



Kinetics and mechanism of the reactions of Ni(II)-N,N-DI-(2-Amino-Ethyl)Oxaldiamide and Ni(II)-N,N-Di-(3-Aminopropyl)Oxaldiamide with Triethylenetetramine Ethylenediaminetetraacetic Acid

by Kim Elizabeth Gilmore

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

Montana State University

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Abstract:

The kinetics and mechanisms of the substitution reactions of nickel (II)-N,N'-di-(2-aminoethyl)oxaldiamide (NiH-2ODEN) and nickel (II)-N,N'-di-(3-aminopropyl)oxaldiamide (NiH-2ODPN) with triethylenetetramine (trien) and ethylenediaminetetraacetic acid (EDTA) have been investigated. The overall rate expressions for the four systems were determined, and the values of the rate constants associated with the reaction pathways identified.

The reactions of both complexes with triethylenetetramine proceed via a direct nucleophilic replacement pathway. Ratios of the rate constants relative to the constant for the unprotonated form of trien are $k_{HT}/k_T = 0.25$ and $k_{H_2T}/k_T = 0.18$ for the reaction of NiH-2ODEN with trien. For the reaction of NiH-2ODPN, $k_{HT}/k_T = 0.55$. The doubly-protonated form of trien does not contribute significantly to the rate for NiH-2ODPN.

The reactions of both complexes with ethylenediaminetetraacetic acid proceed via a proton-assisted nucleophilic pathway. The ratio of the constant for diprotonated EDTA to the constant for monoprotonated EDTA is 35 for the reaction with NiH-2ODEN. The corresponding ratio for the NiH-2ODPN reaction is 100. The fully deprotonated form of EDTA does not react appreciably with either complex.

Ligand-independent constants include a solvent-assisted dissociation constant, k_{H_2O} and constants associated with several proton-limited pathways. The value of k_{H_2O} for NiH-2ODEN is 0.0014 s^{-1} , and 0.001 s^{-1} for NiH-2ODPN. The value of the constant which describes the formation of a protonated intermediate is $6.1 \times 10^6 \text{ M}^{-1}$ for NiH-2ODEN, and $2.0 \times 10^7 \text{ M}^{-1}$ for NiH-2ODPN. The outside protonation constant for the intermediate, k_3 , has a value of $7.0 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for NiH-2ODEN, and $7.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for NiH-2ODPN. The intermediate also reacts via a hydrogen ion-independent pathway.

The value of the rate constant associated with this process, k_2 , is 0.035 s^{-1} for NiH-2ODEN and 0.20 s^{-1} for NiH-2ODPN.

KINETICS AND MECHANISM OF THE REACTIONS OF Ni(II)-N,N'-DI-(2-AMINO-
ETHYL)OXALDIAMIDE AND Ni(II)-N,N'-DI-(3-AMINOPROPYL)OXALDIAMIDE
WITH TRIETHYLENETETRAMINE AND ETHYLENEDIAMINETETRAACETIC ACID

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ABSTRACT

The kinetics and mechanisms of the substitution reactions of nickel(II)-N,N'-di-(2-aminoethyl)oxaldiamide (NiH_2ODEN) and nickel(II)-N,N'-di-(3-aminopropyl)oxaldiamide (NiH_2ODPN) with triethylenetetramine (trien) and ethylenediaminetetraacetic acid (EDTA) have been investigated. The overall rate expressions for the four systems were determined, and the values of the rate constants associated with the reaction pathways identified.

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Ligand-independent constants include a solvent-assisted dissociation constant, $k_{\text{H}_2\text{O}}$, and constants associated with several proton-limited pathways. The value of $k_{\text{H}_2\text{O}}$ for NiH_2ODEN is 0.0014 s^{-1} , and 0.001 s^{-1} for NiH_2ODPN . The value of the constant which describes the formation of a protonated intermediate is $6.1 \times 10^6 \text{ M}^{-1}$ for NiH_2ODEN , and $2.0 \times 10^7 \text{ M}^{-1}$ for NiH_2ODPN . The outside protonation constant for the intermediate, k_3 , has a value of $7.0 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for NiH_2ODEN , and $7.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for NiH_2ODPN . The intermediate also reacts via a hydrogen ion-independent pathway. The value of the rate constant associated with this process, k_2 , is 0.035 s^{-1} for NiH_2ODEN and 0.20 s^{-1} for NiH_2ODPN .

INTRODUCTION

The field of bioinorganic chemistry has mushroomed over the last three decades. An increasing appreciation of the role that metals play in biological systems has led to a great number of studies on the formation, stability, structure, and reactivity of metal-containing compounds of biological origin and of various model systems. A few examples of some relatively common biomolecules serve to show the diversity of metals involved and the truly essential part they play in the life of organisms.

Hemoglobin and myoglobin are the molecules responsible for oxygen transport and storage in most of the higher animals. The active sites of both molecules contain an iron(II) atom bound to a porphyrin ring, called a heme group. The heme group is nestled in a hydrophobic pocket provided by the surrounding protein, which protects the iron atom from the irreversible oxidation which occurs in the presence of water. An interesting variation is seen in some crustaceans, which employ a copper-containing protein for the process of oxygen transport.

Other examples include chlorophyll, the photosynthetic compound found in green plants, which consists of a magnesium atom complexed by a modified porphyrin ring. Vitamin B₁₂ contains a cobalt(III) atom, complexed by a corrin ring (another modified porphyrin ring system). Finally, the pancreatic enzyme carboxypeptidase A contains

a zinc atom bound by the side-chain functional groups of three amino acids within the active site of the enzyme.

In all of these biological molecules, the metal atom is bound by a number of nitrogen, oxygen, and sulfur donors from the organic portion of the molecule. The method of binding helps control the electronic state of the metal atom, and, in some cases, the steric configuration of the molecule which enters to interact with it (generally during enzymatic action). This control, in turn, rigidly defines the mode and rate of reaction in which the molecule participates, hence the extreme specificity of these biological molecules. It is a desire to further understand the action of these systems that has inspired the multitude of studies which have appeared in the literature in the recent past.

Studies of this subject are not new. The discovery of iron-containing compounds in the blood was made in the late 1800's. Jørgensen's and Werner's investigations into the nature of complex ions took place around the turn of the century and laid the foundations for coordination chemistry as we know it. The analytical techniques currently available, as well as the interest of such diverse groups as biologists and solid state physicists, physical chemists and biochemists, have greatly enhanced our abilities to study and understand the problems presented by these systems.

Crystallographic structure determinations show that metals bound in porphyrin or porphyrin-like ring structures are complexed

by nitrogen donors in square-planar fashion, due to the rigid planar structure and configuration of the ring system.¹ The complex is further attached to the protein portion of the molecule by coordination to one or both of the axial positions of the metal by nitrogen-, oxygen-, or sulfur-containing groups on the protein. The heme group in hemoglobin is bound through histidyl nitrogen, leaving the remaining site free to bind molecular oxygen. In cytochrome C, the heme group is coordinated to nitrogen from histidine and sulfur from methionine. In an interesting variation, the cobalt atom in vitamin B₁₂ is coordinated to the four planar nitrogen donors of the corrin ring, with axial positions occupied by imidazole nitrogen and a labile carbon atom of the deoxyribose moiety.

In biomolecules where the metal atom is not rigidly confined by a porphyrin-like ring, greater variety in coordination configuration can be found. In ferredoxins, the iron atoms are tetrahedrally coordinated to sulfur atoms from nearby cysteine residues. Coordination of zinc in carboxypeptidase A is also tetrahedral. Very little is known structurally about copper-containing biomolecules, although a partially completed structure determination indicates that in plastocyanin, coordination by four residues (two histidine, one cysteine, one methionine) is very distorted, neither planar nor tetrahedral.²

Several investigators have sought to explore the behavior of these systems by studying various model systems. A large volume of information is available on the formation and reactions of complexes

of trace metals with amino acids and short polypeptide chains. In the systems discussed above, coordination is through functional groups present in the side chains of the amino acids involved. There is now clear evidence that copper(II) and certain other metal ions can form bonds with deprotonated amide nitrogens in the polypeptide backbone itself. Freeman and co-workers have performed X-ray structural determinations on a number of complexes of Ni(II), Cu(II), and Co(III) with various deprotonated peptide segments.³⁻⁷ These studies confirm the presence of metal-N(peptide) bonds. Careful electron spin resonance (ESR) studies performed on Cu(II)-triglycine and -tetraglycine agree that the coordinated peptide nitrogens are deprotonated in solution.⁸⁻¹¹

Copper(III)-peptide complexes have generated a good deal of interest in recent years. This oxidation state is not common for copper, and it was felt for some time that species containing copper(III) were transitory in nature. It has been determined that peptide coordination facilitates the formation of copper(III) and that these complexes are slow to react with acids and nucleophiles.¹²⁻¹⁴ By contrast, analogous complexes of copper(II) react rapidly with these agents.

Margerum and co-workers have studied copper(III)-peptide complexes extensively, investigating the effects of various conditions on the electrode potential (E°) of the Cu(II)-Cu(III) redox couple and the electron transfer reactions which occur. N-peptide coordination has a large stabilizing effect, substantially

reducing E° values compared with complexes with carboxylate or imidazole donors.¹⁵ Copper(III)-peptide complexes appear to favor one-electron transfer reactions, as both Cu(II) and Cu(III) are stabilized by square-planar coordination. Cu(I) favors tetrahedral coordination, and thus two-electron transfers are not observed for these complexes.¹⁵

It is proposed that copper(III) is present in the active form of galactose oxidase.¹⁶⁻¹⁸ Coordination of the metal in the active site has not been established, but the mechanism appears to involve a two-electron transfer to the substrate molecule. Copper is found in several other enzymes, and Margerum suggests that the Cu(II)-Cu(III) couple be considered as an alternative to the Cu(I)-Cu(II) redox cycle in some biological redox reactions of copper.¹⁵

Arrangement of the ligands about the central metal atom varies with the identity of the donors in metal-peptide complexes. At low pH, prior to amide deprotonation, coordination is through the terminal amine and relatively weak-field carboxylate and peptide oxygen groups. Octahedral geometries are found under these conditions, with water molecules occupying any sites left free by the peptide chain. The ease of peptide hydrogen ionization is shown below.^{19,20}

	Pd(II)	>	Cu(II)	>	Ni(II)	>	Co(II)
pH	3-4		4-6		7-8		10-11

Above the specified pH, stronger-field amide nitrogens displace the

coordinated carboxylate groups. This generally results in square-planar complexes for tripeptides and longer chain oligopeptides, although some copper(II) complexes exhibit tetragonally-distorted octahedral geometries with axially coordinated carboxylate groups. Dramatic color changes often accompany the change in configuration. It should be noted that dipeptides can form bis(dipeptide) complexes with octahedral geometries as well.

Structural studies show that there is a considerable degree of double-bond character in the C-N bond of the coordinated peptide group. Free peptide groups have average C-O and C-N bond distances of 1.24 and 1.325 Å, respectively, while coordinated peptides have slightly longer C-O bonds (~1.26 Å) and shorter C-N bonds (1.30 Å). This suggests that the negative charge is shared by the oxygen and nitrogen atoms. One result is that this group tends to be more rigid with respect to rotation than in the free peptide. Metal-N(peptide) bonds tend to be somewhat shorter than metal-N(amine) bonds within the same complex. Average bond lengths for several copper(II) complexes show the difference: 1.92 Å for Cu-N(peptide) and 2.00 Å for Cu-N(amine).¹² The peptide nitrogen's strength as a ligand field donor is also reflected in the spectral properties of the complexes. This group is high in the spectrochemical series, and λ_{max} values are shifted to lower wavelengths as a result. Absorption maxima for these complexes generally fall between 400 nm and 440 nm.

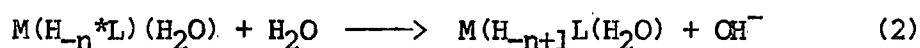
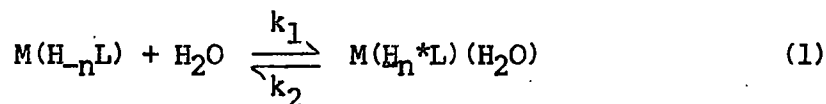
Some interesting comparisons can be drawn from the stability constants and protonation constants of some polyglycine complexes of Ni(II) and Cu(II). Log K values for the formation of copper(II)-triglycine and copper(II)-tetraglycine are 5.5 and 5.4, respectively,²¹ while the value for both corresponding nickel complexes is 3.7.^{22,23} Deprotonation of the amide nitrogens in the copper complexes is successive, each one more difficult than the last. For the triglycine complex, pK_a values are 5.4 and 6.6. This pattern is not seen in nickel complexes, however. The second deprotonation in the analogous complex (pK_a 7.7) is actually easier than the first (pK_a 8.8). Apparently, coordination of the first peptide nitrogen assists further N(peptide) bonding due to the extreme favorability of square-planar complex formation with Ni(II).²²

Reactions of copper(II)-peptide complexes in general proceed faster than the analogous nickel(II) complexes. The reaction of copper(II)-triglycine with acid is an order of magnitude faster than the corresponding reaction of nickel(II)-triglycine. The trend is even more marked when reaction with the nucleophile triethylene-tetramine (trien) is considered; values for copper-triglycine are three orders of magnitude greater than those for the nickel-triglycine reaction.²⁴

Before doing a detailed comparison of the reaction rates of some of these complexes, it is valuable to examine the various ways in which their substitution reactions tend to occur. There are a

number of pathways available for the transfer of the metal atom from one ligand environment to another. The reactivity patterns observed generally include a combination of two or more of the following pathways: solvent-assisted dissociation, nucleophilic attack by the incoming ligand, and proton-transfer limited substitution.

The solvent-assisted pathway is independent of incoming ligand concentration. The following reaction sequence has been proposed.



M is the central metal atom, L is the polypeptide fragment, n is the number of coordinated deprotonated peptide nitrogens, and (H_n^*L) indicates the presence of a free deprotonated-peptide nitrogen. The first step is seen as nucleophilic attack by a solvent molecule on the deprotonated peptide nitrogen, followed by rapid protonation of that nitrogen by another solvent molecule.²⁴ It is even possible that this takes place as a concerted process. Once the metal-peptide nitrogen bond has been broken, dissociation of the coordinated ligand is rapid, and the metal atom is scavenged by the incoming ligand.

During nucleophilic replacement by multidentate ligands, the incoming ligand attaches itself directly to the metal atom, generally through a weak out-of-plane coordination. Dissociation of

a terminal position of the coordinated ligand is followed by the rate-determining equatorial coordination of the incoming ligand. Peptide bond breakage of the original ligand occurs only after the rate determining step.^{25,26}

A number of factors affect the rate of nucleophilic replacement in metal-peptide complexes. The first is the influence of the number of metal-N(peptide) bonds present in the complex. The reaction of copper complexes containing one such bond with trien is too fast to measure by stopped-flow techniques. The rate constant for unprotonated trien with $\text{Cu}(\text{H}_2\text{GGG})^-$ containing two metal-N(peptide) bonds is $1.1 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$. Addition of a third such bond in $\text{Cu}(\text{H}_3\text{GGGG})^{2-}$ decreases its reactivity with trien sharply; dependence on trien is absent and the rate is first-order in the copper complex only. A similar trend is observed for nickel complexes.²⁴

A study of the reaction of ethylenediamine (en), diethylenetriamine (dien), and trien with $\text{Cu}(\text{H}_2\text{GGG})^-$ indicates that the terminal amine position of the peptide is the last displaced and that substitution begins with the carboxylate or peptide groups in these complexes.^{25,27} Several characteristics are important in determining the nucleophilic reactivity of incoming ligands. Among these are the coordinating strength of the donor groups, chelating ability of the ligand, and steric factors governing the approach of the donor groups to the kinetically important metal coordination sites.

Rate constants for reactions of copper triglycine with trien and ethylenediaminediacetic acid (EDDA) are $1.1 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$ and $3.7 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$.²⁴ Since the nucleophiles are structurally similar in many respects, it seems likely that the greater rate observed with trien is due to the presence of four nitrogen donors contrasted with EDDA's two terminal carboxylate groups, which do not coordinate as strongly.

The structure of the ligand can produce steric effects which can affect the rate of nucleophilic attack. Ligands containing primary or secondary amines are good nucleophiles, although secondary amines often react somewhat slower. Ligands containing tertiary amines are sterically hindered from coordinating at the planar position of metal-peptide complexes without extensive dissociation or displacement of the peptide chain. For this reason, ethylenediaminetetraacetic acid (EDTA) is a fairly poor nucleophile. It generally reacts as a coordinating acid or a scavenger in reactions catalyzed by other agents.

The importance of chelate effects in the reactions of these complexes can be seen by comparing reaction rates of nickel-triglycine with ammonia, en, dien, and trien. The rate constant for ammonia is small, while reaction with en proceeds 2,100 times faster. Rates with dien and trien are nearly the same as with en, indicating that the formation of one chelate ring, occurring before the rate-determining step, is responsible for the acceleration in rate in all cases. Also, pH effects in these reactions show that

metal-N(peptide) bond breakage does not occur before the rate-determining step.²⁴

Steric characteristics of the oligopeptide can also determine the ease of nucleophilic approach. A series of complexes of copper with various tripeptides including GGG, LGG, GLG, LGL and GAG (G = glycine, L = leucine, and A = alanine) were studied in their reactions with polyamines. A decrease in rate is observed with the presence of the methyl side-chain of alanine and the isobutyl side-chain of leucine. It is interesting that the decrease in rate is much more pronounced when leucine is the second or third amino acid in the chain (nearer the carboxylate end) than when it is in the first position (at the terminal amine end).^{28,29} This supports the assertion that substitution begins at the carboxylate end of the tripeptide.

A variation on the nucleophilic pathway is proton-assisted nucleophilic attack. Direct nucleophilic replacement is characterized by dependence on nucleophile concentration and increasing reaction rate with increasing pH. This is because the deprotonated forms of the ligand are better nucleophiles. Conversely, complexes which react via a proton-assisted nucleophilic pathway exhibit increasing reaction rates with decreasing pH. An example is copper glycylglycylhistidine. The coordinated imidazole nitrogen of this complex is much more difficult to displace than the terminal carboxylate group in CuH_2GGG^- . As a result, direct nucleophilic replacement by trien is seven orders of magnitude

slower, while the proton-assisted pathway is the major substitution pathway observed.^{30,31}

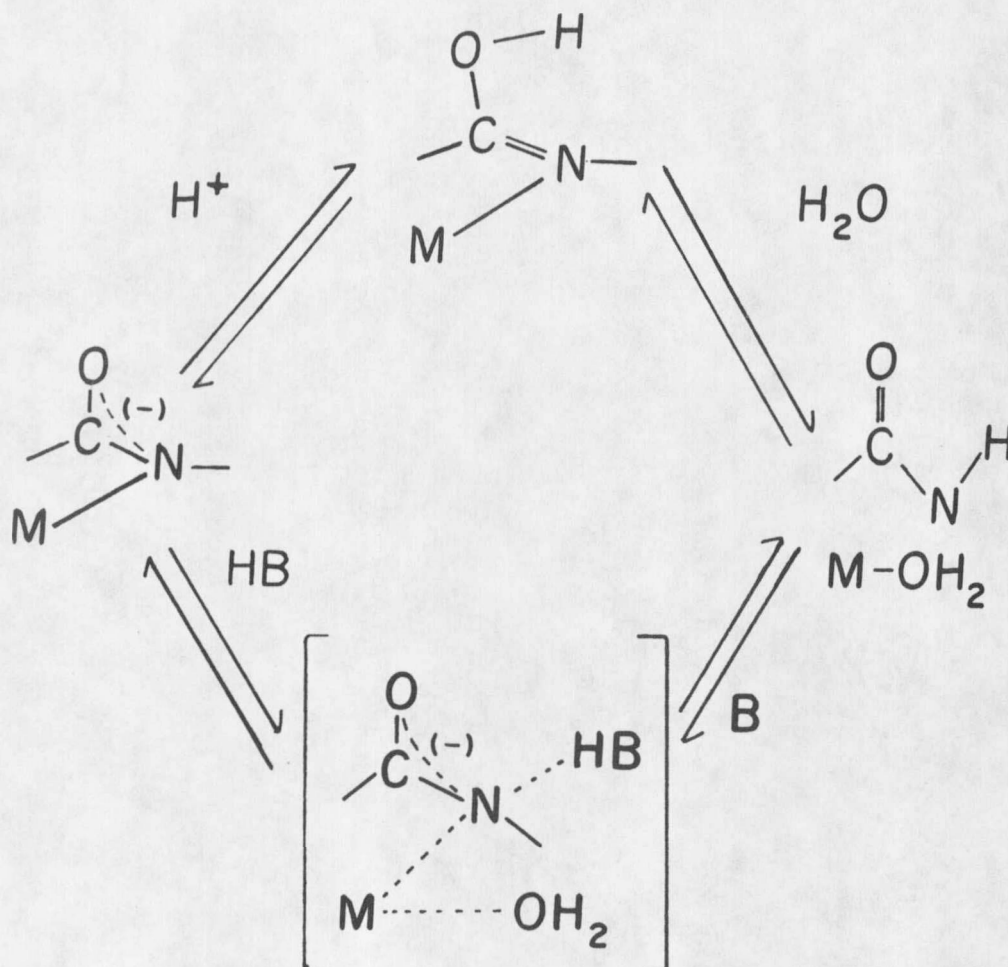
Not surprisingly, protonated forms of the ligand are more effective in this pathway. Reaction probably involves proton transfer to the peptide nitrogen just prior to or during initial ligand coordination to the metal. Protonation of the peptide nitrogen causes rupture of the metal-N(peptide) bond. This, in turn, causes dissociation of the peptide fragment, followed by coordination of the incoming ligand.

There are two major types of proton-transfer limited substitutions observed. The first is general acid catalyzed substitution, where the protonation step is rate-determining. The second, specific hydrogen ion catalysis, involves a protonation equilibrium, followed by the rate-determining bond breakage.³²

It has been proposed that reactions exhibiting general acid catalysis proceed via an inside protonation mechanism,²² which is shown in Figure 1. In this mechanism, the peptide nitrogen is protonated directly, and metal-N(peptide) bond breakage is thought to be concurrent. Reaction rate depends on buffer concentration in reactions of this type.

Specific catalysis by hydrogen ion proceeds via an outside protonation mechanism,³³ also shown in Figure 1. Protonation of the peptide oxygen is rapid, followed by transfer of the proton to the peptide nitrogen with breakage of the metal-N(peptide) bond. The amount of intramolecular reorganization required for the transfer

OUTSIDE PROTONATION PATHWAY

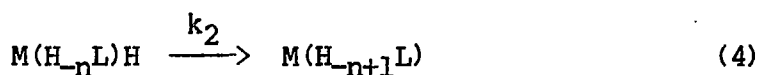
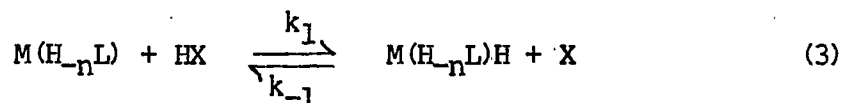


INSIDE PROTONATION PATHWAY

Figure 1. Alternate pathways for the proton-transfer reactions of metal-N(peptide) complexes.

makes the overall process slower than general acid catalysis. No buffer dependence is observed in reactions of this type. In both cases, the metal ion is scavenged by the incoming ligand after the rate-determining step has occurred.

Paniago and Margerum have proposed a general mechanism for the protonation of metal peptide complexes which is shown below.³³ Four different cases are discussed to show how this mechanism includes reactions of the types discussed previously.



The species $M(H_{-n}L)H$ refers to an intermediate which is protonated without cleavage of any metal-N(peptide or amide) bonds. The mechanism postulates that either protonation (Equation 3) or metal-N(peptide) bond breakage (Equation 4) could be rate-determining, depending on the complex and the acid.

In the case where the concentration of $M(H_{-n}L)H$ is negligible and $k_2 \approx k_{-1}[X]$, the steady-state approximation can be used. In this instance, catalysis by HX and inhibition by X are observed. This behavior is seen in the reaction of NiH_2GGG^- with HCO_3^- and CO_3^{2-} .

When the concentration of $M(H_{-n}L)H$ is negligible and $k_2 \gg k_{-1}[X]$, general acid catalysis is observed. The rate-determining

step occurs with formation of the protonated intermediate. The rearrangement of this species to form $M(H_{n+1}L)$ is fast relative to the proton transfer step.

When the concentration of $M(H_nL)H$ is negligible and $k_2 \ll k_{-1}[X]$, the condition previously described as specific hydrogen ion catalysis is observed. Equation 3 may be regarded as a rapid pre-equilibrium, and $K_H[H^+] = k_1[HX]/k_{-1}[X]$, where K_H is the protonation constant for $M(H_nL)H$. This pattern is observed for reactions of NiH_3GGG^{2-} and NiH_3GGGa^- , which contain an additional N(peptide or amide) group coordinated to the metal, as compared with NiH_2GGG^- . The additional nitrogen coordination slows the metal-nitrogen bond cleavage.

Conditions can exist where the concentration of $M(H_nL)H$ is appreciable. When this occurs and $k_2 \ll k_{-1}[X]$, the reaction rate levels off as the pH decreases, and the reactant is converted to the protonated species. This behavior is observed for NiH_3GGG^{2-} below pH 4.

An examination of the reactivity patterns of several related complexes will serve to illustrate further the conditions under which the various pathways just described are observed. Table 1 gives rate constants reported for the systems under discussion, and the structures of the complexes can be found in Figure 2.

Nickel-triglycine (NiH_2GGG^-) has been studied extensively, including proton transfer reactions^{22,34} and ligand exchange reactions with trien and EDTA.³⁵ As mentioned earlier, steric

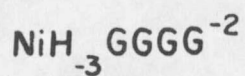
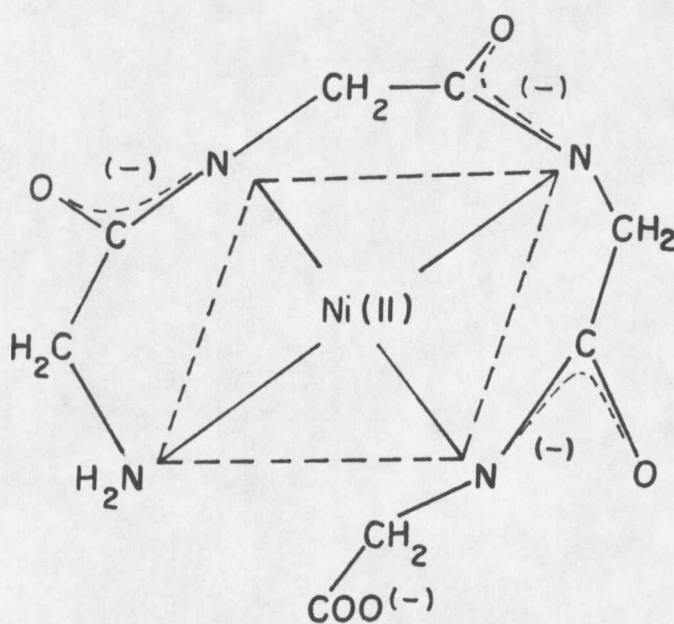
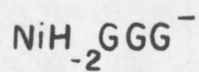
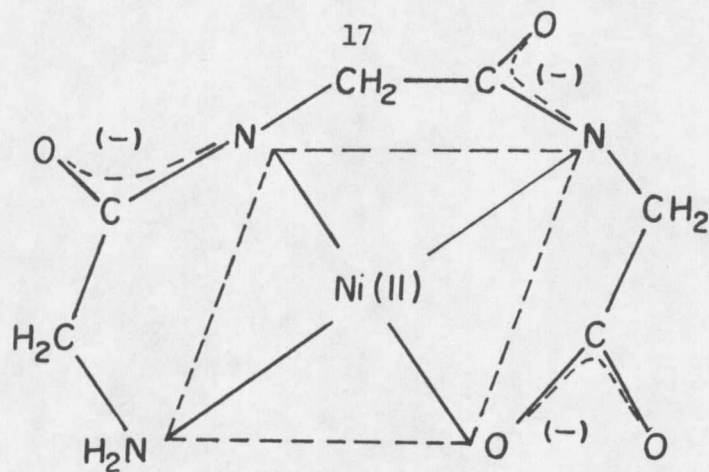
Const.	NiGGG	NiGGGG(33)	NiGGGa(33)	NiGGa(26)	NiGGaCN	NiGGalut(39)	NiGGhis(40)	NiDGEN
k_{H_2O} (s^{-1})	0.086(34))	1.6×10^{-5}		3.1	8.0×10^{-5} (36)	5.6×10^{-2}	8×10^{-5}	2.1×10^{-4} (42) 3×10^{-4} (41)
k_H ($M^{-1}s^{-1}$)	9.5×10^4 (34)	7.1×10^4	3.3×10^4		4.3×10^3 (36)	800	3×10^4	8.5×10^3 (41)
k_T ($M^{-1}s^{-1}$)	1.7×10^4 (35)				13.5(38)			
k_{HT} ($M^{-1}s^{-1}$)	1.8×10^4 (35)				11.6(38)			0.63*(41)
k_{H_2T} ($M^{-1}s^{-1}$)	9.0×10^2 (35)							0.046**(41)
k_Y ($M^{-1}s^{-1}$)	~6(35)							3.33×10^{-3} (42)
k_{HY} ($M^{-1}s^{-1}$)	negligible(35)							8.13×10^{-3} (42)

* k_{HT}/k_T

** k_{H_2T}/k_T

† Acronyms for the complexes do not specify the number of dissociated hydrogen ions or the charge of the complex.

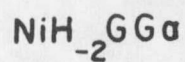
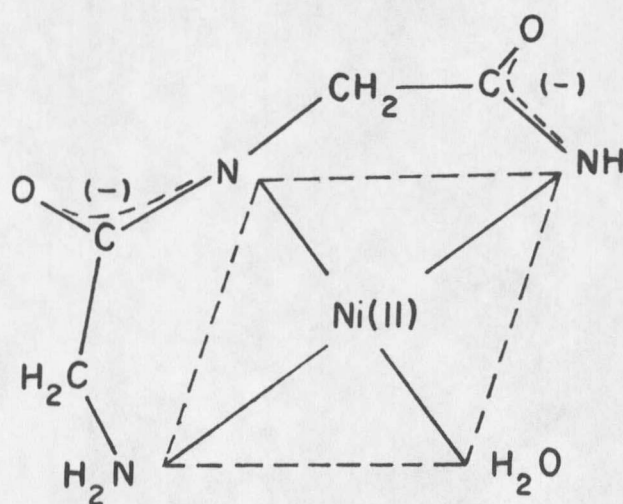
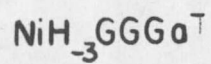
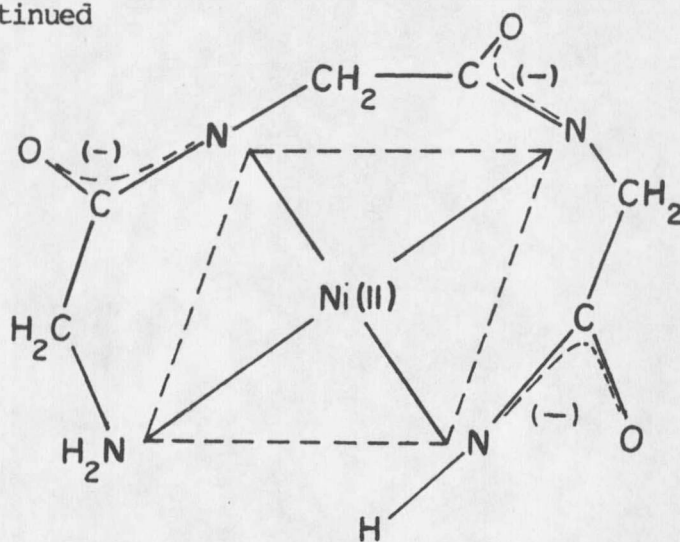
Table 1. Rate constants for some peptide and peptide-amide complexes of Ni(II).[†]



Structures of nickel(II) triglycine (NiH_2GGG^-) and
nickel(II) tetraglycine ($\text{NiH}_3\text{GGGG}^{2-}$)

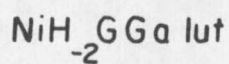
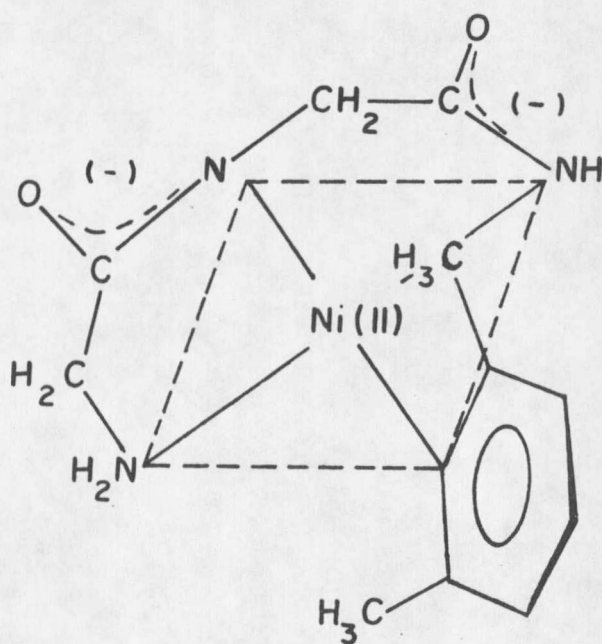
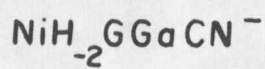
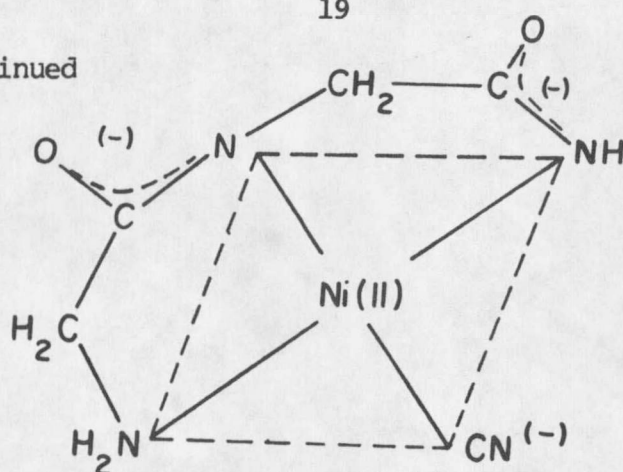
Figure 2. Structures of several nickel(II) complexes.

Figure 2 continued



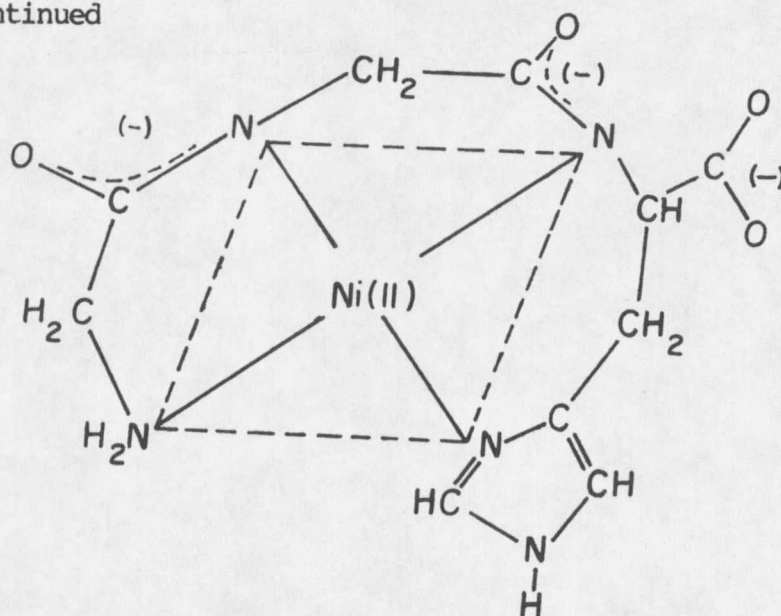
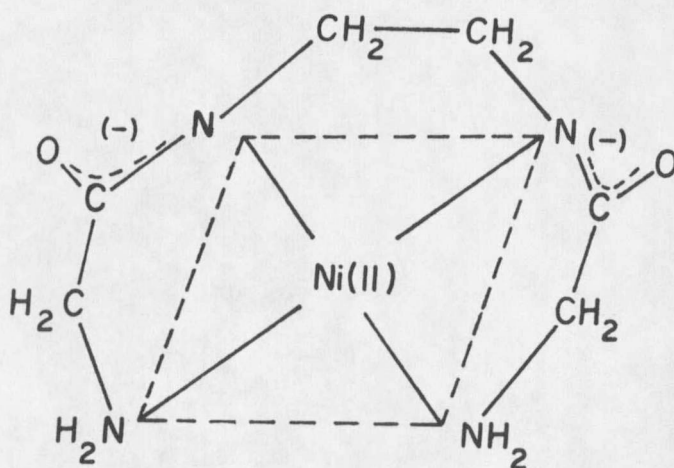
Structures of nickel(II)triglycinamide (NiH_2GGa^-) and nickel(II)diglycinamide (NiH_2GGa)

Figure 2 continued



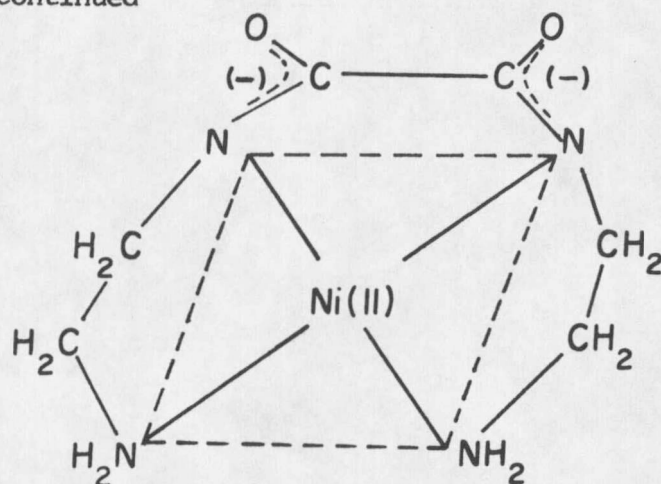
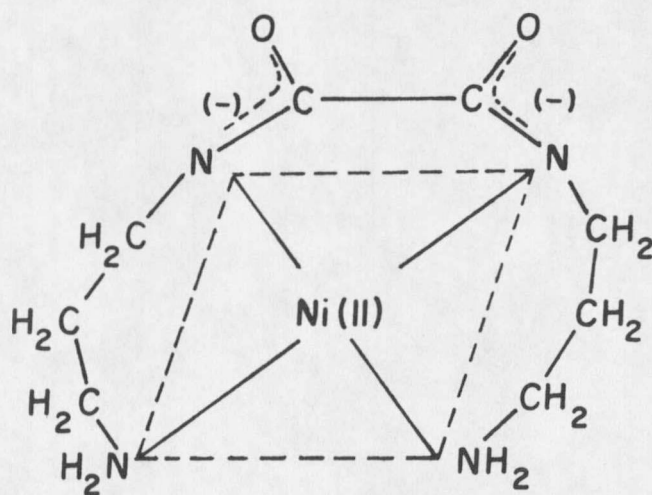
Structures of nickel(II)diglycinamide-cyanide ($\text{NiH}_2\text{GGaCN}^-$)
and nickel(II)diglycinamide-2,6-lutidine
($\text{NiH}_2\text{GGa lut}$)

Figure 2 continued

 NiH_2GGhis  NiH_2DGEN

Structures of nickel(II)diglycylhistidine ($\text{NiH}_2\text{GGhis}^-$)
and nickel(II)diglycylethylenediamine (NiH_2DGEN)

Figure 2 continued

 NiH_2ODEN  NiH_2ODPN

Structures of nickel(II)-N,N'-di(2-aminoethyl)oxaldiamide
 (NiH_2ODEN) and nickel(II)-N,N'-di(3-aminopropyl)oxaldiamide
 (NiH_2ODPN)

considerations make EDTA a poor nucleophile. A dependence on $[H_2EDTA]$ was reported, although a resolved rate constant is not available, indicating that EDTA may react as a coordinating acid in this system. Relative magnitudes of the constants for the various forms of trien indicate that it reacts as a nucleophile. This complex exhibits general acid catalysis in its reaction with acids. There is a solvent-assisted dissociation pathway as well.

By contrast, the reactions of nickel-tetraglycine (NiH_3GGGG)²⁻ and nickel-triglycinamide (NiH_2GGGa)⁻ with acid show specific hydrogen ion catalysis.³³ As indicated earlier, the rate constant for this step is somewhat smaller than the corresponding one for NiH_2GGG ⁻. Constants for these two systems are deceptively similar in magnitude. The k_H values reported in Table 1 are actually combinations of outside protonation and proton-transfer bond-breakage constants. The outside protonation constant for NiH_3GGGG ²⁻ is 50 times greater than that for NiH_3GGGa ⁻, while the subsequent dissociation constant is decreased by a similar factor. It is believed that the free carboxylate group in the protonated NiH_2GGGG ⁻ species is able to form an internally H-bonded cyclic species (see Figure 3) which is more stable than the protonated NiH_2GGGa ⁻ species. This accounts for the greater ease in protonation. It would also explain the slower nickel-N(peptide) bond cleavage. The cyclic intermediate would be slower to rearrange and transfer the proton to the peptide nitrogen. Also, any initial metal-N(peptide) bond weakening due to the outside protonation is

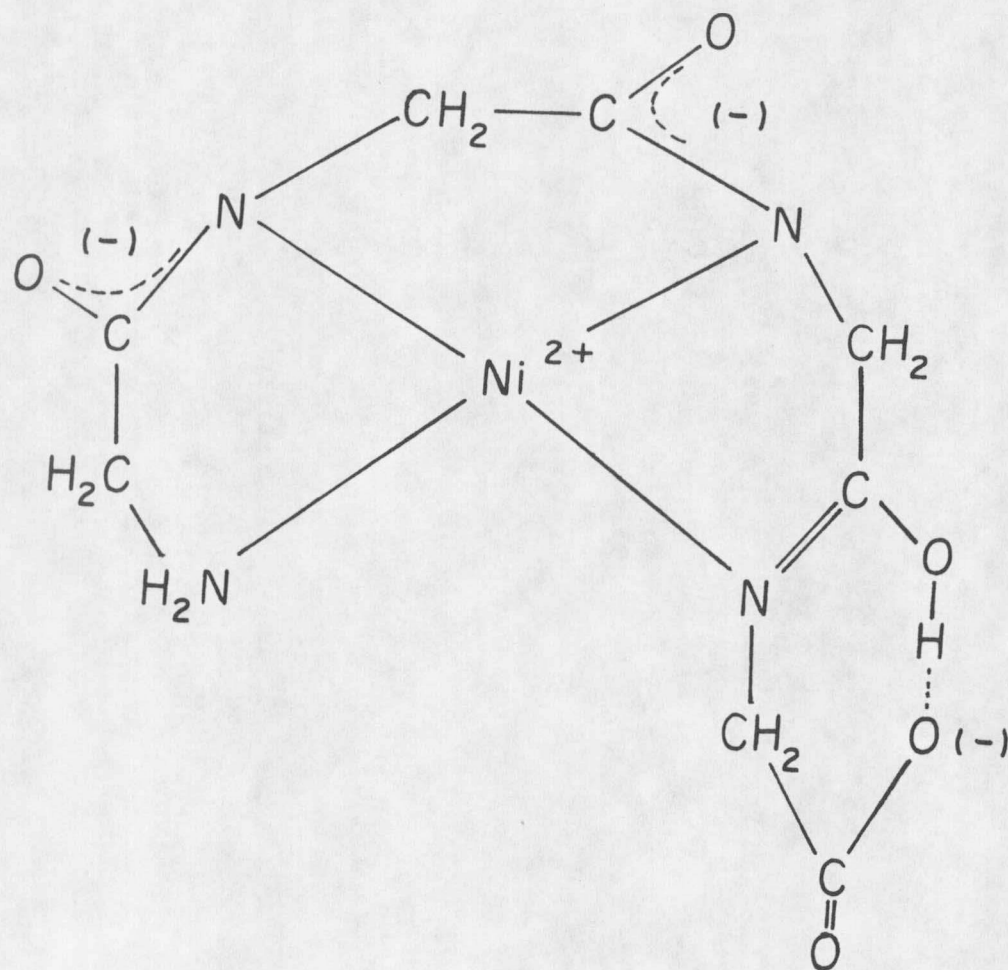


Figure 3. Proposed structure of $(\text{NiH}_3\text{GGGG})\text{H}$.

lessened by charge distribution throughout the ring in the intermediate.

Although no constant for the solvent dissociation pathway is reported for $\text{NiH}_3\text{GGGa}^-$, the $k_{\text{H}_2\text{O}}$ value for $\text{NiH}_3\text{GGGG}^{2-}$ is more than three orders of magnitude smaller than the corresponding constant for NiH_2GGG^- . This could reflect either greater stability in complexes with four coordinated nitrogens as opposed to three, or the greater lability of coordinated carboxylate in the dissociation which follows metal-peptide bond breakage.

The nickel-diglycinamide complex (NiH_2GGa) has three nitrogen donors coordinated in the plane of the metal atom, with H_2O coordinated in the fourth position. The decreased stability of the complex is reflected in the dissociative rate constant, which is nearly two orders of magnitude greater than that reported for NiH_2GGG^- .²⁶ The absence of a third chelate ring in NiH_2GGa probably contributes to this as much as the greater ligand field strength of carboxylate in the fourth position of the triglycine complex. Once NiH_2GGa 's peptide nitrogen is displaced, further dissociation of the peptide is rapid.

Replacement of coordinated H_2O by cyanide imparts considerable stability to the cyano(glycylglycinamido)nickelate complex ($\text{NiH}_2\text{GGaCN}^-$). This is readily apparent upon comparison of $k_{\text{H}_2\text{O}}$ values for the two systems.³⁶ The cyano complex shows specific hydrogen ion catalysis in its reaction with acids.³⁷ The reaction is slower than observed for the other complexes discussed, including

those with amide or peptide nitrogen in the fourth position. Reaction with the nucleophile trien is also slower than that of NiH_2GGa .³⁸

The reactions of the ternary complex of 2,6-lutidine with NiH_2GGa have been studied in an attempt to determine the effect of sterically hindering the axial positions of the complex on its kinetic behavior. When 2,6-lutidine is coordinated in the fourth planar position about the nickel atom, the methyl groups tend to block axial coordination sites.³⁹ It is expected that the rate of nucleophilic attack will be decreased. It is interesting that this axial hindrance also decreases the rate of reaction with acid. Further, the reaction is specific acid catalyzed, when comparison of ligand field stabilization with other similar complexes predicts general acid catalysis for $\text{NiH}_2\text{GGalut}$. Raycheba and Margerum propose that axial solvation of the complex plays a greater part in the general acid mechanism than in the specific acid mechanism in view of these results.³⁹

The behavior of the nickel-glycylglycyl-L-histidine complex ($\text{NiH}_2\text{GGhis}^-$) is rather more complex than the systems previously discussed.⁴⁰ In its reaction with acids, it exhibits both general acid and proton-assisted mechanisms. In the range of pH 5-7, protonation of the second peptide nitrogen is rate-limiting, with a shift of rate-determining step to protonation of the first peptide nitrogen with high general acid concentration. Below pH 5, reaction proceeds via formation of outside protonated species. In its

reaction with trien, proton-assisted nucleophilic replacement is observed between pH 5 and 8. Above pH 8, reaction proceeds via the direct nucleophilic pathway. Above pH 10.5, the rate of reaction is inhibited by OH^- . The authors postulate that this is due to reversibility of an equilibrium step with water, as there is no spectral evidence of formation of a mixed hydroxide species.⁴⁰

Comparison of the rate constants with those of NiH_2GGG^- shows the effect of the coordinated imidazole group in $\text{NiH}_2\text{GHis}^-$ which replaces the carboxylate group in NiH_2GGG^- . The solvent dissociation constant is three orders of magnitude smaller for $\text{NiH}_2\text{GHis}^-$, as are the general acid constants (not shown). The difference in specific hydrogen constants is not as great. The ability of $\text{NiH}_2\text{GHis}^-$ to form an internally H-bonded structure, as does $\text{NiH}_3\text{GGGG}^{2-}$, may contribute to the relative increase in the magnitude of the k_{H} term. Resolved constants for the reaction of $\text{NiH}_2\text{GHis}^-$ with trien are not available, but this reaction proceeds five orders of magnitude more slowly than does the corresponding NiH_2GGG^- reaction at a comparable pH. It is clear that the less-easily displaced imidazole group markedly affects the reactivity of this complex.

The structure of the nickel-diglycylethylenediamine complex (NiH_2DGEN) is somewhat different from the peptide and peptide-amide complexes discussed so far. Both terminal groups are coordinated amines, and both peptide oxygens are located in the side-chains, giving the complex greater symmetry. Table 1 shows that this

complex has a solvent dissociation constant an order of magnitude greater than those observed for $\text{NiH}_3\text{GGGG}^{2-}$, $\text{NiH}_2\text{GGaCN}^-$, and $\text{NiH}_2\text{GGhis}^-$, but 300 times smaller than for NiH_2GGG^- . Its reaction with acid is specific hydrogen ion catalyzed, with a rate constant somewhat smaller than those of $\text{NiH}_3\text{GGGa}^-$ and $\text{NiH}_2\text{GGhis}^-$.

The ligand exchange reactions of NiH_2DGEN with trien^{41} and EDTA^{42} have been studied. The fact that k_{HY} is larger than k_{Y} indicates that EDTA follows a proton-assisted nucleophilic mechanism. The behavior of this complex with trien is not simple. The authors propose an initial equilibrium step prior to reaction with the nucleophile,⁴¹ resulting in trien constants which cannot be clearly resolved. Ratios of the reactivity of the various protonated forms indicate that direct nucleophilic substitution takes place.

The complexes under investigation in this work bear some structural resemblance to the NiH_2DGEN complex. Examination of the reactions of these symmetrical complexes, which contain the same linkages as those found in polypeptide complexes, shows that relatively minor structural variations produce large changes in the rate of reaction and the reactivity pattern observed. Certain complexes exhibit general acid catalysis, while others show specific hydrogen ion catalysis. Direct nucleophilic replacement, proton-assisted nucleophilic substitution, and solvent-assisted pathways have been observed for various members of this family of

complexes. The reactions of the two complexes under study with trien and EDTA will be examined in detail.

STATEMENT OF THE PROBLEM

The various pathways available to metal-peptide complexes in their reactions with acids and polyamide ligands have been discussed in the previous chapter. They include dissociative, nucleophilic, and proton-transfer limited pathways.

The nickel complexes currently under study form yellow, square-planar complexes above $\text{pH} = 9.0$. Both contain two peptide oxygens in the backbone of the complex. Nickel- $\text{N,N}'$ -di-(2-aminoethyl)oxal-diamide (NiH_2ODEN) has two carbons in each side chain, forming five-membered chelate rings. Nickel- $\text{N,N}'$ -di-(3-aminopropyl)oxal-diamide (NiH_2ODPN) has three carbons in each side chain, forming six-membered rings. The complexes have amine groups coordinated in both terminal positions, and deprotonated peptide nitrogens coordinated in the backbone positions. The additional plane of symmetry present in NiH_2DGEN is also present in these complexes.

Several factors are expected to affect the reactivity of these complexes. The adjacent carbonyl groups in the backbone lend a rigidity to this portion of the ligand which could affect the ease of ring-opening during substitution. The more flexible carbon side-chains, compared with NiH_2DGEN 's side-chains which contain peptide oxygens, will produce an as yet unknown effect on the reactivity of the complexes, as will the change from five- to six-membered rings. The reactions of NiH_2ODEN and NiH_2ODPN with trien and EDTA have

been studied in order to more fully understand the effects of these structural variations on mechanism and rate of reaction.

EXPERIMENTAL.

Apparatus

Fast reactions (all reactions with NiH_2ODPN and low pH reactions with NiH_2ODEN) were monitored spectrally by means of a Durrum Model D-103 stopped-flow instrument. A schematic diagram of the instrument is shown in Figure 4. The visible light source was powered by a Beckman DU Power Supply, and the ultraviolet light source was powered by a Beckman Hydrogen Lamp Power Supply. Monochromatic light of the desired wavelength was produced by a Beckman DU spectrophotometer. Light passed through the observation cell (path length = 2 cm), and the non-absorbed portion struck the photomultiplier tube. The signal produced in the photomultiplier traveled via coaxial cable to the oscilloscope to be recorded. Data was collected by a Tektronic type 564 storage oscilloscope. An offset voltage was applied to adjust the oscilloscope screen to maximum sensitivity. Reactants were placed in the drive syringes. The plunger applied pressure to both syringes simultaneously, and the reactants were driven through a mixing chamber and into the observation cell. Sufficient excess solution passed through the cell to flush it of previous reactants and products. The excess flowed through to the stopping syringe. The system was closed, so the stopping syringe moved as it filled until it impacted with a barrier, abruptly stopping the flow. Impact of the stopping syringe

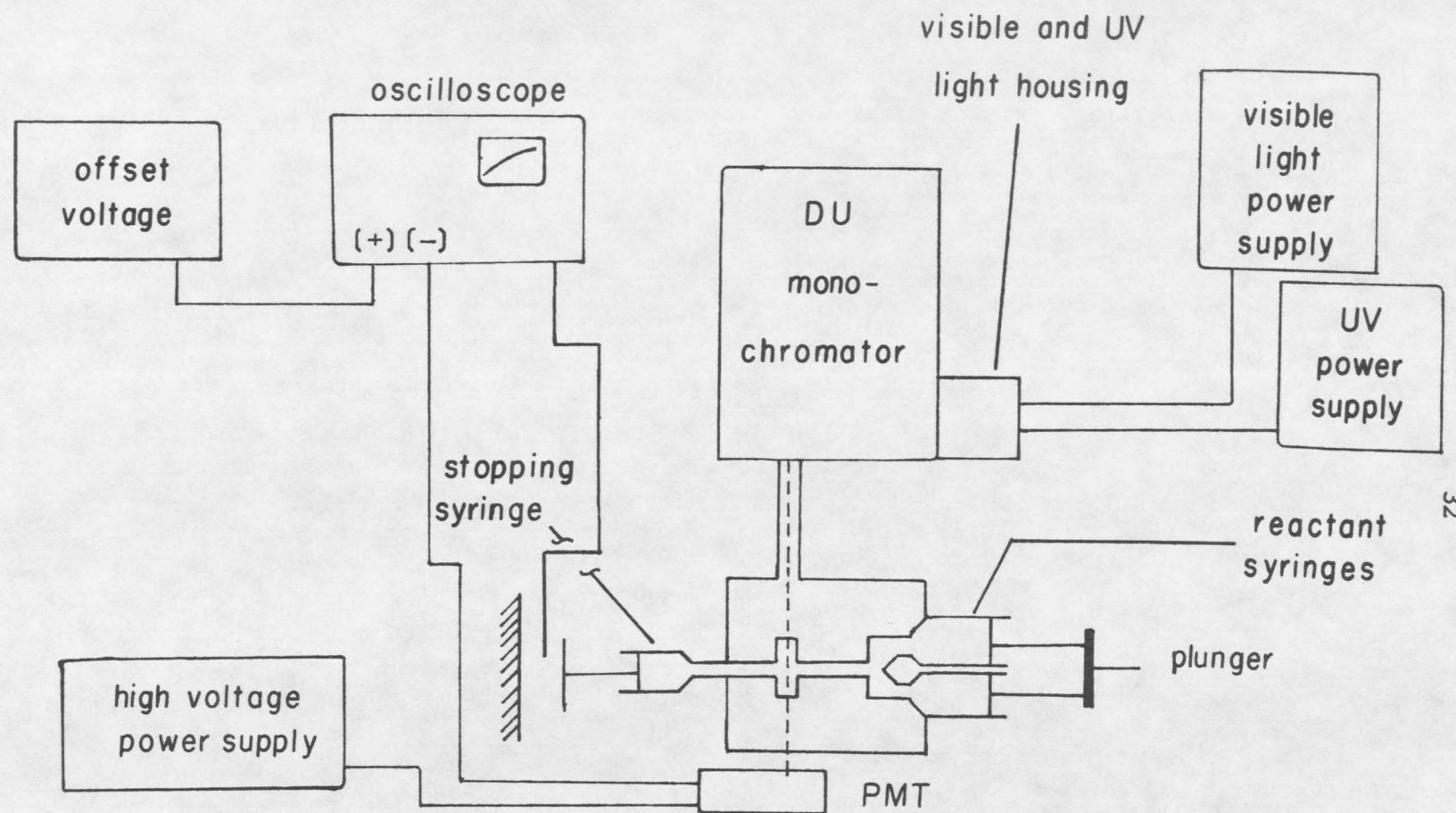


Figure 4. Schematic diagram of stopped-flow apparatus.

initiated data collection. The drive syringes, mixing chamber, and observation cell were maintained at a constant temperature of 25.0°C by a thermostatted bath housing.

Slower reactions were monitored by means of a Varian Model 634S UV-Visible Spectrophotometer. This is a double-beam instrument which allows measurements in absorbance, percent transmittance, or concentration to be taken over a range of 190 nm to 900 nm. Measurements at fixed wavelength or by automatic scanning are possible with this instrument. Kinetic measurements were done at a fixed wavelength using matched 2 cm quartz cells with doubly distilled water in the reference cell. Spectral characterization of the reactants was done using the scanning mode. Data were collected by an associated Varian Model 9176 Strip-Chart Recorder.

An Orion 91-05 combination pH electrode in association with a Corning 130 pH meter was used for all pH measurements except those performed using tris buffer. An Altex #531820 combination pH electrode with a ceramic junction was used for the tris measurements. The instrument was calibrated using VWR Scientific standard pH buffer solutions.

Reagents

Stock Solutions. A stock solution of $\text{Ni}(\text{ClO}_4)_2$ was prepared by dissolving the twice recrystallized salt in doubly distilled water. The solution concentration was determined to be $1.00 \times 10^{-1} \text{ M}$ by means of an EDTA titration, using solid 0.2% murexide indicator.⁴³

Anhydrous sodium perchlorate was prepared in the following manner. The hydrated salt was dissolved in boiling doubly distilled water and filtered. The solution was cooled, and the crystals collected were recrystallized once more from doubly distilled water. The second crop of crystals was lyophilized for 8 hours, then stored in a vacuum dessicator. A 1.0 M stock solution was prepared by dissolving a predetermined weight in doubly distilled water.

Stock buffer solutions were prepared as follows. A sufficient amount of dried, recrystallized sodium borate was dissolved in doubly distilled water to make a 0.10 M solution. Solutions of tris(hydroxymethyl)aminomethane (tris) and sodium acetate, also 0.10 M, were prepared in a similar fashion. The 0.10 M solution of picoline buffer was prepared by dissolving an appropriate weight of practical grade 2-methylpyridine (2-picoline).

The disulfate salt of triethylenetetramine was prepared in the following manner. Technical grade trien was purified by vacuum distillation at 0.5 mm mercury. Two equivalents of concentrated sulfuric acid were added dropwise to one equivalent of the purified trien dissolved in three volumes of ice-cold toluene. An ice-bath was used to maintain the temperature of the mixture throughout the reaction. After the addition was complete, the mixture was stirred for one hour. The precipitate obtained was filtered, dried, and twice recrystallized from doubly distilled water.⁴⁴

A stock solution of approximately 0.10 M trien was prepared by dissolving an analytically weighed amount of the disulfate salt in

doubly distilled water. A small amount of dilute NaOH was added for complete solution of the trien salt. The solution was standardized using the mole ratio method. Varying amounts of the trien solution were added to a fixed amount of $9.75 \times 10^{-2} \text{ M Cu(ClO}_4)_2$. The concentration of Cutrien^{2+} formed was determined spectrophotometrically at 575 nm. A 0.05 M acetate buffer was used to maintain the pH at 4.8, and ionic strength was maintained at 0.10 M with sodium perchlorate.

The recrystallized disodium salt of ethylenediaminetetraacetic acid (EDTA) was dissolved in doubly distilled water to produce an approximately 0.10 M stock solution. The solution was standardized by the CaCO_3 method⁴⁵ using ErioChrome Black T as the indicator.

Ligands. The ligands $\text{N,N'-di-(2-aminoethyl)oxaldiamide}$ (ODEN) and $\text{N,N'-di-(3-aminopropyl)oxaldiamide}$ (ODPN) were synthesized by the method of Hill and Raspin.⁴⁶ Approximately 0.087 moles of diethyl oxalate were added dropwise with stirring to 0.60 moles of ethylenediamine (en) to form ODEN. The same excess of 1,3-propylenediamine (pn) was used to form ODPN. The mixture was held at 0°C for one hour, then allowed to stand at room temperature for two days. Excess en (or pn) and ethyl alcohol were removed by evaporation under reduced pressure. The remaining solid was washed with cold absolute ethanol. The dihydrochloride salt was formed by dissolving the precipitate in methanol which was then bubbled with HCl gas. The resultant white powder was collected and dried.

Ligands were characterized by elemental analysis and carbon-13 nuclear magnetic resonance (NMR) spectroscopy.

Table 2 contains the names and abbreviations of all chemicals used, as well as suppliers and compound purity.

Reactant Solutions. The initial complexes were formed by adding a 50% excess of ODEN or ODPN to a solution containing an aliquot of the nickel stock solution. For the majority of the kinetic measurements, the concentration of the complex solution was such that dilution with an equal volume of incoming ligand solution during the reaction produced a solution where $[\text{Ni}]_{\text{T}} = 5.0 \times 10^{-4} \text{ M}$. Ionic strength was maintained at 0.10 M with NaClO_4 . The solution was bubbled with nitrogen to prevent formation of mixed complexes with oxygen during the slow adjustment of pH with dilute NaOH to approximately pH = 9.0. For reactions where the reaction pH $\geq$ 9.0, the complex solution was buffered with 0.005 M sodium borate. For pH-jump experiments conducted at pH < 9.0, the complex solution was unbuffered. After the final pH had been attained, the solution was brought to volume with deoxygenated doubly distilled water, mixed thoroughly, bubbled once more with nitrogen, and placed in a water bath thermostatted at 25.0°C.

Trien and EDTA solutions were prepared in a similar manner. Reaction concentrations (after 1:1 dilution) ranged from 1×10^{-3} to $7 \times 10^{-3} \text{ M}$. An aliquot of the stock solution was diluted with deoxygenated doubly distilled water. Ionic strength was again maintained at 0.10 M with NaClO_4 . The appropriate buffer was also

Name	Abbreviation
N,N'-di-(2-aminoethyl)oxaldiamide	ODEN ^{a, c}
N,N'-di-(3-aminopropyl)oxaldiamide	ODPN ^{b, c}
Nickel(II)perchlorate	Ni(ClO ₄) ₂ ^{d, j}
Copper(II)perchlorate	Cu(ClO ₄) ₂ ^{d, j}
Triethylenetetramine	trien ^{e, j}
Ethylenediaminetetraacetic acid	EDTA ^{f, j}
Sodium perchlorate	NaClO ₄ ^{g, j}
Sodium borate	Na ₂ B ₄ O ₇ ·10 H ₂ O ^{h, j}
Tris(hydrogenmethyl)aminomethane	tris ^{i, j}
2-Methylpyridine	2-picoline ^{f, k}

^a Elemental Analysis	Expected Value	Value Found
Carbon	29.39 %	29.17%
Hydrogen	6.53%	6.51%
Nitrogen	22.86%	22.73%

^b Elemental Analysis	Expected Value	Value Found
Carbon	34.91%	33.13%
Hydrogen	7.27%	7.41%
Nitrogen	20.36%	19.97%

^cGalbraith Laboratories, Inc., Knoxville, Tennessee

^dG. Frederick Smith Chemical Company

^eKodak Chemical Company

^fMatheson, Coleman, and Bell Chemical Company

^gFluka AG, Chemische Fabrike

^hJ. T. Baker Chemical Company

ⁱSigma Chemical Company

^jReagent grade

^kPractical grade

Table 2.. Names of compounds used and their abbreviations.

added, and the pH adjusted to the desired value with dilute NaOH, bubbling with nitrogen as before. For experiments conducted above pH 9.0, 0.005 M sodium borate buffer was used. For pH-jump experiments conducted below pH 9.0, the following buffer conditions were used for the indicated pH ranges: 0.01 M tris buffer for pH 7.4-8.8; 0.01 M 2-picoline buffer for pH 5.5-7.1; and 0.01 M sodium acetate for pH 4.5-5.0. Ligand solutions were brought to volume, bubbled, and thermostatted as described earlier.

In a typical pH-jump experiment, the unbuffered NiH_2ODPN solution was prepared with an initial pH of approximately 9.0. The complex solution was mixed with an equal volume of EDTA solution buffered at some pH, for example, 5.80. The final pH of this mixture was 5.89 for an EDTA concentration of 1×10^{-3} . In reactions where the ligand concentration was higher, the change in pH upon mixing was smaller, probably due to the greater buffering capacity of the ligand solution.

Experiments were performed varying the nickel complex concentration relative to ligand concentration to establish the order of complex dependence for the reaction. The reaction was found to have a first-order dependence on nickel complex concentration.

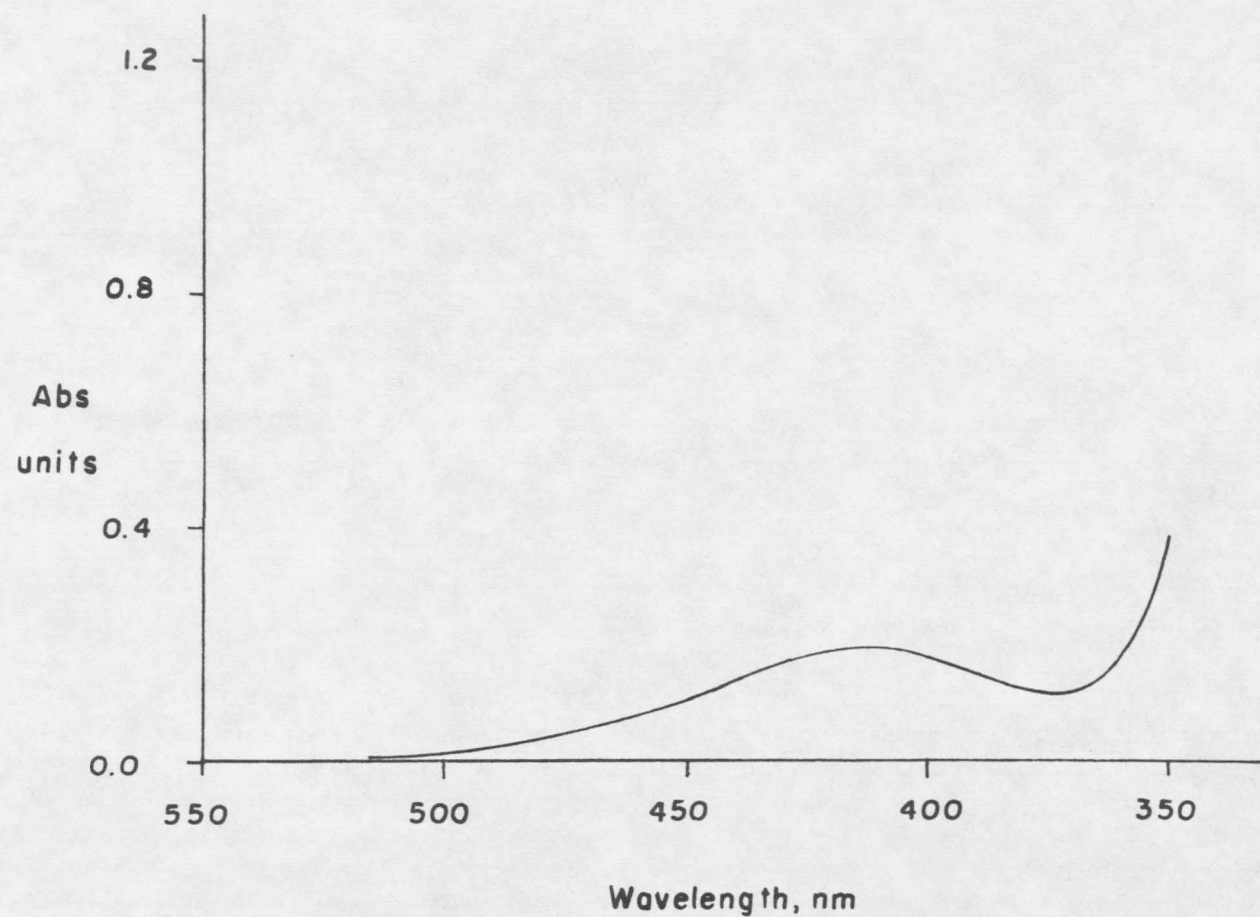
Kinetic Measurements

Spectral Characteristics. Both complexes show weak absorption in the 400-450 nm range of the visible region. NiH_2ODEN has an absorption maximum at $\lambda = 414$ nm with an absorbtivity coefficient

$\epsilon = 187 \text{ M}^{-1} \text{ cm}^{-1}$. The absorption maximum for NiH_2ODPN is at $\lambda = 453 \text{ nm}$, $\epsilon = 67 \text{ M}^{-1} \text{ cm}^{-1}$. It was decided to monitor the kinetics of these systems in the ultraviolet region, where both complexes show much stronger absorption. Spectra for the two complexes in both regions appear in Figure 5. Absorption maxima and absorptivity coefficients are as follows: for NiH_2ODEN , $\lambda_{\text{max}} = 307 \text{ nm}$ and $\epsilon = 2980 \text{ M}^{-1} \text{ cm}^{-1}$; for NiH_2ODPN , $\lambda_{\text{max}} = 293 \text{ nm}$ and $\epsilon = 3270 \text{ M}^{-1} \text{ cm}^{-1}$. The kinetics of the systems were investigated by monitoring the decrease in absorbance as the original ligand was displaced. There was no appreciable absorption for NiEDTA or Nitrien at these wavelengths.

Reaction Conditions. Fast reactions were monitored by the stopped-flow apparatus as described previously. The 100% transmittance position was established before each set of reactions using the non-absorbing reactant, either trien or EDTA . The reaction trace was stored by the oscilloscope, which was triggered by the action of the stopping syringe. Data from the oscilloscope display was manually transcribed as percent transmittance versus time. All transmittance values were converted to absorbance for further data manipulation.

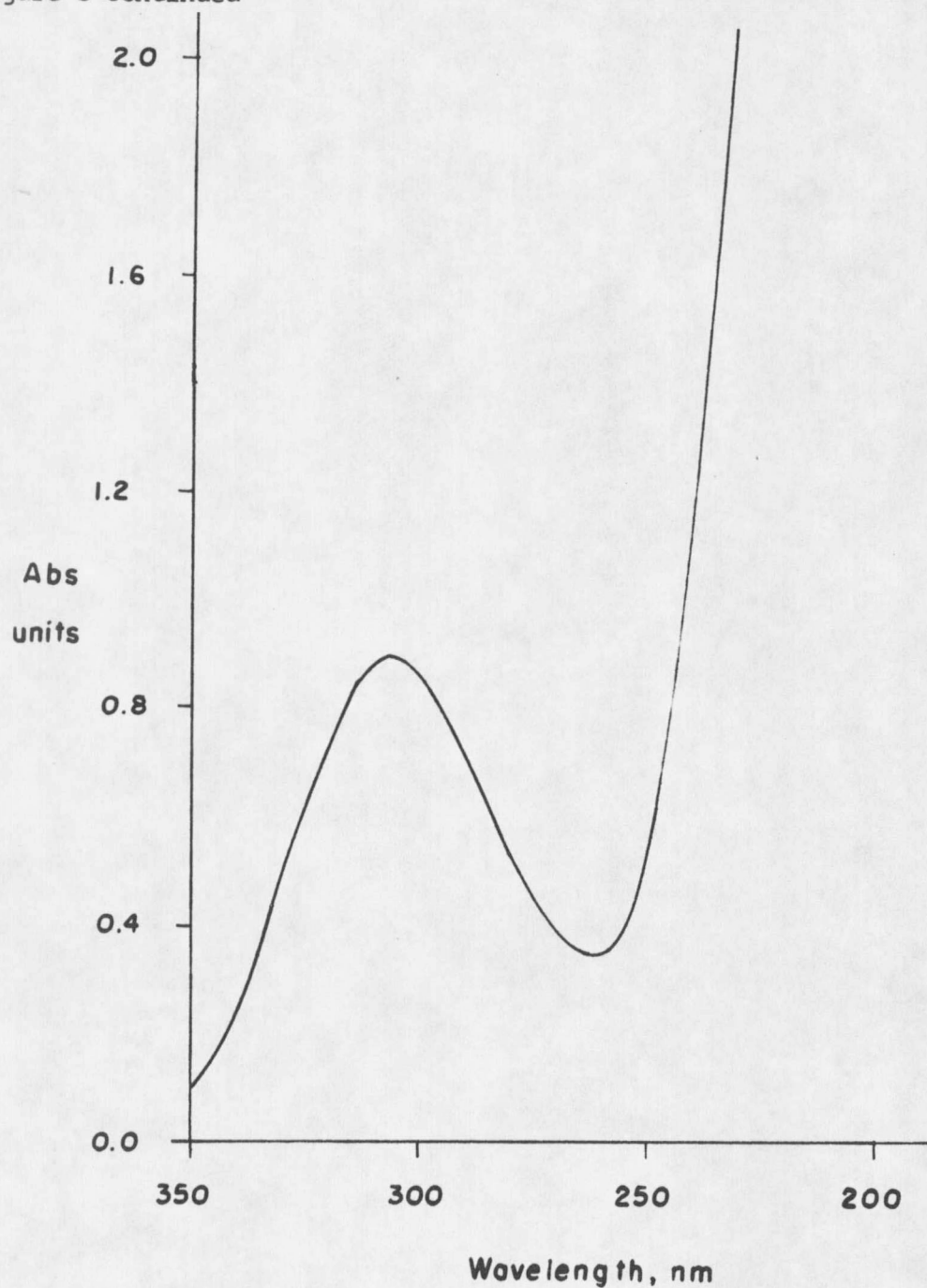
A Varian spectrophotometer was used to monitor the slower reactions. Equal volumes of the reactants were dispensed into a small beaker using volumetric pipets. The solution was bubbled with nitrogen to exclude oxygen while it was stirred mechanically to



Visible absorption spectrum of NiH₂ODEN
[Ni]_T = 1.0×10^{-3} M
Cell path length = 1 cm

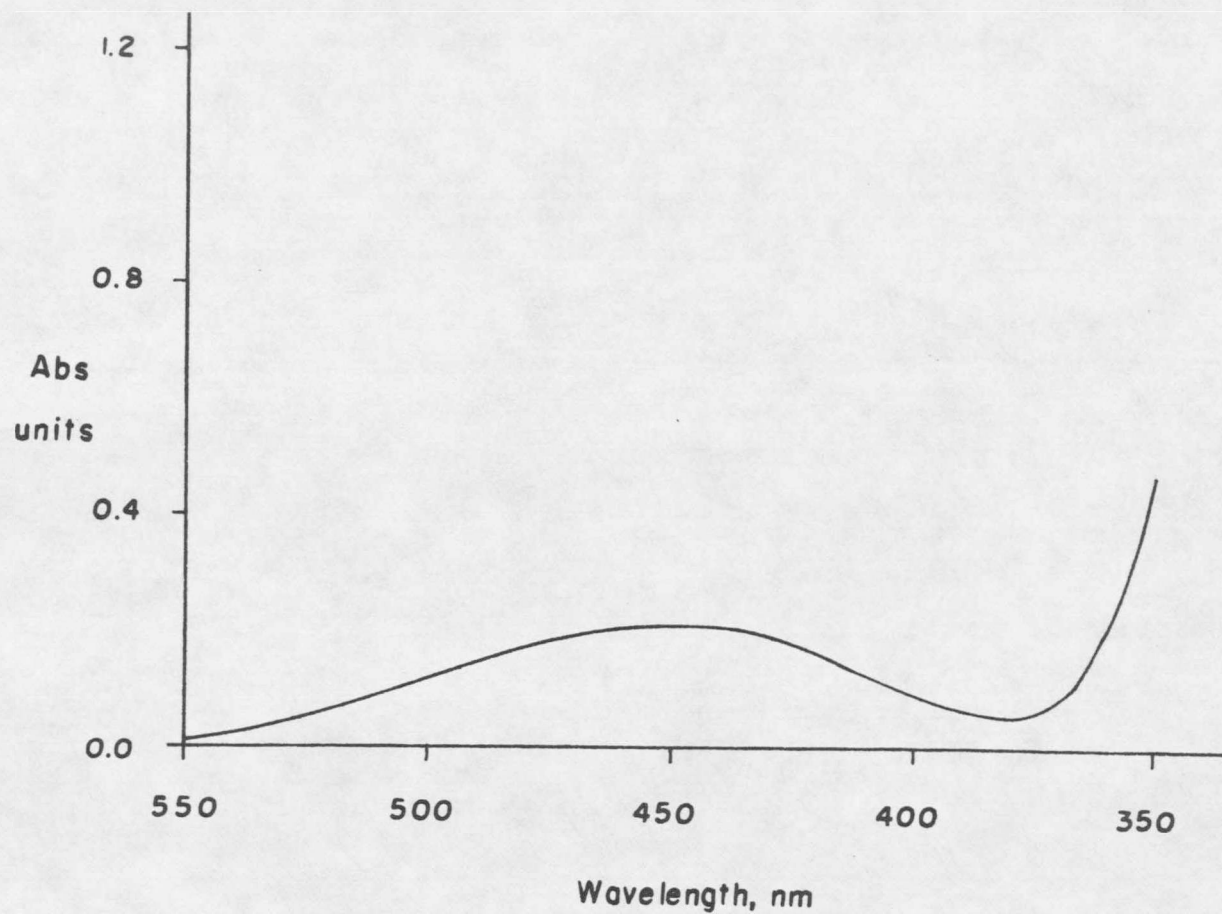
Figure 5. Absorption spectra for NiH₂ODEN and NiH₂ODPN.

Figure 5 continued



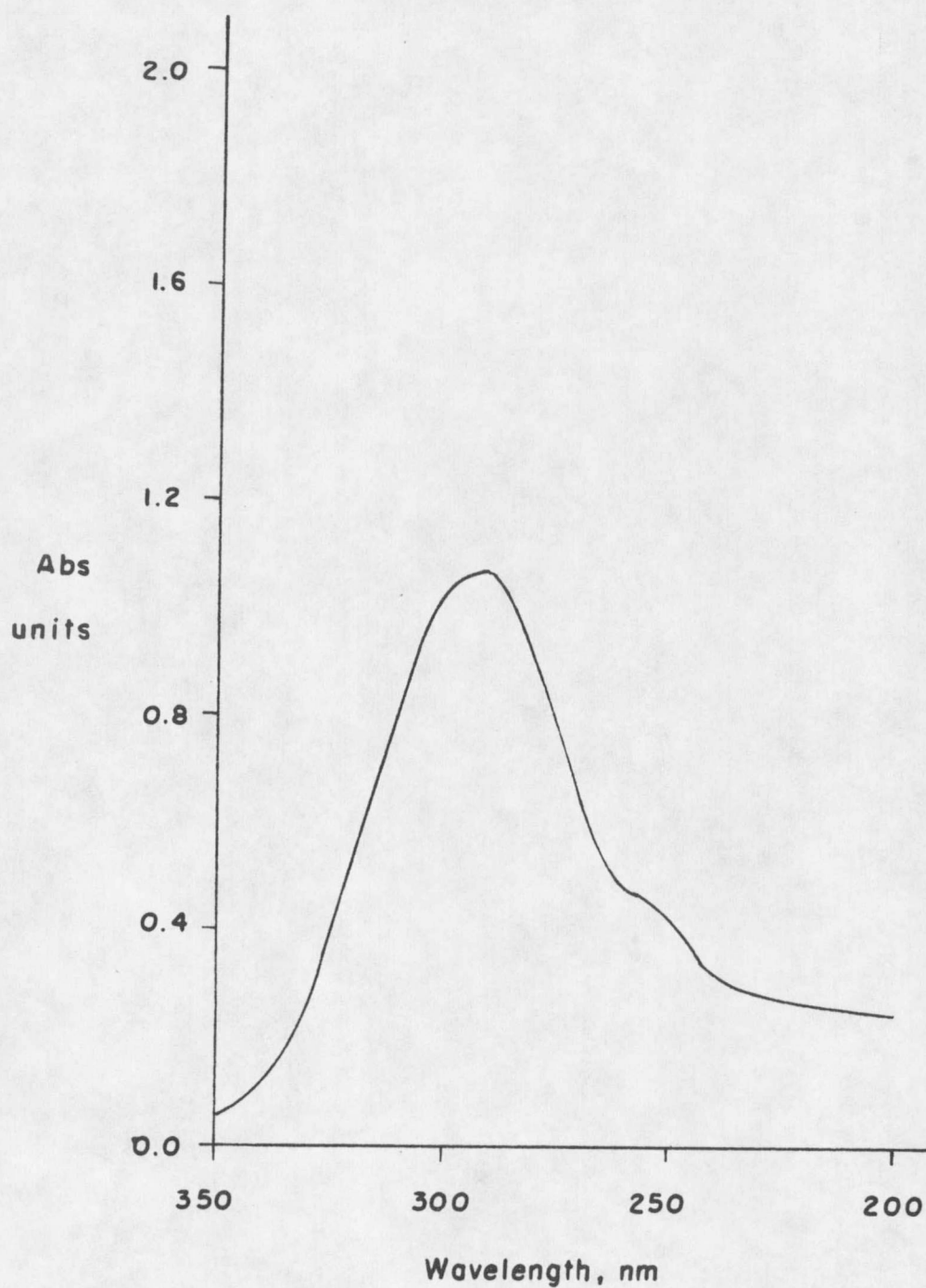
Ultraviolet absorption spectrum of NiH₂ODEN
[Ni]_T = 3.0×10^{-4} M
Cell path length = 1 cm

Figure 5 continued



Visible absorption spectrum of NiH₂ODPN
[Ni]_T = 3.5×10^{-4} M
Cell path length = 10 cm

Figure 5 continued



Ultraviolet absorption spectrum of NiH_2ODPN
 $[\text{Ni}]_{\text{T}} = 1.0 \times 10^{-4} \text{ M}$
Cell path length = 10 cm

ensure thorough mixing. The solution was then transferred to a spectrophotometric cell in order to monitor the progress of the reaction. Less than a minute elapsed during the addition of the second reactant, mixing, and transfer to the cell. The strip chart recorder, initiated at the moment of first contact between reactants, produced a permanent record of the reaction traces. Data were transcribed and treated as described above.

Experimentally determined pH values were converted to $[H^+]$ values using activity coefficients calculated from the extended Debye-Hückel equation.⁴⁷

RESULTS

The Reaction of NiH_2ODEN with Trien

All four systems were studied by maintaining the incoming ligand concentration in large excess of the complex concentration, thus preserving pseudo-first-order conditions. The reactions were monitored spectrophotometrically, following the disappearance of the complex. Indications are that at greater than ten-fold excess ligand concentration, the reactions follow first-order kinetics.

The reaction of NiH_2ODEN with trien was studied over a pH range of 9.88 to 4.46. Plots of the quantity $-\ln(A_\infty - A_t)$ versus time (where A_t is the absorbance at any time t , and A_∞ is the absorbance at infinite time, or completion of the reaction) were linear. The slopes of these plots are the pseudo-first-order rate constants, k_{obs} , and Equation 5 expresses the first-order dependence of rate on the nickel complex concentration.

$$\text{Rate} = \frac{-d[\text{Ni}]_T}{dt} = k_{\text{obs}} [\text{Ni}]_T \quad (5)$$

Table 3 lists the values of k_{obs} , with corresponding pH and $[\text{trien}]_T$ values for the NiH_2ODEN -trien system. Values for k_{obs} are averages of at least three runs under the same experimental conditions.

10^3 [Trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
1.0	0.00479		9.88	1.32×10^{-10}	0.00477	
2.0	0.0090	0.0001	9.88	1.32×10^{-10}	0.00880	
5.0	0.0218		9.88	1.32×10^{-10}	0.0206	
7.0	0.0304		9.88	1.32×10^{-10}	0.0283	
1.0	0.00407		9.58	2.63×10^{-10}	0.00389	
2.0	0.00781		9.58	2.63×10^{-10}	0.00705	
5.0	0.017	0.001	9.58	2.63×10^{-10}	0.0164	
7.0	0.0245		9.58	2.63×10^{-10}	0.0225	
1.0	0.00293	0.00004	9.20	6.31×10^{-10}	0.00288	
2.0	0.0053	0.0001	9.20	6.31×10^{-10}	0.00504	
5.0	0.0123	0.0002	9.20	6.31×10^{-10}	0.0115	
7.0	0.0162	0.0001	9.20	6.31×10^{-10}	0.0157	
1.0	0.002556	0.000006	8.89	1.29×10^{-9}	0.00234	
2.0	0.00434	0.00009	8.89	1.29×10^{-9}	0.00397	
5.0	0.0094	0.0003	8.89	1.29×10^{-9}	0.00881	
7.0	0.0124	0.0007	8.89	1.29×10^{-9}	0.0120	
1.0	0.00221	0.00009	8.60	2.51×10^{-9}	0.00205	
2.0	0.00401		8.60	2.51×10^{-9}	0.00339	
5.0	0.00823		8.60	2.51×10^{-9}	0.00738	
7.0	0.0108		8.60	2.51×10^{-9}	0.0100	
1.0	0.00418		8.11	7.76×10^{-9}	0.00182	0.00167

Table 3. Concentrations and k_{obs} for the reaction of NiH₂ODEN with trien.

Table 3 continued

10^3 [Trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
2.0	0.00568	0.00005	8.09	8.13×10^{-9}	0.00293	0.00175
5.0	0.0100		8.03	9.33×10^{-9}	0.00626	0.00200
7.0	0.0119		8.01	9.77×10^{-9}	0.00846	0.00208
1.0	0.00721		7.73	1.86×10^{-8}	0.00172	0.00378
2.0	0.0091	0.0002	7.72	1.90×10^{-8}	0.00274	0.00386
5.0	0.0138		7.66	2.19×10^{-8}	0.00579	0.00438
7.0	0.0161		7.64	2.29×10^{-8}	0.00780	0.00456
1.0	0.0092	0.0004	7.46	3.47×10^{-8}	0.00165	0.00651
2.0	0.01172	0.00006	7.42	3.80×10^{-8}	0.00260	0.00701
5.0	0.0161		7.37	4.26×10^{-8}	0.00544	0.00770
7.0	0.0188		7.30	5.01×10^{-8}	0.00730	0.00875
1.0	0.0250		6.65	2.24×10^{-7}	0.00123	0.0223
2.0	0.0236		6.60	2.51×10^{-7}	0.00175	0.0235
5.0	0.0267		6.54	2.88×10^{-7}	0.00332	0.0249
7.0	0.0282		6.50	3.16×10^{-7}	0.00437	0.0259
1.0	0.0289		6.22	6.02×10^{-7}		0.0325
2.0	0.030	0.001	6.21	6.16×10^{-7}		0.0328
5.0	0.0309	0.0002	6.16	6.92×10^{-7}		0.0340
7.0	0.0324	0.0008	6.15	7.08×10^{-7}		0.0342
1.0	0.0353		5.94	1.15×10^{-6}		0.0397
2.0	0.0367		5.92	1.20×10^{-6}		0.0403
5.0	0.0371		5.92	1.20×10^{-6}		0.0403

Table 3 continued

10^3 [Trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
7.0	0.0369		5.88	1.32×10^{-6}		0.0415
1.0	0.0433		5.73	1.86×10^{-6}		0.0465
2.0	0.0442		5.70	2.00×10^{-6}		0.0477
5.0	0.0458		5.68	2.09×10^{-6}		0.0484
7.0	0.0463		5.66	2.19×10^{-6}		0.0493
1.0	0.060	0.002	5.41	3.89×10^{-6}		0.0628
2.0	0.0586		5.47	3.39×10^{-6}		0.0589
5.0	0.0591		5.43	3.72×10^{-6}		0.0614
7.0	0.0643		5.39	4.07×10^{-6}		0.0641
1.0	0.0840		5.09	8.13×10^{-6}		0.0944
2.0	0.0879		5.06	8.71×10^{-6}		0.0987
5.0	0.100		4.97	1.07×10^{-5}		0.113
7.0	0.111		4.93	1.17×10^{-5}		0.121
1.0	0.128		4.85	1.41×10^{-5}		0.138
2.0	0.136		4.86	1.38×10^{-5}		0.136
5.0	0.159		4.78	1.66×10^{-5}		0.157
7.0	0.173		4.75	1.78×10^{-5}		0.165
1.0	0.216		4.58	2.63×10^{-5}		0.228
2.0	0.211		4.56	2.75×10^{-5}		0.236
5.0	0.262		4.49	3.24×10^{-5}		0.272
7.0	0.301		4.46	3.47×10^{-5}		0.289

The pseudo-first-order rate constant is actually a collection of constants reflecting the dependence of the rate on the concentrations of several species, which may include the incoming ligand, hydrogen ion, buffers present in the system, and the solvent itself. Often, only one or two of these species contribute significantly to the rate within a certain pH range. Thus, these constants may be extracted from the k_{obs} term by determining the dependence of that term on the concentration of the significant contributor within the indicated pH range.

The ligand dependence of the reaction was determined by examining the reactions conducted above pH = 8.5. Plots of k_{obs} versus $[\text{trien}]_{\text{T}}$ were not linear; and so simple first-order dependence on ligand concentration is not found in this system. Curves approach linearity in the lower ligand concentration range, but as ligand concentration increases, the rate falls off markedly. Plots of the quantity $1/k_{\text{obs}}$ versus $1/[\text{trien}]_{\text{T}}$ are also not linear. These curves also approach linearity in the lower range, but fall away from the projected line as the quantity $1/[\text{trien}]_{\text{T}}$ increases.

Similar systems are known to exhibit behavior described by reaction via parallel paths, some dependent on ligand concentration and others ligand-independent. If the constants describing ligand-dependent and ligand-independent pathways are near enough in magnitude, then both pathways will make a noticeable contribution to the rate. In order to examine both pathways, their individual contributions to the rate must be separated. A solvent-assisted

dissociative pathway is a ligand-independent pathway commonly found in analogous systems. Such a pathway makes a constant contribution to the rate throughout the pH range, regardless of ligand or substrate concentrations. If such a pathway were present in the mechanism for this system, the subtraction of a constant term from k_{obs} will allow the determination of the ligand dependence. The value of this constant, $k_{\text{H}_2\text{O}}$ was determined by calculating values of A , equal to the quantity $1/k_{\text{obs}} - k_{\text{H}_2\text{O}}$. An optimum value for $k_{\text{H}_2\text{O}}$ was found which produced linear plots of A versus $1/[\text{trien}]_{\text{T}}$ throughout the pH range of pH = 8.5 and above (Figure 6). These plots have non-zero intercepts and slopes from which the constants describing the ligand dependence of the system may be extracted. Equation 6 is the equation for the lines in Figure 6, where k_i is the intercept, and k_{slope} is the slope of each line.

$$\frac{1}{k_{\text{obs}} - k_{\text{H}_2\text{O}}} = k_i + k_{\text{slope}} \left(\frac{1}{[\text{trien}]_{\text{T}}} \right) \quad (6)$$

Equations 7 and 8 show a mechanism consistent with the behavior found in this pH range. Equation 7 is the solvent-assisted dissociative pathway mentioned above. Equation 8 is the ligand-dependent pathway, where an equilibrium forming some intermediate complex species precedes the rate-determining reaction with trien.



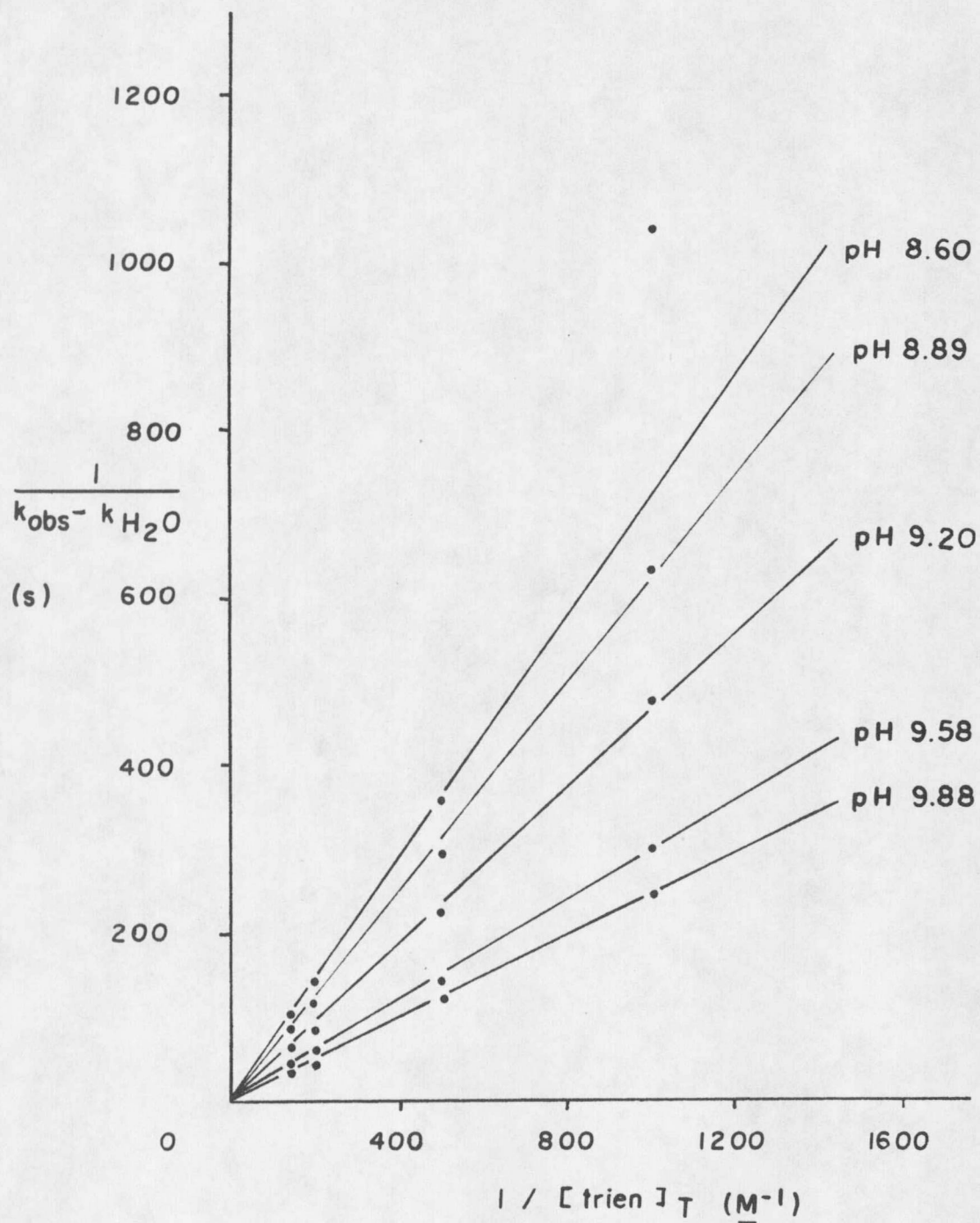
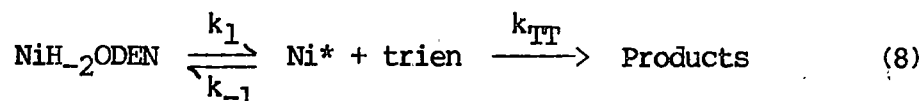


Figure 6. Dependence of k_{obs} on $[\text{trien}]_{\text{T}}$ for the reaction of NiH_2ODEN with trien.



A steady-state treatment can be performed on the intermediate species Ni^* . The resulting expression for the ligand dependence of k_{obs} is given in Equation 9, having previously subtracted the contribution of $k_{\text{H}_2\text{O}}$ from k_{obs} .

$$k_{\text{obs}} - k_{\text{H}_2\text{O}} = \frac{k_1 k_{\text{TT}} [\text{trien}]_{\text{T}}}{k_{-1} + k_{\text{TT}} [\text{trien}]_{\text{T}}} \quad (9)$$

Inversion of this expression allows the assignment of the k_i and k_{slope} values obtained earlier, as shown in Equations 10 and 11.

$$k_i = \frac{1}{k_1} \quad (10)$$

$$k_{\text{slope}} = \frac{k_{-1}}{k_1 k_{\text{TT}}} \quad (11)$$

The constant k_{TT} can be further resolved into constants pertaining to the various protonated forms of trien. The weighted regression portion of the Statistical Package for the Social Sciences (SPSS)⁴⁸ was utilized to solve Equation 12 for k_{T}/k_{-1} , k_{HT}/k_{-1} , and $k_{\text{H}_2\text{T}}/k_{-1}$ values. Values for k_1

$$\frac{1}{k_1 k_{\text{slope}}} = \frac{k_{\text{T}} \alpha_{\text{trien}} + k_{\text{HT}} \alpha_{\text{Htrien}^+} + k_{\text{H}_2\text{T}} \alpha_{\text{H}_2\text{trien}^{2+}}}{k_{-1}} \quad (12)$$

and k_{slope} were obtained from Figure 6. Fractions of the different

forms of trien present at the pH values where the system was studied were obtained using Equations 13, 14, and 15 and the values for K_1 , K_2 , K_3 , and K_4 found in Table 4.

$$\alpha_{\text{trien}} = \frac{K_1 K_2 K_3 K_4}{K_1 K_2 K_3 K_4 + K_1 K_2 K_3 [H^+] + K_1 K_2 [H^+]^2 + K_1 [H^+]^3 + [H^+]^4} \quad (13)$$

$$\alpha_{\text{Htrien}^+} = \frac{K_1 K_2 K_3 [H^+]}{K_1 K_2 K_3 K_4 + K_1 K_2 K_3 [H^+] + K_1 K_2 [H^+]^2 + K_1 [H^+]^3 + [H^+]^4} \quad (14)$$

$$\alpha_{\text{H}_2\text{trien}^{2+}} = \frac{K_1 K_2 [H^+]^2}{K_1 K_2 K_3 K_4 + K_1 K_2 K_3 [H^+] + K_1 K_2 [H^+]^2 + K_1 [H^+]^3 + [H^+]^4} \quad (15)$$

Equilibrium	Equilibrium constant
$\text{H}_4\text{trien}^{4+} \rightleftharpoons \text{H}^+ + \text{H}_3\text{trien}^{3+}$	$K_1 = 10^{-3.25}$
$\text{H}_3\text{trien}^{3+} \rightleftharpoons \text{H}^+ + \text{H}_2\text{trien}^{2+}$	$K_2 = 10^{-6.56}$
$\text{H}_2\text{trien}^{2+} \rightleftharpoons \text{H}^+ + \text{Htrien}^+$	$K_3 = 10^{-9.08}$
$\text{Htrien}^+ \rightleftharpoons \text{H}^+ + \text{trien}$	$K_4 = 10^{-9.74}$

Table 4. Trien equilibria and equilibrium constants.^{49a}

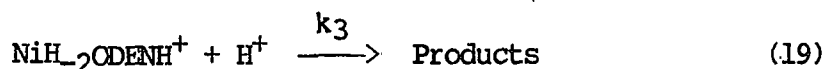
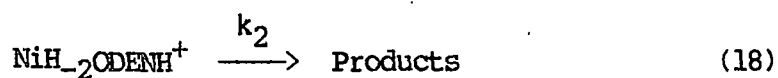
The general rate expression for this system for the pH range above pH = 8.5 is shown in Equation 16.

Rate =

$$\left(k_{\text{H}_2\text{O}} + \frac{k_1 (k_{\text{T}}^{\alpha} \text{trien}^+ + k_{\text{HT}}^{\alpha} \text{Htrien}^+ + k_{\text{H}_2\text{T}}^{\alpha} \text{H}_2\text{trien}^{2+}) [\text{trien}]_{\text{T}}}{k_{-1} + (k_{\text{T}}^{\alpha} \text{trien}^+ + k_{\text{HT}}^{\alpha} \text{Htrien}^+ + k_{\text{H}_2\text{T}}^{\alpha} \text{H}_2\text{trien}^{2+}) [\text{trien}]_{\text{T}}} \right) [\text{Ni}]_{\text{T}} \quad (16)$$

In the range below pH = 8.5, rate dependence on trien diminishes. In this region, the rate begins to increase with decreasing pH, contrasted with the decreasing rate with decreasing pH observed at pH values greater than pH = 8.5. The hydrogen ion dependence of the rate in this region was determined by plotting k_i^* (k_{obs} values extrapolated to zero trien concentration for each pH value studied) versus $[H^+]$. Examination of Figure 7 shows that the hydrogen ion dependence of this system is not simple. There is a linear portion in the region of high $[H^+]$ which has a non-zero intercept. The hydrogen ion dependence falls off sharply at lower $[H^+]$.

This suggests a protonation equilibrium producing a species designated NiH_2ODENH^+ . The protonated species can proceed to products via dissociation or further protonation, as expressed in Equations 17, 18, and 19.



If the pathways shown in Equations 18 and 19 were the only routes which contributed to product formation in the low pH region, the rate of the reaction could be expressed as in Equation 20.

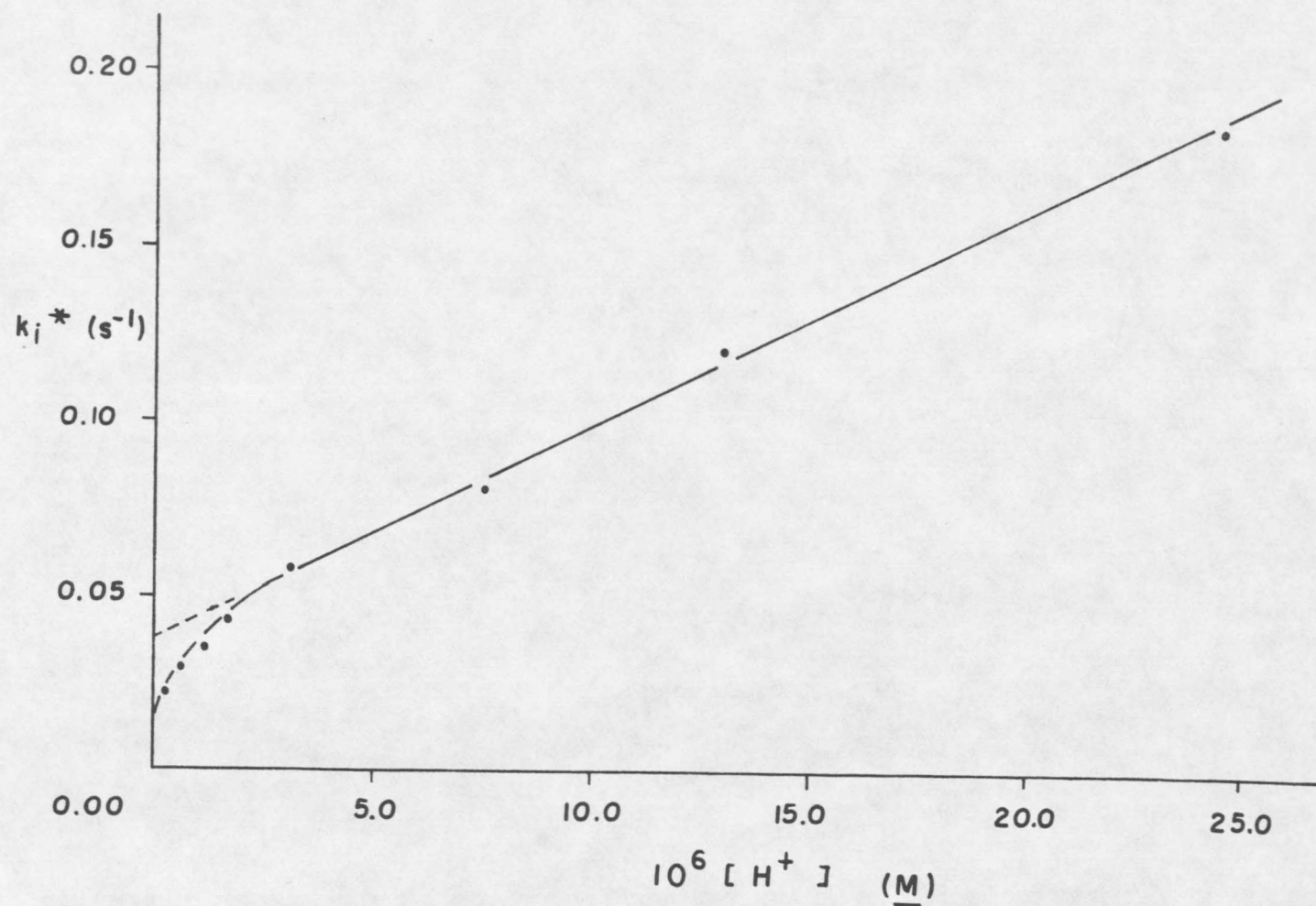


Figure 7. Dependence of $k_i^* [\text{H}^+]$ for the reaction of NiH_2ODEN with trien.

$$\text{Rate} = (k_2 + k_3[\text{H}^+])[\text{NiH}_2\text{ODENH}^+] \quad (20)$$

From this expression, k_3 is the slope of the linear portion and k_2 is the non-zero intercept. The value for K_H cannot be fully resolved from the data.

In the high pH region, it was assumed that $[\text{Ni}]_T = [\text{NiH}_2\text{ODEN}]$. With decreasing pH, the protonation equilibrium pathway becomes a significant competitor for the activated species Ni^* , and a more accurate representation of $[\text{Ni}]_T$ is given by Equation 21.

$$[\text{Ni}]_T = [\text{NiH}_2\text{ODEN}] + [\text{Ni}^*] + [\text{NiH}_2\text{ODENH}^+] \quad (21)$$

It is possible to derive an expression for the rate of reaction based on the three species in Equation 21 and the reaction pathways followed by each species. This expression is quite complex, however, and does not allow resolution of rate constants associated with the various reaction pathways. Certain assumptions can be made, based on the observed kinetics, which simplify the expression considerably.

The first of these assumptions is that, as the pH decreases, the ligand-dependent pathway is no longer competitive with the pathways in Equations 18 and 19. As a result, only the protonated fraction of $[\text{Ni}]_T$ need be considered significant in product formation below a certain pH. Equation 21 can be used to formulate an expression for this fraction, which is shown in Equation 22.

$$\alpha_{\text{NiH}_2\text{ODENH}^+} = \frac{K_1 K_H [\text{H}^+]}{1 + K_1 + K_1 K_H [\text{H}^+]} \quad (22)$$

A second assumption is that the concentration of the intermediate complex, Ni^* , is negligible. The result of this assumption is that the K_1 term in the denominator of Equation 22 may be ignored. Consequently, a value for $K_1 K_H$ may be determined using the low $[\text{H}^+]$ data in Figure 7.

As mentioned earlier, the protonated fraction may proceed to products via either of the pathways found in Equations 18 and 19. The rate expression for the low pH region, with the assumptions discussed above, is found in Equation 23.

$$\text{Rate} = \left[(k_2 + k_3 [\text{H}^+]) \left(\frac{K_1 K_H [\text{H}^+]}{1 + K_1 K_H [\text{H}^+]} \right) \right] [\text{Ni}]_T \quad (23)$$

The rate expressions in Equations 16 and 23 have been used to predict rate constants for the appropriate pH ranges. There is a region of overlap between pH 8.1 and 6.5 where values are generated by both rate expressions and listed separately. These values can be found in the last columns of Table 3. In this system, it is apparent that there is a region which requires consideration of contributions from both hydrogen ion and ligand-dependent pathways for accurate prediction. This can be seen by comparing the observed values with the values predicted by the two expressions. Figure 8 is a plot of k_{obs} versus pH for reactions carried out with a total trien concentration of $7.0 \times 10^{-3} \text{ M}$. The lines are generated from

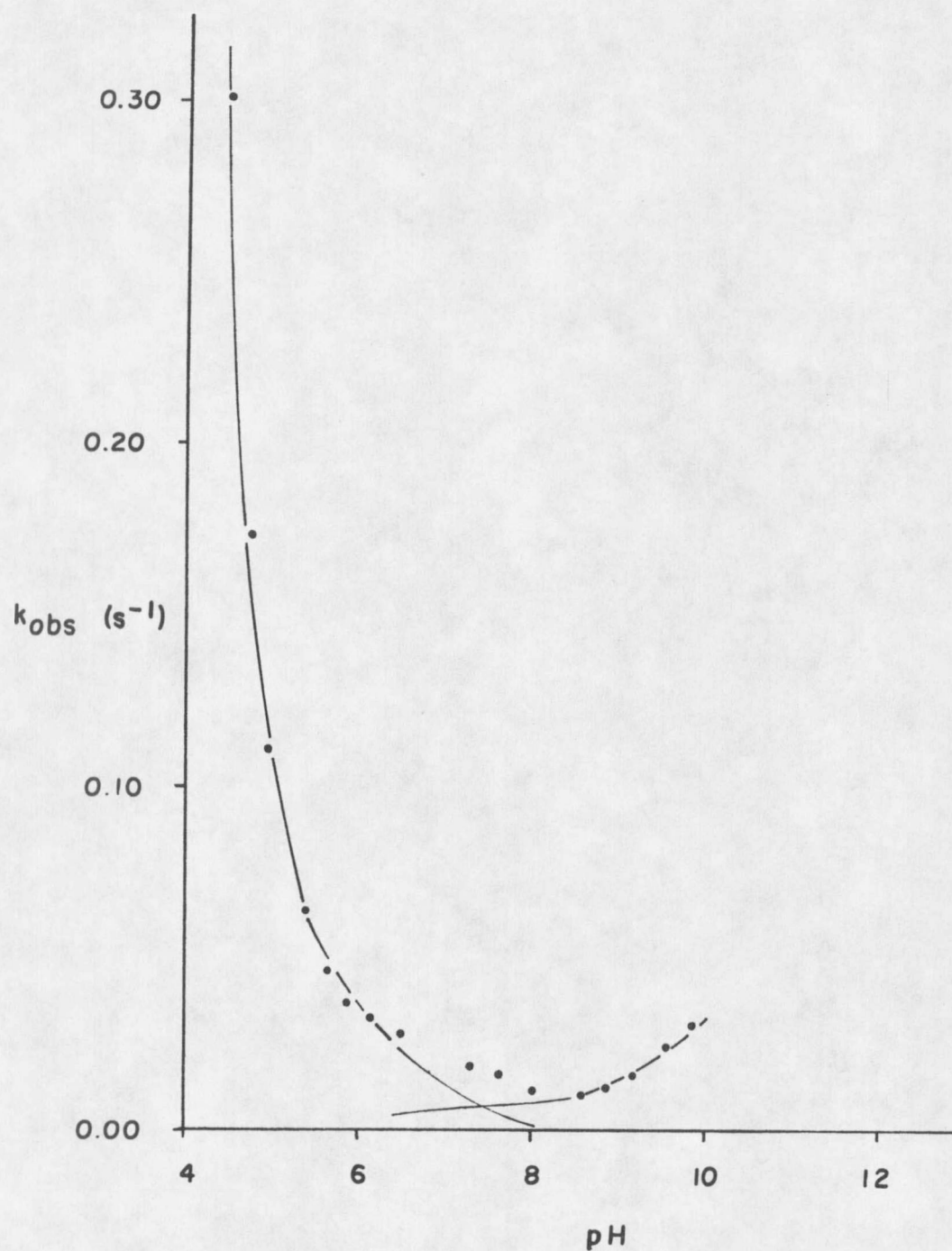


Figure 8. Dependence of observed rate constants on pH for the reaction of NiH_2ODEN with trien.

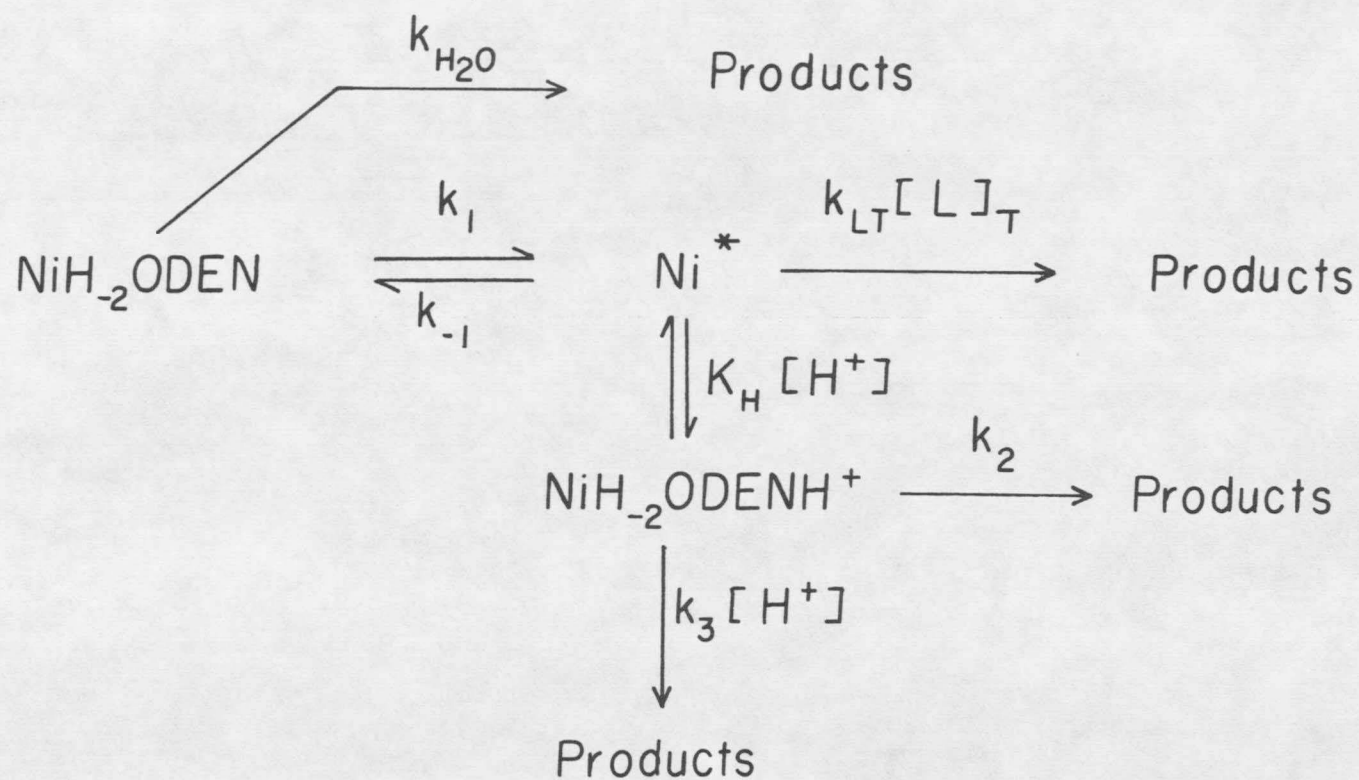
the predicted values. Similar plots can be generated for the other trien concentrations from the data in Table 3. Owing to the complexity of the rate expression which is derived from the mechanism (without simplifying assumptions), it is impossible to predict quantitatively in the region where both ligand and hydrogen ion-dependent pathways contribute to the rate.

In Figure 8, the increase in rate above pH 8.5 is due to nucleophilic attack by $\text{H}_2\text{trien}^{2+}$, Htrien^+ and trien , while the increase in rate below pH 5.4 is due to specific hydrogen ion catalysis. In the region between pH 5.4 and 8.5, nucleophilic replacement, dissociation of the protonated species, and specific hydrogen ion catalysis contribute to the rate in varying degrees, depending on the pH.

A summary of the rate constants for this system is found in Table 5. The full mechanism is shown in Figure 9.

$k_{\text{H}_2\text{O}} = 0.0014 \pm 0.0006 \text{ s}^{-1}$	
$k_1 = 0.7 \pm 0.3 \text{ s}^{-1}$	
$k_2 = 0.035 \pm 0.002 \text{ s}^{-1}$	
$k_3 = (7.0 \pm 0.4) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$	
$K_1 K_H = (6.1 \pm 0.3) \times 10^6 \text{ M}^{-1}$	
$k_T/k_{-1} = 8 \pm 1 \text{ M}^{-1}$	
$k_{\text{HT}}/k_{-1} = 2 \pm 1 \text{ M}^{-1}$	$k_{\text{HT}}/k_T = 0.25$
$k_{\text{H}_2\text{T}}/k_{-1} = 1.4 \pm 0.7 \text{ M}^{-1}$	$k_{\text{H}_2\text{T}}/k_T = 0.18$

Table 5. Rate constants for the reaction of NiH_2ODEN with trien .



8

Figure 9. Proposed mechanism for the reaction of $\text{NiH}_{-2}\text{ODEN}$ with ligands.

The Reaction of NiH_2ODEN with EDTA

This system was studied over a pH range of 9.96 to 4.84. Reactions were run under pseudo-first-order conditions, with $[\text{EDTA}]_T \gg [\text{NiH}_2\text{ODEN}]$. Plots of $-\ln(A_\infty - A_t)$ were linear, and the slopes of these plots were taken as the pseudo-first-order rate constants, k_{obs} . Table 6 summarizes these constants with the corresponding pH and $[\text{EDTA}]_T$ values. Again, values for k_{obs} are averages of at least three runs. Equation 5 expresses the dependence of the rate on nickel complex concentration.

The ligand dependence of the reaction was determined by considering the reactions studied in the pH range above pH = 8.0. Plots of k_{obs} versus $[\text{EDTA}]_T$ were not linear. Inverse plots ($1/k_{\text{obs}}$ versus $1/[\text{EDTA}]_T$) were also not linear. As with the NiH_2ODEN -trien system, plots of the quantity $(1/k_{\text{obs}} - k_{\text{H}_2\text{O}})$ versus $1/[\text{EDTA}]_T$ were found to be linear (Figure 10). An expression similar to Equation 6 can be written for this system (Equation 24).

$$\frac{1}{k_{\text{obs}} - k_{\text{H}_2\text{O}}} = k_i + k_{\text{slope}} \left(\frac{1}{[\text{EDTA}]_T} \right) \quad (24)$$

A mechanism similar to that proposed for the high pH region of the NiH_2ODEN -trien system is consistent with the patterns for this system as well (Equations 7 and 8). An expression for the ligand dependence of k_{obs} , similar to Equation 9, is

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
1.0	0.00100		9.96	1.10×10^{-10}	0.00294	
2.0	0.00153	0.00006	9.96	1.10×10^{-10}	0.00384	
5.0	0.00315	0.00007	9.95	1.12×10^{-10}	0.00628	
7.0	0.00475		9.93	1.17×10^{-10}	0.00773	
1.0	0.00199		9.48	3.31×10^{-10}	0.00324	
2.0	0.00304	0.00004	9.49	3.24×10^{-10}	0.00443	
5.0	0.00643		9.47	3.39×10^{-10}	0.00754	
7.0	0.0087	0.0006	9.44	3.63×10^{-10}	0.00933	
1.0	0.00407		8.91	1.24×10^{-9}	0.00346	
2.0	0.00582		8.91	1.23×10^{-9}	0.00481	
5.0	0.0103	0.0003	8.91	1.23×10^{-9}	0.00833	
7.0	0.0118	0.0002	8.92	1.21×10^{-9}	0.0103	
1.0	0.00550		8.51	3.09×10^{-9}	0.00362	
2.0	0.0080	0.0002	8.51	3.09×10^{-9}	0.00510	
5.0	0.0141		8.49	3.24×10^{-9}	0.00891	
7.0	0.0165		8.46	3.47×10^{-9}	0.0110	
7.0	0.0172	0.0009	8.51	3.09×10^{-9}	0.0110	
1.0	0.0103		7.88	1.32×10^{-8}	0.00423	0.00276
2.0	0.0142		7.87	1.35×10^{-8}	0.00621	0.00282
5.0	0.0199		7.85	1.41×10^{-8}	0.0110	0.00294
7.0	0.0232		7.82	1.51×10^{-8}	0.0135	0.00313

Table 6. Concentrations and k_{obs} for the reaction of NiH_2ODEN with EDTA.

Table 6 continued

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
7.0	0.0240		7.82	1.51×10^{-8}	0.0135	0.00313
1.0	0.0130		7.59	2.57×10^{-8}	0.00492	0.00504
2.0	0.0162		7.58	2.63×10^{-8}	0.00743	0.00514
5.0	0.0210		7.57	2.69×10^{-8}	0.0132	0.00524
7.0	0.0220		7.54	2.88×10^{-8}	0.0160	0.00556
7.0	0.0250		7.55	2.82×10^{-8}	0.0160	0.00546
2.0	0.0260		6.64	2.29×10^{-7}	0.0188	0.0225
5.0	0.0283		6.59	2.57×10^{-7}	0.0272	0.0237
7.0	0.0286		6.57	2.69×10^{-7}	0.0299	0.0242
1.0	0.0329		6.27	5.37×10^{-7}	0.0167	0.0313
2.0	0.0323		6.28	5.25×10^{-7}	0.0232	0.0311
5.0	0.0333		6.25	5.62×10^{-7}	0.0309	0.0318
7.0	0.0346		6.23	5.89×10^{-7}	0.0330	0.0323
1.0	0.0348		6.00	1.00×10^{-6}	0.0196	0.0381
2.0	0.0357		5.98	1.05×10^{-6}	0.0261	0.0386
5.0	0.0386		5.96	1.10×10^{-6}	0.0329	0.0392
7.0	0.0382		5.95	1.12×10^{-6}	0.0346	0.0394
1.0	0.0436		5.78	1.66×10^{-6}	0.0210	0.0447
2.0	0.0429		5.77	1.70×10^{-6}	0.0274	0.0451
5.0	0.0443		5.75	1.78×10^{-6}	0.0337	0.0458
7.0	0.0447		5.73	1.86×10^{-6}	0.0353	0.0465
1.0	0.0523		5.52	3.02×10^{-6}		0.0560

Table 6 continued

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
2.0	0.0541		5.49	3.24×10^{-6}		0.0577
5.0	0.0564		5.47	3.39×10^{-6}		0.0589
7.0	0.057	0.001	5.46	3.47×10^{-6}		0.0595
1.0	0.128		4.88	1.32×10^{-5}		0.132
2.0	0.127		4.87	1.35×10^{-5}		0.134
5.0	0.134		4.86	1.38×10^{-5}		0.136
7.0	0.144		4.84	1.44×10^{-5}		0.140

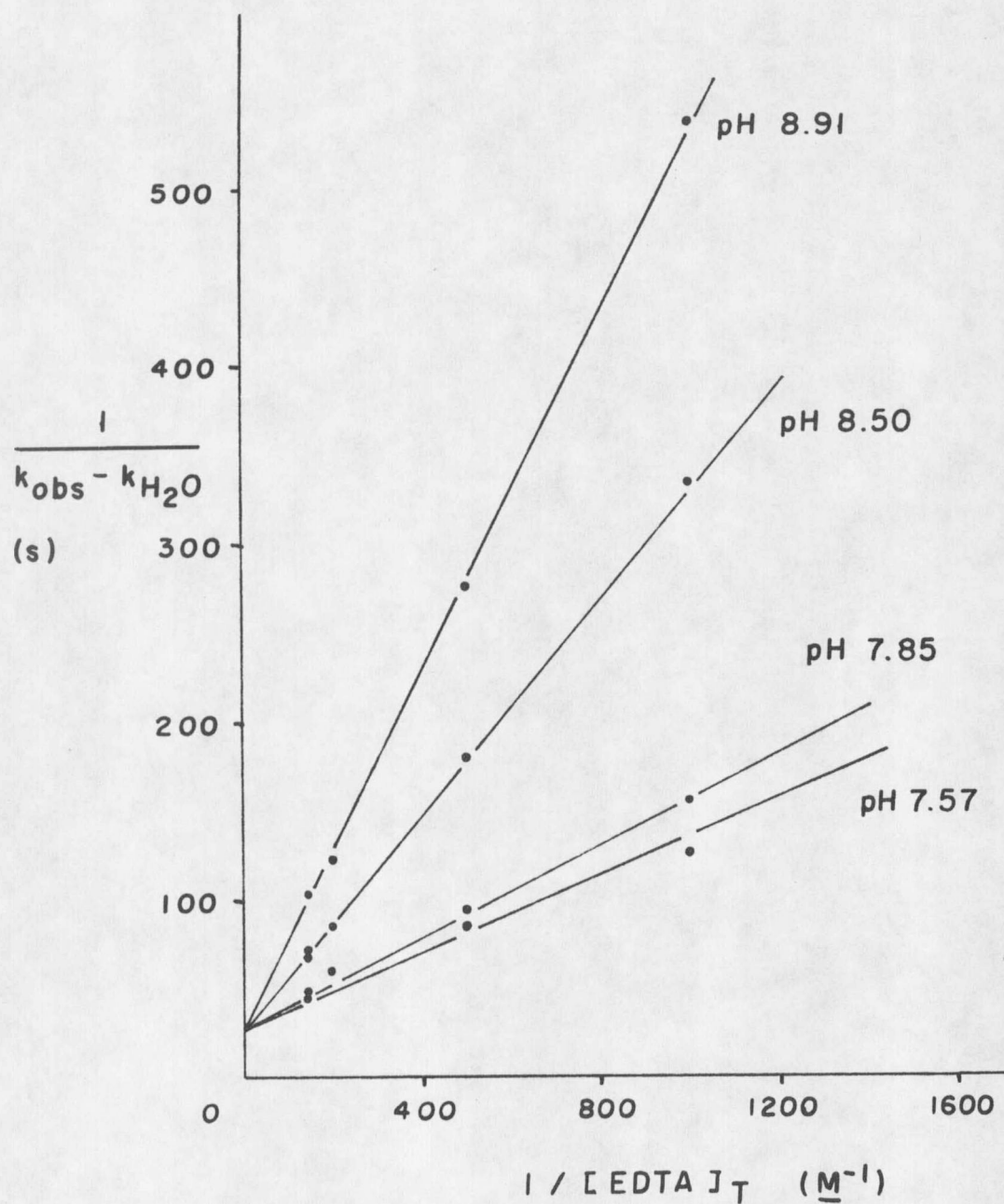


Figure 10. Dependence of k_{obs} on $[\text{EDTA}]_T$ for the reaction of NiH_2ODEN with EDTA.

given by Equation 25.

$$k_{\text{obs}} - k_{\text{H}_2\text{O}} = \frac{k_1 k_{\text{YT}} [\text{EDTA}]_{\text{T}}}{k_{-1} + k_{\text{YT}} [\text{EDTA}]_{\text{T}}} \quad (25)$$

The constants k_i and k_{slope} can be assigned as was discussed in the previous section (Equations 26 and 27).

$$k_i = \frac{1}{k_1} \quad (26)$$

$$k_{\text{slope}} = \frac{k_{-1}}{k_1 k_{\text{YT}}} \quad (27)$$

The weighted regression portion of the SPSS program was again used to solve Equation 28 for k_{HY}/k_{-1} and $k_{\text{H}_2\text{Y}}/k_{-1}$ values. The fully deprotonated form of EDTA did not make a significant contribution to the reaction rate in this system.

$$\frac{1}{k_1 k_{\text{slope}}} = \frac{k_{\text{Y}}^{\alpha} \text{EDTA}^{4-} + k_{\text{HY}}^{\alpha} \text{HEDTA}^{3-} + k_{\text{H}_2\text{Y}}^{\alpha} \text{H}_2\text{EDTA}^{2-}}{k_{-1}} \quad (28)$$

Fractions of the different protonated forms of EDTA (α values) were obtained from expressions similar to Equations 13, 14, and 15 using K values found in Table 7.

The general rate expression for the pH range above pH = 8.0 is given in Equation 29.

Equilibrium		Equilibrium constant
H_6EDTA^{2+}	$\rightleftharpoons H^+ + H_5EDTA^+$	$K_1 = 10^{0.0}$
H_5EDTA^+	$\rightleftharpoons H^+ + H_4EDTA$	$K_2 = 10^{-1.5}$
H_4EDTA	$\rightleftharpoons H^+ + H_3EDTA^-$	$K_3 = 10^{-2.0}$
H_3EDTA^-	$\rightleftharpoons H^+ + H_2EDTA^{2-}$	$K_4 = 10^{-2.68}$
H_2EDTA^{2-}	$\rightleftharpoons H^+ + HEDTA^{3-}$	$K_5 = 10^{-6.11}$
$HEDTA^{3-}$	$\rightleftharpoons H^+ + EDTA^{4-}$	$K_6 = 10^{-10.17}$

Table 7. EDTA equilibria and equilibrium constants.^{49b}

$$\text{Rate} = \left(k_{H_2O} + \frac{k_1 (k_{HY}^{\alpha} HEDTA^{3-} + k_{H_2Y}^{\alpha} H_2EDTA^{2-}) [EDTA]_T}{k_{-1} + (k_{HY}^{\alpha} HEDTA^{3-} + k_{H_2Y}^{\alpha} H_2EDTA^{2-}) [EDTA]_T} \right) [Ni]_T \quad (29)$$

In the range below pH = 8.0, the rate dependence on EDTA diminishes. A slow increase in rate is observed with decreasing pH above pH = 8.0, but below this value, the rate increases with decreasing pH much faster than is predicted by ligand dependence alone. This increase is especially marked below pH = 6.0. A plot of k_i^* (k_{obs} values extrapolated to zero EDTA concentration) versus $[H^+]$, shown in Figure 11, is similar to Figure 7 for the NiH_2OEDN -trien system. The same mechanism is proposed for this system (see Equations 17, 18, and 19). Values for k_2 , k_3 , and K_1K_H are obtained in the same manner as described in the previous section, and the same simplifying assumptions are made. The general rate expression for the low pH region is found in Equation 23.

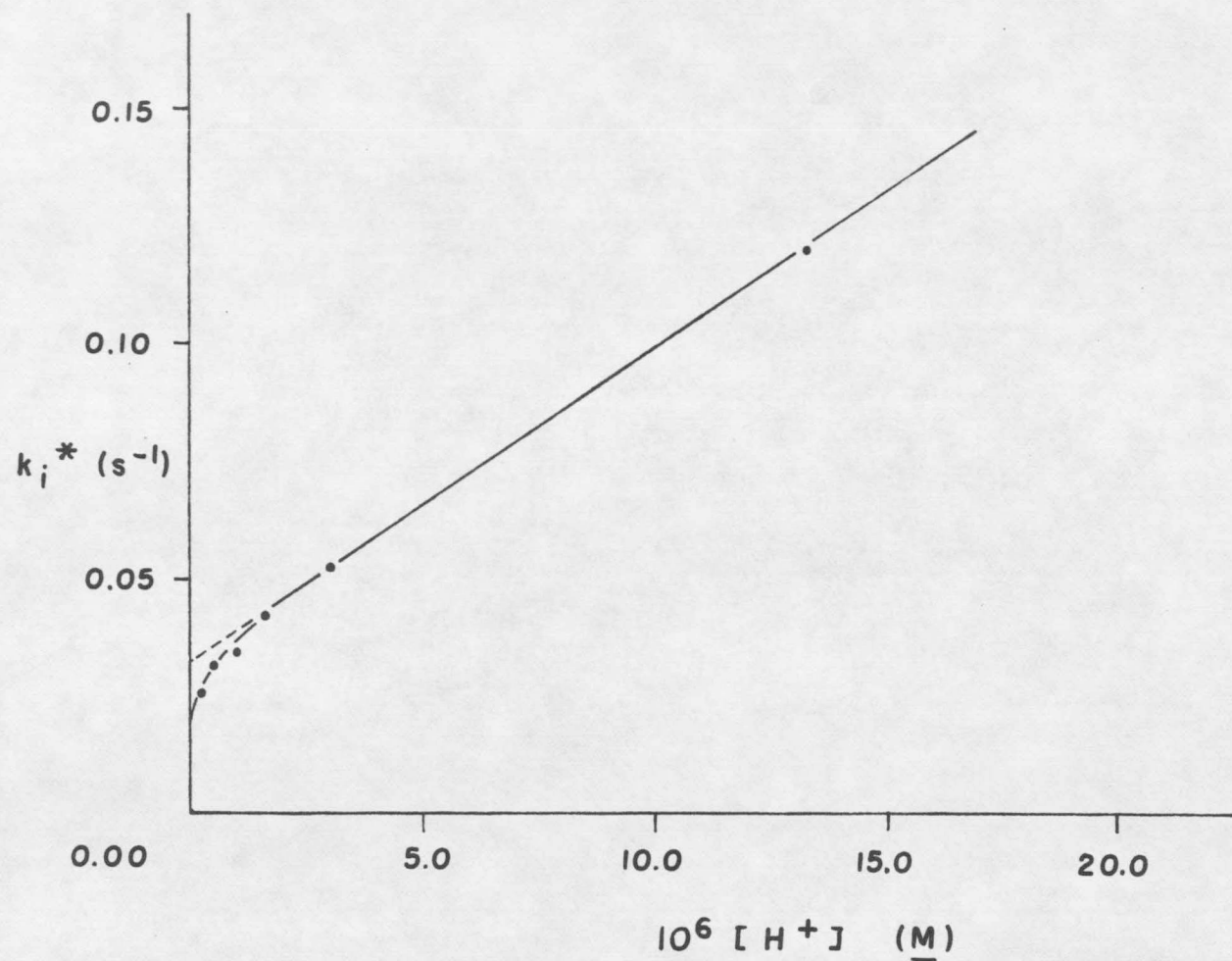


Figure 11. Dependence of k_i^* on $[\text{H}^+]$ for the reaction of NiH_2ODEN with EDTA.

Equations 23 and 29 have been used to predict rate constants for the appropriate pH regions, with a region of overlap between pH 5.46 and 7.88 where both expressions are used. These values are listed in Table 6. In this system, also, there is an indeterminate region where both hydrogen ion- and ligand-dependent pathways contribute to the overall rate of reaction. A plot of k_{obs} versus pH with lines generated from the predicted values is shown in Figure 12. The region between pH 8.0 and 9.88 is dominated by proton-assisted nucleophilic replacement, while in the region below pH 5.5, the rate is due to specific hydrogen ion catalysis. In the region between pH 5.5 and 8.0, contributions from HEDTA^{3-} , $\text{H}_2\text{EDTA}^{2-}$, hydrogen ion, and dissociation of the protonated species determine the rate of reaction.

A summary of the rate constants for this system is found in Table 8. The full mechanism is shown in Figure 9.

$k_{\text{H}_2\text{O}}$	$= 0.0014 \pm 0.0006 \text{ s}^{-1}$	
k_1	$= 0.038 \pm 0.005 \text{ s}^{-1}$	
k_2	$= 0.035 \pm 0.002 \text{ s}^{-1}$	
k_3	$= (7.0 \pm 0.4) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$	
$K_1 K_H$	$= (6.1 \pm 0.3) \times 10^6 \text{ M}^{-1}$	
k_{HY}/k_{-1}	$= (4 \pm 1) \times 10^1 \text{ M}^{-1}$	
$k_{\text{H}_2\text{Y}}/k_{-1}$	$= (1.4 \pm 0.5) \times 10^3 \text{ M}^{-1}$	$k_{\text{H}_2\text{Y}}/k_{\text{HY}} = 35$

Table 8. Rate constants for the reaction of NiH_2ODEN with EDTA.

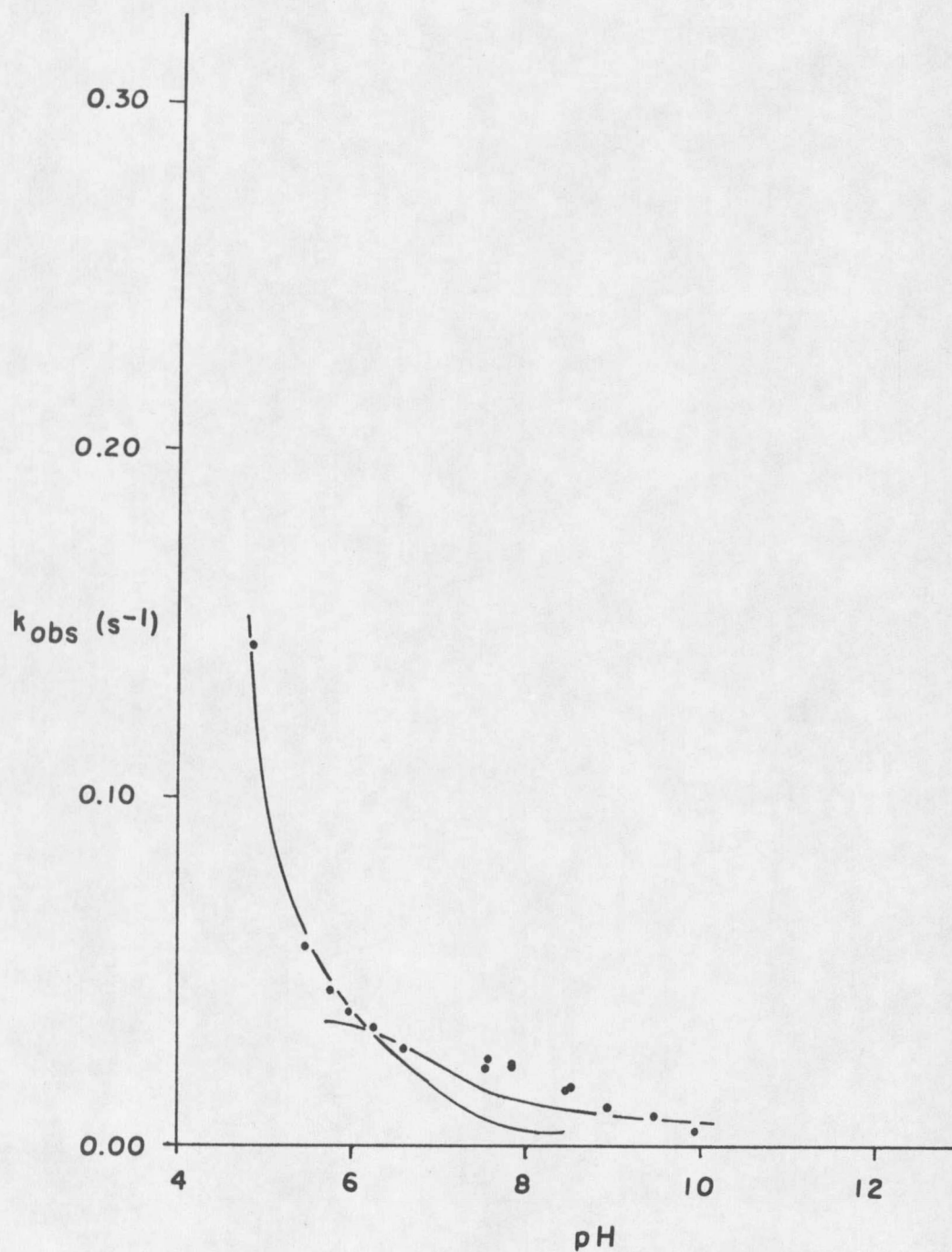


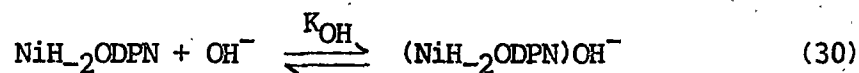
Figure 12. Dependence of observed rate constants on pH for the reaction of NiH_2ODEN with EDTA.

The Reaction of NiH_2ODPN with Trien

Experiments were conducted over a pH range of 11.52 to 4.74. Reactions were again run under pseudo-first-order conditions, and plots of $-\ln(A - A_t)$ were linear. Pseudo-first-order rate constants (k_{obs}) were obtained from these plots, and Equation 5 expresses the rate in terms of nickel complex concentration. Table 9 lists k_{obs} values, with corresponding pH and $[\text{trien}]_T$ values.

As with the system discussed previously, plots of k_{obs} versus $[\text{trien}]_T$ for pH values above pH = 8.0 were not linear, but plots of $(1/k_{\text{obs}} - k_{\text{H}_2\text{O}})$ versus $1/[\text{trien}]_T$ were (Figure 13). Equation 6 is valid for these reactions, and the mechanism in Equations 7 and 8 describes this system also in the region between pH 8.0 and 9.8. The ligand dependence expression is given by Equation 9, and assignment of k_i and k_{slope} by Equations 10 and 11, respectively. Equations 12, 13, 14, and 15, with values from Table 4, were used to obtain values for k_T/k_{-1} and k_{HT}/k_{-1} . The doubly-protonated form of trien did not make a significant contribution to the rate in this system.

Above pH = 9.8, the rate decreases sharply with increasing pH. Spectral studies show a decrease in absorbance at 293 nm (λ_{max}) with increasing pH, corresponding to a decrease in the concentration of the reactive complex species. A simple equilibrium with hydroxide ion producing a non-reactive species is proposed to account for the rate behavior and spectral data (Equation 30).



10^3 [trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
1.0	0.081	0.004	11.50	3.16×10^{-12}	0.0772	
2.0	0.161		11.52	3.02×10^{-12}	0.135	
5.0	0.373		11.51	3.09×10^{-12}	0.271	
7.0	0.515		11.51	3.09×10^{-12}	0.332	
1.0	0.118		11.00	1.00×10^{-11}	0.169	
2.0	0.231		11.01	9.77×10^{-12}	0.304	
5.0	0.538		11.00	1.00×10^{-11}	0.608	
7.0	0.696		11.00	1.00×10^{-11}	0.746	
1.0	0.205		10.37	4.26×10^{-11}	0.279	
2.0	0.393		10.37	4.26×10^{-11}	0.512	
5.0	0.833		10.39	4.07×10^{-11}	1.01	
7.0	1.13		10.39	4.07×10^{-11}	1.25	
1.0	0.235		10.06	8.71×10^{-11}	0.291	
2.0	0.444	0.007	10.06	8.71×10^{-11}	0.537	
5.0	0.969		10.08	8.32×10^{-11}	1.08	
7.0	1.31		10.07	8.51×10^{-11}	1.35	
1.0	0.260		9.76	1.74×10^{-10}	0.271	
2.0	0.473	0.003	9.78	1.66×10^{-10}	0.502	
5.0	1.01		9.78	1.66×10^{-10}	1.04	
7.0	1.33	0.02	9.77	1.70×10^{-10}	1.31	
1.0	0.20	0.01	9.39	4.04×10^{-10}	0.212	

Table 9. Concentrations and k_{obs} for the reaction of NiH₂ODPN with trien.

Table 9 continued

10^3 [trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
2.0	0.42	0.01	9.41	3.90×10^{-10}	0.400	
5.0	0.91	0.04	9.41	3.86×10^{-10}	0.866	
7.0	1.18		9.41	3.86×10^{-10}	1.11	
1.0	0.171		9.20	6.31×10^{-10}	0.169	
2.0	0.313		9.20	6.31×10^{-10}	0.323	
5.0	0.662		9.20	6.31×10^{-10}	0.718	
7.0	0.868		9.20	6.31×10^{-10}	0.936	
1.0	0.138		9.00	1.00×10^{-9}	0.129	
2.0	0.246		9.00	1.00×10^{-9}	0.249	
5.0	0.577		9.00	1.00×10^{-9}	0.568	
7.0	0.691		9.00	1.00×10^{-9}	0.751	
1.0	0.106	0.001	8.82	1.51×10^{-9}	0.0938	0.00589
2.0	0.204	0.004	8.82	1.51×10^{-9}	0.182	0.00589
5.0	0.410		8.78	1.66×10^{-9}	0.426	0.00646
7.0	0.542		8.77	1.70×10^{-9}	0.571	0.00662
1.0	0.0663		8.52	3.02×10^{-9}	0.0542	0.0115
2.0	0.117	0.001	8.51	3.09×10^{-9}	0.106	0.0118
5.0	0.255		8.49	3.24×10^{-9}	0.253	0.0123
7.0	0.317		8.48	3.31×10^{-9}	0.346	0.0126
1.0	0.056	0.001	8.14	7.24×10^{-9}	0.0239	0.0260
2.0	0.0824		8.13	7.41×10^{-9}	0.0465	0.0265
5.0	0.154		8.08	8.32×10^{-9}	0.113	0.0294

Table 9 continued

10^3 [trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
7.0	0.188		8.03	9.33×10^{-9}	0.156	0.0325
1.0	0.0556		7.87	1.35×10^{-8}	0.0125	0.0445
2.0	0.0762		7.84	1.44×10^{-8}	0.0239	0.0470
5.0	0.123		7.78	1.66×10^{-8}	0.0579	0.0528
7.0	0.142		7.75	1.78×10^{-8}	0.0802	0.0559
1.0	0.0843		7.46	3.47×10^{-8}	0.00529	0.0922
2.0	0.0962		7.44	3.63×10^{-8}	0.00957	0.0951
5.0	0.129		7.36	4.36×10^{-8}	0.0224	0.108
7.0	0.150		7.31	4.90×10^{-8}	0.0308	0.116
1.0	0.302		6.58	2.63×10^{-7}	0.00136	0.327
2.0	0.333		6.56	2.75×10^{-7}	0.00172	0.337
5.0	0.382		6.51	3.09×10^{-7}	0.00280	0.364
7.0	0.423		6.48	3.31×10^{-7}	0.00352	0.381
1.0	0.500		6.24	5.75×10^{-7}		0.565
2.0	0.487		6.24	5.75×10^{-7}		0.565
5.0	0.53	0.02	6.21	6.16×10^{-7}		0.595
7.0	0.579		6.20	6.31×10^{-7}		0.606
1.0	0.926		5.93	1.17×10^{-6}		1.00
2.0	0.921		5.94	1.15×10^{-6}		0.985
5.0	0.971		5.90	1.26×10^{-6}		1.06
7.0	1.05		5.88	1.32×10^{-6}		1.11
1.0	1.36		5.70	2.00×10^{-6}		1.60

Table 9 continued

10^3 [trien] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
2.0	1.39		5.71	1.95×10^{-6}		1.56
5.0	1.43		5.69	2.04×10^{-6}		1.63
7.0	1.53		5.68	2.09×10^{-6}		1.66
1.0	2.44		5.51	3.09×10^{-6}		2.39
2.0	2.64		5.48	3.31×10^{-6}		2.54
5.0	2.80		5.45	3.55×10^{-6}		2.72
7.0	3.01	0.04	5.42	3.80×10^{-6}		2.90
1.0	10.26		4.85	1.41×10^{-5}		10.32
2.0	11.70		4.83	1.48×10^{-5}		13.82
5.0	13.44		4.74	1.82×10^{-5}		13.27
7.0	13.64		4.74	1.82×10^{-5}		13.27

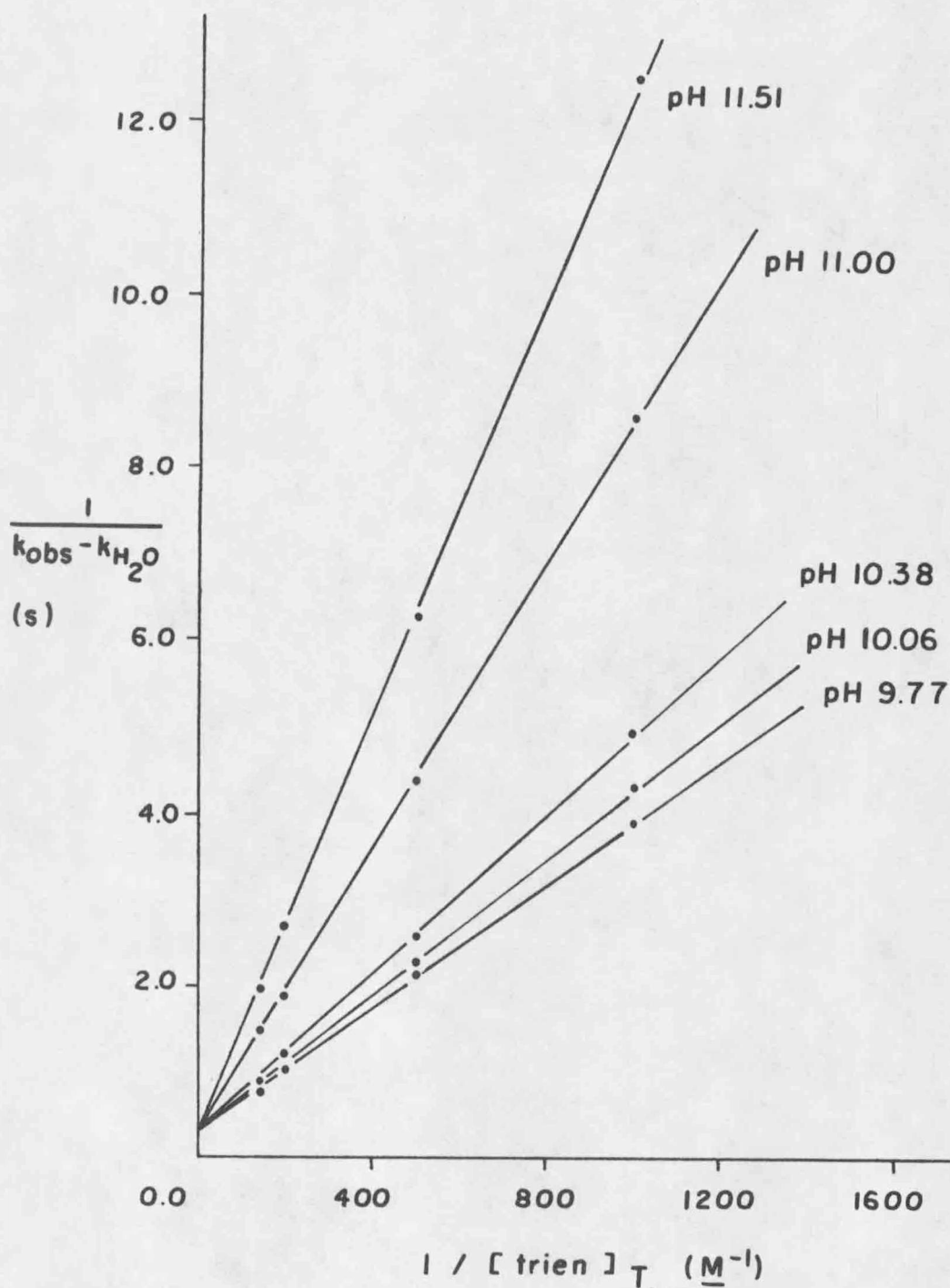


Figure 13. Dependence of k_{obs} on $[\text{trien}]_T$ for the reaction of NiH_2ODPN with trien .

The rate expression for the region above pH 8.0 is given in Equation 31.

$$\text{Rate} = \left(k_{\text{H}_2\text{O}} + \frac{k_1 (k_{\text{T}}^{\alpha} \text{trien} + k_{\text{HT}}^{\alpha} \text{Htrien}^+) [\text{trien}]_{\text{T}}}{k_{-1} + (k_{\text{T}}^{\alpha} \text{trien} + k_{\text{HT}}^{\alpha} \text{Htrien}^+) [\text{trien}]_{\text{T}}} \right) \left(\frac{1}{1 + K_{\text{OH}} [\text{OH}^-]} \right) [\text{Ni}]_{\text{T}} \quad (31)$$

Below pH 8.0, rate dependence on trien decreases, and the rate levels off with decreasing pH. Below pH 7.0, the rate begins to increase with decreasing pH, with the rate of increase becoming large below pH 6.0. The plot of k_1^* versus $[\text{H}^+]$ for this system (Figure 14) is similar to analogous plots for the two systems discussed previously (Figures 7 and 11). The mechanism proposed for those systems (Equations 17, 18, and 19) is consistent with the low pH behavior of the $\text{NiH}_2\text{ODPN-trien}$ system. Values for k_2 , k_3 and $K_1 K_{\text{H}}$ were obtained in the same manner as described previously. The general rate expression is given by Equation 23.

The rate expressions in Equations 23 and 31 have been used to predict rate constants, as in earlier sections. The predicted values can be found in Table 9. The plot of k_{obs} versus pH (Figure 15) shows only a small region between pH 7.5 and 8.0 where predicted values from neither the high pH nor the low pH expression match observed values closely. Above pH 8.0, direct nucleophilic replacement by trien and Htrien^+ determine the rate of reaction, although formation of a non-reactive species with hydroxide inhibits the rate above pH 9.8. Below pH 6.5, the rate is predominantly due to specific hydrogen ion catalysis. Between pH 6.5 and 8.0, the

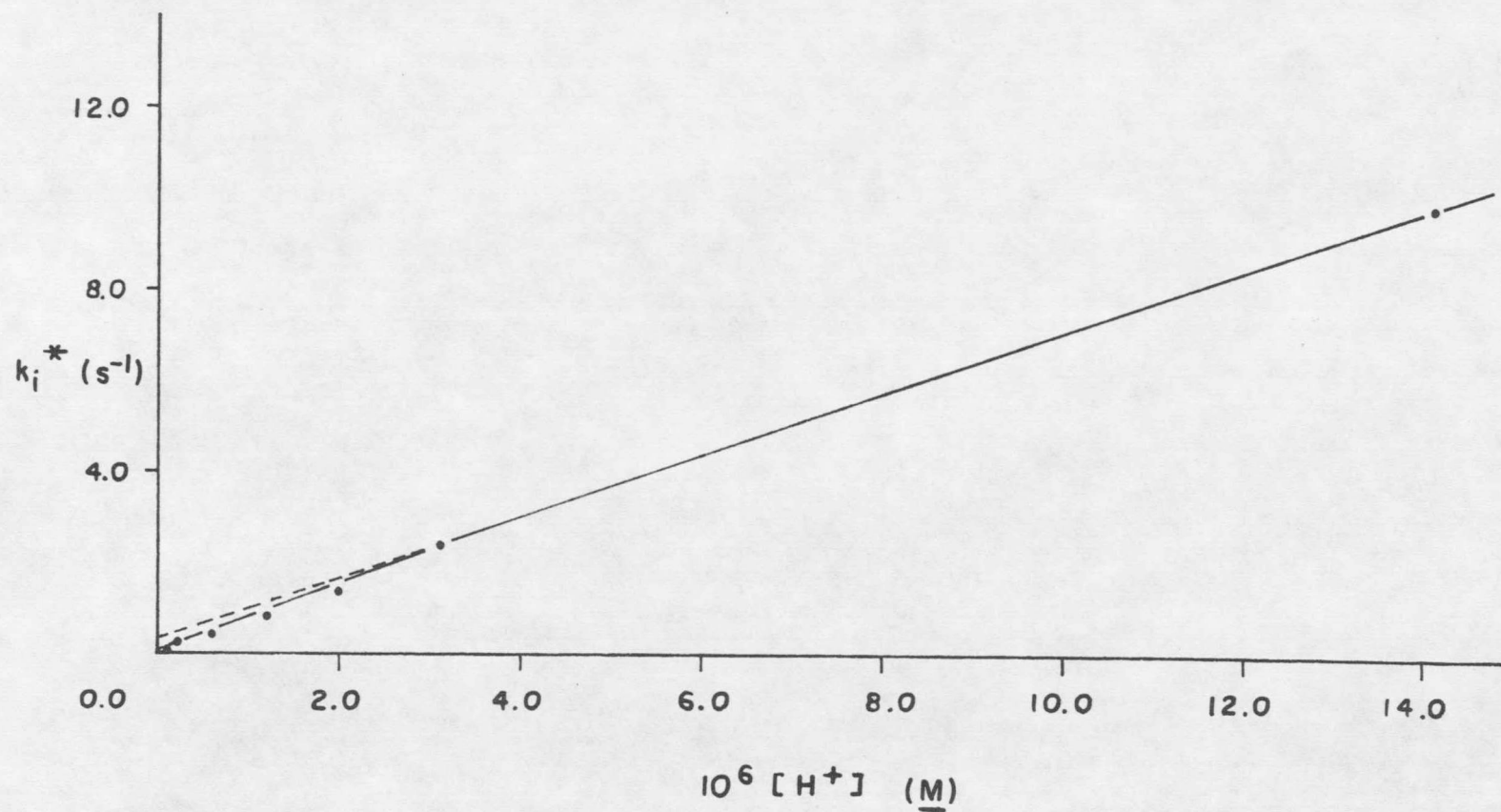


Figure 14. Dependence of k_i^* on $[\text{H}^+]$ for the reaction of NiH_2ODPN with trien.

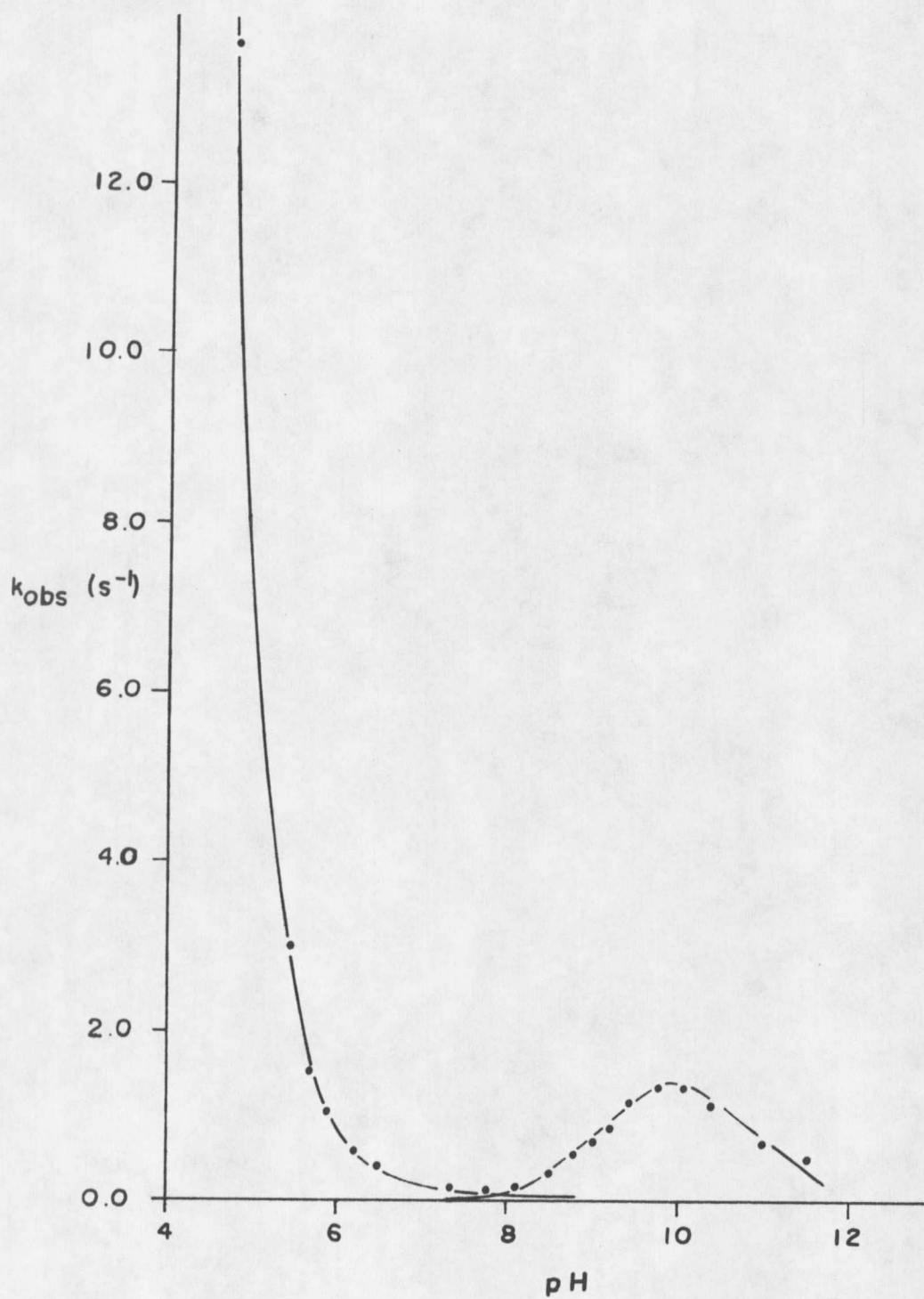


Figure 15. Dependence of observed rate constants on pH for the reaction of NiH_2ODPN with trien.

rate is largely unchanged and probably due to solvent-assisted dissociation, with a contribution from dissociation of the protonated species increasing somewhat as pH decreases.

Table 10 gives a summary of the rate constants for this system. The full mechanism for the reaction of NiH_2ODPN with ligands is shown in Figure 16.

$k_{\text{H}_2\text{O}}$	$= 0.0010 \pm 0.0001 \text{ s}^{-1}$	
k_1	$= 4.0 \pm 0.3 \text{ s}^{-1}$	
k_2	$= 0.20 \pm 0.02 \text{ s}^{-1}$	
k_3	$= (7.2 \pm 0.3) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$	
$K_1 K_H$	$= (2.0 \pm 0.1) \times 10^7 \text{ M}^{-1}$	
k_T/k_{-1}	$= (1.1 \pm 0.1) \times 10^2 \text{ M}^{-1}$	
k_{HT}/k_{-1}	$= (6.0 \pm 0.4) \times 10^1 \text{ M}^{-1}$	$k_{\text{HT}}/k_T = 0.55$
K_{OH}	$= (1.3 \pm 0.4) \times 10^3 \text{ M}^{-1}$	

Table 10. Rate constants for the reaction of NiH_2ODPN with trien.

The Reaction of NiH_2ODPN with EDTA

This system was studied over a pH range of 10.37 to 4.85. Pseudo-first-order conditions were maintained and plots of $-\ln(A_\infty - A_t)$ versus time were linear. Pseudo-first-order rate constants are listed with corresponding pH and $[\text{EDTA}]_T$ values in Table 11. Equation 5 expresses the rate in terms of complex concentration.

Plots of k_{obs} versus $[\text{EDTA}]_T$ for pH values above pH 7.8 were not linear. Linear plots were obtained for the quantity $(1/k_{\text{obs}} - k_{\text{H}_2\text{O}})$

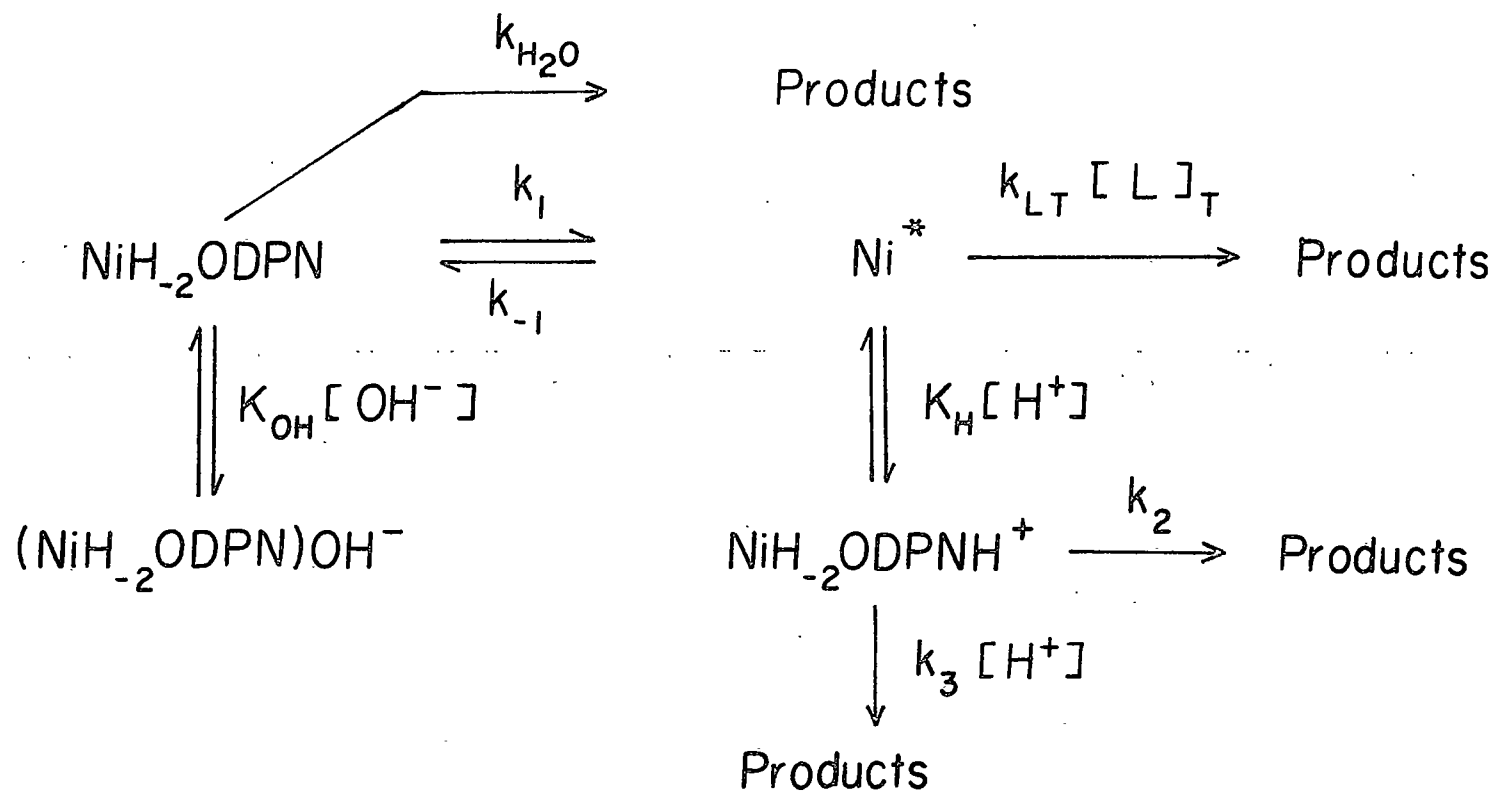


Figure 16. Proposed mechanism for the reaction of $\text{NiH}_{-2}\text{ODPN}$ with ligands.

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
1.0	0.00142		10.33	4.64×10^{-11}	0.00467	
2.0	0.00248	0.00002	10.37	4.31×10^{-11}	0.00795	
5.0	0.00532		10.36	4.35×10^{-11}	0.0162	
7.0	0.0057	0.0002	10.35	4.44×10^{-11}	0.0206	
1.0	0.00356		9.91	1.23×10^{-10}	0.00798	
2.0	0.00580		9.91	1.23×10^{-10}	0.0138	
5.0	0.0116	0.0002	9.88	1.31×10^{-10}	0.0268	
7.0	0.0152	0.0004	9.93	1.17×10^{-10}	0.0324	
1.0	0.011	0.002	9.51	3.07×10^{-10}	0.0105	
2.0	0.0151	0.0004	9.52	3.04×10^{-10}	0.0179	
5.0	0.0297	0.0004	9.53	2.98×10^{-10}	0.0331	
7.0	0.0354		9.53	2.98×10^{-10}	0.0396	
1.0	0.0143		9.00	1.00×10^{-9}	0.0128	
2.0	0.0211		9.00	1.00×10^{-9}	0.0218	
5.0	0.0390		9.00	1.00×10^{-9}	0.0385	
7.0	0.0500		9.00	1.00×10^{-9}	0.0454	
1.0	0.0227	0.0009	8.52	3.02×10^{-9}	0.0159	0.0115
2.0	0.0333		8.51	3.09×10^{-9}	0.0262	0.0118
5.0	0.0515		8.50	3.16×10^{-9}	0.0443	0.0120
7.0	0.0615		8.48	3.31×10^{-9}	0.0511	0.0126
1.0	0.0548		7.88	1.32×10^{-8}	0.0277	0.0438

Table 11. Concentrations and k_{obs} for the reaction of NiH_2ODPN with EDTA.

Table 11 continued

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
2.0	0.0664		7.87	1.35×10^{-8}	0.0414	0.0446
5.0	0.0825		7.86	1.38×10^{-8}	0.0593	0.0454
7.0	0.0898		7.85	1.41×10^{-8}	0.0647	0.0462
1.0	0.0815		7.57	2.69×10^{-8}	0.0380	0.0767
2.0	0.0914		7.57	2.69×10^{-8}	0.0522	0.0767
5.0	0.105		7.54	2.88×10^{-8}	0.0675	0.0807
7.0	0.111		7.52	3.02×10^{-8}	0.0715	0.0835
1.0	0.159		7.22	6.02×10^{-8}	0.0587	0.133
2.0	0.173		7.12	7.58×10^{-8}	0.0691	0.153
5.0	0.208		7.04	9.12×10^{-8}	0.0773	0.172
7.0	0.226		7.01	9.77×10^{-8}	0.0791	0.179
1.0	0.348		6.56	2.75×10^{-7}	0.0710	0.337
2.0	0.371		6.53	2.95×10^{-7}	0.0769	0.353
5.0	0.407		6.49	3.23×10^{-7}	0.0810	0.374
7.0	0.452		6.48	3.31×10^{-7}	0.0818	0.381
1.0	0.595		6.29	5.13×10^{-7}		0.519
2.0	0.560		6.27	5.37×10^{-7}		0.537
5.0	0.621		6.25	5.62×10^{-7}		0.555
7.0	0.620		6.26	5.50×10^{-7}		0.546
1.0	0.96		5.98	1.05×10^{-6}		0.912
2.0	1.01		5.96	1.10×10^{-6}		0.949
5.0	1.00		5.94	1.15×10^{-6}		0.985

Table 11 continued

10^3 [EDTA] _T , M	k_{obs} s ⁻¹	σ	pH	[H ⁺], M	k_{pred}	
					high pH	low pH
7.0	1.08		5.94	1.15×10^{-6}		0.985
1.0	1.41		5.81	1.55×10^{-6}		1.27
2.0	1.52		5.80	1.58×10^{-6}		1.30
5.0	1.52		5.78	1.66×10^{-6}		1.35
7.0	1.57	0.02	5.77	1.70×10^{-6}		1.38
1.0	2.6	0.1	5.49	3.24×10^{-6}		2.49
2.0	2.83		5.49	3.24×10^{-6}		2.49
5.0	3.02		5.45	3.55×10^{-6}		2.72
7.0	3.08		5.44	3.63×10^{-6}		2.78
1.0	10.26		4.89	1.29×10^{-5}		9.45
2.0	10.17		4.88	1.32×10^{-5}		9.67
5.0	11.63		4.85	1.41×10^{-5}		10.32
7.0	12.22		4.85	1.41×10^{-5}		10.32

versus $1/[\text{EDTA}]_T$ (Figure 17). Equation 23 is valid for this system. A mechanism similar to that described in Equations 7, 8, and 30 is consistent with the behavior of this system in the pH range above pH = 7.8. The expression for the ligand dependence is given by Equation 25, and the assignment of k_i and k_{slope} by Equations 26 and 27. Equation 28, values from Table 7, and expressions similar to those in Equations 13, 14, and 15 were used to obtain values for k_{HY}/k_{-1} and $k_{\text{H}_2\text{Y}}/k_{-1}$. As with the $\text{NiH}_2\text{ODEN-EDTA}$ system, the fully deprotonated form of EDTA made no significant contribution to the rate. The general rate expression for the pH range above pH 7.8 is given by Equation 32.

$$\text{Rate} = k_{\text{H}_2\text{O}} + \left(\frac{k_1 (k_{\text{HY}}^\alpha \text{HEDTA}^3 + k_{\text{H}_2\text{Y}}^\alpha \text{H}_2\text{EDTA}^2) [\text{EDTA}]_T}{k_{-1} + (k_{\text{HY}}^\alpha \text{HEDTA}^3 + k_{\text{H}_2\text{Y}}^\alpha \text{H}_2\text{EDTA}^2) [\text{EDTA}]_T} \right) \left(\frac{1}{1 + K_{\text{OH}} [\text{OH}^-]} \right) [\text{Ni}]_T \quad (32)$$

Below pH 7.5, the rate dependence on EDTA decreases, and the rate increases with decreasing pH faster than predicted by the ligand-dependent expression alone. Figure 18 shows the plot of k_i^* versus $[\text{H}^+]$, which resembles analogous plots for the other three systems (Figures 7, 11, and 14). The same mechanism for the low pH region is proposed (Equations 17, 18, and 19), and the general rate expression is given by Equation 23. Values of k_2 , k_3 , and $K_1 K_{\text{HY}}$ were obtained as described previously.

The expressions in Equations 23 and 32 have been used to predict rate constants for this system; these values are listed in

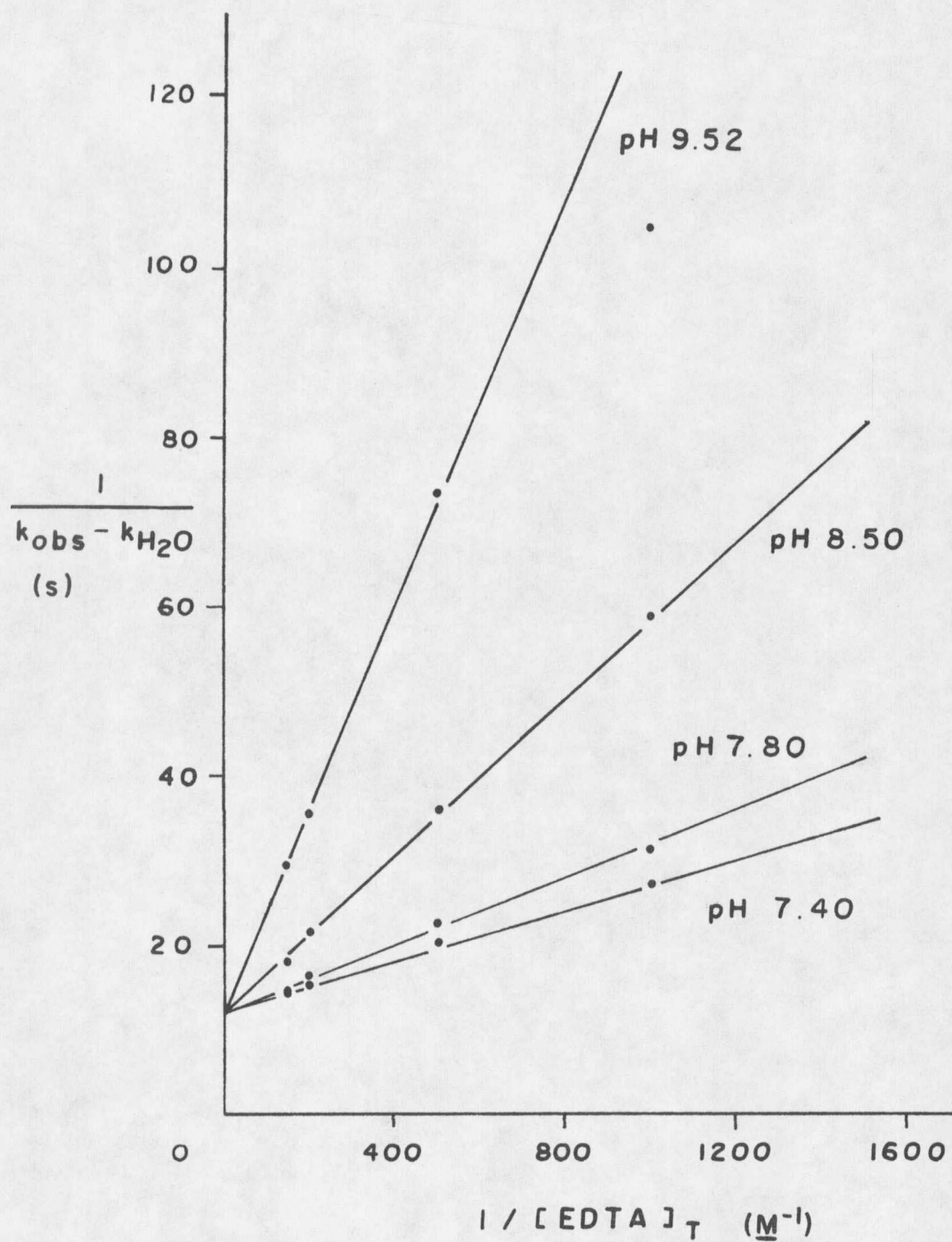


Figure 17. Dependence of k_{obs} on $[\text{EDTA}]_{\text{T}}$ for the reaction of NiH_2ODPN with EDTA.

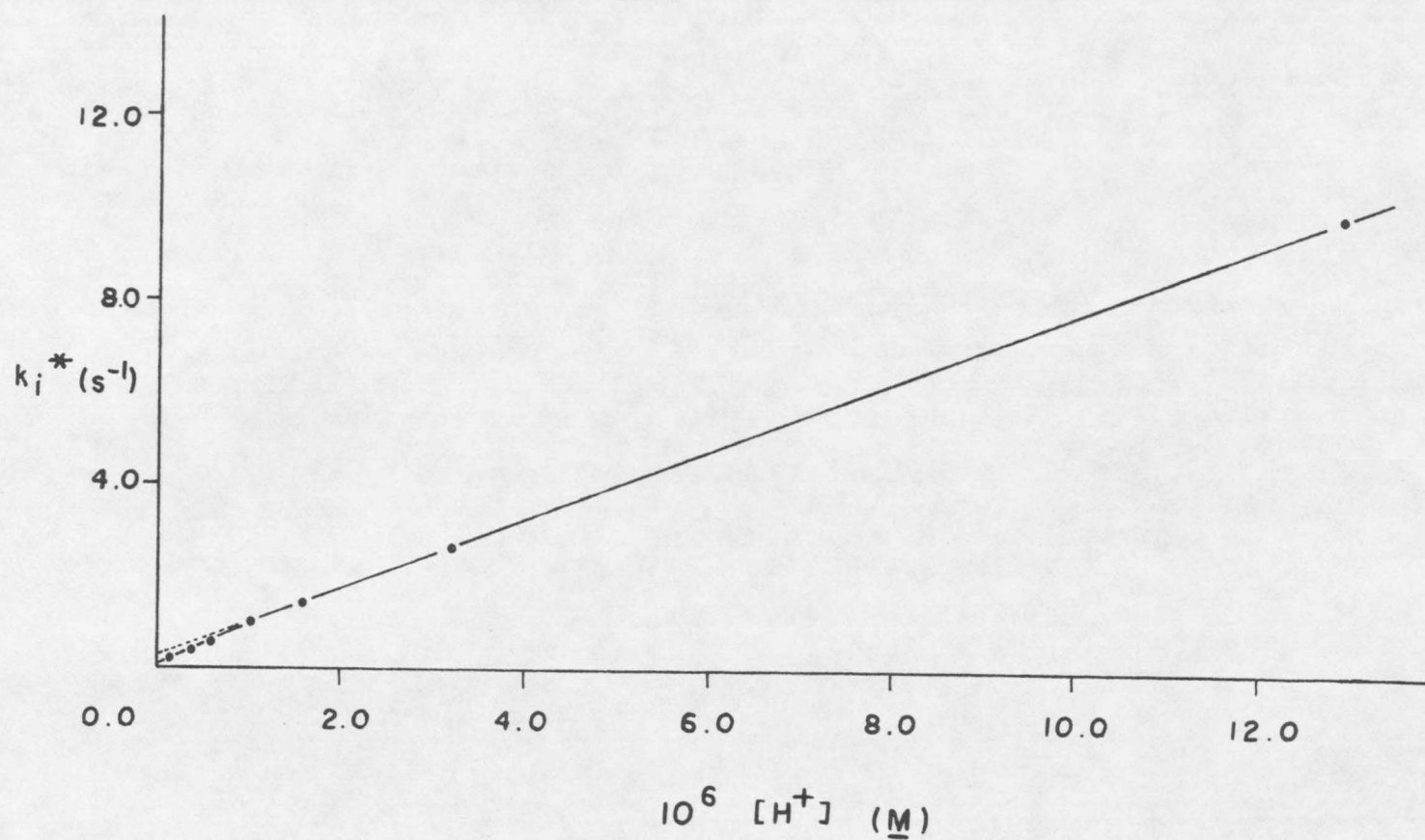


Figure 18. Dependence of k_i^* on $[H^+]$ for the reaction of NiH_2ODPN with EDTA.

Table 11. The plot of k_{obs} versus $[\text{H}^+]$ (Figure 19) shows the comparison of observed and predicted values. The slow increase in rate from pH = 10.37 to pH = 7.80 and rate dependence on HEDTA^{3-} and $\text{H}_2\text{EDTA}^{2-}$ suggest proton-assisted nucleophilic replacement in this pH region. Below pH = 6.50 the rate is predominantly due to specific hydrogen ion catalysis. Solvent-assisted dissociation, dissociation of the protonated intermediate, and a small amount of dependence on $\text{H}_2\text{EDTA}^{2-}$ contribute to the rate in the intermediate region between pH 6.5 and 7.8.

A summary of the rate constants for this system can be found in Table 12. Figure 16 shows the mechanism proposed for the reaction of NiH_2ODPN with EDTA.

$k_{\text{H}_2\text{O}}$	$= 0.0010 \pm 0.0001 \text{ s}^{-1}$	
k_1	$= 0.083 \pm 0.002 \text{ s}^{-1}$	
k_2	$= 0.20 \pm 0.02 \text{ s}^{-1}$	
k_3	$= (1.2 \pm 0.3) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$	
$K_1 K_H$	$= (2.0 \pm 0.1) \times 10^7 \text{ M}^{-1}$	
k_{HY}/k_{-1}	$= (1.6 \pm 0.6) \times 10^2 \text{ M}^{-1}$	
$k_{\text{H}_2\text{Y}}/k_{-1}$	$= (1.6 \pm 0.3) \times 10^4 \text{ M}^{-1}$	$k_{\text{H}_2\text{Y}}/k_{\text{HY}} = 100$
K_{OH}	$= (1.3 \pm 0.4) \times 10^3 \text{ M}^{-1}$	

Table 12. Rate constants for the reaction of NiH_2ODPN with EDTA.

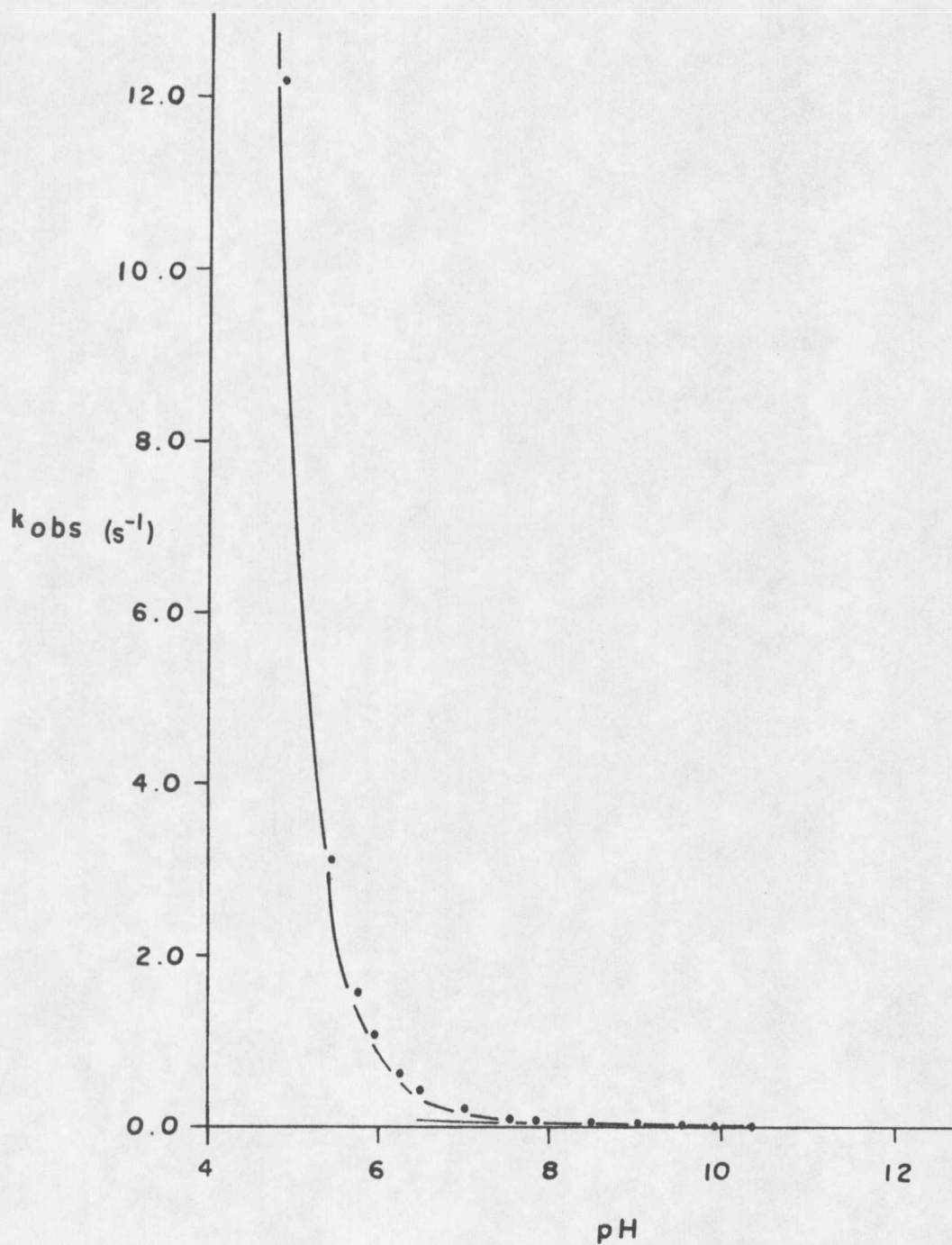


Figure 19. Dependence of observed rate constants on pH for the reaction of NiH_2ODPN with EDTA.

DISCUSSION

The Reaction of NiH_2ODEN with Ligands

The complex NiH_2ODEN reacts with replacing ligands via a variety of parallel and interconnected pathways. As the mechanism in Figure 9 shows, there are two major reactive species in this system, each dominating the reaction within a certain pH range. In the high pH range, the square-planar, doubly-deprotonated species designated NiH_2ODEN is the predominant species, reacting via parallel ligand-dependent and ligand-independent pathways. In the low pH range, the square-planar complex is first converted to a protonated intermediate, designated $\text{NiH}_2\text{ODENH}^+$, which may proceed to products via parallel hydrogen ion-dependent and hydrogen ion-independent pathways. Each of these pathways will be discussed in detail.

Solvent-Assisted Dissociative Pathway. Evidence for a ligand-independent pathway arose from the inability to determine a simple ligand dependence for the rate in the high pH range. Parallel paths making contributions similar in magnitude to the rate in this pH range would explain the difficulty in finding a simple relationship between k_{obs} and ligand concentration. Removal of the contribution from the ligand-independent pathway is necessary before the ligand dependence may be examined.

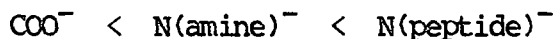
There is no evidence for buffer dependence in this system throughout the pH range studied. Therefore, a likely choice for the identity of the ligand-independent pathway is solvent-assisted dissociation. Such a pathway would make a constant contribution to the rate regardless of pH. The rate constant (k_{H_2O}) was obtained by finding an optimum value for which the quantity $(1/k_{obs} - k_{H_2O})$, when plotted versus $1/[ligand]_T$, produced linear plots (allowing determination of the ligand dependence). The value of k_{H_2O} for the NiH_2ODEN system is 0.0014 s^{-1} .

Examination of Table 1 shows that the dissociation constant for this system is more than an order of magnitude smaller than that of nickel-triglycine ($k_{H_2O} = 0.086 \text{ s}^{-1}$) and more than three orders smaller than that of nickel-diglycinamide ($k_{H_2O} = 3.1 \text{ s}^{-1}$). The dissociative constants reported for nickel-tetraglycine, nickel-cyanoglycylglycinamide, and nickel-diglycylethylenediamine are one to two orders smaller than that found for NiH_2ODEN ($NiGGGG$: $1.6 \times 10^{-5} \text{ s}^{-1}$; $NiGGaCN$: $8.0 \times 10^{-5} \text{ s}^{-1}$; $NiDGEN$: $2.1 \times 10^{-4} \text{ s}^{-1}$, $3 \times 10^{-4} \text{ s}^{-1}$).

The solvent-assisted dissociative pathway is postulated to involve nucleophilic displacement of the peptide nitrogen by solvent, followed by rapid protonation by solvent of the very basic displaced nitrogen. Dissociation of the coordinated ligand and association of the incoming ligand follows this displacement step.²⁴ The preceding comparison of dissociation constants indicates that NiH_2ODEN 's terminal amine slows dissociation relative to NiH_2GGG^- 's

terminal carboxylate group and NiH_2GGA 's absence of a third chelate ring. The terminal peptide nitrogen in $\text{NiH}_3\text{GGG}^{2-}$ and cyanide in $\text{NiH}_2\text{GGaCN}^-$ slow dissociation even further. The lability of the NiH_2ODEN complex with regard to solvent-assisted dissociation is intermediate between the more labile NiH_2GGG^- and the more stable $\text{NiH}_3\text{GGG}^{2-}$.

An examination of the ligand field stabilization of these three complexes shows the same trend as that noted with rate of dissociation. Paniago and Margerum³³ state that the relative order of the three terminal groups under discussion in the spectrochemical series is as follows:



Spectral properties reflect the stabilization which results from coordination of the different groups (see Table 13). For a d^8 square-planar complex in a strong field, the crystal-field stabilization energy is $24.6 Dq$.⁵⁰ Spectral transitions are approximately half that value,³³ and so the difference of $2.6 \text{ kcal mol}^{-1}$ between NiH_2GGG^- and NiH_2ODEN translates to somewhat more than 5 kcal increase in stability for NiH_2ODEN .

The NiH_2DGEN complex is structurally very similar to NiH_2ODEN . Both complexes contain two terminally-bonded amine groups. Further, all chelate rings in both complexes are five-membered. The complexes differ only in the position of the peptide oxygens: in the backbone for NiH_2ODEN and in the side-chains for

Complex	λ_{max} , nm	Spectral Transition kcal mol ⁻¹
NiH ₂ GGG ⁻ (33)	430	66.4
NiH ₃ GGG ²⁻ (33)	412	69.3
NiH ₂ DGEN (41)	410	69.7
NiH ₂ ODEN	414	69.0
NiH ₂ ODPN	453	63.1

Table 13. Absorption maxima and spectral transitions for some nickel(II) complexes.

NiH₂DGEN (see Figure 2). Apparently, this difference in peptide oxygen position lends the DGEN complex greater stability, reflected in the slower dissociation rate and spectral properties as well (Table 13).

Ligand-Dependent Pathways

Reaction with Trien: Examination of Figure 8 shows that the rate decreases with decreasing pH above pH = 8.5. This behavior is seen with direct nucleophilic replacement by the incoming ligand, where unprotonated forms of the ligand are more effective nucleophiles than are protonated forms. A simple first-order dependence on ligand concentration, characterized by linear k_{obs} versus [trien]_T plots, was not found in this system. However, inverse plots (when the contribution from the ligand-independent pathway had been removed before inversion) were found to be linear. This implies an equilibrium step preceding the rate-determining reaction with the ligand. The formation of an intermediate form of

the complex, Ni^* , is postulated to involve dissociation of a terminal amine group. The rate constant for ring-opening for ethylenediamine coordinated to $Ni(II)$ is 0.15 s^{-1} ,⁵¹ in reasonable agreement with the value of k_1 (0.7 s^{-1}) obtained for the reaction of NiH_2ODEN with trien.

Following the dissociation of a terminal amine group, trien may coordinate initially in one of two ways: 1) weak axial association, followed by strong in-plane coordination in the vacant position, or 2) direct in-plane coordination with trien's terminal amine. The importance of the chelate effect in determining reaction rate in other studies³⁵ favors the first of these modes. In either case, it is the in-plane coordination which is important in initiating substitution;²⁴ breakage of the peptide nitrogen which follows this step does not occur prior to the rate-determining step in reactions of analogous complexes.³⁵

The ligand-dependent constants are reported as ratios of k_T , k_{HT} , or k_{H_2T} to k_{-1} , the constant describing the reassociation of the terminal amine, because this mechanism does not allow separation of these two constants. Ratios of k_{HT} to k_T and k_{H_2T} to k_T allow us to examine the relative effectiveness of the various forms of trien as nucleophiles in this system and also permit comparison with other systems. For NiH_2ODEN , $k_{HT} = 0.25\text{ }k_T$, and $k_{H_2T} = 0.18\text{ }k_T$. This trend is to be expected from the nucleophilic nature of the ligand-dependence in this system. In the reaction of the structurally similar NiH_2DGEN with trien, the ratios are $k_{HT}/k_T = 0.63$ and

$k_{H_2T}/k_T = 0.046$. NiH_2ODEN 's k_{HT} constant is somewhat smaller, relative to NiH_2DGEN , but the k_{H_2T} constant is considerably larger. The larger k_{H_2T} ratio may indicate a small degree of proton assistance to the nucleophilic replacement of NiH_2ODEN by H_2trien^{2+} .

Reaction with EDTA: Figure 12 shows that the rate of reaction of NiH_2ODEN with EDTA increases slowly with decreasing pH in the range above $pH = 8.5$. This pattern of behavior is consistent with a proton-assisted nucleophilic displacement mechanism. Pearson and Pagenkopf⁴² postulate that in the reaction between NiH_2DGEN and EDTA, $HEDTA$ is able to transfer a proton to the imide nitrogen prior to or during the rate-determining step, facilitating the substitution process. A similar sequence is envisioned for the reaction with NiH_2ODEN .

As in the reaction with trien, a simple first-order dependence on EDTA concentration was not found. Inverse plots were again found to be linear (when the ligand-independent contribution was removed prior to inversion), suggesting equilibrium formation of an intermediate nickel complex followed by reaction with EDTA. Comparison of k_1 values for the two ligands shows an unexpected discrepancy. If the same activation step were taking place, k_1 values for the reaction of NiH_2ODEN with trien and EDTA should be the same. The difference of more than an order of magnitude (trien: $k_1 = 0.7 \text{ s}^{-1}$; EDTA: $k_1 = 0.038 \text{ s}^{-1}$) clearly indicates that this is not the case. Use of molecular models shows that approach by EDTA is less sterically hindered if two positions are free. This may be

accomplished in one of two ways: 1) dissociation of both terminal amines, or 2) dissociation of a terminal amine, followed by dissociation of the first peptide nitrogen. The magnitude of the difference in k_1 values for the two ligands suggests that dissociation of the peptide nitrogen is the more likely choice. Dissociation of a second terminal amine, with energy barriers presumably equivalent to those associated with the first dissociation, is unlikely to reduce the value of k_1 sufficiently. The sequential unwrapping of the coordinated ligand more reasonably accounts for the magnitude of the change. The backbone of this complex, containing two adjacent peptide oxygens, is expected to have greater rigidity than the side-chains, so the opening of this second chelate ring could be much slower than the opening of the first ring.

Following the activation step, EDTA is able to approach the nickel center and initiate substitution. Axial association or coordination by carboxylate is a reasonable first step in this process, as EDTA's amine nitrogen is in good position for equatorial coordination as a result. An adjacent site is also available for coordination of a second carboxylate group following coordination of the amide nitrogen. Proton transfer to the remaining coordinated peptide nitrogen by protonated forms of EDTA occurs at some point after the initial coordination.

As with the trien reaction, the ligand-dependent constants are reported as ratios of k_y to k_{-1} , etc. In contrast with other

systems, the fully deprotonated form of EDTA makes no significant contribution to the rate. This is further evidence that proton assistance of the nucleophilic replacement process is required in this system. The ratio of k_{H_2Y} to k_{HY} is 35. Comparison of this system with the reaction of NiH_2DGEN with EDTA is not possible, as that system was not studied in a pH range which allowed determination of a k_{H_2Y} term.

Proton-Limited Pathway. Figures 8 and 12 show that below pH = 6.5, the rate of reaction increases dramatically with decreasing pH. This pattern is observed in reactions of NiH_2ODEN regardless of the identity of the incoming ligand. It is clear that the rate is proton-limited in this pH range. Plots of k_{obs} versus hydrogen ion concentration (Figures 7 and 11) indicate that a variety of protonation pathways are available in this system. The curvature at the low $[H^+]$ end of the plot is indicative of a protonation equilibrium. In this region, the rate of reaction is limited by the formation, via the protonation equilibrium, of a new reactive species. The constant descriptive of this process is designated K_H . The resultant species may react via two parallel pathways. The linear portion of Figures 8 and 12 at higher $[H^+]$ indicates that one of these pathways has a first-order dependence on hydrogen ion concentration. The non-zero "intercept" of this linear portion indicates that another pathway, independent of hydrogen ion concentration, is also available to the new protonated reactive species.

As was discussed earlier, two general patterns of hydrogen ion-controlled behavior are observed in metal-peptide systems: general acid catalysis and specific hydrogen ion catalysis. General acid catalysis is characterized by rate dependence on the concentration of buffers present. In the reactions of NiH_2ODEN with ligands, no buffer dependence was observed, and so specific hydrogen ion catalysis is proposed to account for the proton-limited behavior observed in this system. Specific hydrogen ion catalysis is thought to proceed via an outside protonation mechanism (Figure 1). Table 1 shows that values of outside protonation constants for complexes whose protonation reactions proceed via specific hydrogen ion mechanisms are in the range of 10^3 - $10^4 \text{ M}^{-1} \text{ s}^{-1}$ ($\text{NiH}_3\text{GGGG}^{2-}$: $7.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$; $\text{NiH}_2\text{GGaCN}^-$: $4.3 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$). The value initially obtained for K_H in the NiH_2ODEN system is $6.1 \times 10^6 \text{ M}^{-1}$, much higher than expected for an outside protonation constant. Another site available for protonation is the dissociated terminal amine group following the activation step (k_1). The protonation constant for ethylenediamine^{49b} is $7.8 \times 10^9 \text{ M}^{-1}$, considerably higher than the NiH_2ODEN constant. However, if the value obtained in this system were equal to the quantity K_1K_H , describing a combination of dissociation and amine protonation steps, this mechanism would explain the magnitude of the observed constant.

Of the two pathways available for further reaction of the protonated species, the constant k_2 has been assigned to the hydrogen ion-independent pathway. This pathway is believed to

involve a dissociative process, probably solvent-assisted. The value of k_2 for this system is 0.035 s^{-1} . This is larger than $k_{\text{H}_2\text{O}}$, the constant for the solvent-assisted dissociation of the initial square-planar complex. This is perhaps not too surprising, as the protonated complex has only three coordinated nitrogens, compared with four in the initial complex. The discussion of the number of metal-nitrogen bonds present in a complex and the effect on that complex's stability, presented in the Introduction, indicated that fewer M-N bonds led to faster reaction rates due to a decrease in ligand field stabilization.²⁴

The constant k_3 is associated with the reaction of the protonated intermediate via further protonation. The value of this constant is $7 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. This is more in line with values of outside protonation constants in other systems, and this step is postulated to involve an outside protonation.

In the general mechanism for protonation of metal-peptide complexes presented in the Introduction (Equations 3 and 4), four cases were discussed in which the relative magnitudes of k_2 , k_{-1} , and the concentration of the intermediate species $\text{M}(\text{H}_{-n}\text{L})\text{H}$ determined the reactivity pattern observed.³³ The pattern observed in the reaction of $\text{NiH}_2\text{ODENH}^+$ with acid is described by Case 3, where the concentration of $\text{M}(\text{H}_{-n}\text{L})\text{H}$ ($\text{NiH}_2\text{ODENH}_2^{2+}$ here) is negligible and $k_2 \ll k_{-1}[\text{X}^-]$. The significant step in determining the rate of reaction is the bond-breakage step, preceded by the "outside" protonation equilibrium, and $k_1[\text{HX}]/k_{-1}[\text{X}^-]$ from Equation 3 becomes

$K_H[H^+]$. The k_3 term in this system is a combination of K_H and k_2 terms from the general mechanism.

The Reaction of NiH_2ODPN with Ligands

Examination of Figures 9 and 16 shows that the reaction mechanism of NiH_2ODPN with ligands resembles the mechanism which describes the NiH_2ODEN system in many ways. In the NiH_2ODPN system, there are again two different reactive species, each predominant within a certain pH range. A doubly-deprotonated, square-planar species designated NiH_2ODPN is the major reactant in the high pH range, and reacts via parallel ligand-dependent and ligand-independent pathways. This system differs from the NiH_2ODEN system in the formation of a non-reactive species above $pH = 9.8$. In the low pH range, a protonated intermediate is formed which reacts via parallel hydrogen ion-dependent and hydrogen ion-independent pathways. A detailed discussion of the reaction pathways of this system follows.

Solvent-Assisted Dissociative Pathway. As with NiH_2ODEN , evidence for a ligand-independent pathway arose from the difficulty in obtaining a simple expression for the ligand dependence of the rate in the high pH region. There is no evidence of buffer dependence in this system, and so a solvent-dissociation pathway was proposed for NiH_2ODPN as well. The value of the constant was determined by the method described in earlier sections. For NiH_2ODPN reactions, the value of k_{H_2O} is 0.0010 s^{-1} .

This is somewhat smaller than the value found for NiH_2ODEN ($k_{\text{H}_2\text{O}} = 0.0014 \text{ s}^{-1}$), although the two values are nearer to each other than to any of the values quoted in Table 1. The complexes contain several common structural features not found in the other complexes discussed, including two terminal amine groups and the location of both peptide oxygen in the backbone of the complex. An examination of the relative stabilities of the two complexes, as evidenced by their spectral properties, indicates that this is not the explanation for the relative magnitudes of the $k_{\text{H}_2\text{O}}$ values. From Table 13, there is a difference of $5.9 \text{ kcal mol}^{-1}$ in the spectral transitions, leading to nearly 12 kcal mol^{-1} greater stability for the NiH_2ODEN complex. From this, one would expect a much smaller $k_{\text{H}_2\text{O}}$ value for NiH_2ODEN relative to NiH_2ODPN .

Use of molecular models allows comparison of the structures of the complexes. The three five-membered chelate rings in NiH_2ODEN lead to a nearly planar arrangement of the carbon rings and an essentially unstrained complex. The two six-membered side-rings in NiH_2ODPN cause a substantial amount of strain. The carbon chains in the side-rings are distorted well out of the plane defined by the metal and its four coordinated nitrogens. This strain could well lead to a lengthening of the M-N(amine) bonds relative to the M-N(peptide) bonds. Such a decrease in bond strength would explain the decreased stability of the complex. A distortion of N-M-N bond angles could also result from the crowding of the side-chains,

leading to a reduced angle in the second chelate (backbone) ring, and larger angles in the first and third rings.

Solvent displacement of the peptide nitrogen is the first step in the solvent-assisted dissociation process. In NiH_2ODEN , the displacement of the peptide nitrogen will lead to dissociation of the ligand without much delay, as this displacement increases the strain on adjacent metal-nitrogen bonds. In NiH_2ODPN , the same step actually decreases the already present strain on the complex, easing some of the angle strain and probably allowing a shortening of one M-N(amine) bond. Subsequent dissociation of the ligand is not favored as strongly as in the case of NiH_2ODEN , and as a result, the overall process occurs at a slightly slower rate.

Ligand-Dependent Pathways

Reaction with Trien: Figure 15 shows that within the pH range of 8.0-9.8, the rate of reaction decreases with decreasing pH. This is consistent with the direct nucleophilic replacement usually seen with trien, as discussed earlier. As in the reaction of NiH_2ODEN with trien, a simple first-order dependence on trien concentration was not found in this system. Inverse plots (with the $k_{\text{H}_2\text{O}}$ term removed before inversion) were linear, indicating that an equilibrium activation step, followed by reaction with trien, could be proposed for this system as well. The activation step is again postulated to involve dissociation of a terminal amine. The rate constant for ring-opening for 1,3-propylenediamine ($8.8 \times 10^{-3} \text{ s}^{-1}$)⁵⁰ is much smaller than the value of k_1 (4.0 s^{-1}) obtained for

the reaction of NiH_2ODPN with trien. However, this value is recorded for ring-opening of an isolated 1,3-propylenediamine molecule coordinated to Ni(II) . It is reasonable to assume that the strain experienced by the terminal amine groups in NiH_2ODPN as members of an extended chelate ring system constrained by square-planar configuration could be much greater. This would lead to a larger dissociative rate. Also, the tabulated value was measured at 0.3°C . A rough temperature correction to 25°C brings the value to within an order of magnitude of the NiH_2ODPN value.

The value of k_1 for the reaction of NiH_2ODPN with trien is nearly a factor of six larger than the analogous value for the NiH_2ODEN system. The increased strain in the six-membered rings in NiH_2ODPN and the possible lengthening, and corresponding weakening, of the bond between nickel and the terminal amine groups probably account for the greater ease in dissociation observed in this system.

Following the dissociation step, trien enters and coordinates via weak axial interaction followed by strong equatorial coordination in the site left vacant by the dissociation, or by direct equatorial coordination. Following this in-plane coordination by trien, the balance of the substitution proceeds rapidly.

As with the NiH_2ODEN -ligand reactions, the ligand-dependent constants are reported as ratios of k_T to k_{-1} , etc. The doubly-protonated form of trien, $\text{H}_2\text{trien}^{2+}$, does not make a significant contribution to the rate with NiH_2ODPN . Thus, only the ratio of

k_{HT} to k_T is available for comparison. The value of this ratio is 0.54, larger than the corresponding ratio for NiH_2ODEN (0.25) and approaching the value obtained for NiH_2DGEN (0.63).

Above $pH = 9.80$, the rate of reaction drops sharply instead of continuing to increase and finally leveling off, as would be expected if the complex were reacting with trien alone. Spectral studies show a decrease in absorbance at $\lambda = 293 \text{ nm}$, the UV absorption maximum for NiH_2ODPN , in this pH range. This is indicative of a decrease in the concentration of the square-planar reactive species. Similar rate behavior has been observed by Storvick and Pagenkopf in their study of the trien reaction with malonamide- N,N' bis-(2-aminoethyl)nickel(II).⁵² They suggest the equilibrium formation of a non-reactive species which contains hydroxide axially coordinated to the nickel center. The equilibrium constant formed for this process in the NiH_2MBAE system ($1.4 \times 10^3 \text{ M}^{-1}$) agrees remarkably well with the value for the constant obtained for NiH_2ODPN ($1.3 \times 10^3 \text{ M}^{-1}$). Accordingly, formation of an analogous species is proposed to account for the rate inhibition observed at high pH in the reaction of NiH_2ODPN with trien.

Reaction with EDTA: Figure 19 shows a very slow increase in rate with decreasing pH in the region above $pH = 8.0$. The proton-assisted nucleophilic replacement mechanism suggested by Pearson and Pagenkopf⁴² and described in the discussion of the $NiH_2ODEN + EDTA$ reaction is again proposed for the reaction of NiH_2ODPN with EDTA. As was found for the other ligand reactions of these two complexes,

plots of the quantity $(1/k_{\text{obs}} - k_{\text{H}_2\text{O}})$ versus $1/[\text{ligand}]_{\text{T}}$ were linear. An activation step followed by interaction with the ligand is again postulated as a reasonable reaction sequence. Also, k_1 values for the reactions of NiH_2ODPN with trien and EDTA were found to differ by a factor of nearly 50. It is suggested that the k_1 value of 0.083 s^{-1} for the EDTA reaction again represents a two-step dissociation process, in which the second ring opening is much slower than the first. The structure of the backbone in both NiH_2ODEN and NiH_2ODPN is the same; this could account for the smaller difference between k_1 values for the EDTA reactions of the two complexes as compared with analogous values for the trien reactions.

The coordination of EDTA to the nickel center following the initial dissociation steps is expected to proceed via the same sequence as that proposed for the NiH_2ODEN reaction. Axial coordination by carboxylate is followed by equatorial coordination of an amine nitrogen. Intramolecular proton-transfer from EDTA to the coordinated peptide nitrogen occurs after the carboxylate coordination step.

Ligand-dependent constants are again reported as ratios of k_Y to k_{-1} , etc. As with the NiH_2ODEN system, the fully deprotonated form of EDTA makes no significant contribution to the rate of reaction. The ratio of $k_{\text{H}_2\text{Y}}$ to k_{HY} is 100, compared with a value of 35 for the NiH_2ODEN system. It is proposed that the decreased stability of the NiH_2ODPN complex makes it more susceptible to

protonation at the peptide nitrogen, and thus more reactive with the more protonated form of EDTA.

Inhibition by hydroxide is also found in the high pH region of this system. Although the decrease in rate is not apparent in Figure 19, inclusion of the K_{OH} term improves the agreement between predicted and observed values (see Table 12). Formation of a non-reactive species containing axially coordinated hydroxide is proposed for this system as well.

Proton-Limited Pathway. Comparison of Figures 8, 12, 15, and 19 show the same rate behavior occurring in all four systems below pH = 6.50. Plots of k_{obs} versus $[H^+]$ for reactions of NiH_2ODPN (Figures 14 and 18) resemble analogous plots for NiH_2ODEN (Figures 7 and 11), although the curvature in the low $[H^+]$ region is much less pronounced. A protonation equilibrium is again proposed to account for this slight deviation from linearity. The linear portion of the plot again indicates a reaction pathway to products that is first-order in hydrogen ion, while the small non-zero intercept of this linear portion suggests a pathway independent of hydrogen ion concentration.

A general acid mechanism is ruled out in this system, due to the absence of buffer dependence in the rate. The value of the equilibrium constant, " K_H ", originally determined for this system ($2.0 \times 10^7 \text{ M}^{-1}$) is again much larger than values for outside protonation constants obtained for metal peptide complexes (Table 1). Protonation of the terminal amine following the activation step

rather than outside protonation involving a peptide oxygen is proposed as the step described as the protonation equilibrium. The protonation constant for 1,3-propylenediamine^{49a} is $3.31 \times 10^{10} \text{ M}^{-1}$, again much higher than the value obtained for NiH_2ODPN . However, a combination of dissociation and protonation equilibria could easily be in the range of 10^7 .

The value for K_1K_H for the NiH_2ODPN system is slightly more than a factor of three greater than the analogous value obtained for the NiH_2ODEN system. As the protonation constant for 1,3-propylenediamine is slightly more than four times greater than the constant for ethylenediamine, this is perhaps not too surprising.

The hydrogen ion-dependent pathway is again proposed to involve dissociation of the protonated intermediate, and the constant k_2 is assigned to this pathway. The value of k_2 for the NiH_2ODPN system is 0.20 s^{-1} , nearly an order of magnitude greater than the NiH_2ODEN value of 0.035 s^{-1} . This is ascribed once again to the decreased stability of the NiH_2ODPN complex as compared with NiH_2ODEN . Dissociation of a terminal amine does not ease a great deal of the strain which gives rise to the decreased stability of the complex; and with only three M-N bonds, the ligand field stabilization is substantially reduced.

The constant k_3 , associated with the reaction of the protonated intermediate via further protonation, is again postulated to involve an outside protonation, although its value, at $7.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, is larger than the protonation constants shown in Table 1. Once again,

this may be due to the strain in the complex. After the protonation has taken place, and the proton transfer from peptide-oxygen to peptide-nitrogen has begun, the M-N bond may be more susceptible to an increased rate of bond breakage and subsequent dissociation of the complex.

In the context of the general mechanism for proton reactions of metal peptide complexes, the NiH_2ODPN system is thought to resemble Case 3, where specific hydrogen ion catalysis is observed and k_3 is a combination of K_H and k_2 terms from the mechanism. The possibility of an increase in the rate of bond breakage subsequent to the "outside" protonation, relative to the NiH_2ODEN system, is consistent with this mechanism.

CONCLUSION

The kinetics and mechanism of the reactions of NiH_2ODEN and NiH_2ODPN with two polyamide ligands, trien and EDTA, have been studied over a wide pH range in order to increase the understanding of the substitution behavior of nickel complexes containing peptide linkages and a variety of other structural elements.

In many respects, the reactivity patterns of the two complexes are similar. In both systems, there is evidence of a solvent-assisted dissociative pathway. The value of $k_{\text{H}_2\text{O}}$, the rate constant for this process, is similar in magnitude for the two complexes. This process is much slower than that observed for NiH_2GGG^- , due to the comparatively rapid dissociation of the terminally coordinated carboxylate group in NiH_2GGG^- contrasted with the terminal amine groups found in the complexes under study. The cyanide group in $\text{NiH}_2\text{GGaCN}^-$ and imidazole nitrogen in $\text{NiH}_2\text{GGhis}^-$ are more tightly bound still, and solvent-assisted dissociation proceeds more slowly for these complexes than for NiH_2ODEN and NiH_2ODPN .

The reactions of the complexes with polyamine ligands proceed via the same series of steps in all cases studied. The rate-determining reaction with the incoming ligand is preceded by an activation equilibrium step, which involves the dissociation of a terminal amine group, or of the amine group and the adjacent peptide nitrogen, depending on the steric requirements of the incoming

ligand. Reactions of both complexes with trien require dissociation of the terminal amine only, and proceed via direct nucleophilic attack. Reactions with EDTA require two dissociative steps prior to initial attack, and are characterized by proton-assisted nucleophilic replacement. Reaction with EDTA is much slower than reaction with trien for these complexes.

Reaction with acids follows the same general mechanism for both complexes as well. Reaction in the low pH range is specific hydrogen ion catalyzed, as no acceleration of reaction rate is observed in the presence of general acids. A protonation equilibrium precedes two parallel routes to products.

As the pH decreases, reaction via the protonation equilibrium is extremely favorable compared with direct ligand substitution. As a result, reaction via the ligand pathway is no longer competitive below a certain pH, and the reaction proceeds solely via the proton-limited pathways for all practical purposes. The magnitude of the rate constant reported for the combination of activation and protonation equilibrium steps is consistent with dissociation and protonation of a terminal amine group. The value is several orders of magnitude too large to be considered as an outside protonation of the original square-planar complex.

The protonated complex proceeds to products via one of two available pathways: a reaction sequence which is independent of hydrogen ion concentration, and one which exhibits first-order dependence on hydrogen ion concentration. It is proposed that the

hydrogen ion-independent pathway involves solvent-assisted dissociation of the protonated complex. This process is more than an order of magnitude faster than the dissociation of the original complex, due to the decreased ligand field stabilization of the protonated complex, which has only three M-N bonds compared with four such bonds in the original complex. The rate of dissociation for NiH_2GGa , which also has three M-N bonds, is two orders of magnitude faster than observed in this study. The peptide oxygens are both located in the backbone of the NiH_2ODEN and NiH_2ODPN complexes, and this gives the second chelate ring much greater rigidity than the peptide and peptide-amide complexes used for comparison. This increased rigidity is postulated to slow the opening of the second chelate ring considerably, accounting for the relatively slower rate of dissociation.

The magnitude of the rate constant associated with the pathway involving reaction via further protonation is comparable to the outside protonation constants of similar peptide and peptide-amide complexes. As a result, it is postulated that this step involves protonation of a peptide oxygen, followed by proton-transfer to the peptide nitrogen and breakage of the M-N bond.

The overall rate of reaction for NiH_2ODPN with ligands and acids is generally one to two orders of magnitude greater than the corresponding rate for reactions of NiH_2ODEN . Spectral characteristics show an $11.8 \text{ kcal mol}^{-1}$ decrease in stability for the NiH_2ODPN complex compared with NiH_2ODEN . This decrease in

stability is thought to arise from steric crowding in the six-membered side-rings of NiH_2ODPN , which could cause stretching of the M-N bonds in an attempt to relieve the strain. This strain, along with the lowered stability of the complex, would render NiH_2ODPN more reactive in relation to NiH_2ODEN .

The investigation of the reactivity patterns of these two complexes has added to the body of knowledge being collected regarding the effects of small structural changes within the coordinated ligand, such as position of peptide oxygens and chelate ring size, on the kinetics and mechanism of reaction. Understanding the relation between structure and reactivity leads to a better appreciation of the inner workings of metal transport in biological organisms.

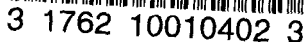
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