12092-47-6; $[Rh(C_8H_{12})Br]_2$, 12092-45-4; CH_3SSCH_3, 624-92-0.

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Thermodynamics and Kinetics of Some Tetra-μ-carboxylato-dirhodium(II) Adduct Formation Reactions

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The thermodynamic and kinetic parameters have been determined for adduct formation reactions of tetra-μ-acetato, tetra-μ-propionato, and tetrakis(μ-methoxyacetato)-dirhodium(II) complexes with 5′-AMP, histidine, imidazole, and pyridine. Tetra-μ-propionato-dirhodium(II) forms more stable adducts than tetra-μ-acetato-dirhodium(II) with all of the ligands studied. With 5′-AMP and imidazole tetrakis(μ-methoxyacetato)-dirhodium(II) forms adducts which are the least stable whereas with histidine the reverse order of stability is observed. The rates of adduct formation among the three rhodium(II) carboxylates are in the order methoxyacetate < acetate < propionate. The presence of more than one donor atom on the adduct-forming ligand increases the foward rate constant by approximately an order of magnitude.

Introduction

For the past few years we have been investigating the biologic activity of several tetra-μ-carboxylato-dirhodium(II) complexes.[1-3] The antitumor activity of these complexes was found to increase with increasing number of carbon atoms in the carboxylate ion.[3] Since the tetra-μ-carboxylato-dirhodium(II) species readily forms adducts with various donor ligands by the replacement of the two axial water molecules, we have been investigating this reaction as a possible source of the anticancer activity. Very little is known about the thermodynamic and kinetic stability of these adducts in aqueous solution particularly with regard to how variations in structural properties and basicity of the carboxylate ions bridging the two rhodium ions affect the bonding characteristics at the two axial positions.

Recently we reported the formation constants for the reactions involving rhodium(II) methoxyacetate, acetate, and propionate and the ligands 5′-AMP, 5′-ADP, and 5′-ATP[4] as well as the detailed thermodynamics for the reaction of these carboxylates with imidazole.[5] In these studies the order of stability of the adducts was the same as the biologic activity, i.e., propionate > acetate > methoxyacetate. However the variation in the stability of the adducts was not nearly as large as that observed for their toxicity and antitumor activity.

The previous studies[4,5] indicate that the lipophilic nature of the bridging carboxylate ion is a dominant factor in determining the order of stability of the adducts. Since the methoxyacetate ion is less basic than the propionate ion, tetrakis(μ-methoxyacetato)-dirhodium(II) adducts should be more stable if an inductive effect was the stability-controlling factor. The thermodynamic studies with imidazole as the

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Table I. Typical Concentration Dependence of Relaxation Times for the $Rh_2(OAc)_4$-5′-AMP System[a]

$10^{-3}C_M$, M	$10^{-3}C_L$, M	$10^{-3}(\bar{M} + \bar{L})$, M	$10^{-3}/\tau$, s^{-1}
1.94	1.96	1.47	5.88
1.92	2.91	1.71	6.25
1.92	3.38	1.92	7.14
1.91	3.85	2.17	7.69
1.90	4.31	2.46	8.70
1.89	4.76	2.77	9.09

[a] $k_f = (2.9 \pm 0.4) \times 10^6\ M^{-1}\ s^{-1}$.

adduct-forming ligand[5] show that the order of stability among the three tetra-μ-carboxylato-dirhodium(II) complexes is determined by the enthalpy of formation. Apparently the two axial water molecules on the propionate complex are more loosely bound due to the lipophilic repulsion of the side chain. If this is true, the rate of adduct formation or water-exchange rate should be faster for the propionate complexes.

In order to determine if the order of stability, propionate > acetate > methoxyacetate, is the same for a variety of ligands and see if the rate of adduct formation is greater for the propionate complex, we have measured the thermodynamic and kinetic parameters for the adduct formation reaction involving several different ligands. This paper reports the result of this investigation.

Experimental Section

Chemicals. The sources of chemicals and the preparation and purification of compounds used in this study have been described previously.[5]

Thermodynamics. An entropy titration technique was employed to determine the formation constants, enthalpies, and entropies of formation for the 1:1 and 1:2 adducts. The details of the instrumentation, procedures, calculations, and data treatment have been described.[5]

Kinetics. The apparatus used in this study is a joule-heating temperature-jump apparatus that employs a spectrophotometric method of detection and has been described previously.[6] All of the determinations were carried out at a room temperature of 23 °C. The temperature rise for the discharge voltage of 20 kV for heating 1 mL of solution between the two electrodes was calculated to be 2 °C. Relaxation times were determined for at least six different solutions with varying concentrations. A typical set of data showing the concentration variations of relaxation time is shown in Table I.

The second-order forward rate constants for the reactions of the type

$$Rh_2X_4{\cdot}2H_2O + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Rh_2X_4{\cdot}L(H_2O) + H_2O$$

where X is a carboxylate ion, were obtained as the slope of the plot of $1/\tau$ against $(\bar{M} + \bar{L} + 1/K_{eq})$ according to the equation

$$1/\tau = k_f(\bar{M} + \bar{L} + 1/K_{eq})$$

where τ is the relaxation time, $\bar{M}$ and $\bar{L}$ are the equilibrium concentrations of the reactants, and K_{eq} is the formation constant. To calculate $\bar{M}$ and $\bar{L}$, use is made of the total concentration of metal ion containing species, C_M, and total ligand concentration, C_L, which are given by

$$C_M = [M] + [ML] + [ML_2]$$

and

$$C_L = [HL^+] + [L] + [ML] + 2[ML_2]$$

where [M] is the concentration of $Rh_2X_4{\cdot}2H_2O$, [ML] the concentration of $Rh_2X_4{\cdot}L(H_2O)$, and $[ML_2]$ the concentration of $Rh_2X_4{\cdot}2L$. With the help of these two expressions and by making use of the equilibrium constants K_1 and K_2 for the formation of $Rh_2X_4{\cdot}L(H_2O)$ and $Rh_2X_4{\cdot}2L$ and the dissociation constant K_a of the ligand, we obtain

$$C_L + [L]\{K_1C_L - K_1C_M - (K_a + [H^+])/K_a\} + [L]^2\{K_1K_2C_L - 2K_1K_2C_M - K_1(K_a + [H]^+)/K_a\} - [L]^3K_1K_2(K_a + [H^+])/K_a = 0$$

Thus from the known values of C_M, C_L, K_1, K_2, K_a, and $[H^+]$, this equation can be solved for the free-ligand concentration [L]. This value can then be used to calculate the equilibrium concentrations of other species.

Results and Discussion

The thermodynamic parameters for the adduct formation reactions are shown in Table II. As mentioned earlier we previously determined the equilibrium constants for the reactions involving the three tetrakis(μ-carboxylato)-dirhodium(II) complexes used in this study and 5′-AMP by a spectrophotometric method.[4] The same order of stability among the three rhodium complexes was obtained in this study. However, the magnitude of the formation constants is somewhat larger. At the present we cannot explain these differences. In using either set of formation constants the thermodynamic parameters change very little and they show the same trends.

One of the reasons for this study was to determine if the order of stability, of adducts found among the three tetra-μ-carboxylato-dirhodium(II) complexes with different ligands, was the same as their biologic activity, i.e., methoxyacetate < acetate < propionate. As can be seen in Table II, tetra-μ-propionato-dirhodium(II) does form more stable adducts than the corresponding acetate complex with 5′-AMP, imidazole, and histidine. However, tetrakis(μ-methoxyacetato)-dirhodium(II) does not show a similar trend. With 5′-AMP and imidazole the methoxyacetate adducts are the least stable but with histidine the reverse is found. In fact there is a rather dramatic increase in the stability of the tetrakis-(μ-methoxyacetato)-dirhodium(II) complex of histidine over

Table II. Summary of Thermodynamic Parameters

Rhodium(II) carboxylate	log K_1	log K_2	$-\Delta H_1$, kcal/mol	$-\Delta H_2$, kcal/mol	ΔS_1, eu	ΔS_2, eu
			Complexation with 5′-AMP			
MeO_2Ac	3.45 ± 0.03	2.70 ± 0.06	5.43 ± 0.09	4.6 ± 0.4	−2.4 ± 1.0	−3.1 ± 2.0
OAc	3.66 ± 0.03	2.66 ± 0.07	5.21 ± 0.06	2.8 ± 0.2	−1.4 ± 1.0	2.7 ± 1.0
Prop	3.78 ± 0.04	2.57 ± 0.04	5.45 ± 0.06	2.0 ± 0.2	−1.0 ± 1.0	5.0 ± 2.0
			Complexation with Imidazole			
MeO_2Ac	3.94 ± 0.03	2.40 ± 0.04	7.30 ± 0.03	3.0 ± 0.3	−6.4 ± 2.0	1.0 ± 2.0
OAc	4.02 ± 0.07	2.48 ± 0.08	7.43 ± 0.03	3.0 ± 0.3	−6.5 ± 2.0	1.2 ± 2.0
Prop	4.07 ± 0.03	2.65 ± 0.07	8.65 ± 0.02	5.3 ± 0.2	−10.5 ± 1.0	−5.7 ± 2.0
			Complexation with L-Histidine			
MeO_2Ac	4.38 ± 0.02	2.79 ± 0.03	7.82 ± 0.02	7.6 ± 0.3	−6.2 ± 1.0	−12.7 ± 2.0
OAc	4.05 ± 0.02	2.69 ± 0.02	7.28 ± 0.02	6.3 ± 0.4	−5.9 ± 1.0	−8.8 ± 2.0
Prop	4.14 ± 0.03	2.71 ± 0.02	6.70 ± 0.02	6.0 ± 0.1	−3.6 ± 1.0	−7.7 ± 2.0
			Complexation with Pyridine			
MeO_2Ac	4.52 ± 0.02	2.81 ± 0.04	7.95 ± 0.03	7.8 ± 0.3	−6.0 ± 1.0	−13.3 ± 2.5

that of the imidazole adduct. Sundberg and Martin,[7] in an extensive review of the interaction of histidine and other imidazole derivatives with metal ions, reported that imidazole in almost all of its complexes acts as a monodentate ligand with N-3, "pyridine nitrogen", as the donor atom except at very high pH. If the same donor atom is involved in the bonding, then the increased stability cannot be explained in terms of the basicity of the ligand since the N-3 nitrogen of imidazole is more basic than the corresponding nitrogen in histidine.

Two possible explanations for the increased stability of the tetrakis(μ-methoxyacetato)-dirhodium(II) adducts of histidine are enhanced π bonding and/or interaction of the alanine moiety of histidine with the side chain of the carboxylate ions. In order to determine if π-bonding is a significant factor in determining the overall stability of these adducts, we determined the thermodynamic parameters for the formation of the tetrakis(μ-methoxyacetato)-dirhodium(II) pyridine adducts. Since the order of π-acceptor ability of the ligands is 5′-AMP < imidazole < histidine < pyridine[8] and the basicity order of the donor atoms of the ligands is 5′-AMP < pyridine < histidine < imidazole, pyridine should form a more stable adduct with the methoxyacetate complex than imidazole if π-bonding is significant. As seen in Table II the pyridine adduct is considerably more stable than the imidazole complex. Unfortunately we could not determine the stability of the pyridine adducts of the acetate and propionate complexes because they are insoluble in water. However, the fact that the histidine adducts of these two complexes are slightly more stable than the corresponding adducts with the more basic imidazole ligand also suggest π bonding is involved.

Since π bonding should be involved to approximately the same extent in the adducts of all three rhodium complexes with a given ligand, the relative stability among the three rhodium complexes must be due to the lipophilic nature of the carboxylate ion side chain to a large degree. The tetra-μ-propionato-dirhodium(II) complex should be less solvated than the methoxyacetate complex because of its lipophilicity. Also the inductive effect of the less basic methoxyacetate ion should result in a strong rhodium–water[6] bond at the two axial positions. Therefore ΔH values for the three imidazole adducts reflect to some degree the differences in energy of solvation. Since more energy is needed to break the metal–water bonds for the methoxyacetate complex, the enthalpy of formation of the imidazole adduct is less favorable. The entropies of formation ΔS_1 and ΔS_2 for the propionate adduct are also more negative which indicates less water of solvation is liberated into the bulk solvent on complexation.

The enthalpy of formation, ΔH_1, is more favorable for the tetrakis(μ-methoxyacetato)-dirhodium(II)–histidine adduct than that for the imidazole complex whereas the reverse is true for the propionate complexes. This is the reason for the different order of stability observed for the two ligands. Comparison of ΔH_1 and ΔS_1 for the imidazole and histidine adducts of tetra-μ-propionato-dirhodium(II) shows that there are large differences in these parameters for the two ligands. This could be due to the alanine moiety of histidine reducing the bond strength because of a steric effect or to repulsion of this polar group by the lipophilic propionate side chain. If it were purely a steric effect, the histidine adduct of the methoxyacetato complex should also be less stable, and since this is not observed, one must conclude that the less favorable enthalpy change, ΔH_1, and the more favorable entropy change, ΔS_1, for the histidine adduct are due to some kind of lipophilic repulsion.

The forward and reverse rate constants for the formation of the 1:1 adducts of the tetra-μ-carboxylato-dirhodium(II) complexes at 23 °C are summarized in Table III. The

Table III. Rate Constants for the Reactions of Tetra-μ-carboxylato-dirhodium(II) Complexes with Different Ligands at 25 °C and pH 7.40

Ligand	Rhodium(II) carboxylate	k_f, M^{-1} s^{-1}	k_r, s^{-1}
5′-AMP	$Rh_2(MeO_2Ac)_4$	$(2.0 \pm 0.4) \times 10^6$	$(1.3 \pm 0.3) \times 10^3$
	$Rh_2(OAc)_4$	$(2.9 \pm 0.4) \times 10^6$	$(1.5 \pm 0.3) \times 10^3$
	Rh_2Prop_4	$(4.4 \pm 0.8) \times 10^6$	$(1.1 \pm 0.2) \times 10^3$
L-Histidine	$Rh_2(MeO_2Ac)_4$	$(4.0 \pm 0.3) \times 10^5$	37 ± 3
	$Rh_2(OAc)_4$	$(3.6 \pm 0.4) \times 10^5$	66 ± 8
	Rh_2Prop_4	$(5.6 \pm 0.9) \times 10^5$	88 ± 12
Imidazole	$Rh_2(MeO_2Ac)_4$	$(6.2 \pm 1.0) \times 10^6$	$(7.0 \pm 1.0) \times 10^2$
	$Rh_2(OAc)_4$	$(7.1 \pm 1.2) \times 10^6$	$(6.8 \pm 1.0) \times 10^2$
	Rh_2Prop_4	$(7.4 \pm 1.4) \times 10^6$	$(6.3 \pm 1.0) \times 10^2$
Pyridine	$Rh_2(MeO_2Ac)_4$	$(6.0 \pm 1.0) \times 10^5$	53 ± 9

forward rate constants for the systems studied are in the range of 10^5–10^6 M^{-1} s^{-1}. It may be pointed out that these systems are unique in that both the metal complex and the adduct-forming ligand are neutral species. For this reason the measured rate constants do not contain a large ion-pair formation constant, K_o, that is involved in rate measurements involving exchange reactions of solvated metal ions and charged ligands. Also the ligand exchange can only occur at the two axial positions of the tetra-μ-carboxylato-dirhodium(II) complexes and cannot involve chelation. Since the following exchange reactions are possible

$$Rh_2X_4 \cdot 2H_2O + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Rh_2X_4 \cdot L(H_2O) + H_2O \quad (1)$$

$$Rh_2X_4 \cdot L(H_2O) + L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RH_2X_4 \cdot 2L + H_2O \quad (2)$$

at high ligand concentration, one could observe one coupled relaxation if the two rates are of the same order of magnitude or two uncoupled relaxation curves if there is enough difference in the two exchange rates. It appears that the latter possibility is the case since we observed two relaxation curves. At a very large concentration of ligand the slow relaxation was found to disappear for all of the systems showing that this is characteristic of reaction 1. The fast relaxation in some cases was found to be characteristic of reaction 2, but no unequivocal data could be obtained because in most of the systems it was found to be in close proximity to the instrument rise time. If the rate of water loss is the rate-determining step, then this qualitative observation that the second step of the reaction is much faster (10–100 times) than the first step indicates labilization of the second axial water molecule on monoadduct formation.

The dimeric rhodium(II) species is stabilized by the bridging carboxylate ions. This strong interaction between the rhodium ions and the equatorial oxygen atom of the carboxylate ions, along with the interactions between the two rhodium ions, apparently gives rise to a system with very high rates of water loss from the axial positions as is evidenced from the rate constants in Table III. The forward rate constants are at least an order of magnitude larger than corresponding reactions of cobalt(II).[9] For example, the forward rate constant, k_f, for the formation of the cobalt(II)–imidazole complex is 1.3×10^5 M^{-1} s^{-1} whereas k_f for the formation of the 1:1 imidazole adduct of the tetra-μ-carboxylato-dirhodium(II) complexes ranges from 6.2×10^6 to 7.4×10^6 M^{-1} s^{-1}.

For the adduct formation reaction with all of the ligands the rates of formation among the three rhodium(II) carboxylates are in the order MeO_2Ac < OAc < Prop. This could be due to either enhanced labilization of the axial water molecules with the slight increased basicity of the bridging acids or a "pushing out" of the water by the more lipophilic carboxylate side chain. The variations of the rate constants

are in the direction one would predict from both of these effects. However the magnitude of the variation is not large and indicates that changing the bridging carboxylate ion has little effect on the rate of water loss.

The variation of the rate constants for a particular carboxylate complex, tetrakis(μ-methoxyacetato)-dirhodium(II), for example, reacting with different ligands is from 4×10^5 to 6.2×10^6 M^{-1} s^{-1} for k_f and from 37 to 1300 s^{-1} for k_r. Though these figures indicate a greater variation in k_r than in k_f thus putting more weight in favor of a dissociative mechanism, the ligand dependency of the rates cannot be overlooked. Whether this results from variations in the extremely small values of K_o, the outer-sphere formation constant, or from participation of the entering ligand in the formation of an activated complex cannot be determined from the available data. It does mean though that the loss of an axial water molecule does not alone determine the rate of these reactions. Though all of the ligands act as monodentate ligands toward the tetra-μ-carboxylato-dirhodium(II) species, the presence of more than one donor atom, as in 5′-AMP or imidazole, increases the rate of formation by an order of magnitude to that with pyridine or histidine where only one binding site is available.

In conclusion, the thermodynamic data show that the order of stability of the adducts formed with nitrogen donor ligands does not always correlate with the biologic activity of these complexes. This does not rule out that simple adduct formation reactions are involved in the anticancer activity of these complexes, but it does show that if it is a factor, only certain types of ligands are involved. Certainly axial bonding with macromolecules such as proteins and polynucleic acids is a completely different situation. In these systems the magnitude and the order of stability of the rhodium(II) complexes will be determined by many factors not present with the monomer units.

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Registry No. $Rh_2(MeO_2Ac)_4 \cdot 2(5'\text{-AMP})$, 56437-38-8; $Rh_2(OAc)_4 \cdot 2(5'\text{-AMP})$, 56437-35-5; $Rh_2(prop)_4 \cdot 2(5'\text{-AMP})$, 56437-37-7; $Rh_2(MeO_2Ac)_4 \cdot 2(\text{imidazole})$, 59532-69-3; $Rh_2(OAc)_4 \cdot 2(\text{imidazole})$, 59532-70-6; $Rh_2(prop)_4 \cdot 2(\text{imidazole})$, 59532-71-7; $Rh_2(MeO_2Ac)_4 \cdot 2(\text{L-histidine})$, 62126-05-0; $Rh_2(OAc)_4 \cdot 2(\text{L-histidine})$, 62154-26-1; $Rh_2(prop)_4 \cdot 2(\text{L-histidine})$, 62154-27-2; $Rh_2(MeO_2Ac) \cdot 2(\text{pyridine})$, 62126-03-8.

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Selenitometal Complexes. 1. Synthesis and Characterization of Selenito Complexes of Cobalt(III) and Their Equilibrium Properties in Solution

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We report the synthesis and characterization of the new selenito complexes $[Co(NH_3)_5OSeO_2](X,Y) \cdot H_2O$, *cis*- and *trans*-$[Co(en)_2(OH_2)OSeO_2H](X,Y)_2 \cdot H_2O$, *cis*-$[Co(en)_2(OH_2)OSeO_2]X \cdot H_2O$, and $[Co(NN)_2O_2SeO]Y \cdot H_2O$ where $X^- = Br^-$, $Y^- = ClO_4^-$, and NN = $NH_2CH_2CH_2NH_2$ (en) or $NH_2CH_2CH_2CH_2NH_2$ (tn). Infrared spectra of the crystalline selenito complexes show that in all complexes the selenito ligand is coordinated exclusively through oxygen, either in a monodentate or in a bidentate form. Acidity constants were determined at 25 °C and in 1.0 M ionic strength, adjusted with sodium perchlorate; for proton release from the aquo ligand in $Co(en)_2(OH_2)OSeO_2^+$, $pK_{aq} = 8.30 \pm 0.05$ for the cis isomer and $pK_{aq} = 7.70 \pm 0.05$ (trans) while for proton release from the hydrogenselenito ligand in $Co(en)_2(OH_2)OSeO_2H^{2+}$, $pK_{a2} = 4.35 \pm 0.05$ (cis) and $pK_{a2} = 4.55 \pm 0.05$ (trans). The overall formation quotient for selenito complexes, Q_s, was determined spectrophotometrically and Q_s varied greatly with pH and the nature of the selenium(IV) species. For four complexes at 25 °C and in 1 M ionic strength, $Q_s = 1.5$–5.4 at pH 1, 16–50 at pH 3, ≥100 at pH 7, and ~5 at pH 11.5. In the pH range 1–3, the biselenite species $HSeO_3^-$, $H_2(SeO_3)_2^{2-}$, and $H_3(SeO_3)_2^-$ all coordinate almost equally, with β values of about 55 for all diaquo complexes and 23 for the monoaquo complex. Below 40 °C, the equilibrium concentration of bidentate selenito complexes existing with monodentate selenito complexes and free selenite is undetectable under all pH conditions. There is no evidence for the existence of bis(selenito) complexes in aqueous media even in the presence of large concentrations of free selenite.

Introduction

Selenium is now recognized[2] as one of the essential trace elements in human and animal nutrition, yet at higher concentrations, selenium can cause acute and chronic poisoning. Much of this evidence has been derived from nutritional, toxicological, and microbiological studies in which sodium selenite has been fed to test animals. Representative examples include growth stimulation and the control of muscular dystrophies in poultry[3,4] and lambs,[5] the fertility of ewes,[6,7] the toxicity to bacteria,[8] the prolonged retention of trace cadmium in mice,[9] and the inhibitory effect upon carcinogenesis in mice.[10]

Despite the biological importance of sodium selenite, very little is known of the properties of sodium selenite as a nucleophile and as a potential ligand in metal complexes. The only selenito complexes previously reported[11] are several red hygroscopic compounds $[Co(en)_2SeO_3]X \cdot nH_2O$, where X^- is Cl^-, Br^-, NO_3^-, or SO_4^{2-}, which were prepared by oxidizing cobalt(II) selenite in the presence of ethylenediamine. The selenito group was considered to be only "weakly bound to the metal center" and "readily removed by hydrolysis".

In contrast, this paper shows that for a number of newly isolated selenito complexes of cobalt(III), the selenito ligand is relatively stable to aquation in acid media and that both