = [\mathrm{H_3O^+}][\mathrm{A^-}][\mathrm{HA}]^{-1}. \qquad (1)$$

(b) The partition of lipoic acid between benzene and the aqueous phase:

$$(\mathrm{HA})_w \rightleftharpoons (\mathrm{HA})_o$$

where the subscripts w and o refer to the aqueous and benzene phases, respectively. The partition constant is defined as

$$K_{\mathrm{D,HA}} = [\mathrm{HA}]_o[\mathrm{HA}]_w^{-1}. \qquad (2)$$

(c) The dimerization of lipoic acid in the organic phase:

$$2(\mathrm{HA})_o \rightleftharpoons (\mathrm{HA})_{2,o}$$

with $(\mathrm{HA})_{2,o}$ denoting the dimeric lipoic acid in the organic phase, and the dimerization constant defined as

$$K_{2,\mathrm{HA}} = [(\mathrm{HA})_2]_o[\mathrm{HA}]_o^{-2}. \qquad (3)$$

Then, the distribution ratio of lipoic acid between benzene and water is written as follows:

$$\begin{aligned} D &= C_{\mathrm{HA},o}C_{\mathrm{HA},w}^{-1} \\ &= K_{\mathrm{D,HA}}(1+2K_{2,\mathrm{HA}}K_{\mathrm{D,HA}}[\mathrm{HA}]_w)(1+K_a[\mathrm{H^+}]^{-1})^{-1}. \qquad (4)\end{aligned}$$

In the lower pH region where the dissociation of lipoic acid in the aqueous phase is negligible, that is, $1 \gg K_a/[\mathrm{H^+}]$, Eq. 4 can be rewritten as follows:

$$D = K_{\mathrm{D,HA}} + 2K_{2,\mathrm{HA}}K_{\mathrm{D,HA}}^2[\mathrm{HA}]_w \qquad (5)$$

As shown in Eq. 5, a linear relationship between the distribution ratio D of lipoic acid and the concentration of unionized lipoic acid in the aqueous phase is expected to hold. Benzene solutions of lipoic acid ranging from 0.025 to 0.7 mol dm^{-3} were equilibrated at 25 °C with 0.01 mol dm^{-3} nitric acid (I=0.1 mol dm^{-3} H, $\mathrm{NaNO_3}$). From the results obtained, the dimerization and partition constants of lipoic acid were determined by the least-squares method according to Eq. 5: $\log K_{2,\mathrm{HA}}=2.51$ and $\log K_{\mathrm{D,HA}}=1.17$, respectively.

On the other hand, the dimerization constant of lipoic acid in benzene is obtained by the vapor pressure osmometry: $\log K_{2,\mathrm{HA}}=2.52$. This value is in good agreement with that determined by the partition experiment. Thus the dimeric lipoic acid prevails in benzene.

Extraction of Copper(II) with Lipoic Acid. If a j-merized copper(II) lipoate $\mathrm{Cu}_j\mathrm{A}_{2j}(\mathrm{HA})_a$ (HA: lipoic acid) is responsible for the extraction, the extraction equilibrium can be expressed as follows:[4]

$$j\mathrm{Cu^{2+}} + 0.5(2j+a)(\mathrm{HA})_{2,o} \rightleftharpoons (\mathrm{Cu}_j\mathrm{A}_{2j}(\mathrm{HA})_a)_o + 2j\mathrm{H^+}$$

with the extraction constant defined as

$$\begin{aligned} &K_{\mathrm{ex}(ja)} = \\ &\quad [\mathrm{Cu}_j\mathrm{A}_{2j}(\mathrm{HA})_a]_o[\mathrm{H^+}]^{2j}[\mathrm{Cu^{2+}}]^{-j}[(\mathrm{HA})_2]_o^{-0.5(2j+a)}. \qquad (6)\end{aligned}$$

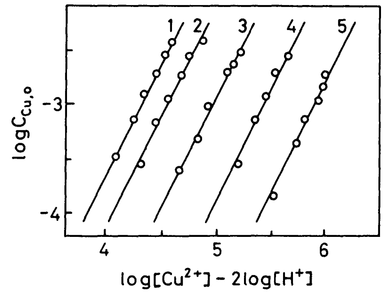

Fig. 1. Determination of the degree of polymerization of copper(II) lipoate. C_{HA}; No. 1: 1.0, No. 2: 0.7, No. 3: 0.4, No. 4: 0.2, No. 5: 0.1 mol dm^{-3}. Solid lines are the straight lines with a slope of 2.

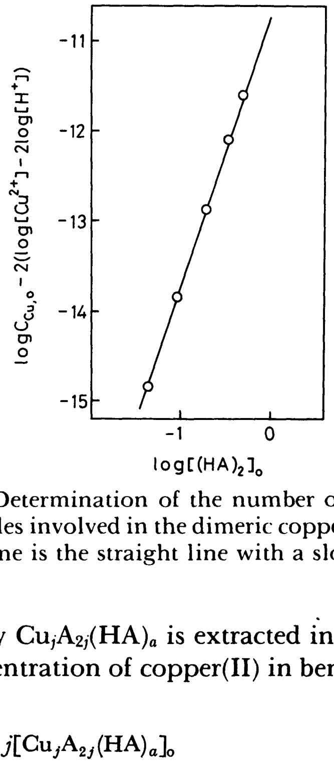

Fig. 2. Determination of the number of lipoic acid molecules involved in the dimeric copper(II) lipoate. Solid line is the straight line with a slope of 3.

When only $\mathrm{Cu}_j\mathrm{A}_{2j}(\mathrm{HA})_a$ is extracted into benzene, the total concentration of copper(II) in benzene is written as follows:

$$\begin{aligned} C_{\mathrm{Cu},o} &= j[\mathrm{Cu}_j\mathrm{A}_{2j}(\mathrm{HA})_a]_o \\ &= jK_{\mathrm{ex}(ja)}[\mathrm{Cu^{2+}}]^j[\mathrm{H^+}]^{-2j}[(\mathrm{HA})_2]_o^{0.5(2j+a)} \qquad (7)\end{aligned}$$

which is rewritten as a logarithmic form:

$$\begin{aligned} \log C_{\mathrm{Cu},o} &= j(\log[\mathrm{Cu^{2+}}] - 2\log[\mathrm{H^+}]) \\ &\quad + 0.5(2j+a)\log[(\mathrm{HA})_2]_o + \log j + \log K_{\mathrm{ex}(ja)}. \qquad (8)\end{aligned}$$

According to Eq. 8, the degree of polymerization of copper(II) lipoate can be obtained from the slope of a plot of $\log C_{\mathrm{Cu},o}$ vs. $(\log[\mathrm{Cu^{2+}}]-2\log[\mathrm{H^+}])$ at a constant $[(\mathrm{HA})_2]_o$. The plot shown in Fig. 1, falls along the straight line with a slope of 2: only the dimeric copper(II) lipoate is responsible for the extraction under the present experimental conditions.

The number of lipoic acid molecules involved in the dimeric copper(II) lipoate is given by the slope of a plot of $\{\log C_{\mathrm{Cu},o}-2(\log[\mathrm{Cu^{2+}}]-2\log[\mathrm{H^+}])\}$ vs. $\log[(\mathrm{HA})_2]_o$. As shown in Fig. 2, the plot falls on the straight line with a slope of 3.0, that is, $(4+a)/2=3$ or $a=2$. Consequently, only $\mathrm{Cu_2A_4(HA)_2}$ is extracted in the present extraction system as in the extraction of copper(II) with decanoic acid in benzene. The extraction constant of the dimeric copper(II) lipoate, $K_{ex(22)}$ can be calculated from the intercept of the plot in Fig. 2. Then the extraction equilibrium for copper(II) lipoate can be expressed as follows:

$$2Cu^{2+} + 3(HA)_{2,o} \overset{K_{ex(22)}}{\rightleftharpoons} (Cu_2A_4(HA)_2)_o + 4H^+$$

with

$$\log K_{ex(22)} = -11.00.$$

Comparison of Lipoic with Decanoic Acids. Both the dissociation constant in the aqueous phase and the dimerization constant in benzene of lipoic acid are similar to those of decanoic acid. This would be attributed to the shielding of the electron-withdrawing effect of the disulfide group by four methylene groups.

The smaller partition constant of lipoic acid than that of decanoic acid suggests that the 1,2-dithiolane ring is more hydrophilic than the pentyl group. The extraction constant stated above is formulated as

$$K_{ex(22)} = K_{D,Cu_2A_4(HA)_2} K_{D,HA}{}^{-6} K_{2,HA}{}^{-3} \beta_{Cu_2A_4(HA)_2} K_a{}^4 \quad (9)$$

where $K_{D,Cu_2A_4(HA)_2}$ and $\beta_{Cu_2A_4(HA)_2}$ denote the partition constant of $Cu_2A_4(HA)_2$ between benzene and water and the overall formation constant of this complex in the aqueous phase defined, respectively as follows:

$$(Cu_2A_4(HA)_2)_w \rightleftharpoons (Cu_2A_4(HA)_2)_o$$

with

$$K_{D,Cu_2A_4(HA)_2} = [Cu_2A_4(HA)_2]_o[Cu_2A_4(HA)_2]_w{}^{-1}$$

and

$$2Cu^{2+} + 4A^- + 2(HA)_w \rightleftharpoons (Cu_2A_4(HA)_2)_w$$

with

$$\beta_{Cu_2A_4(HA)_2} = [Cu_2A_4(HA)_2]_w[Cu^{2+}]^{-2}[A^-]^{-4}[HA]_w^{-2}.$$

From the additive nature of the molar cohesive energy and molar volume of ligand in a complex, the partition constant of a complex MA_n can be approximately correlated to that of the ligand HA as follows[6]: $K_{D,MA_n} \simeq K_{D,HA}{}^n$. Since a similar relation, namely, $K_{D,Cu_2A_4(HA)_2} \simeq K_{D,HA}{}^6$ can be presumed to hold also for the present extraction system, the overall formation constant can be approximated as follows:

$$\beta_{Cu_2A_4(HA)_2} \simeq K_{ex(22)} K_{2,HA}{}^3 K_a^{-4}. \quad (10)$$

On the other hand, taking into account the electrostriction of ligands in the complex, that is, $V_{Cu_2A_4(HA)_2} = 6 \times 0.95 V_{HA}$, the partition constant of $Cu_2A_4(HA)_2$ can be approximated as follows: $\log K_{D,Cu_2A_4(HA)_2} \simeq 5.7 \log K_{D,HA}$. Then, the overall formation constant, $\beta_{Cu_2A_4(HA)_2}$ can be calculated by the following relation:

$$\beta_{Cu_2A_4(HA)_2} \simeq K_{ex(22)} K_{D,HA}{}^{0.3} K_{2,HA}{}^3 K_a^{-4}. \quad (11)$$

The results for lipoic and decanoic acids obtained from these relations are listed in Table 1 together with other constants. As can be seen from Table 1, the value of the overall formation constant of the dimeric copper(II) lipoate in the aqueous phase is close to that of the dimeric copper(II) decanoate. This suggests strongly that in the dimeric copper(II) lipoate the copper(II) ions coordinate not to the disulfide group, but to the carboxyl group of lipoic acid in the same manner as in the dimeric copper(II) decanoate.

Table 1. Comparison of Various Constants of Lipoic with Decanoic Acids

Constants	Lipoic Acid	Decanoic Acid
pK_a	4.85[a]	4.92[c,d]
$\log K_{D,HA}$	1.17[b]	2.80[c,d]
$\log K_{2,HA}$	2.51	2.41[d]
$\log K_{ex(22)}$	−11.00[b]	−11.36[c,e]
$\log \beta_{Cu_2A_4(HA)_2}$	15.93[b,f]	15.55[c,f]
	(16.28)[g]	(16.39)[g]

a) The value is estimated from the data in 50% (v/v) dioxane-water mixture.[2] b) Ionic strength 0.1 mol dm^{-3} (NO_3^-). c) Ionic strength 0.1 mol dm^{-3} (ClO_4^-). d) Ref. 7. e) Ref. 4. f) Calculated by Eq. 10. g) The values in the parentheses are evaluated by taking into account the electro-striction of ligands in the complex (Eq. 11).

In the visible region, the spectrum of copper(II) lipoate in benzene grossly resembles that of copper(II) decanoate in the presence of an excess of the respective acid, that is, copper(II) lipoate shows an absorption peak at 680 nm assigned to a so-called metal-ligand interaction. In the UV region, the spectra for copper(II) lipoate and decanoate in benzene differ from each other, because of the difference in the spectra between lipoic and decanoic acids. This result will also support that copper(II) ions coordinate to the carboxylate group in the dimeric copper(II) lipoate.

In general, soft metal ions like silver(I) ion have a tendency to coordinate to the disulfide moiety. Then we have attempted to study the extraction of silver(I) ion with lipoic acid in carbon tetrachloride. Disappointingly, silver(I) ion could not be extracted, and a white precipitate formed which would be a decomposition product of lipoate. It can be presumed that coordination of silver(I) ion to the disulfide moiety causes cleavage of the disulfide link.

To conclude, lipoate ion coordinates to copper(II) with the carboxylate group without a remarkable participation of the disulfide moiety in the coordination.

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