



Kinetics and mechanism of the reactions of Ni(II)-N,N-diglycyl-ethylenediamine and Ni(II)-malonamide-N,N-bis-(2-aminoethyl) with triethylenetetramine
by Jonathan Paul Storvick

A thesis submitted in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE
in CHEMISTRY

Montana State University

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Abstract:

The kinetics and mechanism of the displacement of the ligands Diglycylethylenediamine (DGEN) and Malonamide-N,N'-bis-(2-aminoethyl) (MBAE) from the Nickel(II) complex by Triethylenetetramine (TRIEN) have been studied. The rate expressions for each reaction were deduced, and the rate constants were evaluated for each reactive species.

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Nickel (II)-Malonamide-N,N'-bis-(2-aminoethyl) was found to react with Triethylenetetramine by a proton-assisted nucleophilic mechanism. Rate constants were $k_T = 1.6 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$, $k_{HT} = 6.7 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{H_2T} = 1.7 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. The reaction switched to a general acid catalyzed mechanism at low pH, $k_{H_3T} = 1.3 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

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KINETICS AND MECHANISM OF THE REACTIONS OF Ni(II)-N,N'-DIGLYCYL-
ETHYLENEDIAMINE AND Ni(II)-MALONAMIDE-N,N'BIS-(2-AMINOETHYL)
WITH TRIETHYLENETETRAMINE

by

JONATHAN PAUL STORVICK

A thesis submitted in partial fulfillment
of the requirements for the degree

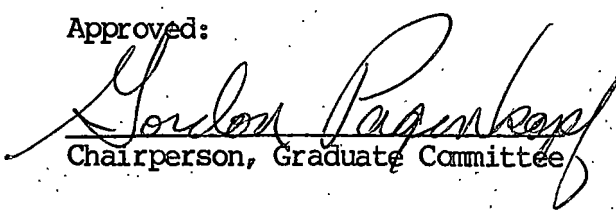
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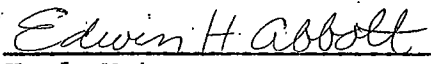
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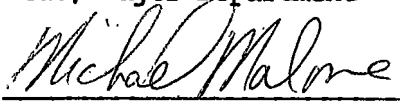
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ABSTRACT

The kinetics and mechanism of the displacement of the ligands Diglycylethylenediamine (DGEN) and Malonamide- N,N' bis-(2-aminoethyl) (MBAE) from the Nickel(II) complex by Triethylenetetramine (TRIE) have been studied. The rate expressions for each reaction were deduced, and the rate constants were evaluated for each reactive species.

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Nickel(II)-Malonamide- N,N' bis-(2-aminoethyl) was found to react with Triethylenetetramine by a proton-assisted nucleophilic mechanism. Rate constants were $k_T = 1.6 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$, $k_{HT} = 6.7 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{H_3O^+ T} = 1.7 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. The reaction switched to a general acid catalyzed mechanism at low pH, $k_{H_3O^+ T} = 1.3 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

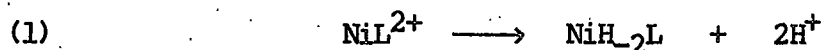
INTRODUCTION

As the literature shows, much interest has been given to the study of metal-polypeptide complexes. Reasons for this lie in the fact that these may be used as models for transport of metals in biological systems (1).

The two metal-ligand complexes which are the focus of this study are Nickel(II)-Diglycylethylenediamine (NiH_2DGEN) and Nickel(II)-Malonamide-N,N'-bis-(2-aminoethyl) (NiH_2MBAE). These complexes are square planar in configuration and have a yellow chromophore associated with them.

Formation of these complexes requires a structural change from octahedral to square planar configuration. This is accomplished by ionization of the peptide hydrogens in basic solution, together with a Ni-O to Ni-N bond rearrangement (2,3). Electronically the Nickel(II) shifts from high spin (paramagnetic) to low spin (diamagnetic) with the increase in field strength of the ligands (4). There is also a shift of the wavelength of maximum absorbance, λ_{max} , in transforming from the blue octahedral complex to the deprotonated yellow square planar complex (5).

The deprotonation reaction is given in Equation 1, where L is the ligand of interest. The structural change for the deprotonation

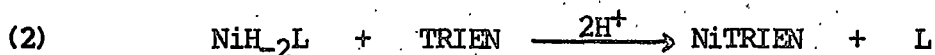


reaction is diagrammed in Figure 1, Copper(II)Triglycine is used as an example (6).

Several metal-ligand complexes have been studied recently and will be used as systems for comparison. These include Copper(II) and Nickel(II) complexes of Triglycine, Tetraglycine, Triglycinamide and Glycylglycylhistidine. The structure of the complexes studied as well as those used for comparison purposes are given in Figure 2.

As you may notice from the structures there are several types of electron donors employed in the formation of the coordinate bonds. Terminal donors include coordinated amine, glycylamide and carboxylate groups. Internally coordinated groups are generally deprotonated amide nitrogens, resulting from the octahedral to square planar conversion.

The reaction studied is given in Equation 2. The reader may



notice that two protons are consumed in the course of the reaction. The transfer of Ni(II) from a deprotonated polypeptide complex to a multidentate ligand environment is accompanied by a change in spin state. The multidentate ligand is coordinated through primary and secondary amine nitrogens to the metal in an octahedral configuration. These types of ligand exchange reactions follow three general mechanisms (7).

The first is a dissociative or replacing ligand independent

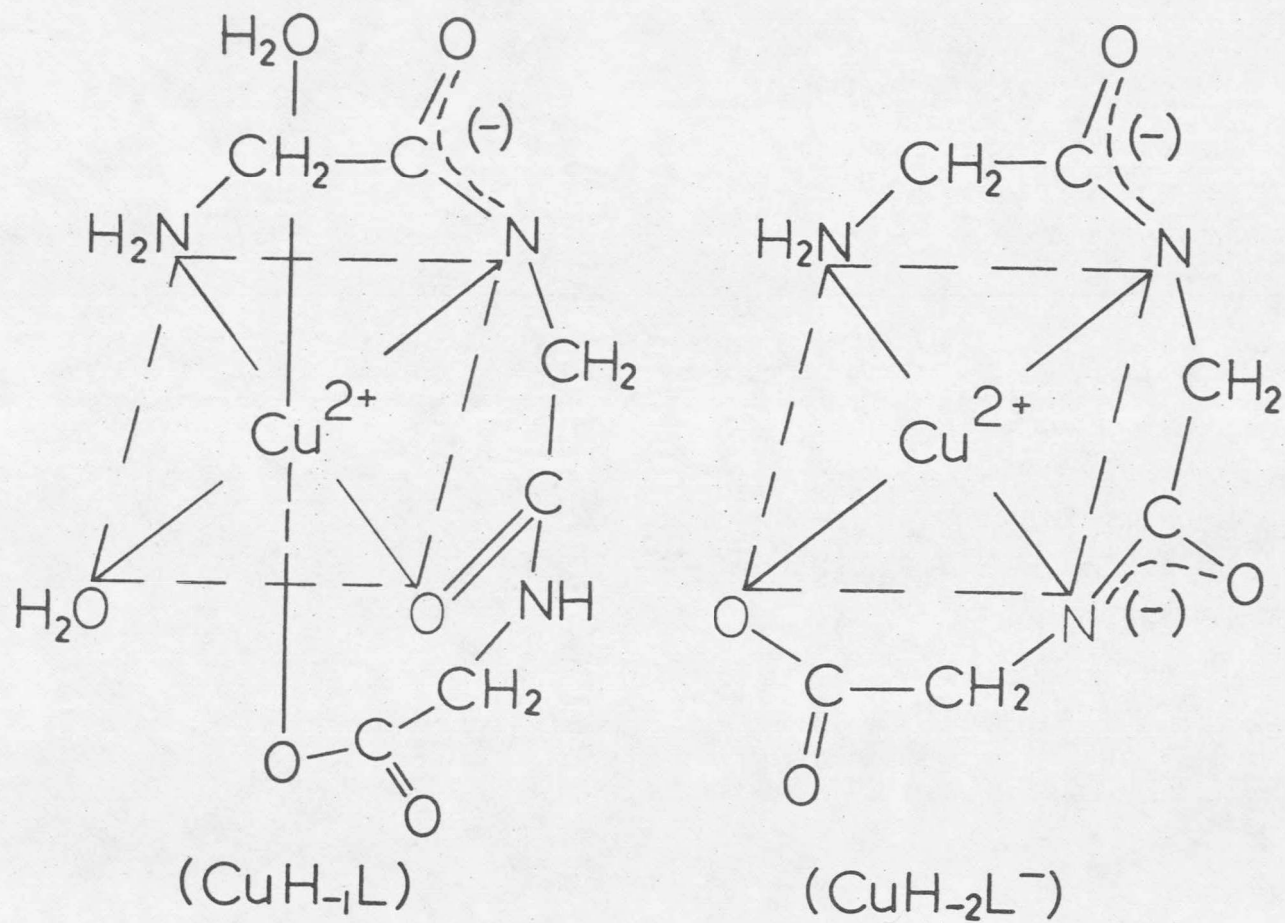
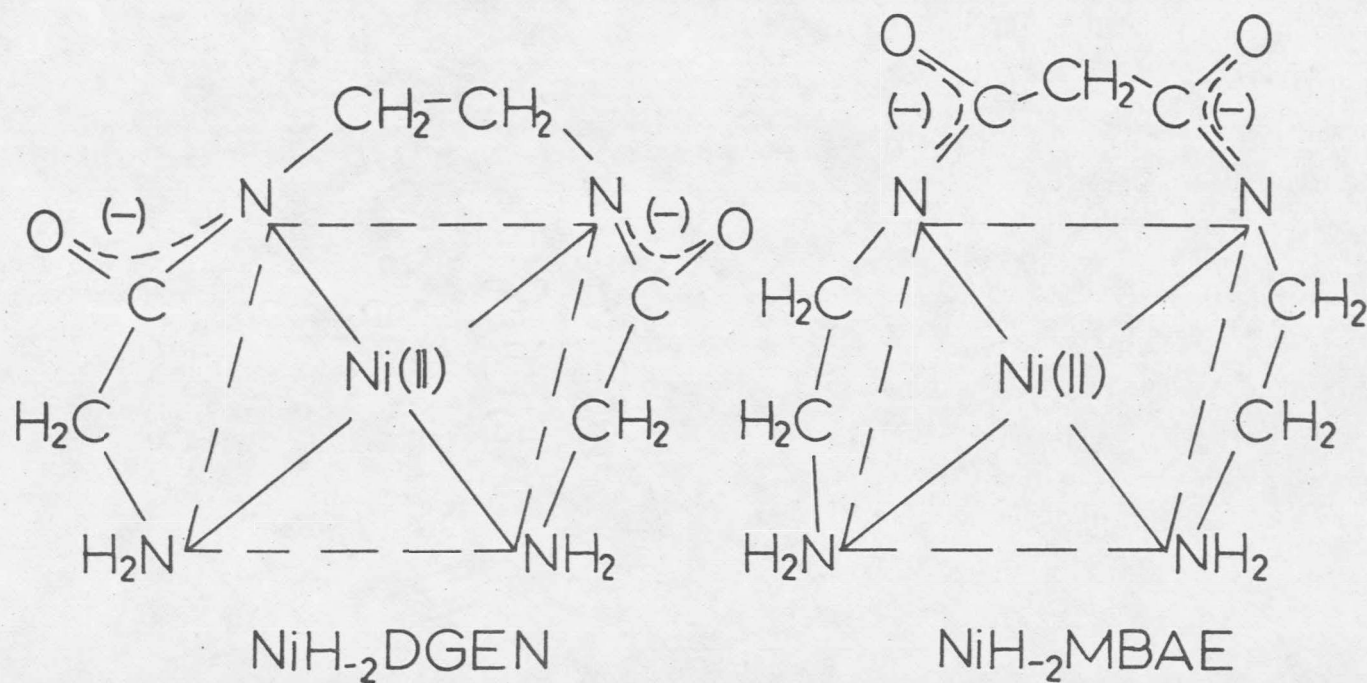


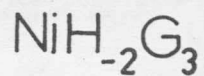
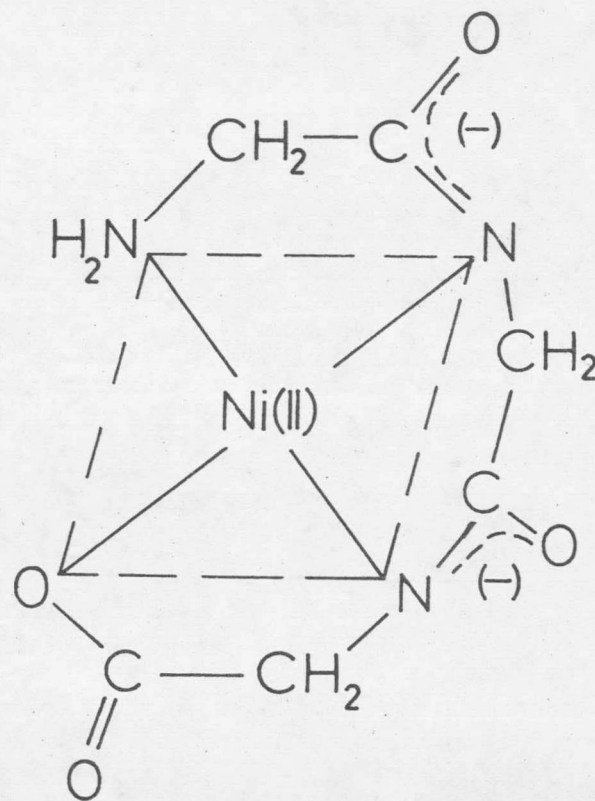
Figure 1. Octahedral-square planar conversion for Copper(II)Triglycine



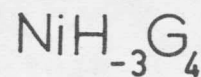
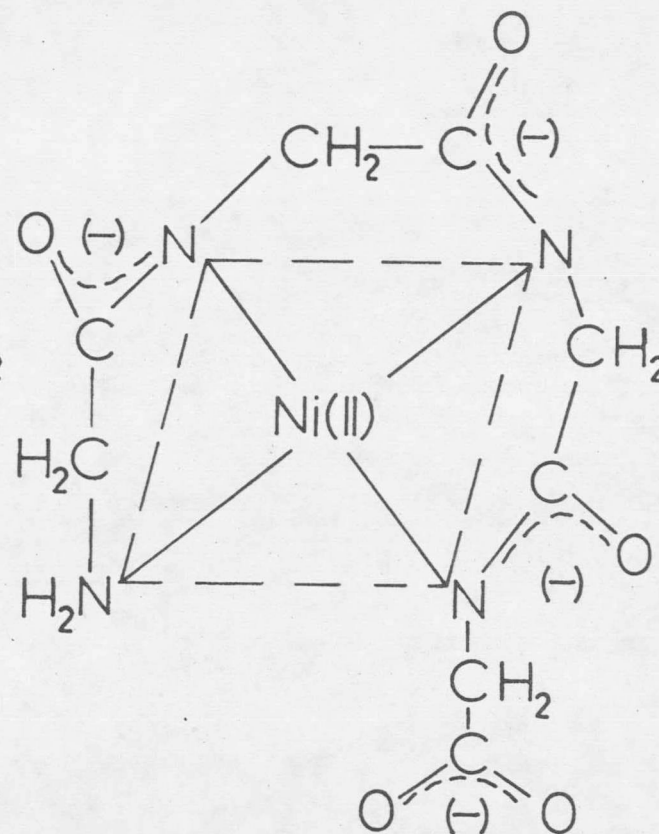
Nickel(II)Diglycylethylenediamine

Nickel(II) -
Malonamide-N-N'bis-(2-aminoethyl)

Figure 2. Structures of several Nickel(II) complexes.

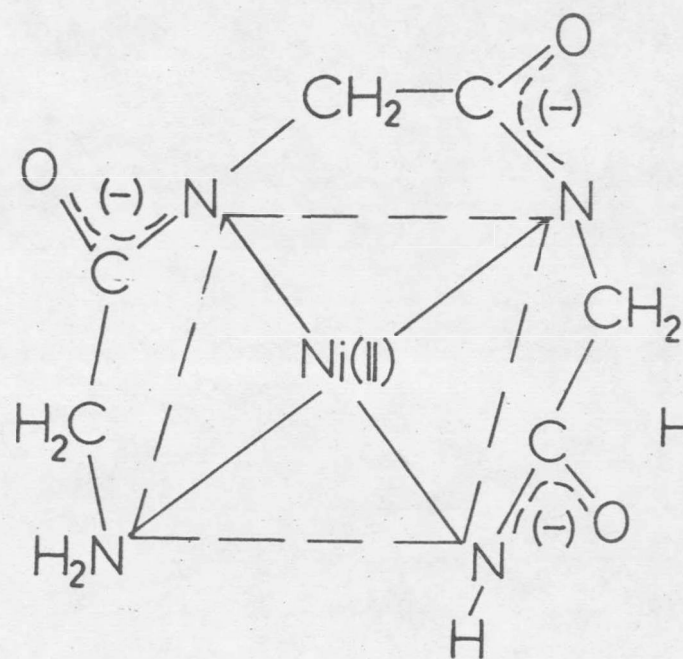


Nickel(II) Triglycine

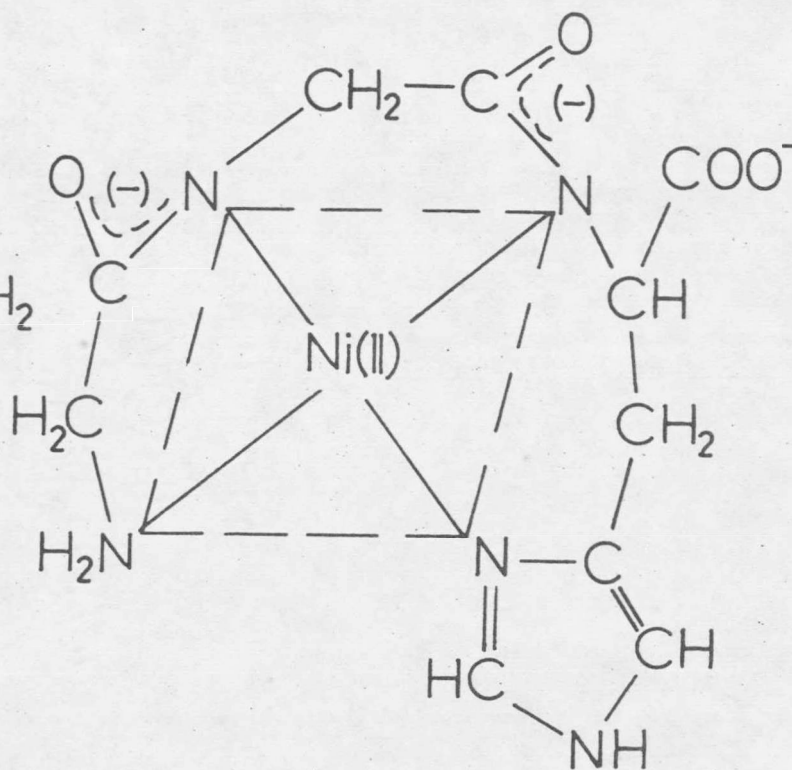


Nickel(II) Tetraglycine

Figure 2. Continued



Nickel(II)-Glycylglycylglycinamide



Nickel(II)-Glycylglycyl-L-histidine

Figure 2. Continued

pathway. The polypeptide unwraps partially from the metal and the replacing ligand rapidly scavenges the binding site(s). The solvent (H_2O) may aid in the dissociation mechanism, or it may be attributable to a molecular rearrangement in the substrate molecule (6). Some examples of dissociative rate constants are $k_d = 5.0 \times 10^{-2} \text{ sec}^{-1}$ for the acid-independent dissociation of Nickel(II)Triglycine (8), and $k_d = 1.8 \times 10^{-3} \text{ s}^{-1}$ for the acid-independent dissociation of Copper(II)Triglycine (6). In the case of Triglycine the dissociation is initiated at a terminal position, this is a typical pattern in dissociation kinetics. These reactions may be catalyzed by coordinating buffer species such as HCO_3^- (9,10).

The second pathway is direct nucleophilic replacement. Here the replacing ligand forms a "weak" out of plane coordination to the square planar complex. A stepwise unwrapping of the peptide from the metal follows, concurrent with formation of coordinate bonds between the nucleophilic replacing ligand and the metal center.

These reactions are characterized by a dependence on the nucleophile concentration, and by an increase in rate with increasing pH (7).

Nitrogen coordination in an equatorial position is necessary for the nucleophilic reactions, as well as the ability of the replacing ligand to form a chelate (11). Multidentate ligands such as Triethylenetetramine and ethylenediaminediacetate are very effective

nucleophiles, whereas mono- and bi-dentate ligands such as NH_3 and ethylenediamine are not as effective.

The existence of a group in the polypeptide complex which is easily displaced from an equatorial site is also important, hence triglycine complexes of Copper(II) and Nickel(II) are susceptible to nucleophilic attack by virtue of their terminal carboxylate coordination. These reactions are subject to steric effects blocking the availability of these equatorial sites (11). Some examples of nucleophilic rate constants are $k_T = 1.1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of TRIEN with Copper(II)Triglycine (11), and $k_{\text{EDTA}} = 3.3 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of EDTA with Nickel(II)-Diglycylethylenediamine (10).

Nucleophilic replacement may also be proton-assisted. These reactions are characterized by an increase in rate with a decrease in pH (from pH ~9 to pH ~6) (7). Here protonated forms of the replacing ligand transfer a proton to a coordinated group of the polypeptide, such as a peptide nitrogen. This intramolecular proton transfer labilizes the group, and renders the complex more susceptible to nucleophilic replacement.

An example of this mechanism is the proton-assisted nucleophilic replacement of Glycylglycylhistidine from the Copper(II) complex by Triethylenetetramine. Here direct nucleophilic replacement is very slow in comparison to Copper(II)Triglycine, as an imidazole

nitrogen is much more difficult to displace than a carboxyl group. The proton assisted pathway is quite favorable however, and a value for the doubly protonated TRIEN replacement has been calculated to be $k_{H_2T} > 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (12).

The third pathway in ligand exchange reactions is rate limited by proton transfer. There are two distinct mechanisms of proton transfer; inside or direct protonation of the peptide nitrogen, and outside protonation of the peptide oxygen (7). These two mechanisms are given in Figure 3 (a,b).

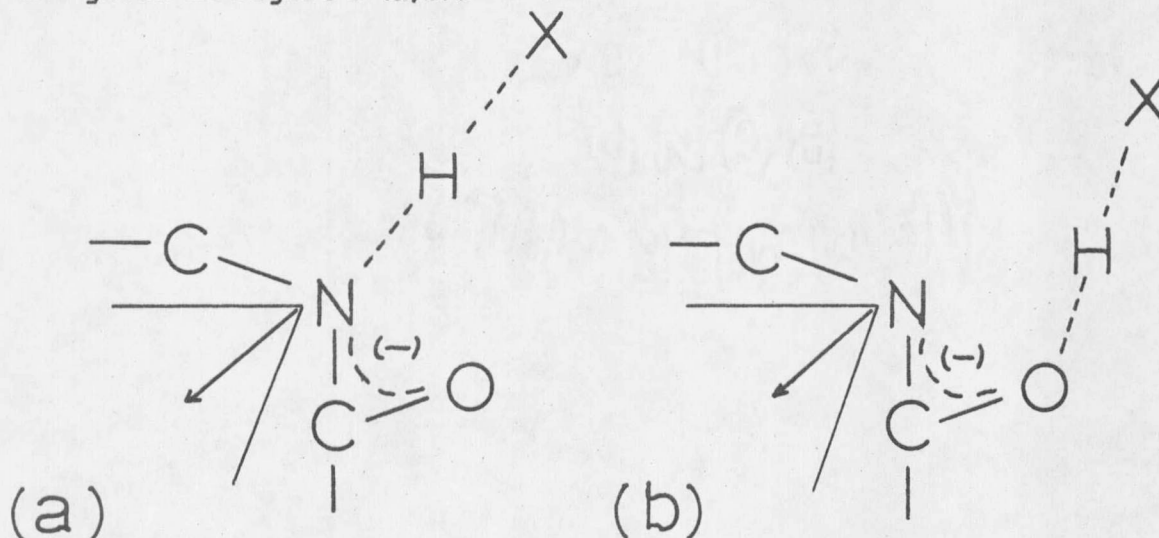


Figure 3. Proton Transfer Limited Mechanisms (a) direct (inside) (b) outside.

Inside protonation occurs simultaneously with metal-peptide nitrogen bond cleavage. This pathway is accelerated by H_3O^+ and by general acids.

The outside protonation pathway is accelerated by H_3O^+ but not by general acids. Here rapid protonation of the peptide oxygen is followed by breaking of the metal-peptide nitrogen bond as the rate determining step. In the presence of replacing ligand the available equatorial site is scavenged and the peptide ligand is displaced (13).

The reaction of Copper(II)Triglycine with acids follows a direct protonation pathway (6). The rate constant for the reaction with H_3O^+ was calculated to be $k_{\text{H}_3\text{O}^+} = 4.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

The reaction of Copper(II)Glycylglycylhistidine with acids does not follow a direct replacement pathway. At low pH evidence has been found supporting the outside protonation kinetic pathway (12). The rate constant for protonation was calculated to be $K_H = 1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.

A general acid catalysis mechanism is determined by studying the reaction in a pH range where the replacing ligand of interest takes on its protonated forms. If an acceleration in the rate is seen at these lower pH values the reaction is general acid catalyzed, and proceeds by the inside protonation pathway.

Specific hydrogen ion catalysis is determined by studying the reaction at lower pH, often by pH-jump methods. If the reaction rate is found to be independent of replacing ligand concentration but still accelerated, a specific hydrogen ion catalyzed mechanism is evidenced. This type of reaction is much slower than normal diffusion controlled

acid-base reactions. The reason for this is the necessity to break and rearrange coordinate bonds after protonation of the peptide oxygen (6).

Factors which determine the reactivity patterns that a ligand replacement reaction will follow may be summarized as follows. The substrate molecule will be examined first, then the replacing ligand.

The metal center of the substrate is particularly important in the overall rate of reaction, for example Copper(II) complexes are generally more reactive than Nickel(II) complexes (8,14).

Terminal donors in the polypeptide also influence the overall rate of reaction. A terminal carbonyl group is much more reactive than a terminal amide nitrogen, which is in turn more reactive than a terminal amine nitrogen.

The crystal field stabilization of a complex also must be taken into consideration. The greater the crystal field stabilization energy, the more sluggish the replacement reaction.

Steric factors must be taken into consideration as well. The displacement of Glycylglycylhistidine from the Copper(II) complex by TRIEN is about 10^7 times slower at pH =9 than the displacement of Triglycine from its Copper(II) complex. The terminal histidine group blocks nucleophilic attack by TRIEN (12).

The properties of the replacing ligand are also important in determining the rate at which a ligand exchange reaction will proceed, as well as the reactivity patterns which it may follow.

In studying the ligand exchange reactions of Copper(II)-Triglycine, Pagenkopf and Margerum found that the structure of the replacing ligand to be critical in determining whether a reaction will proceed by a nucleophilic or a general acid catalyzed mechanism (11).

It is evidenced that coordination of either a carboxylate or an amine group to an axial position is not sufficient, but rather, an entering ligand coordinating to an equatorial position, that occupied initially by the carboxyl group, is necessary to effect the nucleophilic mechanism. In this study it was observed that TRIEN and ethylenediaminediacetate (EDDA) react as nucleophiles with Copper(II)Triglycine. Conversely Nitrilotriacetate and Ethylenediaminetetraacetate do not react as nucleophiles due to steric hindrance in coordination at the equatorial site. These two ligands possess tertiary amine groups which require more space to coordinate than what is allowed for in this system, hence they react by a general acid catalyzed mechanism.

This concludes a discussion of the types of reactivity patterns involved in ligand exchange reactions. Let us now focus our attention to the specific problem of this work, the elucidation of the kinetics and mechanism of the reactions of TRIEN with NiH_2DGEN and NiH_2MBAE .

STATEMENT OF THE PROBLEM

In the preceeding section the major ligand exchange reactivity pattern of Cu(II) and Ni(II) polypeptides have been discussed. These reactions have been observed to proceed by dissociative, nucleophilic and proton transfer mechanisms. This study intends to investigate how a change in internal configuration of the substrate complex affects the reactivity patterns of the ligand exchange reaction.

Nickel(II)-N,N'-Diglycylethylenediamine (NiH_2DGEN) and Nickel(II)-Malonamide-N,N'-bis-(2-aminoethyl) (NiH_2MBAE) are two complexes which differ in basic structure from the glycyl- and glycylamide complex. NiH_2DGEN has the peptide linkages located on the sides of the complex, with NiH_2MBAE the peptide linkages are located on the backbone of the complex. They both have a plane of symmetry through the metal center and the middle of the backbone, unlike the glycyl- and glycylamide complexes which do not (Figure 2). What effect these structural differences may have on reactivity patterns is unknown.

The reactions of TRIEN with NiH_2DGEN and NiH_2MBAE have been studied in an effort to focus in on this problem.

EXPERIMENTAL SECTION

Apparatus

Spectral data were obtained using a Varian Series 634 spectrophotometer and chart recorder. The instrument is fitted with thermostatted cell compartments.

A Radiometer Model PHM26C pH meter with an Orion 91-05 combination pH electrode was used to measure pH. The instrument was calibrated using VWR Scientific standard pH buffer solutions.

Reagents

$\text{Ni}(\text{ClO}_4)_2$ was recrystallized twice from double distilled water. A $9.91 \times 10^{-2} \text{M}$ stock solution was prepared by dissolving the salt in double distilled water and standardized by EDTA titration (15).

Anhydrous sodium perchlorate was prepared by dissolving a weight of hydrated sodium perchlorate in boiling double distilled water, filtering the solution through a millipore ($.45 \mu\text{m}$) filter, evaporating to dryness and heating in a 50°C oven for several hours. To prepare a 2.00M solution of sodium perchlorate, one mole was dissolved and diluted to 500 ml with double distilled water.

A 0.10M sodium borate solution was prepared by dissolving the required weight of sodium borate in the required volume of double distilled water.

Triethylenetetramine was converted to its disulfate salt by adding 2.0 moles of concentrated sulfuric acid dropwise to 1.0 moles of

triethylenetetramine dissolved in toluene. The temperature was maintained at 0°C using an ice bath. The mixture was stirred for one hour, the precipitate was filtered off and recrystallized twice from double distilled water.

A TRIEN stock solution was prepared by dissolving a weight of TRIEN in the required amount of double distilled water. A small amount of dilute sodium hydroxide was required for the solution. The solution was standardized by mole ratio at 550 nm using 0.101M CuSO_4 and a 0.05 M acetate buffer, pH = 4.8.

The ligand Diglycylethylenediamine (DGEN) was synthesized by the method of Cottrell and Gill (16). Addition of 22.7 g ClCH_2COCl in 60 ml CHCl_3 to 14.7 g ethylenediamine in 100 ml CHCl_3 dropwise with cooling gave 59% $\text{C}_2\text{H}_4(\text{NHOOCH}_2\text{Cl})_2$, m.p. 175°C. The solid was filtered, extracted with hot absolute ethanol and then recrystallized in hot absolute ethanol.

A mixture of 14.1 g of above and 105 g $(\text{NH}_4)_2\text{CO}_3$ in 90 ml H_2O and 120 ml conc. NH_4OH was kept 18 hr at room temperature, and heated 4 hr at 55°C. The solution was filtered, and the remaining filtrate was roto-evaporated to dryness. The remaining solid was extracted with 300 ml absolute ethanol under reflux. The residue was dissolved in the minimum quantity of water and poured into 200 ml absolute ethanol. The precipitate was filtered off and recrystallized from aqueous ethanol. The yield was 70% of the dihydrochloride salt, m.p. 246°C.

Malonamide- N,N' bis-(2aminoethyl) (MBAE) was synthesized by the method of Heijiro Ojima and Kiyoko Yamada (17). Diethylmalonate (8.01 g) was added slowly with stirring to 6.0 g ethylenediamine in 20 ml absolute ethanol. The mixture was stirred and heated to 110–120°C for 30 minutes, 30 ml water was added to the mixture. The solution was filtered and the precipitate was converted to the dihydrochloride salt by decomposing with concentrated HCl. None of the common solvents tried were effective in recrystallization of the salt (e.g. absolute or aqueous ethanol, methanol or acetone). The yield was improved by decreasing the amount of water added after heating (5 ml rather than 30 ml) and also by cutting down the amount of absolute ethanol as solvent in the mixing step by one half.

The ligands were characterized by carbon 13 NMR and by elemental analysis (18). The names and abbreviations of all the chemicals used are found in Table I, along with the manufacturer and the compounds' purity.

Complexes were formed by the addition of 50% excess ligand to a Nickel(II)perchlorate solution. The ionic strength was adjusted to $\mu = 0.10$ with 2M sodium perchlorate. It has been shown in previous studies that these systems are oxygen sensitive (19), so the solution was then bubbled with nitrogen.

Dilute NaOH was utilized to bring up the pH slowly. When the solution was within the required pH range it was buffered with sodium

Table I. Names of Compounds Used and Their Abbreviations.

Name	Abbreviation
N,N'-Dicyclicethylenediamine	DGEN ^a
Malonamide-N,N'-bis-(2-aminoethyl)	MBAE ^b
Nickel (II) perchlorate	Ni(ClO ₄) ₂ ^{c,h}
Copper (II) sulfate	CuSO ₄ ·5H ₂ O ^{d,h}
Triethylenetetramine	TRIEN ^{e,h}
Sodium perchlorate	NaClO ₄ ·aq ^{f,h}
Sodium borate	Na ₂ B ₄ O ₇ ·10H ₂ O ^{g,h}

^a Elemental Analysis	Expected Value	Value Found
Carbon	29.16%	30.16%
Hydrogen	6.53%	6.70%
Nitrogen	22.67%	21.05%

^b Elemental Analysis	Expected Value	Value Found
Carbon	32.19%	30.00%
Hydrogen	6.95%	7.07%
Nitrogen	21.45%	20.64%

^c G. Frederick Smith Chemical Company^d Mallinckrodt Chemical Company^e Kodak Chemical Company^f Fluka Ag. Chemische Fabrik^g J. T. Baker Chemical Company^h Reagent Grade

borate, the total boron concentration was 0.005 M. After final pH adjustment the solution was diluted to volume, filtered to remove turbidity, bubbled with nitrogen, and placed in a water bath at 25°C. The concentration of the complex was between 7.0×10^{-4} M and 1.4×10^{-3} M.

TRIEN solutions were prepared by taking an aliquot of TRIEN stock solution. The ionic strength was adjusted to $\mu = 0.10$ with 2M sodium perchlorate, the pH was brought up with dilute sodium hydroxide. These solutions were likewise buffered with sodium borate ($B_T = 0.005$ M). They were diluted to volume after final pH adjustment, bubbled with nitrogen and placed in a water bath at 25°C. Concentrations of the TRIEN solutions were generally $3-4 \times 10^{-2}$ M.

Kinetic Measurements

The NiH_2DGEN complex exhibits an absorption maximum at 410 nm, $\epsilon = 220 \text{ M}^{-1} \text{ cm}^{-1}$; the NiH_2MBAE exhibits an absorption maximum at 440 nm, $\epsilon = 35 \text{ M}^{-1} \text{ cm}^{-1}$. The reactions were followed at these wavelengths, monitoring the decrease in absorbance with time as the ligand was displaced.

Initiation of the reaction was achieved by the addition of 3 to 25 ml TRIEN solution to 25 to 50 ml of the substrate solution. The solutions were then stirred together for an unspecified amount of time under nitrogen, and placed in the spectrophotometer cells. 5 cm cells

were used for NiH_2DGEN , and 10 cm cells were employed for NiH_2MBAE . Ionic strength was maintained at 0.10M NaClO_4 and the temperature was maintained at 25°C .

The reaction rates were measured over a range of $4\text{--}15 \times 10^{-3}\text{M}$ TRIEN concentrations, and a range of $4\text{--}8 \times 10^{-4}\text{M}$ Ni total concentrations.

A_t will be defined as the absorption at time t , A_∞ is the absorption that does not change with time, i.e., the absorption when the reaction is complete.

$A_t - A_\infty$ is a function of the substrate concentration. Plots of $-\ln(A_t - A_\infty)$ versus time were linear, indicating pseudo first order kinetics. The slopes of these plots are the pseudo first order rate constants, k_{obs} .

The observed rate constants were plotted versus Trien_t concentrations, to yield the second order rate constants, k_{slope} . Intercepts of these plots are designated as k_i .

Experimentally determined pH values were converted to $[\text{H}^+]$ values using activity coefficients calculated from the extended Debye-Huckel equations (20).

Second order rate constants, k_{slope} , were fitted to the rate expression using a non-linear least squares computer program: LLJAC. The program has input options available to accept initial estimates. This was done in the case of TRIEN reaction with NiH_2MBAE , as without

the initial estimates two of the four rate constants were calculated to be negative numbers. The initial estimates were weighted the same as experimental points. Table 2 lists equilibria and their constants used in this study.

Table 2. Equilibria and Equilibrium Constants.

Equilibrium	Equilibrium Constant
$\text{HTRIEN}^+ \rightleftharpoons \text{H}^+ + \text{TRIEEN}$	$K_{a1} = 10^{-9.74} \text{ (21)}$
$\text{H}_2\text{TRIEEN}^{2+} \rightleftharpoons \text{H}^+ + \text{HTRIEN}^+$	$K_{a2} = 10^{-9.08} \text{ (21)}$
$\text{H}_3\text{TRIEEN}^{3+} \rightleftharpoons \text{H}^+ + \text{H}_2\text{TRIEEN}^{2+}$	$K_{a3} = 10^{-6.56} \text{ (21)}$
$\text{NiDGEN}^{2+} \rightleftharpoons \text{NiH}_2\text{DGEN} + 2\text{H}^+$	$K_{1ab} = 10^{-16.04} \text{ (5)}$
$\text{NiMBAE}^{2+} \rightleftharpoons \text{NiH}_2\text{MBAE} + 2\text{H}^+$	*

*Equilibrium Constant unavailable in literature.

RESULTS

Determination of the General Rate Expression for the Reaction of TRIEN with NiH_2DGEN

The general rate expression for the displacement of DGEN from the Nickel(II) complex was determined by observing the rate as a function of TRIEN concentration over a pH range of 6.57 to 9.89. A six to forty fold excess in TRIEN_t over $[\text{NiH}_2\text{DGEN}]$ was present at the beginning of each reaction. Plots of $-\ln(A_t - A_\infty)$ versus time were linear, indicating the reaction was first order in substrate concentration. This may be expressed as Equation 3.

$$(3) \quad \text{Rate} = k_{\text{obs}} [\text{NiH}_2\text{DGEN}]$$

Table 3 gives the observed rate constants, k_{obs} for each pH and each $[\text{TRIEN}]_t$. Figure 4 shows the relationship between k_{obs} and $[\text{TRIEN}]_t$ at the pH values where the reaction was studied. The non-zero intercept and linearity of the plots allowed for a breakdown of the constant k_{obs} as shown in Equation 4.

$$(4) \quad \text{Rate} = \{k_i + k_s\} [\text{NiH}_2\text{DGEN}]$$

Under pseudo first order conditions we may describe k_s as in Equation 5 where k_{slope} is the slope calculated from the plots in

$$(5) \quad k_s = k_{\text{slope}} [\text{TRIEN}]_t$$

Figure 1. k_{slope} then is the overall second order rate constant for the reaction. Substituting for k_s in Equation 4 we get:

$$(6) \quad \text{Rate} = \{k_i + k_{\text{slope}} [\text{TRIEN}]_t\} [\text{NiH}_2\text{DGEN}]$$

Table 3. Concentrations of Species and k_{obs} for the Reaction of TRIEN with NiH_2DGEN .

Run #	$10^4[\text{NiH}_2\text{DGEN}]_0$	pH	$10^3[\text{TRIEN}]_t$	$10^3k_{\text{obs}} (\text{s}^{-1})$
2-44-1	6.61	6.57	8.98	3.39
2-44-2	6.20	6.62	11.8	3.43
2-44-3	5.66	6.67	15.4	3.48
2-44-4	4.96	6.70	20.2	3.48
1-59-1	6.34	7.85	8.86	1.07
1-59-2	5.87	7.85	11.5	1.32
1-60-1	5.29	7.85	14.8	1.53
1-60-2	4.53	7.85	19.0	1.88
1-56-1	6.90	8.45	5.78	1.41
1-55-1	6.34	8.45	8.86	1.79
1-56-2	5.87	8.45	11.5	2.32
1-57-1	4.76	8.45	17.7	3.31
1-66-1	7.21	8.94	4.03	2.10
1-66-2	6.61	8.94	7.38	3.35
1-67-1	6.10	8.94	10.2	3.98
1-67-2	3.66	8.94	12.7	4.72
1-78-1	6.61	8.94	3.88	1.68
1-78-2	6.10	8.94	5.37	2.27
1-78-3	5.66	8.94	6.64	2.73
1-79-1	5.29	8.94	7.75	3.02
1-49-1	6.34	9.35	8.86	5.15
1-49-2	5.29	9.35	14.8	7.33
1-49-3	6.90	9.35	5.78	3.68
1-49-4	5.87	9.35	11.5	6.07
1-85-1	6.90	9.35	6.07	4.20
1-85-2	6.34	9.35	9.30	5.92
1-86-1	5.87	9.35	12.1	7.17
1-86-2	5.29	9.35	15.5	8.48
1-64-1	5.29	9.89	14.8	12.3
1-64-2	5.87	9.89	11.5	10.6
1-65-1	6.34	9.89	8.86	8.43
1-65-2	6.90	9.89	5.78	5.47

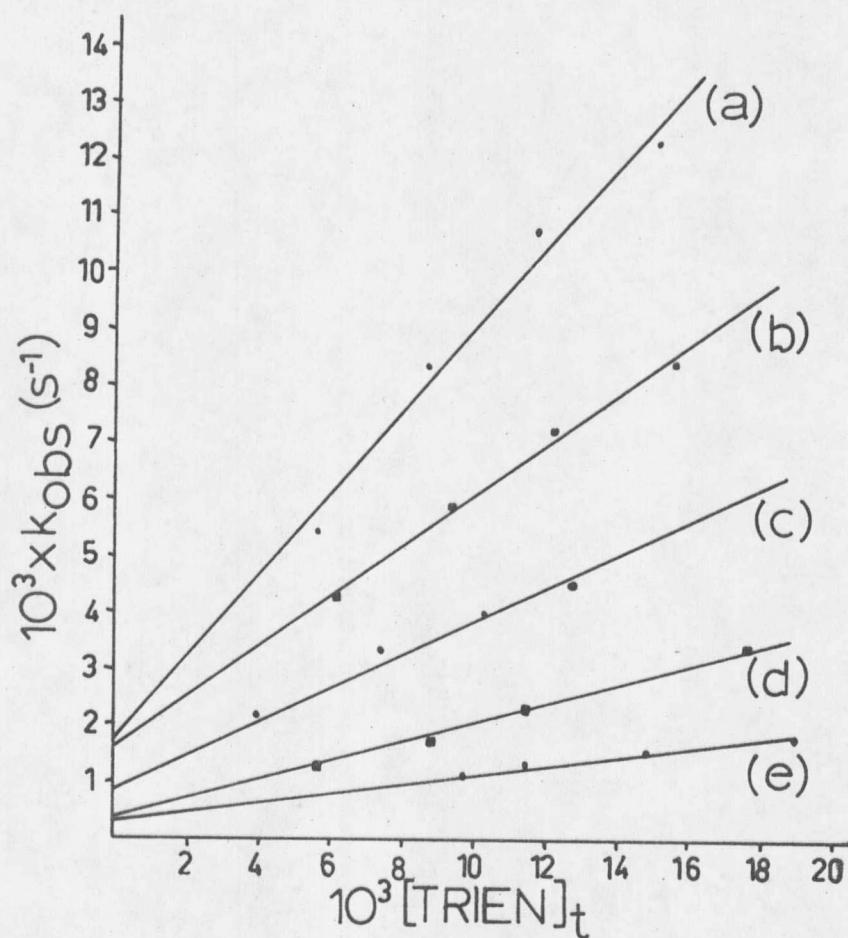


Figure 4. Dependence of k_{obs} on $[\text{TRIEN}]_t$ for the reaction of TRIEN with NiH_2DGEN .

	pH	$10^3 k_i \text{ (s}^{-1}\text{)}$	$k_{\text{slope}} \text{ (M}^{-1}\text{s}^{-1}\text{)}$
a)	9.89	1.6	0.735
b)	9.35	1.4	0.438
c)	8.94	0.67	0.322
d)	8.45	0.45	0.161
e)	7.85	0.37	0.080

In the pH range where the reaction was studied, TRIEN takes on several forms. At low pH doubly and triply protonated TRIEN are the predominant species. At higher pH monoprotonated TRIEN and TRIEN itself predominate. The relationship between $[\text{TRIEN}]_t$ and each of its species is given in Equation 7.

$$(7) \quad [\text{TRIEN}]_t = [\text{TRIEN}] + [\text{HTRIEN}^+] + [\text{H}_2\text{TRIEN}^{2+}] + [\text{H}_3\text{TRIEN}^{3+}]$$

The triply protonated form of TRIEN was omitted in the formation of the rate expression as the rate was found to be TRIEN independent at pH 6.57 to 6.70. However, it was included in the calculation of the speciation of TRIEN, as it amounted to about 5% of the $[\text{TRIEN}]_t$ at pH 7.85.

Using the α values for each contributing species as given in Equations 8-11, the second order rate constants, k_{slope} , were fitted to the expression given in Equation 12.

$$(8) \quad \alpha_{\text{TRIEN}} = \frac{[\text{TRIEN}]}{[\text{TRIEN}]_t}$$

$$(9) \quad \alpha_{\text{HTRIEN}^+} = \frac{[\text{HTRIEN}^+]}{[\text{TRIEN}]_t}$$

$$(10) \quad \alpha_{\text{H}_2\text{TRIEN}^{2+}} = \frac{[\text{H}_2\text{TRIEN}^{2+}]}{[\text{TRIEN}]_t}$$

$$(11) \quad \alpha_{\text{H}_3\text{TRIEN}^{3+}} = \frac{[\text{H}_3\text{TRIEN}^{3+}]}{[\text{TRIEN}]_t}$$

$$(12) \quad k_{\text{slope}} = k_t \alpha_{\text{TRIEN}} + k_T \alpha_{\text{HTRIEN}^+} + K_{\text{H}_2\text{T}} \alpha_{\text{H}_2\text{TRIEN}^{2+}}$$

The computerized non-linear least squares analysis yielded values for the rate constants of $k_T = 9.9 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$, $k_{HT} = 5.5 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$, and $k_{H_2T} = 7.8 \times 10^{-2} \text{M}^{-1} \text{s}^{-1}$. Table 4 is a comparison of the k_{slope} calculated using these constants with the experimentally determined values. Figure 5 given the dependence of k_{slope} on pH for the NiH_2DGEN system.

The value of the intercept k_i was found to increase with increasing pH. At this point we felt the buffer may have some effect, and increased the buffer concentration by a factor of 10. The increase in buffer concentration corresponded to a definite increase in the rate.

In this pH range (7.85-9.89) boric acid and dihydrogen borate anion are in equilibrium. As the intercept k_i increased with increasing dihydrogen borate anion concentration, the relationship between the two was investigated. The concentration of H_2BO_3^- was calculated using α values, $B_T = 0.005 \text{ M}$ and $\text{pK}_a = 9.24$ for boric acid (20). The dependence of k_i on $[\text{H}_2\text{BO}_3^-]$ is shown in Figure 6. The intercept of the plot is the dissociative rate constant, $k_d = 2.4 \times 10^{-4} \text{s}^{-1}$. The slope is the rate constant for H_2BO_3^- catalysis, $k' = 3.7 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$.

pH jump experiments without the use of a buffer were employed in the lower pH range. This was necessary as the complex doesn't form below pH 8. The value of k_{obs} was found to increase at pH = 6.70, and

Table 4. Calculated k_{slope} from pH Speciation of TRIEN for NiH_2DGEN .

pH	$k_{\text{slope}} \text{M}^{-1}\text{s}^{-1}$	$k_{\text{slope}}(\text{calc}) \text{M}^{-1}\text{s}^{-1}$	% deviation	$10^3 k_i (\text{s}^{-1})$
7.85	0.080	0.095	19	0.37
8.45	0.161	0.158	2	0.45
8.94	0.322	0.288	11	0.67
9.37	0.438	0.468	7	1.4
9.89	0.735	0.728	<1	1.6

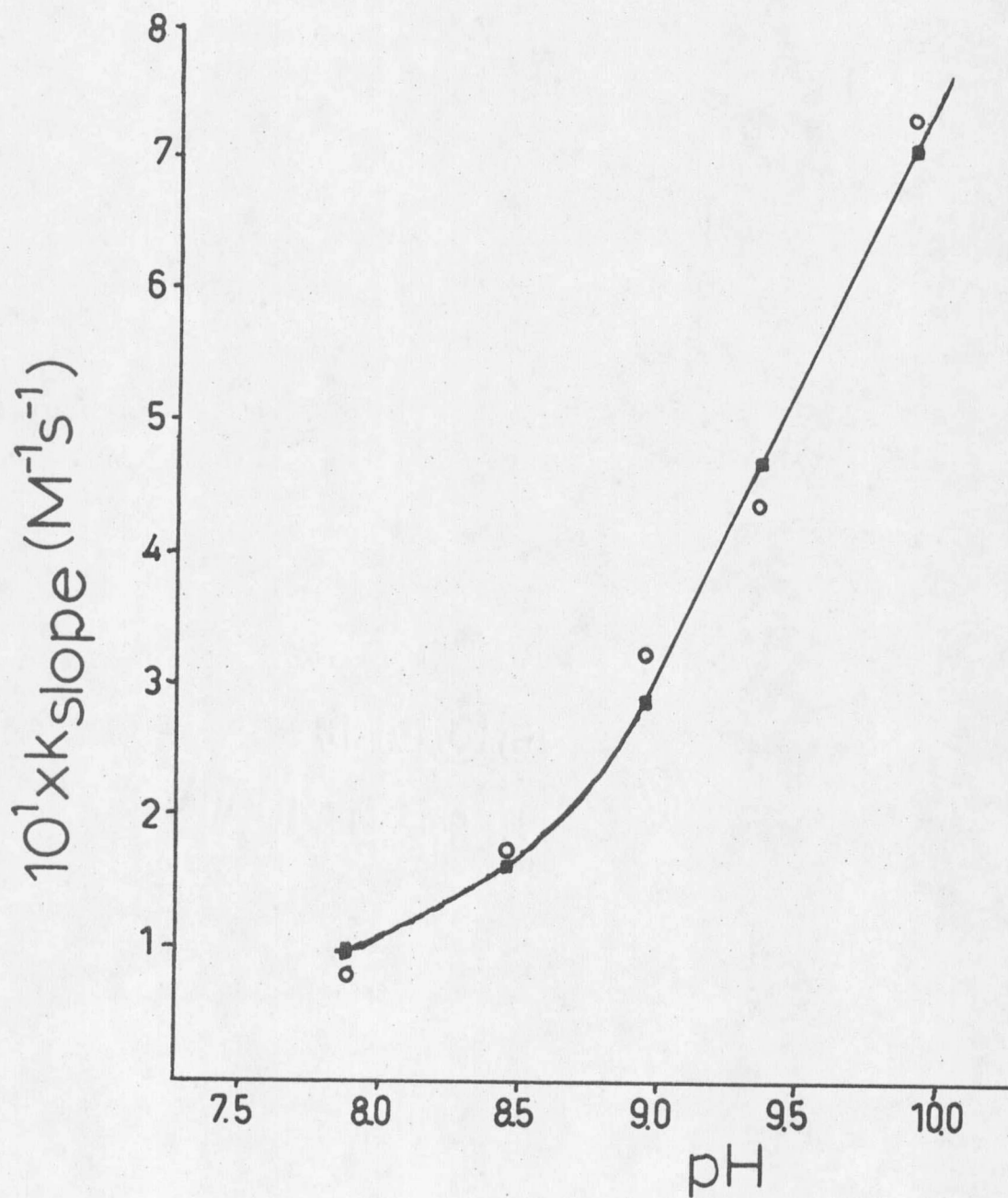


Figure 5. Dependence of k_{slope} on pH for the TRIEN reaction with NiH_2DGEN .

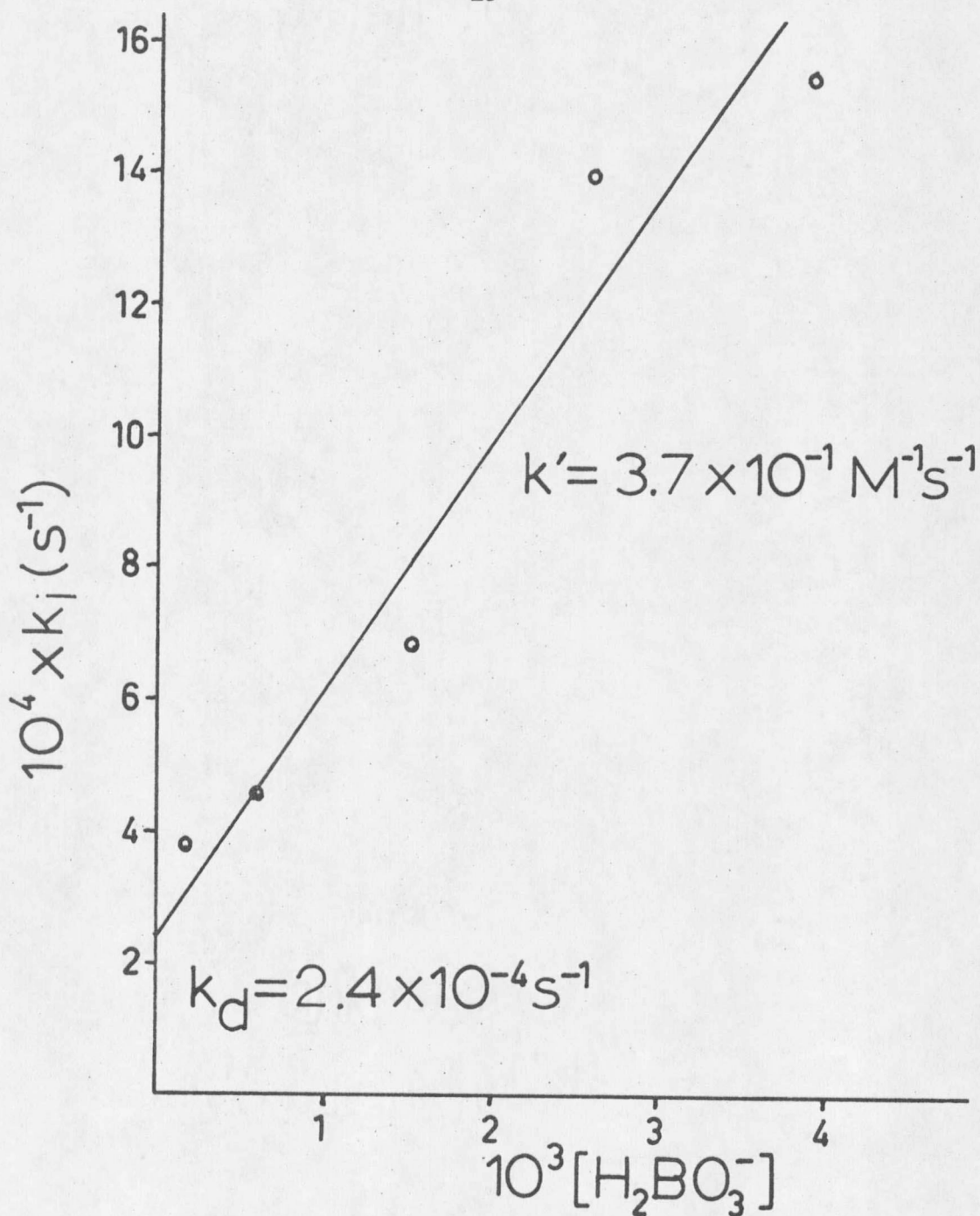


Figure 6. Dependence of k_i on $[\text{H}_2\text{BO}_3^-]$ for the TRIEN reaction with NiH_2DGEN .

no TRIEN dependence was observed at this pH. The value of k_{obs} was used to calculate the specific hydrogen ion catalysis rate constant,

$$k_{\text{H}_3\text{O}^+}.$$

The relationship given in Equation 13

$$(13) \quad k_{\text{obs}} = k_d + k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+]$$

may be rearranged and solved for $k_{\text{H}_3\text{O}^+}$.

$$(14) \quad k_{\text{H}_3\text{O}^+} = \frac{k_{\text{obs}} - k_d}{[\text{H}_3\text{O}^+]} = 1.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$$

Inclusion of all these constants into the rate equation yields:

$$(15) \quad \text{Rate} = \{k_d + k'[\text{H}_2\text{BO}_3^-] + k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+] + k_{\text{T}}[\text{TRIEN}] + k_{\text{HT}}[\text{HTRIEN}^+] + k_{\text{H}_2\text{T}}[\text{H}_2\text{TRIEN}^{2+}]\} [\text{NiH}_2\text{DGEN}]$$

The rate constants are summarized in Table 5. As a final check the observed rate constants k_{obs} , were plotted versus pH, shown in Figure 7. The minimum was observed around pH = 7.8. Below this pH the increase in k_{obs} is due mainly to specific hydrogen ion catalysis. Above this pH the increase in k_{obs} is due to an increase in the concentrations of nucleophilic species of TRIEN, and a corresponding decrease in the concentrations of the non-reactive protonated forms of TRIEN.

Table 5. Rate Constants for the Reaction of TRIEN with NiH_2DGEN .

$$k_d = 2.4 \times 10^{-4} \text{ s}^{-1}$$

$$k_i = 3.7 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$$

$$k_T = 9.9 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{HT} = 5.5 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{H_2T} = 7.8 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$$

$$k_{H_3O} = 1.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$$

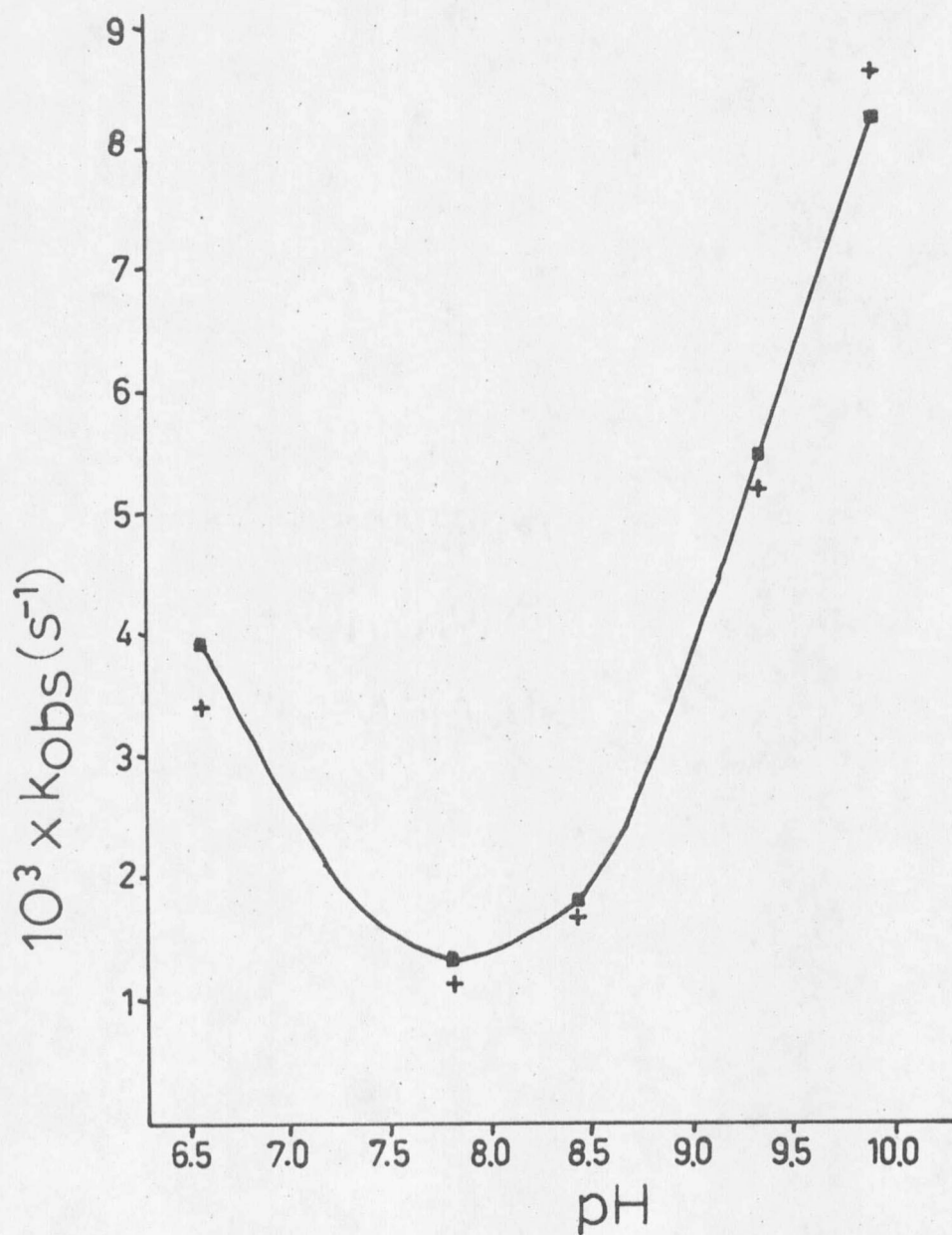


Figure 7. Dependence of k_{obs} on pH for the TRIEN reaction with NiH_2DGEN . $[\text{TRIEN}]_t = 8.86 \times 10^{-3} \text{M}$, $B_T = .005 \text{M}$

DISCUSSION

Mechanism of the Reaction of TRIEN with NiH_2DGEN

The rate of reaction of TRIEN with NiH_2DGEN was found to increase with increasing pH from pH ≈ 7.8 to pH ≈ 9.9 . Below pH ≈ 7.8 the reaction rate was observed to increase with decreasing pH to pH ≈ 6.6 . The reaction in this pH range was found to be independent of TRIEN concentration, ruling out a general acid catalyzed mechanism (i.e., $\text{H}_3\text{TRIEN}^{3+}$ is not a reactant). A replacing ligand independent pathway was also observed and was found to be enhanced by a buffer species with increasing pH. The mechanisms associated with all of these observations will be explored in the following paragraphs.

The fact that the rate of reaction increases with increasing pH from pH ≈ 7.8 to pH ≈ 9.9 is conclusive evidence for a nucleophilic mechanism. The calculated rate constants decrease with increasing protonation of the nucleophile (TRIEN) according to a pattern reported in other studies (8). For the reaction of TRIEN with Ni(II)Triglycine the rate constants $k_T = 1.7 \times 10^4 \text{M}^{-1}\text{s}^{-1}$ and $k_{\text{HT}} = 1.8 \times 10^4 \text{M}^{-1}\text{s}^{-1}$ are roughly equivalent. The rate constant $k_{\text{H}_2\text{T}} = 9.0 \times 10^2 \text{M}^{-1}\text{s}^{-1}$ is about an order of magnitude smaller. The reason for this is the binding sites of doubly-protonated TRIEN are occupied and reduced effectiveness as a nucleophile is evidenced.

A similar reactivity pattern has been found in this study. The calculated rate constants decrease with increasing protonation;

$k_T = 9.9 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$, $k_{HT} = 5.5 \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$, and $k_{H_2T} = 7.8 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

Again k_{H_2T} is about an order of magnitude smaller than k_T . The rate constants for the nucleophilic replacement of Triglycine are over 10,000 times larger than those calculated for the replacement of DGEN. This is due to the fact that a terminal carboxyl group is much more reactive than a terminal amine.

The rate constants for the reaction of TRIEN with NiH_3GGa are $k_T = 7.4 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{HT} = 0.10 \text{ M}^{-1} \text{ s}^{-1}$, where $\mu = 1 \text{ M NaClO}_4$ (22). The reactivity of this complex is on the same order of magnitude as NiH_2DGEN , as the complexes are quite similar in structural stability (i.e. both have four nitrogen donors).

The rate of reaction increased with decreasing pH from $\text{pH} \approx 7.8$ to $\text{pH} \approx 6.6$. This observation coupled with the fact that the replacement was independent of TRIEN concentration is conclusive evidence for a specific hydrogen ion catalyzed mechanism. Here a proton is transferred to a carboxyl oxygen, followed by Nickel-peptide nitrogen bond cleavage and scavenging of the binding site by the replacing ligand. The value of the rate constant, $k_{\text{H}_3\text{O}^+} = 1.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, was found to be roughly in agreement with a previously reported value of $k_{\text{H}_3\text{O}^+} = 1.82 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ (23)

The non-zero intercepts of the plots of k_i versus $[\text{TRIEN}]_t$ were

indicative of a replacing ligand independent pathway. The fact that the intercept values increased with increasing pH led us to suspect an interaction of a buffer species increasing the rate of dissociation with increasing pH.

Our of plane coordination of a buffer species has been reported in previous studies (9,10). The coordinating buffer acts as an acid, donating a proton to the amide nitrogen, thus facilitating metal-nitrogen bond cleavage and henceforth the dissociation of the complex. In general, acids which have the capacity to coordinate and donate a proton simultaneously are very effective catalysts for dissociation reactions. Often they are many times more reactive than one would suspect from pK_a values (9).

The rate constant for hydrogen carbonate catalysis of the TRIEN displacement of Triclycine from the Nickel(II) complex is $194 \text{ M}^{-1}\text{s}^{-1}$. This may be compared to the rate constant for dihydrogen borate catalysis of the TRIEN displacement of DGEN from the Nickel(II) complex, $k' = 3.7 \times 10^{-1} \text{ M}^{-1}\text{s}^{-1}$. The reason the HCO_3^- catalysis rate constant is so much higher is that it is aiding in the dissociation of a much more reactive substrate. In this study it appears that H_2BO_3^- coordinates to the NiH_2DGEN complex in an axial position. Donation of a proton to the amide nitrogen facilitates Nickel-nitrogen bond cleavage, and the site is rapidly scavenged by the nucleophilic replacing ligand.

The dissociative rate constant is the intercept of the plot of k_i versus $[H_2BO_3^-]$, that is where $H_2BO_3^-$ no longer aids in the dissociation of the complex. The value of this constant was calculated to be $k_d = 2.4 \times 10^{-4} s^{-1}$. A comparison of the dissociative rate constant with the value previously reported for the reaction of EDTA with NiH_2DGEN (10), $k_d = 2.1 \times 10^{-1} s^{-1}$, showed excellent agreement within experimental error. It has been shown that TRIEN reacts with NiH_2DGEN by several parallel paths. Each of these pathways contribute differently to the overall rate of reaction depending on the pH where the reaction is carried out. These pathways are summarized in Figure 8, the proposed mechanism for this reaction.

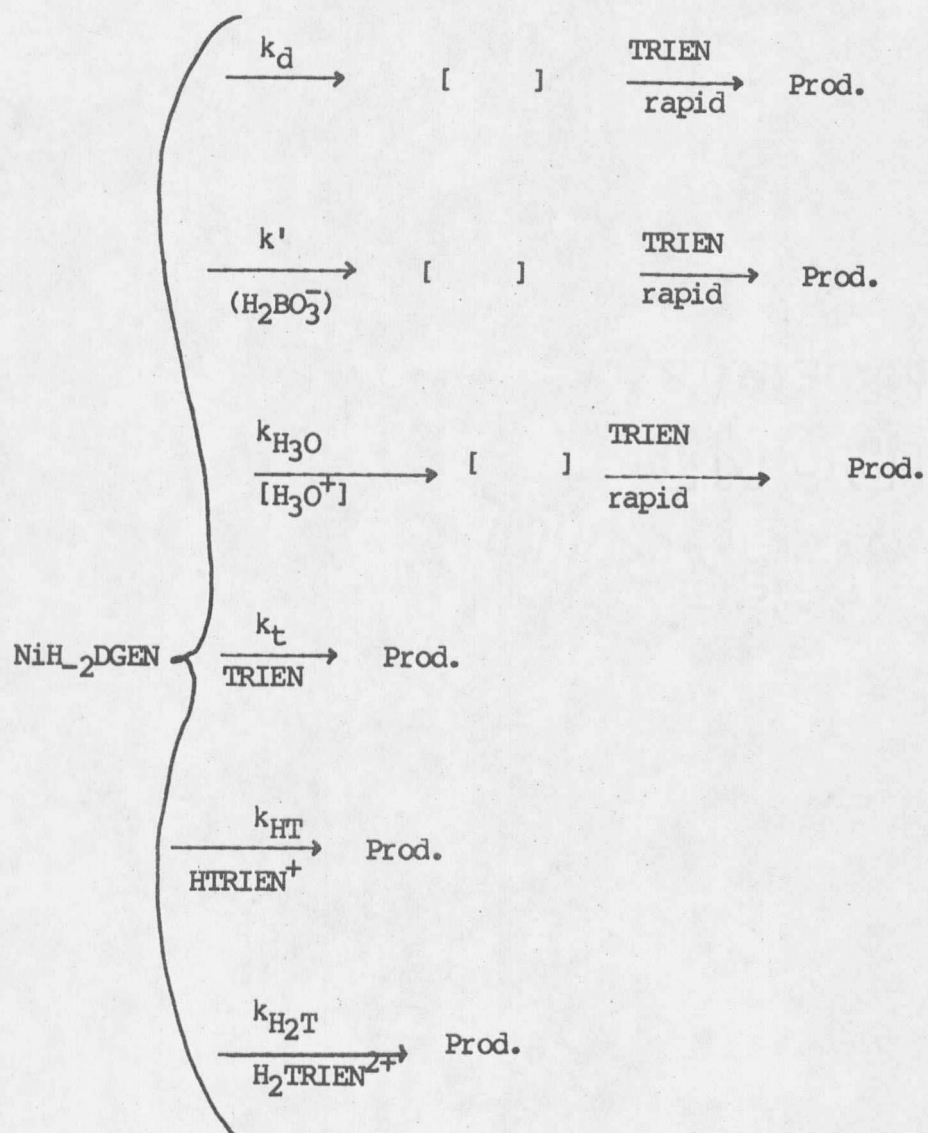


Figure 8. Proposed mechanism for the reaction of TRIEN with Ni_2DGEN .

RESULTS

Determination of the General Rate Expression for the Reaction of TRIEN with NiH_2MBAE

The rate expression for the reaction of TRIEN with NiH_2MBAE was determined in much the same manner as for the reaction with NiH_2DGEN . At 4-16 fold excess in TRIEN concentration over $[\text{NiH}_2\text{MBAE}]$ was present at the beginning of each reaction. Plots of $-\ln(A_t - A_\infty)$ versus time were linear, indicating the reaction was first order in substrate concentration. This may be expressed as in Equation 16.

$$(16) \quad \text{Rate} = k_{\text{obs}} [\text{NiH}_2\text{MBAE}]$$

Table 6 gives the observed rate constants, k_{obs} for each pH and each $[\text{TRIEN}]_t$. Figure 9 shows the relationship between k_{obs} and $[\text{TRIEN}]_t$ at the pH values where the reaction was studied. The non-zero intercept and linearity of the plots allowed for a breakdown of the constant k_{obs} as shown in Equation 17.

$$(17) \quad \text{Rate} = \{k_i + k_s\} [\text{NiH}_2\text{MBAE}]$$

Under pseudo first order conditions we may describe k_s as in Equation 18

$$(18) \quad k_s = k_{\text{slope}} [\text{TRIEN}]_t$$

where k_{slope} is the slope calculated from the plots in Figure 6. k_{slope} is the overall second order rate constant for the reaction. Making the proper substitutions into Equation 17 we get:

$$(19) \quad \text{Rate} = \{k_i + k_{\text{slope}} [\text{TRIEN}]_t\} [\text{NiH}_2\text{MBAE}]$$

Table 6. Concentration of Species and k_{obs} for the Reaction of TRIEN with NiH_2MBAE

Run #	$10^4[\text{NiH}_2\text{MBAE}]_0$	pH	$10^3[\text{TRIEN}]_t$	$10^3k_{\text{obs}}\text{s}^{-1}$
2-11-1	12.1	8.50	5.05	9.50
2-11-2	11.6	8.50	6.74	13.4
2-12-1	10.8	8.50	9.33	16.9
2-12-2	9.71	8.50	12.1	20.8
2-14-1	11.6	8.63	6.07	6.70
2-14-2	10.8	8.63	8.09	8.95
2-15-1	9.71	8.63	10.9	12.6
2-15-2	8.83	8.63	13.2	15.2
2-5-1	11.6	8.94	6.74	4.68
2-5-2	10.8	8.94	8.98	6.17
2-6-1	9.71	8.94	12.1	7.98
2-6-2	8.83	8.94	14.7	10.3
2-7-1	11.6	9.39	6.74	3.83
2-7-2	10.8	9.39	9.98	5.60
2-8-1	9.71	9.39	12.1	6.23
2-8-2	8.83	9.39	14.7	7.45
2-9-1	11.6	9.92	6.74	3.87
2-9-2	10.8	9.92	8.98	4.83
2-10-1	9.71	9.92	12.1	6.13
2-10-2	8.83	9.92	14.7	6.98
2-22-3	10.8	10.5	8.09	4.30
2-23-1	9.71	10.5	10.9	5.05
2-23-2	8.83	10.5	13.2	5.95
2-23-3	8.09	10.5	15.2	6.85
2-20-1	11.6	11.0	6.07	2.55
2-20-2	10.8	11.0	8.09	3.13
2-20-3	9.71	11.0	10.9	4.18
2-21-1	8.83	11.0	13.2	4.62
2-21-2	10.8	11.5	8.09	1.90
2-21-3	9.71	11.5	10.9	2.63
2-22-1	8.83	11.5	13.2	3.08
2-22-2	8.09	11.5	15.2	3.45

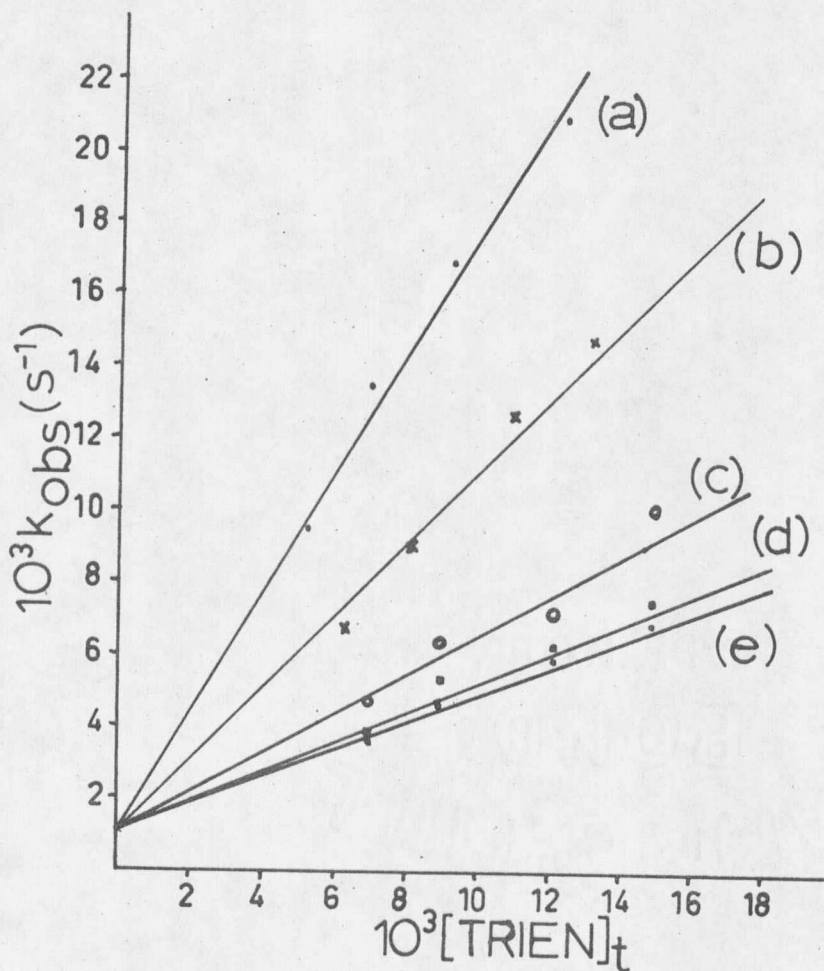


Figure 9. Dependence of k_{obs} on $[\text{TRIEN}]_t$ for the reaction of TRIEN with NiH_2MBAE .

	pH	$10^3 k_i (\text{s}^{-1})$	$k_{\text{slope}} (\text{M}^{-1} \text{s}^{-1})$
a)	8.50	1.0	1.71
b)	8.63	1.0	1.01
c)	8.94	1.0	0.58
d)	9.39	1.0	0.43
e)	9.92	1.0	0.40

The rate of reaction was observed to decrease with increasing pH. Using the α values for TRIEN described previously, with the inclusion of the triply protonated form, $\text{H}_3\text{Trien}^{3+}$, the second order rate constants, k_{slope} , were fit to the expression given in Equation 20.

$$(20) \quad k_{\text{slope}} = k_{\text{T}}^{\alpha} \text{TRIEN} + k_{\text{HT}}^{\alpha} \text{HTRIEN}^{+} + k_{\text{H}_2\text{T}}^{\alpha} \text{H}_2\text{TRIEN}^{2+} + k_{\text{H}_3\text{T}}^{\alpha} \text{H}_3\text{TRIEN}^{3+}$$

Employing the experimental points as well as initial guesses of the rate constants, a non-linear least squares program computed values for the rate constants of $k_{\text{T}} = 1.6 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$, $k_{\text{HT}} = 6.7 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$, $k_{\text{H}_2\text{T}} = 1.7 \times 10^{-2} \text{M}^{-1} \text{s}^{-1}$, and $k_{\text{H}_3\text{T}} = 1.3 \times 10^2 \text{M}^{-1} \text{s}^{-1}$. Table 7 gives a comparison of the experimentally determined k_{slopes} and those values calculated using the rate constants above. Figure 20 is a plot of k_{slope} versus pH, the solid line is calculated using the computed rate constants and Equation 20.

As the intercept of the k_{obs} versus $[\text{TRIEN}]_{\text{t}}$ plots remained constant, the value of $1.0 \times 10^{-3} \text{s}^{-1}$ was taken for the dissociative rate constant, k_{d} . There was no indication of buffer enhancement of the rate, and no indication of specific hydrogen ion catalysis in the pH range studied.

The reaction rate was observed to decrease at very high pH. Table 8 gives the relationship between k_{i} and pH at high hydroxide ion concentration. As hydroxide ion inhibition was evident, the expression given in Equation 21 was chosen to account for this.

Table 7. Calculated k_{slopes} from the pH Speciation of TRIEN for NiH_2MBAE .

pH	$k_{\text{slope}} \text{M}^{-1} \text{s}^{-1}$	$k_{\text{slope}} (\text{calc}) \text{M}^{-1} \text{s}^{-1}$	% deviation	$10^3 k_i$
8.50	1.7	1.6	6	1.0
8.63	1.0	1.2	20	1.0
8.94	5.8×10^{-1}	6.4×10^{-1}	10	1.0
9.39	4.3×10^{-1}	4.4×10^{-1}	5	1.0
9.92	4.0×10^{-1}	3.7×10^{-1}	8	1.0

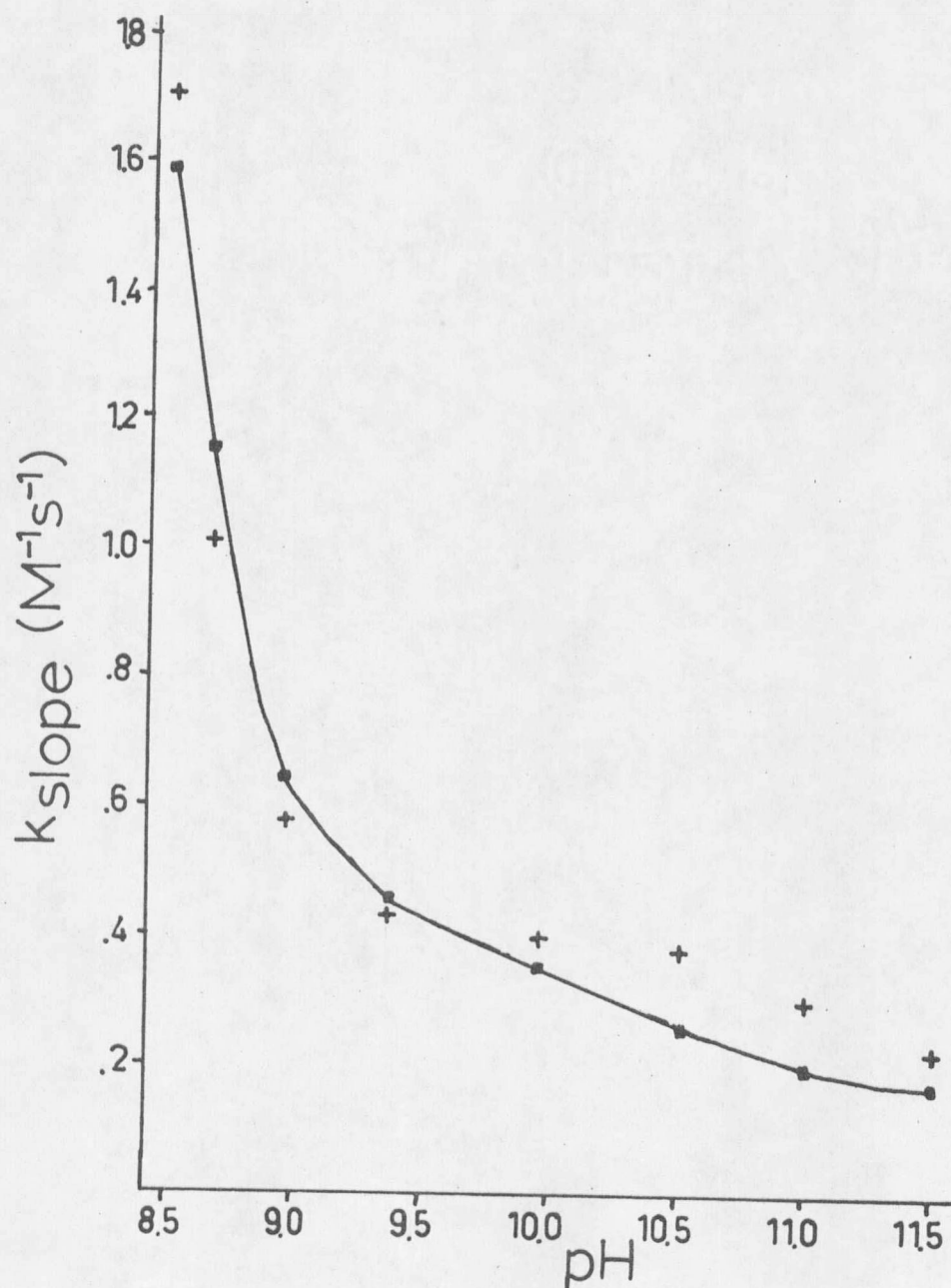


Figure 10. Dependence of k_{slope} on pH for the TRIEN reaction with NiH_2MBAE .

Table 8. Relationship Between k_i and pH at High Hydroxide Ion Concentration for the TRIEN Reaction with NiH_2MBAE .

pH	$[\text{H}^+]$	$[\text{OH}^-]$	k_i	$\left(\frac{k_d}{k_i}\right) - 1$
10.5	3.81×10^{-11}	2.62×10^{-4}	$1.0 \times 10^{-3} \text{ s}^{-1}$	0.00
11.0	1.20×10^{-11}	8.33×10^{-4}	$7.0 \times 10^{-4} \text{ s}^{-1}$	0.43
11.5	3.81×10^{-12}	2.62×10^{-3}	$2.0 \times 10^{-4} \text{ s}^{-1}$	4.00

$$(21) \quad k_i = k_d \left(\frac{1}{1 + K[\text{OH}^-]} \right)$$

The equation may be arranged as in Equation 22.

$$(22) \quad \left(\frac{k_d}{k_i} \right) - 1 = K[\text{OH}^-]$$

Plotting $\left(\frac{k_d}{k_i} \right) - 1$ versus $[\text{OH}^-]$, the equilibrium constant K_1 was evaluated to be $1.4 \times 10^3 \text{ M}^{-1}$. (Figure 11).

The overall rate law is given in Equation 23, Table 9 is a summary of the constants previously evaluated.

$$(23) \quad \text{Rate} = \{k_d + k_T[\text{TRIEN}] + k_{HT}[\text{HTRIEN}^+] + k_{H_2T}[\text{H}_2\text{TRIEN}^{2+}] + k_{H_3T}[\text{H}_3\text{TRIEN}^{3+}]\} \left(\frac{1}{1 + K_1[\text{OH}^-]} \right) [\text{NiH}_2\text{MBAE}]$$

As a final check the observed rate constants, k_{obs} , were plotted versus pH, as shown in Figure 12. The observed rate constants decreased with increasing pH. This is conclusive evidence for a proton assisted reactivity pattern.

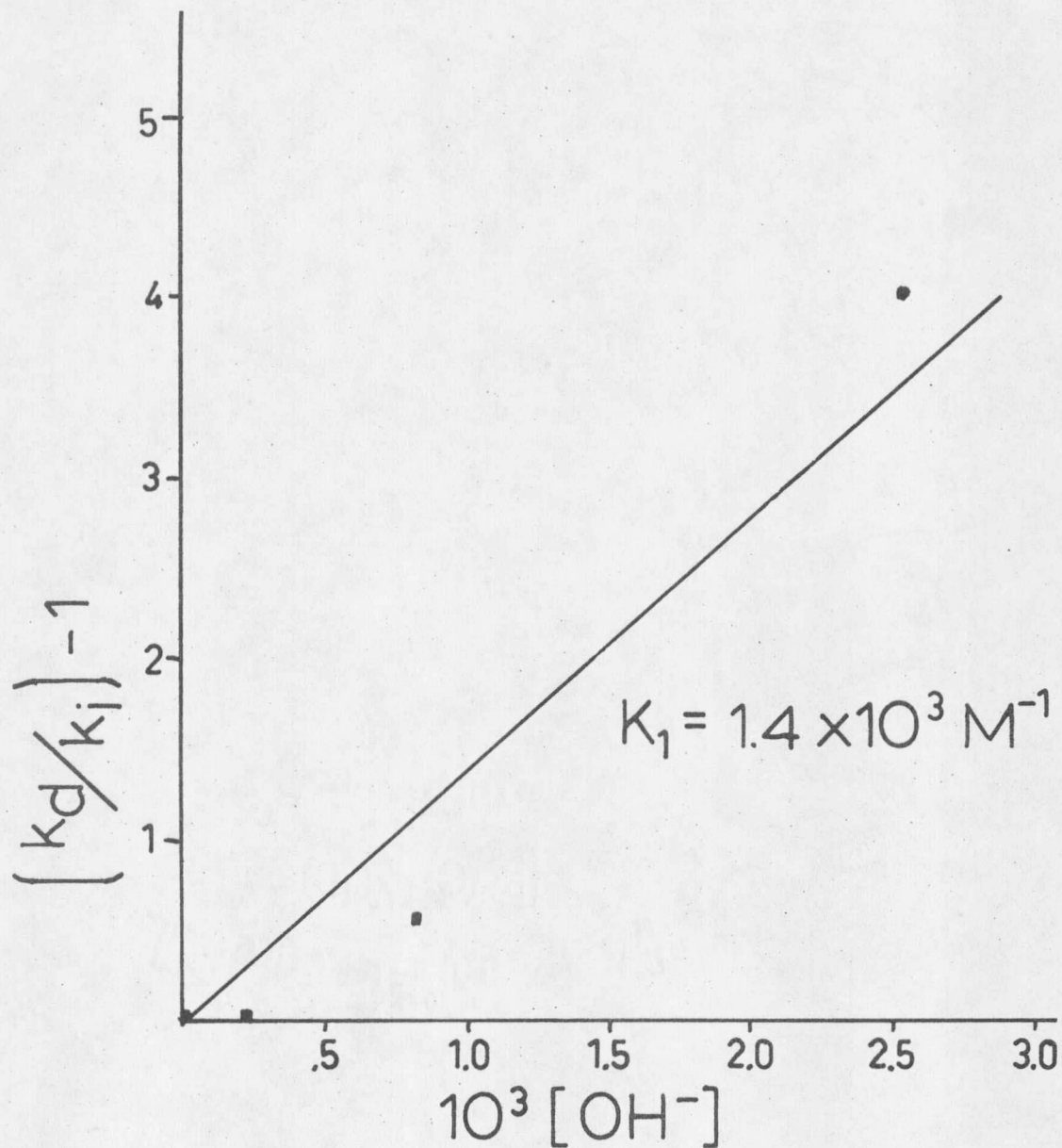


Figure 11. Evaluation of the equilibrium constant K_1 for hydroxide inhibition of the rate of the reaction of TRIEN with NiH_2MBAE .

Table 9. Rate Constants for the Reaction of TRIEN with NiH_2MBAE .

$$k_d = 1.0 \times 10^{-3} \text{s}^{-1}$$

$$k_T = 1.6 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$$

$$k_{HT} = 6.7 \times 10^{-1} \text{M}^{-1} \text{s}^{-1}$$

$$k_{H_2T} = 1.7 \times 10^{-2} \text{M}^{-1} \text{s}^{-1}$$

$$k_{H_3T} = 1.3 \times 10^2 \text{M}^{-1} \text{s}^{-1}$$

$$K_1 = 1.4 \times 10^{-4} \text{M}^{-1}$$

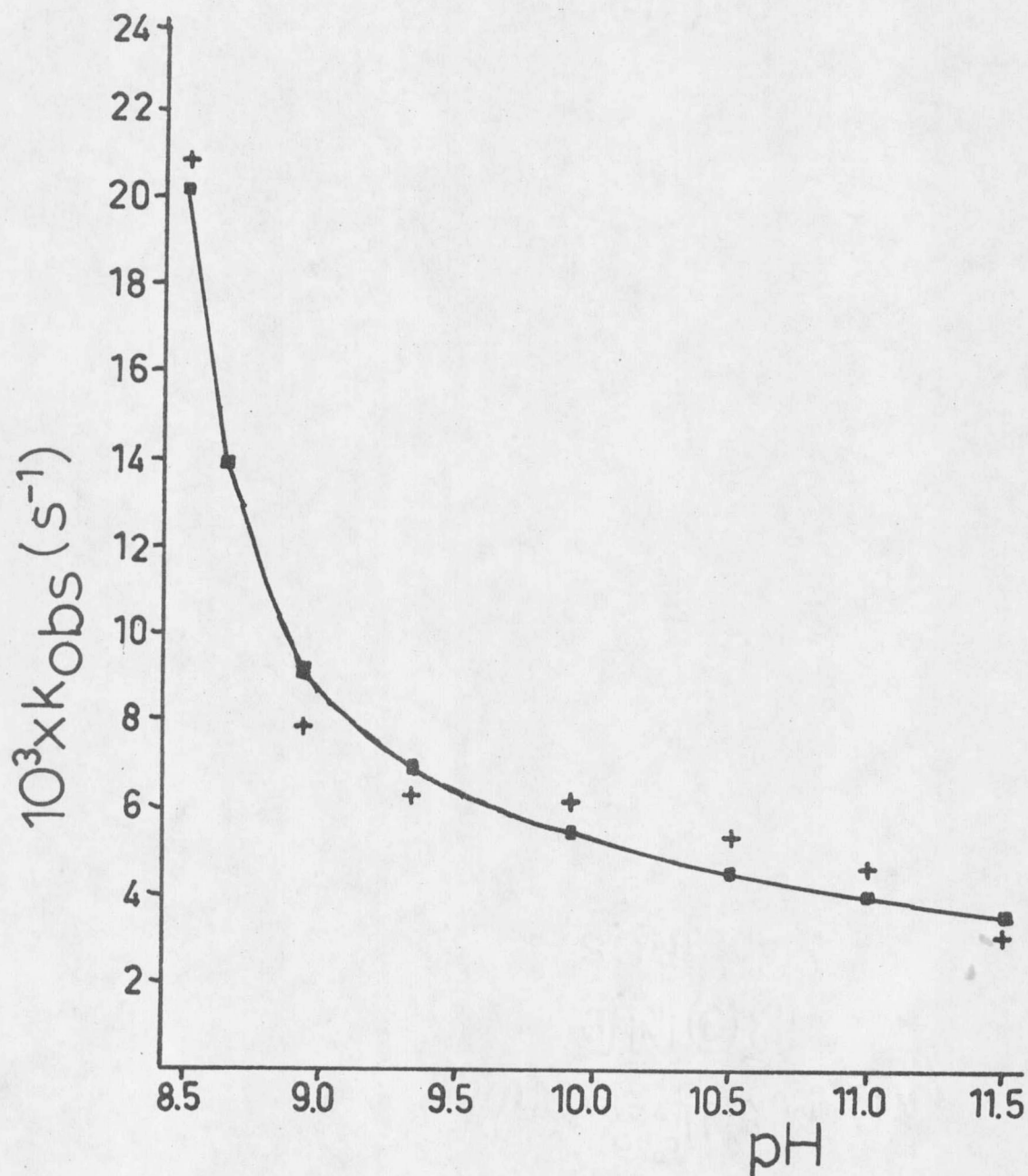


Figure 12. k_{obs} vs pH for the reaction of TRIEN with NiH_2MBAE
 $[\text{TRIEN}]_{\text{T}} = 1.21 \times 10^{-2} \text{ M}$, $B_{\text{T}} = 0.005 \text{ M}$.

DISCUSSION

Mechanism of the Reaction of TRIEN with NiH_2MBAE

TRIEN reacts with NiH_2MBAE faster at low pH. This reactivity pattern is similar to that reported for the reaction of TRIEN with $\text{Cu(II)Glycylglycyl-L-histidine}$ (12), and with $\text{Ni(II)-glycylglycyl-L-histidine}$ (24). In these studies a proton assisted nucleophilic mechanism is proposed, and direct nucleophilic attack is reduced. When nucleophiles can react by displacing an equatorial carboxylate group the reactions are much faster (i.e. TRIEN reaction with CuH_2GGG and NiH_2GGG) than when deprotonated imidazole nitrogens must be displaced (8,11).

When direct nucleophilic attack is unfavorable a proton may be added to a peptide nitrogen, rendering the molecule more susceptible to reaction with nucleophiles. Mono-protonated TRIEN is the most effective of the TRIEN species at facilitating this reaction. A proton is donated to the amide nitrogen, Nickel-nitrogen bond cleavage results and the site is rapidly scavenged. The direct nucleophilic attack on NiH_2MBAE is slow, and consequently $k_{\text{HT}} > k_{\text{T}}$.

Doubly-protonated TRIEN is a very weak acid. Although it can protonate an amide nitrogen similar to HTRIEN^+ , the remaining mono-protonated TRIEN (after the loss of 1 proton) is not an effective nucleophile as one binding site is occupied. For this reason the rate constant $k_{\text{H}_2\text{T}}$ is less than k_{T} , and very much smaller than k_{HT} .

The rate of reaction was too fast to be measured without the use of a stopped-flow apparatus below $\text{pH} = 8.50$. This led us to believe that the reaction switched to a general acid catalysis mechanism in the lower pH range. The calculated value of $k_{\text{H}_3\text{T}}$ supported this conjecture, it was found to be the largest rate constant for this reaction by a factor of over 100. Here again protons are transferred to amide nitrogens facilitating Nickel-nitrogen bond cleavage. A similar reactivity pattern has been reported for the reaction of EDTA with Copper(II)Triglycine (11). Here EDTA will react with CuH_2GGG only after a proton has been transferred to the peptide nitrogen of the triglycine complex.

In addition to the proton-assisted nucleophilic mechanism and general acid catalysis mechanism, a replacing ligand independent pathway was also observed. The intercept k_i , remained constant throughout the pH 8.50-9.92 range. The value of k_i was chosen as the dissociative rate constant, $k_d = 1.0 \times 10^{-3} \text{ s}^{-1}$. There was no evidence for buffer enhancement of the rate, or for specific hydrogen ion catalysis.

At the higher pH values (10.5-11.5) there is a decrease in reactivity exemplified in the slope as well as the intercept of the k_{obs} versus $[\text{TRIEN}]_t$ plots. This leads one to suspect inhibition by hydroxide ion, presumably through coordination in an axial position. This is explained in the rate law by the inclusion of the term

$\frac{1}{1 + K_1[\text{OH}^-]}$, where $K_1 = 1.4 \times 10^3 \text{M}^{-1}$. This term has an effect on reducing the overall rate only when hydroxide ion concentration is high.

Figure 13 is a proposed mechanism for the reaction of TRIEN with NiH_2MBAE . The parallel pathways are evident from the distinct reactivity pattern shown. TRIEN effects the displacement by a proton-assisted nucleophilic mechanism, which switches to a general acid catalyzed mechanism at low pH.

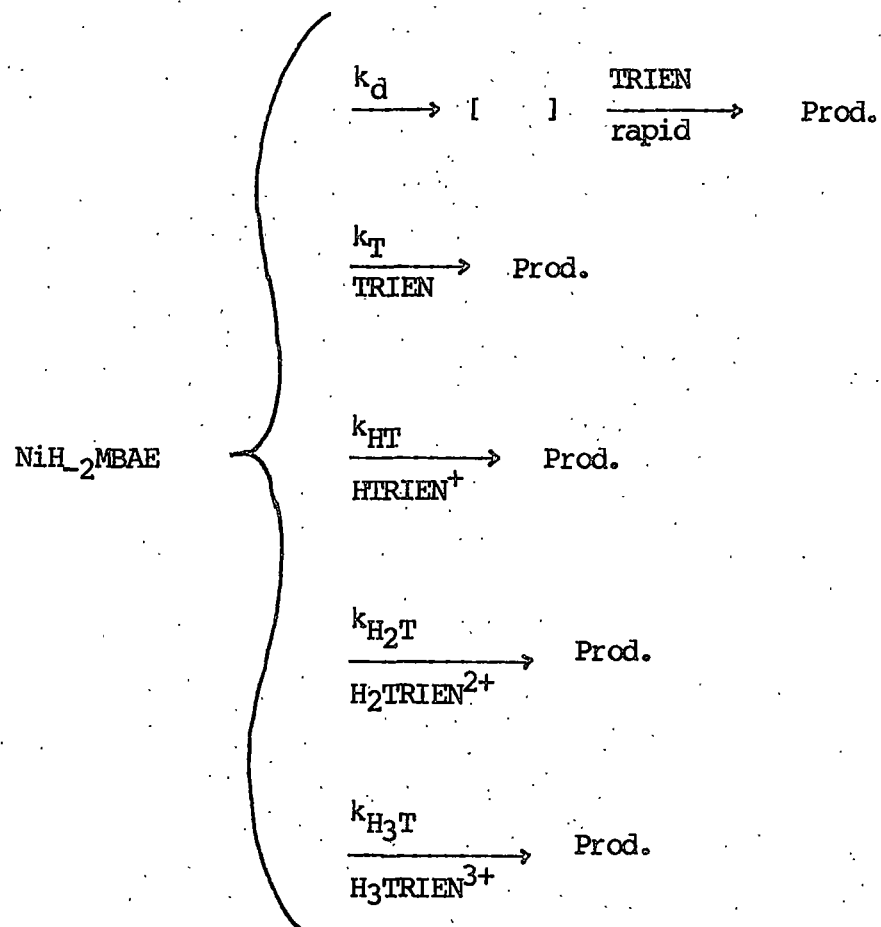


Figure 13. Proposed mechanism for the reaction of TRIEN with NiH_2MBAE .

CONCLUSION

It has been shown that the two complexes studied display quite different reactivity patterns. The reasons for this difference must involve the structural dissimilarities of the two complexes. The NiH_2MBAE complex has the peptide linkages located on the backbone of the square planar complex, and displays a 5,6,5-membered ring structure. Alternatively the NiH_2DGEN complex has the peptide linkages located on the sides of the square planar complex, and displays a 5,5,5-membered ring structure.

Perhaps the largest difference between the two is that both carbonyl oxygens are located on the same ring for NiH_2MBAE but on opposite rings for NiH_2DGEN . This must effect the crystal-field stabilization of the complexes, which is evidenced by the difference in absorption spectra. NiH_2MBAE has $\lambda_{\text{max}} = 440\text{nm}$, $\epsilon = 35\text{M}^{-1}\text{cm}^{-1}$; NiH_2DGEN absorbs at a shorter wavelength (higher energy), $\lambda_{\text{max}} = 410\text{nm}$, and also has a larger molar absorptivity coefficient, $\epsilon = 220\text{M}^{-1}\text{cm}^{-1}$.

Experimentally it has been shown that TRIEN reacts with NiH_2MBAE by a proton-assisted nucleophilic mechanism. This switches to a general acid catalyzed mechanism, at lower pH, which proceeds by inside protonation of the peptide nitrogen.

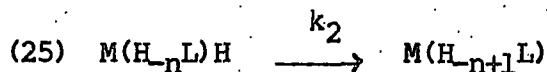
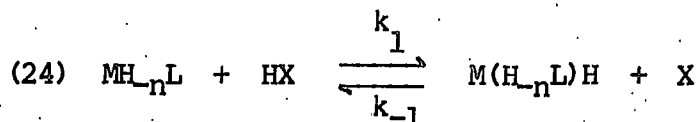
Alternatively TRIEN has been found to react with NiH_2DGEN by a nucleophilic mechanism. This switches to specific hydrogen ion

catalysis (independent of TRIEN) at lower pH, which proceeds by outside protonation of the carbonyl oxygen.

From the different reactivity patterns displayed by the two seemingly quite similar complexes, several questions arise. Why does TRIEN react with NiH_2DGEN by a direct nucleophilic mechanism, but reacts with NiH_2MBAE by a proton-assisted nucleophilic mechanism? What is the reason for specific hydrogen ion catalysis of the reaction with NiH_2DGEN , but the reaction with NiH_2MBAE is general acid catalyzed at lower pH?

It is evident from previous studies that axial coordination is important for nucleophilic displacement of these metal ligand complexes (11). The 6-membered ring on the backbone of the NiH_2MBAE complex has two carbonyl oxygens protruding in an axial orientation, space filling models show the ring to be slightly puckered. This configuration might presumably be blocking toward axial coordination of an approaching nucleophile, which could be part of the reason proton-transfer and metal-peptide nitrogen bond cleavage preceeds coordination of the nucleophile to the metal.

Paniago and Margerum present the following mechanism for protonation of metal peptide complexes:



where the species $\text{M}(\text{H}_{-n}\text{L})\text{H}$ indicates an intermediate protonated complex without cleavage of any metal-N (peptide or amide) bonds (9).

It is evident from spectral data that the NiH_2DGEN complex has greater ligand-field stabilization. The metal-peptide nitrogen bonds are probably more stable partially due to the fact that the carbonyl oxygens are located on opposite sides of the substrate molecule.

According to the mechanism presented above, the relative values of k_2 and k_{-1} are of significance. Paniago and Margerum (9) postulate that as the metal-peptide nitrogen bonds become more stable, the k_2 values become smaller, and the reaction with acids shifts from general acid catalyzed to specific hydrogen ion catalyzed. It is felt that this is an explanation for the different reactivity patterns displayed by the two complexes and their reaction with acids. Unfortunately, thermodynamic data is not available for NiH_2MBAE , as this may possibly substantiate the arguments presented here.

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