

Studies on the Sulfur-containing Chelating Agents. XLIV.¹⁾ Kinetic Study of Ligand Exchange Reaction of Mercury-Aminopolycarboxylate with Monothiodibenzoylmethane by Solvent Extraction Method

NOBUKO NAKANISHI, AKIRA YOKOYAMA, and HISASHI TANAKA

Faculty of Pharmaceutical Sciences, Kyoto University²⁾

(Received September 20, 1974)

The kinetics of ligand exchange reaction of mercury-aminopolycarboxylates (Hg-Y) with monothiodibenzoylmethane (SBB) is studied by solvent extraction method. EDDA, NTA, EDTA-OH, DPTA-OH, EDTA, methyl-EDTA, GEDTA and DTPA are used as aminopolycarboxylic acid. The reaction rate is determined by the measurements of the radioactivity of ²⁰³Hg in the aqueous phase. From the respective dependencies of the rate constant on the concentrations of hydrogen ion, SBB and Y, the formation of the mixed ligand complex was approved in the reaction mechanism. The values of the rate constants and stability constants of Hg-Y are found to be correlated each other with a few exceptions such as the cases of EDTA-OH and DPTA-OH, and the rate determining step is considered to be involved in the step of the dissociation of aminopolycarboxylic acid. The usefulness of the solvent extraction method for the kinetic study of complex formation was proved through the result presented here.

Monothiodibenzoylmethane (abbreviated as SBB hereafter) is regarded as the most advantageous reagent for the solvent extraction of some metal ions among various monothio- β -diketones, its high partition coefficient,^{3,4)} and the high stability of some metal complexes being considered. Previously, we established a radioisotope dilution method⁵⁾ for the determination of trace amount of mercury, applying SBB as an extractant, and determined⁴⁾ the stability and extraction constants of mercury complex of SBB. Recently, monothio- β -diketones have been actively studied from various points of view,⁶⁾ however the detailed information of the complex formation of SBB is scarce. In an attempt to get some information on the complex formation of SBB with various metal ions in the presence of other chelating agents, we investigated the mechanism of the complex formation of SBB with mercury in the presence of aminopolycarboxylic acid through the kinetic study by the use of the solvent extraction method.⁷⁾

Experimental

Materials—Reagent grade Hg(OAc)₂ was used to prepare approximately 1.0×10^{-3} M solution, which was standardized by EDTA titration. When this solution was diluted to a proper concentration, trace amount of ²⁰³Hg in the form of Hg(OAc)₂ purchased from The Radio Chemical Center was added. SBB was synthesized and purified by the method reported previously.⁸⁾ Aminopolycarboxylic acids listed in Chart 1 were obtained from Dojindo Co. Ltd.. Acetate and borax-mannitol buffer solutions were used. The ionic strength

- 1) Part XLIII: M. Chikuma, A. Yokoyama, Y. Ooi, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **23**, 507 (1975).
- 2) Location: Yoshida, Shimoadachi-cho, Sakyo-ku, Kyoto.
- 3) E. Uhlemann, B. Schuknecht, K.D. Busse, and V. Pohn, *Anal. Chim. Acta*, **56**, 185 (1971).
- 4) A. Yokoyama, N. Nakanishi, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **20**, 1855 (1972).
- 5) H. Tanaka, N. Nakanishi, Y. Sugiura, and A. Yokoyama, *Bunseki-kagaku*, **17**, 1428 (1968).
- 6) M. Cox and J. Darken, *Coord. Chem. Rev.*, **7**, 29 (1971); S.E. Livingstone, *Coord. Chem. Rev.*, **7**, 59 (1971).
- 7) P.R. Subbaraman, M.C. Sister, and H. Freiser, *Anal. Chem.*, **41**, 1878 (1969); I.P. Alimarin, Y.A. Zolotov, and V.A. Bodnya, *Pure. Appl. Chem.*, **25**, 667 (1971); T. Sekine and Y. Komatsu, *Bunseki-kagaku*, **23**, 222 (1974).
- 8) A. Yokoyama, S. Kawanishi, M. Chikuma, and H. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **15**, 540 (1967)

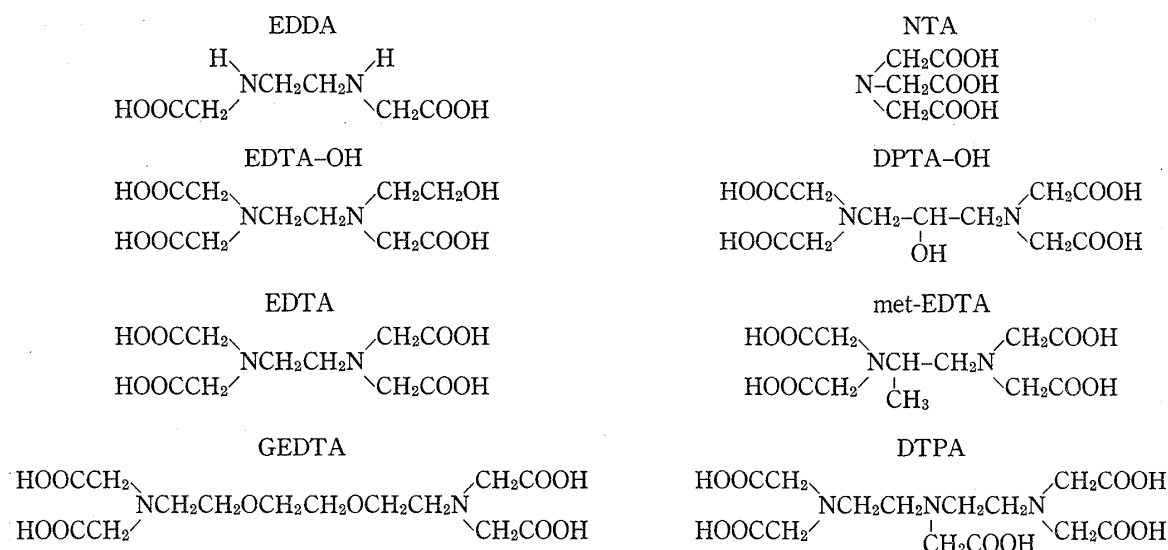


Chart 1. Structure of Aminopolycarboxylic Acid

of the solution was adjusted to 0.1 by NaNO_3 . CHCl_3 was shaken with water, distilled and saturated with buffer solution before use. Distilled and deionized water was used.

Apparatus—Solvent extraction was carried out in a 500 ml three necked flask which was dipped in a water bath thermostated at $25.0 \pm 0.5^\circ$ by Yamato Labo Stirrer with Tokyo Rika Kikai Vacuum Stirrer. Measurement of radioactivity was made with a Fujitsu well type scintillation counter Model ATS-121 for a period of time necessary to obtain total counts of at least 10000. A Hitachi-Horiba Model F-5 type pH meter was used for the pH measurements.

Procedure—A 100 ml aliquot of a solution containing radioactive $\text{Hg}(\text{OAc})_2$, aminopolycarboxylic acid and buffer solution was placed in a 500 ml three necked flask and stirred vigorously with an equal volume of CHCl_3 solution of SBB. At proper time interval, 3 ml of aqueous phase was taken and allowed to stand for 10 min, and a 2 ml aliquot of the solution was taken into a plastic tube for the counting of the radioactivity, $\{A_{\text{Hg}}\}_a$. Finally pH of the aqueous phase was measured. The concentration of mercury in the aqueous phase is shown as follows.

$$[\text{Hg}]_a = \frac{\{A_{\text{Hg}}\}_a}{\{A_{\text{Hg}}\}_T} [\text{Hg}]_T$$

$[\text{Hg}]_a$: concentration of mercury in the aqueous phase

$[\text{Hg}]_T$: total concentration of mercury

$\{A_{\text{Hg}}\}_a$: radioactivity of ^{203}Hg in the aqueous phase

$\{A_{\text{Hg}}\}_T$: initial radioactivity of ^{203}Hg in the aqueous phase

The speed of the stirring was adjusted to achieve the constant extraction rate, by the check of the relation between the radioactivity in the aqueous phase and the stirring speed.

Results

Dependence of the Concentration of Mercury in the Aqueous Phase

A linear correlation was found between $\log[\text{Hg}]_a$ and time, when the concentration of SBB in the organic phase and that of aminopolycarboxylic acid in the aqueous phase, and pH were kept constant. Some of the results obtained are shown in Fig. 1 and 2. The reaction is first order with respect to concentration of mercury. Pseudo first order rate constant, k_{obs} , was determined from the slope of the line.

pH Dependence

Between pH 3 and 5, Fig. 3 shows the relationship between k_{obs} and $[\text{H}^+]$, in which the straight line intercepts the k_{obs} axis. On a pH range from 6 to 8, as shown in Fig. 4, k_{obs} vs. $1/[\text{H}^+]$ plot gives also a straight line which intercepts the k_{obs} axis at the same value as observed in Fig. 3, but never through the origin.

Dependence on the Concentration of SBB in the Organic Phase

The concentration of SBB in the organic phase being varied, pseudo first order rate constants were determined in both acid and alkaline solutions. The plots of k_{obs} vs. $[\text{SBB}]_0$ are shown in Fig. 5 and 6, which give a straight line through the origin.

Dependence on the Concentration of Aminopolycarboxylic Acid

The concentration of aminopolycarboxylic acid (Y) in the aqueous phase being varied, pseudo first order rate constants were determined in both acid and alkaline solutions. The plots of $\log k_{\text{obs}}$ vs. $[\text{Y}]$ are shown in Fig. 7 and 8, which are parallel to the $[\text{Y}]$ axis.

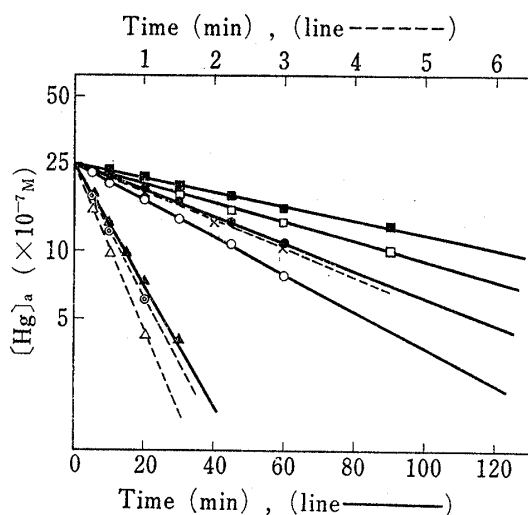


Fig. 1. Relationship between $\log [\text{Hg}]_a$ and Reaction Time at Acidic Region

- : GEDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 3.85
 - : DTPA SBB = $3.0 \times 10^{-4} \text{ M}$ pH 4.21
 - : met-EDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 4.44
 - : EDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 4.22
 - ▲: EDTA-OH SBB = $5.0 \times 10^{-5} \text{ M}$ pH 4.86
 - ×: NTA SBB = $5.0 \times 10^{-5} \text{ M}$ pH 4.89
 - ⊙: EDDA SBB = $2.5 \times 10^{-5} \text{ M}$ pH 4.92
 - △: DPTA-OH SBB = $1.0 \times 10^{-4} \text{ M}$ pH 4.37
- ($\text{Hg}_T = 2.5 \times 10^{-6} \text{ M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{ M}$)

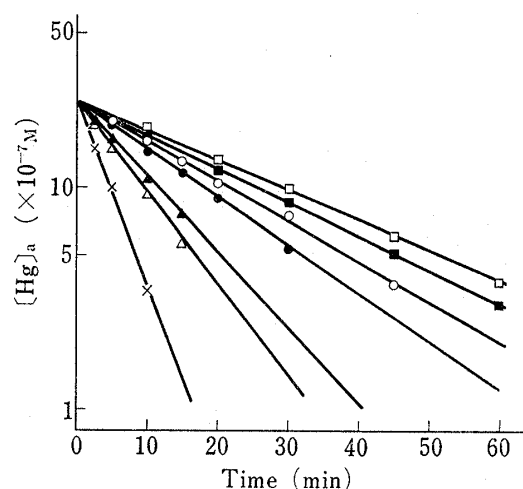


Fig. 2. Relationship between $\log [\text{Hg}]_a$ and Reaction Time at Alkaline Region

- : met-EDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 7.75
 - : GEDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 8.35
 - : DTPA SBB = $3.0 \times 10^{-4} \text{ M}$ pH 7.80
 - : EDTA SBB = $1.0 \times 10^{-4} \text{ M}$ pH 7.71
 - ▲: EDTA-OH SBB = $5.0 \times 10^{-5} \text{ M}$ pH 7.06
 - △: DPTA-OH SBB = $1.0 \times 10^{-4} \text{ M}$ pH 7.30
 - ×: NTA SBB = $5.0 \times 10^{-5} \text{ M}$ pH 7.53
- ($\text{Hg}_T = 2.5 \times 10^{-6} \text{ M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{ M}$)

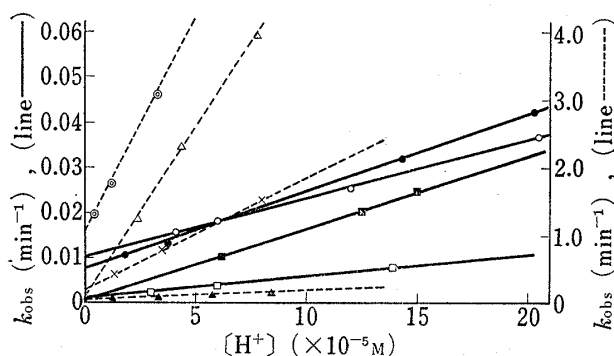


Fig. 3. Relationship between k_{obs} and $[\text{H}^+]$ at Acidic Region

- ⊙: EDDA SBB = $2.5 \times 10^{-5} \text{ M}$
 - ▲: EDTA-OH SBB = $5.0 \times 10^{-5} \text{ M}$
 - : DTPA SBB = $3.0 \times 10^{-4} \text{ M}$
 - △: DPTA-OH SBB = $1.0 \times 10^{-4} \text{ M}$
 - : EDTA SBB = $1.0 \times 10^{-4} \text{ M}$
 - : GEDTA SBB = $1.0 \times 10^{-4} \text{ M}$
 - ×: NTA SBB = $5.0 \times 10^{-5} \text{ M}$
 - : met-EDTA SBB = $1.0 \times 10^{-4} \text{ M}$
- ($\text{Hg}_T = 2.5 \times 10^{-6} \text{ M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{ M}$)

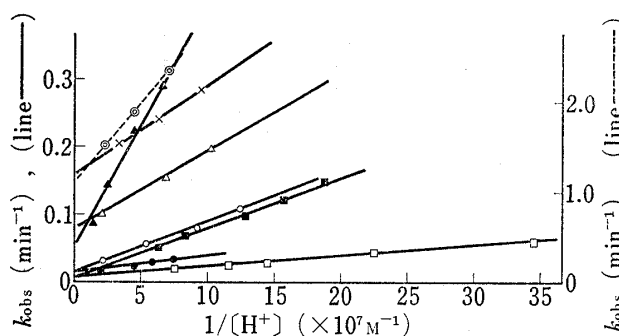


Fig. 4. Relationship between k_{obs} and $1/[\text{H}^+]$ at Alkaline Region

- ⊙: EDDA SBB = $2.5 \times 10^{-5} \text{ M}$
 - ▲: EDTA-OH SBB = $5.0 \times 10^{-5} \text{ M}$
 - : DTPA SBB = $3.0 \times 10^{-4} \text{ M}$
 - △: DPTA-OH SBB = $1.0 \times 10^{-4} \text{ M}$
 - : EDTA SBB = $1.0 \times 10^{-4} \text{ M}$
 - : GEDTA SBB = $1.0 \times 10^{-4} \text{ M}$
 - ×: NTA SBB = $5.0 \times 10^{-5} \text{ M}$
 - : met-EDTA SBB = $1.0 \times 10^{-4} \text{ M}$
- ($\text{Hg}_T = 2.5 \times 10^{-6} \text{ M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{ M}$)

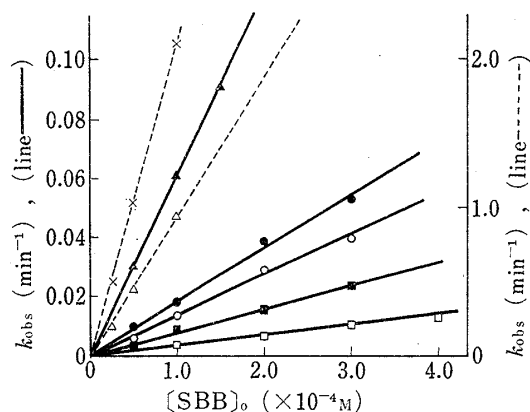


Fig. 5. Relationship between k_{obs} and $[\text{SBB}]_0$ at Acidic Region

×: DPTA-OH pH 4.37 ○: met-EDTA pH 4.44
 △: NTA pH 4.89 ■: GEDTA pH 3.85
 ▲: EDTA-OH pH 4.86 □: DTPA pH 4.21
 ●: EDTA pH 4.22
 ($\text{Hg}_T = 2.5 \times 10^{-6} \text{M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{M}$)

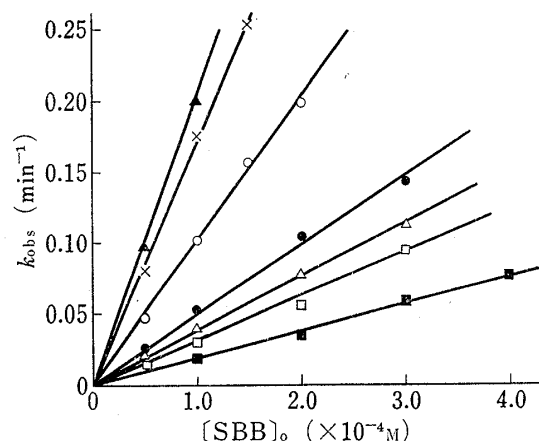


Fig. 6. Relationship between k_{obs} and $[\text{SBB}]_0$ at Alkaline Region

▲: NTA pH 7.53 △: GEDTA pH 8.35
 ×: EDTA-OH pH 7.06 □: met-EDTA pH 7.75
 ○: DPTA-OH pH 7.30 ■: DTPA pH 7.80
 ●: EDTA pH 7.71
 ($\text{Hg}_T = 2.5 \times 10^{-6} \text{M}$, $\text{Y}_T = 1.0 \times 10^{-3} \text{M}$)

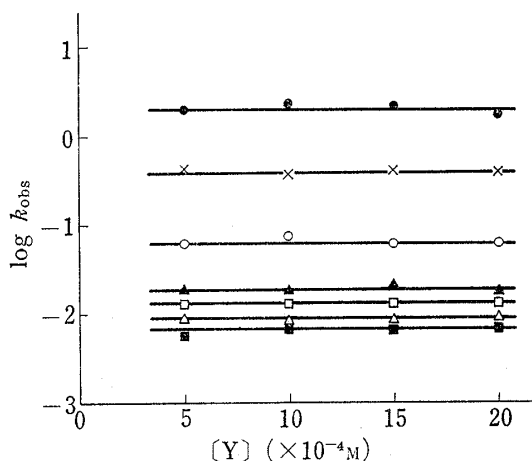


Fig. 7. Relationship between $\log k_{\text{obs}}$ and $[\text{Y}]$ at Acidic Region

●: DPTA-OH SBB = $1.0 \times 10^{-4} \text{M}$ pH 4.37
 ×: NTA SBB = $5.0 \times 10^{-5} \text{M}$ pH 4.89
 ○: EDTA-OH SBB = $5.0 \times 10^{-5} \text{M}$ pH 4.86
 ▲: EDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 4.22
 □: met-EDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 4.44
 △: DTPA SBB = $3.0 \times 10^{-4} \text{M}$ pH 4.21
 ■: GEDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 3.85
 ($\text{Hg}_T = 2.5 \times 10^{-6} \text{M}$)

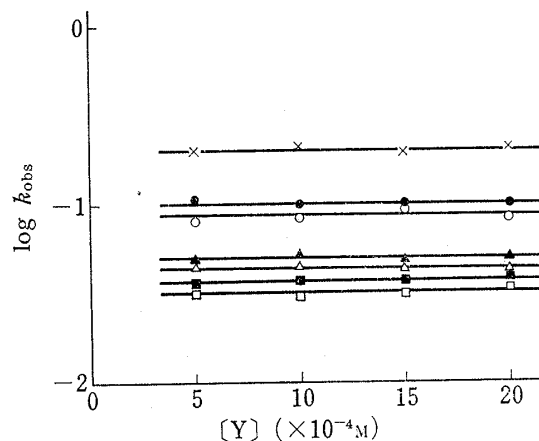


Fig. 8. Relationship between $\log k_{\text{obs}}$ and $[\text{Y}]$ at Alkaline Region

×: NTA SBB = $5.0 \times 10^{-5} \text{M}$ pH 7.53
 ●: DPTA-OH SBB = $1.0 \times 10^{-4} \text{M}$ pH 7.30
 ○: EDTA-OH SBB = $5.0 \times 10^{-5} \text{M}$ pH 7.06
 ▲: EDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 7.71
 △: DTPA SBB = $3.0 \times 10^{-4} \text{M}$ pH 7.80
 ■: GEDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 8.35
 □: met-EDTA SBB = $1.0 \times 10^{-4} \text{M}$ pH 7.75
 ($\text{Hg}_T = 2.5 \times 10^{-6} \text{M}$)

Discussion

From above results, the rate of the decrease of the concentration of mercury in the aqueous phase is expressed as equation (1).

$$-\frac{d[\text{Hg}]_a}{dt} = \left\{ k_0 \frac{1}{[\text{H}^+]} + k_1 + k_2 [\text{H}^+] \right\} [\text{Hg}]_a [\text{RSH}]_0 \quad (1)$$

$[\text{RSH}]_0$: total SBB concentration in the organic phase k_0, k_1, k_2 : observed rate constants

Further, the reaction rate is independent of the concentration of aminopolycarboxylic acid, $[\text{Y}]$. In the aqueous phase, mercury is considered to be present in the form of the complex of aminopolycarboxylic acid completely under the experimental condition, that means $[\text{Hg}] \ll$

[Y], their high stability constants, $k_{\text{Hg-Y}}$,^{9,10} shown in Table I being taken into account. Thus $[\text{Hg}]_a$ is considered to be equal to $[\text{HgY}]$, and the equation (1) is expressed as equation (2).

$$-\frac{d[\text{HgY}]}{dt} = \left\{ k_0 \frac{1}{[\text{H}^+]} + k_1 + k_2[\text{H}^+] \right\} [\text{HgY}][\text{RSH}]_0 \quad (2)$$

$[\text{HgY}]$: total mercury aminopolycarboxylate concentration in the aqueous phase.

Equation (3) can be derived from equation (2),

$$-\frac{d[\text{HgY}]}{dt} = \{ k_0 + k_1[\text{H}^+] + k_2[\text{H}^+]^2 \} \frac{P_r}{K_a} [\text{HgY}][\text{RS}^-] \quad (3)$$

where

$$[\text{RS}^-] = \frac{K_a[\text{RSH}]_0}{P_r[\text{H}^+]}$$

P_r , partition coefficient and K_a , acid dissociation constant, are expressed as follows. The value of $\log P_r/K_a$ was found to be 13.0.⁴⁾

$$P_r = \frac{[\text{RSH}]_0}{[\text{RSH}]}$$

$$K_a = \frac{[\text{RS}^-][\text{H}^+]}{[\text{RSH}]}$$

$[\text{RSH}]$: SBB concentration in the aqueous phase

The value of $\log K_0$, $\log K_1$ and $\log K_2$ are shown in Table I, together with those of $\log K_{\text{Hg-Y}}$.

TABLE I. Rate Constants and Stability Constants for Mercury-Aminopolycarboxylates

	$\log k_0$	$\log k_1^a)$	$\log k_1^b)$	$\log k_2$	$\log K_{\text{Hg-Y}}$
EDDA	-4.1	4.6	4.6	9.4	10.16
NTA	-4.56	3.6	3.5	8.53	14.6
EDTA-OH	-4.11	3.0	3.0	7.31	20.1
DPTA-OH	-4.95	2.9	2.9	8.70	20.17
EDTA	-5.14	2.0	2.0	6.08	21.80
Met-EDTA	-5.43	1.9	2.0	6.24	21.70
GEDTA	-5.63	1.9	1.9	5.65	23.12
DTPA	-5.53	1.0	1.1	5.74	27.0

($\text{HgT}=2.5 \times 10^{-6}\text{M}$, $\text{YT}=1.0 \times 10^{-3}\text{M}$)

a) data from Fig. 3

b) data from Fig. 4

The equation (3) expresses that the ligand exchange reaction can proceed *via* three pathways which depend on the hydrogen ion concentration with zero, the first and the second order, respectively. Furthermore, independency of the concentration of aminopolycarboxylic acid on the reaction rates excludes the possibility of the dissociation of mercury aminopolycarboxylate complex before SBB coordinates with mercury. In other words, it is expected that this ligand exchange reaction proceeds through the formation of the mixed ligand complex. In fact, the formation of the mixed ligand complex involving mercury, SBB and other complexing agent such as aminopolycarboxylic acid was confirmed spectrophotometrically.¹¹⁾

9) L.G. Sillen and A.E. Martell, "Stability Constants of Metal Ion Complexes," Supple .1, the Chemical Society, London, 1971.

10) R.S. Saxena, *J. Inorg. Nucl. Chem.*, **30**, 3369 (1968); L.C. Thompson and S.K. Kundra, *ibid.*, **28**, 2945 (1966).

11) A. Yokoyama, N. Nakanishi, and H. Tanaka, unpublished.

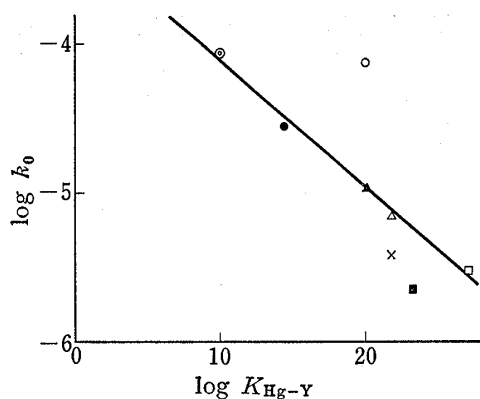


Fig. 9. Relationship between $\log k_0$ and $\log K_{\text{Hg-Y}}$

⊙: EDDA ▲: DPTA-OH ■: GEDTA
●: NTA △: EDTA □: DTPA
○: EDTA-OH ×: met-EDTA

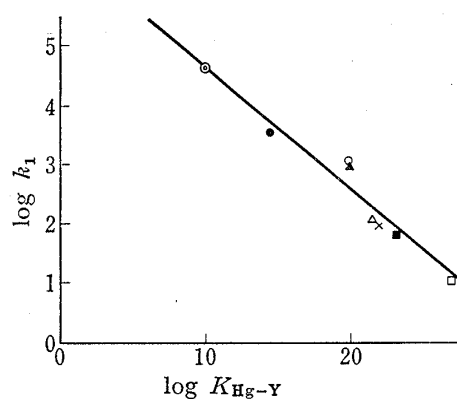


Fig. 10. Relationship between $\log k_1$ and $\log K_{\text{Hg-Y}}$

⊙: EDDA ▲: DPTA-OH ■: GEDTA
●: NTA △: EDTA □: DTPA
○: EDTA-OH ×: met-EDTA

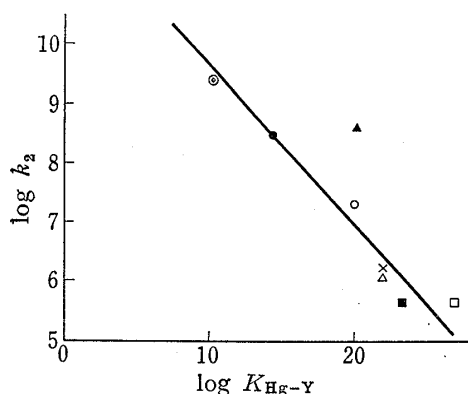


Fig. 11. Relationship between $\log k_2$ and $\log K_{\text{Hg-Y}}$

⊙: EDDA ▲: DPTA-OH ■: GEDTA
●: NTA △: EDTA □: DTPA
○: EDTA-OH ×: met-EDTA

With respect to the structure of mercury aminopolycarboxylate complex, the structure of mercury complex of CyDTA investigated by Margerum, *et al.*¹²⁾ can be referred. In this complex, mercury was not completely surrounded by the coordination cage of ligand molecule, but as in lanthanum-EDTA, it can have an exposed coordination side. The reaction mechanism which involves the coordination of SBB with mercury through the exposed side in the aminopolycarboxylate complex before the dissociation of aminopolycarboxylic acid seems to be reasonable by considering the similar structure in the mercury aminopolycarboxylates presented here to that of lanthanum-EDTA. The rate determining step may be involved in the step of the dissociation of aminopolycarboxylic acid, which is made easier through the formation of the coordination between SBB and mercury.

The value of the rate constants and stability constants of mercury aminopolycarboxylate complexes were found to be correlated each other a few exceptions such as the values of k_0 and k_2 in the cases of EDTA-OH and DPTA-OH, respectively. A close concern of the rate determining step to the dissociation of aminopolycarboxylic acid from the SBB-aminopolycarboxylate-mercury mixed ligand complex is suggested from the results in Fig. 9–11, which show the increase of the stability constant leads to the decrease of the reaction rate, except for the cases of EDTA-OH and DPTA-OH. The exceptional results in EDTA-OH and DPTA-OH can not be clearly interpreted in this study.

Thus, the present results suggest that the dissociation of aminopolycarboxylic acid from the mixed ligand complex is an important step in this ligand exchange reaction. The formation of the mixed ligand mercury complex¹³⁾ which involves protein, mercury and a complexing agent has been discussed in vivo transport of mercury in connection with the use of aminopoly-

12) D.L. Janes and D.W. Margerum, *Inorg. Chem.*, **5**, 1135 (1966).

13) J.L. Sudmeier and J.J. Pesek, *Anal. Biochem.*, **41**, 39 (1971); J.L. Sudmeier and J.J. Pesek, *Inorg. Chem.*, **10**, 860 (1971).

carboxylic acid as an antidote against the poisoning caused by mercury¹⁴⁾ and also as a radio-pharmaceutical.¹⁵⁾ The present results may add some basic informations for the discussion of the behavior of mercury complex of aminopolycarboxylic acid in the biological system.

14) E.D. Weinberg, "Metal-Bindine in Medicine," Iippincott, Philadelphia, 1960.

15) H. Ueda and M. Iio, "Kakuigaku," Ishiyaku-Shuppan Co., Tokyo, 1971.