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Effect of Noncoordinative Axial Blocking on the Stability and Kinetic Behavior of Ternary 2,6-Lutidine–Nickel(II)–Oligopeptide Complexes

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Ternary 2,6-lutidine complexes in aqueous solution are formed with a variety of nickel(II) and copper(II) deprotonated-peptide species. Although the lutidine complex of aquonickel is too weak to measure, an equilibrium constant of 112 M^{-1} is observed for the reaction of lutidine with nickel diglycinamide to form the square-planar [Ni($H_{-2}G_2a$)lut] species. The reactions of the [Ni($H_{-2}L$)lut] species (where L is G_2a or triglycine) indicate that the two methyl groups of lutidine block axial coordination to nickel and hinder both the nucleophilic attack by trien and the solvent accessibility needed for acid attack. The lutidine–copper(II)–peptide complexes are substantially less stable than the corresponding nickel(II) species and are proposed to be five-coordinate in nature.

Introduction

Although 2,6-dimethylpyridine (2,6-lutidine) can form complexes of copper(II)[1-5] and nickel(II)[6] in the solid state, the coordination of the ligand has been too weak to measure in aqueous solution.[7] In fact, 2,6-lutidine has been useful as a noncomplexing buffer at pH 6–8. Hence, it was noted with some surprise in an earlier study[8] that moderate concentrations of 2,6-lutidine inhibit the reaction of nickel(II) glycylglycylglycine, Ni($H_{-2}G_3$)$^-$, with EDTA. In the present study we report the ability of 2,6-lutidine to form ternary complexes with copper(II) and nickel(II) oligopeptides in aqueous solution. Copper(II) complexes with nitrogen bases are usually more stable than nickel(II) complexes, but this is not the case for the interaction of 2,6-lutidine (lut) with the metal–diglycinamide complexes, where the [$Ni^{II}(H_{-2}G_2a)$lut] complex forms more readily than the [$Cu^{II}(H_{-2}G_2a)$lut] complex.

The ternary lutidine–peptide complexes of Ni(II) have interesting kinetic properties because the methyl groups of the coordinated lutidine tend to block the axial coordination sites, effectively limiting the attack of nucleophiles. It is interesting that acid attack also is inhibited.

Copper(II) and nickel(II) promote the ionization of peptide hydrogens from oligopeptides with the formation of deprotonated-N(peptide)–metal bonds.[9-13] The Ni(II) complexes of triglycine (G_3), tetraglycine (G_4), and triglycinamide (G_3a) are yellow, diamagnetic, square-planar species for the fully deprotonated forms.[8,12,14] The rates of acid reaction with the complexes have shown evidence of both specific-acid and general-acid catalyses, depending on the nature of the complex.[8,15,16] Nucleophilic attack by polyamines, polyaminocarboxylates, and other ligands also have been studied.[17-19]

In the present work, the ability of 2,6-lutidine to complex copper(II)– and nickel(II)–oligopeptide complexes is examined as well as the kinetic reactivity of [$Ni^{II}(H_{-2}G_2a)$lut] and [$Ni^{II}(H_{-2}G_3)$lut]$^-$.

Experimental Section

Reagents. Reagent grade pyridine, α-picoline (2-methylpyridine), and 2,6-lutidine were used, and aqueous stock solutions were standardized with $HClO_4$ by using methyl orange indicator. The γ-picoline (4-methylpyridine) was purified by distillation under reduced pressure. Ethylpyridinium bromide was standardized argentimetrically. Stock solutions of $Ni(ClO_4)_2$ and $Cu(ClO_4)_2$ were prepared from the twice recrystallized salts and standardized with EDTA by using murexide indicator.[20] Sodium perchlorate solutions were prepared by the neutralization of Na_2CO_3 with concentrated $HClO_4$ followed by several hours of boiling to remove dissolved carbon dioxide and then filtered through a sintered-glass filter. The commercially available (Sigma Chemical Co., St. Louis, Mo.) diglycinamide hydrochloride contained a 1–2 mol % tetraglycinamide hydrochloride (G_4a·HCl) impurity. The reactions of the metal complexes of G_4a[21] are distinctly different from those of G_2a, and this impurity had no effect on the results obtained.

The hydrogen ion concentration was determined by using the relationship $-\log [H^+] = pH - 0.11$ for all experiments performed at an ionic strength of 0.10 ($NaClO_4$).[22] At an ionic strength of 1.0 ($NaClO_4$) the $[H^+]$ concentrations were determined by using the relationship $-\log [H^+] = pH + 0.29$.[21]

Spectrophotometric Determinations of Equilibrium Constants. The visible absorption spectra of solutions containing the metal–peptide complex (ML) and varying concentrations of the added ligand, Z, (where Z is lutidine, pyridine (py), γ-picoline (γ-pic), ethylpyridinium ($Etpy^+$), or bromide ion) were recorded at 25.0 °C with a Cary 14 spectrophotometer using a 0–0.5 slide wire. The equilibrium constants were calculated by an iterative linear least-squares procedure. Absorbance data were evaluated by using eq 1, which describes the

$$(\epsilon_{ML} - \epsilon_{obsd})/[Z] = (\epsilon_{obsd} - \epsilon_{MLZ})K_{app} \quad (1)$$

equilibrium given in eq 2 prior to correction for the presence of hydroxy

$$ML + Z \overset{K}{\rightleftharpoons} MLZ \quad (2)$$

species of ML in the pH range 9–11. The equilibrium constant, K_{app}, and the molar extinction coefficient, ϵ_{MLZ}, were obtained from the slope and intercept of a plot of $(\epsilon_{ML} - \epsilon_{obsd})/[Z]$ vs. ϵ_{obsd} and recal-

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Table I. Spectrophotometrically Determined Equilibrium Constants[a]

complex	ligand[b]	K,[c] M^{-1}
A. Copper Complexes		
$Cu(H_{-3}G_3a)^-$	lut	4.5 ± 0.6
	γ-pic	6.8 ± 0.4
	py	2.3 ± 0.4
$Cu(H_{-2}G_3)^-$	lut	4.0 ± 0.6
	py	2.1 ± 0.3[d]
	Br^-	~0.1[e]
	$Etpy^+$	<1[f]
$Cu(H_{-2}G_2a)$[g]	lut	6.3 ± 0.9
	py	44 ± 7
	$Etpy^+$	<0.8[h]
$Cu(aq)^{2+}$	lut	<10
$Co(en)_3^{3+}$	lut	<0.3
B. Nickel(II) Complexes		
$Ni(H_{-3}G_3a)^-$	lut	<2
$Ni(H_{-2}G_3)^-$	lut	11 ± 1
$Ni(H_{-2}G_2a)$[g]	lut	112 ± 5
	py	262 ± 8

[a] μ = 0.10 ($NaClO_4$); 25.0 °C; $[ML]_T = (0.5\text{–}2.0) \times 10^{-3}$ M; pH 9–11. [b] [Ligand] = (3.0–49) × 10^{-2} M. [c] Average value of K ($ML + Z \rightleftarrows MLZ$). Upper limits evaluated by assuming less than 10% complex formation. [d] μ = 1.0 ($NaClO_4$). [e] μ = 3.0 ($NaClO_4$). [f] μ = 0.16 (NaBr). [g] Corrected for the presence of hydroxy species.[14] [h] μ = 0.26 (NaBr).

culated until the difference in two successive values of both K_{app} and ϵ_{MLZ} was less than 1%. The initial estimate of the equilibrium constant, whether larger or smaller than the final value, had no effect on the magnitude of the result obtained by this procedure.

Kinetic Experiments. All nickel(II)–peptide solutions were freshly prepared each day. In order to maximize the amount of the ternary complexes formed with lutidine, we adjusted the pH to approximately 10.5. Upon mixing with acid (acetic acid, glycine, maleic acid, oxalic acid, or perchloric acid) or with a triethylenetetramine (trien) solution, we observed a rapid decrease in the absorbance, corresponding to the loss of $Ni(H_{-2}G_2a)$ or $Ni(H_{-2}G_3)^-$ not complexed by lutidine or pyridine. The rates of formation and disappearance of the $[Ni(H_{-2}G_2a)lut]$ and $[Ni(H_{-2}G_3)lut]^-$ complexes were followed at 430 nm by using a computer-interfaced[23] Durrum stopped-flow spectrophotometer. The $[Ni(H_{-2}G_2a)OH^-]$ and $[Ni(H_{-2}G_2a)py]$ complexes were observed at 454 and 426 nm, respectively.

The observed pseudo-first-order rate constant, k_{obsd}, is defined by the expression $-d[Ni(H_{-2}L)lut]/dt = k_{obsd}[Ni(H_{-2}L)lut]_{total}$ where L is diglycinamide (G_2a) or triglycine (G_3) and $[Ni(H_{-2}L)lut]_{total}$ is equal to the sum of the concentrations of the lutidine–nickel–peptide species in solution. The k_{obsd} values were obtained by using an on-line nonlinear least-squares computer program and are the average of at least four kinetic runs.

Results and Discussion

Copper(II)–Peptide Complexes. The spectrophotometrically determined equilibrium constants for the formation of ternary complexes with the copper peptides are given in Table I, section A. In each case investigated, complexation with lutidine resulted in a shift of the visible absorption maximum to shorter wavelengths (Table II). Complexes formed by $Cu(H_{-2}G_3)^-$ with hydroxide ion and bromide ion result in a shift of the visible maximum to longer wavelengths,[18] as is expected for a species in which either an axial solvent molecule has been replaced by a stronger donor or an equatorial carboxylate by a weaker donor.

Although the $Cu(H_{-2}G_2a)$ species has an equatorial coordination site which is not available in either $Cu(H_{-2}G_3)^-$ or $Cu(H_{-3}G_3a)^-$, the equilibrium constants with lutidine are all very similar, suggesting that an equatorial coordination site is not required for the formation of the copper(II)–lutidine ternary complexes. If an equatorial coordination position was required, the equilibrium constant observed for the reaction of $Cu(H_{-3}G_3a)^-$ with lutidine would be expected to decrease by an order of magnitude when the pH is raised from 10 to 11, but it remains constant.

Table II. Visible Absorption Characteristics of Some Copper(II)- and Nickel(II)–Peptide Complexes[a]

complex	λ_{max}, nm	ϵ, M^{-1} cm^{-1}
$Cu(H_{-3}G_3a)^-$	517	144[24]
$Cu(H_{-3}G_3a)lut^-$	512	143
$Cu(H_{-3}G_3a)(\gamma\text{-pic})^-$	517	134
$Cu(H_{-3}G_3a)py^-$	512	133
$Cu(H_{-2}G_3)^-$	555	149[25]
$Cu(H_{-2}G_3)lut^-$	545	147
$Cu(H_{-2}G_3)py^-$	550	93
$Cu(H_{-2}G_3)Br^{2-}$	555[b]	149[b]
$Cu(H_{-2}G_3)OH^{2-}$	578	95[8]
$Cu(H_{-2}G_2a)H_2O$	580	78[24]
$Cu(H_{-2}G_2a)OH^-$	575	81[24]
$Cu(H_{-2}G_2a)lut$	545	82
$Cu(H_{-2}G_2a)py$	555	127
$Ni(H_{-2}G_3)^-$	430	260[8]
$Ni(H_{-2}G_3)lut^-$	432	222
$Ni(H_{-2}G_3)OH^{2-}$	457	167[8]
$Ni(H_{-2}G_2a)OH^-$	454	137[24]
$Ni(H_{-2}G_2a)lut$	430	165
$Ni(H_{-2}G_2a)py$	426	164

[a] μ = 0.10 ($NaClO_4$); 25.0 °C. [b] μ = 3.0 ($NaClO_4$); for $Cu(H_{-2}G_3)^-$; λ_{max} 545 nm; ϵ 153 M^{-1} cm^{-1}.

The possibility of outer-sphere complexes between lutidine and the copper–peptide species can be discounted as the source of the spectrophotometrically detected complexation reactions observed in this study. If hydrogen bonding between the basic form of lutidine and the terminal amine was responsible for the observed spectral shifts, a similar effect would be expected to occur between lutidine and $Co(en)_3^{3+}$.[26] No such effect is detectable. Hydrogen bonding to an axial solvent molecule would result in a shift of the absorption maximum to longer wavelengths, which is in the opposite direction to that observed for the copper–peptide–lutidine species. Finally, if a "stacking" or a "hydrophobic" interaction was occurring, the ethylpyridinium ion ($Etpy^+$) ought to cause a similar spectral shift. $Etpy^+$ ion did not alter the visible absorption spectrum of either the $Cu(H_{-2}G_2a)$ or the $Cu(H_{-2}G_3)^-$ species.

Since an equatorial coordination site is not required for the formation of the ternary lutidine–copper(II)–peptide complexes and since outer-sphere complexes cannot account for the observed spectral changes, these ternary complexes must be at least five-coordinate. The crystal structure of the bis(2-nitroacetophenonato)(2,6-lutidine)copper(II) has recently shown that the Cu^{2+} ion lies in the center of a distorted square pyramid.[1] In this case, however, the lutidine molecule is located in a basal rather than an apical position.

The crystal structures for a variety of copper–peptide complexes show that the Cu atom is frequently five-coordinate and is displaced by 0.1–0.2 Å above the plane formed by the peptide moiety.[27,28] Space-filling models indicate that a distorted square-pyramidal geometry is sterically possible for the ternary copper(II)–peptide–lutidine complexes. Displacement of the copper atom from the mean plane of the peptide moiety would favor ternary complexes of this type. The structure proposed for the $Cu(H_{-3}G_3a)lut^-$ species is given as I. An analogous structure is also proposed for the Cu-

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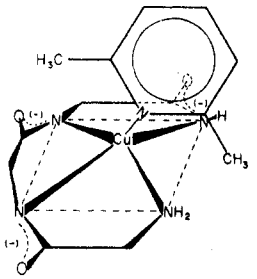


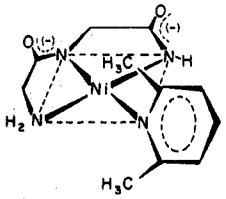
I, proposed structure: $Cu(H_{-3}G_3a)lut^-$

$(H_{-2}G_3)lut^-$ species; however, the $Cu(H_{-2}G_2a)lut$ species may exist with the lutidine in an equatorial position. The large increase in the stability of the pyridine complex with $Cu(H_{-2}G_2a)$ compared to $Cu(H_{-2}G_3)^-$ and $Cu(H_{-3}G_3a)^{2-}$ suggests that an equatorial site may be used for the $Cu(H_{-2}G_2a)py$ species.

Shifts of the visible absorption maximum accompanying the formation of five-coordinate from four-coordinate copper(II) complexes are normally to lower energy (pentaamine effect).[24,29] The lutidine complexes examined here show a reversal of this trend, although the corresponding hydroxide ion and bromide ion complexes do not. The different spectral behavior of the lutidine complexes can be rationalized in terms of metal (d_{xz}, d_{yz}) to ligand (lutidine π^*) π back-bonding. This is consistent with the previous suggestions of π back-bonding in the pyridine[30–32] and lutidine[33,34] complexes of first-row transition-metal ions.

Nickel(II)–Peptide Complexes. Although the stability constants have been determined for a number of substituted pyridines with $Ni(aq)^{2+}$, hydrolysis and the inherent weakness of $Ni(lut)^{2+}$ prevent the determination of the stability of the 2,6-lutidine complex.[7] The equilibrium constants, K_1, for the formation of the $Ni(py)^{2+}$ and $Ni(\alpha\text{-pic})^{2+}$ complexes from $Ni(aq)^{2+}$ are $10^{1.85}$ M^{-1} and less than 10 M^{-1}, respectively.[7b] For $Ni(lut)^{2+}$ K_1 is smaller still. In contrast to this, the equilibrium constants for the formation of the $Ni(H_{-2}G_2a)py$ and $Ni(H_{-2}G_2a)lut$ complexes from $Ni(H_{-2}G_2a)$ are $10^{2.4}$ M^{-1} and $10^{2.05}$ M^{-1} (Table IB). Hence, the presence of an added ligand (triglycine or diglycinamide) not only prevents hydrolysis but also enhances the ability of nickel(II) to form complexes with 2,6-lutidine.

The $Ni(H_{-2}G_2a)lut$ complex is 10 times more stable than the $Ni(H_{-2}G_3)lut^-$ species (Table IB). In both cases the visible absorption maximum occurs at approximately 430 nm (Table II), which is characteristic of many low-spin square-planar nickel(II) deprotonated-peptide complexes. In contrast to the copper(II) species, the $Ni(H_{-2}G_2a)lut$ and $Ni(H_{-2}G_3)lut^-$ complexes appear to be square planar. Although lutidine is a substantially stronger base than is pyridine,[35] the stabilities of the $Ni(H_{-2}G_2a)lut$ and $Ni(H_{-2}G_2a)py$ complexes are not greatly different, indicating that the steric effect of the lutidine methyl groups is such that relatively weak axial interactions (i.e., solvation) are inhibited in the $Ni(H_{-2}G_2a)lut$ species. This situation is more pronounced in the case of copper(II). While the $Ni(H_{-2}G_2a)py$ complex is twice as stable as the $Ni(H_{-2}G_2a)lut$ species, the $Cu(H_{-2}G_2a)py$ species is 20 times more stable than its lutidine analogue. The proposed structure of the $Ni(H_{-2}G_2a)lut$ species is given as II. An analogous



II, proposed structure: $Ni(H_{-2}G_2a)lut$

structure has been reported for the potassium salt of trichloro(2,6-lutidine)platinate(II).[36]

Acid Decomposition Reactions. The rates of disappearance of the $Ni(H_{-2}L)lut$ species, where L is G_2a or G_3^-, were studied from $-\log [H^+] = 7$ to 0.4. The value of the observed pseudo-first-order rate constant, k_{obsd}, was independent of the buffer used, indicating that the acid dissociation reactions of both $Ni(H_{-2}H_2a)lut$ and $Ni(H_{-2}G_3)lut^-$ are specific-acid catalyzed.

For $Ni(H_{-2}G_2a)lut$, the observed acid dissociation rate constant is independent of the acidity above $-\log [H^+] = 5$ and displays a first-order $[H^+]$ dependence below $-\log [H^+] = 4$ (Figure 1, curve A). The absence of general-acid catalysis suggests that an outside-protonated species forms prior to the rate-determining nickel–peptide bond cleavage as is also the case for the reactions of $Ni(H_{-3}G_4a)^-$ [21] and of $Ni(H_{-3}G_4)^{2-}$ and $Ni(H_{-3}G_3a)$ with acid.[15]

The mechanism proposed for the reaction of $Ni(H_{-2}G_2a)lut$ with acid is given (for L = G_2a) in eq 3–5. The observed

$$Ni(H_{-2}L)lut \xrightarrow{k_{0d}} \text{products} \qquad (3)$$

$$Ni(H_{-2}L)lut + H^+ \underset{}{\overset{K_{1H}}{\rightleftharpoons}} Ni(H_{-2}L)lut{\cdot}H \qquad (4)$$

$$Ni(H_{-2}L)lut{\cdot}H \xrightarrow{k_{1d}} \text{products} \qquad (5)$$

first-order rate constant is defined by eq 6. The values determined for k_{0d} and $K_{1H}k_{1d}$ are $(5.6 \pm 0.1) \times 10^{-2}$ s^{-1} and 800 ± 5 M^{-1} s^{-1}, respectively.

$$k_{obsd} = (k_{0d} + K_{1H}k_{1d}[H^+])/(1 + K_{1H}[H^+]) \qquad (6)$$

The presence of the free carboxylate group in the $Ni(H_{-2}G_3)lut^-$ species results in a slightly more complex acid-dissociation behavior (Figure 1, curve B). For $Ni(H_{-2}G_3)lut^-$, the value of the observed acid-dissociation rate constant goes through a minimum at $-\log [H^+] = 3$. This behavior is indicative of the formation, in appreciable concentrations, of an outside-protonated species, $Ni(H_{-2}G_3)lut{\cdot}H$. Above $-\log [H^+] = 4$, the reactant is $Ni(H_{-2}G_3)lut^-$, while, below $-\log [H^+] = 3$, the reactant is $Ni(H_{-2}G_3)lut{\cdot}H$.

As was the case for the $Ni(H_{-2}G_2a)lut$ complex, k_{obsd} for the reaction of $Ni(H_{-2}G_3)lut^-$ with acid is independent of the buffer used. The proposed reaction mechanism is given by eq 3–5 and eq 7 and 8, where L is the triglycinate ion (G_3^-). In terms of this mechanism, k_{obsd} is given by eq 9. Resolution

$$Ni(H_{-2}L)lut{\cdot}H + H^+ \underset{}{\overset{K_{2H}}{\rightleftharpoons}} Ni(H_{-2}L)lut{\cdot}2H \qquad (7)$$

$$Ni(H_{-2}L)lut{\cdot}2H \xrightarrow{k_{2d}} \text{products} \qquad (8)$$

$$k_{obsd} = \frac{k_{0d} + K_{1H}[H^+](k_{1d} + K_{2H}k_{2d}[H^+])}{1 + K_{1H}[H^+](1 + K_{2H}[H^+])} \qquad (9)$$

of the data yields values of 3.5 ± 0.1 s^{-1}, 0.8 ± 0.1 s^{-1}, and 544 ± 8 M^{-1} s^{-1} for k_{0d}, k_{1d}, and $K_{2H}k_{2d}$, respectively. The first outside-protonation constant, K_{1H}, is $10^{3.6}$ M^{-1}, while the

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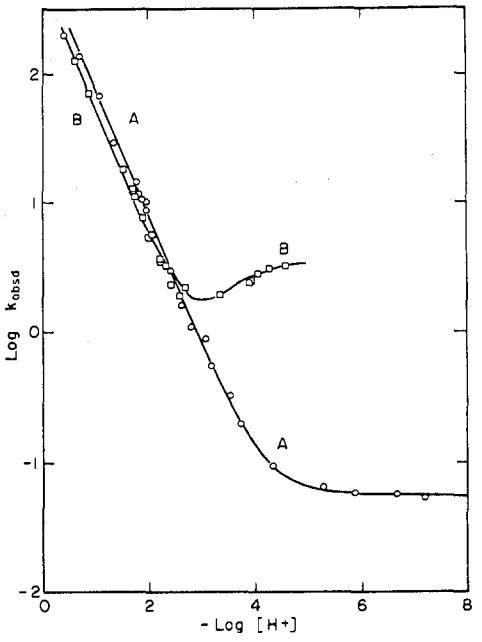

Figure 1. Effect of acidity on the dissociation rate of the $Ni(H_{-2}L)lut$ complexes: (A) $Ni(H_{-2}G_2a)lut$; (B) $Ni(H_{-2}G_3)lut^-$ (μ = 1.0 ($NaClO_4$), 25.0 °C, λ 430 nm).

second outside-protonation constant, K_{2H}, could not be determined for the same reasons that K_{1H} could not be evaluated for the $Ni(H_{-2}G_2a)lut$ complex.

The value of log K_{1H} (3.6) for $Ni(H_{-2}G_3)lut^-$ is similar to the protonation constant ($10^{3.4}$)[37] of the carboxylate group of the free triglycinate ligand. It is larger than the log K_{1H} values observed for $Ni(H_{-3}G_3a)$ (2.3)[15] and $Ni(H_{-3}G_4a)$ (2.4)[21] but smaller than the value of 4.2 found for the $Ni(H_{-3}G_4)^{2-}$ complex. Intramolecular hydrogen bonding between the deprotonated peptide oxygen and the free carboxylate group of the tetraglycinate ligand (G_4^-) has been shown to be the cause of the increased outside-protonation constant for $Ni(H_{-3}G_4)^{2-}$.[15] Similar effects have also been observed for several copper(II)–peptide complexes.[38] In the absence of metal ions, the carboxylate group of polypeptide ligands can exist in either a cis or a trans orientation with respect to the peptide oxygen of the amino acid residue adjacent to the C-terminal end. The carboxylate protonation constant for the cis configuration, which is capable of forming an intramolecular hydrogen bond, is 0.3–0.5 log unit larger than that for the trans conformation, which cannot form an intramolecular hydrogen bond in the protonated form.[39] Thus, intramolecular hydrogen bonding between a protonated carboxylate group and a peptide oxygen occurs even if the peptide is not coordinated to a metal ion. It is, therefore, reasonable to expect internal hydrogen bonding to play a significant role in the formation of the outside-protonated $Ni(H_{-3}G_3)lut{\cdot}H$ species (Figure 2B).

Participation of the triglycinate carboxylate group in a hydrogen bond is also consistent with the observation that the first-order dissociation rate constant for the $Ni(H_{-2}G_3)lut{\cdot}H$ species (k_{1d} = 0.8 s^{-1}) is smaller than that for the $Ni(H_{-2}G_3)lut^-$ complex (k_{0d} = 3.5 s^{-1}). The hydrogen-bonded carboxylate group of $Ni(H_{-2}G_3)lut{\cdot}H$ (Figure 2B) cannot assist the dissociation reaction of the complex, while the free carboxylate of $Ni(H_{-2}G_3)lut^-$ (Figure 2A) can assist the dissociation of the lutidine molecule by undergoing an internal associative reaction to form $Ni(H_{-2}G_3)^-$ (Figure 2D). Although 0.10 M acetate ion does not affect the dissociation rate, the carboxylate group of the coordinated triglycinate ion does because of the kinetic chelate effect.[40,41] Ligand-exchange reactions of $Ni(H_{-2}G_3)^-$,[17] $Cu(H_{-2}G_3)^-$,[19] and $Ni(CN)_4^{2-}$ [41] are substantially more rapid when the exchanging ligand is a polydentate amine or an aminocarboxylate rather than ammonia or an acetate ion.

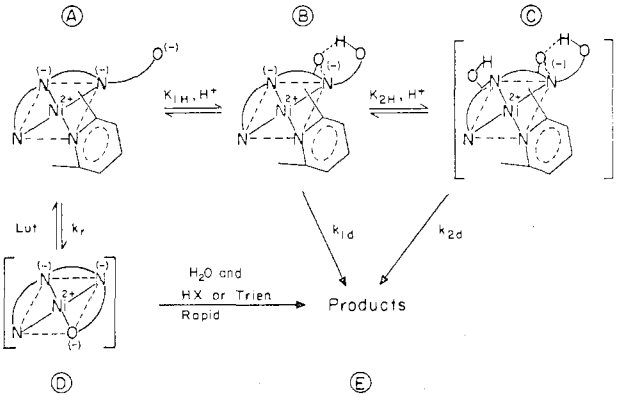

Figure 2. Reaction scheme proposed for the acid dissociation of $Ni(H_{-2}G_3)lut^-$.

Once $Ni(H_{-2}G_3)^-$ is formed (species D in the mechanism given in Figure 2), it reacts rapidly with acid. The specific-acid rate is much faster[42] than that of the $Ni(H_{-2}G_3)lut^-$ complex, and the $Ni(H_{-2}G_3)^-$ reaction is general acid catalyzed.[15] The effect of lutidine coordination is to reduce the H^+ attack on $Ni(H_{-2}G_3)^-$ by a factor of 17 despite the fact that the carboxylate group is no longer coordinated. Furthermore, the reactivity of $Ni(H_{-2}G_2a)lut$ with H^+ is a factor of 63 less than that of $Ni(H_{-2}G_3)^-$.

The ability of the methyl groups of 2,6-lutidine to sterically hinder the axial coordination positions of the nickel ion in the $Ni(H_{-2}G_2a)lut$ complex is very important. At $-\log [H^+]$ = 5.5, $Ni(H_{-2}G_2a)lut$ dissociates with a first-order rate constant, k_{obsd}, of 0.06 s^{-1} and is independent of the buffer. At the same pH for the $Ni(H_{-2}G_2a)py$ complex, k_{obsd} is 30.2 s^{-1} when 0.05 M acetic acid (pK_a = 4.5)[43] is used and is 2.85 s^{-1} when 0.05 M MES (pK_a = 6.27)[44,45] is used. Thus, the ability of the lutidine methyl groups to limit the accessibility of the axial coordination sites in the $Ni(H_{-2}G_2a)lut$ complex causes its dissociation reaction with acid to be specific acid catalyzed, while the $Ni(H_{-2}G_2a)py$ complex displays very marked general-acid catalysis.

The general mechanism previously proposed for the transfer of protons to deprotonated nickel(II)–peptide complexes accounts for four types of kinetic behavior.[15] Whether or not general-acid catalysis is observed depends to a large degree on the ligand field stabilization of the nickel–peptide complex, and, therefore, it depends on the stability of the complex. In previous examples the more stable the complex, the more likely that specific-acid catalysis and slower dissociation rates would be observed. In the present case, however, the more stable $Ni(H_{-2}G_2a)py$ complex still shows general-acid catalysis, while the less stable $Ni(H_{-2}G_2a)lut$ complex is specific acid catalyzed. This emphasizes the importance of axial solvation. That is, the transition-state complex of the general-acid-catalyzed reaction pathway, which involves proton transfer directly to

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the peptide nitrogen, is more solvated than is the transition-state complex of the specific-acid-catalyzed reaction pathway, which involves protonation of a peptide oxygen prior to the dissociative cleavage of the metal–N(peptide) bond. The solvent accessibility of the axial coordination sites is, however, still of importance in the specific-acid-catalyzed reaction. While the cyanide complex of nickel diglycinamide is 10^5 times more stable[46,47] than the lutidine complex, $K_{1H}k_{1d}$ is 5 times larger for the $Ni(H_{-2}G_2a)CN^-$ complex.[48]

The first outside-protonation constant for $Ni(H_{-2}G_2a)$lut (K_{1H}) and the second outside-protonation constant of $Ni(H_{-2}G_3)lut^-$ (K_{2H}) could not be determined for one of two reasons. Either (1) the value of these protonation constants is less than 2 M^{-1} or (2) successive protonations mask the effect. The first possibility requires that the added steric hindrance and reduced solvation resulting from the presence of the 2,6-lutidine in the $Ni(H_{-2}G_2a)$lut and $Ni(H_{-2}G_3)lut^-$ complexes dramatically decrease the value of the outside-protonation constants. For a number of palladium(II)–,[49] nickel(II)–,[15,21] and copper(II)–peptide[38] complexes the value of K_{1H} is in the range of 10^2 to 10^3 M^{-1}. On the other hand the K_{1H} value for $Ni(H_{-2}G_3)^-$ is less than 10^2 M^{-1},[42] and the first and second outside-protonation constants for the bis(diglycinato)cobalt(III) anion, $Co(H_{-1}G_2)_2^-$, are $10^{1.46}$ and $10^{0.1}$, respectively.[50] Therefore, the metal environment is important in determining the ease of protonation of the peptide oxygens. Although a protonation constant of less than 2 M^{-1} is surprising, it is possible that blocking the axial solvent coordination greatly lowers the value in the absence of internal hydrogen bonding.

Normally, the first-order $[H^+]$ dependence changes to a zero-order dependence when an outside-protonated species is found in appreciable concentrations. However, the second possibility is that successive outside protonations are accompanied by compensating increases in reactivity such that deviation from a first-order $[H^+]$ dependence is not detected. A recent investigation[21] of the acid dissociation of the deprotonated nickel(II)–tetraglycinamide complex, $Ni(H_{-3}G_4a)^-$, has shown that although three protons successively alter the reactivity of the $Ni(H_{-3}G_4a)^-$ complex, the changes in the observed rate constant, k_{obsd}, are not as dramatic as might be expected. If a similar situation occurs for the reactions of $Ni(H_{-2}G_2a)$lut and $Ni(H_{-2}G_3)lut^-$ with acid, it is possible that the outside-protonation constants have not been observed.

Reactions with Triethylenetetramine. Triethylenetetramine (trien) behaves as a strong nucleophile in its reactions with a variety of metal–peptide complexes.[17] The typical reaction behavior leads, at constant pH, to an observed pseudo-first-order rate constant of the form: $k_{obsd} = k_r + k_{trien}[trien]_T$. This is also the case for the reaction of trien with the $Ni(H_{-2}L)Z$ ternary complexes.

In the case of the $Ni(H_{-2}G_2a)$lut species (μ = 1.0 ($NaClO_4$); $-\log [H^+] = 10.5$), values of 0.059 s^{-1} and 0.28 M^{-1} s^{-1} are obtained for k_r and k_{trien}, respectively. At an ionic strength of 0.10 ($NaClO_4$) and $-\log [H^+] = 10.37$, k_r and k_{trien} are 0.115 s^{-1} and 0.19 M^{-1} s^{-1}. For the $Ni(H_{-2}G_2a)$-α-pic complex k_{trien} is 1.6×10^3 M^{-1} s^{-1} (μ = 1.0 ($NaClO_4$); $-\log [H^+] = 10.8$; $(0.45–1.8) \times 10^{-2}$ M trien) and for the $Ni(H_{-2}G_2a)$py complex k_{trien} is 1.0×10^4 M^{-1} s^{-1} (μ = 1.0 ($NaClO_4$); $-\log [H^+] = 10.5$; $(4.5–9.0) \times 10^{-3}$ M trien). Only the dissociative pathway, k_r = 3.5 s^{-1}, is observed for the reaction of the $Ni(H_{-2}G_3)lut^-$ complex with trien ($-\log [H^+] = 10.7$; $(0.645–6.45) \times 10^{-2}$ M trien).

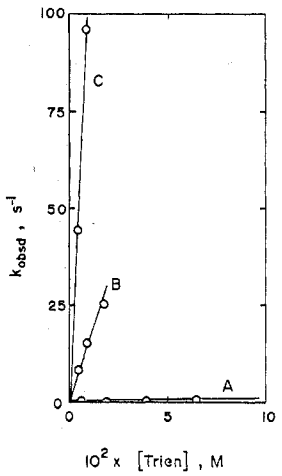

Figure 3. Comparison of the susceptibility of the ternary $Ni(H_{-2}G_2a)Z$ complexes to nucleophilic attack by trien, where Z is (A) lut, (B) α-pic, and (C) py.

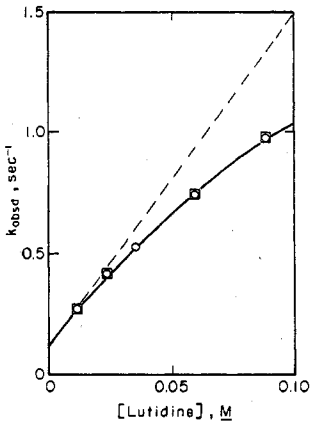

Figure 4. Reversible formation of the $Ni(H_{-2}G_2a)$lut complex at μ = 0.10 ($NaClO_4$), 25.0 °C, and λ 430 nm: (○) $-\log [H^+] = 9.67$; (□) $-\log [H^+] = 10.17$.

Figure 3 shows the effect of steric blocking on the susceptibility of the $Ni(H_{-2}G_2a)Z$ complexes to nucleophilic attack by trien. The blocking of one axial position (α-pic vs. py) results in a sixfold decrease in reactivity. Blocking both axial sites (lut vs. α-pic) reduces the rate constant of nucleophilic attack by trien by an additional factor of 5000.

Reversible Formation of $Ni(H_{-2}G_2a)$lut. When excess lutidine is added to $Ni(H_{-2}G_2a)$ under conditions where there is only partial formation of $Ni(H_{-2}G_2a)$lut (i.e., reversible formation as shown in eq 10), the expected pseudo-first-order

$$Ni(H_{-2}G_2a) + lut \underset{k_r}{\overset{k_f}{\rightleftharpoons}} Ni(H_{-2}G_2a)lut \qquad (10)$$

rate constant is $k_{obsd} = k_f[lut] + k_r$. However, as the plot of k_{obsd} against lutidine in Figure 4 shows, this simple dependence is not found. At low lutidine concentrations the ratio of the slope to intercept (k_f/k_r) is 112 M^{-1}, in agreement with the equilibrium studies (Table I), but at higher lutidine concentrations the k_f value appears to decrease. Furthermore, the observed rate constant has no pH dependence at pH 9.6–10.2, which is unexpected since the previously reported[14] pK_a values are 8.52, 9.35, and 10.53 for the formation of $Ni(H_{-1}G_2a)^+$, $Ni(H_{-2}G_2a)$, and $Ni(H_{-2}G_2a)OH^-$, respectively, and, therefore, the species reacting with lutidine would be expected to change with pH.

When $Ni(H_{-2}G_2a)OH^-$ solutions, which are initially at pH 10.5–11, are subjected to 2:1 dilutions, only a very slow ($t_{1/2} > 10^3$ s) equilibration reaction is observed. Similarly, the

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Table III. Summary of Kinetically Evaluated Constants[a]

constant	Ni($H_{-2}G_2a$)lut	Ni($H_{-2}G_3$)lut$^-$	Ni($H_{-2}G_3$)$^-$ [b]
k_{od} (k_r or k_{-2}), s^{-1}	5.6×10^{-2} [c]	3.5	5×10^{-2} [d]
K_{1H}, M^{-1}	<5	$10^{3.6}$	$<10^2$ [e]
k_{1d}, s^{-1}	$>1.6 \times 10^2$	0.8	
$K_{1H}k_{1d}$, M^{-1} s^{-1}	8.0×10^2	3×10^3	5×10^4 [f]
K_{2H}, M^{-1}		<5	
k_{2d}, s^{-1}		$>1 \times 10^2$	
$K_{2H}k_{2d}$, M^{-1} s^{-1}		5.4×10^2	
k_2, s^{-1}	3.3	...	...
K_1, M^{-1}	4.1	...	...
k_{trien}, M^{-1} s^{-1}	0.28	<2	1.7×10^4 [g]
k_{trien}, M^{-1} s^{-1}	1×10^4 (for Ni($H_{-2}G_2a$)py)		
k_{trien}, M^{-1} s^{-1}	2×10^3 (for Ni($H_{-2}G_2a$)-α-pic)		

[a] $\mu = 1.0$ ($NaClO_4$); 25.0 °C. [b] $\mu = 0.10$ ($NaClO_4$). [c] k_{od} (k_r or k_{-2}) = 0.12 s^{-1} at $\mu = 0.10$. [d] Reference 8. [e] Reference 42. [f] In addition, these reactions are general acid catalyzed, and at high acidity the $[H^+]^2$ term is observed.[42] [g] Reference 17.

pseudo-first-order rate constant for the reaction of Ni($H_{-2}G_2a$)OH^- with CyDTA (3.9×10^{-3} M; pH 11, $\mu = 1.0$ ($NaClO_4$)) is 2.5×10^{-3} s^{-1}. Both of these results indicate that at high pH the Ni($H_{-2}G_2a$)OH^- dissociation reaction is slow.

Potentiometric titrations have shown that the only yellow species is Ni($H_{-2}G_2a$)OH^-, and it was postulated[14] that the protonation of this species results in the formation of Ni($H_{-2}G_2a$)H_2O. However, the reaction rate for this process (eq 11) would be expected to be very rapid, since it involves H^+

$$Ni(H_{-2}G_2a)OH^- + H_2O \rightleftarrows Ni(H_{-2}G_2a)H_2O + OH^- \quad (11)$$

transfer to the oxygen of a coordinated hydroxide ion. The square planar to octahedral conversion which occurs in the course of reaction 11 is also expected to be rapid.[51] The above experiments show that the actual reaction is not rapid, and hence we postulate that the thermodynamically stable species is Ni($H_{-1}G_2a$)OH rather than Ni($H_{-2}G_2a$)H_2O. This proposal requires the assignment of the first and third potentiometrically determined pK_a values[14] of 8.52 and 10.53 to the deprotonation of the peptide nitrogens and the second pK_a (9.35) to the hydrolysis of a coordinated water molecule. Although the protonation constants, log K_H, for most hydroxynickel species are in the range of 10–11, a value of 9.3 has been reported[52] for the reaction: $Ni(OH)ATP^{3-} + H^+ \rightleftarrows NiATP^{2-}$

The necessity of making and breaking nickel–N(peptide) bonds accounts for the sluggishness of the CyDTA reaction and for the slow equilibration observed in the dilution experiments. Also, the behavior of the lutidine reaction can be understood in terms of a reaction mechanism (eq 12 and 13)

$$Ni(H_{-1}G_2a)OH + lut \overset{K_1}{\rightleftarrows} Ni(H_{-1}G_2a)(OH)lut \quad (12)$$

$$Ni(H_{-1}G_2a)(OH)lut \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} Ni(H_{-2}G_2a)lut \quad (13)$$

in which nickel(II)–N(peptide) bond formation becomes rate limiting at high lutidine concentrations. The resolved values of K_1, k_2, and k_{-2} are 4.06 ± 0.05 M^{-1}, 3.3 ± 0.6 s^{-1}, and 0.12 ± 0.1 s^{-1}, respectively, at $\mu = 0.1$ M ($NaClO_4$).

Since we see no kinetic evidence for appreciable concentrations of [Ni($H_{-2}G_2a$)H_2O], the equilibrium constant, K = 112 M^{-1}, for the addition of lutidine to nickel diglycinamide is defined by $K = [Ni(H_{-2}G_2a)lut]/[Ni(H_{-1}G_2a)OH][lut]$, while the value of K' ($K' = [Ni(H_{-2}G_2a)lut]/[Ni(H_{-2}G_2a)][lut]$) is at least an order of magnitude larger.

Summary of Reaction Pathways. The kinetic parameters evaluated for the reactions of Ni($H_{-2}G_2a$)lut and Ni($H_{-2}G_3$)lut$^-$ are summarized in Table III along with those of Ni($H_{-2}G_3$)$^-$ for comparison. The ternary nickel complexes display a number of common features in their reaction behavior. The axial coordination sites of both complexes are sterically blocked by the lutidine methyl groups. As a consequence, the effectiveness of trien as a nucleophile toward these Ni(H_{-2}L)lut complexes is greatly diminished in comparison with that observed for the unhindered Ni($H_{-2}G_2a$)py complex or for Ni($H_{-2}G_3$)$^-$. Not only is specific-acid catalysis observed in each case but also the first outside-protonation constants (K_{1H}) are found to be smaller than is the case for metal–peptide complexes in which the axial sites are not blocked.

The effect of the carboxylate group of the triglycine molecule is seen in both the kinetic and the equilibrium behavior of its nickel complexes. The species formed by the addition of 2 equiv of base (to a 1:1 Ni–ligand mixture) in excess of that required to consume all ligand ionizable protons is dramatically different for the nickel diglycinamide and triglycine complexes. When triglycine is the ligand, a yellow, diamagnetic, square-planar nickel complex, Ni($H_{-2}G_3$)$^-$, is formed. In this complex (Figure 3, species D), the metal is ligated by an amine, two deprotonated peptide nitrogens, and a carboxylate oxygen. When diglycinamide is the ligand, an octahedral complex, Ni($H_{-1}G_2a$)OH, in which the nonsolvent donor groups are an amine, one deprotonated peptide nitrogen, and a hydroxide ion, is formed. The effect of the carboxylate group is also seen in the kinetic behavior of the lutidine-containing ternary complexes. The ability of the carboxylate group of the triglycine molecule to form an internal hydrogen bond increases the value of the outside-protonation constant for Ni($H_{-2}G_3$)lut$^-$ compared to that of Ni($H_{-2}G_2a$)lut. In addition the carboxylate group's ability to assist the dissociation of the Ni($H_{-2}G_3$)lut$^-$ complex by undergoing an internal substitution reaction is inhibited by the formation of the hydrogen bond. As a result, a minimum is observed in the plot (Figure 1) of log k_{obsd} vs. –log $[H^+]$ at –log $[H^+]$ = 3.

Conclusions

(1) Lutidine forms ternary complexes with both copper(II) and nickel(II) peptides. Low-spin, square-planar nickel(II) complexes are formed, while some of the copper(II) appear to be five-coordinate. This behavior reflects the reduced steric constraints experienced by square-planar, d^8 nickel(II) complexes relative to that of tetragonal, d^9 copper(II) complexes.

(2) The equilibrium constant for the formation of a nickel diglycinamide ternary complex with lutidine is at least 20 times larger than that of its copper(II) analogue.

(3) The ability of 2,6-lutidine to sterically hinder (without coordination) the axial coordination positions of the Ni($H_{-2}G_2a$)lut species causes the acid dissociation reaction to be specific acid rather than general acid catalyzed. This indicates that axial solvation of the transition-state complex is more extensive in the general-acid-catalyzed reaction pathway than in the specific-acid-catalyzed pathway.

(4) The steric hindrance caused by the methyl groups of 2,6-lutidine reduces the susceptibility of the Ni($H_{-2}G_2a$)lut complex to attack by nucleophiles. trien is almost 10^5 times slower to react with Ni($H_{-2}G_2a$)lut than it is with either Ni($H_{-2}G_2a$)py or Ni($H_{-2}G_3$)$^-$.

(5) The thermodynamically stable nickel(II)–diglycinamide species formed by the consumption of 2 equiv of base contains only one nickel(II)–deprotonated peptide nitrogen bond. The other equivalent of base if present as a coordinated hydroxide ion.

Acknowledgment. This investigation was supported by

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Registry No. $Cu(H_{-3}G_3a)lut^-$, 72658-92-5; $Cu(H_{-3}G_3a)(\gamma\text{-pic})^-$, 72658-93-6; $Cu(H_{-3}G_3a)py^-$, 72658-94-7; $Cu(H_{-2}G_3)lut^-$, 72658-95-8; $Cu(H_{-2}G_3)py^-$, 72658-96-9; $Cu(H_{-2}G_3)Br^{2-}$, 72658-97-0; $Cu(H_{-2}G_2a)lut$, 72658-98-1; $Cu(H_{-2}G_2a)py$, 72658-99-2; $Ni(H_{-2}G_3)lut^-$, 72659-00-8; $Ni(H_{-2}G_2a)lut$, 72692-63-8; $Ni(H_{-2}G_2a)py$, 72659-01-9; $Ni(H_{-2}G_2a)(\alpha\text{-pic})$, 72659-02-0; $Ni(H_{-3}G_3a)^-$, 34722-97-9; $Cu(aq)^{2+}$, 14946-74-8; $Co(en)_3^{3+}$, 14878-41-2; trien, 112-24-3; lut, 108-48-5.

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Normal- and High-Pressure Kinetics and Mechanism of the Cis–Trans Isomerization of $PtXR(PEt_3)_2$ Complexes. Evidence for an Initial Solvolysis Step

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It has been previously postulated that the spontaneous cis–trans isomerization of $PtXR(PEt_3)_2$, where R = alkyl or aryl groups and X = halides, occurs through the three-coordinate intermediate $PtR(PEt_3)_2^+$, which is in a steady state during the reaction. High-pressure kinetics have now revealed a ΔV^* value of -12 cm^3 mol^{-1} for the first step in this mechanism. Therefore this step must be considered to be associative. Kinetics at atmospheric pressure show that the intermediate species is not in a steady state, but rather a preequilibrium exists. These data are consistent with an initial solvolysis step and also establish that the rate of solvolysis of *cis*-$PtXR(PEt_3)_2$ is faster than the rate of the subsequent isomerization reaction. A ΔV^* value of $+7.7$ cm^3 mol^{-1} was found for the isomerization reaction. This can be interpreted either as a dissociation of the intermediate *cis*-$PtR(MeOH)(PEt_3)_2^+$ or as an intramolecular rearrangement of this species.

Introduction

The catalyzed cis–trans isomerization of square-planar d^8 complexes is believed to proceed, depending on the conditions, either via pseudorotation of a five-coordinate intermediate or through a consecutive displacement of ligands.[1] The spontaneous cis–trans isomerization in polar solvents most likely follows the latter mechanism with the solvent acting as a catalyst.

Romeo et al.[2] studied the spontaneous isomerization

$$cis\text{-}PtXR(PEt_3)_2 \xrightarrow{MeOH} trans\text{-}PtXR(PEt_3)_2 \qquad (1)$$

(R = alkyl, aryl, or substituted aryl groups and X = Cl or Br), as well as various substitution reactions of these cis complexes:[2]

$$cis\text{-}PtBrR(PEt_3)_2 + Y^- \xrightarrow{MeOH} cis\text{-}PtYR(PEt_3)_2 + Br^- \qquad (2)$$

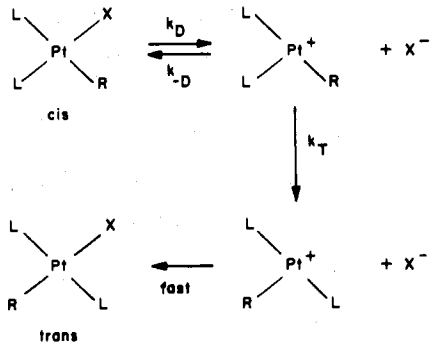
(Y = halide or pseudohalide). Surprisingly they found that, with the exception of R = mesityl, the observed isomerization rate constant for reaction 1 is much smaller than the corresponding solvolysis rate constant for reaction 2. Only in the case of R = mesityl are the rate constants equal. Furthermore, these isomerization reactions were shown[2] to have small absolute ΔS^* values, except for R = mesityl where $\Delta S^* = -92$ J K^{-1} mol^{-1}. The authors therefore postulated a dissociative mechanism for these reactions (Scheme I).

With use of the steady-state approximation, the following rate law was derived:

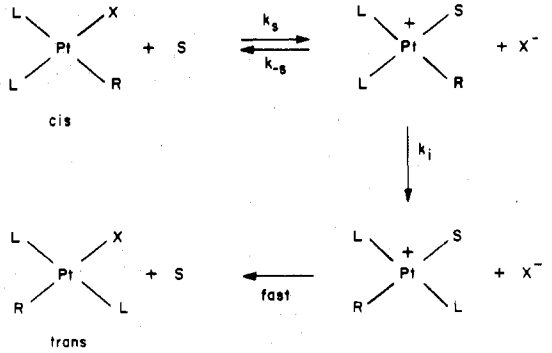
$$k_{obsd} = k_D k_T/(k_{-D}[X^-] + k_T) \qquad (3)$$

As predicted by eq 3, mass law retardation was found when halide ions were introduced into the reaction solution.[2] Since k_{obsd}(reaction 1) $\simeq k_s$(reaction 2) for R = mesityl, it was also proposed that the substitution reactions of the *cis*-PtX(mesityl)$(PEt_3)_2$ complexes follow a dissociative mechanism.

Scheme I



Scheme II



Recently an alternative explanation was proposed involving a rapid preequilibrium rather than the steady-state approximation for reaction 1 (Scheme II), leading to rate law 4.[3]

$$k_{obsd} = k_i K_s/([X^-] + K_s) \qquad (4)$$

With use of the available [Br$^-$] dependence data[2] for reaction 1, k_i and K_s were calculated.[3] As the k_s values are

(1) Louw, W. J. *Inorg. Chem.* **1977**, *16*, 2147 and references therein.
(2) (a) Faraone, G.; Ricevuto, V.; Romeo, R.; Trozzi, M. *J. Chem. Soc. A* **1971**, 1877. (b) Romeo, R.; Miniti, D.; Trozzi, M. *Inorg. Chim. Acta* **1975**, *14*, L15. (c) Romeo, R.; Miniti, D.; Trozzi, M. *Inorg. Chem.* **1976**, *15*, 1134. (d) Romeo, R. *Ibid.* **1978**, *17*, 2040.
(3) van Eldik, R.; Palmer, D. A.; Kelm, H. *Inorg. Chem.* **1979**, *18*, 572.

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