Reactivity of *cis*-Bis(glycinato ester)tetraammineruthenium(III) in Acidic Solutions

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Abstract

The complexes *cis*-$[(NH_3)_4Ru(NH_2CH_2COOR)_2](PF_6)_2$ ($R = CH_3$, $CH_2C_6H_5$) and *cis*-$[(NH_3)_4Ru(NH_2CH_2COOC_2H_5)_2](CF_3SO_3)_2$ have been prepared. Fast oxidation of the ruthenium ion to Ru(III) was followed by a first order pH dependent reaction that produced $[(NH_3)_4\overline{RuNH_2CH_2COO}]^{2+}$ as the only product. A mechanism that depicts linkage isomerization of one of the glycine ester ligands from the N-bound to the O-bound isomer as the initial stage is suggested. This mechanism is consistent with the experimental observations of a linear relationship between $(k_{obs})^{-1}$ and $[H^+]^{-1}$, and with the presence of $[(NH_3)_4\overline{RuNH_2CH_2COO}]^{2+}$ as the sole product of the reaction.

Introduction

Ruthenium complexes of amino acids and their derivatives serve as models for two kinds of interactions that exist in metalloproteins: metal ion–apoprotein interactions, and interactions between the metal ion and substrates of metalloenzymes.

The inertness of ruthenium ions in their two major oxidation states – II and III – enables detailed studies of mechanisms and intermediates in these systems. These facts are exploited when ammineruthenium species are attached to various proteins in order to study intramolecular electron transfer processes involving metalloproteins [1–3] and as probes of various properties of proteins [4].

Former studies of systems which involved ammineruthenium complexes of amino acids and their derivatives revealed interesting reactivity modes. Thus, N-bound glycinepentaammineruthenium(III) demonstrated a remarkable isomerization to the O-bound isomer [5]. When ethyl glycinate was the ligand, isomerization was followed by hydrolysis of the ester, and the O-bound glycinate complex was produced [6]. Analogous complexes of glycinamides and dipeptides showed another remarkable reaction which involved formation of a N,O-bound chelate, concomitant with dissociation of an ammonia ligand [7]. None of these reactions has a parallel in the chemistry of analogous complexes of the inert metal ion Co(III) [8], or any other inert metal ion [9].

Thus far, ammineruthenium complexes which contain one molecule of glycine, glycinamide or their derivatives, bound either as monodentate ligands, or chelated as bidentate ligands, have been studied [5–7, 10]. Here we present the results of a study of tetraammineruthenium complexes which contain two amino acid ester ligands N-bound *cis* to each other. In the Ru(III) state, these complexes react to produce the N,O-bound chelate of the parent amino acid. This is a different reactivity pattern from that demonstrated by pentaammineruthenium(III) complexes which contain a single glycinato ester ligand, and is more similar to the reactivity mode of pentaammineruthenium(III) complexes which contain a single glycinamide derivative as a ligand.

Experimental

Chemicals and Reagents

Chloropentaammineruthenium(III) chloride was prepared from ruthenium trichloride [11], and was purified by recrystallization from 0.1 M HCl. *cis*-Diaquotetraammineruthenium(III) trifluoromethanesulfonate was prepared from chloropentaammineruthenium(III) chloride as described before [10a, 12]. The hydrochloride salts of methyl glycinate and ethyl glycinate and the *p*-toluenesulfonate salt of benzyl glycinate were purchased from Sigma.

The neat esters were prepared [12] as follows: a suspension of the ester salt in ether was bubbled with dry NH_3 for ~10 min and then with argon for another 10 min. The resulting suspension was dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated. The esters were kept below 0 °C and were used as soon as possible in order to avoid dimerization.

CF_3SO_3H (Fluka, purum) was distilled under reduced pressure, in an ungreased apparatus, and kept in a desiccator at 4 °C. $CF_3SO_3Na \cdot H_2O$ was prepared

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TABLE 1. Ru Analysis[a] Results of the Bis(glycine ester)tetraammineruthenium(II) Complexes, and Yields of $[(NH_3)_4\overline{RuNH_2CH_2COO}]^{2+}$ Produced after their Oxidation

Complex	Ru (%)		Purity (%)	Glycinate chelate yield[b]
	calc.	found		
$[(NH_3)_4Ru(NH_2CH_2CO_2CH_3)_2](PF_6)_2$ (I)	15.7	13.6 ± 0.4	87 ± 3	90 ± 3
$[(NH_3)_4Ru(NH_2CH_2CO_2CH_2C_6H_5)_2(PF_6)_2$ (II)	12.8	13.0 ± 0.3	102 ± 3	105 ± 3
$[(NH_3)_4Ru(NH_2CH_2CO_2C_2H_5)_2](CF_3SO_3)_2$ (III)	15.0	14.3 ± 0.4	95 ± 3	94 ± 3

[a]By the method of Marchant *et al.* [14]. [b]Determined from the absorption at 288 nm ($\epsilon = 1.9 \times 10^3$ M^{-1} cm^{-1}), based on the weighted amount of the complex [10a].

by neutralizing CF_3SO_3H with NaOH (10 M) and drying in a vacuum desiccator over NaOH.

Argon was freed of oxygen by passing it through a bubbling tower containing a Cr^{2+} solution. When used in syntheses in non-aqueous solvents, argon was dried by passing it through a bubbling tower containing concentrated H_2SO_4, and then it was saturated with the solvent vapor by passage through a bubbling tower containing the solvent.

All other chemicals were reagent grade, and were used as received. Deionized water that was distilled from an all-glass apparatus was used throughout.

Preparation of Complexes

cis-Bis(methyl glycinate) tetraammineruthenium-(II) hexafluorophosphate (**I**) its bis(benzyl glycinate) analogue (**II**) and the trifluoromethanesulfonate salt of the bis(ethyl glycinate) complex (**III**), were prepared by a procedure similar to that of Diamond [12]. 200 mg of *cis*-$[(NH_3)_4Ru(H_2O)_2](CF_3SO_3)_3$ were dissolved in 2 ml of argon saturated methanol, in a Zwickel flask [13]. Zinc amalgam was added, and reduction was allowed to proceed for ~20 min. When preparing complex **III** the solution was transferred at this point by means of a positive argon pressure to a bubbling flask that was attached to the Zwickel flask, and 0.2 ml of the ligand was syringed in. A colour change and precipitation commenced almost immediately. After ~30 min the solution was filtered, and the yellow precipitate was washed with dry ether. In the preparation of complexes **I** and **II** the ligands were added to the solution in the Zwickel flask, after reduction. A colour change from dark orange to yellow was observed, but no precipitate formed. This solution was transferred to a bubbling flask which contained 1 ml of a saturated solution of NH_4PF_6 in methanol that was previously saturated with argon. A precipitate started to form immediately. The solution was cooled in ice and filtered and the yellow precipitate washed with dry ether. Cyclic voltammetry and square wave voltammetry proved each of the three complexes to contain a single electroactive species.

The percentage of ruthenium in fresh samples of the complexes was determined by the method of Marchant *et al.* [14]. The results are summarized in Table 1 which also presents the yields of the glycinato chelate produced by the reactions of the oxidized complexes (*vide infra*). The results indicate that complexes **I** and **III** are contaminated with some impurity that does not contain ruthenium, is not electrochemically active, and is transparent in the UV and visible regions of the spectrum. Elementary analysis of complex **III** yielded the following results: C, 16.9; H, 4.2; N, 11.8. Calc.: C, 17.8; H, 4.5; N, 12.5%, consistent with 95 ± 3% purity, as obtained by the Ru analysis.

Analytical Methods

UV spectra were recorded on a Perkin-Elmer 555 recording spectrophotometer. pH was measured with a homemade digital pH-meter using a Metrohm 147 combined electrode.

Electrochemical Measurements

Cyclic and square wave voltammograms were recorded using a homemade multipurpose polarographic analyzer, and a Hewlett-Packard model 7045B X-Y recorder. The electrochemical cell was of the conventional two-compartment design in which the reference cell was isolated from the test solution by means of a glass frit. A carbon-paste working electrode, platinum wire auxiliary electrode and Ag/AgCl in saturated KCl reference electrode were used. All experiments were performed in argon saturated solutions. The concentrations of complexes were $(1-2) \times 10^{-3}$ M, and the ionic strength was kept at 0.1 M. Potentials were converted to normal hydrogen scale by adding 0.197 V.

Kinetic Measurements

Kinetics were followed spectrophotometrically. The temperature was kept at 20 ± 0.5 °C using a Haake E52 thermostat.

Results

cis-Bis(glycinato ester)tetraammineruthenium(II) Complexes

The *cis* configuration of the starting $[(NH_3)_4Ru(H_2O)_2]^{3+}$ complex, excess of ligand, and the high stereospecificity of $[(NH_3)_4RuL_2]^{2+}$ substitutions [15], suggest that only the *cis* disubstituted complexes were produced. This was verified by the electrochemical results which showed a single electroactive species in cyclic and square wave voltammograms. The half wave potentials (at 0.1 M CF_3SO_3H) are: 0.290 ± 0.005 V, 0.270 ± 0.005 V and 0.270 ± 0.005 V *versus* NHE for **I**, **II** and **III** respectively. These values are 0.1–0.15 V more positive than the $E_{1/2}$ values of $[(NH_3)_5RuNH_2CH_2COX]^{2+/3+}$ couples (X = OC_2H_5, NHR) [5, 10a, c] which in turn are 0.07–0.12 V higher than the $E_{1/2}$ value of $[(NH_3)_6Ru]^{2+/3+}$ [16]. Thus, successive substitution of the ammineruthenium center by amino acid derivatives gradually increases its redox potential.

Products of the Reaction of the Ru(III) Complexes

Solutions of complexes **I**, **II** and **III** were oxidized by a slight (~5%) excess of $Na_2S_2O_8$. After the oxidation process (which is completed within 1 s under the experimental conditions) was over, further absorption changes in the UV spectra of the solutions were detected. The spectra obtained when no further spectral changes could be observed were identical with the spectrum of glycinatotetraammineruthenium(III) [10a], and indicated 100% yield for its production from the bis(glycinato ester) complexes (Table 1). Electrochemical analysis of the product solutions revealed a single electroactive species with $E_{1/2}$ = –0.010 V at pH 1, which shifted to +0.020 V at pH 3. These values are identical with the values featured by the glycinato chelate [10a]. The oxidation and reduction waves had identical intensities, a fact which suggests that glycine is bound only as a bidentate ligand, since monodentate O-bound glycinate is very labile in the Ru(II) state, and aquates before being oxidized [5]. In order to verify that the glycinato chelate is indeed the only product, zinc amalgam was added to the product solution which was then stirred for several minutes. After removal of the amalgam, the solution was oxidized with air, and its UV spectrum was compared to its spectrum before this treatment. No change could be detected. This proves that no aquation takes place in the Ru(II) state, consistent with the presence of chelated glycinate as the only product of the reaction.

Kinetics of the Reactions of the Ru(III) Complexes

Solutions of the Ru(II) complexes ($(2–5) \times 10^{-4}$ M) were oxidized with ~5% excess of $Na_2S_2O_8$, and their spectra were monitored between 200 and 400 nm as a function of time at several pH values. The absorption increased in the whole of this spectral range, and a peak at 288 nm grew in at the expense of a flat and lower peak at ~270 nm that was featured immediately after oxidation. First order plots were linear for at least 3 halflives. The results are summarized in Table 2. Plots of the rate constants as a function of H^+ concentration (see Fig. 2) show rate saturation at low pH (see 'Discussion').

TABLE 2. Kinetic Results for the Reaction of $[(NH_3)_4Ru(NH_2CH_2COOR)_2]^{3+}$ Complexes[a]

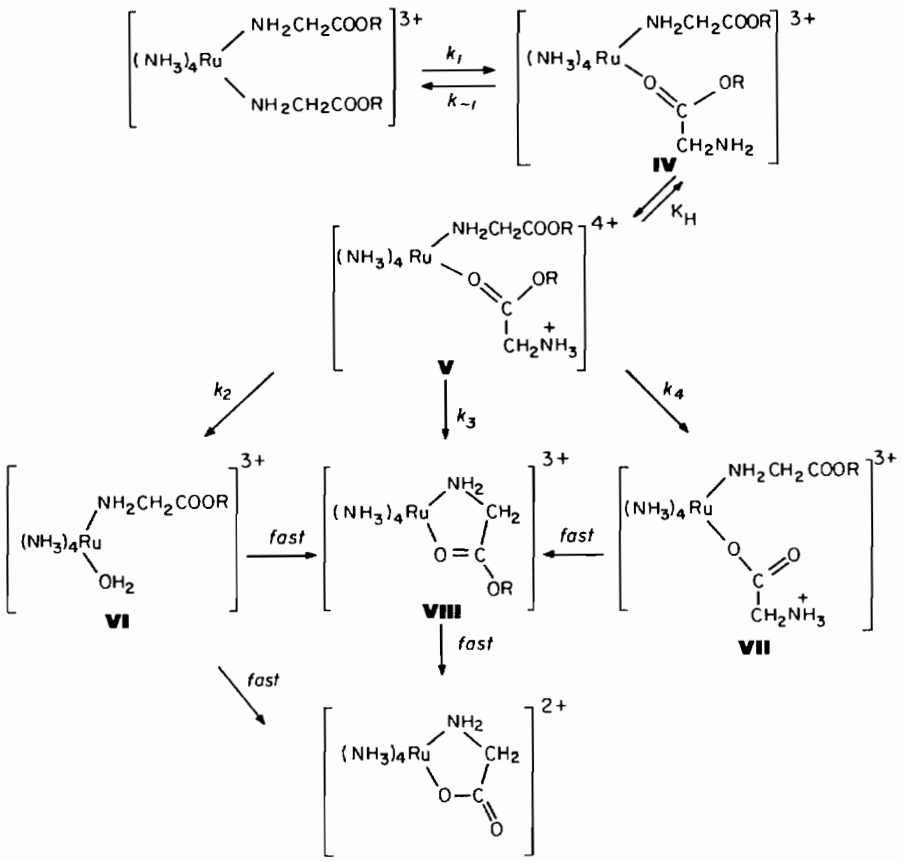
R	$[H^+]$ (M)				
	$10^3 \times k_{obs}$ (s^{-1})				$10^3 \times k_1$ (s^{-1})[b]
	0.1	0.01	0.003	0.001	
CH_3	1.7	1.3	1.0	0.47	1.8
C_2H_5	2.0	1.6	1.2	0.55	2.1
$CH_2C_6H_5$	2.1	1.9		0.68	2.2

[a] 20 ± 0.5 °C, μ = 0.1 M ($CF_3SO_3H + CF_3SO_3Na$). [b] Calculated from the intercepts of the lines in Fig. 2.

Discussion

Ruthenium complexes of amino acids and amino acids derivatives demonstrate a variety of interesting chemical reactivity patterns. Linkage isomerization of bound amino acid [5], linkage isomerization followed by ester hydrolysis of bound amino acid ester [6], chelation of monodentately bound amido derivatives of amino acids [7], hydrolysis of chelated amino acid amide in solutions of acidic pH [10d] and deprotonation of the α-carbon of chelated amino acid amides below neutral pH [10c] were all observed for Ru(III) complexes. None of these reactions has a parallel in the chemistry of the inert metal ion Co(III) [8]. Some of these reactivity modes (e.g. chelation of glycinamide derivatives concomitant with dissociation of a NH_3 ligand, and linkage isomerization of glycine and ethyl glycinate) are quite outstanding for an inert metal center such as Ru(III) [17].

Ru(III) bound amino acids and amino acid esters undergo linkage isomerization from the N-bound isomer to the O-bound isomer [5, 6]. Ru(III) N-bound amino acid amides undergo a different reaction – chelation by an attack of the carbonyl oxygen on the metal ion, which brings about dissociation of an ammonia ligand [7]. The present study demonstrates the ability of Ru(III) monodentate N-bound amino acid ester molecules to form a N,O-bound chelate, and to initiate dissociation of a ligand from the Ru(III) center. Chelation may take place, provided that two amino acid ester molecules are bound to the Ru(III) ion, so that one of the ester molecules and not a NH_3 ligand dissociates from the metal center in the course of the reaction.



Scheme 1.

Scheme 1 is suggested to represent the various modes of production of the glycinato chelate from the bis(glycinato ester) Ru(III) complexes. This Scheme is similar to schemes suggested for the hydrolysis of monodentate ethyl glycinate [6], and for the aquation path of complexes of glycinamide derivatives [7], and leads to eqn. (1).

$$k_{obs} = \frac{k_1(k_2 + k_3 + k_4)K_H[H^+]}{k_{-1} + (k_2 + k_3 + k_4)K_H[H^+]} \quad (1)$$

Equation (1) explains the rate saturation observed at low pH values (Fig. 1). Plots of $(k_{obs})^{-1}$ *versus* $[H^+]^{-1}$ yield straight lines (Fig. 2) as expected. From the intercepts of these lines values of k_1, the rate of isomerization of the N-bound glycinate ester to the O-bound isomer, were calculated. These values, which are presented in Table 2, are similar to the values obtained for analogous reactions of glycine [5] and of ethyl glycinate [6] bound to $(NH_3)_5Ru^{III}$.

$[(NH_3)_5RuNH_2CH_2COOC_2H_5]^{3+}$ transforms into the O-bound isomer with a rate constant of 1.14×10^{-3} s^{-1} [6]. The rate constant measured in the present work for the complex with two N-bound ethyl glycinate ligands is 2.1×10^{-3} s^{-1}, about twice as large. Taking into account the statistical factor of 2, the rates are essentially identical.

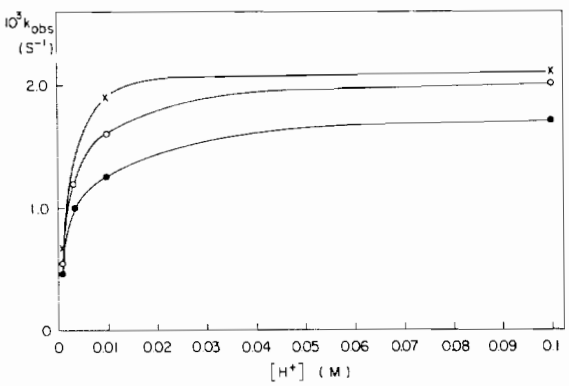


Fig. 1. Observed rate constant *vs.* H^+ concentration in the reaction of *cis*-$[(NH_3)_4Ru(NH_2CH_2COOR)_2]^{3+}$: ●, R = CH_3; ○, R = C_2H_5; x, R = $CH_2C_6H_5$.

Intermediates **IV** and **V** are anologous to the intermediates suggested in the hydrolysis/aquation of (ethyl glycinate) pentaammineruthenium(III) [6]. The complex produced by isomerization of one of

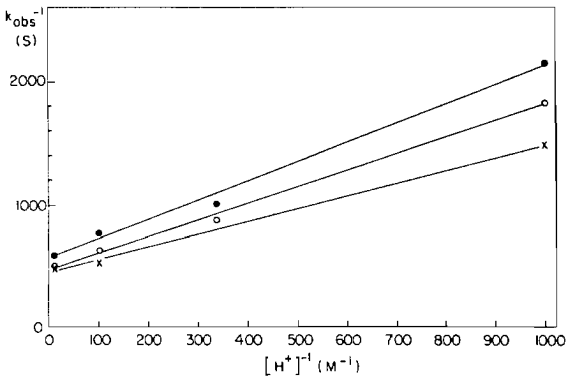


Fig. 2. $(k_{obs})^{-1}$ *vs.* reciprocal value of H^+ concentration in the reaction of *cis*-$[(NH_3)_4Ru(NH_2CH_2COOR)_2]^{3+}$: ●, R = CH_3; ○, R = C_2H_5; x, R = $CH_2C_6H_5$.

the ester molecules can undergo aquation to yield **VI** (k_2), or it can produce the N,O-bound chelate **VIII**, either directly (k_3) or after initial hydrolysis of the monodentate O-bound ester **VII** (k_4). The chelated ester (**VIII**) is then hydrolyzed to the final product in a fast process. The final chelated glycinato product can also be produced from the aquation product **VI** either directly, by an attack of the Ru-bound water molecule on the carbonyl oxygen (C–O bond cleavage), or via intermediate **VIII**, by an attack of the carbonyl oxygen on the ruthenium ion, and dissociation of the water molecule (Ru–O bond cleavage). The final product of all possible reaction paths is the glycinato chelate, as observed experimentally.

Figure 1 demonstrates rate saturation as a function of $[H^+]$, which leads to a pH independent rate when $[H^+] > 0.1$ M. A similar situation obtains for $[(NH_3)_5RuNH_2CH_2COOC_2H_5]^{3+}$ only in solutions 10 times more concentrated in H^+ [6]. Independence of pH should occur when $k_{-1} \ll (k_2 + k_3 + k_4)K_H[H^+]$, in the denominator of eqn. (1). The constants k_{-1} and K_H are the same for the mono and bis substituted ethyl glycinate complexes. The only difference lies in the term connected with the path leading to chelation by substitution of the O-bound glycinato ligand by the carbonyl oxygen of the second ester ligand (k_3). Thus, k_3 should be larger than k_2 and k_4, and is probably the main (though not the only) path leading to the final product. This is also consistent with the faster rate of reaction of the bis substituted complexes as compared to the mono substituted complex, under conditions where the rate is pH dependent.

The linearity of the lines in Fig. 2 indicates that direct substitution of one N-bound glycinato ester ligand by the carbonyl oxygen of the other glycinato ester ligand does not occur. Such a path would contribute a pH independent term to k_{obs}, which would cause non-linearity of the lines plotted in Fig. 2. Substitution of the amino group of the ester ligand could be easier than that of NH_3, because of its lower affinity toward Ru(III) [18].

Conclusions

Ammineruthenium(III) complexes that contain a single N-bound glycine or ethyl glycinate ligand, produce monodentate O-bound glycinato complexes [5, 6]. Analogous complexes of glycinamide and its derivatives produce N,O-bound chelates of the amide derivatives [7]. The bis(glycine ester) complexes studied here, also produce a chelated product, and in that resemble the behaviour of the glycinamide complexes. The mechanism, though, is similar to that of the mono substituted ester complex. The different products are the result of the presence of a second N-bound glycine ester ligand which can form a N,O-bound chelate by substitution of either a water molecule or the other (monodentate O-bound) ester molecule.

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