A Kinetic Study of the Isotopic Exchange of Indium in Indium N-2-Hydroxyethylethylenediamine-N, N′, N′-triacetate Complex in Water

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(Received April 13, 1963)

As an extension of the kinetic study of the isotopic exchange of co-ordination compounds of the d^{10} structure, the present authors have studied the kinetics of indium *N*-2-hydroxyethylethylenediamine-*N*,*N*′,*N*′-triacetate (henceforth written as EDTA-OH with a formula H_3Z) using indium 114 m as tracer. It was previously reported that the exchange rate is measurably slow in an acid solution of pH 2 to 4 but very fast in more acid solutions.¹⁾ The exchange kinetics is quite different from that of the corresponding gallium complex,²⁾

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1) K. Saito and M. Tsuchimoto, This Bulletin, 35, 368 (1962).

2) K. Saito and M. Tsuchimoto, *J. Inorg. Nucl. Chem.* 23, 71 (1961).

and also from that of indium ethylenediamine-*N*,*N*,*N'*,*N'*-tetraacetate (henceforth written as EDTA with a formula H_4Y).[3]

This paper gives the results of a kinetic study of the indium EDTA-OH complex $[InZ\cdot OH_2]\cdot H_2O$ with indium in neutral and basic media, and they are compared with the findings regarding the related complexes mentioned above.

Experimental

Preparation of the Complex. — Radioactive EDTA-OH complex of indium was prepared from indium 114 m. (Ammersham; specific activity: 10 μc. per mg.) and extra pure EDTA-OH (Dotite EDTA-OH).[1] The specific activity was 0.41 μc. per mg.

Procedure for Kinetic Runs and Measurement of Radioactivity. — The method was principally the same as that used in the previous work. Uncomplexed indium hydrolyses in aqueous solutions with a pH value of more than 4, and the kinetics was always studied in the presence of tartrate. In neutral solutions up to pH 8.0, 0.0035 M tartrate sufficed to keep 10^{-3} M indium in the aqueous phase, whereas as much as 0.05 M tartrate was required at pH 11. Since tartrate is present in a doubly de-protonated form in the pH region higher than 5, the given figures indicate the concentration of $C_4H_4O_6^{2-}$.

The reaction was very slow in neutral solutions at 25°C, and the kinetics was studied at 40°C. The separation with 8-quinolinol was effected with more ease at this temperature, the separation-induced zero-time exchange being negligible.

Results

The exchange constant, *R*, is expressed by McKay's formula:

$$R=-2.303\cdot\frac{ab}{a+b}\cdot\frac{\log(1-F)}{t}$$

where *a* and *b* are the molar concentrations of the uncomplexed indium and of the indium EDTA-OH complex respectively, *t* is the lapse of time, and *F* the fraction of reaction. The kinetics was entirely different in basic and in neutral media. The *R* values, however, are independent of *a* and are proportional to *b*, regardless of the pH value. Such relationships are graphically shown in Figs. 1 and 2. Hence, the reaction constant, *k*, is expressed by *R*/*b* and has a dimension of T^{-1} in the given concentration range.

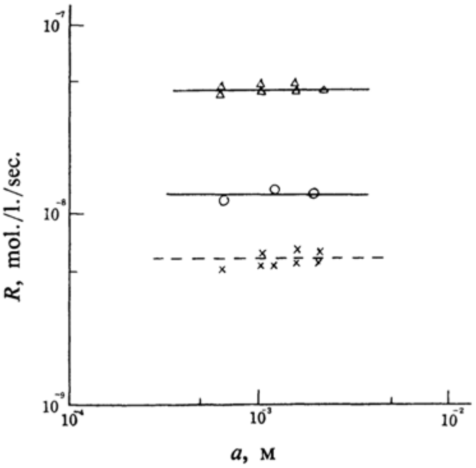

Fig. 1. Relationship between the exchange rate *R* and the concentration of uncomplexed indium *a*.
$\mu=0.30$ (KNO_3); *b*, 1.20×10^{-3} M; Tartrate concn., 0.060 M.
—○— pH, 10.08; 25°C; Barbiturate, 0.0375 M
—△— pH, 8.54; 25°C; Glycine, 0.0625 M
--×-- pH, 7.33; 40°C; Barbiturate, 0.0375 M

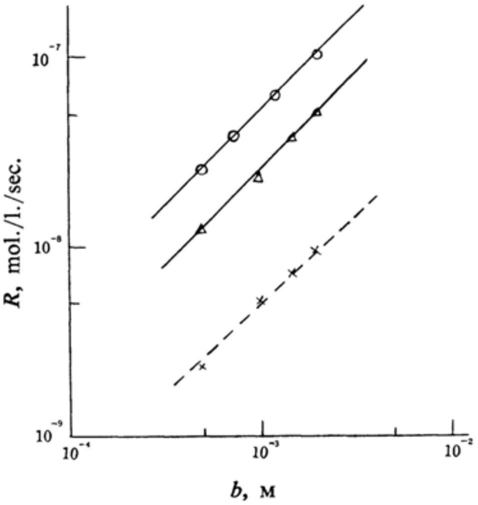

Fig. 2. Relationship between the exchange rate *R* and the concentration of the indium EDTA-OH complex *b*.
$\mu=0.30$ (KNO_3); *a*, 1.20×10^{-3} M; Tartrate concn. 0.060 M
—○— pH, 10.70; 25°C; Barbiturate, 0.0375 M
—△— pH, 8.40; 25°C; Glycine, 0.0625 M
--×-- pH, 7.33; 40°C; Barbiturate, 0.0375 M

Exchange in Basic Media.—The pH dependence of *k* in basic media buffered with various agents, including barbiturate, *p*-hydroxybenzoate and glycine, is shown in Fig. 3. The *k* values are proportional to the hydroxide ion concentration regardless of the kind of buffering agent, and the rate constant is expressed by $R=k'\cdot b[OH^-]$. The dependence of the *k'* value upon the concentration of tartrate and the buffering agents is shown in Table I for barbiturate and *p*-hydroxybenzoate solution and in Fig. 4 for glycine solution. The rate

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[3] K. Saito and M. Tsuchimoto, ibid., in press.

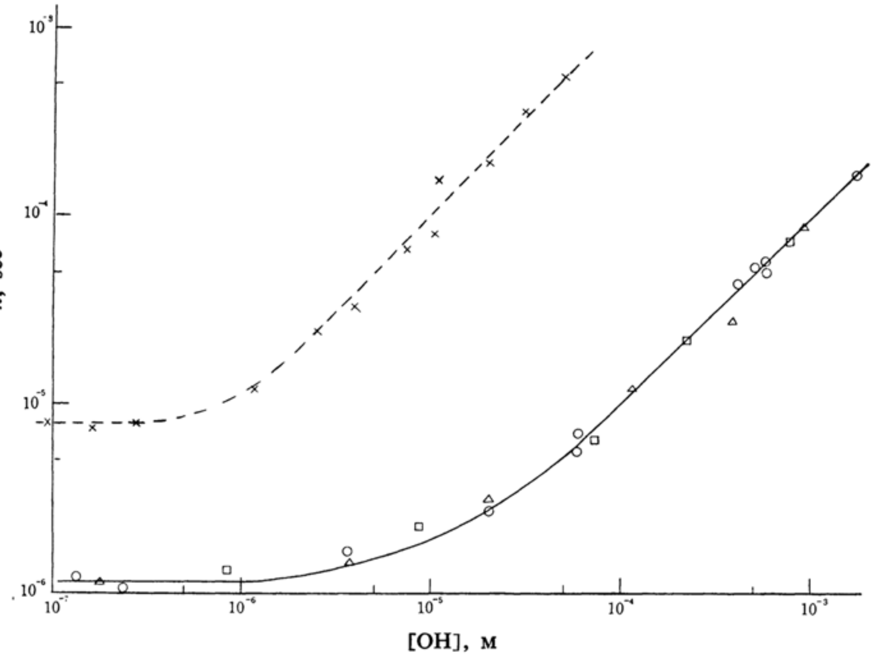

Fig. 3. Relationship between the exchange rate constant k and the hydroxide ion concentration in basic media.
25°C; $\mu=0.30$ (KNO_3); Tartrate concn., 0.060 M
—○— In 0.0375 M barbiturate
—△— In 0.0125 M p-hydroxybenzoate
—□— In 0.2 M NH_3 containing 0.032 M NH_4NO_3
--×-- In 0.0625 M glycine

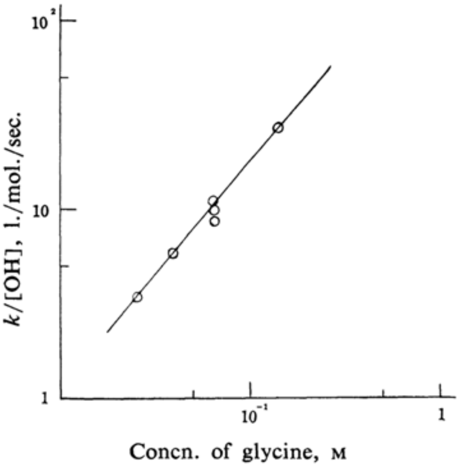

Fig. 4. Influence of the concentration of glycine upon the exchange rate constant k. 25°C; pH, 8.33; $\mu=0.30$ (KNO_3); tartrate, 0.060 M

TABLE I. INFLUENCE OF BUFFERING AGENTS UPON THE EXCHANGE RATE CONSTANT IN BASIC SOLUTIONS*

Buffer	Concn. of buffer, M	μ (KNO_3)	$k/[OH^-]$ l./mol./sec.
Na barbiturate	0.025	0.30	0.102
	0.0375	0.30	0.0985
	0.100	0.30	0.175
p-Hydroxybenzoate	0.0075	0.30	0.132
	0.0125	0.30	0.103
	0.0200	0.30	0.187
Ammonia	0.2 (0.032 M NH_4NO_3)	0.30	0.108
Glycine**	0.0625	0.10	9.55
	0.0625	0.30	9.61
	0.0625	0.55	9.21
	0.0625	0.10 (KCl)	10.6
	0.0625	0.55 (KCl)	11.5

* 25°C; Tartrate concn., 0.060 M; Its concentration has little influence upon the rate. (data omitted).

** The influence of the concentration. of glycine is shown in Fig. 4. Change in ionic strength affects the rate to a very small extent in other buffers, too (data omitted).

is affected by the concentration of tartrate and of the former two agents to a small extent. On the other hand, it increases linearly with increase in the concentration of glycinate. The influence of the ionic

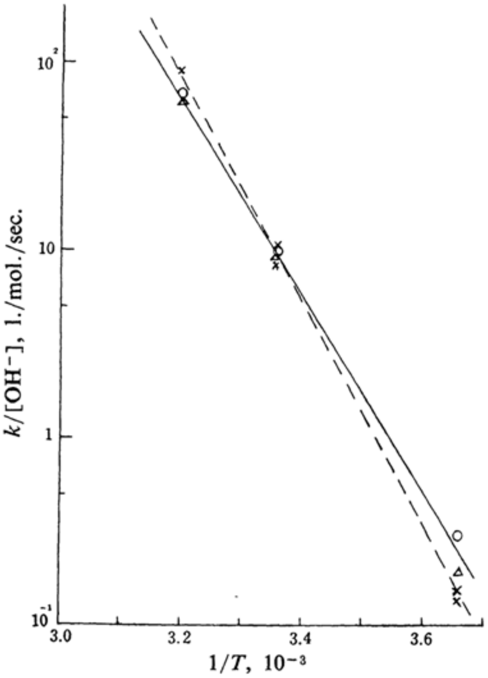

Fig. 5. Temperature dependence of the exchange rate constant in basic media.
$\mu=0.30$ (KNO_3) ; Tartrate concn., 0.060 M
—○— In 0.0375 M barbiturate
—△— In 0.0125 M *p*-hydroxybenzoate
--×-- In 0.0625 M glycine

strength is small, regardless of the kind of buffering agent used. The temperature dependence in various solutions is shown in Fig. 5; the E_A values are 25 and 27 kcal./mol. in barbiturate (or *p*-hydroxybenzoate) and in glycine solution respectively.

Exchange in Neutral Solutions. — In the pH region from 4 to 8, the exchange reaction proceeds much more slowly than in basic or more acid media; the time taken for one kinetic run was sometimes more than one week, even at 40°C. Hence, the experimental

TABLE II. INFLUENCE OF BUFFER AND IONIC STRENGTH UPON THE EXCHANGE RATE CONSTANT IN THE NEUTRAL REGION*

Buffer	Concn. of buffer, M	μ (KNO_3)	k 10^{-5} sec^{-1}
None	—	0.25	1.38
NaN_3	0.025	0.25	1.52
p-Hydroxybenzoate	0.0125	0.25	1.55
Barbiturate	0.0375	0.25	1.30**
	0.0375	0.10	1.22
	0.0375	0.10 (KCl)	1.25
	0.0375	0.55	1.28
	0.0375	0.55 (KCl)	1.73

* 40°C ; Tartrate concn., 0.060 M ; pH, 6.13

** Mean value of 12 observations ; max. 1.47×10^{-5}, min. 1.09×10^{-5} sec^{-1}

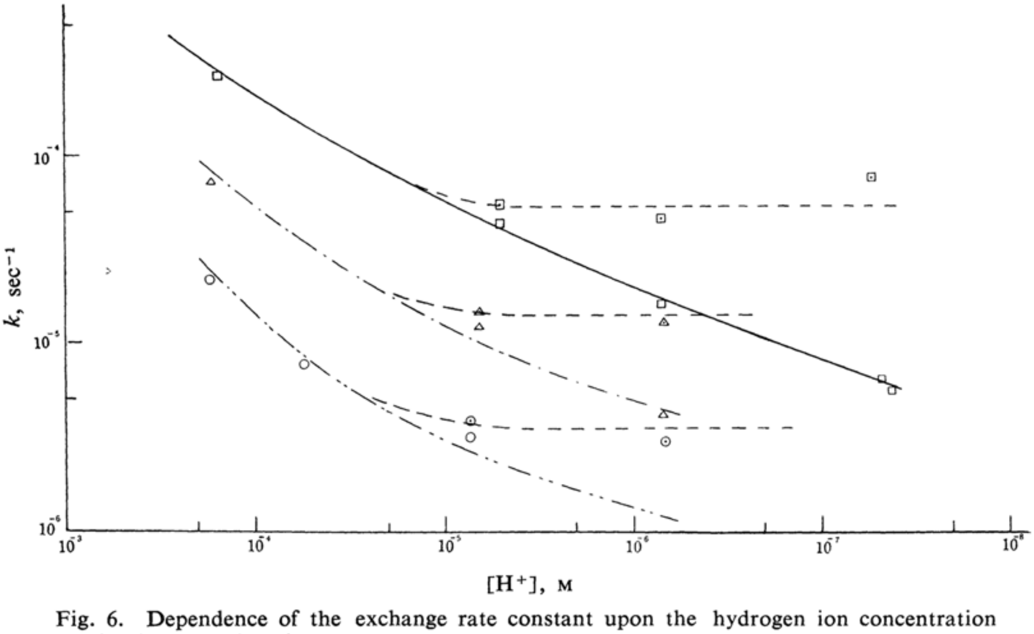

Fig. 6. Dependence of the exchange rate constant upon the hydrogen ion concentration in the neutral region.
40°C ; $\mu=0.25$ (KNO_3); no buffer other than tartrate
—··—○—··— In 0.0035 M tartrate ———⊙———
—·—·△·—·— In 0.0175 M tartrate ———⟁———
————□———— In 0.060 M tartrate ———⊡———

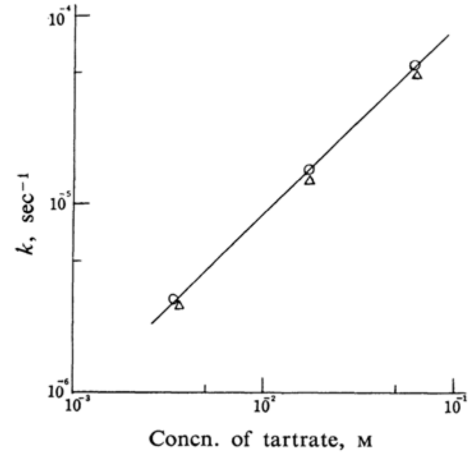

Fig. 7. Relationship between the exchange rate constant *k* and the concentration of tartrate in the neutral region.
40°C; $\mu=0.25$ (KNO_3)
—○— pH 5.15 —△— pH 6.15

error may be greater. In Fig. 6, the *k* values are plotted against the hydrogen ion concentration. At a given concentration of tartrate, the rate constant decreases with rise of pH value. The influence of tartrate ions is shown in Fig. 7. (see Discussion). The influence of the buffer and that of the ionic strength are tabulated in Table II. The *k* values do not appear to be affected significantly by these factors. On the other hand, the rate increases linearly with an increase in the concentration of glycine, as Fig. 8 shows. The temperature dependence of *k*, which is illustrated in Fig. 9, indicates that the Arrehenius activation energy is 19.2 kcal. per mol. in a tartrate solution, with or without barbiturate, and 24.7 kcal. per mol. in the presence of glycine.

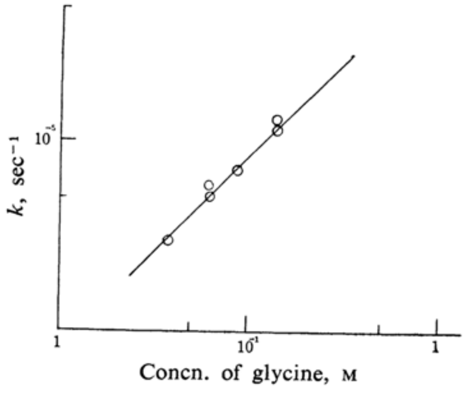

Fig. 8. Influence of the concentration of glycine upon the exchange rate constant in the neutral region.
25°C; $\mu=0.25$ (KNO_3); pH, 7.04; Tartrate concn., 0.060 M

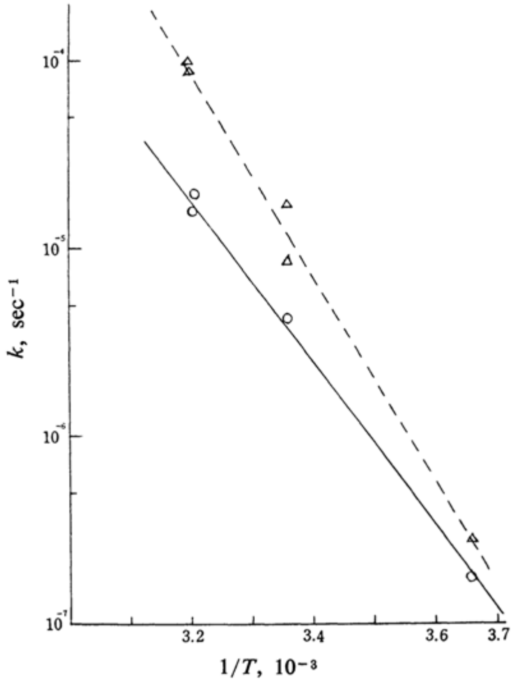

Fig. 9. Temperature dependence of the exchange rate constant in the neutral region.
$\mu=0.25$ (KNO_3); 0.060 M tartrate
—○— Without glycine
--△-- In 0.0625 M glycine

Discussion

The kinetics of the exchange of the indium EDTA-OH complex is quite different from that of the indium EDTA, gallium EDTA or gallium EDTA-OH complex. In neutral solutions, the last three undergo isotopic exchange at an immeasurably slow rate, while the rate for the first-mentioned complex is measurable, although very small as compared with that in an acid or a basic solution. In basic solutions, *k* is proportional to the hydroxide ion concentration regardless of the kind of buffering agent used (see Table III).

The uncomplexed indium (initially nonradioactive) is present in solutions of a pH more than 4 in the form of a tartrate complex. However, the state of this indium species does not appear to be important in discussing the reaction mechanism because the exchange rate, *R*, is independent of the concentration of uncomplexed indium.

Exchange in Basic Media. — The indium EDTA-OH has a co-ordinated water, and the dissociation constant to give a proton is 3.6×10^{-6} at 25°C and 5.0×10^{-6} at 40°C. Hence, in basic solutions of pH higher than 8, most of the complex is present in the form of

TABLE III. COMPARISON OF KINETIC DATA FOR INDIUM EDTA AND EDTA-OH COMPLEX AT 25°C

Media		In-EDTA	In-EDTA-OH
	R	$k'\cdot b\cdot[\text{H}^+]^3$	$k'\cdot b\cdot[\text{H}^+]^1$
Acid	k'	4.3×10 l^3/mol^3/sec.	1.0×10^{-2} l./mol./sec.
	E_A	18 kcal./mol.	11 kcal./mol.
	R	$< 10^{-10}$ mol./l./sec.	$k\cdot b\cdot[\text{H}^+]^0$
Neutral	k	immeasurably slow	1.3×10^{-5} sec^{-1}
	E_A	——	19 kcal./mol.
	R	$k'\cdot b\cdot[\text{OH}^-]^2$	$k'\cdot b\cdot[\text{OH}^-]^1$
Basic	k'	5.2×10^1 l^2/mol^2/sec.	1.1×10^{-1} l./mol./sec.
	E_A	25 kcal./mol.	25 kcal./mol.

For simplicity values under representative conditions are given. Details of the experimental conditions are seen in other tables and figures.

hydroxo complex $[\text{InZ}\cdot\text{OH}]^-$. Since the exchange rate constant, k, is little affected by buffering agents with different structures, such as barbiturate, *p*-hydroxybenzoate and ammonia, the exchange in solutions containing these buffers appears to involve the exchange of the hydroxo complex. Thus, the exchange seems to proceed as follows:

$$[{}^*\text{InZ}\cdot\text{OH}]^- + \text{OH}^- \rightleftarrows [{}^*\text{InZ}\cdot\text{O}]^{2-} + \text{H}_2\text{O}$$

(equilibrium to form a conjugate base)

$$\begin{tikzcd} {[{}^*\text{InZ}\cdot\text{O}]^{2-}} \arrow[r, shift left, "\text{slow}"] & {[{}^*\text{InO}\cdot\text{aq.}]^{+} + \text{Z}^{3-}} \arrow[l, shift left, "\text{fast}"] \arrow[d, shift left, dashed] \\ & {[\text{In}\cdot\text{tart}_x]^{n}} \arrow[u, shift left, dashed] \end{tikzcd}$$

(rapid exchange of In)

These equations can be simplified as follows:

$$[{}^*\text{InZ}\cdot\text{O}]^{2-} + [\text{In}\cdot\text{tart}_x]^{n} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftarrows}} [\text{InZ}\cdot\text{O}]^{2-} + [{}^*\text{In}\cdot\text{tart}_x]^{n}$$

Such processes can be alternatively expressed in a somewhat different way as follows:

$$[{}^*\text{InZ}\cdot\text{OH}]^- + \text{OH}^- \rightarrow [{}^*\text{InZ}\cdot(\text{OH})_2]^{2-}$$

(attack with hydroxide ions as the rate-determining step)

$$[{}^*\text{InZ}\cdot(\text{OH})_2]^{2-} + [\text{In}\cdot\text{tart}_x]^{n} \rightleftarrows [\text{InZ}\cdot(\text{OH})_2]^{2-} + [{}^*\text{In}\cdot\text{tart}_x]^{n}$$

(fast exchange)

Recently, Hoard, Smith and Lind⁽⁴⁾ suggested that EDTA complexes of such tervalent metal ions as aluminum, chromium and iron have co-ordination number 7 in the crystalline state. Generally, EDTA-OH forms very similar complexes to EDTA with tervalent metal ions, so that it would not be unreasonable to assume a process involving the attack with hydroxide ions to form an intermediate with co-ordination number 7.

The formation of such an intermediate can also be postulated when it is assumed that the indium EDTA-OH complex has one other mole of co-ordinated water in an aqueous solution. The dissociation constant to give second proton would be so small as compared with that for the first proton that a labile dihydroxo complex is present only as an intermediate state in strongly basic solutions.

$$[{}^*\text{InZ}\cdot(\text{OH}_2)_2] \rightleftarrows [{}^*\text{InZ}\cdot\text{OH}_2\cdot\text{OH}]^- + \text{H}^+$$

(dissociation of the first proton)

$$[{}^*\text{InZ}\cdot\text{OH}_2\cdot\text{OH}]^- + \text{OH}^- \rightleftarrows [\text{InZ}\cdot(\text{OH})_2]^{2-} + \text{H}_2\text{O}$$

(equilibrium to form a labile dihydroxo complex (conjugate base) as a reaction intermediate)

Nevertheless, nothing decisive can be stated as to the validity of one of the alternative expressions.

Amidst other buffering agents, glycine increases the rate to a marked extent and k' is proportional to the glycine concentration. Such an observation suggests that the reaction mechanism is different from that mentioned above. Acceleration of the exchange reaction by glycine is also seen in the case of the indium EDTA complex, which gives quite different kinetics in the presence and in the absence of glycine.[3] The co-ordinated water in the $[\text{InY}\cdot\text{OH}_2]^-$ complex is rather easily replaced by other ligands, including halogens and ammonia. In a very similar complex, $[\text{InZ}\cdot\text{OH}_2]$, the water could also be replaced (although with more difficulty) and the following equilibrium is very likely established in aqueous solutions:

$$[{}^*\text{InZ}\cdot\text{OH}_2] + \text{NH}_2\text{CH}_2\text{CO}_2\text{H} \rightleftarrows [{}^*\text{InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2\text{H}] + \text{H}_2\text{O}$$

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4) J. L. Hoard, G. S. Smith and M. Lind, "Advances in the Chemistry of the Co-ordination Compounds," Ed. by S. Kirschner, McMillan Co., New York (1961), p. 296.

With rise of the pH value, the co-ordinated glycine will liberate a proton to give a complex anion, $[\text{*InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2]^-$, which predominates in the given pH region. This anionic complex would interact with hydroxide ions to give a conjugate base, and the exchange reaction would involve a dissociation of the conjugate base.

$$[\text{*InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2]^- + \text{OH}^- \rightleftarrows [\text{*InZ}\cdot\text{NHCH}_2\text{CO}_2]^{2-} + \text{H}_2\text{O}$$

(equilibrium to form a conjugate base)

$$[\text{*InZ}\cdot\text{NHCH}_2\text{CO}_2]^{2-} + [\text{In}\cdot\text{tart}_x]^n \xrightleftharpoons[\text{fast}]{\text{slow}} [\text{InZ}\cdot\text{NHCH}_2\text{CO}_2]^{2-} + [\text{*In}\cdot\text{tart}_x]^n$$

The alternative expression, involving an intermediate with co-ordination number 7 can be similarly written.

Exchange in Neutral Solution. — In the pH region from 4 to 7, the rate constant is much less affected by the pH. In more acid solutions, k values are proportional to the hydrogen ion concentration;[1] this effect is observed at pH below 5. In the acid region, the rate increases in the presence of such acidic radicals as citrate and acetate, and a mechanism involving the replacement of the co-ordinated water by an acid radical was postulated.[1] In the pH region from 5 to 8, the dissociation of co-ordinated water is appreciable, and the effective concentration of the aquo indium EDTA-OH complex $[\text{InZ}\cdot\text{OH}_2]$ would be decreased to decrease the b value. If the observed k values were corrected on the basis of the effective b values calculated from the dissociation constant, the curves would be as those indicated by broken lines in Fig. 6; i. e., k is independent of the pH at a given concentration of tartrate.

The k vs. tartrate ($\text{C}_4\text{H}_4\text{O}_6^{2-}$, written as "tart" henceforth) concentration curve in Fig. 7 indicates that the corrected k value is proportional to the concentration of tartrate, regardless of the pH. Since the presence of such buffering agents as barbiturate, p-hydroxybenzoate and azide (except glycine) does not affect the k value, the replacement of co-ordinated water by tartrate could play an important role in exchange the mechanisms.

$$[\text{*InZ}\cdot\text{OH}_2] + \text{tart}^{2-} \rightleftarrows [\text{*InZ}\cdot\text{tart}]^{2-} + \text{H}_2\text{O}$$

(equilibrium to form a mixed complex)

If such species underwent isotopic exchange with uncomplexed indium at a measurable rate, the kinetics would be satisfactorily accounted for.

$$[\text{*InZ}\cdot\text{tart}]^{2-} + [\text{In}\cdot\text{tart}_x]^n \xrightleftharpoons[\text{fast}]{\text{slow}} [\text{InZ}\cdot\text{tart}]^{2-} + [\text{*In}\cdot\text{tart}_x]^n$$

Generally co-ordinated hydroxide ions are replaced by other ligands with much more difficulty than co-ordinated water, so that the formation of the tartrate complex $[\text{*InZ}\cdot\text{tart}]^{2-}$ from the hydroxo complex would not be significant. Hence, the correction of the observed k values on the basis of the effective b values at pH 5 to 8 (broken lines in Fig. 6) would be legitimate. With rise of the pH value, such a species is overwhelmed by the hydroxo complex $[\text{InZ}\cdot\text{OH}]^-$, which undergoes isotopic exchange at a greater rate through the mechanism mentioned before. Throughout the whole pH range, barbiturate and p-hydroxybenzoate do not seem to participate in the exchange reaction.

Acceleration of the exchange reaction by glycine is also observed in the neutral region from pH 5 to 8. Since the rate is independent of the pH in this region, even in the presence of glycine and most glycine is present in an un-ionized form, the formula $[\text{*InZ}\cdot\text{NH}_2\text{CH}_2\cdot\text{CO}_2\text{H}]$ would be feasible as an intermediate.

$$[\text{*InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2\text{H}] + [\text{In tart}_x]^n \xrightleftharpoons[\text{fast}]{\text{slow}} [\text{InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2\text{H}] + [\text{*In}\cdot\text{tart}_x]^n$$

With rise of the pH value, the co-ordinated glycine would lose a proton to give an anionic complex, $[\text{InZ}\cdot\text{NH}_2\text{CH}_2\text{CO}_2]^-$, which undergoes isotopic exchange through the formation of the conjugate base at a greater rate, as mentioned before.

As has been discussed in this and the preceding paper, the indium EDTA-OH complex is more labile than the indium EDTA complex, as Table III shows. No such difference was observed between the corresponding gallium complexes,[2] which give kinetics similar to that of the indium EDTA complex. Hence, the lability of the indium EDTA-OH complex is rather exceptional amidst similar complexes.

Summary

1) The kinetics of the isotopic exchange of the indium EDTA-OH complex with uncomplexed indium has been studied in neutral and basic solutions, with $^{114\text{m}}\text{In}$ as tracer.

2) The exchange rate is independent of the concentration of uncomplexed indium and proportional to that of the EDTA-OH complex, giving the relationship $R = k\cdot b$.

3) In a basic solution buffered by barbiturate, p-hydroxybenzoate, or ammonia, the k

value is proportional to the concentration of hydroxide ions and is little affected by the buffer. The Arrhenius activation energy is 25 kcal. per mol., and a mechanism involving the dissociation of hydroxo complex $[InZ\cdot OH]^-$ as the rate-determining step was postulated. The exchange is accelerated by glycine.

4) In a neutral solution with a pH value below 8, the rate is small but measurable. It is independent of the pH value and is little affected by barbiturate or *p*-hydroxybenzoate, and the activation energy is 19 kcal. per mol. The dissociation of a mixed complex containing tartrate as one of the ligands, $[InZ\cdot C_4H_4O_6]^{2-}$, appears to be the rate-determining step. Glycine accelerates the exchange reaction.

5) The feature of the isotopic exchange of the indium EDTA–OH complex is quite different from that of the EDTA complex; the former seems to be much more labile than the latter and similar gallium complexes.

The authors wish to thank the Ministry of Education for its grant-in-aid.

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