METAL COMPLEXES RELATED TO VITAMIN B_6 CATALYSIS AND TETRAAZA-[14], [15], AND [16]- MACROCYCLES —— POTENTIAL MODELS FOR PORPHYRINS AND CORRINS

by

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METAL COMPLEXES RELATED TO VITAMIN B_6 CATALYSIS AND SYNTHESIS OF TETRAAZA-[14], [15], and [16]- MACROCYCLES —— POTENTIAL MODELS FOR PORPHYRINS AND CORRINS

by

Georgia Nan Weinstein

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ABSTRACT

PART 1

Metal Complexes Related to Vitamin B_6 Catalysis

Chapter 1.. Historical introduction to Vitamin B_6 Complexes.

Chapter 2. The aldimine complexes N-(Salicylidene)glycinato and valinatozinc(II), N-(pyridoxylidene)valinatocopper(II) monohydrate and N-(3-Hydroxopyridyl-2-methylene)valinatocopper(II) hemihydrate have been prepared from L-valine. Synthetic methods and characterization data are given. Also prepared were the bis-chelate amino acid ester complexes, Bis[N-(2-ethyoxycarbonyl-1-propyl)salicylaldiminato]copper(II) and Bis[N-(3-ethyoxycarbonyl-2-propyl)salicylaldiminato]copper(II). The inertness of these two complexes to H-D exchange contrasts with the ready exchange in the absence of base of the complexes derived from α-amino acids. This result shows that facile exchange and racemization properties of Bis[N-(alkoxycarbonylalkyl)-salicylaldimino]metal(II) complexes derivedprincipally from the direct attachment of the electron-withdrawing HC=NM and $COOC_2H_5$ groups to the asymmetric center. The base-catalyzed racemization rates of four copper(II)-aldimine complexes in 95% ethanol at 50° were found to increase in the order N-Salicylidene-L-valinatocopper(II), Cu(sal-L-val)<<N-Pyridoxylidene-L-valinatocopper(II)≤ N-3-Hydroxopyridyl-2-methylene-L-valinatocopper(II)<N-4-NO_2-Salicylidene-L-valinatocopper(II). This order is essentially the

same as that of qualitative catalytic effectiveness of the constituent o-hydroxyarylcarbonyl compounds in nonenzymatic transamination and reinforces in semiquantitative fashion the prevailing model of ligand electronic features requisite to catalytic activity of these compounds.

Chapter 3. The ketimine complexes 2-o-Hydroxybenzyliminopropionatocopper(II) and zinc(II), M(hba-prop), 2-o-Hydroxybenzyliminoisovaleratocopper(II), Cu(hba-ival), and 2(α-Methyl-o-hydroxybenzyliminopropionato- and isovaleratocopper(II) have been prepared. Synthetic methods and characterization data are given. The base-catalyzed tautomerization (transamination) rates of Cu(hba-prop) and Cu(hba-ival) in 95% ethanol at 50° were found to be ~150 times faster than the racemization rate for the aldimine complex Cu(sal-L-val).

PART II

Synthesis of Tetraaza-[14], [15], and [16]- Macrocycles ——

Potential Models for Porphyrins and Corrins

Symmetrical tetraaza macrocycles with 14-, 15-, and 16-membered chelate rings have been synthesized by a simple two step, non-template procedure in which a 1,2-dithiolium salt is reacted with ethylene- or trimethylenediamine. The nickel complexes 6,13-Diphenyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,-13-tetraenenickel(II), 6,14-Diphenyl-1,4,8,12-tetraazacyclopentadeca-4,6,12,14-tetraenenickel(II), and 7,15-Diphenyl-1,5,-9,13-tetraazahexadeca-5,7,13,15-tetraenenickel(II) have been prepared from the corresponding ligands. Synthetic methods and characterization data are given.

Thesis Supervisor: Dr. Richard H. Holm

Title: Professor of Chemistry

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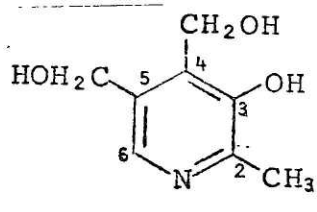
PART I

CHAPTER I

Introduction to Vitamin B_6 Metal Complexes

Vitamin B_6-containing enzymes catalyze a large number of transformations of α-amino and α-keto acids including transamination, racemization, decarboxylation and β-elimination. Many of these reactions are also catalyzed by metal ions in nonenzymatic systems.[1] The first part of this thesis is concerned with the nonenzymatic catalysis of racemization and transamination. Of particular interest are the structural features of vitamin B_6 essential to catalysis; these are explored through quantitative racemization studies. The role of the metal ion in nonenzymatic catalysis is considered, and the relative rates of racemization and tautomerization of aldimine and ketimine complexes, respectively, are compared for related systems. An historical introduction is presented to acquaint the reader with concepts fundamental to understanding the research presented.

Vitamin B_6 is not the name for one specific molecule, but refers to a group of related compounds.



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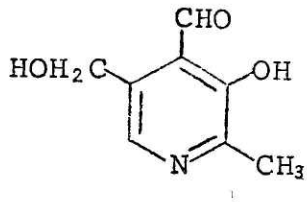

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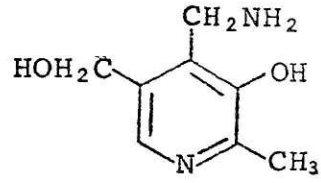

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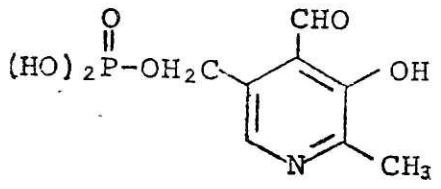

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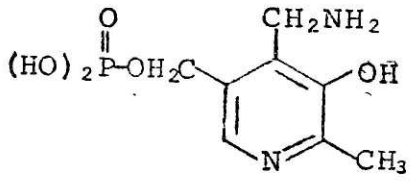

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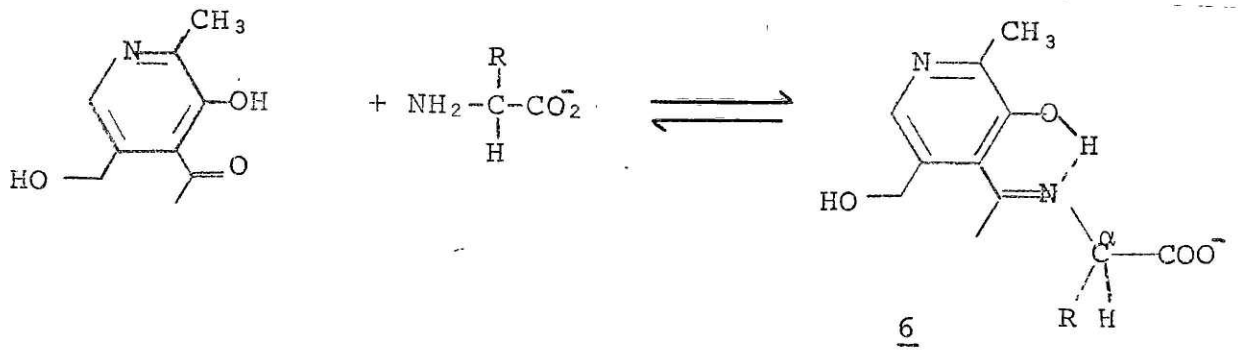
Pyridoxine (1) was the first to be isolated in 1938; it was fully characterized through structural determination and *in vitro* preparation by the end of 1939. However Snell found in 1942 that there were other natural materials which also cured dermatitis in rats and promoted faster growth than pyridoxine in lactic acid bacteria. Through *in vitro* synthesis these were found to be pyridoxal (2) and pyridoxamine (3). The phosphate groups of 4 and 5 are essential for the coenzymatic activity of vitamin B_6; it is postulated that the phosphate group is necessary for attachment to the enzyme.[2-5] The most important function of vitamin B_6-dependent enzymes is to catalyze transformations of α-amino acids. Both pyridoxal and pyridoxamine react to form Schiff base compounds:



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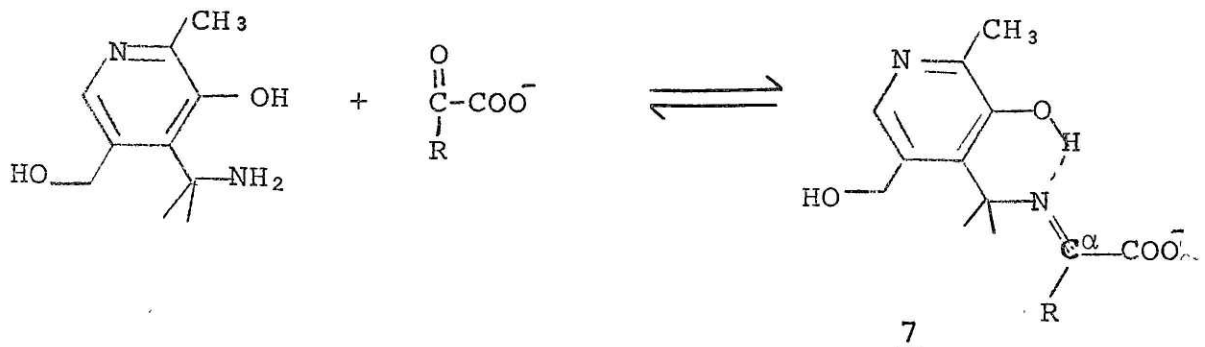

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Aldimine type compounds (6) are formed from pyridoxal and an amino acid and ketimine type compounds (7) are formed from pyridoxamine and a keto acid. The Schiff bases 6 and 7 are tautomers differing only in the position of a double bond and a hydrogen atom.

The first observation that reactions catalyzed by vitamin B_6 enzymes could be reproduced nonenzymatically came in 1945 when Snell autoclaved pyridoxal with amino acids and noted the formation of pyridoxamine and a keto acid.[6] The coupling of the forward and reverse reactions (1) and (2) results in the overall transamination reactions:

(1) amino acid$_1$ + pyridoxal $\rightleftarrows$ keto acid$_1$ + pyridoxamine

(2) keto acid$_2$ + pyridoxamine $\rightleftarrows$ amino acid$_2$ + pyridoxal

(3) amino acid$_1$ + keto acid$_2$ $\rightleftarrows$ amino acid$_2$ + keto acid$_1$

In 1952 Snell found that the transamination reaction was catalyzed by metal ions.[7] This finding prompted great interest in the reactions of metal ions with pyridoxal and amino acids, especially since it was thought at the time that a metal ion might be present at the active site of vitamin B_6 enzymes. There has been, however, no proof that metals are present at the active site of these enzymes, and in one enzyme, glutamic-aspartic transaminase, direct assay has shown that there is less than 0.4 mole of metal ion per mole of active site.[8] The reactions of Schiff base metal complexes, however, continue to be of interest as inorganic reactions of great diversity. Also, the metal ion may simulate some of the features of enzymatic active sites by promoting Schiff base formation and by increasing the lability

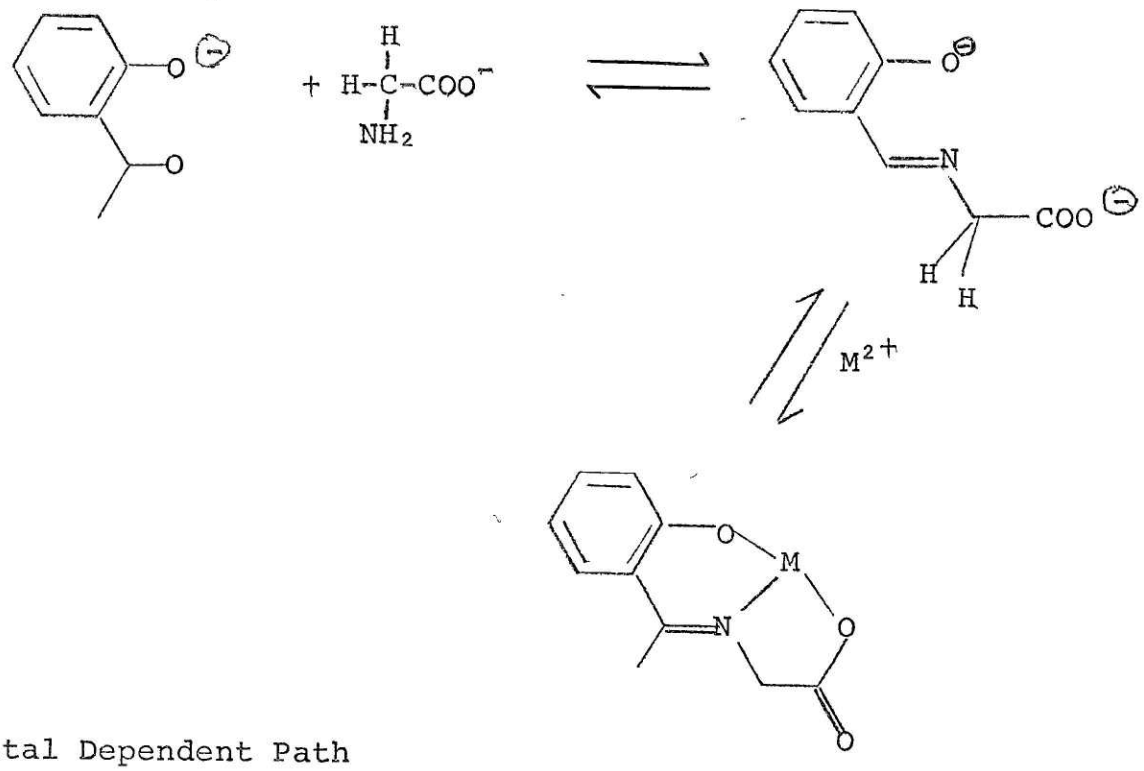
of bonds formed by the α-carbon in metal complexes of compounds of type 6.

The question of whether the metal ion actually catalyzes the formation of the Schiff base, or simply acts in effect as a stabilizing trap for the intermediate carbinolamine and final product, but does not kinetically catalyze the reaction, has been studied most thoroughly for the system M(sal-gly).*[9,10] Salicylaldehyde has the same functional groups for metal complexation as pyridoxal, o-OH and CHO, but has a simpler electronic spectrum and undergoes fewer side reactions because it lacks the ring constituents of pyridoxal. Using pH-stat and spectrophotometric techniques in aqueous solution at pH 5-9, Leussing et al.[9,10] have shown that the effect of metal complexation on Schiff base formation depends on the metal ion present. For some metals (Cu^{+2}, Ni^{+2}, Co^{+2}) there is a metal-independent path only, while for others there is both a metal-independent and a metal-dependent path (Mg^{+2}, Mn^{+2}, Zn^{+2}, Cd^{+2}, Pb^{+2}). The two pathways are illustrated in Scheme 1. Those metals effective in catalyzing the metal-dependent pathway share the common feature of having no partially filled d-orbitals. Complexes of these metal ions are therefore likely to be labile in solution and to impose few geometrical constraints on the ligands. The salicylaldehyde and glycine can thus be bound to the metal in the proper spatial relationship for carbinolamine formation and subsequent rapid dehydration to occur. Although the reaction scheme described

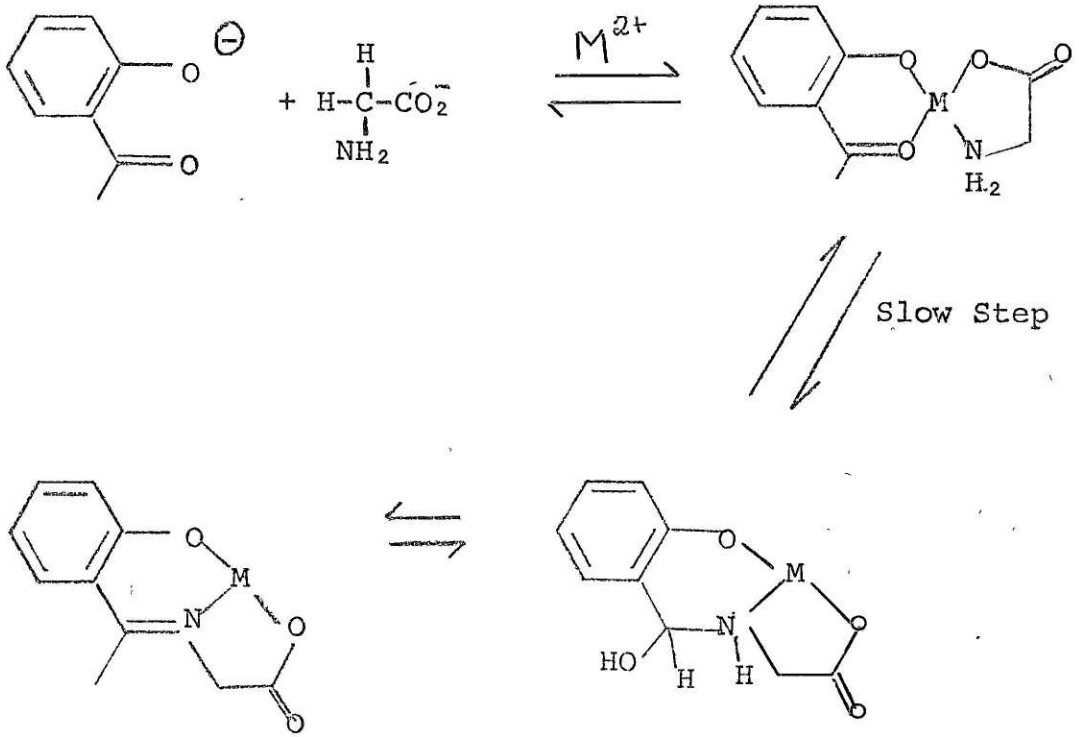
*Abbreviations are listed at the end of Part I

SCHEME 1.

Metal Independent Path

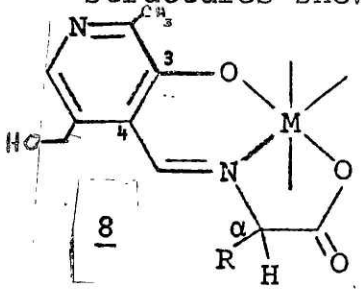


Metal Dependent Path



above may not be general for all o-hydroxyarylcarbonyl and amino acid reactants, the system PLP:glu:Cu^{2+} shows only metal-independent Schiff base formation at pH 4.[11]

Metal complexes of the tridentate Schiff base ligand can have a 2:1 or a 1:1 ligand:metal ratio. This work is primarily concerned with the 1:1 complexes. Relevant examples are the complexes formed from pyridoxal, 3-hydroxy-2-pyridinealdehyde, and salicylaldehyde and amino acids, which have the general structures shown below:



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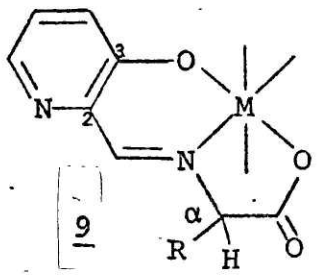

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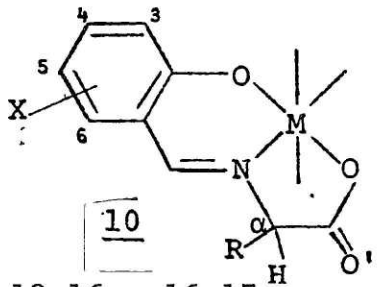

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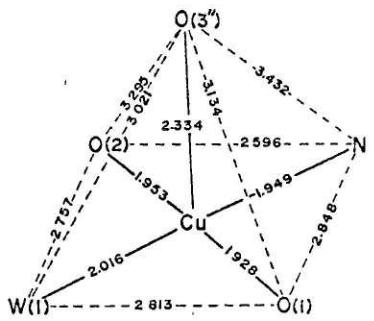
A number of aldimine complexes of types 8,[12-16] 9,[16,17] and 10[16,18-22] and some with the pyridine ring protonated[15-17] have been isolated with metal ions such as Mn(II), Cu(II), and Zn(II). The crystal structures of [Cu(sal-gly)(H_2O)]·0.5 H_2O,[23] 11, Cu(pyr-DL-val),[24] 12, and Cu(Ppyr-DL-Phala)(H_2O)],[25] 13, have been determined. In each case there is square pyramidal coordination around the metal with the Schiff base occupying three of the coordination positions in the basal plane. In 11 the fourth



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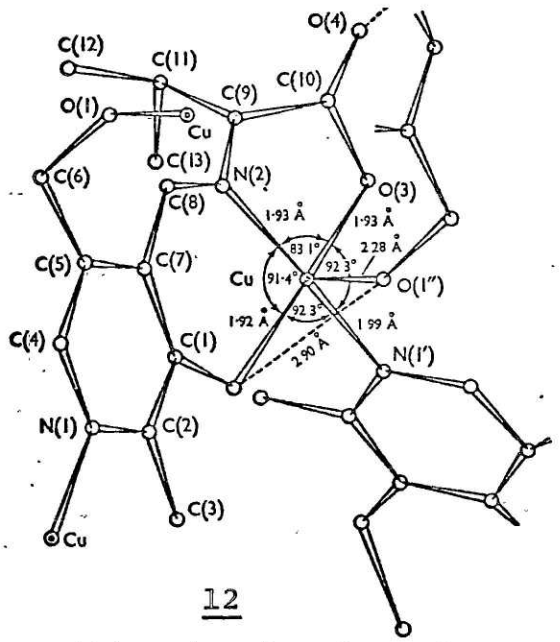

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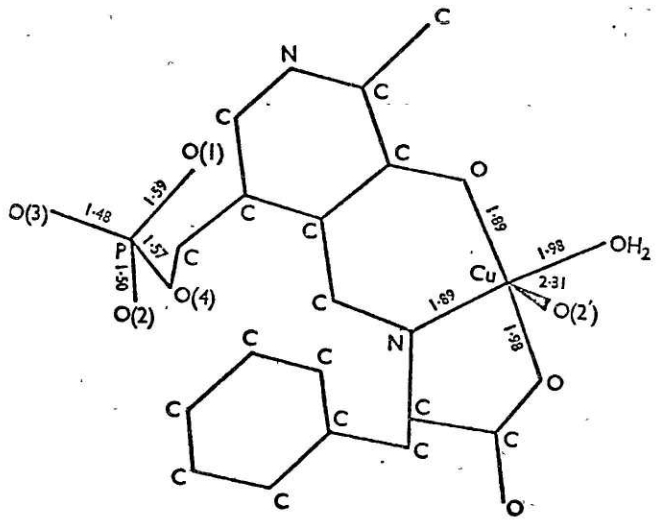

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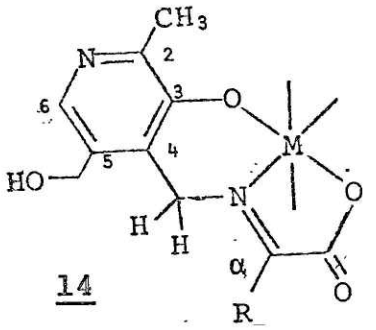
position in the plane is occupied by a water molecule and the apical oxygen is the free carbonyl oxygen from another molecule. The fourth basal position in the pyridoxylidine complexes is occupied by a pyridine nitrogen, or a water molecule, and the apical position by a hydroxymethyl, 12, or a phosphate 13, oxygen molecule. Only a few attempts to isolate ketimine type complexes 14 and 15 have been reported[20,26] and no structural



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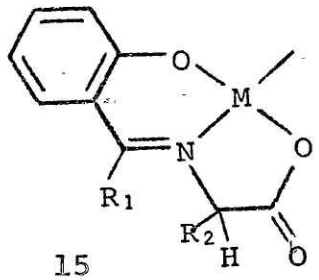

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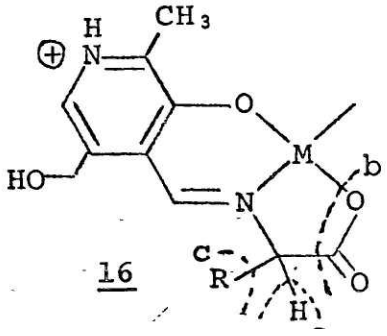
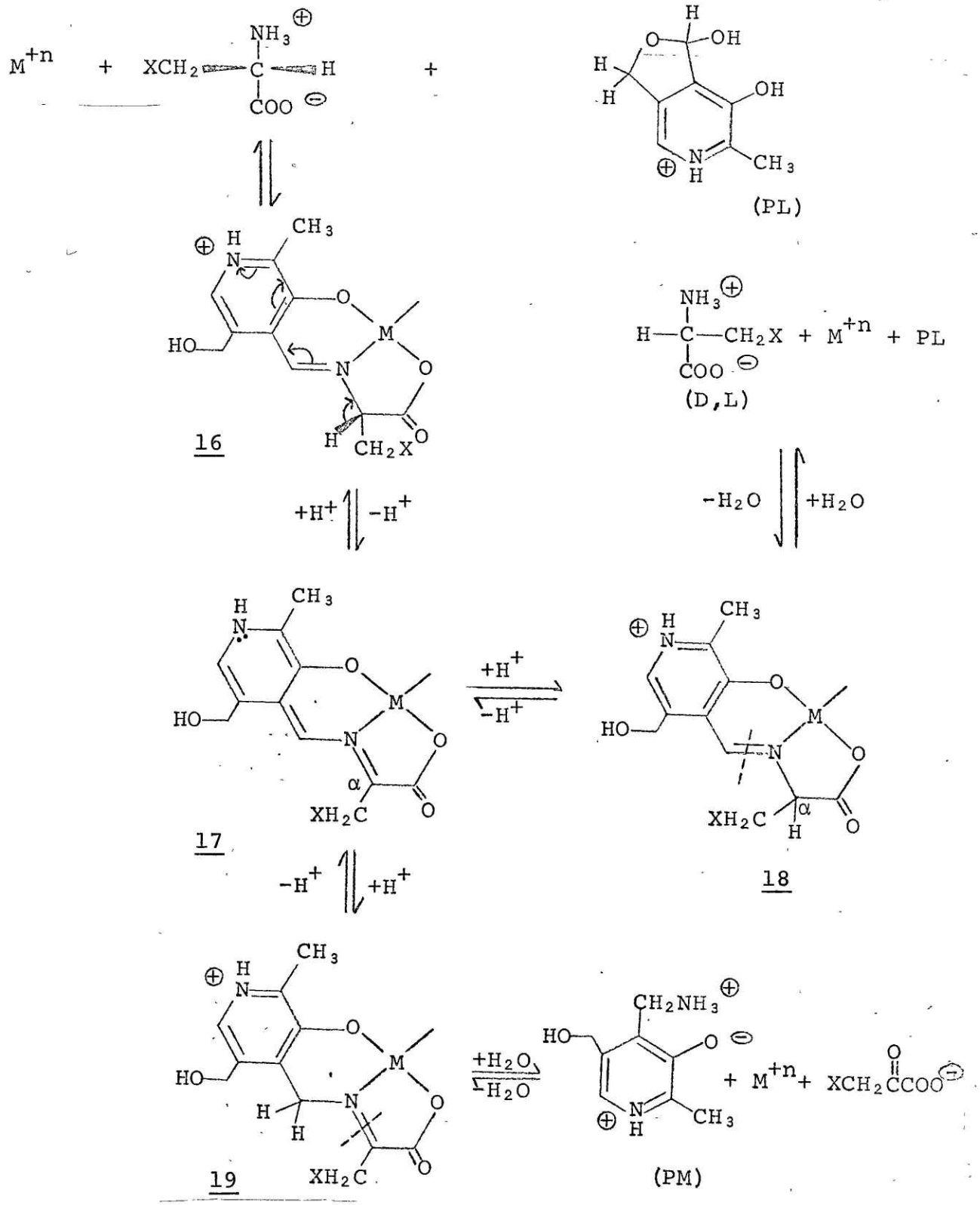
determinations have been done. It is assumed throughout that the structure is probably similar to that of the aldimine with the Schiff base acting as a planar tridentate ligand.

The reactions of the amino acids in complexes of type 8 and 16

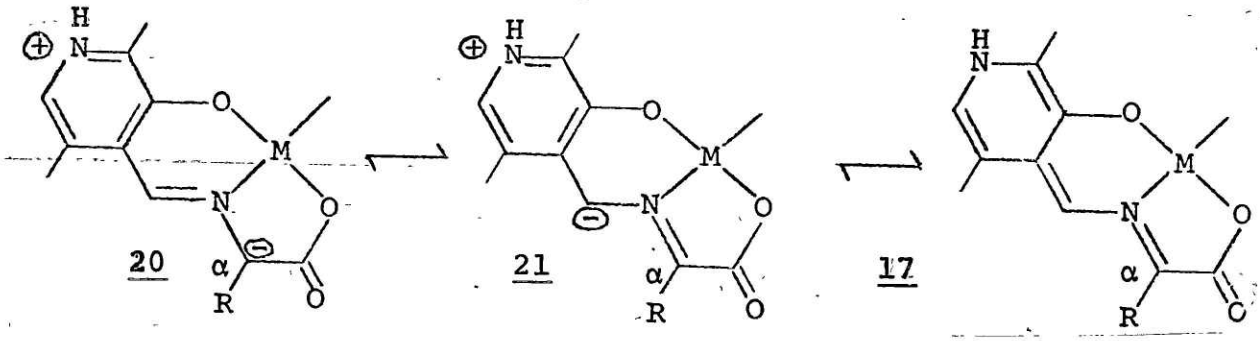


16

have been grouped by Snell[4] according to the bond broken during the initiation of the reaction. A partial listing of the reactions of α-amino acids catalyzed by pyridoxal and metal ions in model systems is given in Table I, which is taken from reference 1. We will be concerned mainly with the transamination and racemization reactions. The mechanism of these reactions was first proposed independently by Braunstein and Sheymakin[4] and Metzler, Ikawa and Snell[27] in 1953-1954 on the basis of model studies with pyridoxal and other o-hydroxyarylcarbonyl compounds, and metal ions as catalysts. The mechanisms proposed in Scheme 2 on the next page involve the formation of a 1:1 or 2:1 aldimine complex followed by the breaking of bond "a" (loss of the α-H) of the condensed amino acid in 8 or 16. If the proton recombines at the α-C in 17, the racemized complex 18 will be produced, if it recombines at the azomethine carbon the ketimine 19 will be formed. Subsequent hydrolysis of the imine bond will give pyridoxal plus racemized amino acid in the former case and pyridoxamine plus keto acid in the latter. The metal is postulated to increase the rate of the reaction in three ways:[1,4] (1) it promotes Schiff base formation in aqueous solution, (2) it increases the lability of the α-C-H bond through the inductive electron-withdrawing effect of the H-C=N-M grouping, (3) it serves to hold the ligand in a planar configuration. The importance of feature (3) is seen after the loss of the α-H when the carbanion formed can be stabilized by resonance 20 ⇌ 21 ↩ 17, in which the

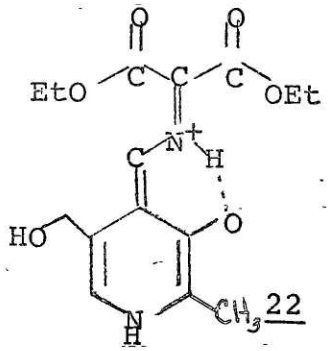


Scheme 2. Mechanisms for Pyridoxal-Catalyzed Transamination and Racemization of L-Amino Acids.



conjugated system extends from the pyridinium nitrogen to the α-C. The electrophilic group on the ring ortho or para to the azomethine function is essential for this resonance stabilization. Thus, while 3-hydroxypyridine-2-and -4-aldehyde catalyze the transamination reaction from glutamate to α-ketoglutarate,[4] salicylaldehyde, which has the ortho hydroxyl and formyl groups essential for metal complexation but does not possess an electron-withdrawing group on the ring, is not catalytically active.[4]

Later studies (vide infra) have lent support to this basic view of the mechanism including the role of the metal, and it has remained remarkably unchanged since its proposal. Recently, this view has been challenged by E. H. Abbott,[28] who claims to have isolated the 1,4-dihydropyridine from pyridoxal and diethylaminomalonate, 22, which is equivalent to resonance form 17. He suggests that the N-H proton can labilize the α-CH and hold the ligand



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planar by hydrogen bonding and that the only important role of the metal is to mask the negative charge on the phenolic oxygen.

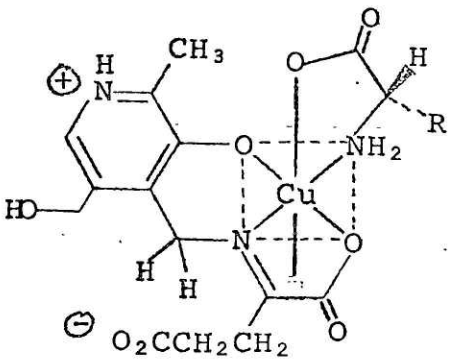
His conclusions have yet to be confirmed by independent studies.

Racemization and transamination of species generated in solution have been studied both qualitatively and quantitatively by spectrophotometric and nuclear magnetic resonance techniques. Nonenzymatic racemization was first observed for L-alanine, L-phenylalanine, and L-valine in systems containing pyridoxal; the rate was increased by the addition of Al(III), Fe(III), or Cu(II).[29] For the system PL:L-ala:Cu(II) or Al(III), racemization is favored over transamination above pH ~9. The pyridine nitrogen is unprotonated at this pH. Racemization at low pH values where transamination is favored probably occurs via formation of 19 and the reverse reaction to 18, followed by hydrolysis, whereas at pH >9 it is not necessary to postulate the formation of the ketimine 19 as an intermediate step. Racemization at high pH (pD ~10) has also been observed by pmr for $Al(pyr\text{-}L\text{-}ala)_2^-$ in D_2O. As racemization occurs and the α-H is replaced by deuterium the alanine methyl doublet becomes a singlet.[30] Racemization rate studies at pH 10 in water have shown that the rate is dependent on the particular metal ion present and on the substituents on the benzene ring in pyridoxal analogues.[31] The fastest rates were observed for Cu^{2+} and for salicylaldehyde with an electron withdrawing group in the 4-position. Substitution with an electron-releasing group produced rates slower than that of salicylaldehyde itself.[31]

The transamination reaction has been studied much more extensively than the racemization reaction. The transamination reaction for α-amino acids, outlined in equations (1)-(3), starts

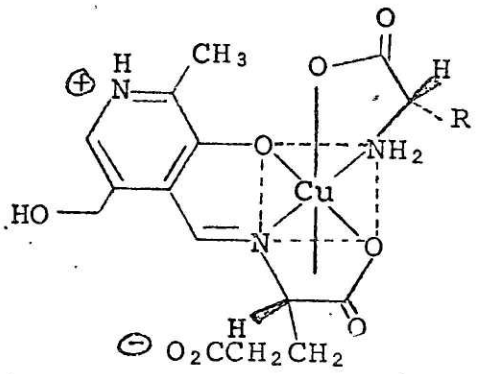
with the formation of an aldimine Schiff base complex 16, breaking of bond "a" to form a resonance stabilized species such as 17, and reprotonation at the azomethine carbon to form a ketimine Schiff base complex, 19, followed by hydrolysis of the imine bond. Upon completion of the reverse reaction of pyridoxamine with a different keto acid to form 19 and a retracing of the steps above, reaction (3) has been completed. Usually the transamination reaction is only studied in one direction, viz , either (1) or (2) is followed since each of these is a transamination reaction in itself.

The metal ion not only increases the rate of transamination,[7] but in one report was found to produce optical selectivity in the transamination between D- or L-alanine or phenylalanine and α-ketoglutarate catalyzed by pyridoxal and Cu(II).[32a] The optically active amino acid was present in excess, and glutamic acid was formed with a 2-3% optical enrichment with the L-form predominant if L-alanine was present. The formation of the optically enriched amino acid must arise from stereoselectivity in the ketimine 19 → aldimine 17 conversion. Such stereoselectivity requires a dissymmetric intermediate which can be formulated as containing the optically active amino acid. This intermediate must be stable for longer than the time required for the tautomerization. The species 23 and 24 are possible structures for the dissymmetric intermediates; hydrolysis of 24 yields L-glutamic acid. Although the optical selectivity is small, it is difficult to imagine there being any selectivity at all without formation of a metal complex.



[Cu(Hpym-glt)(L-aa)]$^-$

23



[Cu(Hpyr-L-glu)(L-aa)]$^-$

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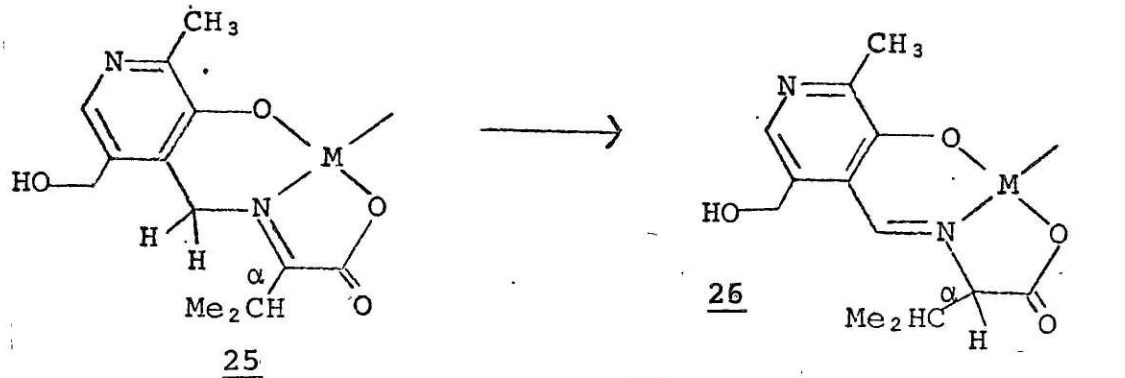
The reaction of metal ions with pyridoxamine and α-ketoglutarate at 100° showed a rate enhancement of 7-35 over the metal-free system.[32b] The efficiency of metal ions as catalysts was found to occur in the following order: Ga(III)>Cu(II)>Al(III)> Fe(II)>Fe(III)≳Zn(II)>In(III)≳Ni(II)>Co(II)>Sc(III). Only slight catalytic activity was observed for the series Cd(II)>Cr(II)>Mn(II)> Mg(II). The order of catalytic activities for the divalent metal ions parallels the order of stability constants for the chelates formed by the reaction $M^{+2}+PL^{-}+val^{-} = M(pyr\text{-}val)$,[15] except for the inversion of Zn(II) and Ni(II). This finding supports the proposed mechanism in which metal chelation with the reactants is the first step in catalysis.

The aldimine→ketimine conversion 16→ 19 was originally proposed on the basis of the formation of uncomplexed transamination products. The first direct evidence of this reaction came from spectral studies of the system PM:pyruvate:Ni(II),[33] and the separation of ketimine and aldimine complexes from the system PL:glycine:Al(III) by paper chromatography.[34] Recent pmr

work has clearly established the existence of both tautomers, and has been useful in measuring total ketimine and aldimine formation as a function of pH, establishing semi-quantitative pKa values for complexes, and providing structural information for those complexes for which ligand exchange is not fast on the pmr time scale.[30,35-40] The reaction ketimine → aldimine is usually followed due to the greater stability and more rapid rate of formation of the aldimine tautomers. The conversion of Al(III)-ketimine complexes[37] in the system PM:pyr:Al(III) to the corresponding aldimine is clearly shown in Fig. 1. The spectrum of the aldimine system PL:ala:Al(III) had been determined in a separate study. A recent spectrophotometric study has shown that in methanol unprotonated complexes from pyridoxamine and α-ketoisovalerate (25) convert to the aldimine 26 by a first order process.[41,42] The catalytic order of the metal ions when added to a preequilibrated mixture of PM and α-ketoisovalerate is Cu(II)>Zn(II)>Ni(II), which is the same as that found



for the PM-glutarate transamination[32b] and is 1000-fold faster than the metal-free rate.[41,42] The reaction rate is increased by the presence of base. An unprotonated form of 17 is suggested as the intermediate which is converted to the aldimine on reprotonation of the α-carbon.

No attempt has been made to be exhaustive in this introduction, as there are several recent reviews on the subject of vitamin B_6 metal complexes.[1,5,43] It should be noted that all previous racemization and transamination rate studies have been done on species generated in solution. In the kinetic studies reported in this thesis, however, preformed, characterized metal complexes which maintain their integrity in solution have been studied, greatly reducing uncertainty as to the identity of the species undergoing reaction. The findings presented herein support the general mechanism proposed for racemization and transamination, while emphasizing both the independence of racemization from transamination at high pH and the stability of the aldimine vs. the ketimine complex.

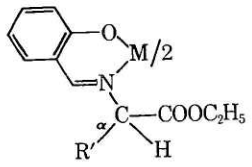
CHAPTER 2

Racemization of Schiff Base Complexes

Introduction

The relation of the structural and electronic properties of pyridoxal and other o-hydroxyarylcarbonyl compounds to their ability to catalyze the transamination[4] reaction in model systems has been discussed in Chapter 1. The minimal features of pyridoxal essential to the nonenzymatic catalysis of transamination are found in 3-hydroxypyridine-2- and -4-aldehydes. It is of interest to see if the same features are necessary for racemization.

The racemization reaction proceeds much faster for Schiff base complexes derived from amino acid esters (27) than for those



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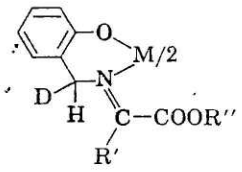
from amino acids (10, X=H).[22,44] In fact, the bis[N-alkoxycarbonylalkyl)salicylaldimino]metal(II) complexes have not been isolated with a high degree of optical activity. If the optically active amino acid ester is reacted with $M(sal)_2$ for as short a time as 30 seconds in ethanol (M=Cu) the metal complex isolated is optically inactive.[22] If the reaction is run in ethanol-1-d hydrogen-deuterium exchange is seen at the α-carbon only; exchange is about 65% complete at the end of the 30 second reaction time.[22] No deuterium substitution is seen at the azomethine carbon. In a related experiment in which the metal complex is made from

bis(2-deuterioformylphenolato)copper(II), $Cu(d\text{-}sal)_2$, there is no loss of deuterium from the azomethine position and no deuterium incorporation at the α-carbon. These findings suggest that the ketimine (28) is not an intermediate in the racemization



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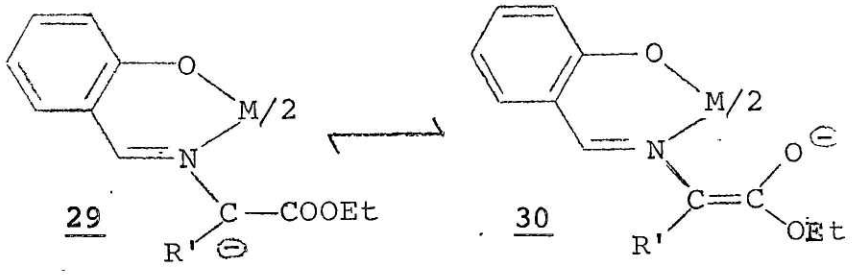
reaction since an equilibrium between 27 and 28 would have to result in the exchange of a deuterium label between the azomethine and α-carbon atoms. The reaction scheme suggested involves loss of a proton from the α-carbon by dissociation or base (B=acetate or ethanol) assistance to form a carbanion which could be stabilized by enolate resonance.[22]



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Experimental Section

Preparation of Complexes. The following groups of complexes were prepared by the indicated procedures. The degrees of hydration n indicated in the preparations were obtained from best fits of the analytical data; independent determinations by weight loss studies were not carried out. All quantities dependent upon formula weights were calculated using these n values. N-Salicylidene-L-valinatocopper(II) sesquihydrate and N-4-NO_2-Salicylidene-L-valinatocopper(II) monohydrate were prepared by Dr. M. J. O'Connor

and reported previously.[16]

N-(Salicylidene)glycinatozinc(II) anhydrous and monohydrate, Zn(sal-gly) and Zn(sal-gly)·H_2O (10, X=H, R=H).- Salicylaldehyde (0.020 mol) was added to the amino acid (0.022 mol) in 30 ml of water and the mixture was warmed to 50°. Solid zinc acetate monohydrate (0.020 mol) was introduced and the mixture was stirred vigorously at 40-60° for ca. 90 min. After cooling to room temperature the crude complex was collected by filtration. The initially isolated species was boiled five times with 100 ml of 95% ethanol and 15 ml water and twice with 100 ml absolute ethanol Drying at 80° (10^{-2} mm) gave the anhydrous complex. The monohydrate was obtained by combining the preceding aqueous ethanol solutions and reducing the volume until white crystals separated. This solution was allowed to stand for 2 weeks; the crystalline complex was collected by filtration and then dried at 80°; both complexes mp >360°.

Anal. Zn(sal-gly)·$0H_2O$, calcd. for $C_9H_7NO_3Zn$: C, 44.57; H, 2.89; N, 5.78. Found: C, 44.67; H, 2.84; N, 5.70.

Zn(zal-gly)·$1H_2O$, calcd. for $C_9H_9NO_4Zn$: C, 41.49; H, 3.46; N, 5.38. Found: C, 41.18; H, 3,44; N, 5.29.

N-(Salicylidene)valinatozinc(II) hemihydrate and monohydrate, Zn(sal-L-val)·$0.5H_2O$ and Zn(sal-L-val)·H_2O (10, X=H, R=$CH(CH_3)_2$).

These complexes were obtained by the procedure used for the glycinato complexes. The initially isolated valinato complex was recrystallized three times from 5:1 v/v ethanol-H_2O and dried to constant weight at 80° (10^{-2} mm). The white product obtained was found to be the hemihydrate. The monohydrate was isolated as

white crystals by volume reduction of the combined aqueous ethanol filtrates.

N-(Pyridoxylidene)valinatocopper(II) monohydrate, Cu(pyr-L-val)·H_2O (8, R=$CH(CH_3)_2$). Pyridoxal was obtained from its hydrochloride (Calbiochem) by treatment with aqueous potassium hydroxide. Hydrated lithium hydroxide (9.50 mmol) was added to a solution of 4.75 mmol of L-valine in 20 ml of degassed methanol at 5° under nitrogen and allowed to react for 1 hr. Pyridoxal (4.75 mmol) was then added and the mixture stirred for 15 min at 5°. An equivalent amount of aqueous cupric nitrate solution was added dropwise, producing almost immediate crystallization of the product. Methanol (ca. 5 ml) was added and after additional stirring for 1 hr the complex was collected by filtration. It was obtained as a dark green solid after washing with ice-cold methanol (3x10 ml) and ether (5x10 ml) and drying at 25°/10^{-2}mm for 24 hrs; mp >360° with decomposition beginning at 235°. Anal. calcd. for $C_{13}H_{18}N_2O_5Cu$: C, 45.15; H, 5.21; H, 8.10. Found: C, 45.16; H, 4.70; N, 7.90.

N-(3-Hydroxopyridyl-2-methylene)valinatocopper(II) hemihydrate, Cu(3,2-hpy-L-val)·$0.5H_2O$ (9, R=$CH(CH_3)_2$). The ligand 3-hydroxypyridine-2-carboxaldehyde was synthesized by a published method[45,46] and purified by vacuum sublimation at 70-80° immediately before use. The complex was prepared by the procedure for the related pyridoxylidene complex. Analytically pure samples were obtained either by washing the precipitated product with methanol and ether or by recrystallizing it from a chloroform-methanol-isobutanol solvent mixture. Dark green crystals were obtained; mp 258-260°.

Anal. Calcd. for $C_{11}H_{13}N_2O_{3.5}Cu$: C, 45.13; H, 4.44; N, 9.57. Found: C, 45.13; H, 4.08; N, 9.52.

Bis[N-(2-ethyoxycarbonyl-1-propyl)salicylaldiminato]Cu(II), Cu(Etaib-sal)$_2$ (31). The ethyl ester hydrochloride of the amino acid was prepared by dissolving 0.010 mol of β-aminoisobutyric acid in 30 ml of absolute ethanol and passing dry hydrogen chloride gas through the solution for 3 hrs. Removal of the solvent gave the crude hydrochloride as an oil. The free ester was obtained by dissolving the oil in 50 ml of dichloromethane and passing dry ammonia gas through the solution for 15 min. Ammonium chloride was filtered off, the dichloromethane evaporated, and 30 ml of absolute ethanol added to the residue. This solution was heated just to the boiling point and bis(salicylaldehydato)Cu(II) (0.0050 mol) added. The reaction was allowed to proceed for 30 sec, the solution filtered, and the brownish-green filtrate evaporated until crystallization began. The solution was maintained at 40° for 1 hr and the product filtered off. It was recrystallized twice from absolute ethanol and dried in vacuo for 3 hrs at room temperature. The pure product was obtained as greenish-brown crystals, mp 122-123°.

Anal. Calcd. for $C_{26}H_{32}N_2O_6Cu$: C, 58.70; H, 6.02; N, 5.27. Found: C, 58.38; H, 6.27; N, 5.10.

Bis[N-(3-ethoxycarbonyl-2-propyl)salicylaldiminato]Cu(II), Cu(Etab-sal)$_2$ (32). Crude 3-aminoethylbutyrate was obtained on a 0.030 mol scale from 3-aminobutyric acid using the method in the preceding preparation. It was reacted with 0.030 mol of salicylaldehyde in 15 ml of dichloromethane for 15 min at room temperature. Removal of solvent gave the Schiff base as a yellow oil which was distilled at 140°/10^{-2} mm. The Schiff base (0.021 mol) was dissolved in 60 ml of dry t-butanol containing 0.025 mol of potassium t-butoxide under a nitrogen atmosphere. Tetraethylammonium tetrabromocuprate(II) (0.013 mol) was added and the reaction allowed to proceed for 3 hrs at 50°. Removal of the

t-butanol yielded a brown tar which was extracted with warm, dry n-heptane. The solvent was removed in vacuo and the resultant brown oil was subjected to pumping at 30-50° for 2 hrs. The complex obtained in this way was found to be of adequate purity. Despite repeated attempts it could not be recrystallized to yield a solid. It could not be prepared in pure form by a method similar to that employed for complex 31.

Anal. Calcd. for $C_{26}H_{32}N_2O_6Cu$: C, 58.70; H, 6.02; N, 5.27. Found: C, 58.65; H, 6.17; N, 5.16.

N-(Salicylidene)-3-aminoisobutyrato-Cu(II), Cu(sal-aib) (33, R = H, R' = CH_3). 3-Aminoisobutyric acid (0.015 mol) was dissolved in 15 ml of water and 0.015 mol of salicylaldehyde added. The yellow solution was heated for 30 min at 60-70° and then 0.015 mol of cupric acetate monohydrate in 20 ml of hot water was added dropwise. The green complex precipitated as the addition was completed. Reaction was allowed to proceed for 1 hr at 60-70° and the solution filtered when hot to yield ca. 3.0 g of product. This material was recrystallized from 300 ml of absolute ethanol and dried to constant weight at 80°/10^{-2} mm. An anhydrous dark green solid was obtained; mp 281-283°.

Anal. Calcd. for $C_{11}H_{11}NO_3Cu$: C, 49.12; H, 4.08; N, 5.21. Found: C, 49.28; H, 4.15; N, 5.08.

N-(Salicylidene)-3-aminobutyrato-Cu(II) hemihydrate, Cu(sal-ab)·$0.5H_2O$ (33, R = CH_3, R' = H). This compound was obtained using the preceding method. It was recrystallized twice from 90% ethanol and obtained as a light green solid after drying at 80°/10^{-2} mm to constant weight; mp 258-260°.

Anal. Calcd. for $C_{11}H_{12}NO_{3.5}Cu$: C, 47.42; H, 4.31; N, 5.03. Found: C, 47.68; H, 4.73; N, 5.26.

Magnetic Measurements. Magnetic moments of representative Cu(II) complexes at 25° were measured by the Faraday method using $HgCo(NCS)_4$ as a calibrant. Moments for four complexes are given in Table II. Additional values are Cu(sal-ab)·$1/2H_2O$, 1.76 BM and Cu(sal-aib), 1.78 BM.

Acidity Measurements. Measurement of apparent hydrogen ion concentrations in 95% or other aqueous ethanol solutions were made with a Radiometer 26 pH meter equipped with a Radiometer combined glass-calomel electrode, which was equilibrated in the particular solvent medium prior to measurement.

Deuterium Exchange Studies of Bis(N-ethoxycarbonylpropylsalicylaldiminato)-Cu(II) Complexes. The deuterium exchange properties of the proton attached to the asymmetric carbon in $Cu(Etaib\text{-}sal)_2$ and $Cu(Etab\text{-}sal)_2$ were investigated under neutral and basic conditions in ethanol-1-d solutions. After the treatments described below the complexes were reisolated, dissolved in carbon tetrachloride, and the Schiff bases freed by passing hydrogen sulfide through the solutions. The precipitated sulfide was removed by filtration, the volume of the solution reduced to ca. 2-3 ml, and the pmr spectrum of the free ligand recorded. A 0.09 M solution of $Cu(Etaib\text{-}sal)_2$ was refluxed for 30 min and a 0.08 M solution containing equimolar ethanol-1-d was refluxed for 17 hrs. Solutions of $Cu(Etab\text{-}sal)_2$ 0.08 M in complex and sodium ethoxide were refluxed for periods up to 17 hrs and a similar solution containing a 1:5 mole ratio of complex to base was refluxed for 30 min. In all cases the pmr spectra revealed no deuterium exchange of the proton in question or of any other protons, and were the same as those of the separately prepared Schiff bases. The following chemical shift data (Hz, CCl_4 solution, TMS reference) were obtained: H(Etaib-sal), -73 (both CH_3's, triplet + doublet), -168 (β-H, quartet), -222 ($N\text{-}CH_2$, doublet), -247 (ester CH_2, quartet), -420 (ring protons), -500 (HC=N); H(Etab-sal),

-69 (ester CH_3, triplet), -74 ($CHCH_3$, doublet), -148 ($CHCH_2$, doublet), -240 (ester CH_2 + α-H, multiplet), -420 (ring protons), -499 (HC=N). All coupling constants are 6-7 Hz.

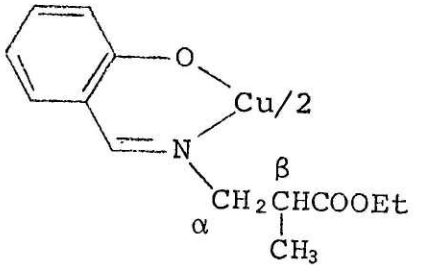
Measurement of Racemization Rates. Rates of racemization of Cu(sal-L-val)·3/2H_2O, Cu(4-NO_2sal-L-val)·H_2O, Cu(3,2-hpy-L-val)·1/2H_2O, and Cu(pyr-L-val)·H_2O were measured polarimetrically in basic 95% ethanol solutions at 50.0 ± 0.1°. A Perkin-Elmer Model 141 Spectropolarimeter and a 10 cm jacketed cell attached to a circulating constant temperature bath were employed. Sample solutions (50 ml) were prepared by dissolving the complex in degassed 95% ethanol and adding a sufficient volume of standardized, degassed stock solution of sodium hydroxide in 95% ethanol to achieve an apparent base concentration equal to within ±2% of that of the complex (usually 1-1.5x10^{-3} M). The ca. 0.05 M stock solution was standardized by pH titration with a 95% ethanol solution of benzoic acid. Measurements of optical rotations of the four complexes were made at 589 mμ and in several cases at 578 and 436 mμ also. At the concentrations employed (cf. Table III) initial rotations ranged from 0.150° to 0.350°. Kinetic runs were carried out for at least two half-lives and some were continued to zero rotation. The average number of measurements per run was 25, and as many as 50 measurements were made for the longer runs. The following control experiments were made for the longer runs. Solutions identical to those used in the kinetic runs, except for the presence of base, were maintained at 50° for times longer than two half-lives of the racemization reaction in basic solutions. In all cases the values of $[\alpha]_{589}$ and the wavelengths and intensities of absorption band maxima in the 210-450mμ region were unchanged. Spectral data are given in Table II. As a check on possible decomposition of the complexes during the kinetic runs, spectra in the 210-800 mμ range were

recorded at the beginning and end of these runs using solutions maintained at 50° and having the same concentrations as those employed in rate measurements. In the 210-450 mμ range no new absorption features were observed, and band intensities changed by ≤6% with changes of <4% observed in most cases. In addition, the absorption, ORD and/or CD spectra of fresh solutions without base and in the presence of equimolar base were compared (cf. Figs. 2 and 3). Only slight changes were found in the ultraviolet absorption spectra and in the visible a weak shoulder was detectable on the trailing edge of the ultraviolet absorption at 490-525 mμ in basic solutions of the four complexes. Band maxima at 640-670 mμ in neutral solutions were shifted by 10-20 mμ to higher energies in the basic solutions. Intensities of these features changed by <10% during kinetic runs except for Cu(3,2-hpy-val)·1/2H_2O, whose bands at 650 mμ and 500 mμ (sh) increased considerably in intensity. Possible sources of spectral differences between neutral and basic solutions are mentioned in the text. To establish that the added base acted as a catalyst and was not consumed during loss of optical activity, glass electrode measurements were made on portions of solutions used in the kinetic runs. Prior to each run solutions were diluted under nitrogen to 50% aqueous ethanol composition using degassed distilled water and the apparent pH determined; the same procedure was followed at the end of each run. A 0.01 M succinic acid buffer in 50% ethanol was employed as a standard.[47] Changes of less than 10% in initial and final readings were found except for solutions of Cu(3,2-hpy-L-val)·1/2H_2O where differences of 10-15% were observed. Plots of log α_{589} vs. time in all cases gave excellent straight lines for at least two half-lives from which pseudo first-order rate constants $k_{r(obsd)}$ (min^{-1}) were obtained by least squares fits of the data. Racemization rate constants were

obtained from the relation $k_r(M^{-1}\ min^{-1}) = k_{r(obsd)}/(OH^-)$. Kinetic data are set out in Table III.

Results and Discussion

Racemization of Bis[N-ethoxycarbonylalkyl)salicylaldiminato]-Metal(II) Complexes. The rapid racemization of complexes of type 27 was proposed to result from the activation of the α-C-H bond by electron-withdrawing properties of the metal azomethine linkage and the carboethoxy group, and from resonance stabilization of the intermediate.[22] In order to discover which of these effects was more important the metal complexes Cu(Etaib-sal)$_2$ (31) and Cu(Etab-sal)$_2$ (32) were prepared. In the former a methylene group has been inserted between the asymmetric carbon and the metal center and in the latter between the asymmetric carbon and the carboethoxy group. Because of the effort involved in making the optically active amino acids, the racemic amino acid esters were used to prepare the complexes, and possible hydrogen-deuterium exchange was monitored. The complexes were refluxed in ethanol-1-d in the presence and absence of base (sodium ethoxide) and then decomposed with hydrogen sulfide. PMR spectra of the free Schiff bases showed no H-D exchange at any position. This same procedure was used to show exchange at the α-carbon



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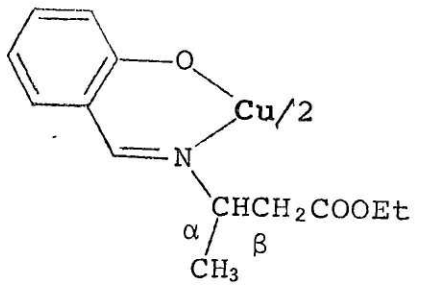

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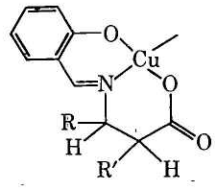
only in the type 27 complexes Cu(Etgly-sal)$_2$,[48] and Cu(Etala-sal)$_2$, Cu(Et-Phala-sal)$_2$ and Zn(Etala-sal)$_2$.[22]

It had been hoped that the lability of the α-proton in 31 or 32 would be decreased just enough so that exchange could be studied on a convenient time scale; obviously the effect was more extreme. Whereas 27 undergoes H-D exchange at the α-carbon in ethanol-1-d with no added base, 31 and 32 are perfectly stable in refluxing ethanol-1-d with added base. Direct attachment of the asymmetric carbon to one or the other of the two electron-withdrawing groups COOEt and HC=N-M is not enough to activate the C-H bonds to exchange. Thus all three features of the asymmetric center in 27, (1) electron withdrawal through the azomethine-metal linkage, (2) electron withdrawal by the carboethoxy group and (3) "enolate" resonance stabilization of the anionic intermediate by the carboethoxy group, appear to be necessary for rapid exchange and racemization to occur.

Schiff Base-Amino Acid-Metal(II) Complexes. The metal complexes of primary interest for the racemization studies are Cu(sal-L-val)·1.5H_2O, Cu(4-NO_2-sal-L-val)·H_2O, Cu(3,2-hpy-L-val)·0.5H_2O and Cu(pyr-L-val)·H_2O, all of which were isolated as crystalline solids. The magnetic and spectral data for these complexes, which is presented in Table II, indicate that they are simple spin-doublet species with electronic spectra similar to those for other Cu(II)-Schiff base complexes obtained from simple amino acids.[15,19-21,49-52] A common Cu(II) chromophore composed of the O_2N donor group from the Schiff base and two or three additional ligands,[23-25] which are probably ethanol or water molecules, is suggested by the appearance of all ligand field absorptions in the visible region in the narrow range 14,900-15,600 cm^{-1}. These complexes all have a negative Cotton effect or negative CD band associated with strong absorption

bands at 25,000-28,000 cm^{-1} which is typical for Cu(pyr-L-aa) and Cu(sal-L-aa) complexes.[50,53] The ORD and CD spectra of a typical complex are presented in Fig. 2. Two Schiff base amino acid complexes having two six-membered rings have also been synthesized. They have the general structure 33 and



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were prepared from 3-aminobutyric acid (R=CH_3,R'=H) and 3-aminoisobutyric acid (R = H, R' = CH_3). Preliminary studies indicated that racemization was slower in these complexes than in those prepared from valine, which is an α-amino acid.

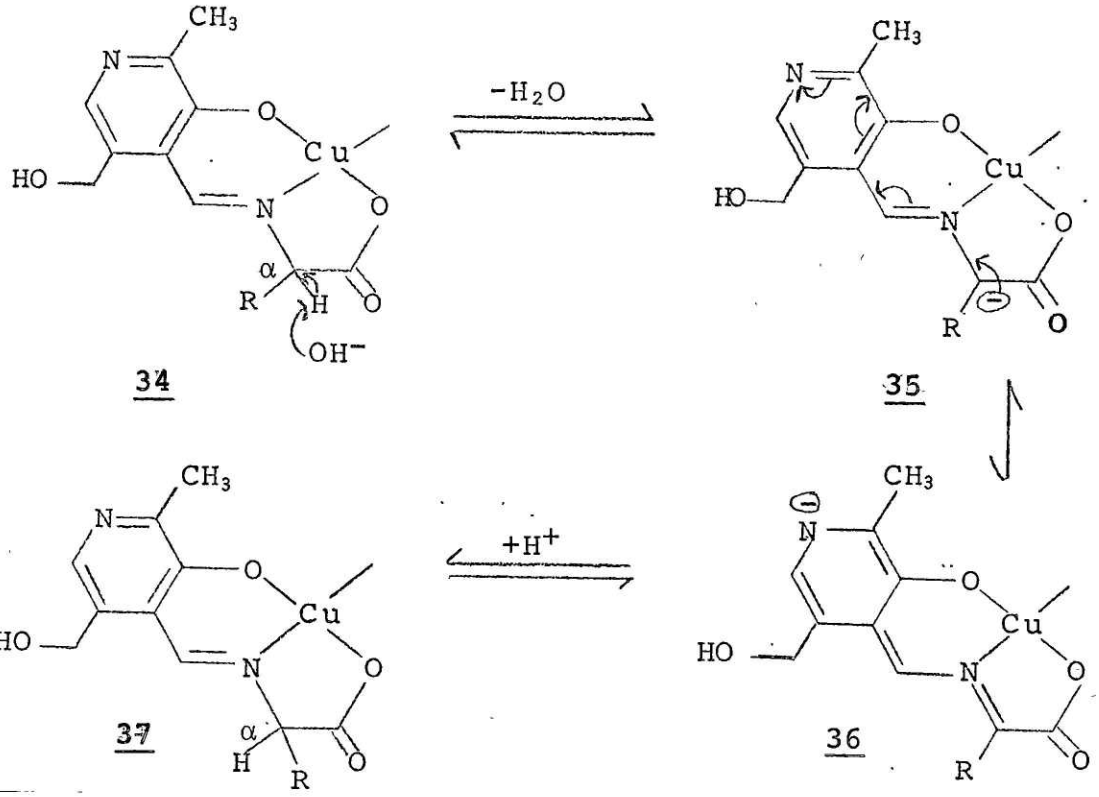
Racemization Kinetics. The purpose of the kinetics measurements has been to obtain a quantitative indication of the activation of the α-C-H bond in a series of 1:1 Schiff base complexes derived from the same amino acid and metal ion, but differing in the o-hydroxyarylcarbonyl ligand component. The latter has been selected according to its reported catalytic activity (pyridoxal, 3-hydroxy-2-pyridinealdehyde, and 4-nitrosalicylaldehyde) or lack of same (salicylaldehyde) in glutamate → α-ketoglutarate transamination at pH ~5 in the presence of Al(III).[27,54] It should be noted here that during the transamination reaction 4-nitrosalicylaldehyde undergoes reduction of the nitro group[54] which could result in oxidative deamination of the amino acid.[43] This compound was chosen for study because it introduced an electron-withdrawing function para to the azomethine function in the Schiff base without altering the basic benzene ring structure of salicylaldehyde. Cu(II) and L-valine were chosen for study because they form complexes whose reaction rates are conveniently studied by polarimetry. Finally, 95% ethanol was employed as a reaction medium in order to prevent the hydrolysis of the imine bond which occurs in water.

The control experiments described in the experimental section demonstrated that (i) racemization does not occur in solutions kept at 50° without added base, (ii) decomposition is slight during the course of the kinetic run, (iii) the apparent base concentration does not show significant change during a kinetic run. The only exception to these statements is for Cu(3,2-hpy-L-val) which does undergo some decomposition during the kinetic run, as evidenced by small changes in the visible region of the electronic spectrum. The rate constants for this complex are therefore considered to be the least reliable. The largest spectral changes were found for neutral solutions compared to solutions with equimolar base and complex at the start of kinetic runs and are illustrated by the ORD, CD, and absorption spectra of Cu(pyr-L-val)·H_2O in Figs. 2 and 3. The origin of these changes is obscure but may be due to the formation of a species such as, e.g., [Cu(pyr-L-val)OH]$^-$ in a labile preequilibrium step prior to onset of the racemization process. No new features or significant intensity alterations of ultraviolet bands which might arise from carbinolamine complexes or hydrolysis products were found in the presence of base.

In order to obtain rate data suitable for comparison, racemization kinetics of the four complexes were determined over the same or nearly the same concentration range of complex and base; the two solutes were maintained at equimolar concentrations in all runs; Pseudo first-order rate constants $k_{r(obsd)}$ and racemization rate constants k_r corresponding to the relation rate = k_r(complex)(OH^-)

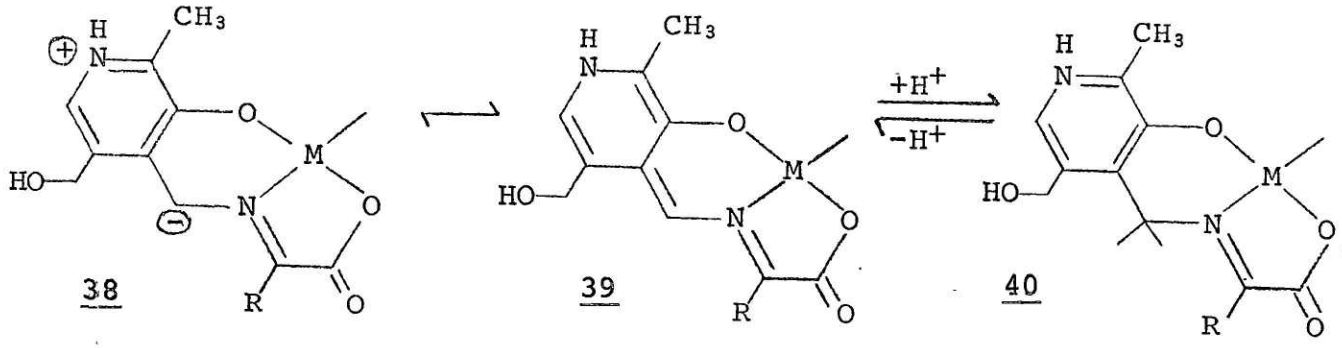
are given in Table III. In the range of ca. $0.7\text{-}1.7\times10^{-3}$ M k_r values are reasonably independent of concentration. The apparent order of racemization rates under these experimental conditions is Cu(4-NO_2sal-L-val)>Cu(3,2-hpy-L-val)>Cu(pyr-L-val)>> Cu(sal-L-val).

The kinetic data indicate that salicylaldehyde is the least effective racemization catalyst of the four o-hydroxy-arylcarbonyl compounds studied. The proposed reaction mechanism provides some explanation of these results; the pyridoxal complex which is used to illustrate the mechanism is unprotonated



at the basic pH of the reaction mixture.[55] In the mechanism proposed the α-proton is lost by base attack in the slow step, and the carbanion formed 35 is stabilized by resonance with 36 in which the negative charge is delocalized onto the ring nitrogen. In 36 the conjugated system extends from the α-carbon to the ring nitrogen. The racemization reaction is completed by reprotonation at the α-carbon to form 37. Since salicylaldehyde lacks an electron-withdrawing group ortho or para to the azomethine function, it cannot be postulated to have a resonance form such as 36. Therefore, formation of the anionic intermediate 35 from the Cu(sal-L-val) complex requires a somewhat higher activation energy than for the other three complexes resulting in a slower rate, provided that pre-exponential factors are similar for all four complexes.

Loss of the α-H is postulated to be the first step in both the transamination and racemization reactions. Racemization and transamination are, however, competitive and distinct processes. The transamination reaction is favored over the racemization reaction at pH values below the pK_a values of the pyridinium nitrogen of the aldimine complexes.[55] A reactive intermediate such as 38 is postulated to be important in the transamination reaction. This intermediate is stabilized by resonance with 39 in which the negative charge is delocalized onto the ring, the reaction is completed by the protonation of the azomethine carbon to form the ketimine tautomer 40. Although



this same reaction sequence could occur for the unprotonated complex during racemization, it is thought to be unlikely since the electronic spectra give no evidence of ketimine formation during the course of the reaction. The presence of an unprotonated ketimine similar to 40 and its rapid tautomerization to the racemized aldimine cannot,however, be completely ruled out by the present data.

The results of this study emphasize two aspects of the electronic factors important in vitamin B_6 catalysis.[4,27] First, the stability of aldimine structures of type 8 (and to a lesser extent 9) during the racemization reaction indicates that racemization is favored over transamination in the absence of the protonated pyridine unit. At low pH values racemization is thought to occur primarily by the reversal of transamination.[4] Second, the order of racemization rates of the four complexes studied in basic solution is the same as the qualitative order found for

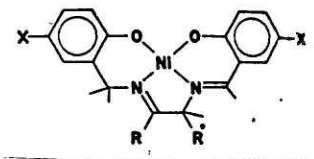
the o-hydroxyarylcarbonyl components as transamination catalysts in acid solution (salicylaldehyde<<4-nitrosalicylaldehyde~3-hydroxy-2-pyridinealdehyde~pyridoxal).[4] This relationship supports the contention that appreciable reaction rates for transamination in acid solution and racemization in basic solution derive from resonance stabilization of the appropriate intermediates (38 ⇌ 39, 35 ⇌ 36), for which an electron-withdrawing group (-N=, $\overset{+}{\underset{H}{N}}$=, -$NO_2$) ortho or para to the azomethine carbon is required.

Torchinskii[50] observed that at pH 8.5 and 65-90° aqueous solutions of Cu(II), pyridoxal, and several optically active amino acids showed a loss of CD intensity. This effect was ascribed without proof to an aldimine→ketimine conversion. Similarly, Johns and Whelan[56] ascribed the α-deuteration of amino acids which they observed in aqueous solutions of Cu(II), salicylaldehyde and amino acids to an aldimine→ketimine→deuterated (racemized) aldimine sequence. There is no necessity to postulate ketimine formation to explain the results of either of these studies; on the basis of our data the conversion of optically active aldimine directly to racemized aldimine via the intermediate 35 ⇌ 36 is suggested. Further investigation of these systems, particularly electronic spectra and H-D exchange studies would be of interest to show if racemization without ketimine formation is a general phenomenon which would explain the results of these and other experiments.

CHAPTER 3

Tautomerization of Schiff Base Complexes

Tautomerization is one of the key reactions of pyridoxal-dependent enzymes, as was discussed in Chapter 1. Although numerous aldimine type metal complexes (8-10) have been isolated, only two ketimine complexes, bis(α-pyridoxyliminopropionato)-Ni(II)[26] and 2-ô-hydroxybenzyliminopropionatocopper(II)[20] have been described previously. Recently nickel complexes with one aldimine and one ketimine type nitrogen ligand (41) have been



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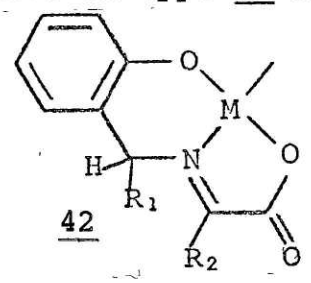
reported.[57] Presumably these complexes were formed by reaction of nickel(II) acetate with the diketimine ligand and subsequent tautomerization of only half of the molecule.

Studies of the tautomerization process are usually approached from the ketimine side, ile., M(pym-ka) →TM(pyr-aa) due to the appreciably greater stability of the aldimine form under ordinary conditions. Tautomerization of ketimine complexes generated in solution has been observed by electronic spectral measurements[33,41,42] and by pmr.[37] In view of the importance of ketimine species and their tautomerization reactions in the proposed mechanism for transamination and other transformations in model

systems,[1] it was considered of interest to prepare several ketimine metal complexes and to study their tautomerization. Complexes of type 42 and 43, rather than those derived from



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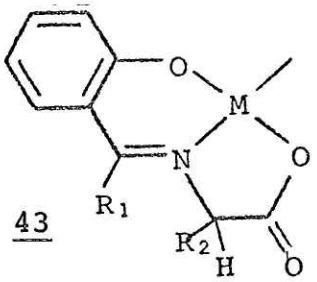

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pyridoxamine and pyridoxal, have been employed due to their greater ease of isolation and higher hydrolytic stability.

Experimental Section

Preparation of Compounds. o-Hydroxybenzylamine (mp 126-127°) and α-methyl-o-hydroxybenzylamine (mp 86-87°) were prepared from the corresponding oximes by reduction with sodium in liquid ammonia.[58] In the following preparations of new complexes the quoted water contents were inferred from best fits of the analytical data; independent determinations by weight loss studies were not carried out.

2-o-Hydroxybenzyliminopropionatocopper(II) Monohydrate, Cu(hba-prop)·H_2O.[59] o-Hydroxybenzylamine (3.3 mmol) was added to 3.3 mmol of pyruvic acid in 5 ml of water and the solution was stirred at 5° for 5 min. At this temperature 20 ml of an aqueous solution containing an equimolar amount of cupric acetate was added dropwise. After an additional 10 min of stirring the light green microcrystalline product was collected and washed with 5 ml of ether; mp 225-226°. Anal. Calcd. for $C_{10}H_{11}NO_4Cu$: C, 44.04; H, 4.04; N, 5.17. Found: C, 44.27; H, 3.85; N, 5.26.

2-o-Hydroxybenzyliminopropionatozinc(II) Hemihydrate, Zn(hba-prop)·1/2H_2O. The Schiff base was prepared by allowing o-hydroxybenzylamine (10 mmol) and sodium pyruvate (10 mmol) to react with stirring in 15 ml of anhydrous methanol for 15 min at 25°. The crude base was collected and dried under vacuum at 25°; mp 178-180°. Zinc acetate dihydrate (2.5 mmol) dissolved in 40 ml of methanol was added to a solution of 2.5 mmol of the Schiff base in 75 ml of methanol. After stirring for 2.5 hr, the product was collected and dried at 25°/0.05 mm; mp >300°. Anal. Calcd. for $C_{10}H_{10}NO_{3.5}Zn$: C, 45.23; H, 3.77; N, 5.28. Found: C, 45.78; H, 3.61; N, 5.37.

2-o-Hydroxybenzyliminoisovaleratocopper(II), Cu(hba-ival). A procedure analogous to that for Zn(hba-prop)·1/2H_2O using α-ketoisovaleric acid was employed except that the ligand was not isolated and was reacted with cupric acetate for 30 min. The complex was obtained as bright green microcrystals; mp 229-230°. Anal. Calcd. for $C_{12}H_{13}NO_3Cu$: C, 50.79; H, 4.60; N, 4.96. Found: C, 50.40; H, 4.70; N, 5.02

N-o-Hydroxyacetophenoneimino-L-alaninatocopper(II) Monohydrate, Cu(hac-L-ala)·H_2O. Potassium hydroxide (1 mmol) in 25 ml of methanol was added to a solution of 1 mmol of L-alanine in 5 ml of methanol. The solution was warmed until all the alanine dissolved, a solution of 1 mmol of o-hydroxyacetophenone in 5 ml of methanol was added, and the mixture stirred at 5° for 10 min.

Ether (20 ml) was added to precipitate any unreacted alanine and the solution was filtered. To the filtrate was added a solution of 0.9 mmol of cupric acetate in 100 ml of methanol, the reaction mixture was stirred for 2 hr, and filtered to remove a small amount of bis(L-alaninato)copper(II). Reduction of the filtrate volume to 5 ml followed by the addition of 10 ml of acetone afforded the crude complex as a deep blue solid. This material was recrystallized from water and dried at 25°, yielding a deep green powdery product; mp 271-273°. Anal Calcd. for $C_{11}H_{13}NO_4Cu$: C, 46.07; H, 4.54; N, 4.89. Found: C, 45.70; H, 4.44; N, 4.80.

2-(α-Methyl-o-hydroxybenzylimino)propionatocopper(II) Monohydrate, Cu(mhba-prop)·H_2O. A procedure analogous to that for Zn(hba-prop)·$1/2H_2O$ was used, except that the complex was precipitated from methanol solution by the addition of isobutanol and n-pentane. The complex was obtained as a green solid after recrystallization from chloroform; mp 350°. Anal. Calcd. for $C_{11}H_{13}NO_4Cu$: C, 46.07; H, 4.54; N, 4.89. Found: C, 45.76; H, 4.44; N, 4.73.

2-(α-Methyl-o-hydroxybenzylimino)isovaleratocopper(II) Hemihydrate, Cu(mhba-ival)·$1/2H_2O$. A preparation analogous to that for the preceding complex was used. The product was recrystallized from ether and dried at 25°; it was obtained as a light green powder; mp 212-215°. Anal. Calcd. for $C_{13}H_{16}NO_{3.5}Cu$: C, 51.06; H, 5.24; N, 4.58. Found: C, 51.35; H, 5.72; N, 4.35.

Physical Measurements. Electronic spectra were obtained on a Cary Model 14 spectrophotometer, magnetic moments were measured

by the Faraday method ($HgCo(NCS)_4$ calibrant), pmr spectra were determined on a Varian T-60 instrument (TMS reference), and a Varian V-4502 spectrometer was employed for epr measurements. All quantities dependent upon formula weights were calculated using those including the water contents specified above.

Rates of Ketimine→Aldimine Conversion. Rates of base-catalyzed tautomerization of Cu(hba-prop)·H_2O and Cu(hba-ival) were measured spectrophotometrically in 95% ethanol solutions at 30.0±0.1° and 50.0±0.1°. Sample solutions (50 ml) were prepared by dissolving the isolated complex in degassed 95% ethanol and adding a sufficient volume of standardized[16] degassed stock solution of sodium hydroxide in 95% ethanol to achieve an apparent base concentration equal to within ±5% of that of the complex (usually $1.5\text{-}2.0\times10^{-4}$ M). The reaction was followed by monitoring the increase in absorption of the ca. 27,320 cm^{-1} band of the aldimine forms (cf. Figure 4 and Table IV). Kinetic runs were carried out for at least two half-lives and the complete electronic spectra at the end of each run showed that most of the ketimine had transaminated with no apparent decomposition. The following control experiments were also performed. Solutions identical with those used in kinetic runs, except for the presence of base, were maintained at 50° for times longer than two half-lives of the transamination reaction in basic solutions. In all cases the energies and intensities of the band maxima in the ultraviolet and

visible regions were unchanged. Plots of $\log(A_{aldimine}-A)$ *vs.* time in all cases gave straight lines from which pseudo first-order rate constants $k_{t(obsd)}$ (min^{-1}) were obtained by least-squares treatment of the data. Tautomerization (transamination) rate constants were obtained from $k_t(\underline{M}^{-1}min^{-1}) = k_{t(obsd)}/(OH^-)$.

Results and Discussion

The ketimine metal complexes M(hba-ka) (42, R_1 = H, R_2 = CH_3, $CH(CH_2)_3$) and M(mhba-ka) (42, R_1 = CH_3, R_2 = CH_3, $CH(CH_3)_2$) have been prepared. This and previous work[16,22] has resulted in the preparation of the following pairs of tautomeric Cu(II) complexes: Cu(hba-prop)·H_2O and Cu(sal-L-ala)·$2H_2O$ (Pair I), Cu(hba-ival) and Cu(sal-L-val)·$3/2H_2O$ (Pair II), and Cu(mhba-prop)·H_2O and Cu(hac-L-ala)·H_2O (Pair III). Pair I was previously reported by Nakahara,[20] but only limited spectral and polarographic data were presented in order to show that the complexes did possess different ligand structures.

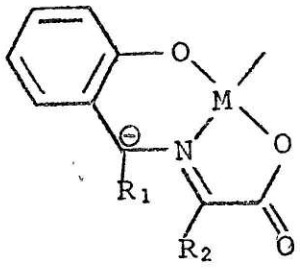
The members of each tautomeric pair may in fact be readily distinguished by their electronic spectra (*cf.* Table 4 and Fig. 4). In particular, complexes with structure 43 possess an intense feature at ~27,500 cm^{-1} whereas the complexes 42 do not have a maximum at this energy, their closest band (~24,000-25,600 cm^{-1}) being considerably less intense. The d-d band in the visible region of the type 42 complexes was consistently found to be at slightly lower energies than the corresponding feature of the complexes

of structure 43. A fourth type 42 complex, Cu(mhba-ival)·1/2 H_2O has also been prepared. Its tautomer, derived from o-hydroxyacetophenone and L-valine, could not be obtained. Other physical data (magnetic moments, infrared frequencies, epr parameters) have not proven satisfactorily characteristic of the members of Pairs I-III. Magnetic moments are somwehat dependent on the extent of hydration,[1] and evidence is accumulating that anhydrous Cu(sal-aa) complexes are antiferromagnetic dimers or polymers in the solid or in non-coordinating solvents.[60] The epr spectra of the Pair II complexes were determined in fluid and frozen (77°K) methanol solution. The following parameters, which afford little differentiation between the two structures, were obtained: Cu(hba-ival)- $\langle g \rangle = 2.1273$, $\langle a \rangle = 0.00636\ cm^{-1}$, $g_{\parallel} = 2.269$, $g_{\perp} = 2.057$, $a_{\parallel} = 0.0180\ cm^{-1}$; Cu(sal-L-val)·3/2$H_2O$ - $\langle g \rangle = 2.125$, $\langle a \rangle = 0.00693\ cm^{-1}$, $g_{\parallel} = 2.257$, $g_{\perp} = 2.059$, $a_{\parallel} = 0.0188\ cm^{-1}$. Values of a refer to $^{63,65}Cu$ hfs; superhyperfine splittings due to nitrogen could not be resolved in either case.

Conclusive structural evidence is provided by the pmr spectra of Zn(hba-prop)·1/2H_2O and Zn(sal-L-ala) which are analogues of the Pair I Cu(II) complexes. The ketimine and the aldimine are readily differentiated by the following pmr data: Zn(hba-prop)·1/2H_2O (pyridine-d_5)-2.49 (3,CH_3), 4.67 (2, CH_2), ~7.1 ppm (4, phenyl); Zn(sal-L-ala)·H_2O (methanol-d_4)- 1.35 (3, doublet (J = 7 Hz), CH_3), 3.97 (1, quartet, CH), ~7.1 (4, phenyl), 8.33 ppm (1, azomethine).

In the ketimine complex there is neither an azomethine proton, nor an α-H, and the resonances of both the methylene protons and α-methyl group are singlets in accord with structure 42.

The tautomerization kinetics of Cu(hba-prop)·H_2O and Cu-(hba-ival) were determined in 95% ethanol solutions containing equimolar sodium hydroxide under conditions closely similar to those employed in the study of the racemization kinetics of Cu(II) Schiff base complexes discussed in Chapter 2. No reaction was observed in water, ethanol, or methanol solutions at 50° for 24 hrs unless base was present. Tautomerization rate constants k_t, which are averages of at least three kinetic runs, were found to be 2.29±0.21 (30°) and 7.16±0.64 $\underline{M}^{-1}min^{-1}$ (50°) for Cu(hba-prop)·H_2O and 0.87±0.11 (30°) and 3.70±0.30 $\underline{M}^{-1}$ min^{-1}(50°) for Cu(hba-ival). The lower rates for the latter presumably reflect the greater degree of steric hindrance of the isopropyl group with regard to base attack on the methylene protons. The value of k_t (50°) for the latter complex is directly comparable with the rate of racemization of its tautomer Cu(sal-$\underline{L}$-val)·$3/2H_2O$ at the same temperature. The ratio k_t/k_r ~150 provides a quantitative demonstration that ketimine→aldimine tautomerization (transamination), presumably proceeding through the anion 44 ⇌ 45 which preferentially protonates at the α-carbon, is a faster process than racemization of the aldimine when determined under similar experimental conditions. The rate of aldimine→ketimine tautomerization, although not yet measured



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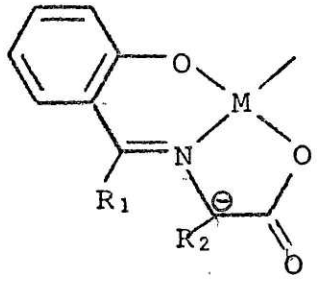

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for the complexes 43, is clearly much less than that of aldimine racemization since no spectral features now known to be associated with M(hba-ka) were observed at any point during the racemization reactions of M(sal-aa). It is also observed that the tautomerization rates of Cu(hba-ka) are qualitatively slower than those of M(pym-ival) (M = Cu(II), Zn(II)) in neutral methanol solutions.[41,42] As discussed in Chapter 2 for the racemization reaction, this situation arises at least in part from the presence of an electron-withdrawing group ortho or para to the $R_1\overset{|}{C}NCR_2$ unit which allows resonance stabilization of anionic intermediates similar to 45.

The tautomerization of a ketimine complex such as 42 (R_1 = H) and subsequent hydrolysis to complete the transamination reaction would presumably give rise to a racemic amino acid. In contrast there is complete optical specifity in the enzymic systems.[61,62] In an effort to produce amino acids with some optical specificity, ketimine complexes were prepared from the potentially resolvable α-methyl-o-hydroxybenzylamine with the goal of seeing if base-assisted proton transfer from an asymmetric center to an α-carbon might result in an optically active product

43. Unexpectedly Cu(mhba-prop)·H_2O and Cu(mhba-ival)·$1/2H_2O$ (42, $R_1 = CH_3$) did not tautomerize when heated in methanol or 95% ethanol at 50-60° for 24 hours, or in a pH 10 aqueous solution at 50° for several hours. The aldimine complex Cu(hac-L-ala)·H_2O was similarly stable.

In summary, the tautomerization rate from ketimine to aldimine metal complex has been found to be much faster than the racemization rate for the corresponding aldimine as shown by the stability of the electronic spectra during the racemization reaction. The minimum ring constituents essential for transamination, the ortho hydroxy and aldehyde groups and an electron withdrawing group ortho or para to the aldehyde[4] are also essential for rapid racemization. The ortho or para electron-withdrawing group on the ring is thought to provide important resonance stabilization in both the racemization and transamination reaction, thereby enhancing the rate of the reaction. Further, research into the properties of isolated ketimine complexes would be of interest. In particular the isolation of complexes with a variety of o-hydroxyarylamine constituents should be attempted in order to study the tautomerization reaction of a series of ketimine complexes and a structural determination should be done on at least one ketimine complex.

Table I Reactions of α-Amino Acids Catalyzed by Pyridoxal and Metal Ions in Model Systems

A. Reactions resulting from labilization of an α-hydrogen (18, bond a)

1. transamination: $RCH(NH_2)COOH + R'COCOOH \rightleftharpoons RCOCOOH + R'CH(NH_2)COOH$
2. racemization: $L\text{-}RCH(NH_2)COOH \rightleftharpoons D\text{-}RCH(NH_2)COOH$
3. β-elimination: dehydration of α-amino-β-hydroxyacids
   $HOCH_2CH(NH_2)COOH \rightarrow CH_3COCOOH + NH_3$
   desulfhydration of cysteine
   $HSCH_2CH(NH_2)COOH \rightarrow CH_3COCOOH + H_2S + NH_3$
4. tryptophan synthesis from serine and indole
5. β-proton exchange: $R_2CHCH(NH_2)COOH \rightleftharpoons R_2CDCD(NH_2)COOH$
6. γ-elimination: desulfhydration of homocysteine
   $HSCH_2CH_2CH(NH_2)COOH \rightarrow CH_3CH_2COCOOH + H_2S + NH_3$
7. Synthesis of α-amino-β-hydroxyacids from glycine and an aldehyde

B. Reactions resulting from labilization of the carboxyl group (18, bond b)

decarboxylation of amino acids

$$RCH(NH_2)COOH \rightarrow RCH_2NH_2 + CO_2$$

C. Reactions resulting from labilization of an R group (18, bond c)

degradation of α-amino-β-hydroxyacids to aldehydes and glycine

$$RCH(OH)CH(NH_2)COOH \rightleftharpoons RCHO + H_2NCH_2COOH$$

D. Oxidative Deamination

$$RCH(NH_2)COOH + O_2 + H_2O \rightarrow RCOCOOH + NH_3 + H_2O_2$$

Table II. Magnetic Moments and Electronic Spectra of Cu(II) Schiff Base-Amino Acid Complexes

Complex	μ_{eff} (BM)[a]	λ_{max} (cm^{-1}) (ε)[b]
Cu(sal-L-val)·3/2H_2O	1.65	45,040 (20,500), 41,150 (21,900), 37,040 (13,800), 27,320 (5030), 15,600 (109)
Cu(4-NO_2sal-L-val)·H_2O	1.75	46,730 (17,700), 40,000 (19,900), 34,970 (14,000), 23,920 (4420), 14,900 (118)
Cu(3,2-hpy-L-val)·1/2H_2O	1.96	46,300 (26,300), 41,150 (13,900), 35,700 (sh, 2860), 27,470 (7960), 15,000 (104)
Cu(H-3,2-hpy-L-val)Br	1.73	46,300 (24,300), 41,150 (13,200), 35,700 (sh, 3100), 27,860 (7490), 14,800 (108)
Cu(pyr-val)·H_2O	1.72	43,480 (21,100), 36,760 (9300), 25,640 (5720), 15,200 (120)

[a]Solid. [b]95% ethanol solution.

Table III. Kinetic Data for the Base-Catalyzed Racemization of Cu(II) Schiff Base-Amino Acid Complexes in 95% Ethanol Solution at 50°

Complex	$\underline{M} \times 10^3$	$k_{r(obsd)}$[a] $min^{-1} \times 10^4$	$k_r = k_{r(obsd)}/(OH^-)$ $\underline{M}^{-1}\ min^{-1}$	k_r av $\underline{M}^{-1}\ min^{-1}$
Cu(sal-L-val)·3/2H_2O	1.67	0.394	0.0236	
	1.56	0.361	0.0231	0.0246
	1.06	0.278	0.0262	
	1.04	0.266	0.0256	
Cu(4-NO_2sal-L-val)·H_2O	1.58	9.25[b]	0.585	
	1.54	8.40	0.546	
	1.08	5.94	0.550	0.558
	0.87	4.90	0.563	
	0.74	4.04	0.547	
Cu(3,2-hpy-L-val)·1/2H_2O	1.54	5.17	0.336	
	1.53	4.95	0.324	0.309
	1.09	3.01	0.276	
	1.00	2.99	0.299	
Cu(pyr-L-val)·H_2O	1.57	3.53	0.225	
	1.56	3.56	0.228	
	1.06	2.53	0.238	0.236
	1.03	2.55	0.248	
	0.77	1.84	0.239	

[a] Determined from α_{589} data; concentrations of complex and sodium hydroxide equal. [b] Determined from α_{578} data.

Table IV. Magnetic and Spectral Data for Tautomeric Cu(II) Complexes

Pair	Complex	μ_{eff}(BM)[a]	λ_{max}, cm^{-1} (ε)[b]
I	Cu(sal-L-ala)·$3H_2O$	1.72	15,500 (111), 27,300 (4,890), 37,310 (12,500), 41,150 (21,100), 45,050 (19,900)
	Cu(hba-prop)·H_2O	1.57	14,790 (153), 25,640 (563), 36,230 (4,700), 43,500 (sh) (8,600)
II	Cu(sal-L-val)·$\frac{3}{2}H_2O$[c]	1.65	15,600 (109), 27,320 (5,030), 37,040 (13,800), 41,150 (21,900), 45,040 (20,500)
	Cu(hba-ival)	1.39	14,820 (128), 24,880 (597), 36,360 (4,540), 43,480 (9,450)
III	Cu(hac-L-ala)·H_2O	1.70	15,820 (101), 27,860 (4,590), 37,590 (11,600), 43,860 (23,400)
	Cu(mhba-prop)·H_2O	1.58	14,930 (127), 24,040 (574), 35,970 (4,460), 42,900 (8,500)
	Cu(mhba-ival)·$\frac{1}{2}H_2O$	1.46	15,390 (104), 24,630 (610), 35,970 (5,410) 42,920 (sh) (9,200)

[a]Solid state, ~25°. [b]95% ethanol solution. [c]Data from ref. 16.

Table V. Abbreviations

ala	free or condensed alanine
ab	free or condensed aminobutyric acid
aib	free or condensed β-aminoisobutyric acid
Etaa-sal	N-ethoxycarbonylalkylsalicylaldimine anion
glu	free or condensed glutamate
glt	free or condensed glutarate
gly	free or condensed glycine
hac-aa	N-o-hydroxyacetophenoneiminoaminoacidato dianion
hba-ka	2-o-hydroxybenzyliminoketoacidato dianion
3h2-hpy-aa	N-(3-hydroxypyridyl-2-methylene)aminoacidato dianion
ival	free or condensed α-ketoisovaleric acid
M	di- or trivalent metal ion
mhba-ka	α-Methyl-o-hydroxybenzyliminoketoacidato dianion
Phala	free or condensed phenylalanine
pl	pyridoxal
plp	pyridoxal phosphate
pm	pyridoxamine
Ppyr	pyridoxylidene phosphate
prop	free or condensed pyruvate
pyr-aa	N-pyridoxylideneamino acidato dianion
pym-ka	α-pyridoxyliminoketoacidato dianion
X-sal-aa	ring-substituted N-salicylideneamino acidato dianion (X = H not explicitly stated)
val	free or condensed valine

Figure Legends

Figure 1. Pmr spectra (100 MHz) of D_2O solutions initially 0.1 M in both pyridoxamine and pyruvate, 0.05M in Al(III):[37] (a) fresh solution showing the formation of free ketimine and the 1:1 Al complex; (b, c) spectra revealing transamination of Al-ketimine complexes to yield 1:1 and 2:1 Al-aldimine species. The three solutions are not at equilibrium. Unprefixed signals refer to free pyridoxamine: Al-A, aluminum aldimine, Al-K, aluminum ketimine complex; SB, side band; X, impurity.

Figure 2. ORD and CD spectra of Cu(pyr-L-val)·H_2O in 95% ethanol in presence of equimolar sodium hydroxide at the beginning of a kinetic run and in the absence of base. CD: -o-o-o-, no base; -ooo-o-, with base; ORD: -Δ-Δ-Δ-Δ no base; Δ-Δ-Δ, with base.

Figure 3. Absorption spectrum of Cu(pyr-L-val)·H_2O in 95% ethanol solution; -:-:-, no base; ———, in presence of equimolar sodium hydroxide at start of kinetic run; ----, in presence of equimolar sodium hydroxide at end of kinetic run.

Figure 4. Electronic spectra of Cu(sal-L-val)·3/2H_2O (---) and Cu(hba-ival) (———) in 95% ethanol solution.

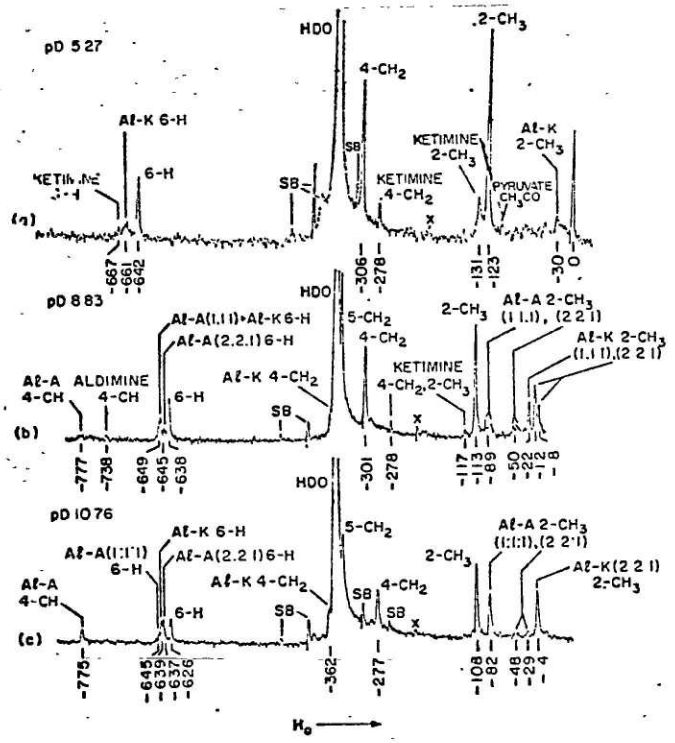

pD 5.27
HDO
4-CH2
2-CH3
Al-K 6-H
6-H
SB
KETIMINE 2-CH3
Al-K 2-CH3
KETIMINE 4-CH2
PYRUVATE CH3CO
(a)
-667
-661
-642
-306
-278
-131
-123
-30
0
pD 8.83
HDO
5-CH2
4-CH2
2-CH3
Al-A 2-CH3 (1 1 1), (2 2 1)
Al-K 2-CH3 (1 1 1),(2 2 1)
Al-A(1.1.1)+Al-K 6-H
Al-A(2.2.1)6-H
Al-A 4-CH
ALDIMINE 4-CH
6-H
Al-K 4-CH2
KETIMINE 4-CH2,2-CH3
SB
(b)
-777
-738
-649
-645
-638
-301
-278
-117
-113
-89
-50
-22
-18
pD 10.76
HDO
5-CH2
Al-K 6-H
Al-A(1.1.1) 6-H
Al-A(2.2.1)6-H
Al-A 4-CH
Al-K 4-CH2
6-H
SB
4-CH2
2-CH3
Al-A 2-CH3 ((1.1.1),(2 2 1)
Al-K(2 2 1) 2-CH3
(c)
-775
-645
-639
-637
-626
-362
-277
-108
-82
-48
-29
-4
H0

Figure 1

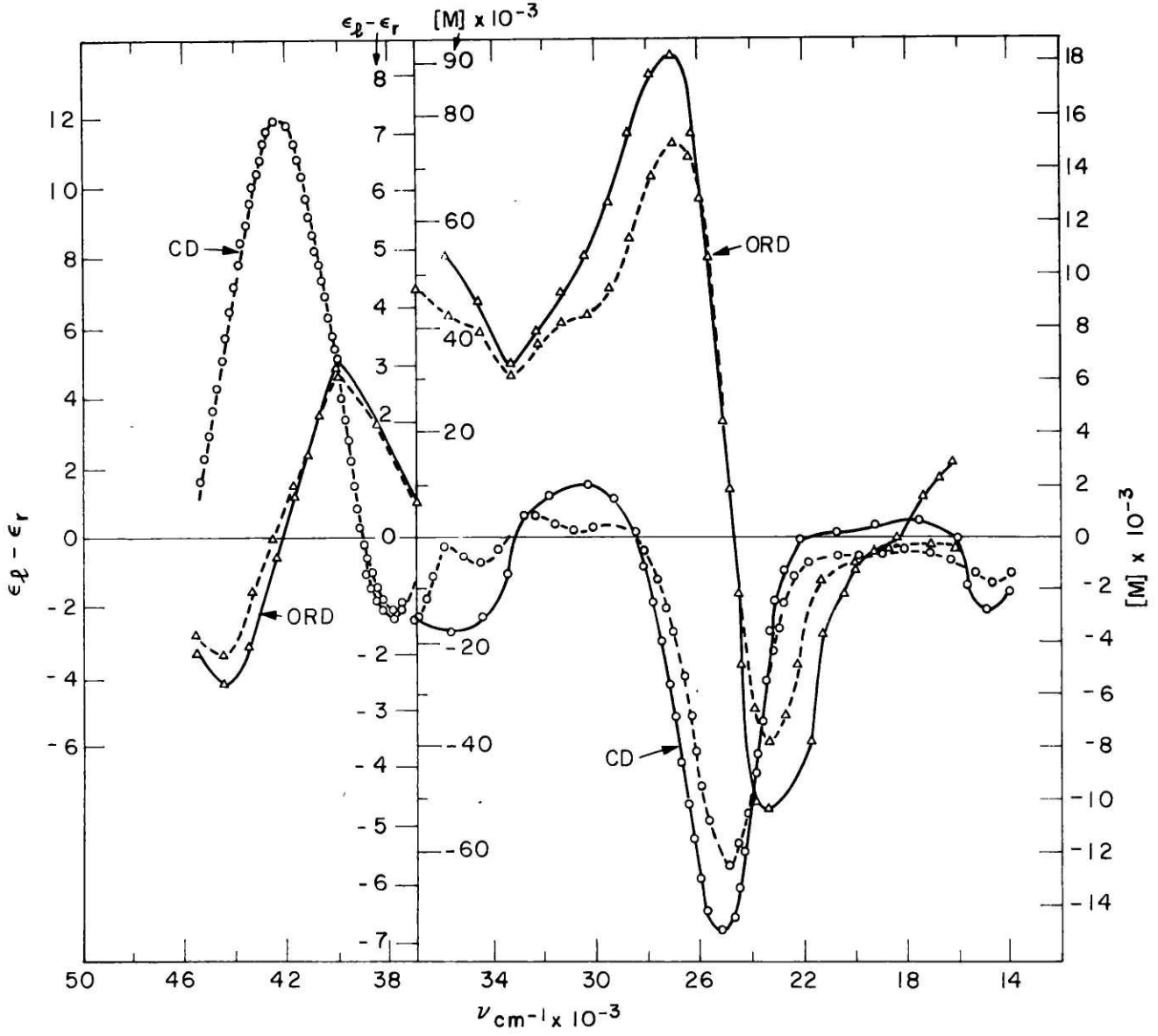
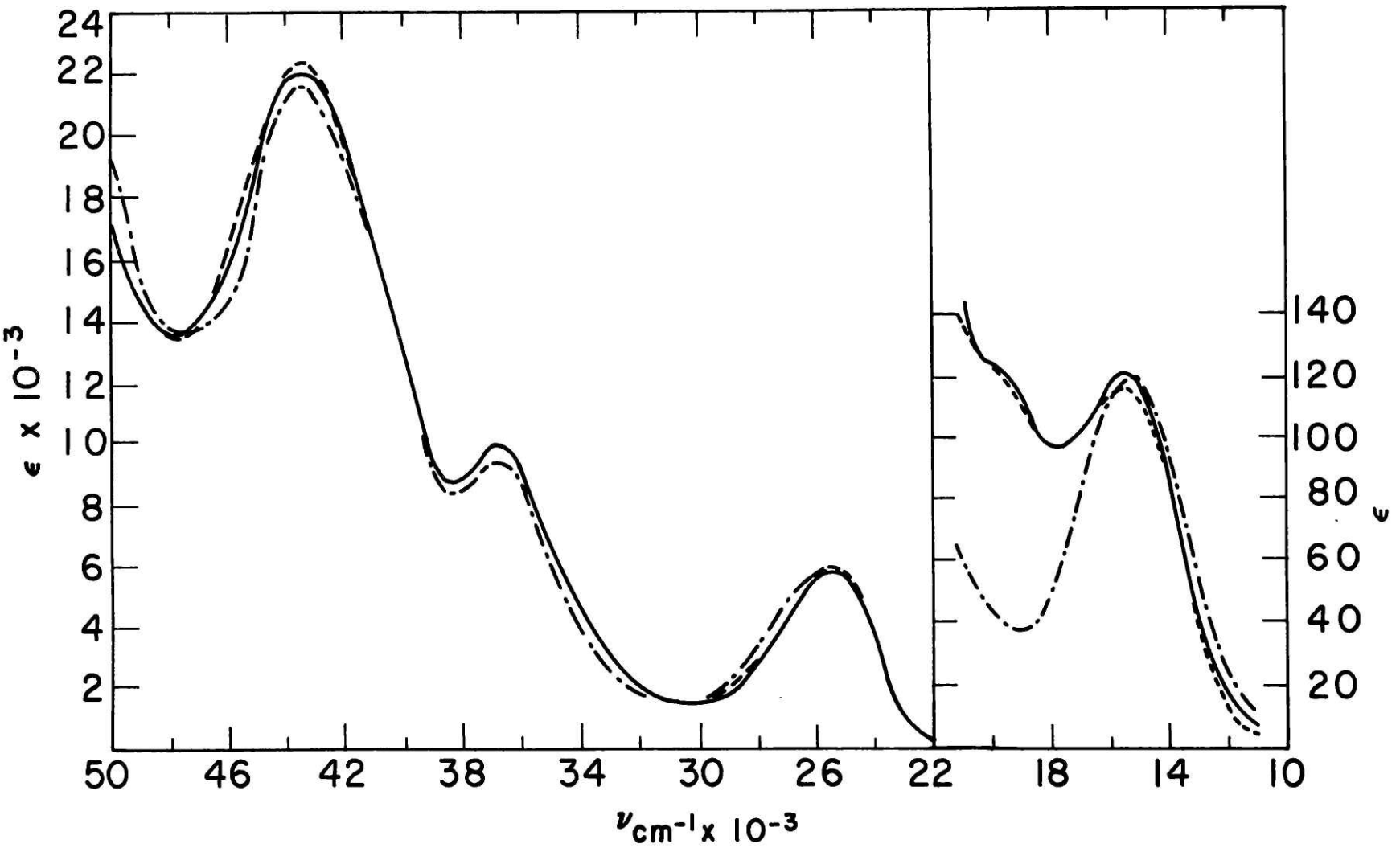

$\epsilon_l - \epsilon_r$
[M] x 10^{-3}
CD
ORD
ORD
CD
$\epsilon_l - \epsilon_r$
[M] x 10^{-3}
$\nu_{cm^{-1}} \times 10^{-3}$

Figure 2


24
22
20
18
16
14
12
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8
6
4
2
ε x 10⁻³
140
120
100
80
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ε
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34
30
26
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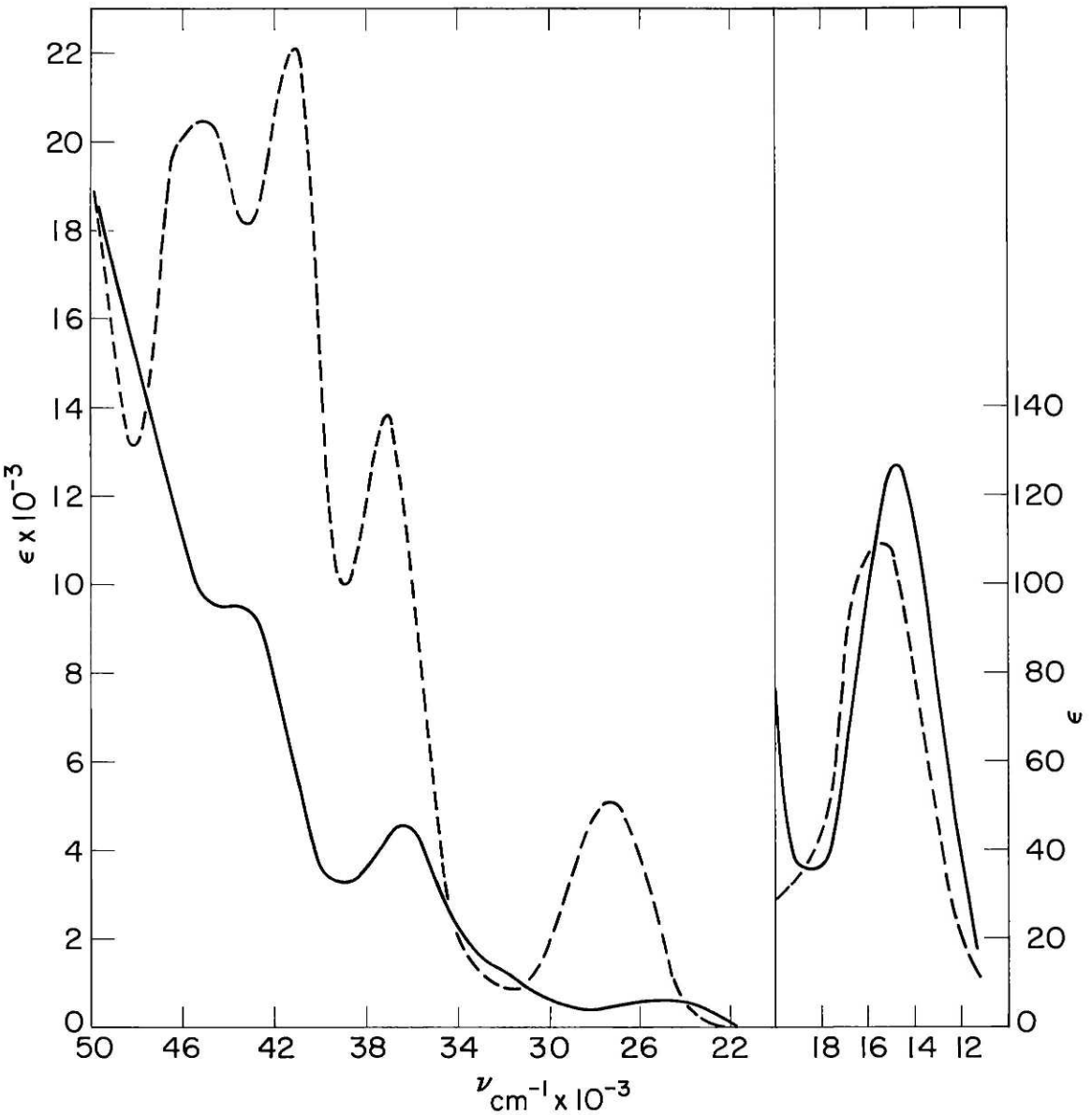
18
14
10
ν cm⁻¹ x 10⁻³

Figure 3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ε x 10⁻³
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40
20
0
ε
50
46
42
38
34
30
26
22
18
16
14
12
ν cm⁻¹ x 10⁻³

Figure 4

REFERENCES PART I

1. R. H. Holm, "Vitamin B_6 Complexes," in "Inorganic Biochemistry," G. L. Eichhorn, Ed., Elsevier Publishing Company, Amsterdam, 1972, Chapt. 31.
2. F. A. Robinson, "The Vitamin Cofactors of Enzyme Systems," Pergamon Press, Oxford, 1966, Chapt. V.
3. A. F. Wagner and K. Folkers, "Vitamins and Coenzymes," Interscience Publishers, New York, N. Y., 1964, Chapt. IX.
4. E. E. Snell, Vitamins and Hormones, 16, 77 (1958).
5. cf. Collected papers in Vitamins and Hormones, 22, 361-884 (1968).
6. E. E. Snell, J. Am. Chem. Soc., 67, 194 (1945).
7. D. E. Metzler and E. E. Snell, J. Am. Chem. Soc., 74, 979 (1952).
8. P. Fasella, G. G. Hammes, and B. L. Vallee, Biochim. Biophys. Acta, 65, 142 (1962).
9. K. S. Bai and D. L. Leussing, J. Am. Chem. Soc., 89, 6126 (1967).
10. D. Hopgood and D. L. Leussing, J. Am. Chem. Soc., 91, 3740 (1969).
11. M. E. Farago and T. Matthews, J. Chem. Soc. A, 609 (1970).
12. J. Baddiley, Nature (London), 170, 711 (1952).

13. D. E. Metzler, J. B. Longenecker, and E. E. Snell, J. Am. Chem. Soc., 76, 639 (1954).

14. H. N. Christensen, J. Am. Chem. Soc., 79, 4073 (1957).

15. L. F. Davis, F. Roddy, and D. E. Metzler, J. Am. Chem. Soc., 83, 127 (1961).

16. G. N. Weinstein, M. J. O'Connor and R. H. Holm, Inorg. Chem., 9, 2104 (1970).

17. D. Heinert and A. E. Martell, J. Am. Chem. Soc., 85, 1334 (1963).

18. R. P. Houghton and D. J. Pointer, J. Chem. Soc., 3302 (1964).

19. A. Nakahara, Bull. Chem. Soc. Japan, 32, 1195 (1959).

20. Y. Nakao, S. Sasaki, K. Sakurai, and A. Nakahara, Bull. Chem. Soc. Japan, 40, 241 (1967).

21. Y. Nakao, K. Sakurai, and A. Nakahara, Bull. Chem. Soc. Japan, 40, 1536 (1967).

22. M. J. O'Connor, R. E. Ernst, J. E. Schoenborn, and R. H. Holm, J. Am. Chem. Soc., 90, 1744 (1968).

23. T. Ueki, T. Ashida, Y. Sasada, and M. Kakudo, Acta Cryst. 22, 870 (1967).

24. J. F. Cutfield, D. Hall and T. N. Waters, Chem. Commun., 785 (1967).

25. G. A. Bentley, J. M. Waters and T. N. Waters, Chem. Commun., 988 (1968).

26. B. E. C. Banks, A. A. Diamantis and C. A. Vernon, J. Chem. Soc., 4235 (1961).

27. D. E. Metzler, M. Ikawa, and E. E. Snell, J. Am. Chem. Soc., 76, 648 (1954).

28. E. H. Abbott, personal communication to R. H. Holm.

29. J. Olivard, D. E. Metzler, and E. E. Snell, J. Biol. Chem., 199, 669 (1952).

30. E. H. Abbott and A. E. Martell, J. Am. Chem. Soc., 92, 5845 (1970).

31. M. Ando and S. Emoto, Bull. Chem. Soc. Japan, 42, 2624, 2628 (1969).

32. (a) J. B. Longenecker and E. E. Snell, Proc. Natl. Acad. Sci. U. S., 42, 221 (1956). (b) J. B. Longenecker and E. E. Snell J. Am. Chem. Soc., 79, 142 (1957).

33. G. L. Eichhorn and J. W. Dawes, J. Am. Chem. Soc., 76, 5663 (1954).

34. P. Fasella, H. Lis, N. Siliprandi and C. Baglioni, Biochim. Biophys. Acta, 23, 417 (1957).

35. O. A. Gansow and R. H. Holm, J. Am. Chem. Soc., 90, 5735 (1968).

36. O. A. Gansow and R. H. Holm, J. Am. Chem. Soc., 91,573 (1969).

37. O. A. Gansow and R. H. Holm, J. Am. Chem. Soc., 91 5984 (1969).

38. E. H. Abbott and A. E. Martell, Chem. Commun., 1501, (1968).

39. E. H. Abbott and A. E. Martell, J. Am. Chem.Soc.,91, 6866 (1969).

40. E. H. Abbott and A. E. Martell, J. Am. Chem. Soc., 91, 6931 (1969).

41. Y. Matsushima and A. E. Martell, J. Am. Chem. Soc., 89, 1322, 1331 (1967).

42. A. E. Martell and Y. Matsushima, in ref. 5, pp. 33-52.

43. T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," vol. II, W. A. Benjamin, Inc., New York (1966).

44. P. Pfeiffer, W. Offerman, and H. Werner, J. Prakt. Chem., 159, 313 (1942)

45. D. Heinert and A. E. Martell, Tetrahedron, 3, 49 (1958).

46. D. Heinert and A. E. Martell, J. Am. Chem. Soc., 81, 3933 (1959).

47. R. G. Bates, "Determination of pH, Theory and Practice," John Wiley and Sons, Inc., New York, N. Y., 1964, Chapt. 8.

48. G. A. Auld and A. Davison, Inorg. Chem., 7, 306 (1968).

49. Y. Matsuo, J. Am. Chem. Soc., 79, 2011 (1957).

50. Yu. M. Torchinskii, Biochemistry (USSR), 31, 909 (1966).

51. Y. Matsushima and A. E. Martell, J. Am. Chem. Soc., 89, 1322 (1967).

52. Y. Matsushima, Chem. Pharm. Bull., 16, 2143 (1968).

53. Yu. M. Torchinskii and L. G. Koreneva, Dokl. Biochem., 155, 110 (1964), Biochem. (USSR), 30, 31 (1965).

54. M. Ikawa and E. E. Snell, J. Am. Chem. Soc., 76, 653 (1954).

55. D. L. Leussing and N. Huq, Anal. Chem., 38, 1388 (1966).

56. R. B. Johns and D. Whelan, Australian J. Chem., 19, 2143 (1966).

57. H. Kanatomi and I. Murase, Inorg. Chem., 11, 1356 (1972).

58. A. P. Terent'ev and N. I. Gusar, J. Gen. Chem. USSR, 35, 124 (1965).

59. This compound was prepared previously but the synthetic conditions were not specified.[20]

60. G. O. Carlisle, J. K. Ganguli, and L. J. Theriot, Inorg. Nucl. Chem. Letters, 7, 527 (1971).

61. H. C. Dunathan, L. Davis, P. G. Kury, and M. Kaplan, Biochemistry, 7, 4532 (1968).

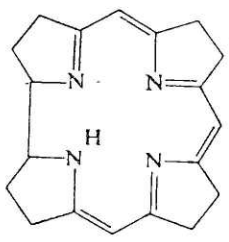
62. M. E. Ayling, H. C. Dunathan, and E. E. Snell, Biochemistry, 7, 4537 (1968).

PART II

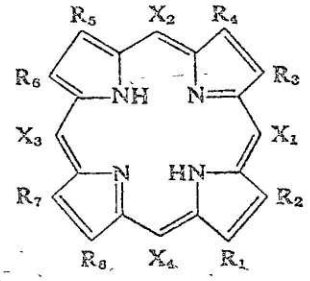
Synthesis of Tetraaza-[14],[15], and [16]-Macrocycles —— Potential Models for Porphyrins and Corrins

Introduction

Efforts to obtain synthetic ring systems resembling naturally occuring macrocycles such as the corrins (1) and porphyrins (2) have led to the recent preparation of



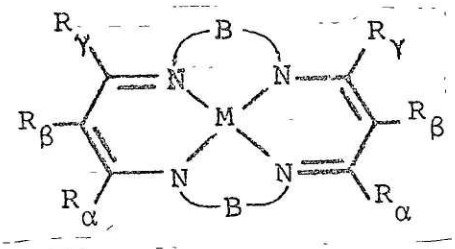
1



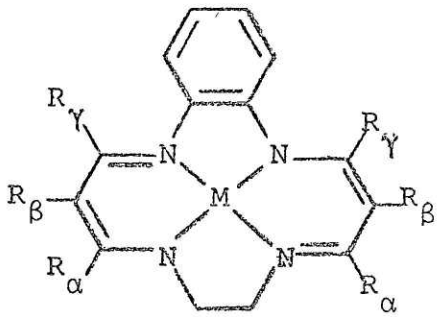
2

a large number of new macrocyclic ligands and their metal(II, III) complexes.[1-4] Although the natural macrocyclic complexes usually contain four conjugated six-membered rings or three six- and one five-membered ring (6-6-6-6 and 6-6-6-5 types, respectively), the majority of the synthetic macrocycles are of the 6-5-6-5 type. These complexes can be classified according to the degree of unsaturation of the π-electronic

structure internal to the chelate rings. They range from the completely unsaturated 16π-electron systems, 3[5-8] and 4[9] to the completely saturated system 11[10] (and C-methyl derivatives thereof[11]) and include the 14-π (5[12] and 6[13,14]), 12-π (7[15,16] and 8[9,12,17,18]), 8-π[11,19,20] (9), and 4-π[11,21,22] (10) systems.. The 6-π and 2-π complexes derived from 10 have also been prepared.[11,19] Complex 8, ($R_\alpha = R_\gamma = CH_3$, $R_\beta = H$)



3 B = o-C_6H_4
4 B = CH=CH



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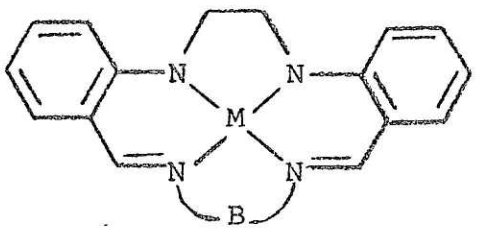
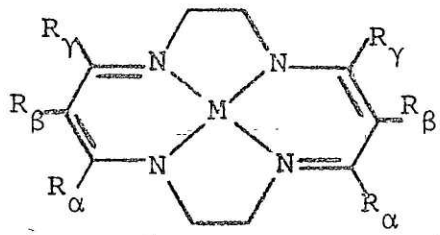


6 B = o-C_6H_4
7 B = $(CH_2)_2$



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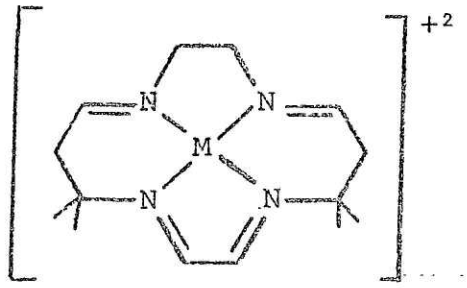
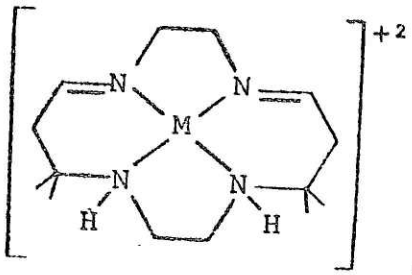
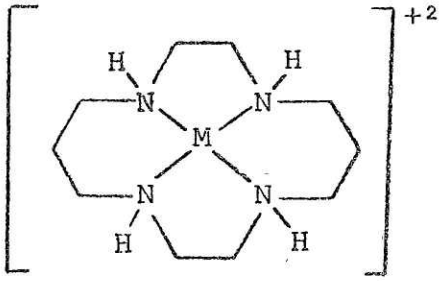


9 (cis, trans)



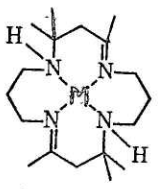
10 (cis, trans)



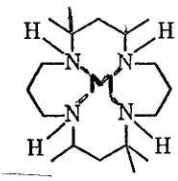
11

is of particular interest because it contains no functional groups (e.g., R_β = COR or COOR), and can be successfully dehydrogenated to the corresponding 16-π complex (4), which is completely conjugated.[9]

The 6-6-6-5 and 6-6-6-6 complexes which have been reported can be classfied according to their ring substituents. The "Curtis macrocycles"[11] (12) result from the condensation of an aliphatic aldehyde or ketone with a diamine in the presence of a metal ion (Ni(II), Cu(II)). The resulting 4-π complexes[11,23] can be hydrogenated to the fully saturated system (13),[11,24] but obviously can never be converted to fully conjugated species because of gem-dimethyl substitution in the

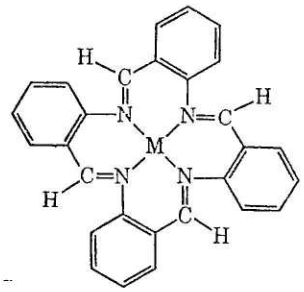


12 (cis or trans)



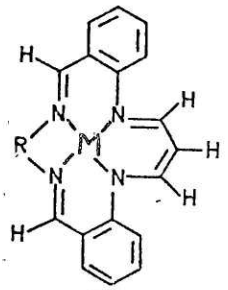
13

4- and 12-positions. The second group of complexes (14-16) contains benzo units fused to the chelate rings and results from the self-condensation of o-aminobenzaldehyde (14[25]) and other condensation reactions of this compound and its derivatives affording (15[26]) and (16[14]). All of the complexes of the third type contain an activating group, COR or COOR, in



, M = Ni, Cu

14



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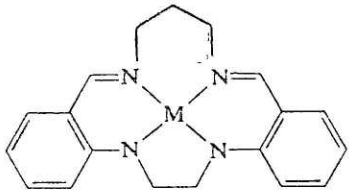
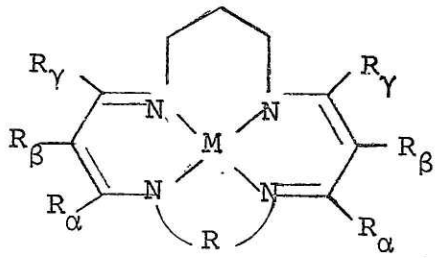
R = -CH₂·CH₂-
R = -CH(Me)·CH₂-
R = *o*-phenylene
R = -CH₂·CH₂·CH₂-



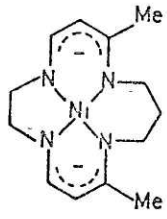
16

the β-position (17).[12,17] Macrocycles 12-17 all have fundamental disadvantages as



17 R = $(CH_2)_{2,3}$

models for thennaturally occuring macrocycles which are both highly conjugated and symmetrical. The benzene ring in complexes 14-16 almost certainly changes the electronic structure of the molecule from that in 1 and 2. Complex 17 has a 12-π ligand system and probably could not be oxidatively dehydrogenated to the 14- or 16-π system of 1 or 2, respectively, because of the possibly interfering functional groups R_β = COR, COOR. In a recent preliminary communication Hipp and Busch[27] reported the removal of these carbonyl-containing groups with mineral acids and subsequent deprotonation of the resulting cation, to form the 12-π system,



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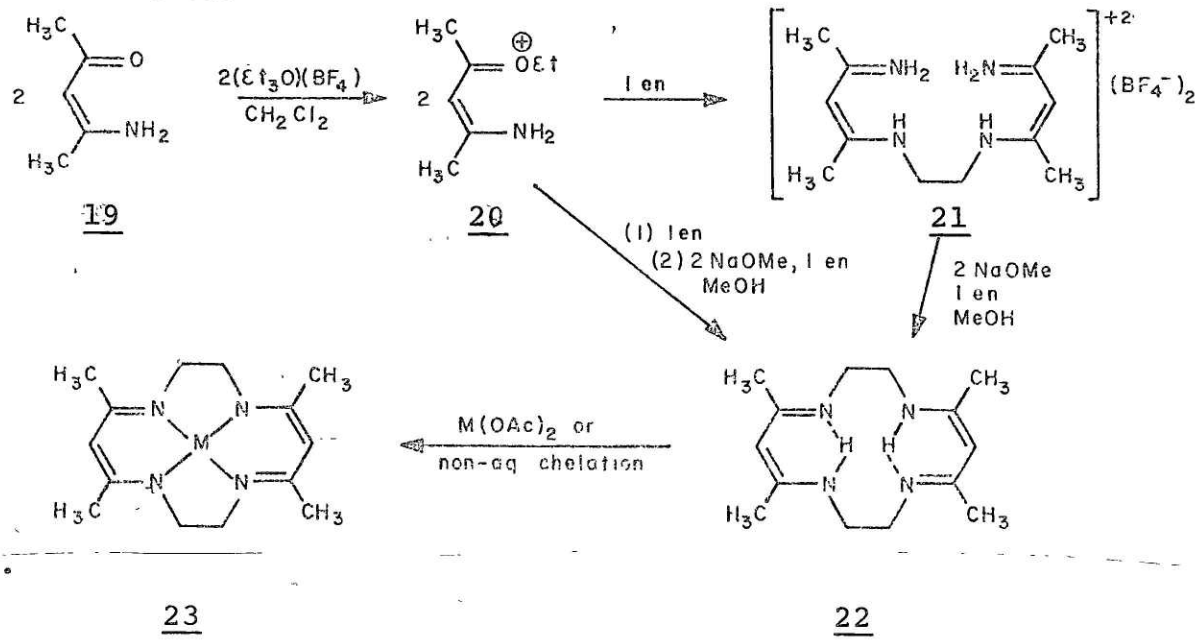
18, which has the potential for being oxidatively dehydrogenated to a 14-π model for corrin.

The objective of the research presented in this part of the thesis has been to find a general method for the synthesis of symmetrical 6-5-6-5, 6-5-6-6, and 6-6-6-6 macrocyclic, tetraaza complexes which could subsequently be oxidatively dehydrogenated to yield 14-π and 16-π systems similar to those of the naturally occuring macrocycles. The most logical route to suitable 6-5-6-6 and 6-6-6-6 ligands appeared to be an extension of the synthetic method employed by Truex and Holm[9] to prepare the 6-5-6-5 ligand 22. However, when

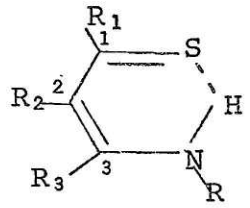


19 20 21

23 22

a preparation parallel to that outlined above was attempted using trimethylenediamine instead of ethylenediamine the only product isolated was the trimer $(C_7H_{12}N_2)_3$ (cf. experimental section).

It has been shown that β-aminothiones (24) can undergo



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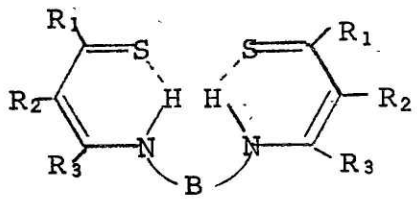
nucleophilic amine attack at C_1 to afford diamines.[28-30] Such reactions suggest a synthetic route to the tetraaza macrocycles via a β-aminothione intermediate. β-aminothiones with a variety of R substituents[28-37] may be prepared from dithiolium salts by direct reaction with monoamines or from O-alkyl β-ketoamine cations and sodium hydrosulfide.[36] The former reaction was considered preferable, since the latter reaction yields a mixture of the S-N and O-N ligands which is sometimes difficult to separate.[38] Ethylenediamine and o-phenylenediamine have been shown to react with a 3,5-diphenyl-1,2-dithiolium salt to give the tetradentate ligand 25 ($R_1 = R_3 = C_6H_5$, $R_2 = H$).[33] Metal complexes of 25 with $R_2 = H$ and $R_1 = R_3 \neq C_6H_5$[33]

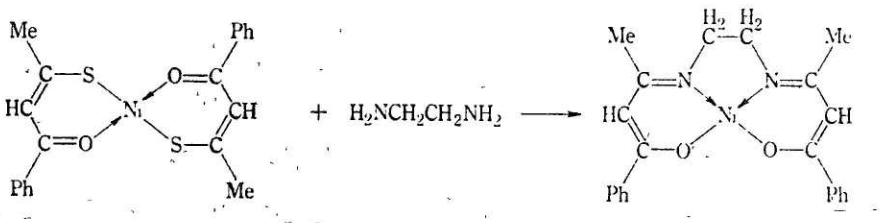


B = C_6H_4
B = $(CH_2)_2$

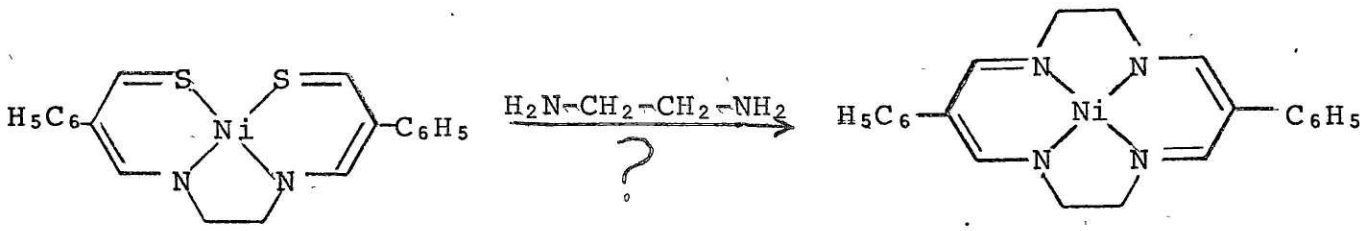
25

or $R_1 = R_3 = CH_3$, B = $(CH_2)_2$,[39] have been reported, but little experimental detail was given. Therefore, before embarking on experiments aimed at closing a symmetrical bis-β-thioamine, ligands of type 25, B = $(CH_2)_{2,3}$, were prepared from 3-phenyl-1,2-dithiolium perchlorate. The ligands and nickel(II) complexes formed as expected, the nucleophilic amine attack occuring at the carbon bonded to hydrogen[28,35] (R_1= C_6H_5, $R_2 = R_3$ = H).

The symmetrical dithiolium salt, 4-phenyl-1,2-dithiolium perchlorate, was chosen as the starting material for more extensive synthetic studies for several reasons. First, it can be made in high yield from inexpensive, easily obtainable starting materials, sulfure and α-methylstyrene,[40,41] and, unlike 3,5-dimethyl-1,2-dithiolium perchlorate,[42] is not explosive. It also offers two possible routes to the macrocycle once 25 (R_1=R_3= H, R_2 = C_6H_5, B = $(CH_2)_2$) is formed. The reaction of bis(3-thiolo-1-phenylbut-2-en-1-one)-nickel(II), 26, with ethylenediamine to yield bis(benzoylacetone)-ethylenediimine)nickel(II), 27,[43] suggested one possible synthetic approach to the closed macrocycle. If N,N'-bis[(2-thioformyl-2-phenylvinyl)ethylenediamine]nickel(II), 28, is reacted

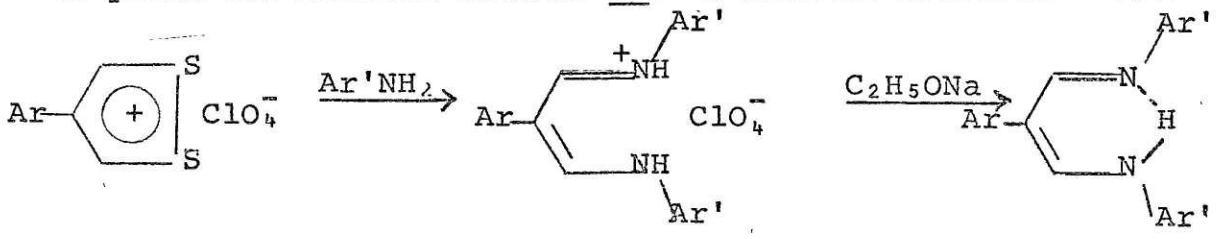


26 27



28 29

with ethylenediamine and the reaction proceeds as for the O-S ligand system, the product should be the macrocyclic complex 29. This reaction sequence should also be possible employing trimethylenediamine as the base to form either a 6-5-6-6 or a 6-6-6-6 complex. The second approach involves a non-template ligand synthesis. The 4-aryl-1,2-dithiolium perchlorates are the only dithiolium saltssreported to react with two moles of aniline[29] or 3-methylaniline[28] to form a diamine perchlorate salt, 30,[28,29] which can be deprotonated to yield the neutral diamine 31. A similar reaction between



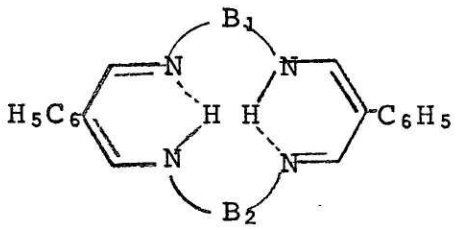
30 31

Ar = C_6H_5, Ar' = C_6H_5, pCH_3-C_6H_4

Ar = pCH_3-C_6H_4, Ar' = pCH_3-C_6H_4

4-phenyl-1,2-dithiolium perchlorate and ethylene or trimethylenediamine would be expected to result in the formation

of the desired macrocyclic ligand 32. Synthesis of the corresponding 6-5-6-5, 6-5-6-6 and 6-6-6-6 macrocycles and their



32 B_1, B_2 = $(CH_2)_2$ or $(CH_2)_3$

Ni(II) complexes were accomplished by this method and are described in the following section.

Experimental Section

Preparation of Compounds. The 3- and 4-phenyl-1,2-dithiolium perchlorates were prepared by published methods.[40,41] Analytical data for new compounds are given in Table I. Pmr and electronic spectral data are summarized in Tables II and III. Structural formulas are set out in the text.

6,8,14,16,22,24-Hexamethyl-1,5,9,13,17,21-hexaazacyclotetracosa-5,7,13,15,21,23-hexaene, H_3(MeHMe(tm)$_3$). To a solution of 30.0 g (0.30 mol) of 4-aminopent-3-en-2-one[44] in 200 ml dry dichloromethane was added 57.0 g (0.30 mol) of triethyloxonium tetrafluoroborate dissolved in 150 ml of dry dichloromethane. The solution was stirred under an atmosphere of dry nitrogen for 30 min. Trimethylenediamine (11.2 g, 0.15 mol), distilled from sodium hydroxide, was added over a 30 min period. The bright

yellow solution was stirred for an additional 3 hr at room temperature. Dichloromethane was removed under reduced pressure and replaced with 400 ml of absolute methanol. To this solution was added 16.2 g (0.30 mol) of sodium methoxide in 150 ml of methanol and immediately thereafter an additional 11.2 g (0.15 mol) of trimethylenediamine was introduced. The reaction was allowed to proceed for 4 hr with stirring during which time ammonia was evolved. Half of the methanol was then removed under reduced pressure and the solution filtered. No product was recovered from the filtrate. White crystals were obtained by extracting the residue with 300 ml of hot chloroform, reducing the volume, and adding methanol. The solid was recrystallized from absolute ethanol to afford 0.50 g of pure product in very low yield (1.2%). No other product was isolated from this reaction. Molecular weight, calculated 414; found 407 (osmometry, chloroform solution). The mass spectrum of a sample independently prepared by S. Koch revealed an intense parent ion peak at m/e 414.

N,N'-Bis(3-phenyl-3-thioxo-1-propenyl)ethylenediamine, H_2(S-PhHH(en)) (25, R_1 = Ph, R_2 = R_3 = H, B = $(CH_2)_2$). 3-Phenyl-1,2-dithiolium perchlorate[41] (2 g, 7 mmol) was suspended in 50 ml absolute ethanol and heated with ethylenediamine (0.4 g, 7 mmol). The mixture was stirred at room temperature for 1 hr, warmed to 60-70° for 3 hr, and the product filtered off. Recrystallization from chloroform yielded orange crystals (0.5 g, 20% yield) which were dried in vacuo for 3 days at 60°.

N,N'-Bis(3-phenyl-3-thioxo-1-propenyl)trimethylenediamine, H_2(S-PhHH(tm)) (25, R_1 = Ph, R_2 = R_3 = H, B = $(CH_2)_3$). was prepared by the same procedure used for the ethylenediamine analog, except that the orange crystalline material was recrystallized twice from a 4:1 chloroform:heptane mixture to afford 0.5 g of product (20% yield).

N,N'-Bis(3-phenyl-3-thioxo-1-propenyl)ethylenediamino-Ni(II), Ni(S-PhHH(en)). To a suspension of the ligand H_2(S-PhHH(en)) (1.6 g, 4.5 mmol) in 20 ml of hot chloroform a solution of nickel acetate tetrahydrate (1.2 g, 4.8 mmol) in 25 ml methanol was added dropwise. The mixture was refluxed for 1 hr and filtered hot to afford a brown powder (1 g, 60% yield) which was purified by recrystallization from acetone, followed by drying in vacuo for 2 days at 60° to yield 0.4 g of pure product. The complex was too insoluble for pmr measurements.

N,N'-Bis(3-phenyl-3-thioxo-1-propenyl)trimethylenediamino-Ni(II), Ni(S-PhHH(tm)). This complex was prepared by the same procedure used for the ethylenediamine analog. The initial product (0.3 g, 70% yield) however, was extremely impure (mp = 55-60°), but was purified by recrystallization from acetone and drying overnight in vacuo at room temperature to afford 0.1 g of complex.

N,N'-Bis(2-thioformyl-2-phenylvinyl)ethylenediamine, H_2(S-PhH(en)), 36). To a suspension of 4-phenyl-1,2-dithiolium perchlorate[41,42] (20.0 g, 70 mmol) in 350 ml absolute ethanol, ethylenediamine (3.1 g, 52 mmol) in 45 ml ethanol was added dropwise over a 1 hr period. The product was deposited as a yellow powder during

the course of the reaction. Filtration of the solution yielded 12.0 g (>90% yield) of the crude product (mp ~150°), 1.0 g of which was purified by recrystallization from chloroform-methanol and from benzene to produce 0.1 g of yellow crystals which were dried for 2 days in vacuo at 80°. The infrared spectrum is shown in Fig. 1. The pmr spectrum was obtained in a Fourier transform mode due to low solubility.

N,N'-Bis(2-thioformyl-2-phenylvinyl)ethylenediamino-Ni(II), Ni(S-HPhH(en)), (28). This complex was prepared in 45% yield from the crude H_2(S-HPhH(en)) ligand by the same procedure used for Ni(S-PhHH(en)). Purification was accomplished by recrystallization from xylene and then from acetone followed by drying in vacuo to yield golden brown crystals. Infrared and pmr spectra are shown in Figs. 2 and 9, respectively.

6,13-Diphenyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene, H_2(HPhH(en)$_2$), (37). To a well-stirred suspension of crude H_2(S-HPhH(en)) (5.0 g, 14 mmol) in 175 ml of hot benzene, ethylenediamine (4.6 g, 78 mmol) in 40 ml benzene was added dropwise during a 1 hr period. The yellow solution was decanted to separate it from an orange oil which formed during the reaction and then cooled to room temperature, yielding a first crop of white crystals. A second crop was obtained by volume reduction of the filtrate followed by the addition of ethanol or methanol; total crude yield was 1.9 g (40%). Recrystallization of 0.6 g from chloroform gave 0.36 g of pure compound. The mass spectrum

revealed an intense parent ion peak at m/e 344. Infrared, pmr, and uv spectra are shown in Figs. 3, 10 and 13 respectively.

6,13-Diphenyl-1,4,8,11-tetraazacyclotetradeca-4,6,11,13-tetraene-nickel(II), Ni(HPhH(en)$_2$), (33). To a solution of the crude ligand (3.1 g, 9.0 mmol) in 10 ml of hot dimethylformamide was added nickel acetate tetrahydrate (2.5 g, 10.0 mmol). The resulting red solution was stirred at 120° for 1/2 hr. After cooling, the red crystalline compound was collected by filtration (3.0 g, 84% yield), purified by recrystallization from chloroform and dried overnight in vacuo at 80° to afford 2.7 g of product. This complex could not be prepared by the reaction of Ni(S-HPhH(en)) with ethylenediamine under a variety of conditions. Infrared, pmr and electronic spectra are presented in Figs. 4, 10, and 13, respectively. The pmr spectrum was taken in CS_2 because the CH_2 protons exchanged with deuterium from the solvent in $CDCl_3$ and CD_2Cl_2.

6,14-Diphenyl-1,4,8,12-tetraazacyclopentadeca-4,6,12,14-tetraene, H_2(HPhH(en)(tm)), (38). Trimethylenediamine (9.0 g, 12 mmol) in 75 ml benzene was added dropwise to a well-stirred suspension of crude H_2(S-HPhH(en)) (20.0 g, 5.7 mmol) in 700 ml of hot benzene. Following the 1 hr addition period, the orange solution was decanted from a red oil. Volume reduction to 300 ml and the addition of 300 ml of absolute ethanol, followed by cooling, led to the separation of the product as yellow crystals. Further crops were obtained by continued volume reduction followed by the addition of

ethanol, total yield 5.4 g, 26%. Contamination with H_2(HPhH-(tm)$_2$) (cf. preparation of this compound) increased with later crops. Two recrystallizations of 3.0 g of crude product from 3:1 v/v ethanol-chloroform yielded 1.9 g of a white crystalline material which gave a satisfactory elemental analysis (cf. Table I). The mass spectrum of this material, however, showed peaks at m/e 419, 372, H_2(HPhH(tm)$_2$), and 344, H_2(HPhH(en)$_2$), as well as at m/e 358 (parent ion peak). Repeated attempts to purify the compound by fractional recrystallization from ethanol or ethanol-chloroform failed. Thin layer chromatography on alumina or silica gel with a variety of solvents failed to indicate conditions under which chromatography would be successful in separating the 6-5-6-5 and 6-5-6-6 macrocyclic ligands. The infrared, pmr, and uvsspectra shown in Figs. 5, 11, and 14, respectively,,are of the analyzed compound.

6,14-Diphenyl-1,4,18,12-tetraazacyclopentadeca-4,6,12,14-tetraene-nickel(II), Ni(HPhH(en)(tm)), (34). The nickel complex was prepared from ligand which had been recrystallized once from 3:1 v/v ethanol-chloroform. The ligand (1.5 g, 4.2 mmol) was dissolved in 90 ml dimethylformamide at 75°, nickel acetate tetrahydrate (1.1 g, 4.5 mmol) added, and the reaction mixture stirred for 1/2 hr at 75°C. After cooling, the shiny,green crystalline material was collected by filtration (1.4 g, 82%), and dried in vacuo for 12 hrs at 140°. This sample analyzed satisfactorily. Calcd. for $C_{23}H_{24}N_4Ni$: C, 66.54; H, 5.83; N, 13.49. Found : C, 66.49; H, 5.85; N, 13.47. However, low resolution mass spec-

trometry showed impurity peaks at m/e 428 and 400, indicating the presence of a ca.3-4% impurity of $Ni(HPhH(tm)_2)$ and a ca. 13-14% impurity of $Ni(HPhH(en)_2)$, respectively. The nickel complex (0.2 g) was therefore purified by column chromatography with about 50% recovery (0.1 g). Two passes through a 39cm x 2.5cm silica gel PF_{254} column with a 2:1 v/v methylene chloride: cyclohexane eluant resulted in elimination of the m/e 428 peak and reduction of the m/e 400 peak to an intensity of less than 1% of the parent ion peak at m/e 414. No impurities above m/e 414 were observed. The product eluted as a narrow green band, leaving behind a brown material at the top of the column. The analysis, infrared, pmr and electronic spectra of the finally purified complex are presented in Table I and Figs. 6, 11 and 14,respectively. The pmr spectrum was obtained in CS_2, because in $CDCl_3$ and CD_2Cl_2 the CH_2 protons of the ethylenediamine moiety exchanged with deuterium and the CH_2 protons from trimethylenediamine were seen as broad peaks instead of sharp multiplets.

7,15-Diphenyl-1,5,9,13-tetraazahexadeca-5,7,13,15-tetraene, $H_2(HPhH(tm)_2)$, (39). Trimethylenediamine (25.3 g, 34.2 mmol) in 75 ml benzene was added dropwise over a 1/2 hr period to a well-stirred suspension of crude $H_2(S\text{-}HPhH(en))$ (20.0 g, 5.7 mmol) in 700 ml of hot benzene. The mixture was allowed to react a further 1/2 hr and the orange solution decanted from a red oil. Volume reduction to 300 ml, followed by the addition of 700 ml ethanol led to the separation of 0.7 g of yellow solid (mp 186-190°) which was mainly $H_2(HPhH(en)(tm))$. The desired product was obtained

by volume reduction to 100 ml, yielding a cream-colored powder (mp 128-140°), which was purified by two recrystallizations from 2:1 v/v chloroform-ethanol. Further crude product was obtained by removing all solvent, adding 50 ml of methanol, and filtering off the powdery material; total crude yield was 6.3 g (30%). This compound has also been prepared by the reaction of trimethylenediamine with H_2(S-HPhH(tm)).[45] The mp, mixed mp, and pmr, ir and uv spectra of the compound reported here are identical with those of the compound prepared by Tang and Holm[45] and characterized by a high resolution mass spectrum with parent ion peak at m/e 372. The ir, pmr, and uv spectra are presented in Figs. 7, 12, and 15, respectively.

7,15-Diphenyl-1,5,9,13-tetraazahexadeca-5,7,13,15-tetraene-nickel(II), Ni(HPhH(tm)$_2$), (35). The ligand employed in this preparation was crude material which was recrystallized once from 2:1 v/v chloroform-ethanol; all operations were performed in a nitrogen atmosphere. To a solution of H_2(HPhH(tm)$_2$) (2.0 g, 5.4 mmol) in 15 ml degassed dimethylformamide at 80°C was added 1.4 g (5.7 mmol) of nickel acetate tetrahydrate in 10 ml dimethylformamide. Upon the addition of 20 drops of trimethylenediamine, green crystals started to separate out of the solution. The reaction mixture was stirred at 80° for 22 hrs, cooled and filtered. The green microcrystalline solid (0.9 g, 39% yield) was washed with 3 x 10 ml degassed ethanol and dried *in vacuo* at room temperature for 16 hrs. If desired, the metal complex

can be recrystallized from dimethylformamide.[45] Using the ligand prepared from H_2(S-HPhH(tm)),[45] a metal complex can be obtained which has mp and infrared, pmr, and electronic spectra identical with those of the complex reported here (cf. Figs. 8, 12 and 15).

Physical Measurements. Electronic spectral data was obtained using a Cary Model 14 spectrophotometer. A Mechrolab Model 302 osmometer operating at 37° was used foremolecular weight measurements in solutions prepared with chloroform. Pmr spectra were obtained on either a Varian T-60 or a Hitachi Perkin-Elmer R-20B spectrometer using TMS asaan internal standard. Accurate chemical shifts for the macrocycles were determined using a frequency counter attached to the spectrometer. Infrared spectra in the 4000-1300 cm^{-1} and 1300-400 cm^{-1} ranges were recorded as Kel-F and nujol mulls, respectively, and calibrated at 1601 cm^{-1} and 906 cm^{-1} using a polystyrene strip.

Mass Spectra. Low resolution mass spectra were taken on a Hitachi Perkin-Elmer RMU-6D spectrometer operating at 70 eV. High-resolution mass spectra were determined using a CEC21-11B double-focusing spectrometer employing photoplate recording and operating at 70 eV. Tabulated below are the principal peaks in the parent ion region of the high-resolution spectra of H_3(MeHMe(tm)$_3$), H_2(HPhH(en)$_2$) and H_2(HPhH(en)(tm)). Given in the tabulation are the assigned isotopes and the observed and calculated exact masses for each.

$H_3(MeHMe(tm)_3)-C_{24}H_{42}N_6$

Ion^+	Obsd.	Calcd.
$^{12}C_{24}{}^{1}H_{40}{}^{14}N_6$	412.33105	412.33138
$^{12}C_{24}{}^{1}H_{41}{}^{14}N_6$	413.33961	413.33934
$^{12}C_{24}{}^{1}H_{42}{}^{14}N_6$	414.34694	414.34704
$^{12}C_{23}{}^{13}C_1{}^{1}H_{42}{}^{14}N_6$	415.34877	415.35036
$^{12}C_{22}{}^{13}C_2{}^{1}H_{42}{}^{14}N_6$	416.35429	416.35389

$H_2(HPhH(en)_2)-C_{22}H_{24}N_4$

Ion^+	Obsd.	Calcd.
$^{12}C_{22}{}^{1}H_{22}{}^{14}N_4$	342.18645	342.18444
$^{12}C_{22}{}^{13}C_1{}^{1}H_{22}{}^{14}N_4$	343.18938	343.18780
$^{12}C_{22}{}^{1}H_{24}{}^{14}N_4$	344.19979	344.20009
$^{12}C_{21}{}^{13}C_1{}^{1}H_{24}{}^{14}N_4$	345.20400	345.20344

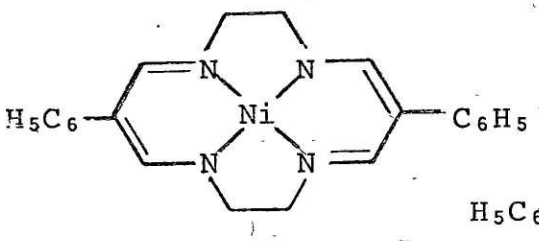
$H_2(HPhH(en)(tm))-C_{23}H_{26}N_4$

Ion^+	Obsd.	Calcd.
$^{12}C_{23}{}^{1}H_{26}{}^{14}N_4$	358.21480	358.21574
$^{12}C_{22}{}^{13}C_1{}^{1}H_{26}{}^{14}N_4$	359.21960	359.21910

The following masses together with the observed (calculated) relative intensities were obtained under low resolution in the parent ion region of Ni(HPhH(en)(tm)): 414,100(100); 415,29.5 (26.8); 416,41.5(39); 417,12.4(10.55); 418,6.7(5.36); 419,1.6 (1.08); 420,1.2(1.1).

Results and Discussion

Symmetrical 6-5-6-5 , 6-5-6-6, and 6-6-6-6 tetraaza macrocyclès and their Ni(II) complexes (33, 34, and 35, respectively) have been synthesized.



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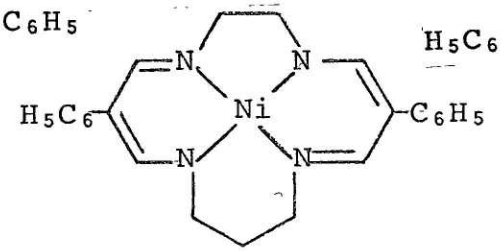

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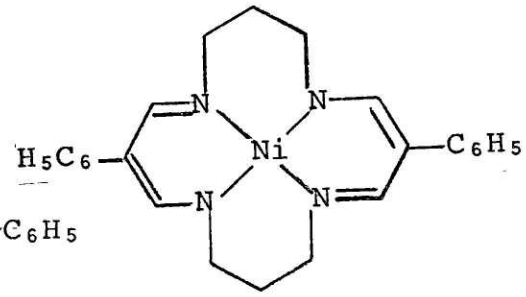

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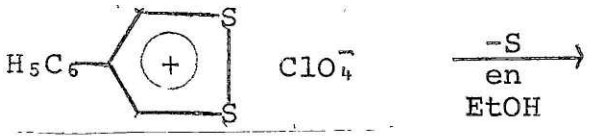
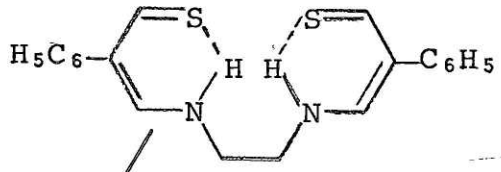
The reactions employed for the non-template ligand syntheses are set out below:





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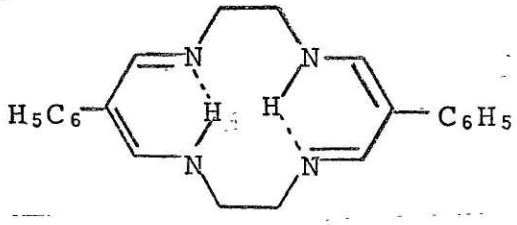

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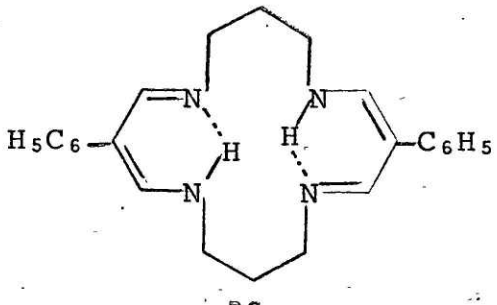
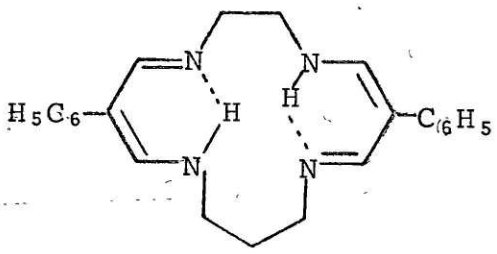
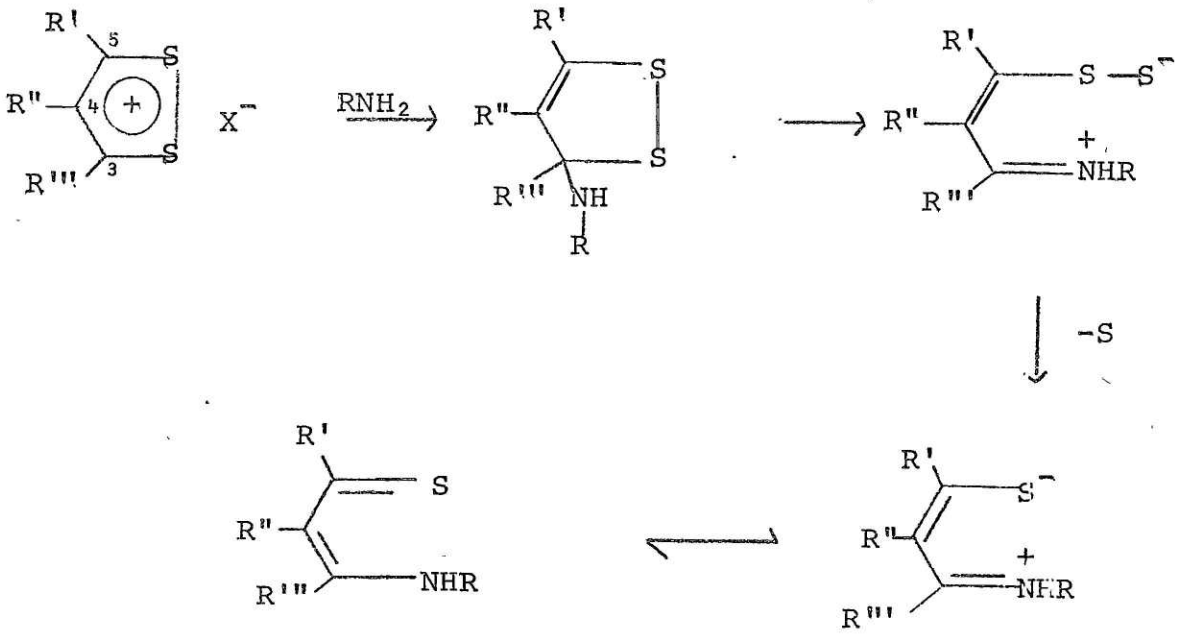


38 and



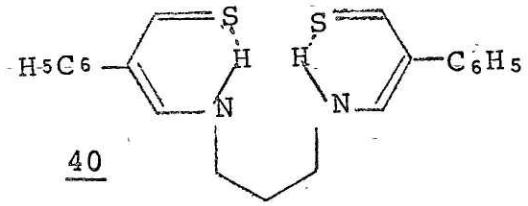
39

The addition of the diamine to the 1,2-dithiolium perchlorate salt is carried out in two steps. In the first step sulfur is liberated and the β-thioamine, 36, is isolated. Presumably the reaction proceeds by the mechanism proposed by Leaver et. al.[29] for nucleophilic attack at C_3 of 1,2-dithiolium salts:



In the second step of the reaction, nucleophilic attack by diamine at the thione carbons of 36 liberates hydrogen sulfide and results in macrocycle formation. The closure reaction could not successfully be carried out in one step in either benzene[45]

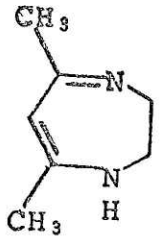
or ethanol. Reaction of 36 with trimethylenediamine yields two products, 38 and 39, which is formed as a result of amine exchange. The amount of each product formed depends on the mole ratio of trimethylenediamine used. The physical properties of the 6-6-6-6 macrocycle 39 are identical with those of the compound prepared by the reaction of H_2(S-HPhH(tm)),[45] 40, with trimethylenediamine and identified by mass spectrometry



40

as the dimer, m/e 372. Mass spectra of the 6-5-6-6 ligand, 38, revealed that both 37 and 39 had formed in the reaction, as well as the product. Also an unidentified impurity with m/e 419 was present. Although the desired 6-5-6-6 macrocycle was present, and the ligand analyzed satisfactorily, it could not be prepared free of the impurities revealed by mass spectrometry. Effort was therefore concentrated on purifying the nickel complex which , like the 6-5-6-5 and 6-6-6-6 complexes, was prepared by reaction of the ligand with nickel acetate tetrahydrate in dimethylformamide. The purification of Ni(HPhH(en)(tm)) was achieved by chromatography on silica gel, resulting in a complex whose mass spectrum showed the parent ion as the highest mass peak at m/e 414, and a less than 1% impurity of Ni(HPhH(en)$_2$) at m/e 400. The agreement of the observed and calculated relative intensities in the parent ion region of the low resolution spectrum of

$C_{23}H_{24}N_4Ni$ (cf. experimental section) supports the assignment of this peak to the nickel complex, Ni(HPhH(en)(tm)). Efforts to prepare the nickel complexes, 33 and 34, by the reaction of Ni(S-HPhH(en)) (28) with ethylenediamine and trimethylenediamine, respectively, were unsuccessful. The complex 28 is stable in refluxing xylene with excess ethylenediamine for 24 hrs, but forms a brown tar when refluxed in neat ethylenediamine or trimethylenediamine for the same period. At lower temperatures 28 is stable to neat amine. No evidence for the formation of the nickel macrocycles from Ni(S-HPhH(en)) was seen. In contrast Ni(S-HPhH(tm)) reacts with neat trimethylenediamine at 25° to eliminate nickel(II) as NiS, and form the macrocycle 39.[45] As mentioned in the introduction, the preparation of the 6-6-6-6 macrocycle $H_2(MeHMe(tm)_2)$ was attempted by a reaction scheme similar to that employed by Truex and Holm[9] for the synthesis of $H_2(MeHMe(en)_2)$, (8, $R_\alpha = R_\gamma = CH_3$, $R_\beta = H$). Molecular weight and spectral data were used by Truex and Holm to show that this compound was not the monomer 2,3-dihydro-5,7-dimethyl-1,4-diazepine[46] which has structure 41



41

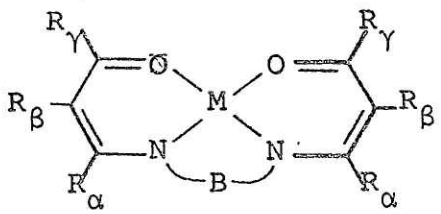
in weakly polar media.[47,48] The only compound isolated in the trimethylenediamine reaction is thought to be the trimer, $H_3(MeHMe(tm)_3)$. The pmr spectrum (cf. Table II) is in accord with this structure or that of the desired compound, $H_2(MeHMe-(tm)_2)$, but both the solution molceular weight (407), and the parent ion mass spectral peak at m/e 414 indicate that a trimer has formed.

Electronic and pmr spectral data (cf. Tables II and III and Figures 9-15) are consistent with the proposed ligand (37-39) and metal complex (33-35) structures.[9] Both the 6-5-6-6 and 6-6-6-6 nickel complexes exhibit a d-d band near 16,500 cm^{-1}, whereas the lowest energy ligand field transition for the 6-5-6-5 complex occurs at 18,200 cm^{-1}. The NH proton resonances which sometimes are either absent,[48-50] or are seen as broad peaks[9,50] in the pmr spectra of β-iminoamines, cannot be found in the spectra of 37 and 39. The strongly deshielded resonance of the NH proton (-10.53 ppm) in 38 is indicative of the existence of hydrogen bonded chelate rings. Upon nickel complex formation the CH and α-CH_2 resonances shift to higher field. The spectra of the complexes consist of the β-H and phenyl resonances at about -7 ppm (relative intensities 4 and 12, respectively), the α-CH_2 absorption at about -3.3 ppm (relative intensity 8), which is a singlet in 33, a triplet plus a singlet in 34 (tm plus en resonances), and a triplet in 35, and the β-CH_2 multiplet at about -1.90 ppm (relative intensity 2 in 34

and 4 in 35). Exact chemical shift data are presented in Table II and the pmr spectra are shown in Figures 9-12. Spectra of the 6-5-6-5 and 6-5-6-6 complexes cannot be taken in the deuterated solvents $CDCl_3$ and CD_2Cl_2 because the methylene protons of the ethylenediamine moiety exchange with deuterium from the solvent within the time necessary to prepare the solution. The sharp singlet at -3.35 ppm in the spectrum of 33 and at -3.25 ppm in the spectrum of 34 in CS_2 is completely absent in the deuterated solvent. Also, the tm-α-CH_2 proton resonance in 34 appears as a broad band in $CDCl_3$ or CD_2Cl_2, instead of the sharp triplet observed in CS_2, or in the spectrum of the ligand in deuterated solvents. The only other example of the exchange of the methylene protons of a 5-membered ring in a macrocyclic complex involved the exchange of the CH_2 protons α to the imine bond in 9, which absorb at 4.68 ppm.[51] The pmr spectrum of this salt showed a loss of the resonances from these methylene protons after 24 hrs in neutral D_2O, or after 5 min in D_2O at pD10.[51] In comparison the methylene protons of the five-membered ring in 33 and 34, which exchange in $CDCl_3$ and CD_2Cl_2 within minutes, are extremely labile.

All of the 6-6-6-6 and 6-5-6-6 macrocyclic complexes previously reported[3] were prepared in the presence of metal ions to form the metal complexes directly. The syntheses described here provide a convenient, two step, non-template route to symmetrical tetraaza macrocycles which have been reacted to form Ni(II) and Cu(II)[45] (6-6-6-6) complexes and presumably

will form stable complexes with other metal ions. This synthetic route not only affords all three macrocycles (6-5-6-5, 6-5-6-6, and 6-6-6-6) in moderate yield from a readily available, inexpensive 1,2-dithiolium salt, but also has the advantage of not dictating the substituents on the macrocycle ring. In the Curtis[11] macrocycles (12), there is always gem-dimethyl substitution in the 4- and 12-positions, while in the Jäger[12,17] 15- and 16-member ring macrocycles (17) R_β always is either COR or COOR; β-ketoamine complexes 42 (M = Ni, Cu)



42

will not cyclize with aliphatic diamines unless R_β is an activating group.[9] The generality of this reaction was increased by Hipp and Busch[27] when they removed R_β to form 18, which like 34 has the maximum symmetry possible for a 6-5-6-6 macrocycle C_{2v}, and has no functional groups.

One of the principal interests in macrocyclic tetraaza complexes of the 6-6-6-6 and 6-5-6-6 types is concerned with their transformations into species whose conjugated ligand structures are related to those of the natural macrocycles such as porphyrins and corrins. The synthesis of complexes with conjugated ligand systems by the oxidative dehydrogenation,[52] of 34 and 35 should be possible. Such reactions with

M(MeHMe(en)$_2$), M = Ni(II) and Cu(II), employing trityl tetrafluoroborate as the oxidizing agent yield the completely conjugated 16-π complex M(MeHMe-2,9-diene).[9] Preliminary studies indicate that Ni(HPhH(tm)$_2$)[45] and Ni(HPhH(en)(tm)) do react with trityl cation. The products of these reactions, however, have not yet been identified. Research into the method and the mechanism of the oxidative dehydrogenation of the metal complexes is being continued. The research described in Part II of this thesis thus provides the starting point for a long-term project which will include the synthesis of a number of macrocycles by the reaction of diamines and 1,2-dithiolium salts, the preparation of conjugated-ligand, symmetrical macrocyclic complexes of the HPhH type, and an in-depth study of the physical properties, particularly the redox behavior of these complexes.

Table I. Characterization Data for Ligands and Complexes

Compound	Mp,[a] °C	Calcd,% C	Calcd,% H	Calcd,% N	Found,% C	Found,% H	Found,% N
H_3(MeHMe(tm)$_3$)	180-182	69.52	10.21	20.27	69.50	10.09	20.23
H_2(S-PhHH(en))	187-188	68.14	5.72	7.95	67.92	5.65	7.74
H_2(S-PhHH(tm))	148-149	68.81	6.05	7.64	68.84	6.13	7.56
Ni(S-PhHH(en))	243-245	58.70	4.43	6.85	58.57	4.45	7.26
Ni(S-PhHH(tm))	210-212	59.60	4.76	6.62	59.56	4.54	6.52
H_2(S-HPhH(en))	183	68.14	5.72	7.95	68.21	5.74	7.96
Ni(S-HPhH(en))	250-251	58.70	4.43	6.85	58.78	4.66	6.48
H_2(HPhH(en)$_2$)	286-289	76.71	7.02	16.29	76.48	7.20	16.29
Ni(HPhH(en)$_2$)	320-322	65.87	5.53	13.77	65.78	5.60	13.83
H_2(HPhH(en)(tm))	220-222	77.06	7.31	15.63	77.29	7.34	15.54
Ni(HPhH(en)(tm))	276-277	66.54	5.83	13.49	66.73	5.90	13.41
H_2(HPhH(tm)$_2$)	146-148	77.38	7.58	15.04	77.23	7.65	15.17
Ni(HPhH(tm)$_2$)	268-270	67.16	6.11	13.05	67.01	6.01	13.22

[a] Sealed tube, uncorrected.

Table II. Pmr Data for Ligands and Complexes

Compound	Solvent	Chemical Shifts, ppm
$H_3(MeHMe(tm)_3)_3$	$CDCl_3$	-1.88(Me and β-CH_2), -3.25[a] (α-CH_2), -4.4 (CH), -11.1[b] (NH)
H_2(S-PhHH(tm))	$CDCl_3$	-2.08[c](β-CH_2), -3.63[d](α-CH_2), -6.52(CH), -6.8(CH), -7.54[c] (Ph), -13.7[b](NH)
Ni(S-PhHH(tm))	$CDCl_3$	-1.9[c] (β-CH_2), -3.78[a](α-CH_2), -6.27(CH), -6.4(CH), -7.5[c](Ph)
H_2(S-HPhH(en))[e]	CD_2Cl_2	-3.70(CH_2), -7.33(CH and Ph), -10.33[f](CH)
Ni(S-HPhH(en))	$CDCl_3$	-3.72(CH_2), -7.35(Ph), -7.56 (CH), -8.17(CH)
H_2(HPhH$(en)_2$)	CD_2Cl_2	-3.60(CH_2), -7.20(Ph), -7.74 (CH)
Ni(HPhH$(en)_2$)	CS_2	-3.35(CH_2), -7.01(Ph), -7.12(CH)
H_2(HPhH(en)(tm))	CD_2Cl_2	-1.90[c](β-CH_2), -3.46(en-CH_2), -3.70[a](tm-α-CH_2), -7.19(Ph), -7.62(CH), -10.53[b](NH)

Table II. Continued

Compound	Solvent	Chemical Shifts, ppm
Ni(HPhH(en)(tm))	$CDCl_3$	-1.90[b] (β-CH_2), -3.31[b] (tm-α-CH_2), -7.11(CH), -7.16(Ph)
Ni(HPhH(en)(tm))	CS_2	-1.87[c] (β-CH_2), -3.13(en-CH_2), -3.33[a] (tm-α-CH_2), -6.91(CH), -6.99(Ph)
H_2(HPhH(tm)$_2$)	CD_2Cl_2	-1.82[c] (β-CH_2), -3.45[a] (α-CH_2), -7.09(Ph), -7.52(CH)
Ni(HPhH(tm)$_2$)	$CDCl_3$	-1.89[c] (β-CH_2), -3.25[a] (α-CH_2), -6.92(CH), -7.18(Ph)
Ni(HPhH(tm)$_2$)	CS_2	-1.87[c] (β-CH_2), -3.21[a] (α-CH_2), -6.72(CH), -6.99(Ph)

[a]Center of triplet. [b]Center of broad peak. [c]Center of multiplet. [d]Center of quartet. [e]$CHDCl_2$ used as internal standard. Spectrum taken on a Hitachi Perkin-Elmer R-20B spectrometer interfaced with a Digilab FTS/NMR-3 data system. [f]Center of doublet.

Table III. Electronic Spectral Data[a]

Compound	λ_{max} cm^{-1} (ε)[b]
H_2(HPhH(en)$_2$)	30,200(22,200), 33,900(30,500)
Ni(HPhH(en)$_2$)[c]	18,200(sh, 500), 20,300(sh, 1,500), 23,300(5,150), 29,100(27,400), 32,100(25,400)
H_2(HPhH(en)(tm))	30,500(21,400), 34,100(26,700)
Ni(HPhH(en)(tm))[c]	16,500(224), 22,200(sh, 3,150), 23,900(5,790), 29,900(33,900), 32,500(sh, 26,600)
H_2(HPhH(tm)$_2$)	29,200(16,900), 34,800(21,300)
Ni(HPhH(tm)$_2$)	13,200(sh, 69), 16,600(157), 25,500(5,540), 30,200(33,000)

[a]Chloroform solution. [b]Apparent values, uncorrected for underlying absorption. [c]Reproducible spectra were not obtained at <14,000 cm^{-1} because of decomposition in ir lamp beam.

Figure Legends

Figure 1. Infrared mull spectrum of H_2(S-HPhH(en)).

Figure 2. Infrared mull spectrum of Ni(S-HPhH(en)).

Figure 3. Infrared mull spectrum of H_2(HPhH(en)$_2$).

Figure 4. Infrared mull spectrum of Ni(HPhH(en)$_2$)

Figure 5. Infrared mull spectrum of H_2(HPhH(en)(tm)).

Figure 6. 4000-1200 cm^{-1} infrared mull spectrum; 1300-400 cm^{-1}, KBr pellet spectrum of Ni(HPhH(en)-(tm)).

Figure 7. Infrared mull spectrum of H_2(HPhH(tm)$_2$).

Figure 8. Infrared mull spectrum of Ni(HPhH(tm)$_2$).

Figure 9. 60 MHz pmr spectrum of Ni(S-HPhH(en)) in d_6-acetone solution.

Figure 10. 60 MHz pmr spectrum of H_2(HPhH(en)$_2$) (upper) in CD_2Cl_2 solution and Ni(HPhH(en)$_2$) (lower) in CS_2 solution.

Figure 11. 60 MHz pmr spectrum of H_2(HPhH(en)(tm)) (upper) in CD_2Cl_2 solution and Ni(HPhH(en)(tm)) (lower) in CS_2 solution.

Figure 12. 60 MHz pmr spectrum of H_2(HPhH(tm)$_2$) (upper) in CD_2Cl_2 solution and Ni(HPhH(tm)$_2$) in $CDCl_3$ solution.

Figure 13. Electronic spectra of H_2(HPhH(en)$_2$) (---) and Ni-(HPhH(en)$_2$) (——) in chloroform solution.

Figure Legends (continued)

Figure 14. Electronic spectra of $H_2(HPhH(en)(tm))$ (---) and $Ni(HPhH(en)(tm))$ (——) in chloroform solution.

Figure 15. Electronic spectra of $H_2(HPhH(tm)_2)$ (----) and $Ni(HPhH(tm)_2)$ (——) in chloroform solution.

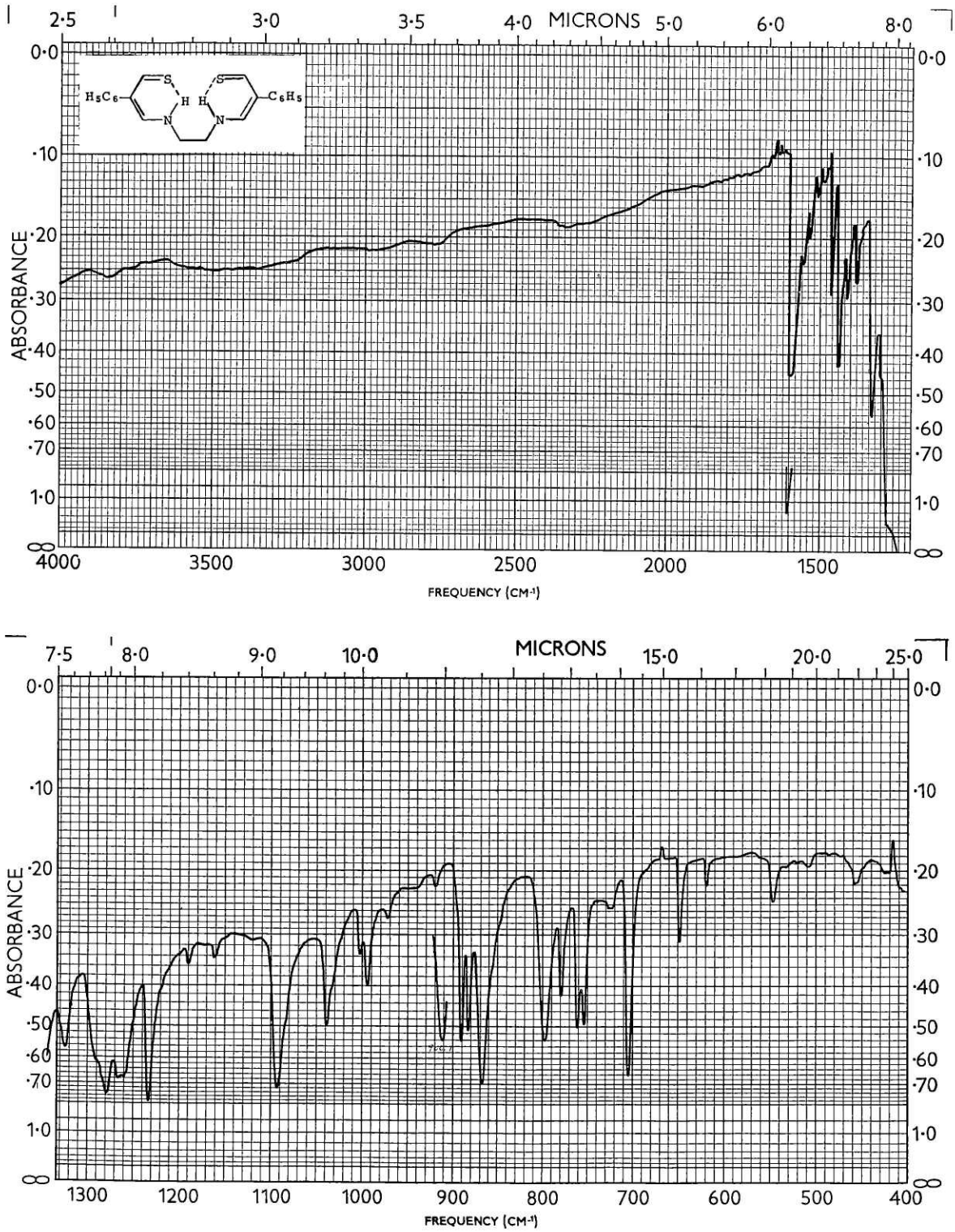

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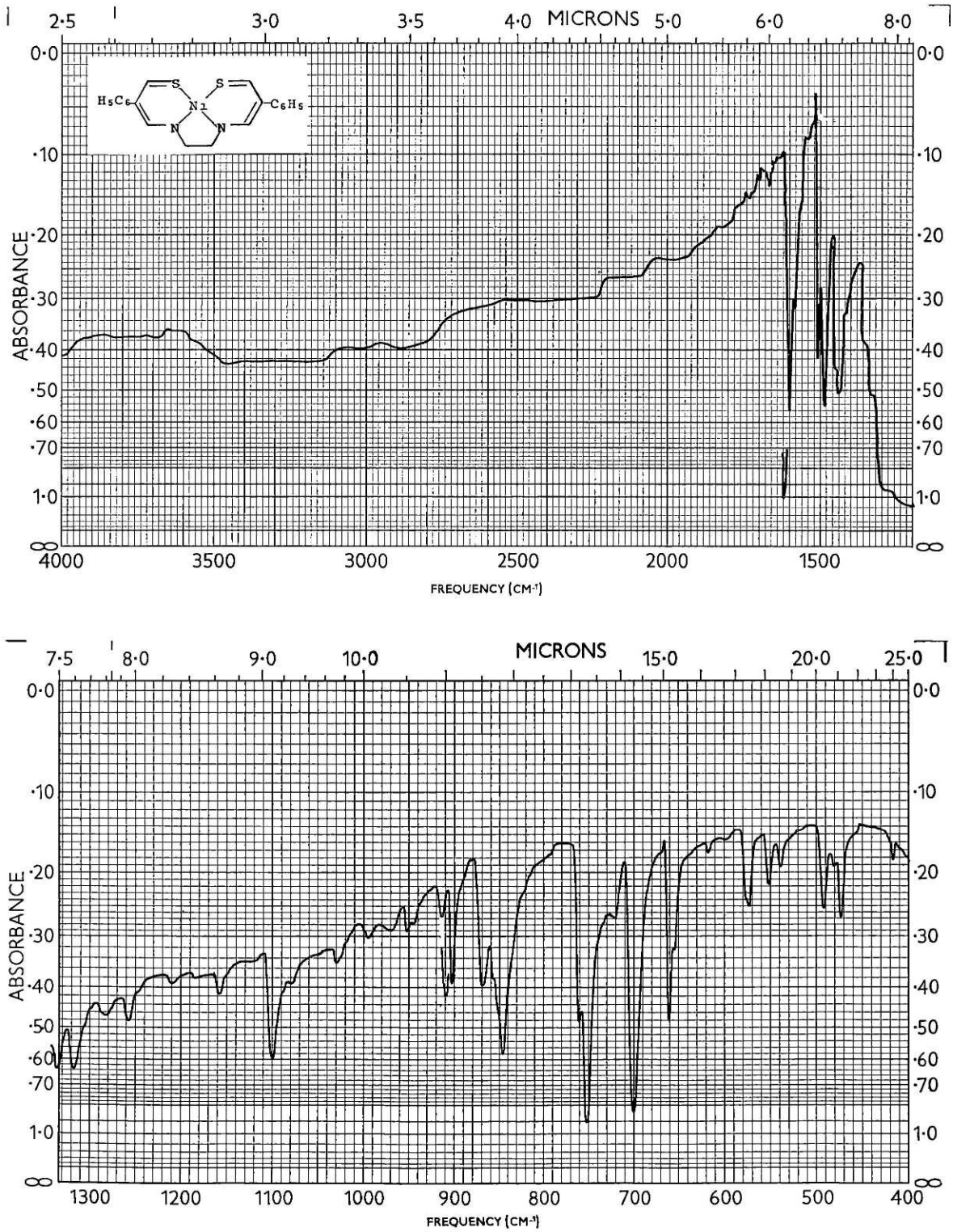
Figure 1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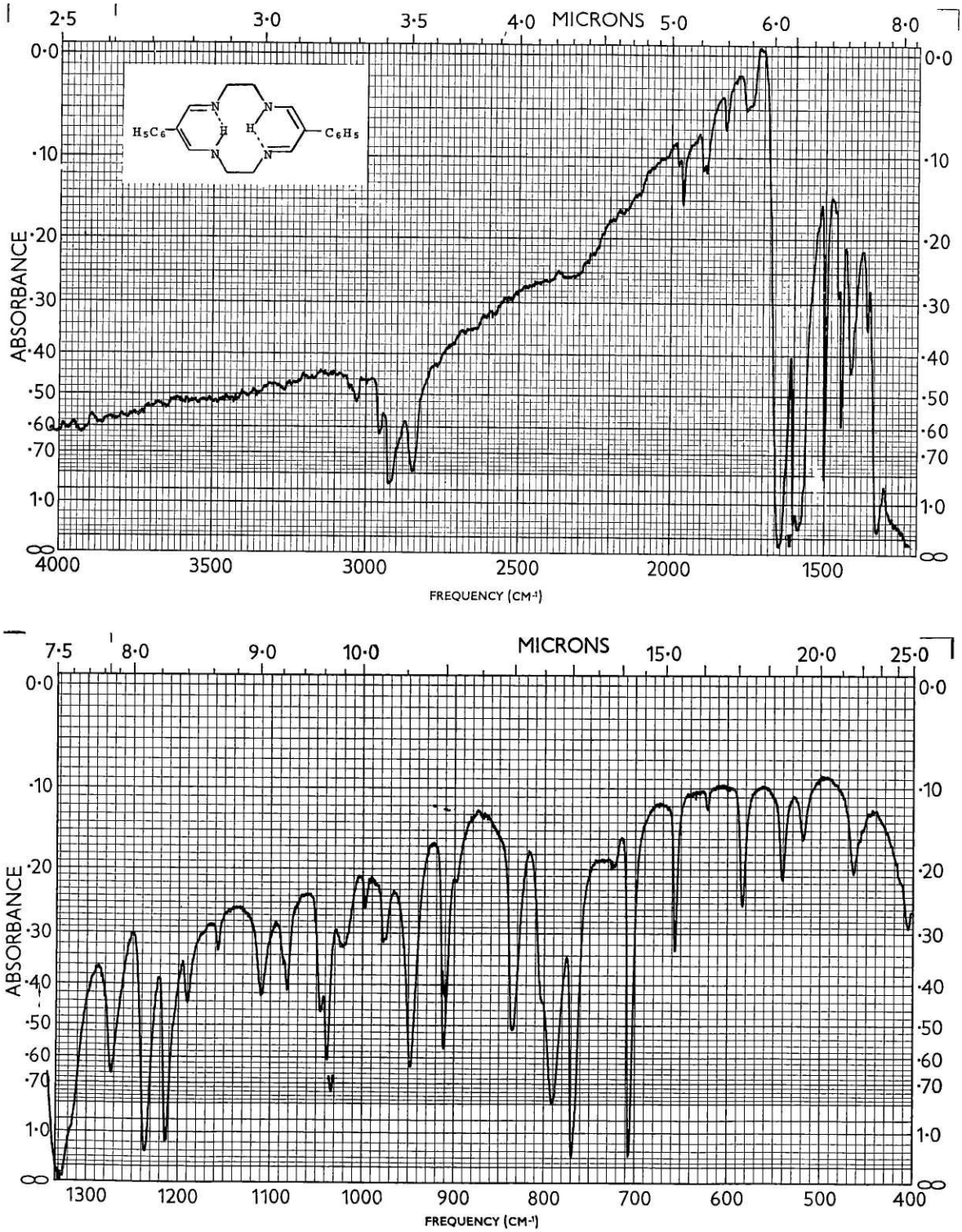
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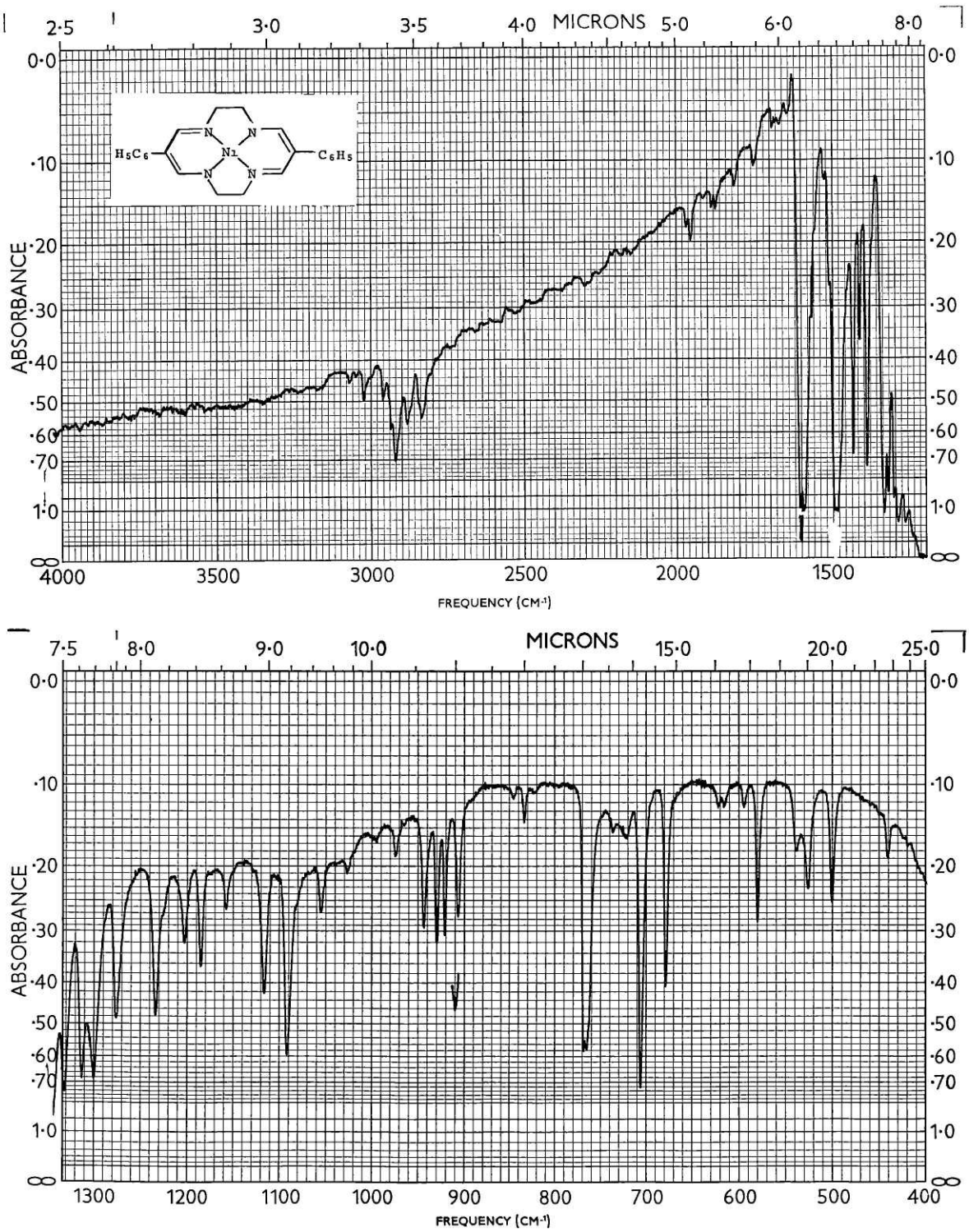
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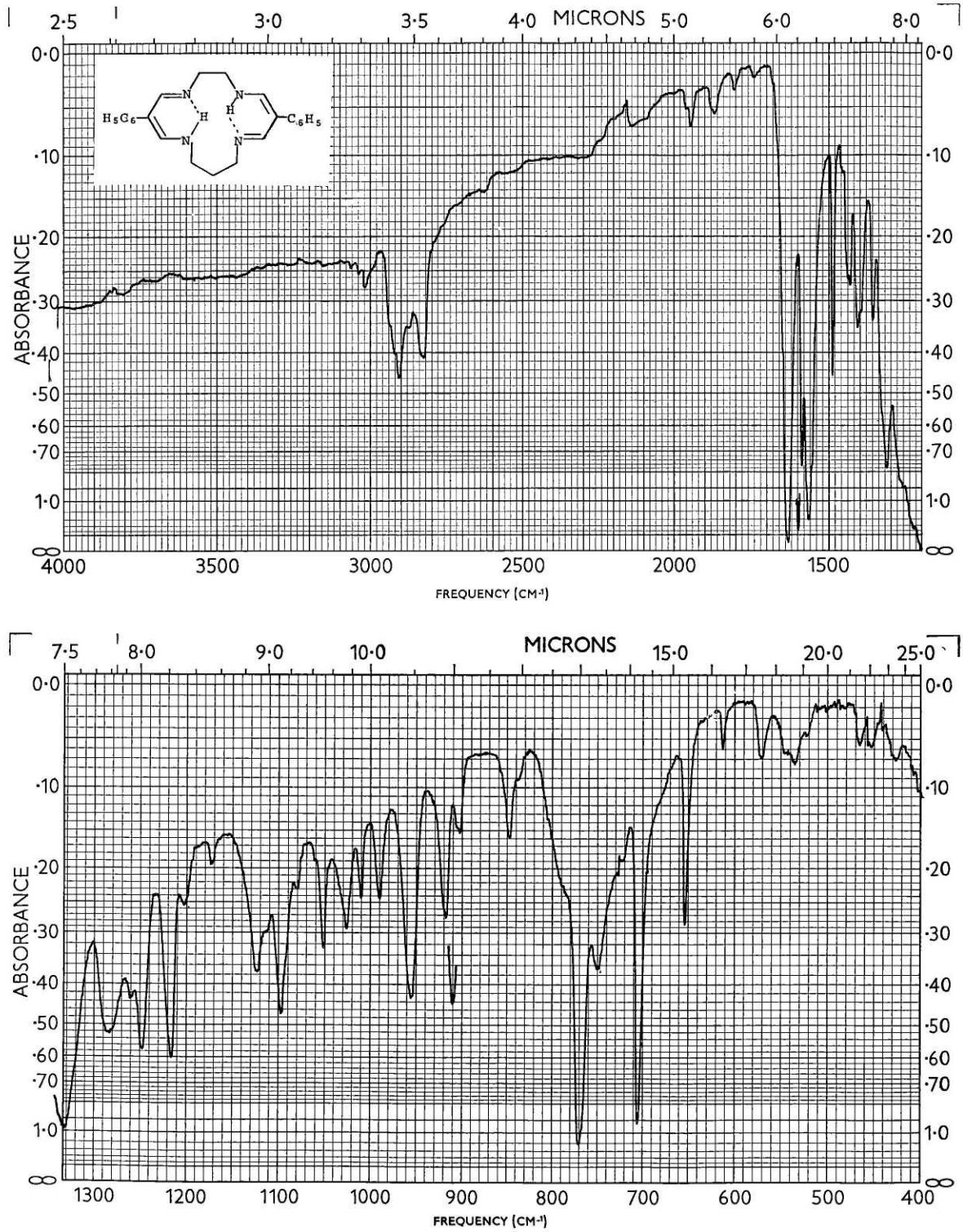
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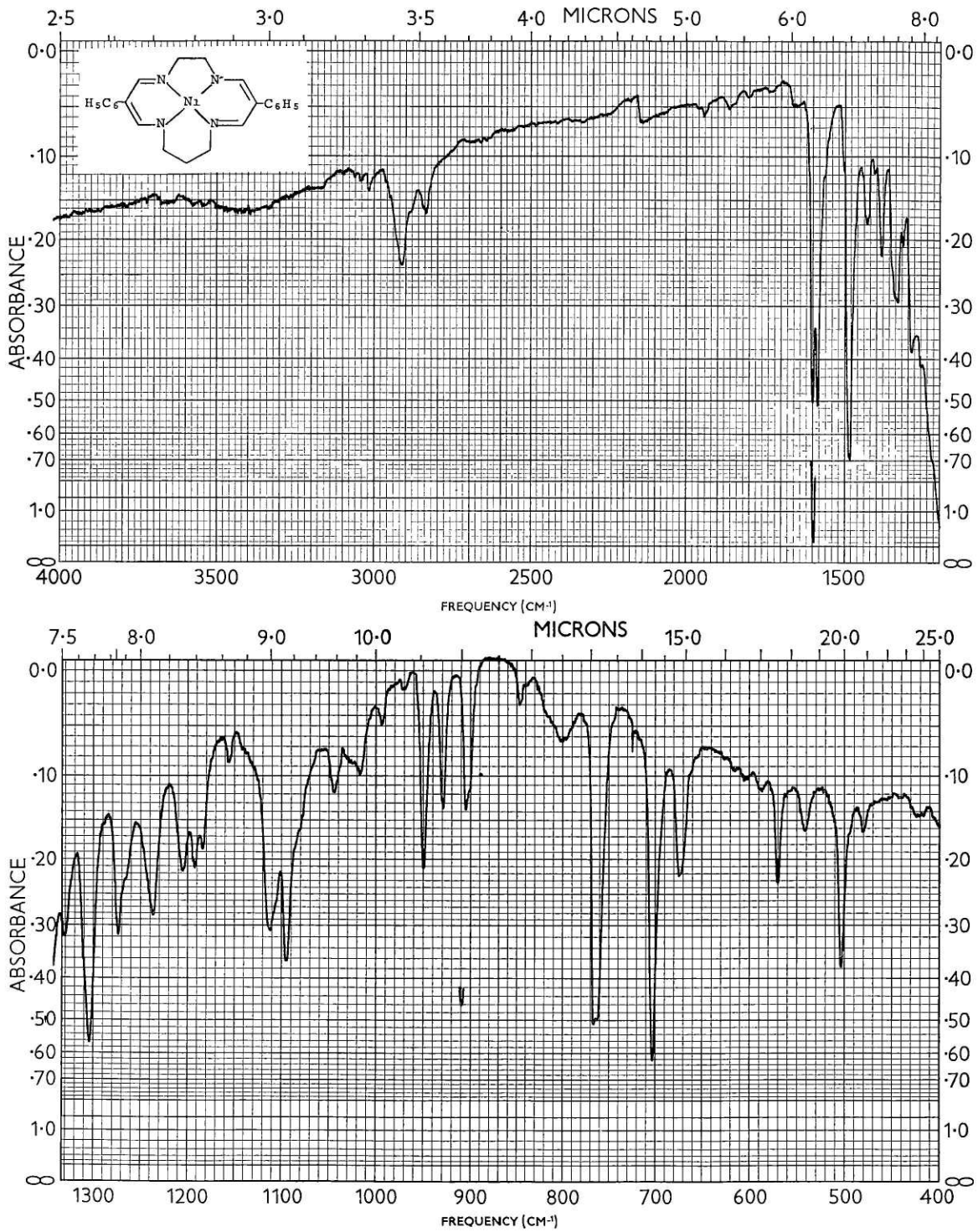
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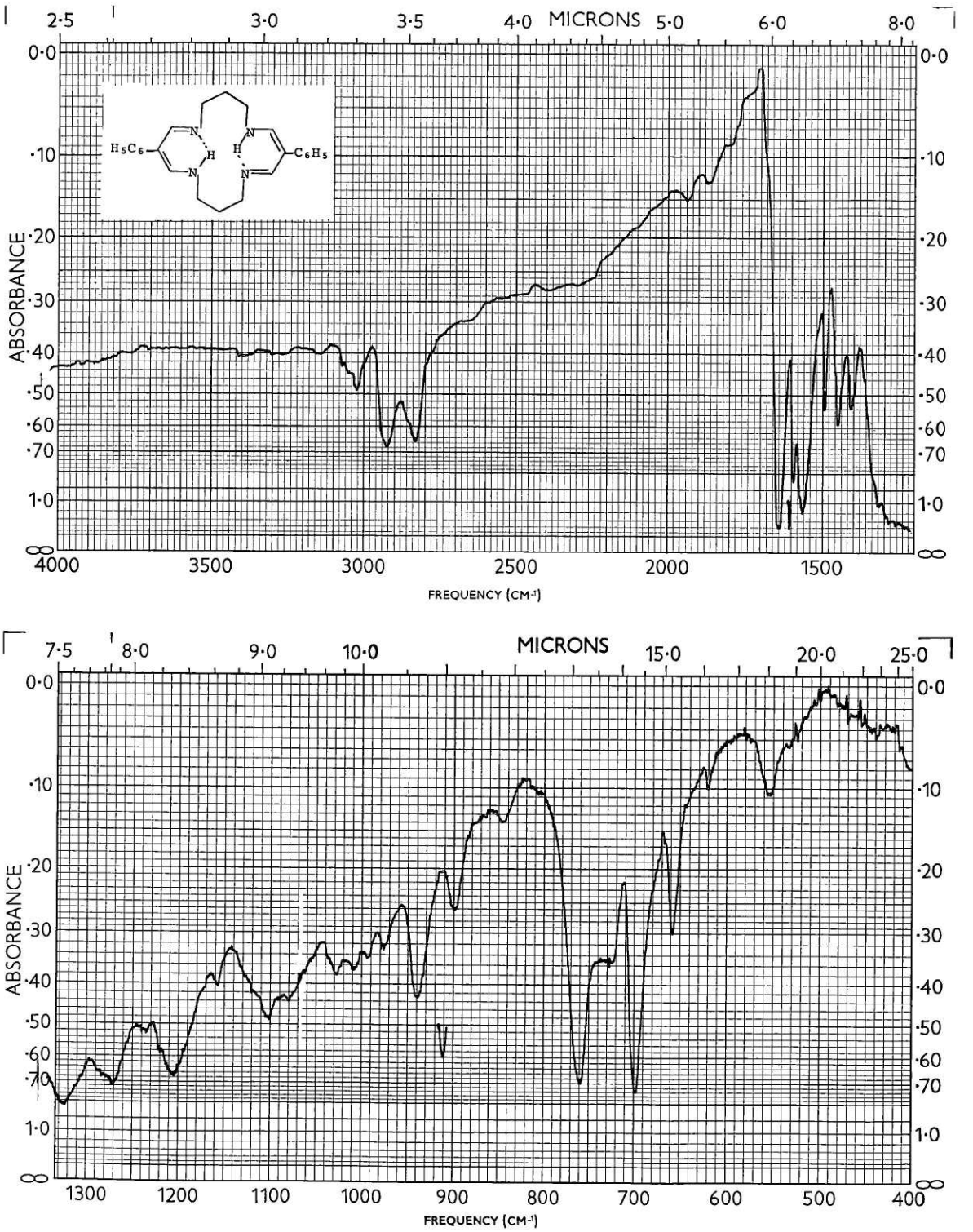
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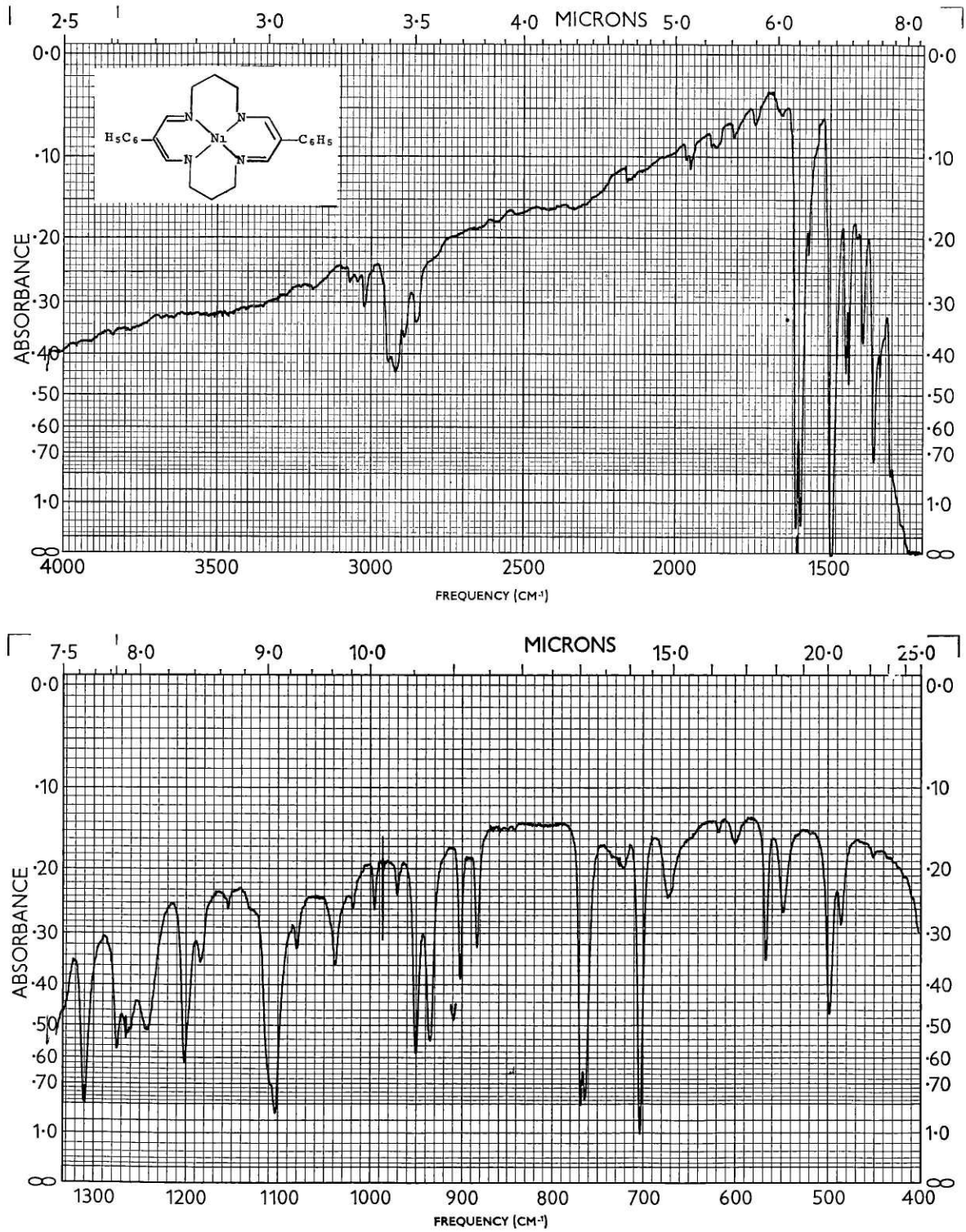
Figure 7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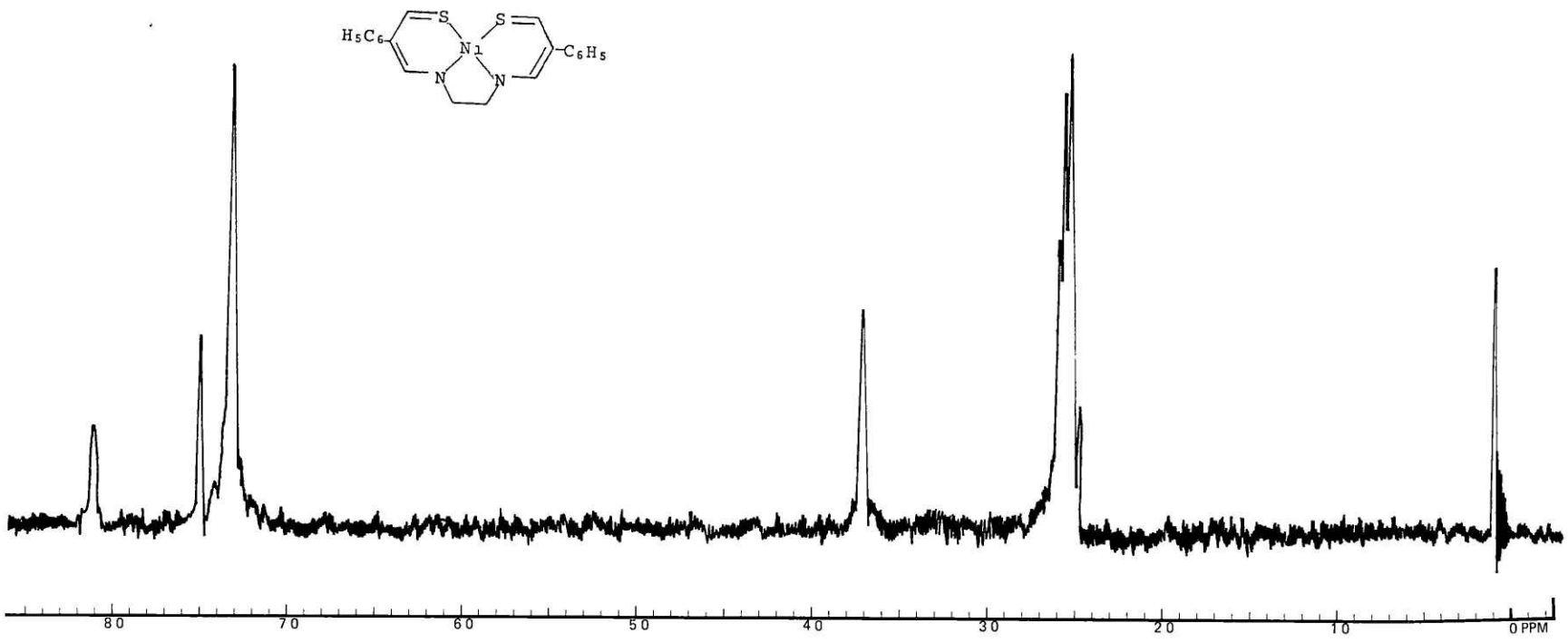

Figure 9

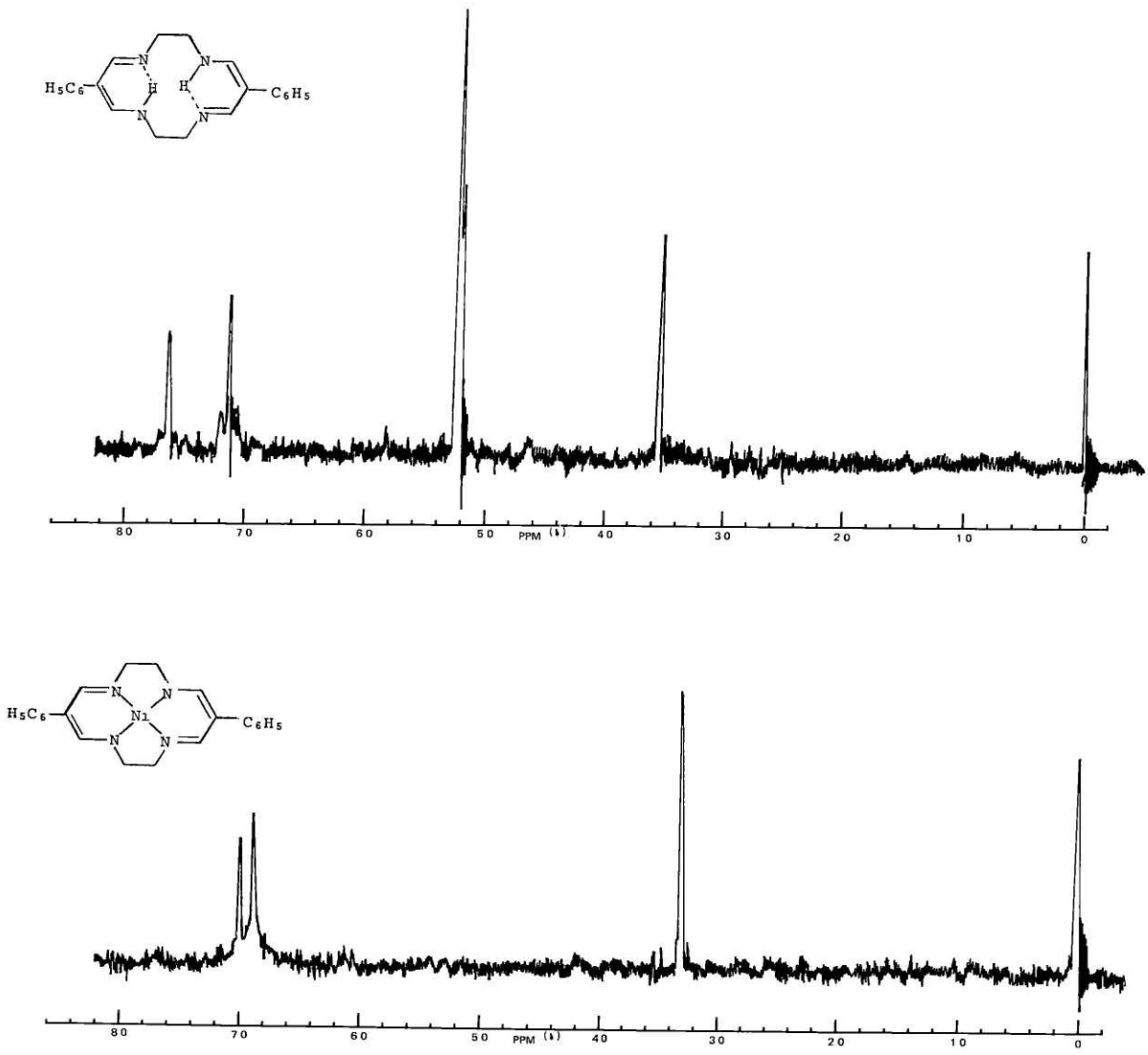
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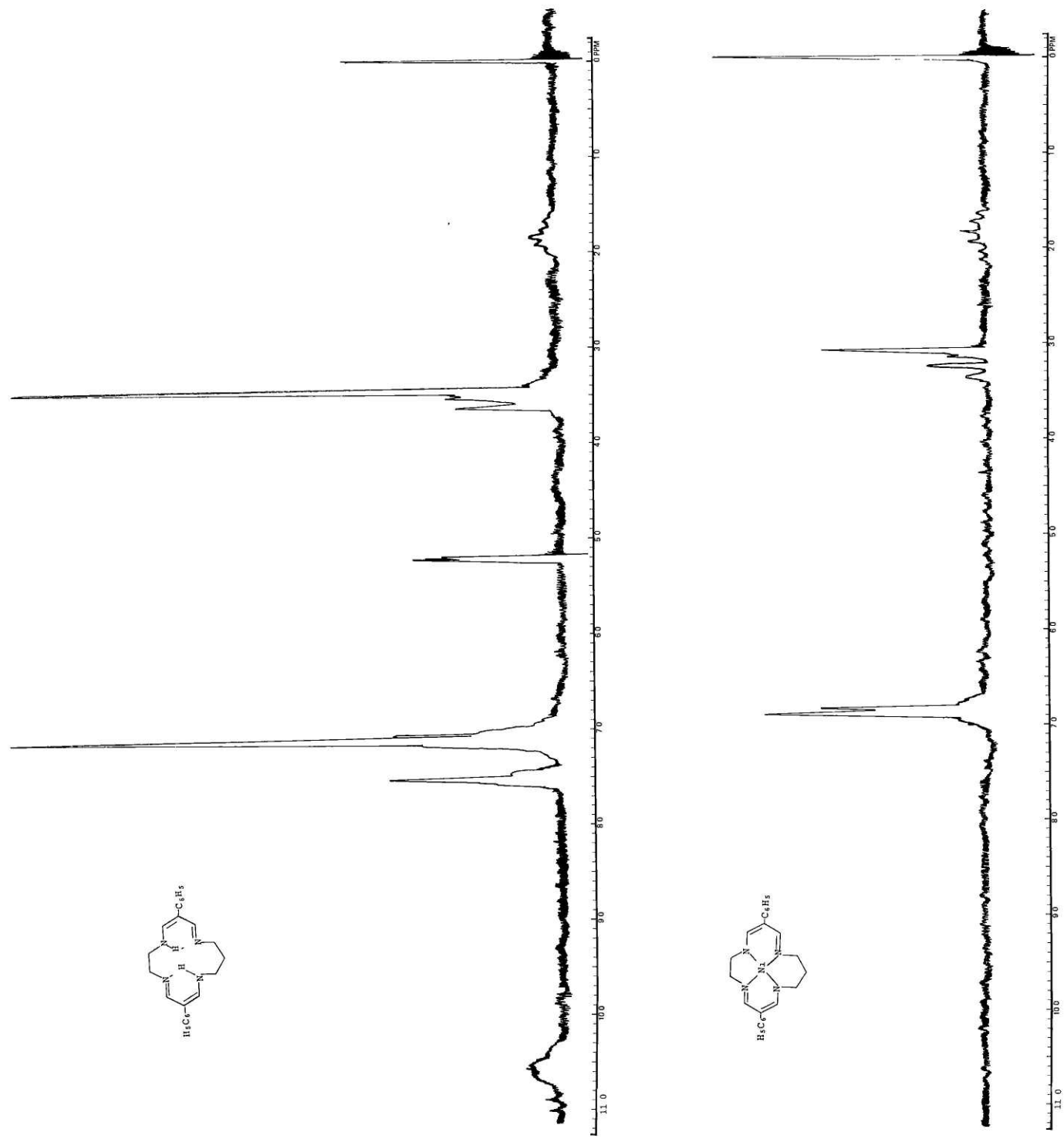
Figure 10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Ni

Figure 11

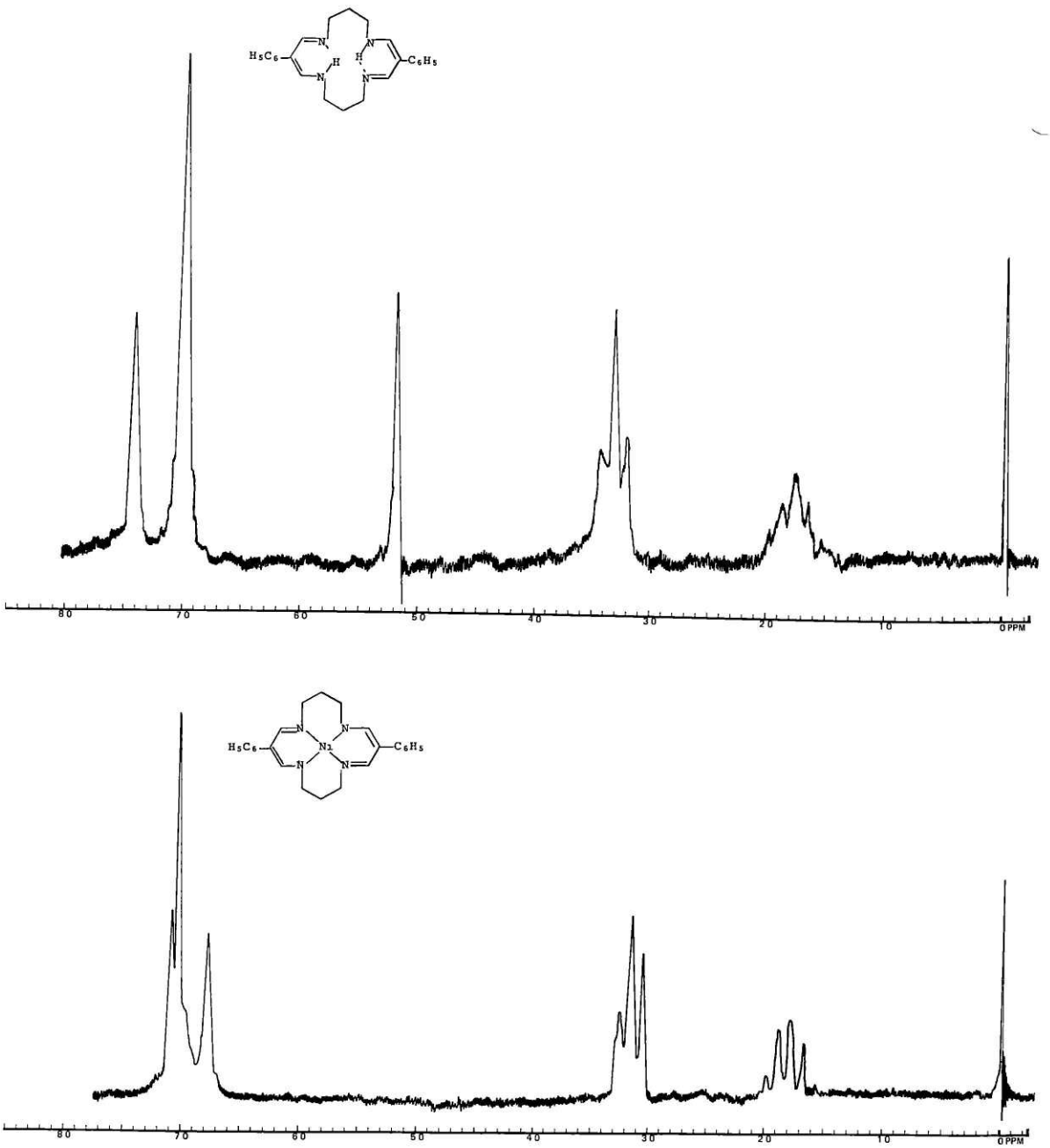
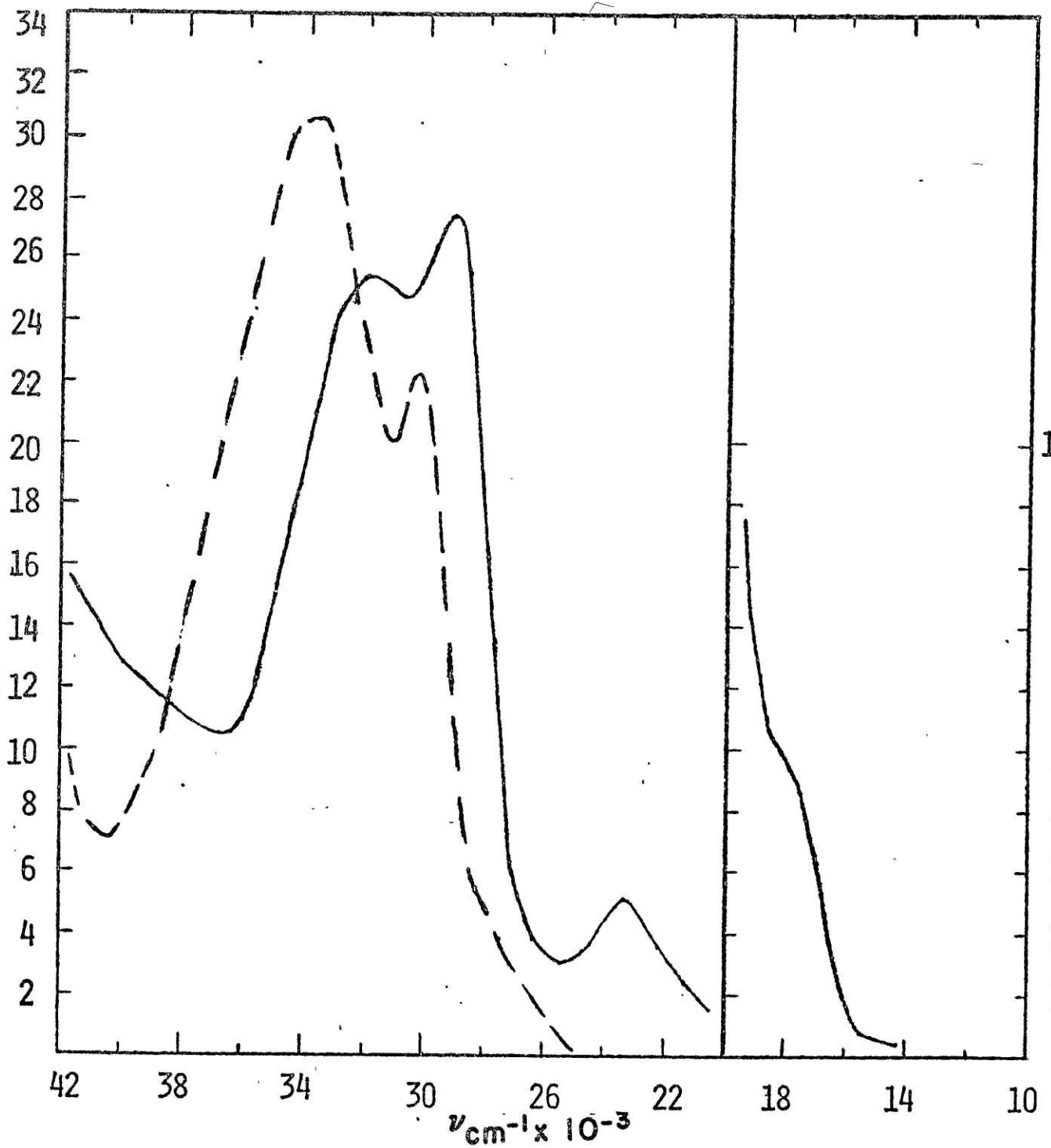


Figure 12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4
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ε x 10⁻³
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800
700
600
500
400
300
200
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ε
42
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34
30
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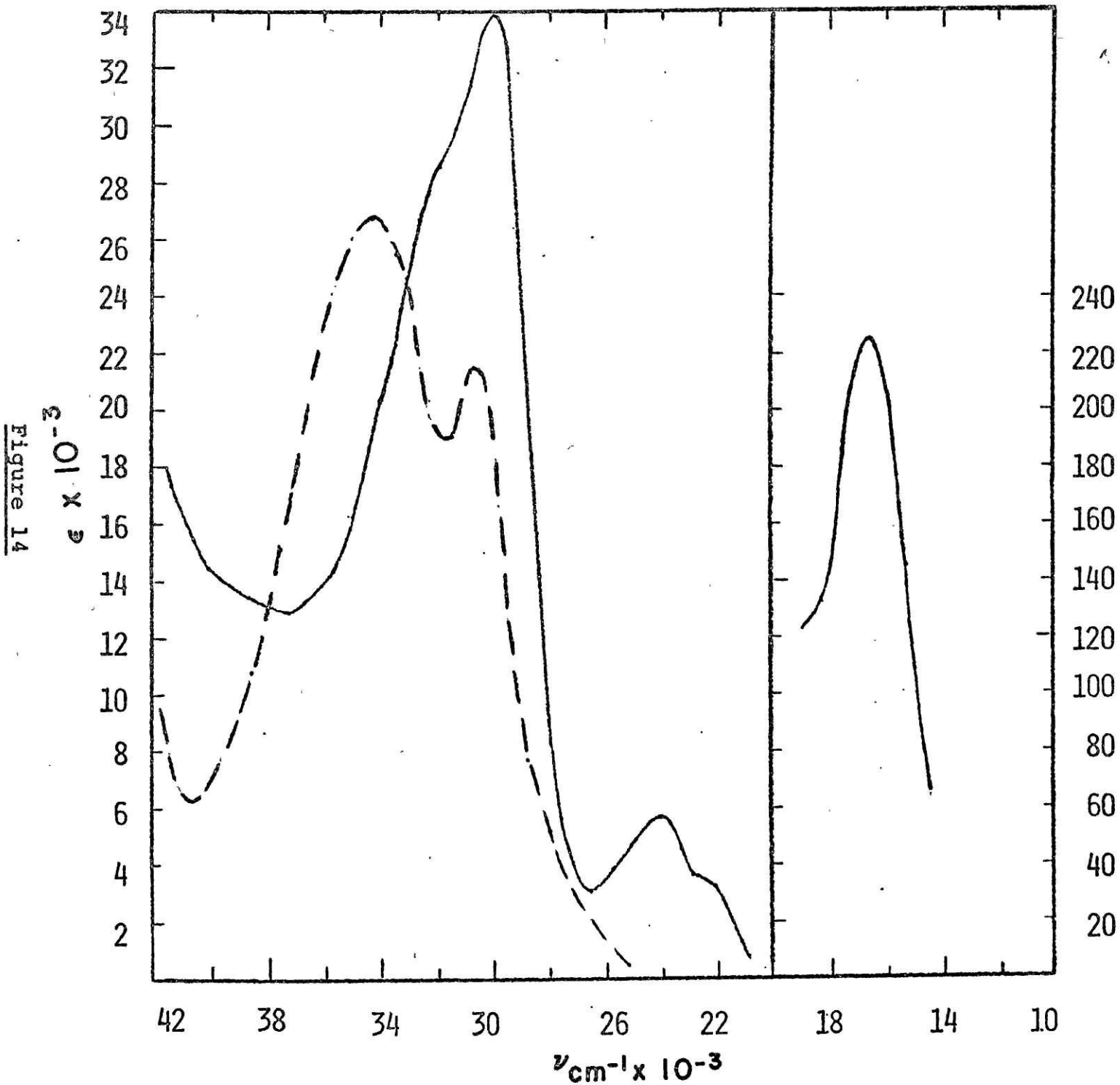
22
18
14
10
ν cm⁻¹ x 10⁻³

Figure 13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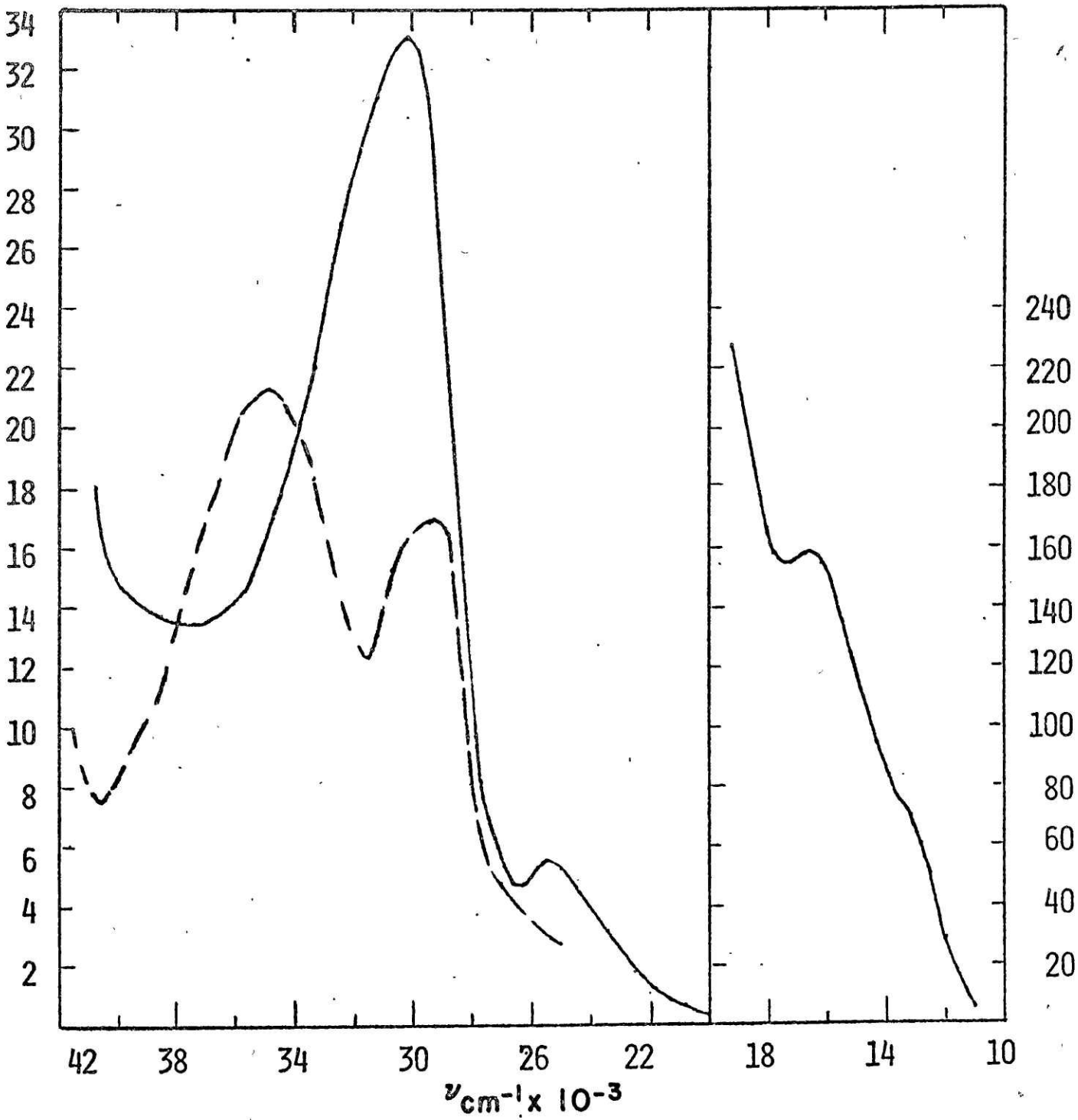
νcm⁻¹ x 10⁻³

Figure 14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ν cm⁻¹ x 10⁻³

Figure 15

REFERENCES PART II

1. D. H. Busch, Helv. Chim. Acta, Fasciculus Extraordinarius Alfred Werner, 174 (1967).
2. D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati, and N. Tokel, Advan. Chem. Ser., 100, 44 (1971).
3. L. F. Lindoy and D. H. Busch, Preparative Inorganic Reactions, 6, 1 (1971).
4. J. P. Candlin, K. A. Taylor, and D. T. Thompson, "Reactions of Transition Metal Complexes," Elsevier Publishing Co., Amsterdam, 1968, pp. 83-99.
5. E.-G. Jager, Z. Chem., 4, 437 (1964).
6. H. Hiller, P. Dimroth, and H. Pfitzner, Ann., 717, 137 (1968).
7. P. Chave and C. L. Honeybourne, Chem. Commun., 279 (1969).
8. E.-G. Jäger, Z. Anorg. Allg. Chem., 364, 177 (1969).
9. T. J. Truex and R. H. Holm, J. Am. Chem. Soc., 94, 4529 (1972).
10. B. Bosnich, M. L. Tobe, and G. A. Webb, Inorg. Chem., 4, 1109 (1965).
11. N. F. Curtis, Coordination Chem. Rev., 3, 3 (1968).
12. E.-G. Jäger, Z. Chem., 8, 30, 470 (1968).
13. M. Green and P. A. Tasker, Chem. Commun., 518 (1968).

14. M. Green and P. A. Tasker, Inorg. Chim. Acta, 5, 17, 65 (1971).

15. D. St. C. Black and M. J. Lane, Australian J. Chem., 23, 2039 (1970).

16. E. Uhlemann and M. Plath, Z. Chem., 9, 234 (1969).

17. E.-G. Jäger, Z. Chem., 8, 392 (1968).

18. P. Bamfield, J. Chem. Soc., A, 2021 (1969).

19. N. F. Curtis, Chem. Commun., 881 (1966).

20. (a) I. E. Maxwell and M. F. Bailey, Chem. Commun. 883 (1966); (b) V. L. Goedken and D. H. Busch, Inorg. Chem., 10, 2679 (1971).

21. L. G. Warner, N. J. Rose, and D. H. Busch, J. Am. Chem. Chem. Soc., 90, 6938 (1968).

22. J. M. Palmer, E. Papaconstantinou, and J. F. Endicott, Inorg. Chem., 8, 1516 (1969).

23. D. A. House and N. F. Curtis, J. Am. Chem. Soc., 86, 223 (1964).

24. E. K. Barefield and D. H. Busch, Inorg. Chem., 10, 1216 (1971).

25. G. Melson and D. Busch, Proc. Chem. Soc., 223 (1963).

26. D. St. C. Black and A. J. Hartshorn, Chem. Commun., 706 (1972).

27. C. J. Hipp and D. H. Busch, Chem. Commun., 737 (1972).

28. C. Paulmier, Y. Mollier, N. Lozach, Bull. Soc. Chim. France, 2463 (1965).

29. D. Leaver, D. M. McKinnon, and W. A. H. Robertson, J. Chem. Soc., 32 (1965).

30. F. Clesse, A. Reliquet, H. Quiniou, C. R. Acad. Sci., Ser. C., 272, 1049 (1971).

31. H. Prinzbach and E. Futterer, Adv. Heterocyclic Chem., 7, 39 (1967).

32. R. Mayer and H. Hartmann, Chem. Ber., 97, 1886 (1964).

33. E. Uhlemann, Z. Naturforsch., 21b, 592 (1966).

34. M. Saquet and A. Thullier, Bull. Soc. Chim. France, 2463 (1965).

35. D. M. McKinnon and E. A. Robak, Can. J. Chem., 46, 1855 (1968).

36. D. H. Gerlach and R. H. Holm, J. Am. Chem. Soc., 91, 3457 (1969).

37. G. L. Coustumer and Y. Mollier, Bull. Soc. Chim. France, 3076 (1970).

38. S. Eaton, personal communication.

39. D. Mc C. Wei and S. C. Cummings, Abstr. of papers, 162nd National Meeting, American Chemical Society, September, 1971, abstr. INOR-136.

40. E. K. Fields, J. Am. Chem. Soc., 77, 4255 (1955).

41. E. Klingsberg, J. Am. Chem. Soc., 83, 2934 (1961).

42. M. Schmidt and H. Schulz, Chem. Ber., 101, 277 (1968).

43. S. H. H. Chaston, S. E. Livingstone, T. N. Lockyer, and J. S. Shannon, Australian J. Chem., 18, 1539 (1965).

44. R. D. Archer, Inorg. Chem., 2, 292 (1963).

45. S. C. Tang and R. H. Holm, unpublished results.

46. C. Schwarzenbach and K. Lutz, Helv. Chim. Acta, 23, 1139 (1940); D. Lloyd and D. R. Marshall, J. Chem. Soc., 2597 (1956).

47. H. A. Staab and F. Vögtle, Chem. Ber., 98, 2701 (1965).

48. E. Daltrozzo and K. Feldman, Ber. Bunsenges. Phys. Chem., 72, 1140 (1968).

49. S. G. McGeachin, Can. J. Chem., 46, 1903 (1968).

50. C. L. Honeybourne and G. A. Webb, Spectrochim. Acta, Part A, 25, 1075 (1969).

51. V. L. Goedken and D. H. Busch, Inorg. Chem., 10, 2679 (1971).

52. L. J. Chinn, "Selection of Oxidants in Synthesis," M. Dekker Publishing Co., New York, 1971, Chap. 6.

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