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STERIC EFFECTS ON THE REACTION OF TRIETHYLENETETRAMINE WITH NICKEL(II)- DIPEPTIDEAMIDE-CYANIDE COMPLEXES

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The reaction of triethylenetetramine with a series of deprotonated nickel(II)-dipeptideamide-cyanide complexes has been investigated. The dipeptideamides include glycylglycineamide, glycyl-L-alanineamide, L-alanylglycineamide, and L-alanyl-L-alanineamide. The respective second order rate constants, at pH 10.6 ± 1 , are $14.4 \text{ M}^{-1} \text{ sec}^{-1}$, $4.20 \text{ M}^{-1} \text{ sec}^{-1}$, $4.85 \text{ M}^{-1} \text{ sec}^{-1}$ and $1.27 \text{ M}^{-1} \text{ sec}^{-1}$. The influence of methyl substitution in the amide chain is discussed.

INTRODUCTION

Nickel(II) and copper(II) complexes of short chain oligopeptides and oligopeptide amides have been the subject of many recent reports. The coordination of nickel and copper to these ligands facilitates the ionization of the amide protons and in general the complexes are deprotonated in solutions that have pH values of seven or greater. The ionization of the amide protons results in complexes that are square planar and in the case of nickel spin paired.

Metal transfer from these complexes is characterized by three general reactivity patterns: proton transfer limited,¹⁻³ direct nucleophilic replacement with polyamines⁴⁻⁶ or cyanide,^{7,8} and proton assisted.⁹ The proton transfer limited and the polyamine reactions are subject to steric selectivity in both the substrate complex¹⁰ and the replacing ligand.^{4,5} Cyanide forms stable 1:1 mixed complexes with the tripeptide and dipeptideamide nickel complexes.^{7,8,11} This report presents the reaction kinetics of triethylenetetramine with a series of substituted nickel-dipeptideamide-cyanide complexes.

EXPERIMENTAL SECTION

Reagents

Nickel(II) perchlorate stock solution was prepared from the twice recrystallized salt. The solution was standardized by EDTA titration using murexide indicator. Triethylenetetramine, trien, was recrystallized as the sulfate salt and standardized spectrophotometrically using standard copper(II).

Dipeptideamide solutions were prepared from the chromatographically pure solid (Mann Research Laboratories, New York, New York and Fox Chemical Company, Los Angeles, California). These solutions were used shortly after preparation. Ionic strength was maintained at 0.10 F with sodium perchlorate. Borate buffer was prepared from the recrystallized salt. Sodium cyanide was prepared from the twice recrystallized salt and standardized by the argentimetric method.

The nickel(II) complexes were prepared fresh for each series of kinetic measurements. The procedure for preparation of the complexes involved the mixing of nickel(II) and ligand solutions so there was at least a 100% excess of ligand. The pH of the resulting solution was slowly adjusted to about 10. At this pH the amide protons are ionized. A stoichiometric amount of sodium cyanide was then added. The amide complexes required about an hour to form. Each complex exhibited absorption maxima in the 405–410 nm and 245–247 nm regions. The pH values were converted to $-\log [\text{H}^+]$ by subtracting 0.10. The acidity constants^{1,2} for trien are $\text{pK}_1 = 9.81$ and $\text{pK}_2 = 9.09$.

Kinetic Measurements

The trien replacement reactions were initiated by mixing 0.5–5.0 ml of trien with 50.0 ml of nickel complex. The trien was added with a syringe or by pipet. The pH of both reactants was adjusted to the desired value prior to mixing. Borate buffer was added to the nickel-complex solutions.

The reactions were monitored spectrophotometrically at 245–247 nm using 10.0 cm absorption

cells and a Cary Model 14 Spectrophotometer. Temperature was maintained at 25.0° C. At least a ten-fold excess of trien over nickel total was maintained in each kinetic run. Rate constants were calculated from plots of $\ln(A-A_\infty)$ vs time. With few exceptions each reported rate constant is the average of three kinetic runs.

RESULTS

Pseudo first order kinetics are observed for the reaction of cyanoglycylglycinamidonicelate(II), $\text{NiH}_2\text{glylaCN}^-$, with excess triethylenetetramine. The dependence of the observed pseudo first order rate constant, k_{obs} , on the trien concentration is shown in Figure 1. The zero intercept indicates that the reaction is proceeding through one path, and the observed rate constants are also independent of $\text{NiH}_2\text{glylaCN}^-$ concentration. A rate equation consistent with these data is shown in Eq. 1. Trien_T is the sum of all

$$\text{Rate} = \frac{-d[\text{NiH}_2\text{glylaCN}^-]}{dt} = k_{\text{Trien}_T}[\text{NiH}_2\text{glylaCN}^-][\text{Trien}_T] \quad (1)$$

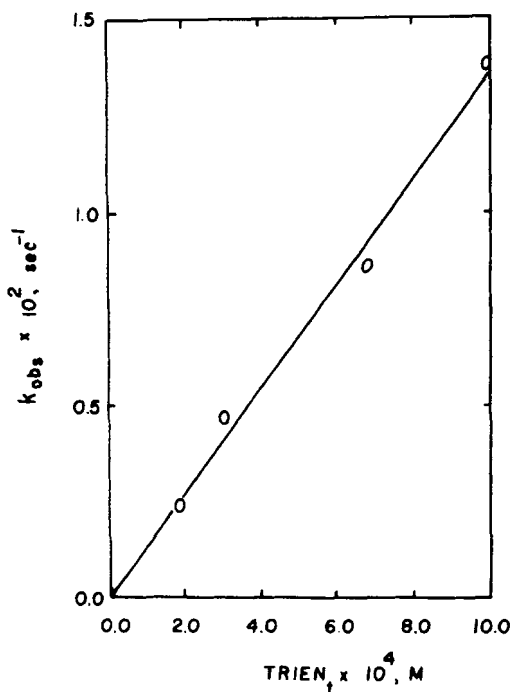


FIGURE 1 Dependence of the pseudo first order rate constants on trien concentration- $\text{NiH}_2\text{GGaCN}^-$ system. $T = 25.0^\circ\text{C}$, $\mu = 0.10 \text{ F NaClO}_4$, $-\log[\text{H}^+] = 10.0$, $[\text{NiH}_2\text{GGaCN}^-] = 9.6 \times 10^{-6} \text{ M}$.

possible trien species, and $k_{\text{obs}} = k_{\text{Trien}_T}[\text{Trien}_T]$.

Hydrogen ion dependence has been studied over the pH range of 9–10.6. In this pH range there are three trien species: trien, Htrien^+ , and $\text{H}_2\text{trien}^{2+}$. All three of these can be reactants, however, the reactivity of $\text{H}_2\text{trien}^{2+}$ is often much less than the other two. For this system its reactivity is too small to be evaluated. Resolution of k_{Trien_T} in Eq. 1 into k_T and k_{HT} can be accomplished in the following manner:

$$k_{\text{Trien}_T} = k_T \alpha_{\text{trien}} + k_{\text{HT}} \alpha_{\text{Htrien}} \quad (2)$$

$$\text{where } \alpha_{\text{trien}} = \frac{[\text{Trien}]}{[\text{Trien}_T]}, \alpha_{\text{Htrien}} = \frac{[\text{Htrien}^+]}{[\text{Trien}_T]}$$

k_T is the rate constant for the reaction with trien and k_{HT} is the rate constant for the reaction with Htrien^+ . Rearrangement and utilization of the trien protonation constants yields

$$k_{\text{Trien}_T} \frac{(K_2 K_1 + K_2 [\text{H}^+] + [\text{H}^+]^2)}{K_2} = k_T K_1 + k_{\text{HT}} [\text{H}^+] \quad (3)$$

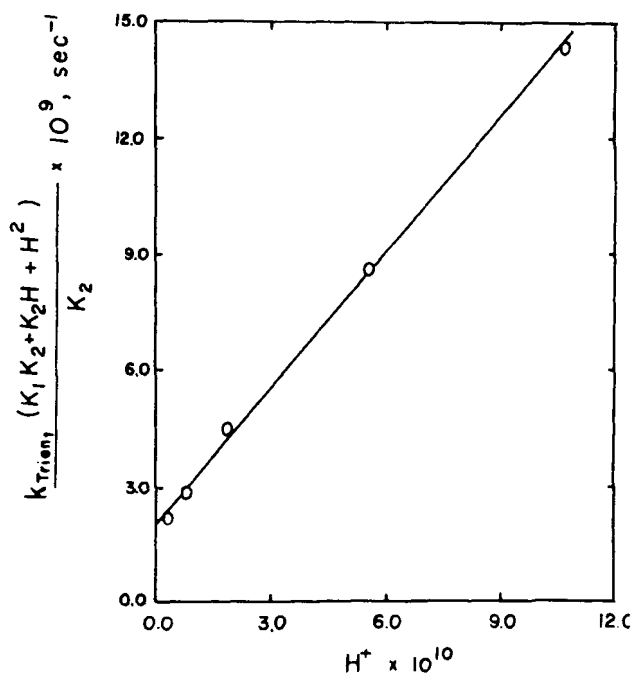


FIGURE 2 Resolution of k_{Trien_T} for $\text{NiH}_2\text{GGaCN}^-$ -Trien system into k_T and k_{HT} , slope = k_{HT} , intercept = $k_T K_1$, $T = 25.0^\circ\text{C}$, $\mu = 0.10 \text{ F NaClO}_4$, see Eq. 3.

A plot of the left side of Eq. 3 versus $[H^+]$ is shown in Figure 2. The slope = k_{HT} and intercept = $k_T K_1$. The line in Figure 2 is the least square fit, $k_T = 13.5 \text{ M}^{-1} \text{ sec}^{-1}$ and $k_{HT} = 11.6 \text{ M}^{-1} \text{ sec}^{-1}$. The resolved rate equation is

$$\text{Rate} = \{k_T[\text{trien}] + k_{HT}[\text{Htrien}^+]\} [\text{NiH}_2\text{glylaCN}^-] \quad (4)$$

The reaction of trien with a variety of substituted dipeptide amides was undertaken in an attempt to evaluate steric requirements of the substrate complex. The rate constants are summarized in Table I. The pH profiles have not been determined for all systems, however, the rate constants reported in Table I are for the same pH range and thus suitable for discussion. The rate data for the dipeptideamide systems is presented in Table II.

DISCUSSION

The reaction of triethylenetetramine with NiH_2 dipeptideamide-cyanide complexes gave no evidence of intermediate species and in all cases the reactions are first order in each reactant. The rate constants increase with pH, indicating that trien is reacting as a nucleophile. If the protonated trien species were acting as acids the pH dependence would be opposite to that observed.

The reaction of trien with $\text{NiH}_2\text{GGaCN}^-$ is considerably slower than the reaction of trien with NiH_2GGA . This is in agreement with the rates of acid independent decomposition of NiH_2GGA and $\text{NiH}_2\text{GGaCN}^-$. In this case NiH_2GGA reacts approximately 4×10^4 times faster.^{13,14} A similar decrease in reactivity is observed as the length of the polypeptide chain is increased. For example the acid independent decomposition rate constants for

NiH_2GGG^- and $\text{NiH}_3\text{GGGG}^{2-}$ are $5.0 \times 10^{-2} \text{ sec}^{-1}$ and $1.6 \times 10^{-5} \text{ sec}^{-1}$, respectively.^{2,3}

In NiH_2GGA and NiH_2GGG^- three of the four square planar coordination sites are occupied by nitrogen donors. The fourth is either water or a carboxylate group. When water is replaced by CN^- to form $\text{NiH}_2\text{GGaCN}^-$ or when the carboxylate group is replaced by another nitrogen donor, as in $\text{NiH}_3\text{GGGG}^{2-}$, there is a shift of one adsorption maxima from approximately 430 nm to 412 nm. This difference represents an increased crystal field stabilization energy of approximately 6 kcal/mole for $\text{NiH}_3\text{GGGG}^{2-}$ and qualitatively accounts for the decreased rate of reaction. Cyanide, being one of the best donors, provides comparable crystal field stabilization when it replaces H_2O in NiH_2GGA and correspondingly accounts for the relative rates of the trien reactions.

The rate constants for the various complexes reveal substantial steric effects due to the dipeptide structure. The difference in substitution rate cannot be attributed to hindered coordination at the axial site since the peptide backbone forces the substituents away from the axial positions. Substitution of a methyl group in either peptide residue results in a comparable reduction in rate. Even though this rate reduction is sizeable, a factor of three, it is smaller than the factor of 85 observed for a similar substitution in CuH_2 -tripeptide complexes.¹⁰ The reduction in rate is attributed to hindered rotation about the C-C and N-C bonds of the peptide backbone which occurs when chelate rings are opened during the rate determining step.

Substitution of methyl groups can alter the basicity of the nitrogen donors, however, comparison of the stability constants for the similar copper(II)-tripeptide complexes^{15,16} reveals no regular trend and thus it is believed that steric interactions during the rotation of chelate rings are the major contributors to the observed rate reduction.

TABLE I
Rate constants for the reaction of Trien with substituted dipeptideamide complexes

Complex	$-\log[H^+]$	k_{Trien} , $\text{M}^{-1} \text{ sec}^{-1}$
$\text{NiH}_2\text{GGaCN}^-$	10.5	14.4
$\text{NiH}_2\text{AGaCN}^-$	10.6	4.85
$\text{NiH}_2\text{GAaCN}^-$	10.7	4.20
$\text{NiH}_2\text{AAaCN}^-$	10.6	1.27

GGa = glycylglycineamide
GAa = glycyl-L-alanineamide
CN⁻ = cyanide ion

AGa = L-alanyl-glycineamide
AAa = L-alanyl-L-alanineamide

TABLE II
Data for reaction of Trien with nickel-dipeptideamide-cyanide complexes
[Complex] = $9.6 \times 10^{-6} M$; T = 25.0°C; $\mu = 0.10 F NaClO_4$

Trien _T 10 ⁴ M	-log[H ⁺]	k _{Trien_T} , M ⁻¹ sec ⁻¹ expt	calc ^c
	NiH ₂ GGaCN ⁻		
1.85	10.00	13.0	11.3
3.50	10.10	13.5	13.2
3.50 ^a	10.15	13.4	12.4
6.85	10.00	12.6	11.9
10.0	10.00	13.7	11.9
3.50	8.97	5.49	5.51
3.50	9.26	8.03	7.88
3.50	9.75	12.0	11.2
3.50	10.08	14.3	12.4
3.50	10.50	14.4	13.1
4.00 ^b	10.36	13.6	13.0
	NiH ₂ AGaCN ⁻		
4.00	10.63	4.78	4.85
7.80	10.65	4.81	4.85
11.5	10.65	4.85	4.85
	NiH ₂ GAaCN ⁻		
4.00	10.73	4.45	4.20
7.80	10.73	4.15	4.20
11.5	10.73	4.17	4.20
	NiH ₂ AAaCN ⁻		
15.6	10.67	1.29	1.27
24.0	10.65	1.28	1.27
30.5	10.65	1.30	1.27

^a [Complex] = 0.48×10^{-6}

^b CN⁻ = 6.0×10^{-5}

^c $k_{\text{Trien}_T}(\text{calc}) = (k_T[\text{trien}] + k_{\text{HT}}[\text{H trien}^+])/[\text{Trien}_T]$

At least one additional reaction pathway is available in the 9–11 pH range.^{11,13} This reaction sequence would involve dissociation of a portion of the amide ligand followed by rapid scavenging of the intermediate by trien. Previous studies indicate that the process is too slow to make a significant contribution to the reaction rates observed in this study. Experimental confirmation is evidenced by the zero intercept in Figure 1.

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