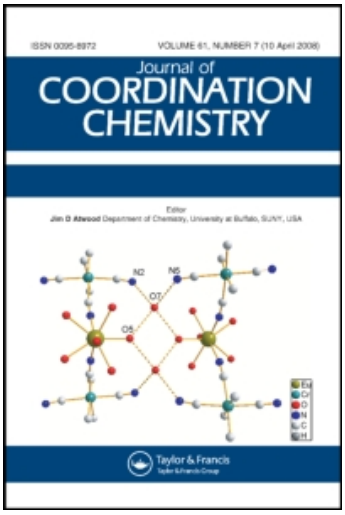

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KINETICS AND MECHANISM OF SUBSTITUTION OF AQUOETHYLENEDIAMINETETRAACETATORUTHANATE (III) WITH CYSTEINE IN AQUEOUS SOLUTION

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Reaction of the edta (ethylenediaminetetraacetate) complex of ruthenium(III) with cysteine has been studied spectrophotometrically as a function of [cysteine], pH (1.3–9.5) and temperature (20–45°) in aqueous solution. Stopped-flow kinetic studies revealed that the substitution is first-order in both reactants. A maximum observed rate constant (k_{obs}) was obtained in the pH region 7.8–8.0 which is in contrast to the characteristic bell-shaped k_{obs}-pH profile for the substitution of Ru(III)-edta reported so far the (where maximum k_{obs} is usually attained in the pH range 4.5–6.0). Activation parameters determined from the temperature dependence of observed rate constants at pH = 5.0 are comparable to those for other thio-ligand substitutions and consistent with the proposed mechanism.

Keywords: Ruthenium(III); edta; cysteine; substitution; kinetics

INTRODUCTION

Recently we engaged in studying the reactivity of the Ru(III)-edta complex with various amino acids. In an earlier paper[1] we reported the interaction of the Ru(III)-edta complex with alanine, phenylalanine and valine. The μ-oxo diruthenium complexes[1] undergo oxidative deamination in the presence of oxygen to give α-keto acids. We now have selected cysteine for the following reasons. Cystine is an amino acid which is formed *via* oxidation by linking two molecules of cysteine through the side chain sulfur atoms. Cystine is much less soluble in water (zwitterionic form of cystine at pH 5.0 is soluble to the extent of 160 mg

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dm^{-3} at 37 °C.[2] The low solubility of cystine has other effects. Cystinurea is a genetic defect that causes patients to excrete high quantity of the amino acid in the urine. Excess insoluble amino acid crystallises to form stones in the kidney, ureter and bladder. Therefore it is of interest to know of the reactivity of cysteine towards metal complexes and whether it undergoes air-oxidation or not in the coordinated state. In this paper we report the kinetics and mechanism of substitution of the Ru(III)-edta complex with cysteine in aqueous solution as a function of ligand concentration, pH and temperature.

EXPERIMENTAL

Materials

$K[Ru^{III}(Hedta)Cl].2H_2O$ was prepared by following the published procedure.[3] All other chemicals used were of A.R. grade. Doubly distilled water was used throughout the experiments.

Instrumentation

Absorption spectra were recorded on a Shimadzu 160 spectrophotometer coupled with a TCC 240A temperature controller. Kinetics of substitution were studied by using a HI-TECH stopped-flow spectrophotometer (SF-51) equipped with a data analyser (Apple IIe) with which kinetic traces could be evaluated. The substitution reaction was monitored at 514 nm. The instrument was thermostatted to ± 0.1 °C. Rate constant data were measured under *pseudo*-first-order conditions of excess ligand (at least 10 fold excess) and corresponding first-order plots were linear for at least 2–3 half-lives. Acetate, phosphate and borate buffers were used to control the pH of the test solutions and pH measurements were carried out with a Digisun pH meter. NaCl was used to adjust the ionic strength of the solutions. Rate constant data are the average of triplicate runs and are reproductible within 4%.

RESULTS AND DISCUSSION

Before describing the experimental results we recapitulate the aqueous chemistry of the Ru(III)-edta complex and various acid dissociation equilibria of cysteine in aqueous solution. $K[Ru^{III}(Hedta)Cl]$ is aquated rapidly when dissolved in water [4] to give $Ru^{III}(Hedta)(H_2O)$, which is stable below pH 2. The $Ru^{III}(Hedta)$

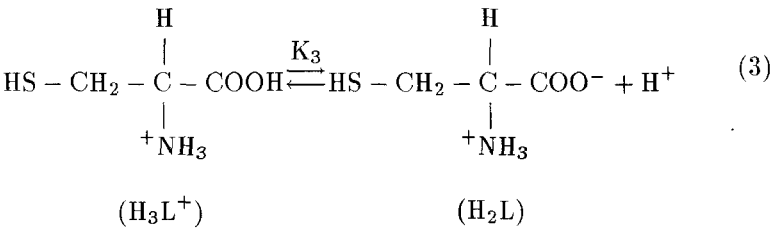
(H_2O) complex shows two pKa values which are associated with the following acid dissociation equilibria.

$$[Ru^{III}(Hedta)(H_2O)] \overset{K_1}{\rightleftharpoons} [Ru^{III}(edta)(H_2O)]^- + H^+ \quad (1)$$

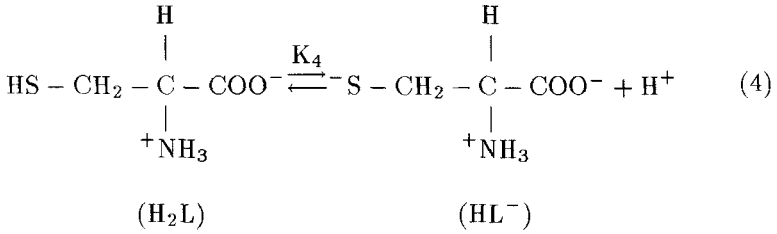
$$[Ru^{III}(edta)(H_2O)]^- \overset{K_2}{\rightleftharpoons} [Ru^{III}(edta)(OH)]^{2-} + H^+ \quad (2)$$

The values of pK_1 and pK_1 at 25 °C are 2.4 and 7.6, respectively.[4–5] The most reactive species towards substitution is $Ru^{III}(edta)(H_2O)^-$, which exists predominantly in the pH range 4.5–6.0.[4–5]

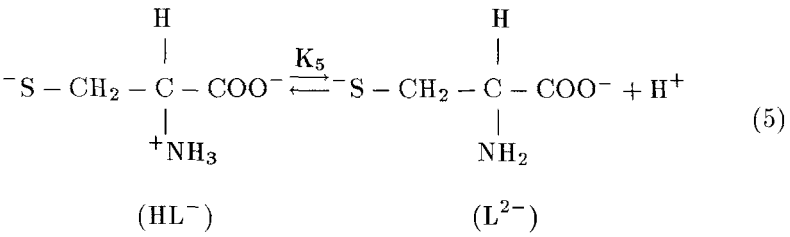
The characteristic acid dissociation equilibria of cysteine are outlined in.[3–5]



$$(H_3L^+) \qquad (H_2L) \quad (3)$$



$$(H_2L) \qquad (HL^-) \quad (4)$$



$$(HL^-) \qquad (L^{2-}) \quad (5)$$

The values of pK_3, pK_4 and pK_5 are 1.9, 8.3 and 10.1, respectively, at 25 °C.[6]

Addition of cysteine to an aqueous solution of Ru(III)-edta causes an immediate colour change from pale-yellow to red. The intense band in visible region (514 nm) is assigned to the LMCT (sulfur to ruthenium)[7] of coordinated cysteine in the [Ru(edta) (cysteine)] complex.

The 1:1 stoichiometry of the reaction was determined spectrophotometrically (at 514 nm) by the mol ratio method. The spectroscopic features of the product

in H_2O did not exhibit any change by exposing it to air or by changing the pH of the solution (except for decrease in absorbance at high pH which due to the base hydrolysis of the product).

Preliminary kinetic studies revealed that the buffer components and NaCl used for maintaining ionic strength did not interfere with the substitution studied here. The rate of reaction was found to be first order with respect to Ru(III)-edta. Values of *pseudo*-first-order rate constant (k_{obs}) increased linearly with increasing [cysteine], with no significant intercept. This indicates that the reverse aquation of the product is negligible under the employed conditions. However, at high pH, base hydrolysis of the substituted product complex was found to be appreciable. The substitution reaction exhibits a typical pH dependence as shown in Figure 1. Considering the substitution lability of various Ru(III)-edta complex in equilibria (1–2) and different reactive forms of cysteine ligand in the studied pH range, the pH dependence of the substitution process may be interpreted in terms of the mechanism outlined in (6–9) for which a rate expression is given in (10).

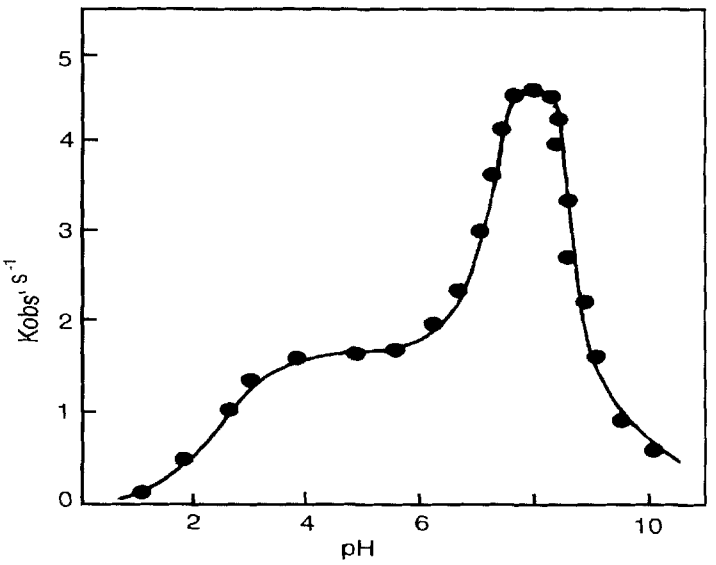


FIGURE 1 Effect of pH on the observed rate constant (k_{obs}) for the substitution-of the Ru(III)-edta complex with cysteine at 30 °C; $[Ru^{III}] = 5 \times 10^{-4}$ M, $\mu = 0.2$ M, $[cysteine] = 5 \times 10^{-3}$ M.

$$Ru^{III}(Hedta)(H_2O) + H_2L \xrightarrow{k_1} Ru^{III} - L \quad (6)$$

$$Ru^{III}(edta)(H_2O)^- + H_2L \xrightarrow{k_2} Ru^{III} - L \quad (7)$$

$$Ru^{III}(edta)(H_2O)^- + HL^- \xrightarrow{k_3} Ru^{III} - L \quad (8)$$

$$Ru^{III}(edta)(OH)^{2-} + HL^- \xrightarrow{k_4} Ru^{III} - L \quad (9)$$

$$k_{obs} = \frac{k_1[H^+]^3 + k_2K_1[H^+]^2 + k_3K_1K_5[H^+] + k_4K_1K_2K_5}{[H^+]^3 + (K_1 + K_2 + K_5)[H^+]^2 + (K_1K_2 + K_2K_5 + K_1K_5)[H^+] + K_1K_2K_5}[H_2L] \quad (10)$$

At low pH (*i.e.*, high $[H^+]$) (10) reduces to $K_{obs} = k_1[H_2L]$, whereas at high pH (*i.e.*, low $[H^+]$) it reduces to $k_{obs} = k_4[H_2L]$. Values of k_1 and k_4 thus obtained are 10±2 $M^{-1}s^{-1}$ and 117±5 $M^{-1}s^{-1}$, respectively. The validity of (10) is substantiated as the theoretical curve (pH-k_{obs} profile), superimposes on that obtained experimentally (Figure 1). Appropriate fit of experimental data results in k_1 = 11±1 $M^{-1}s^{-1}$, k_2 = 352±12 $M^{-1}s^{-1}$, k_3 = 2036±117 $M^{-1}s^{-1}$ and k_4 = 122±3 $M^{-1}s^{-1}$.

The first inflection in k_{obs} *vs* pH (Figure 1) occurs at pH = pK_1 (2.4). This means that the rates of substitution of $Ru^{III}(Hedta)(H_2O)$ with H_3L^+ and H_2L do not differ much. Values of observed rate constant (k_{obs}) remains constant over pH range 4–6, but in contrast to earlier findings, rate of reaction is found to increase with increasing pH above 6 (Figure 1). The second inflection appears at pH = pK_2 (7.6). A bell-shaped pH dependence of rate constant with maximum reactivity in the pH range 4–6 was reported earlier for substitution of the Ru(III)-edta system. The reason for the decrease in rate constant above pH 6 was explained[4–5] in terms of the formation of $Ru^{III}(edta)(OH)^{2-}$, which is comparatively less labile towards substitution. The intriguing feature of the present reaction can be explained in terms of the reaction between two reactive species (*7*). Here, an increase in pH generates $Ru^{III}(edta)(OH)^{2-}$ even though the rate is increased due to formation of HL^-, which is most reactive form of cysteine. Maximum reactivity of the system is observed over a very small pH range (7.8–8.0). Although the concentration of $Ru^{III}(edta)(H_2O)^-$ is small in comparison with that of $Ru^{III}(edta)(OH)^{2-}$ in the above mentioned pH range, the reaction (*7*) still adds substantially to the overall rate. Further increase in pH from 8 to 10 causes a sharp decrease in rate.

The decrease once again demonstrates the lower lability of $Ru^{III}(edta)(OH)^{2-}$ towards substitution, (9), even though the ligand is present in its most reactive form (HL^-). It is important to note here that at high pH the substituted product $Ru^{III}(edta)$ (cysteine) is not stable and undergoes base hydrolysis.

The effect of temperature on k_{obs} was studied at pH 5.0. The rates and activation parameters are summarised in Table I along with data for other thio-

ligands. Values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are quite comparable to those reported earlier (Table I) and are indicative of an associative mode of activation as proposed earlier.

TABLE I Rate and activation parameters for thioligand substitution of Ru^{III} (edta)$(H_2O)^-$ at pH 5.0

Ligand	$k^a/M^{-1}\ s^{-1}$	$\Delta H^{\neq}$ *(kJ mol^{-1})*	$\Delta S^{\neq}$ *(Jk^{-1}mol^{-1})*	*Ref*
thiourea	2970	22	−105	5
dimethyl thiourea	1450	25	−107	5
tetramethylthiourea	154	30	−107	
thiocyanate	270	37	−75	5
thiosulfate	2.94[b]			7
dimethylsulfoxide	11			10
2-marcaptoryridine	10500	24	−84	8
4,6-dimehtyl-2-marcaptopyrmidine	7800[b]	29	−76	9
cysteine	332	36	−129	This work

[a]25 °C.[b]30 °C

In conclusion, the present work describes the rapid binding of Ru(III)-edta to cysteine at a pH of physiological interest to form a stable, water-soluble, substituted complex which does not undergo air oxidation for several hours. Our experimental results may be useful in developing a metal-based drug for cystinurea.

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