Palladium and Platinum Complexes of Vitamin B_6

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Abstract

Palladium and platinum complexes of pyridoxamine, pyridoxine and pyridoxal have been prepared. The structures of the complexes $PtCl_2PM.H_2O$, trans-$PdCl_2(PN)_2$ and $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ have been determined by use of single crystal x-ray studies. The compounds $PdCl_2PM$, trans-$PdCl_2(PN)_2$, cis-$PdCl_2(PN)_2$ and cis $PdCl_2(PL)_2$ were also studied by use of carbon-13 nmr spectroscopy. All the complexes have also been characterised by use of infrared spectral studies.

In the complexes, $PtCl_2PM.H_2O$ and $PdCl_2PM$, the ligand pyridoxamine is chelated to the metal through the aminomethyl nitrogen and the phenolate oxygen atoms whereas in the complexes, trans-$PdCl_2(PN)_2$, cis-$PdCl_2(PN)_2$ and cis-$PdCl_2(PL)_2$ the vitamin B_6 ligands are coordinated to the metal through the pyridine ring nitrogen. The compounds $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ and $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$ have no direct metal-ligand bonding. In all the complexes, the metal maintains a square planar coordination except in $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ where the metal is octahedrally coordinated.

PM = pyridoxamine

$[PMH_2]^{2+}$ = diprotonated pyridoxamine

PN = pyridoxine

PL = pyridoxal

PLH^+ = protonated pyridoxal

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Chapter I

INTRODUCTION

History and structures of vitamin B_6

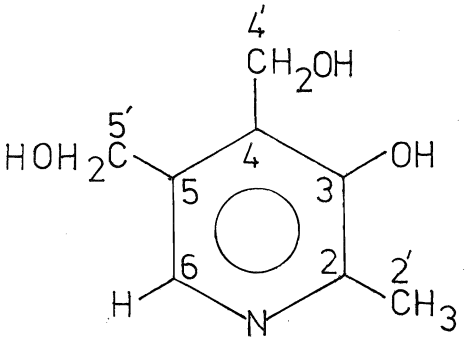
The role of vitamins in the nutrition and metabolic processes of man has long been discovered since the olden days when sailors on long voyages reportedly developed scurvy. However, it was not until 1934 that vitamin B_6 activity was defined.[1] Since initial experimental studies were done on rats, vitamin B_6 was regarded as that part of the vitamin B-complex responsible for the cure of a specific dermatitis developed by rats on a vitamin free diet supplemented with vitamin B_1 and lactoflavin.

Vitamins are necessary for the normal health and development of the animal organism and also for bacteria and other microorganisms. Symptoms of vitamin deficiency result from partial failure of one or more metabolic functions for which the missing vitamin is essential. The general characteristics of vitamin B_6 deficiency in animals include retarded growth, acrodynia, anemia, epileptiform convulsions and partial alopecia. Deficiency of pyridoxine results in a decrease in serum protein synthesis. Much nutritional evidence indicates that vitamin B_6 is in some way concerned with fat metabolism. Vitamin B_6 deficient animals show a lower capacity to transform protein into fat and also decrease in the storage of liver cholesterol.[2] Certain strains of bacteria and yeasts have been reported[3] to grow on one or more forms of vitamin B_6 as the sole or predominant source of carbon and nitrogen.

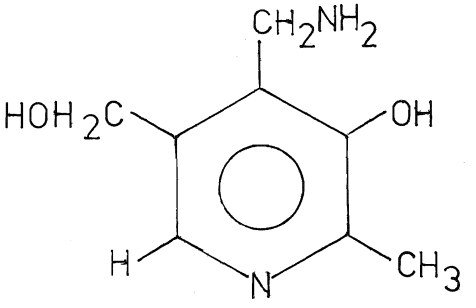
By the middle of 1938, pyridoxine was isolated from rice bran,[4] rice[5] and yeast.[6] With the isolation of pyridoxine achieved, a complete structure determination was effected.[7] The first synthesis of the vitamin was then undertaken.[8,9,10] Later, an improved method of synthesis was carried out by Jones and Kornfield.[11] Several other syntheses have been described.[12,13] Snell[14] and his group in the course of their studies of the effects of pyridoxine on microorganisms discovered pyridoxine-like substances with even greater growth-promoting activity than pyridoxine. These were the corresponding aldehyde, pyridoxal and amine, pyridoxamine. From later work by Snell[15] and his group, it was established that the main metabolically active form of the vitamin B_6 compounds is pyridoxal-5-phosphate, also known as codecarboxylase. However, pyridoxamine-5-phosphate is also an important coenzyme for transaminases.[16] The structures of the vitamin B_6 and their phosphate derivatives are shown in Figure 1. It has been observed that animals respond to all three vitamins. The same situation exists in many fungi and bacteria that require vitamin B_6. Thus, there must exist mechanisms for interconverting the three derivatives. Figure 2 represents the metabolic interrelationship of vitamin B_6 in animal tissue as suggested by Wada and Snell.[17]

Pyridoxal, pyridoxamine and pyridoxine are naturally occurring free forms of vitamin B_6. The vitamin also occurs naturally as pyridoxamine-5-phosphate and pyridoxal-5-phosphate. Pyridoxine is less abundant in most tissues than the other forms of vitamin B_6.

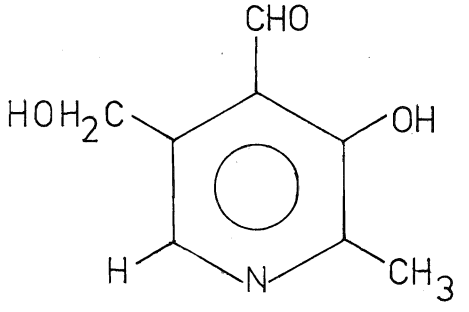
Figure 1. Vitamin B_6 and phosphate derivatives.



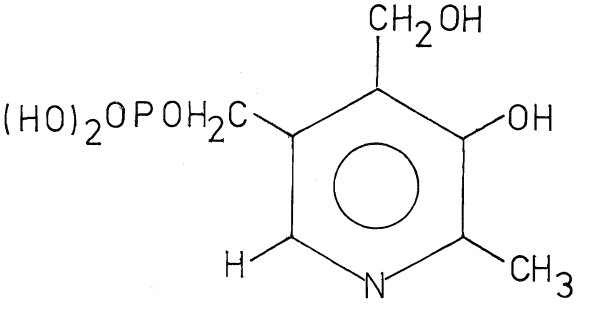
PYRIDOXINE (PN)



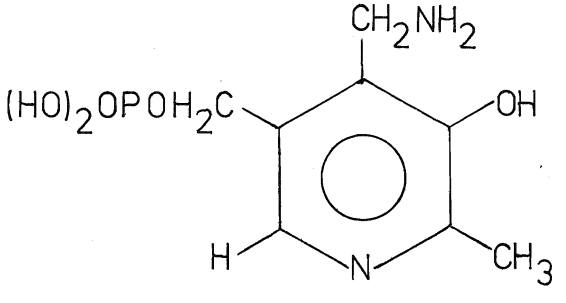
PYRIDOXAMINE (PM)



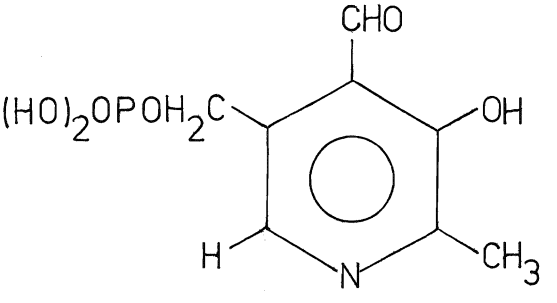
PYRIDOXAL (PL)



PYRIDOXINE PHOSPHATE (PNP)

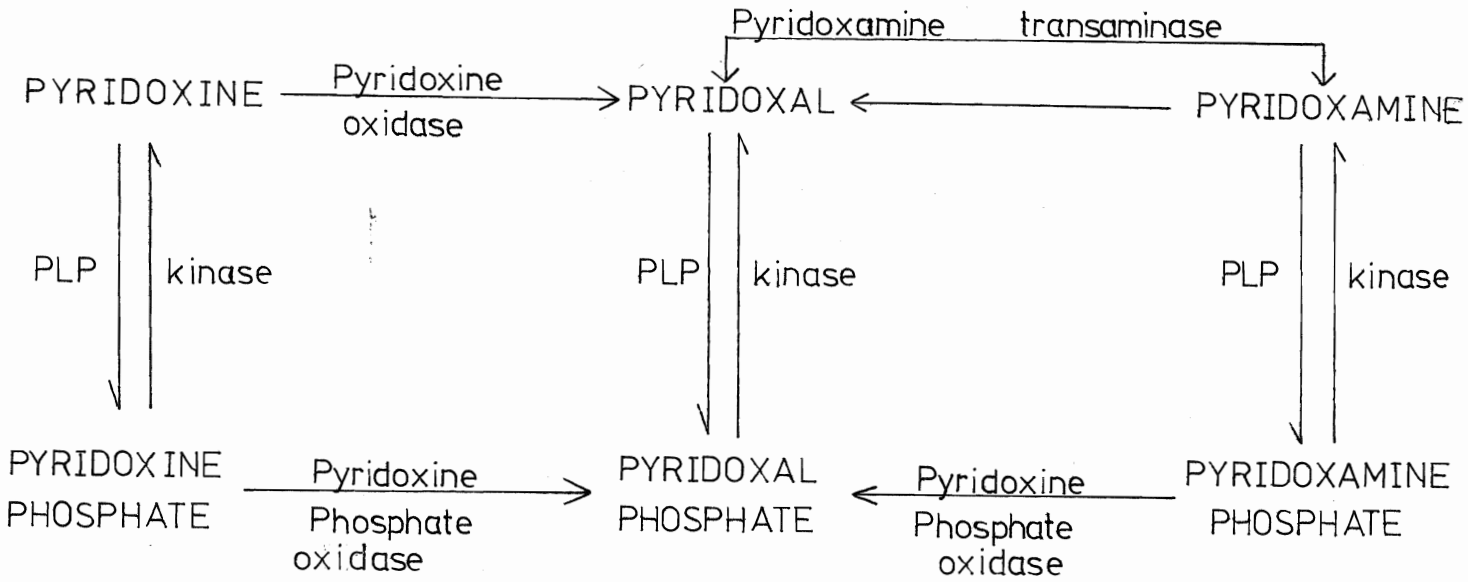


PYRIDOXAMINE PHOSPHATE (PMP)



PYRIDOXAL PHOSPHATE (PLP)

Figure 2. The metabolic interrelationship of vitamin B_6 in animal tissues.



The vitamin B_6 compounds in neutral aqueous solutions have been found to exhibit tautomerism.[18,19,20] Although in such solutions the dipolar ionic forms predominate, a significant amount of the uncharged forms also are present. In alcoholic solution the uncharged form predominates.[19] ^{13}C nmr spectra of the vitamin B_6 compounds in aqueous solution indicate that the ionization of the pyridinium and phenolic groups take place in well separated steps and that the compounds exist as zwitterions in neutral aqueous solution.[21] In neutral solid, pyridoxamine exists as the dipolar ionic form with the amine nitrogen protonated.[22] Pyridoxine, however, exists as the uncharged species.[23] X-ray single crystal studies[24] and infrared spectrum[25] of PMHCl have shown that the pyridoxamine cations PMH^+ have a deprotonated phenolic group and protonated ring and amino nitrogen atoms. Figures 3 and 4 show the tautomeric forms of pyridoxine and pyridoxamine respectively. The acid strength of the phenolic group has been found to follow the order pyridoxamine > pyridoxamine-5-phosphate > pyridoxal-5-phosphate > pyridoxal > pyridoxine, while the base strength for the heterocyclic ring nitrogen atom follows the inverse order.[26]

The vitamin B_6 compounds are involved in a number of extremely important metabolic reactions of the α-amino acids. Pyridoxal-5-phosphate, the biocatalytically active or coenzyme form of vitamin B_6 functions in non-oxidative enzymatic transformations of amino acids and catalyzes such reactions as transamination[27,28,29,30] between α-amino acids and α-keto acids, racemization[31,32] of α-amino acids, decarboxylation,[23] β-elimination[33,34] and γ-elimination.[33,35] The enzymatic transamination

Figure 3. Tautomeric forms of pyridoxine.

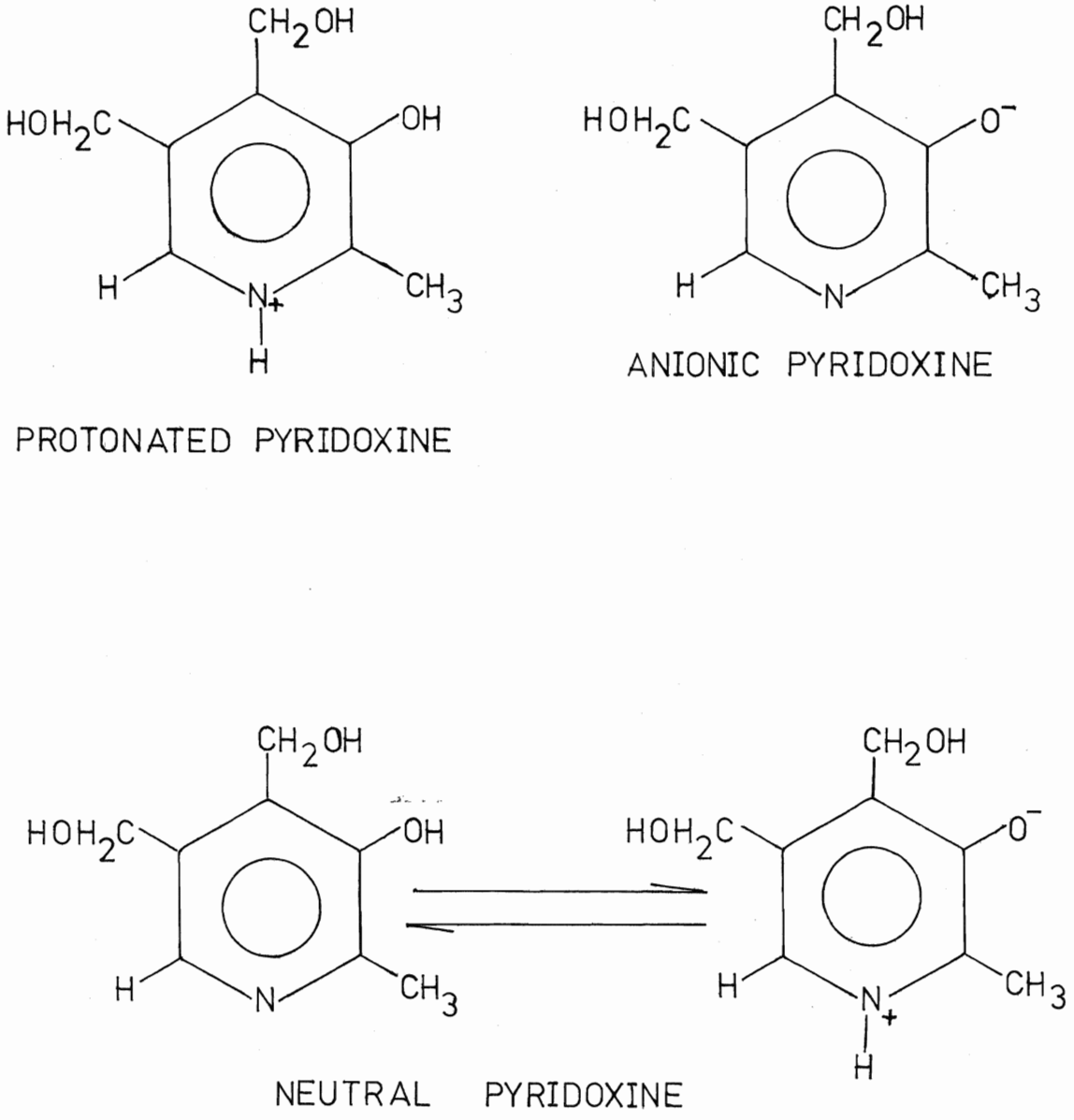
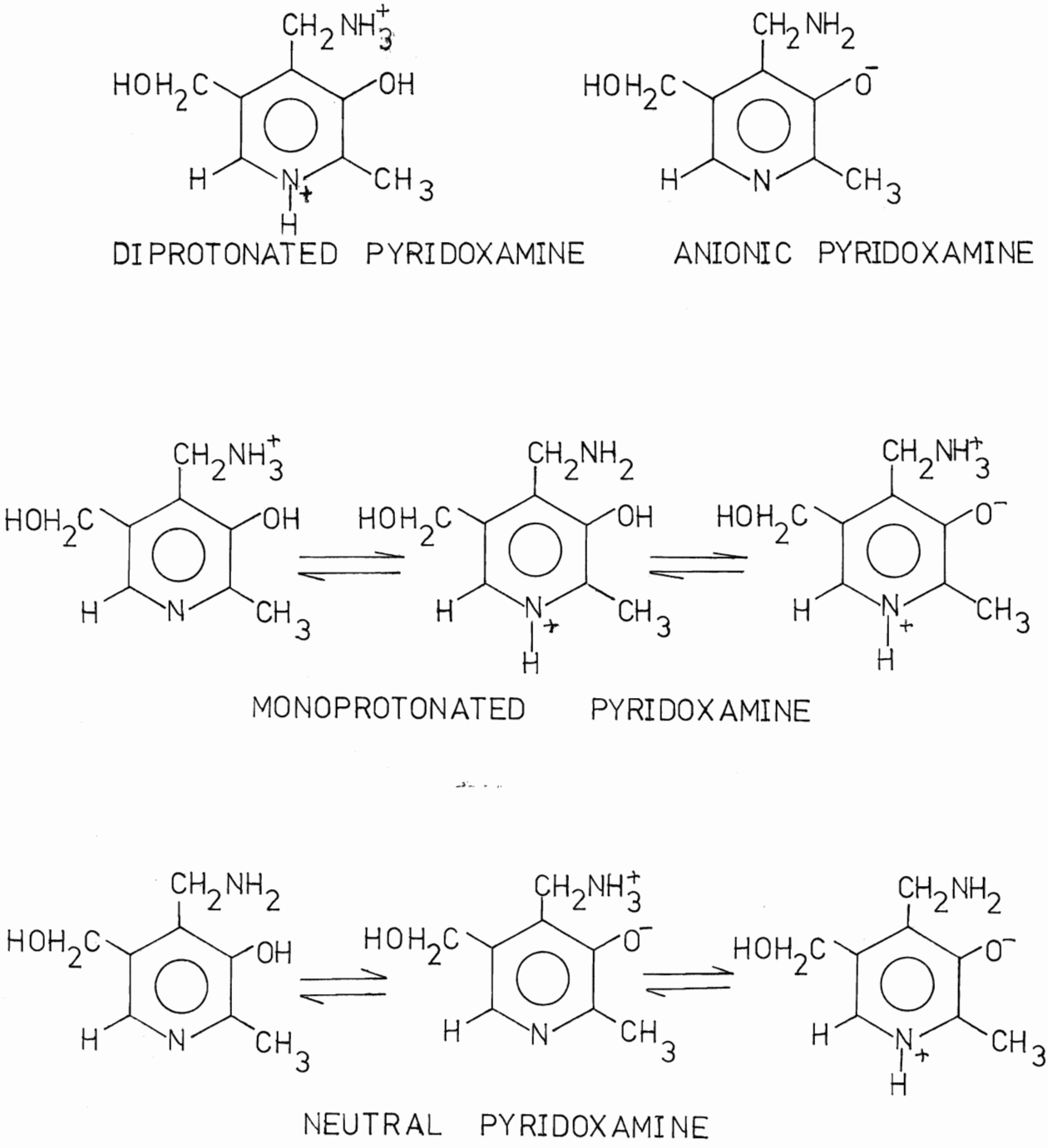


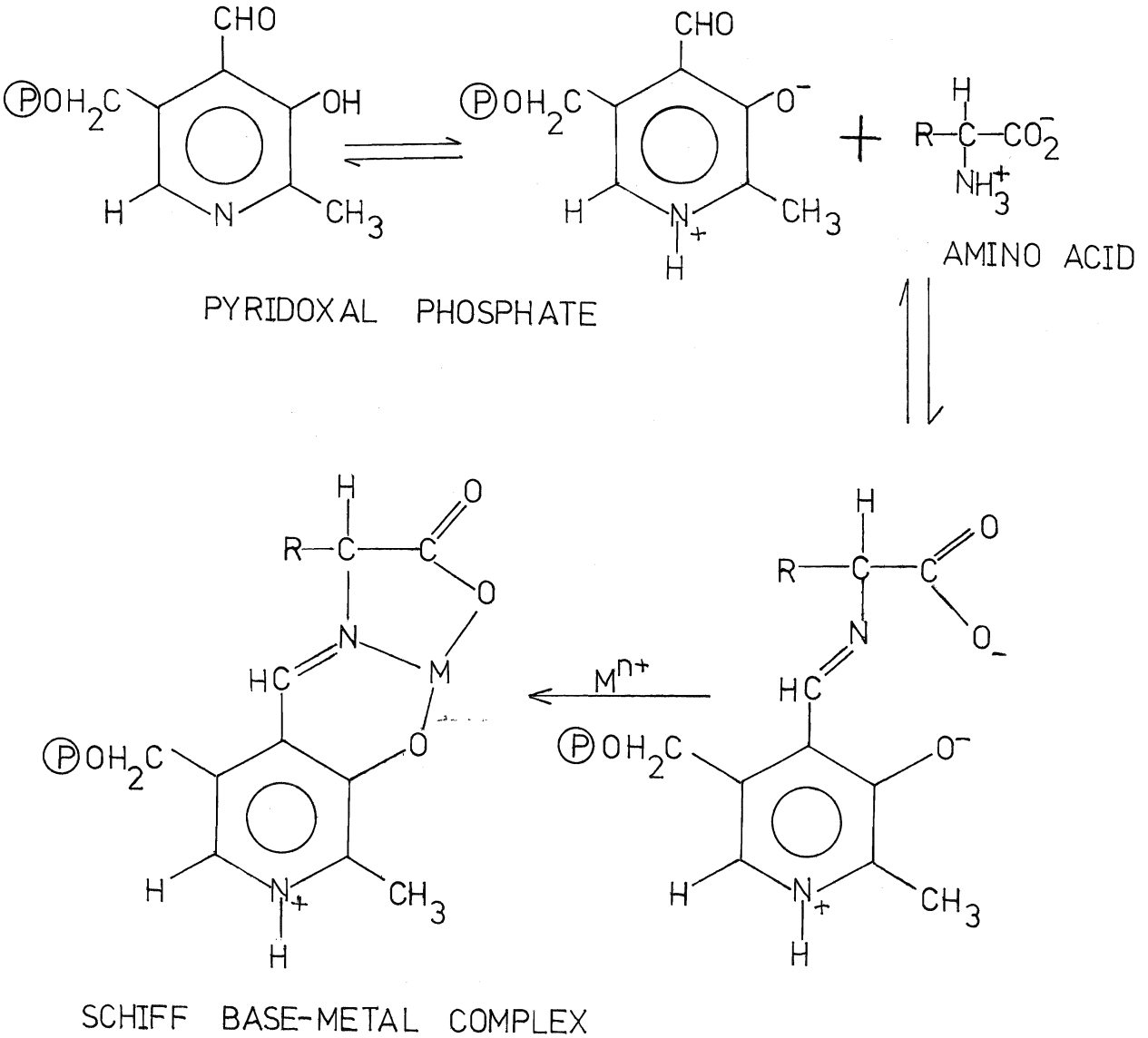
Figure 4. Tautomeric forms of pyridoxamine.



reaction between an α-amino acid and an α-keto acid catalyzed by pyridoxal phosphate has been well studied. These studies led Snell[33] and coworkers to propose a mechanism for the reaction. It involves a reaction of the aldehyde function of the vitamin and the amino group of the amino acid to form a Schiff base as an intermediate. It has been observed[35] that pyridoxal-5-phosphate catalyzed the transamination of α-amino acids in the presence of metal ions such as Cu(II), Fe(III), Al(III), and in the absence of enzymes. On the basis of these observations, non-enzymatic transamination of α-amino acids by pyridoxal-5-phosphate was visualised as proceeding through the formation of the metal chelate containing the Schiff base. Some other typical enzymatic amino acid transformations have been reproduced in non-enzymatic systems. These include the decarboxylation and racemization reactions. Because the non-enzymatic reactions parallel the enzymatic reactions closely, it has been suggested that both reactions proceed through the same mechanism. The non-enzymatic reactions have thus become suitable model reactions for the study of the enzymatic reactions.[37] Figure 5 shows the general mechanism for the formation of the Schiff base-metal complex.

According to the mechanism, a Schiff base is initially formed from pyridoxal-5-phosphate and the α-amino acid. The Schiff base is stabilised by chelating to the metal. The reaction that follows depends on the ability of the electron attracting groups in the chelated complex to withdraw electrons from the region of the α-carbon of the amino acid. The imines derived from the amino acids are prone to cleavage of one of three

Figure 5. General mechanism for the formation of Schiff base-metal complex.



bonds to the α-carbon since the conjugated pyridine system acts as an electron sink. In the enzymatic reactions, a key function of the enzyme is to orient the bond to be broken in the substrate-cofactor complex perpendicular to the plane of the extended conjugated system. If an enzyme orients the amino acid-pyridoxal-5-phosphate or Schiff base complex such that the carboxyl group is perpendicular to the conjugated system, stereoelectronic effects favour decarboxylation. Recent model studies[38] show that in the non-enzymatic reactions, the rate of racemization and hydrogen exchange at the α-carbon of the amino acid-pyridoxal-5-phosphate Schiff base is determined by the proportion of conformer having the C_α-H_α bond orthogonal to the π-system. Such stereoelectronic requirements enable pyridoxal-5-phosphate dependent enzymes to enhance reaction rates and control specificity of bond cleavage by proper conformation orientations. In the pyridoxal-5-phosphate catalyzed enzymatic reaction, reactions seem to occur predominantly on only one side of the enzyme-bound substrate cofactor complex.[39] Figures 6 and 7 show the transamination and decarboxylation processes respectively in the non-enzymatic reactions.

The catalytic roles of the metal ions in the non-enzymatic reactions were first suggested by Longenecker and Snell[40] as follows:

(i) the metal ion maintains the planarity of the Schiff base molecule to facilitate the electron displacement process,

(ii) the metal ion reinforces the displacement of electrons toward the pyridine nitrogen,

(iii) the metal ion acts as a template and thus helps in the formation

Figure 6. Pyridoxal-5-phosphate in transamination.

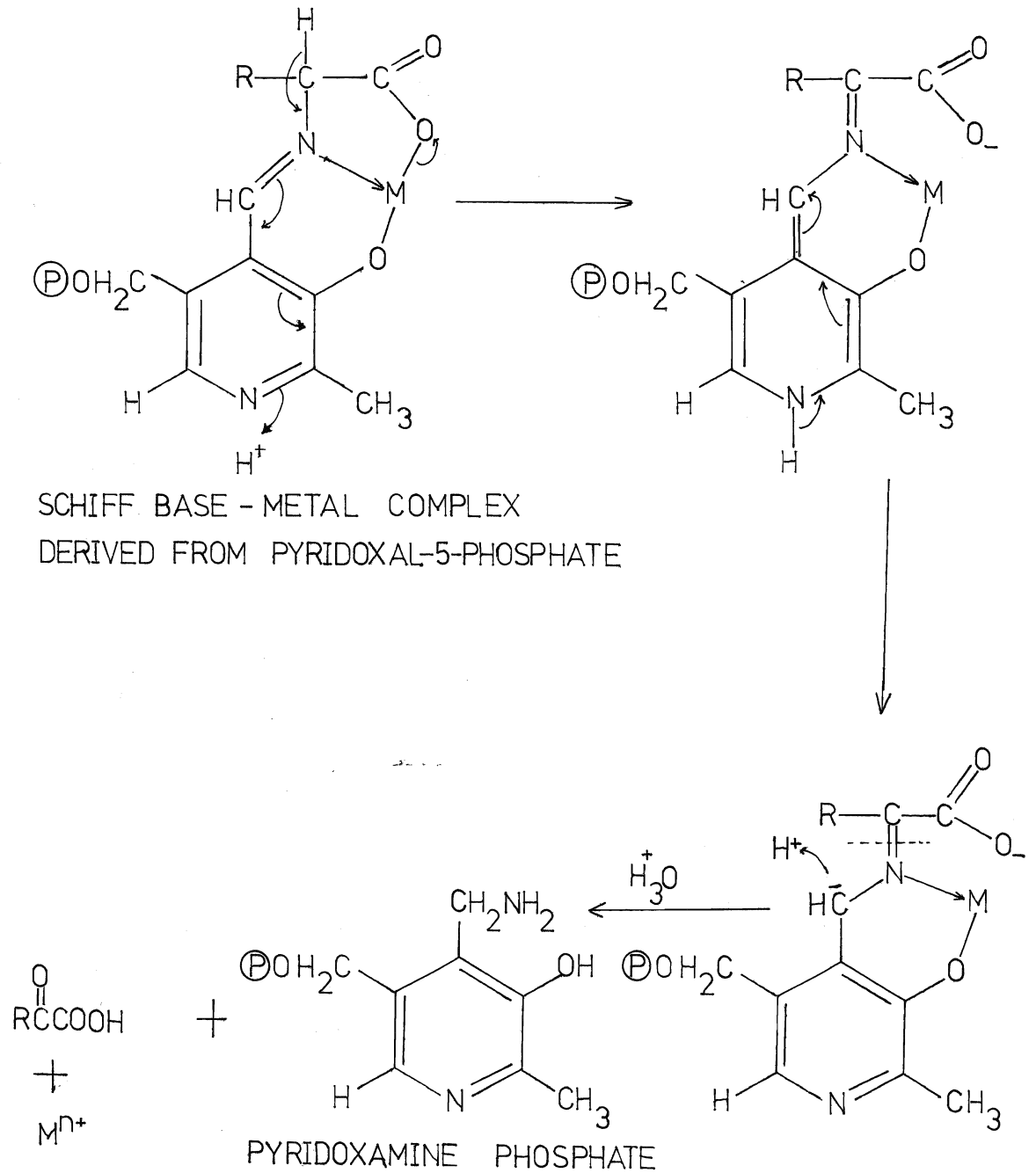
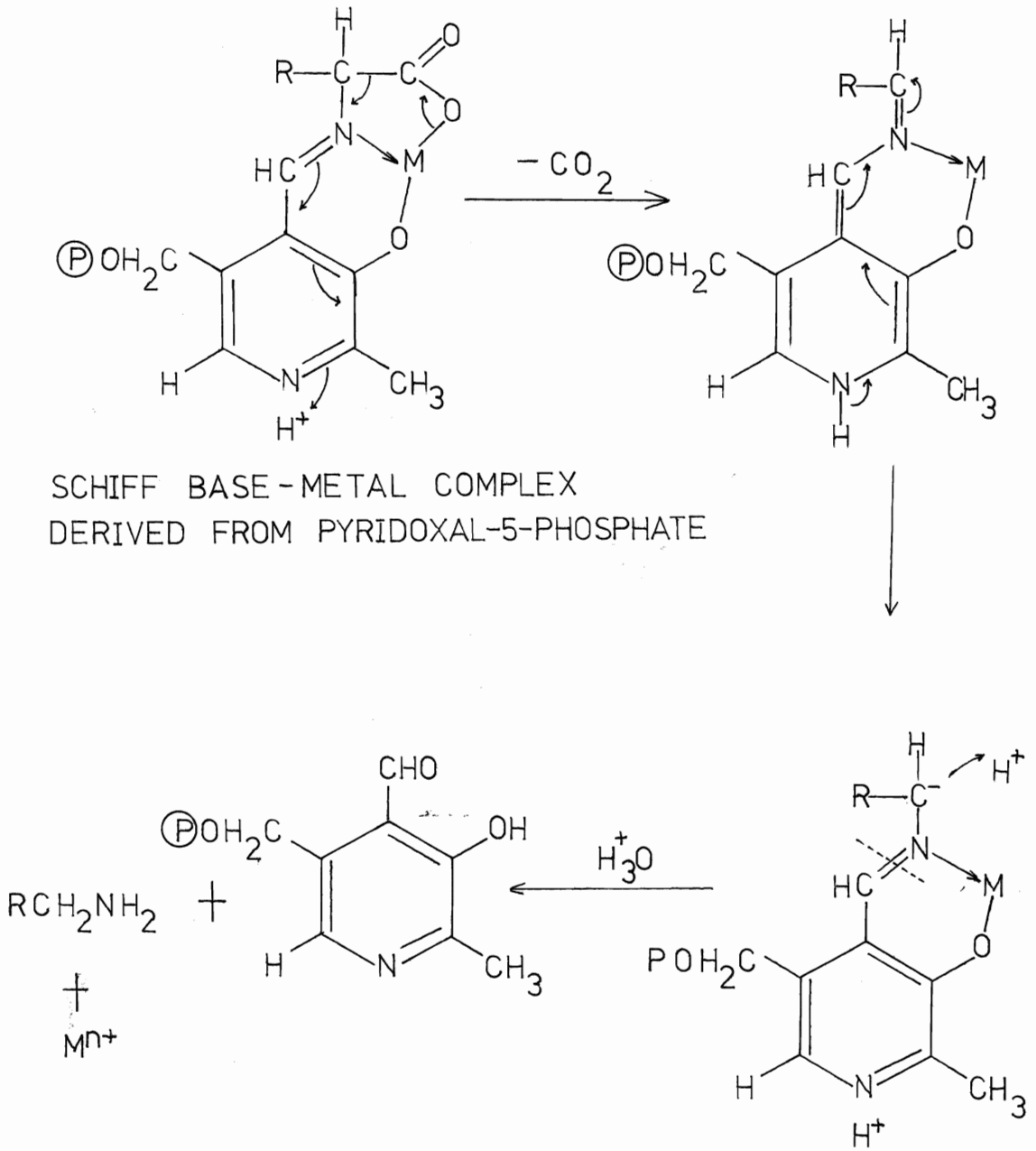


Figure 7. Pyridoxal-5-phosphate in decarboxylation.



of the Schiff base,

(iv) by stabilizing the intermediate the metal ion can promote hydrolysis of the Schiff base.

Since the Schiff base ligand is tridentate, complexes with 2:1 and 1:1 ligand:metal stoichiometry can be formed. Crystal structures[41] of the hydrated complexes, bis(pyridoxylidene-DL-valinato)nickel (II) and bis(pyridoxylidene-L-valinate)zinc (II) show that both compounds consist of discrete molecules with octahedral metal ions bonded to two tridentate Schiff bases. The structure of the Cu(II)-pyridoxylidene complex Cu(pyr-DL-val)[42] also indicates that the Schiff base is tridentate and planar.

For many of the reactions involving pyridoxal-5-phosphate, Cu(II) has been found to be much more effective catalyst than Co(II), Ni(II), Zn(II), Fe(II) or Al(III). The order of catalytic activity as established by Longenecker and Snell[40] is Cu(II) > Al(III) > Fe(II) > Fe(III) > Zn(II) > Ni(II) > Co(II). A small catalytic activity was observed for the series Cd(II) > Cr(II) > Mn(II) -> Mg(II).

Binding of Metal Ions to the B_6 vitamins.

Studies of the binding of metal ions with vitamin B_6 compounds in the absence of amino acids are of particular interest. Since the vitamin B_6 compounds exist in solution as tautomers, chelation to the metal ion depends very much on the pH of the solution or the predominant form of the tautomer present. The compounds of vitamin B_6 may act either as unidentate ligands

and bind the metal ion through the pyridine nitrogen or as a bidentate ligand and chelate the metal ion by the phenolate oxygen and the nitrogen or oxygen at the adjacent group in the 4'-position. There is also the possibility of unidentate binding through the phenolate oxygen. Stability constant determinations[43] of Cu(II) and Ni(II) complexes with pyridoxal gave values which were of comparable magnitude with those of Cu(II) and Ni(II) complexes with pyridine, picoline and 3-hydroxy-methylpyridine. This led to the conclusion that pyridoxal acts as a monodentate ligand and that the heterocyclic ring nitrogen atom was the ligand atom. A later study[44] of the complex equilibria of Mn(II), Ni(II) and Co(II) with pyridoxine and pyridoxal led to the assumption that pyridoxine and pyridoxal make use of the meta-oxy atom in the formation of the complexes.

There is little doubt about the liganding sites in pyridoxamine. As the amino methyl group in pyridoxamine is much more basic than the hydroxymethyl and hydrated aldehyde groups in pyridoxine and pyridoxal respectively, pyridoxamine forms much more stable chelate ring structures than the other ligands. However, a polarographic determination of the stability constants[45] of Cd(II) and Zn(II) complexes with pyridoxamine gave results which imply that pyridoxamine can act as a monodentate ligand and coordinate Zn(II) through the heterocyclic nitrogen atom. The study did not exclude the possibility that the ligand may chelate Zn(II) through the meta-oxy group and the nitrogen atom of the amino group, but in such case mixed monodentate and bidentate complexation of the ligand to Zn(II) may occur.

The crystal structure[46] of a pyridoxamine complex of Zn(II), $[Zn(PM)_2(H_2O)_2](NO_3)_2$ shows that the zinc atom lies on a center of symmetry and is chelated to the aminomethyl nitrogen and the phenolate oxygen of pyridoxamine zwitterion. Recent crystal structure[47,48] and infrared[25] studies of copper complexes of anionic and neutral pyridoxamine show that the copper atoms are chelated to the pyridoxamine ligand through the 4-(aminomethyl) and the phenolate groups of a pyridoxamine zwitterion.

Complexes of pyridoxal-5-phosphate and pyridoxamine-5-phosphate with Cu(II), Co(II) and Zn(II) have been prepared by Farago et al.[49] Their study indicates no case of the pyridine nitrogen involved in coordination. Nuclear magnetic resonance studies[50] using ^{31}P, ^{1}H and ^{13}C of the pyridoxal-5-phosphate-Mn(II) system indicates a structure for the metal PLP complex in which the metal ion is simultaneously bound to the phosphate and the aldehyde oxygens.

The liganding site in pyridoxine seems to depend on the type of solvent medium used. A ^{13}C nmr study has shown that coordination of the metal ions by pyridoxine is through the phenolic oxygen and the oxygen at the adjacent group in the 4'-position in aqueous solution. In water-dimethylsulfoxide mixture, the pyridine nitrogen becomes a more effective donor and with increasing proportions of dimethylsulfoxide some cations are coordinated by dimethylsulfoxide rather than pyridoxine.[51] Single crystal x-ray structure and ^{13}C nmr solution (D_2O) studies[52] of $Cd(PN)Cl_2$ indicate that the pyridoxine molecule is bidentate and chelated to the cation through the phenolic oxygen and the oxygen at the adjacent hydroxymethyl group.

Goals of the Research

Even though there is sufficient evidence for the occurrence of a monodentate coordination of the heterocyclic nitrogen atom to the cation in solution, such complexes have not yet been isolated in the cyrstalline form. Synthesis of such complexes in the crystalline form would be a tremendous step towards the elucidation of their crystal and molecular structures. Such structures could be compared to the normal chelated ones to see what effect the various coordination sites have upon the ligand structure. It would also be interesting to know what effect the heterocyclic nitrogen-metal bond will have on electron displacement process from the α-carbon of the Schiff base intermediates.

In this work, palladium and platinum complexes of pyridoxine, pyridoxal and pyridoxamine and their acid forms have been synthesized. Infrared, ^{13}C nmr and single crystal x-ray diffractometry studies have been done on some of the complexes obtained. It is interesting to note that for the first time, a metal-pyridoxine complex has been obtained in the crystalline form in which the ligand is monodentate and the heterocyclic nitrogen atom is coordinated to the metal.

Chapter II

EXPERIMENTAL

CHEMICALS:

Potassium tetrachloropalladate, K_2PdCl_4, and potassium tetrachloroplatinate, K_2PtCl_4 were purchased from Alfa Products. Palladium(II) chloride, $PdCl_2$, was obtained from Matheson, Coleman and Bell. Pyridoxal hydrochloride, pyridoxamine dihydrochloride and pyridoxal-5-phosphate were purchased from Sigma Chemicals. Pyridoxine hydrochloride was purchased from Eastman Kodak Company.

All reagents were used without further purification.

INSTRUMENTATION:

Infrared spectra in the 4000 cm^{-1} to 200 cm^{-1} range were recorded on a Perkin-Elmer 225 grating infrared spectrophotometer. The samples were prepared as mulls in Nujol. Potassium bromide discs and caesium iodide discs were used to record spectra in the range 4000 cm^{-1} to 600 cm^{-1} and 600 cm^{-1} to 200 cm^{-1} respectively. The spectra were calibrated with polystyrene and the peaks were measured from the chart. ^{13}C nuclear magnetic resonance spectra were obtained at 15.08 MHz on a Bruker WP-60 FT NMR spectrometer at a temperature of 300°K and flip angle of 30° using 0.5 Hz of line broadening. A sweep width of 3759 Hz and a 1.1 second acquisition time were used. Samples were prepared in DMSO-d_6. The internal standard was either TMS or DMSO. The number of scans varied from 2000 to 32000.

Oscillation photographs were taken on a Picker X-ray generating instrument using a Weissenberg camera from Charles Supper Company and No-screen medical x-ray films from Kodak. The films were exposed for about 20 minutes to CuK_α radiation (λ = 1.542 Å). The Weissenberg photographs were taken using nickel filtered CuK_α radiation with exposure times of 12-24 hours. The photographs were indexed and approximate unit cell dimensions and space group were obtained by following the procedures outlined in Stout and Jensen.[53] The crystals were then transferred to a CAD-4 diffractometer and the structures were determined by Professor M. F. Richardson.

ELEMENTAL ANALYSIS:

Elemental analyses were done by Galbraith Laboratories Inc., Knoxville, Tennessee, and Guelph Chemical Laboratories, Guelph, Ontario, and Mikronanalytisches Laboratorium, Bonn, Germany. The analytical results are shown in Table 1.

SYNTHESIS OF COMPOUNDS:

Neutral pyridoxamine, pyridoxine and pyridoxal were prepared by adding aqueous sodium hydroxide solution to the aqueous solutions of the acid forms of the ligands until the pH was between 7 and 8. The precipitated crystals were filtered and washed with water. They were recrystallised in water.

Table 1. Analytical Data

Compound	Found C	H	N	Cl	Metal	Calculated C	H	N	Cl	Metal
$PdCl_2.PM$ $C_8H_{12}N_2O_2PdCl_2$	27.60	3.74	7.72	19.91		27.80	3.50	8.10	20.60	
$PtCl_2.PM.H_2O$ $C_8H_{14}N_2O_3PtCl_2$	21.28	3.11	6.20	16.32		21.24	3.10	6.19	15.71	
$PdCl_2.(PL)_2$ $C_{16}H_{18}N_2O_6PdCl_2$	37.39	4.23	5.43			37.54	3.52	5.48		
<u>trans</u>-$PdCl_2(PN)_2$ $C_{16}H_{22}N_2O_6PdCl_2$	36.90	4.44	5.40	12.89		37.23	4.27	5.43	13.77	
<u>cis</u>-$PdCl_2(PN)_2$ $C_{16}H_{22}N_2O_6PdCl_2$	37.47	4.49	5.57			37.23	4.27	5.43	13.77	
$[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$ $C_8H_{16}N_2O_3PdCl_4$	21.93	3.79	6.38	32.40	23.10	22.02	3.67	6.42	32.57	24.30
$[PLH^+]_2[PtCl_6]^{2-}.2H_2O$ $C_{16}H_{26}N_2O_9PtCl_6$	24.34	3.17	3.45	25.74	22.76	24.62	3.08	3.59	27.30	25.00

Synthesis of $PdCl_2$.PM

K_2PdCl_4 (0.5 g) was dissolved in water (20 mL). PM.$2H_2O$ (0.3 g) was dissolved in warm water (20 mL) and then added to the Pd solution while stirring. A few drops of 0.1 M NaOH solution were added until the pH ≃ 7. The yellow precipitate produced was filtered, washed with water and ethanol. The product was air dried. Several attempts were made to recrystallise the product in various solvents but no crystals were produced. The yellow powder was always obtained. The same yellow powder was obtained at pH 8-9.

$PdCl_2$.PM crystals grown in gel

The gel was formed by titrating 0.5 M NaOH with a 0.5 M sodium metasilicate solution to a pH of 7.5. A solution of K_2PdCl_4 (0.2 g) in water (20 mL) was then added and stirred to ensure thorough mixing. The resulting solution was placed into 50 mL test tubes and allowed to set. About 20 mL of solution was placed in each test tube. The gel set in about 30 minutes.

PM.$2H_2O$ (0.15 g) was dissolved in warm water (20 mL). The solution was allowed to cool to room temperature. Five mL of the PM.$2H_2O$ solution was carefully added to each tube without damaging the gel at the interface. The tubes were lightly stoppered and placed in a closed cupboard. Yellow crystals up to 3 mm in length were produced by the end of two weeks.

Synthesis of $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$

$PdCl_2$ (0.1 g) was added to 0.1 M HCl (10 mL) and benzene (10 mL). The mixture was stirred until all the $PdCl_2$ dissolved. PM (0.1 g) was then added, and stirring continued for two hours. The resulting clear solution was kept in the fume hood to concentrate. Large yellowish-brown needlelike crystals developed. The crystals were filtered, washed with water and finally with acetone and air dried.

Synthesis of $PtCl_2.PM.H_2O$

K_2PtCl_4 (0.25 g) was dissolved in water (10 mL). $PM.2H_2O$ (0.25 g) was dissolved in warm water (30 mL) and allowed to cool to room temperature. The $PM.2H_2O$ solution was added in drops to the Pt solution while stirring. The pH was brought to 7 by addition of a few drops of NaOH solution. The resulting solution was stirred for 15 minutes and then kept in a closed cupboard to ensure slow evaporation. Yellow needlelike crystals were obtained after 2-3 days. The crystals were filtered and washed with water followed by ethanol and air dried.

Synthesis of $[PLH^+]_2[PtCl_6]^{2-}.H_2O$

K_2PtCl_4 (0.5 g) and PLHCl (0.5 g) were added to water (30 mL). The mixture was heated while stirring for about 10 minutes. The resulting solution was allowed to cool and then filtered. The filtrate was kept in the fume hood to evaporate. Orange platelike crystals formed after a day. The crystals were filtered and washed with water and allowed to dry in air.

Synthesis of trans-$PdCl_2(PN)_2$

K_2PdCl_4 (0.3 g) was dissolved in water (20 mL). PN (0.4 g) was dissolved in water (20 mL) and then added in drops to the Pd solution while stirring. The pH of the solution was adjusted to 7 by carefully adding a few drops of NaOH solution. The resulting solution was kept in a closed cupboard to ensure slow evaporation. Small yellow needlelike crystals developed after a day. The crystals were filtered and washed with water and air dried.

There is an immediate precipitation of yellow powder compound if the pH is slightly above 7. At high pH, the precipitate dissolves. Such solutions never produced crystals, but rather gave a thick yellow paste.

Synthesis of cis-$PdCl_2(PN)_2$

K_2PdCl_4 (0.8 g) was dissolved in water (20 mL). PN (0.6 g) was dissolved in water (15 mL). The PN solution was then added in drops to the Pd solution while stirring. The pH of the resulting solution was 6. The solution was left in a closed cupboard to evaporate. Yellow platelike parallelepiped crystals were obtained after a day. The crystals were filtered and washed with water, and finally with ethanol. They were air dried.

Synthesis of cis-$PdCl_2(PL)_2$

K_2PdCl_4 (0.4 g) was dissolved in water (20 mL). PL (0.4 g) was dissolved in warm water (20 mL). The PL solution was allowed to cool to room temperature and then added dropwise to the palladate solution while

stirring. A few drops of NaOH solution were added until the pH was 7, whereupon a yellow precipitate appeared. Stirring was continued for 10 minutes and the precipitate was filtered, washed with water followed by ethanol and then air dried.

Attempts were made to grow crystals of the above product from gel as described in the synthesis of $PdCl_2PM$, but that resulted in bundles of minute crystals unsuitable for single crystal x-ray studies.

Attempted reaction of K_2PtCl_4 with Pyridoxine

K_2PtCl_4 (0.25 g) was dissolved in water (10 mL). An aqueous solution of PN (0.2 g in 10 mL water) was added in drops to the platinate solution while stirring. The pH was adjusted to 7 by addition of a few drops of 0.1 N NaOH solution. The resulting solution was stirred for about 30 minutes, and then kept in a closed cupboard to ensure slow evaporation. Red needlelike crystals developed after 2 days. An infrared spectrum indicated that the crystals are K_2PtCl_4.

A second attempt was made by refluxing the solution for 30 minutes, but PtO deposited during and after refluxing. Other attempts under various pH conditions and in different solvents yielded no good results.

Attempted reactions of $[Pt(H_2O)_4]^{2+}$ with vitamin B_6

A solution of $[Pt(H_2O)_4]^{2+}$ in 1 N $HClO_4$ was prepared as reported by Okeya and Kawaguchi.[54] Portions of the $[Pt(H_2O)_4]^{2+}$ solution were treated separately with equimolar amounts of pyridoxine, pyridoxal, pyridoxal-5-

phosphate and pyridoxamine. The solutions were stirred for 30 minutes and then kept in the fume hood to evaporate. White crystals separated out from the orange-yellow solution. The crystals were filtered and washed with water, and dried in air. The infrared spectra indicate the formation of the acid forms of the ligands.

New reaction mixtures were prepared and attempts made to neutralise the solutions by addition of aqueous NaOH solution. It was not possible to raise the pH above 3. PtO precipitated out of the solution when NaOH solution was added.

Reactions of vitamin B_6 with $[Pd(dien)H_2O](ClO_4)_2$

(a) Synthesis of $PdI_2.H_2O$

A solution of K_2PdCl_4 (1.5 g) in water (40 mL) was heated to about 90°C. Excess KI was added to precipitate virtually insoluble $PdI_2.H_2O$ which was filtered, washed with water and dried in air.

(b) Synthesis of [Pd(dien)I]I

A few drops of water was added to $PdI_2.H_2O$ (1.6 g) to form a thick paste. About 0.2 mL of dien was added in dropwise with stirring. The resultant mixture was baked to dryness on a steam bath. The solid was extracted with water at 90°C. The unreacted $PdI_2.H_2O$ was separated by filtration and the yellow filtrate was evaporated on a steam bath until crystals appeared. The solution was cooled to 5°C and the crystalline

product was filtered, washed with water and dried in air. The infrared spectrum of the product was the same as reported by Watt and Klett.[55]

(c) Synthesis of $[Pd(dien)H_2O](ClO_4)_2$

A suspension of [Pd(dien)I]I (0.8 g) in water (10 mL) was treated with $AgClO_4$ (0.72 g). A rapid precipitation of AgI occurred. The solution was heated for about 12 minutes on a boiling water bath to ensure complete reaction before filtering off the AgI precipitate. The precipitate was washed with about 20 mL of hot water and the combined filtrate was concentrated to 10 mL on a boiling water bath.

(d) Attempted synthesis of $[Pd(dien)vitB_6](ClO_4)_2$

The $[Pd(dien)H_2O](ClO_4)_2$ solution obtained in (c) was divided into three equal portions. Equimolar amounts of solutions of pyridoxal, pyridoxine and pyridoxamine were added separately to the three solutions. Each resultant solution was stirred vigorously for one hour and then left in the fume hood to evaporate. The vitamin B_6 compounds separated out from the yellow solution. More vigorous conditions such as prolonged stirring and heating on boiling water bath produced no complexation.

Chapter III

RESULTS AND DISCUSSION

Synthesis:

The vitamin B_6 compounds were reacted with the palladium and platinum chlorides under different pH conditions. In very acidic conditions, pH = 2, pyridoxamine reacted with the palladium to form brown needlelike crystals. Results of the elemental analysis, shown in Table 1, indicate that the compound has the molecular formula $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$. It looks probable from the formula that there is no direct metal-pyridoxamine bonding. The cation $[PMH_2]^{2+}$ is formed in acidic medium with both the pyridine and the amino nitrogens protonated. Under such conditions, the cation $[PMH_2]^{2+}$ formed the salt with the tetrachloropalladate anion $[PdCl_4]^{2-}$. The salt crystallises out of solution with a molecule of water. At neutral pH, the reaction between pyridoxamine and potassium tetrachloropalladate results in an immediate precipitation of yellow powdered compound. The elemental analysis shows that the yellow powder has the molecular formula $PdCl_2PM$. Under similar conditions, the reaction between pyridoxamine and potassium tetrachloroplatinate produced yellow needlelike crystals after two days. The elemental analysis gave the formula $PtCl_2PM.H_2O$. At pH between 8 and 9, the same yellow powdered compound was obtained in the reaction of pyridoxamine and potassium tetrachloropalladate, but in the case of potassium tetrachloroplatinate, no precipitate could be isolated when the reaction was carried out at a pH between 8 and 9.

The reaction of pyridoxine with potassium tetrachloropalladate produced some interesting results. At neutral pH, the reaction yielded yellow small needlelike crystals after one day. The elemental analysis gave the molecular formula $PdCl_2(PN)_2$. There was an immediate precipitation of yellow powdered compound when the pH was slightly above 7. The infrared spectrum of the powder was the same as that of the yellow needlelike crystals, therefore the powder was not submitted for elemental analysis since it was thought to be the same as the crystalline product obtained at pH 7. At pH above 8, there was no product isolated. The solution on standing formed a thick yellow paste. At pH 6, pyridoxine reacted with the palladate to form yellow platelike crystals. When the crystals were examined under the microscope, they were observed to be flat parallelepipeds with well defined edges. However, the elemental analysis gave the molecular formula $PdCl_2(PN)_2$ which is the same as that obtained for the needlelike crystals obtained at pH 7.

The reaction of pyridoxine with potassium tetrachloroplatinate under similar conditions as used for the palladate and also under more vigorous conditions produced no analogous products. In most cases, the potassium tetrachloroplatinate crystallised out of solution.

Pyridoxal reacted with potassium tetrachloropalladate to produce a yellow complex which precipitates out of solution immediately at pH 7. The elemental analysis indicates that the complex has the molecular formula $PdCl_2(PL)_2$. A mixture of solutions of pyridoxal and potassium tetrachloroplatinate at pH 7-8 on standing overnight, deposited a brown-yellow powder. The product was thought not to be pure, so no elemental analyses were

performed. The infrared spectrum of this product showed a strong band at 1770 cm^{-1}. Some attempts were made to obtain a purer product from this reaction, but with no success. At pH 3-4, pyridoxal formed orange platelike crystals with the platinate after a day. The elemental analysis gave the molecular formula $[PLH^{+}]_2[PtCl_6]^{2-}.H_2O$.

Pyridoxal-5-phosphate produced no complexes with the palladate and the platinate under the reaction conditions employed. The reaction of potassium tetrachloropalladate with pyridoxal-5-phosphate at pH 7 produced greenish needlelike crystals. However, the infrared spectrum of the product did not indicate the presence of pyridoxal-5-phosphate. The product turned out to be the palladate which crystallised out of solution. Similarly, the platinate crystallised out of solution without forming a complex with the ligand.

Various other methods were employed with the aim of producing complexes that might have the pyridine ring nitrogen of the vitamin B_6 compounds directly bonded to the metal. It was thought that by blocking three of the liganding sites in square planar Pd(II) or Pt(II) with a strong tridentate chelating ligand as diethylenetriamine, and occupying the fourth site with a solvent that forms a relatively weak bond to the metal, it might be possible for the vitamin B_6 ligands to substitute the weakly bonded solvent by forming a monodentate bond to the metal. The diethylenetriamine palladium(II)-aquo complex used did not produce a complex with any of the vitamin B_6 ligands under the reaction conditions employed. The vitamin B_6 compounds were also unreactive towards $[Pt(H_2O)_4]^{2+}$. The reactions of

$[Pt(H_2O)_4]^{2+}$ with the vitamin B_6 compounds were carried out in very strong acidic medium in which case all the liganding sites of the vitamin B_6 compounds were protonated. This resulted in the acid forms of the vitamin B_6 compounds crystallising out from the solution. Attempts to neutralise the acid solutions resulted in precipitation of PtO.

Crystallographic study of the complexes

The crystal data for the compounds trans-$PdCl_2(PN)_2$, $PtCl_2PM.H_2O$ and $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ are shown in Table 2.

trans-$PdCl_2(PN)_2$: The single crystal x-ray study shows that the pyridoxine ligands are directly bonded to the metal atom through the heterocyclic ring nitrogen. The molecules lie on centres of symmetry. The Pd atoms are square planar with the two chlorine atoms trans to each other. The structure is shown in Figure 8. The bond distances and angles in trans-$PdCl_2(PN)_2$ are shown in Tables 3 and 4 respectively. The bond distances and angles in the free ligand are also shown. The Pd-N bond distance is 2.030(3) Å. Clark and Palenik[56] have observed that the Pd-N distances found in square planar palladium(II) complexes in which the Pd-N bond is neither sterically hindered nor trans to a very strong metal-ligand bond are in the range 1.99-2.04 Å. The value obtained for trans-$PdCl_2(PN)_2$ is within this range and agrees well with other[57,58] palladium-pyridine nitrogen bond distances. A bond distance of 1.365(4) Å found for the C(2)-O(1) bond indicates that the phenolic group is protonated. This value is comparable to that obtained for the free ligand (1.374(4) Å)

Table 2. Crystal Data

	trans-$PdCl_2(PN)_2$	$[PLH^+]_2[PtCl_6]^{2-}.H_2O$	$PtCl_2PM.H_2O$
Formula	$PdCl_2C_{16}H_{22}N_2O_6$	$PtCl_6C_{16}H_{20}N_2O_6.H_2O$	$PtCl_2C_8H_{12}N_2O_2.H_2O$
M.W.	515.40	760.40	452.10
Crystal System	monoclinic	triclinic	orthorhombic
a (Å)	5.271(2)	7.355(2)	7.028(1)
b (Å)	17.263(2)	8.534(2)	12.788(1)
c (Å)	10.269(1)	11.555(2)	13.435(2)
α (°)	90.00	71.73(2)	90.00
β (°)	95.41(2)	73.10(2)	90.00
γ (°)	90.00	66.79(2)	90.00
V ($Å^3$)	930.25	621.26	1207.46
Space group	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$
d_{obs} (g/cm^3)	1.78	2.025	2.46
d_{calc} (g/cm^3)	1.84	2.032	2.49
Z	2	1	4
R	0.030	0.059	0.030
R_w	0.034	0.056	0.031

Cell dimensions determined from 25 accurately centered reflections, MoKα radiation, on a CAD-4 diffractometer.

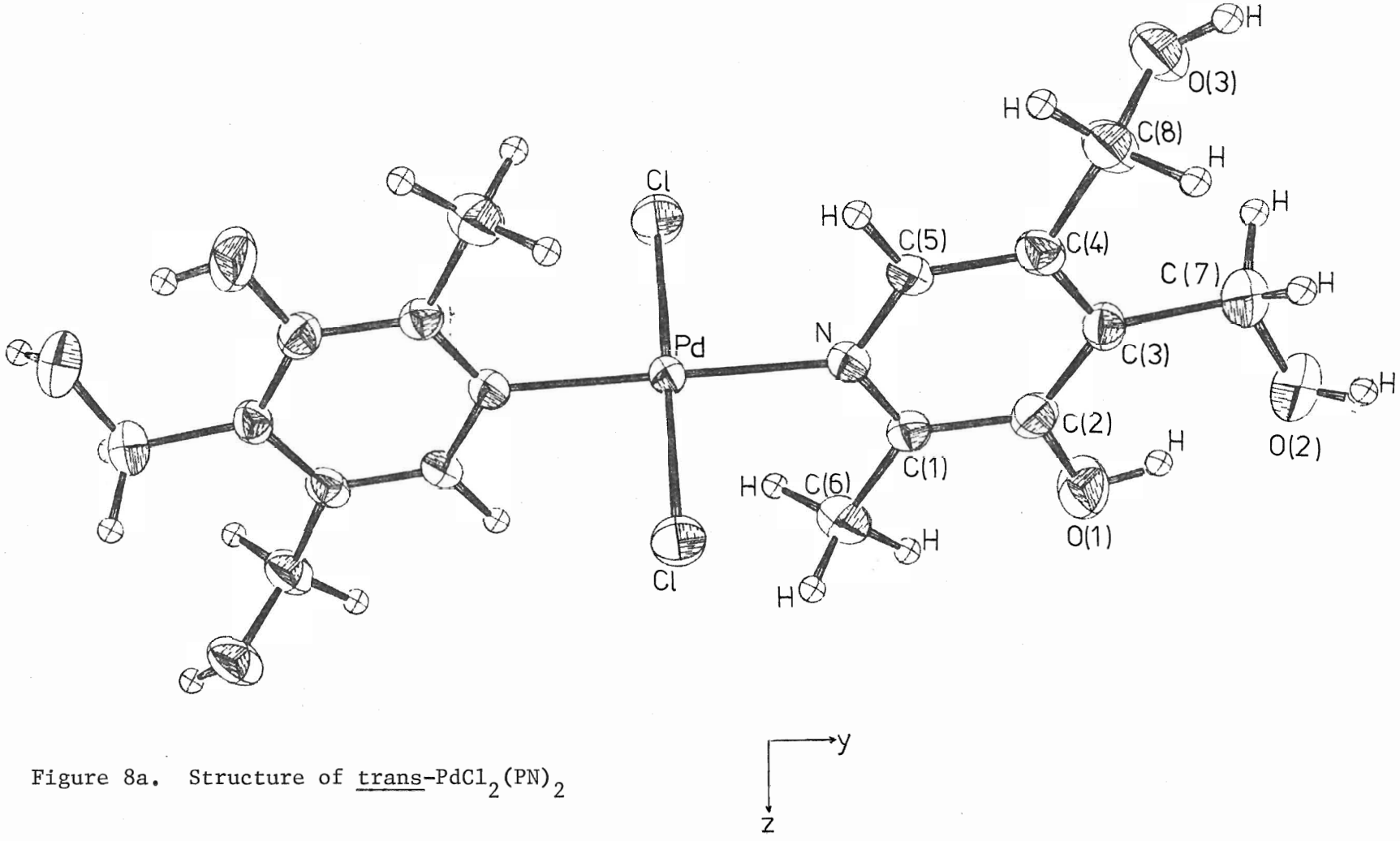


Figure 8a. Structure of <u>trans</u>-$PdCl_2(PN)_2$

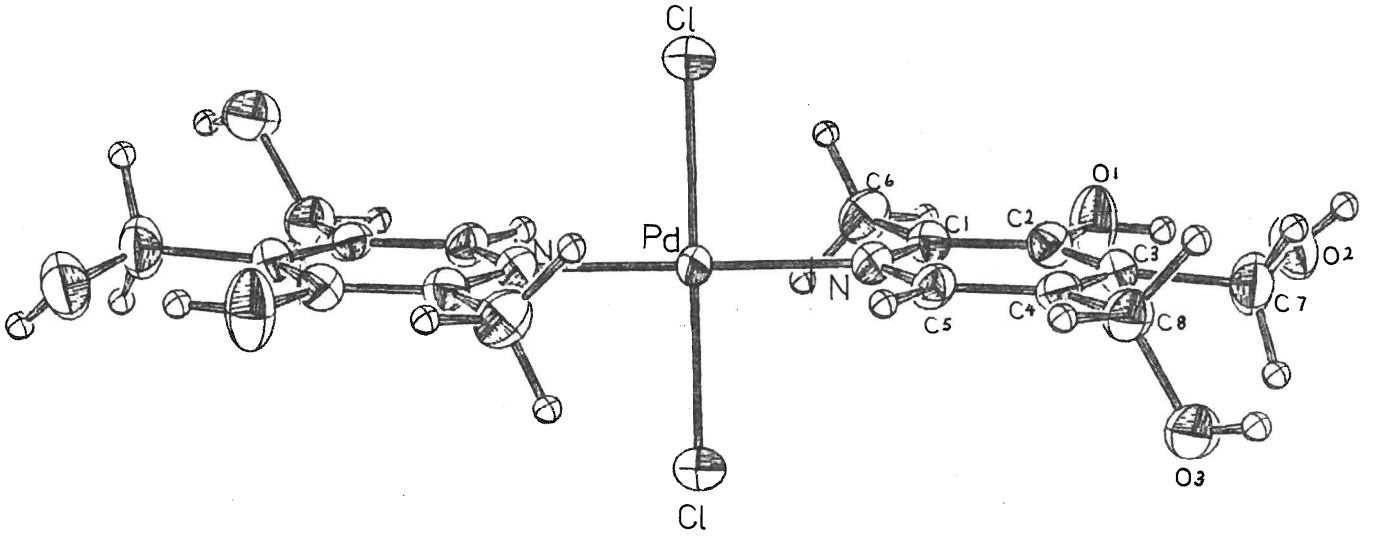


Figure 8b. Structure of <u>trans</u>-$PdCl_2(PN)_2$ plotted on projection perpendicular to the $PdCl_2N_2$ plane.

Table 3. Bond lengths in trans-$PdCl_2(PN)_2$ and in the free ligand

	trans-$PdCl_2(PN)_2$ (Å)	free ligand[23] (Å)
C(1)-C(2)	1.406(5)	1.394(5)
C(2)-C(3)	1.382(5)	1.389(5)
C(3)-C(4)	1.407(5)	1.401(5)
C(4)-C(5)	1.385(5)	1.370(5)
C(5)-N	1.335(4)	1.340(5)
N-C(1)	1.347(4)	1.332(4)
C(1)-C(6)	1.489(5)	1.507(5)
C(2)-O(1)	1.365(4)	1.374(4)
C(3)-C(7)	1.514(5)	1.518(5)
C(7)-O(2)	1.426(5)	1.391(5)
C(4)-C(8)	1.511(5)	1.521(5)
C(8)-O(3)	1.429(5)	1.422(4)
Pd-N	2.030(3)	
Pd-Cl	2.314(1)	

Table 4. Bond angles in trans-$PdCl_2(PN)_2$ and in the free ligand

	trans-$PdCl_2(PN)_2$ (°)	free ligand[23] (°)
C(2)-C(1)-N	119.2(3)	120.8(3)
C(6)-C(1)-C(2)	120.4(3)	120.5(3)
C(6)-C(1)-N	120.3(3)	118.7(3)
C(1)-C(2)-O(1)	115.1(3)	117.3(3)
C(3)-C(2)-O(1)	123.2(3)	122.3(3)
C(3)-C(2)-C(1)	121.6(3)	120.3(3)
C(7)-C(3)-C(2)	123.8(3)	121.8(3)
C(7)-C(3)-C(4)	118.9(3)	120.6(3)
C(5)-C(4)-C(3)	118.7(3)	118.6(3)
C(8)-C(4)-C(3)	122.3(3)	120.3(3)
C(8)-C(4)-C(5)	119.0(3)	121.1(3)
C(3)-C(7)-O(2)	112.2(3)	111.2(3)
C(4)-C(8)-O(3)	109.6(3)	112.2(3)
C(4)-C(5)-N	122.9(3)	123.3(3)
C(4)-C(3)-C(2)	117.3(3)	117.7(3)
C(5)-N-C(1)	120.2(3)	119.3(3)
C(1)-N-Pd	122.2(2)	--
C(5)-N-Pd	117.6(2)	--
N-Pd-Cl	90.6(1)	--

which was observed[23] to have an unionised phenolic group. It is, however, longer than those found in complexes with deprotonated phenolic group as in $Cu(PM\text{-}H)_2.2H_2O$[48] and (pyr-DL-valinato)Cu(II)[59] where values of 1.330(3) Å and 1.310(9) Å respectively were obtained. The C(5)-N-C(1) bond angle in trans-$PdCl_2(PN)_2$ is 120.2°. In the free ligand, this angle is 119.3° as expected for a non-protonated pyridine ring.[60] In pyridoxine monohydrochloride where the pyridine ring nitrogen is protonated, the C(5)-N-C(1) bond angle was found[61] to be 124.7°. Since the pyridine ring nitrogen is coordinated to the metal in trans-$PdCl_2(PN)_2$, it might be expected that coordination will lead to the opening of the C(5)-N-C(1) bond angle to a value comparable to that obtained in PNHCl. It looks as if coordination of the ring nitrogen atom to the metal had no significant effect on the C(5)-N-C(1) bond angle. Comparison of the bond distances in the coordinated and free ligand shows no appreciable difference between the two values.

The pyridine ring is capable of π-bonding with the filled d-orbitals of the central metal atom[62] so that electron deficiency that might have resulted over the ring from the pyridine nitrogen-metal bond is replenished. Such a situation will tend to keep the π-electrons delocalised over the ring system approximately constant. The pyridoxine ligand might be capable of similar back-bonding and therefore offset the effect of the palladium-pyridine nitrogen bond on the ring. Another possible explanation might be the effect of the larger size of palladium compared to hydrogen, thus preventing the opening of the C(5)-N-C(1) bond angle on coordination.

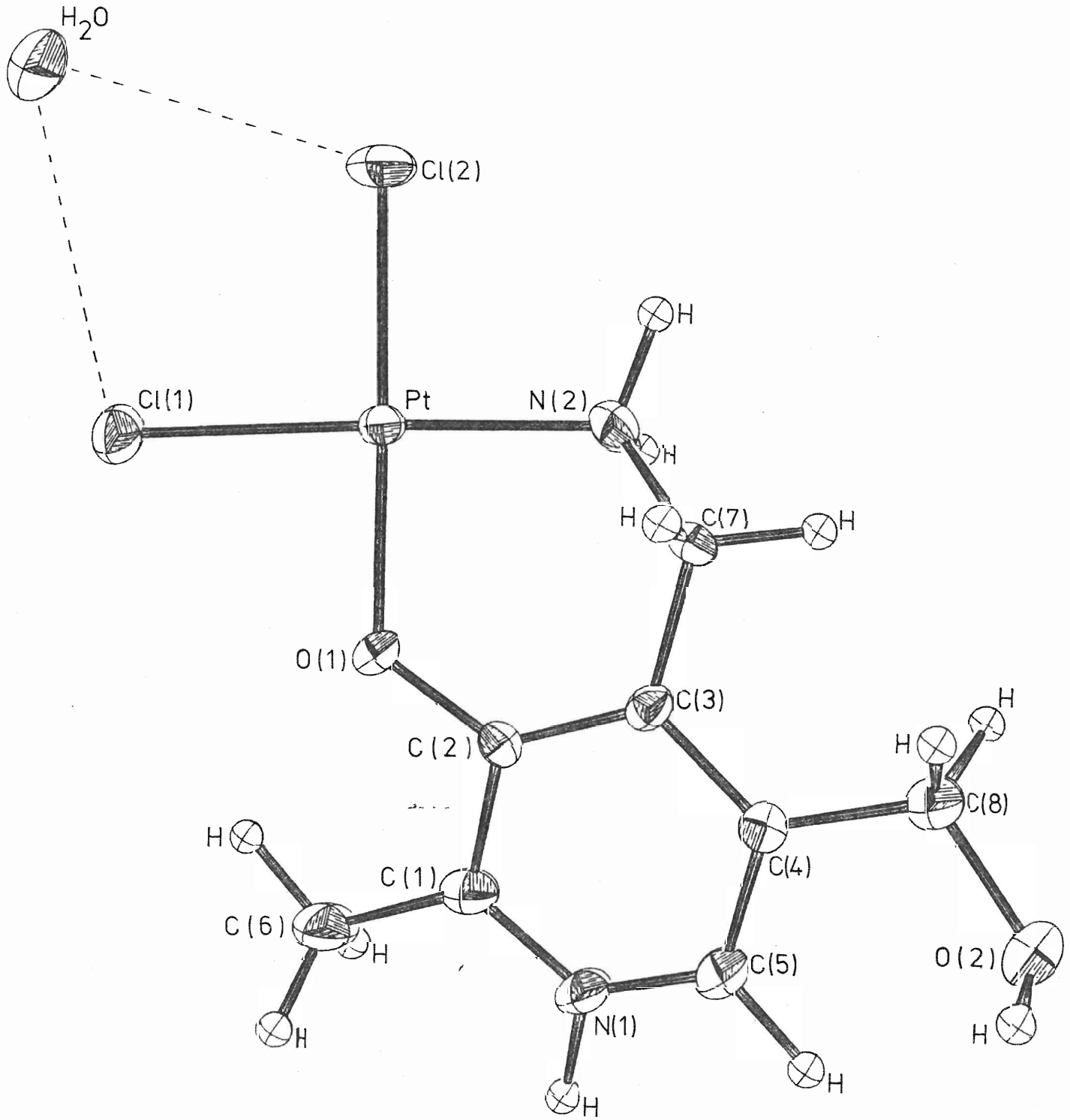
$PtCl_2PM.H_2O$: The bond distances and angles are shown in Table 5. The crystal structure shows that the platinum atom is square planar and is chelated to pyridoxamine through the phenolate oxygen and the aminomethyl nitrogen atoms. The pyridine ring nitrogen is protonated. The structure of the complex is shown in Figure 9. The Pt-O(1) and Pt-N(2) bond distances are 2.015(4) Å and 2.031(6) Å respectively. Also the Pt-Cl(1) and Pt-Cl(2) distances are 2.313(2) Å and 2.286(2) Å respectively. These values agree well with other[63,64,65] Pt-O, Pt-N and Pt-Cl bond distances. The short Pt-Cl(2) distance compared with Pt-Cl(1) distance is expected since the Pt-Cl(2) bond is trans to a stronger metal-oxygen bond. The bond angles and distances in the coordinated pyridoxamine are similar to those found[46,48] in the zinc and copper complexes of pyridoxamine.

$[PLH^+]_2[PtCl_6]^{2-}.H_2O$: The structure shows that both pyridoxal groups are protonated at the pyridine ring nitrogen atoms. The phenolic groups are unionised. Each pyridoxal molecule exists in the hemiacetal form. The bond distances and angles are shown in Table 6. The C(5)-N-C(1) bond angle is 126.3° as expected for protonated pyridine ring nitrogen. The angle is higher than that obtained for trans-$PdCl_2(PN)_2$, but compares favourably with values obtained for PNHCl (124.7°) by Bacon and Plant[61] and for PMHCl (125.1°) by Longo and Richardson.[24] The platinum is octahedrally coordinated in the $[PtCl_6]^{2-}$ anion with an average Pt-Cl distance of 2.32 Å. The Cl(2) and Cl(2') atoms are hydrogen bonded through N-H of the pyridoxal cations. Figures 10 and 11 show the structures of the $[PLH^+]$ and $[PtCl_6]^{2-}$ groups in $[PLH^+]_2[PtCl_6]^{2-}.H_2O$.

Table 5. Bond distances and angles in $PtCl_2PM.H_2O$.

	Distance (Å)		Angle (°)
C(2)-O(1)	1.342(7)	C(5)-N(1)-C(1)	125.2(6)
C(8)-O(2)	1.444(8)	C(2)-C(1)-N(1)	116.4(6)
C(5)-N(1)	1.319(9)	C(6)-C(1)-N(1)	121.1(6)
C(1)-N(1)	1.334(8)	C(6)-C(1)-C(2)	122.4(6)
C(7)-N(2)	1.487(9)	C(1)-C(2)-O(1)	112.8(5)
C(6)-C(1)	1.495(9)	C(3)-C(2)-O(1)	126.7(5)
C(1)-C(2)	1.429(8)	C(3)-C(2)-C(1)	120.4(6)
C(3)-C(2)	1.407(8)	C(4)-C(3)-C(2)	118.8(6)
C(4)-C(3)	1.402(8)	C(7)-C(3)-C(2)	122.1(5)
C(7)-C(3)	1.501(8)	C(7)-C(3)-C(4)	119.1(6)
C(4)-C(5)	1.403(9)	C(5)-C(4)-C(3)	118.0(6)
C(8)-C(4)	1.490(9)	C(8)-C(4)-C(3)	122.3(6)
C(1)-C(6)	1.495(9)	C(8)-C(4)-C(5)	119.7(6)
		C(4)-C(5)-N(1)	120.8(6)
Pt-Cl(1)	2.313(2)	C(3)-C(7)-N(2)	114.2(5)
Pt-Cl(2)	2.286(2)	C(4)-C(8)-O(2)	113.3(6)
Pt-O(1)	2.015(4)	C(2)-O(1)-Pt	124.9(4)
Pt-N(2)	2.031(6)	N(2)-Pt-O(1)	90.9(2)
		N(2)-Pt-Cl(2)	90.4(2)
		N(2)-Pt-Cl(1)	177.8(2)
		O(1)-Pt-Cl(2)	177.8(2)
		O(1)-Pt-Cl(1)	86.9(1)
		Cl(2)-Pt-Cl(1)	91.8(1)

Figure 9. Structure of $PtCl_2PM.H_2O$

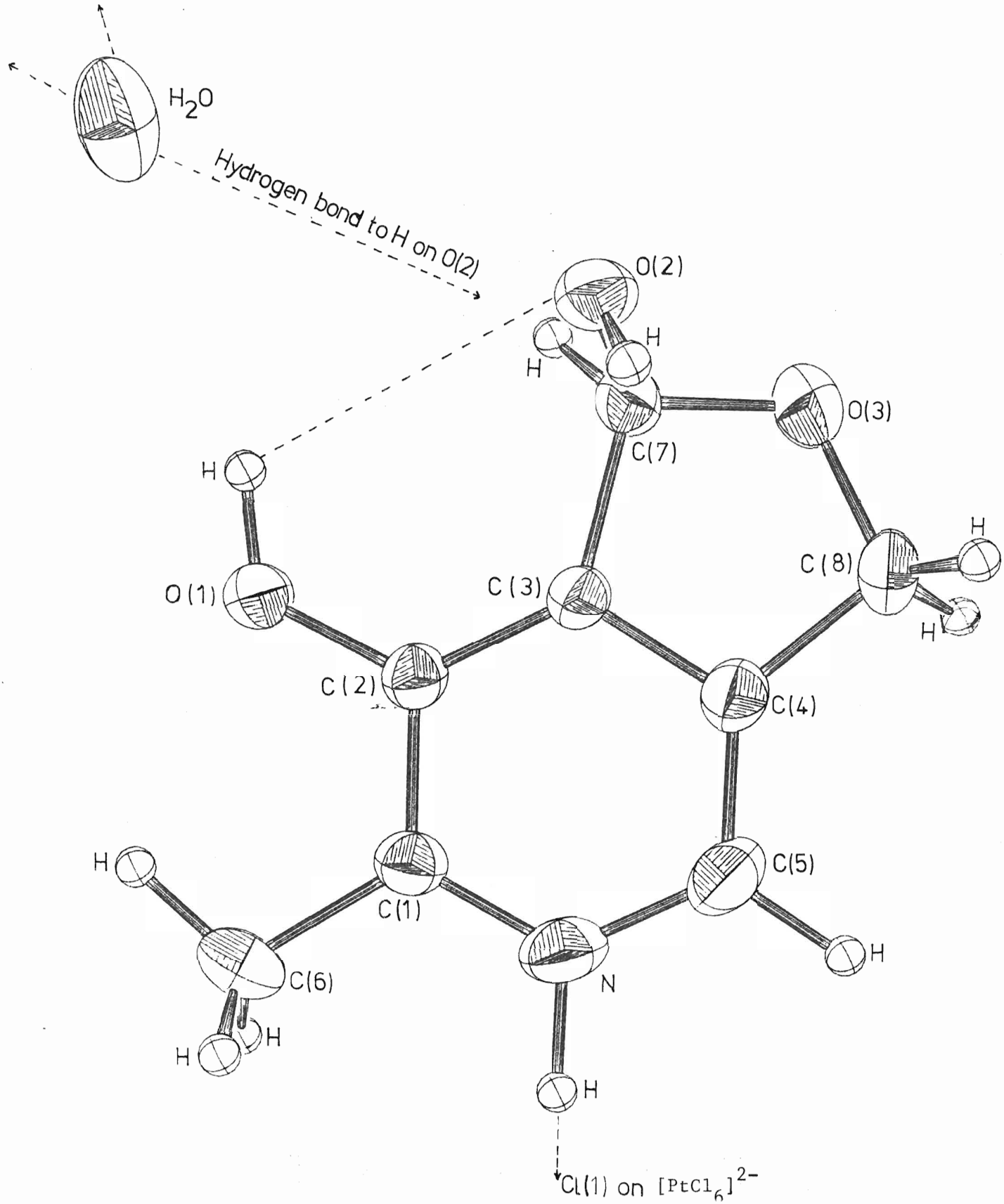


----- = hydrogen bonding

Table 6. Bond distances and angles in $[PLH^+]_2[PtCl_6]^{2-}.H_2O$

	Distance (Å)		Angle (°)
C(1)-C(2)	1.416(9)	C(5)-N-C(1)	126.2(6)
C(2)-C(3)	1.384(8)	C(2)-C(1)-N	118.2(6)
C(3)-C(4)	1.387(9)	C(4)-C(5)-N	116.9(7)
C(4)-C(5)	1.381(10)	C(6)-C(1)-N	120.0(7)
C(5)-N	1.344(11)	C(6)-C(1)-C(2)	121.8(7)
N-C(1)	1.334(10)	C(1)-C(2)-O(1)	116.4(6)
C(1)-C(6)	1.493(10)	C(1)-C(2)-C(3)	117.1(6)
C(2)-O(1)	1.334(8)	C(4)-C(8)-O(3)	103.8(6)
C(3)-C(7)	1.517(9)	C(8)-C(4)-C(5)	131.1(7)
C(7)-O(2)	1.408(9)	C(8)-C(4)-C(3)	109.2(6)
C(7)-O(3)	1.404(8)	C(8)-O(3)-C(7)	111.2(5)
C(4)-C(8)	1.496(10)	C(5)-C(4)-C(3)	119.7(7)
C(8)-O(3)	1.443(10)	C(2)-C(3)-C(7)	130.0(6)
		C(4)-C(3)-C(7)	108.0(6)
Pt-Cl(1)	2.319(2)	C(4)-C(3)-C(2)	121.9(6)
Pt-Cl(2)	2.322(2)	O(3)-C(7)-O(2)	112.5(6)
Pt-Cl(3)	2.314(2)	C(3)-C(7)-O(2)	110.3(5)
		C(3)-C(7)-O(3)	104.1(5)
		C(3)-C(2)-O(1)	126.5(5)
		Cl(2)-Pt-Cl(1)	90.6(1)
		Cl(3)-Pt-Cl(1)	89.4(1)
		Cl(3)-Pt-Cl(2)	88.7(1)

Figure 10. Structure of $[PLH^+]$ in $[PLH^+]_2[PtCl_6]^{2-}.H_2O$



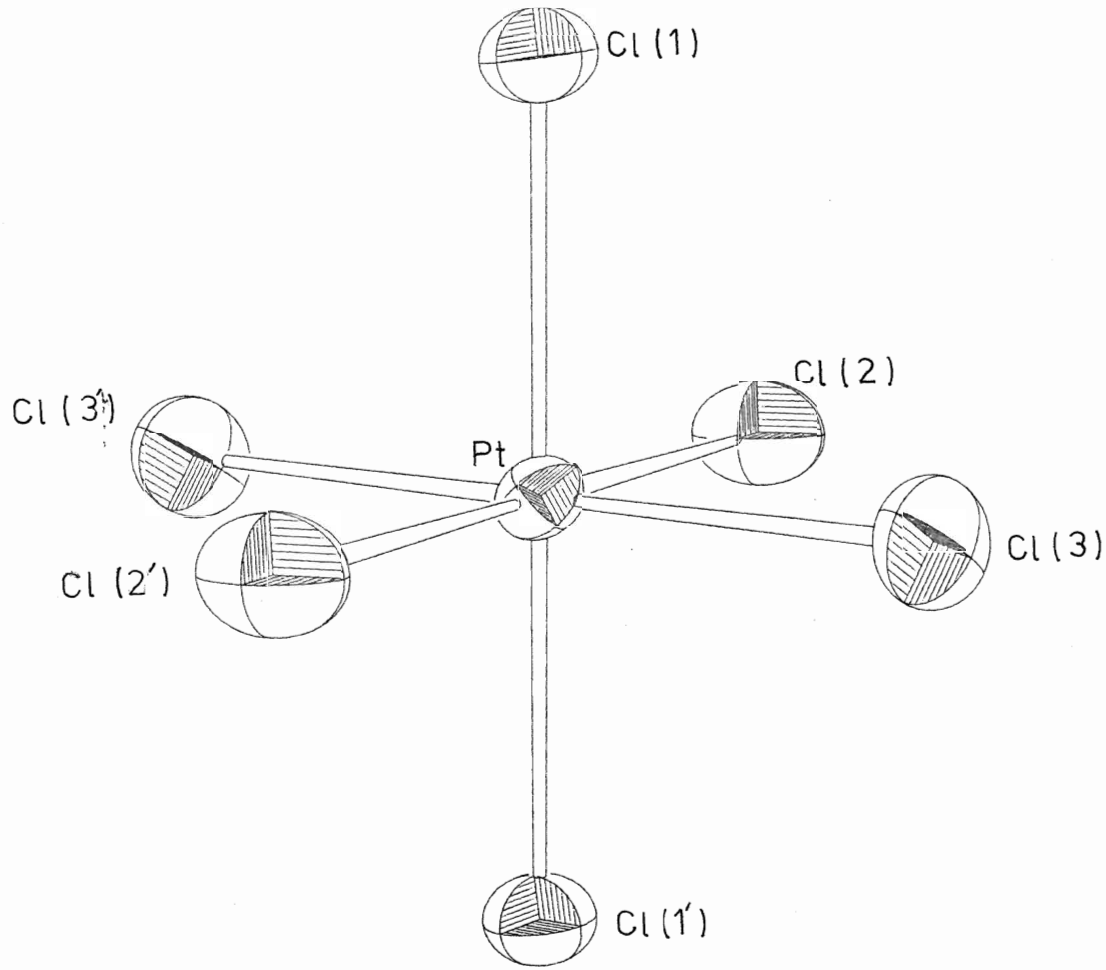


Figure 11. Structure of $[PtCl_6]^{2-}$ in $[PLH^+]_2[PtCl_6]^{2-}.H_2O$

$PdCl_2PM$ and cis-$PdCl_2(PL)_2$: Crystals of $PdCl_2PM$ and cis-$PdCl_2(PL)_2$ were grown in gels. The yellow needlelike crystals obtained for $PdCl_2PM$ were found to have minute crystals on their surfaces and therefore could not be used for single crystal x-ray studies. In the case of cis-$PdCl_2(PL)_2$, bundles of minute crystals which were unsuitable for crystallographic studies were obtained from the gel.

Infrared spectra of the ligands:

The vibrational spectra of pyridine, pyridinium ion and substituted pyridines have been well documented.[63,64,65,66,67,68] By comparison of the spectra of the vitamin B_6 compounds with those of pyridine, pyridinium ion and the substituted pyridines, some vibrational frequencies in the vitamin B_6 compounds have been assigned.[25,69]

The following paragraphs are meant to point out the major features in the infrared spectra of the ligands. These features will then be used to show the possible structures of the complexes.

There are four characteristic bands near 1630, 1610, 1535 and 1485 cm^{-1} in the spectra of the pyridine compounds. These peaks are associated with the ring breathing frequencies. The occurrence of HOH and HNH bending modes of about 1650 and 1600 cm^{-1}, however, makes the identification of the pyridine peaks at 1630 and 1610 cm^{-1} difficult. The four ring breathing modes of pyridine and substituted pyridines have been observed to shift to higher frequencies in pyridinium salts. The ring modes are of variable intensities and depend on the substituents. The band at about 1535 cm^{-1} is present in all the protonated pyridine compounds.

The infrared spectrum of neutral pyridoxal, Figure 12, has been discussed by Heinert and Martell.[69] They noted that the C=O stretching band is absent and attributed this to the occurrence of pyridoxal predominantly in the hemiacetal form. Three weak and sharp bands between 2100 and 2000 cm^{-1} have been considered as indication of the dipolar nature of the compound in the crystalline state. There is no free O-H band. Bands at about 3175, 3090 and 2740 cm^{-1} have been assigned to the chelated O-H and intermolecular O...H-N bands. The band of 1540 cm^{-1} suggests that the pyridine ring nitrogen is protonated. Figure 13 shows the structure of crystalline pyridoxal as proposed by Heinert and Martell.[69]

The infrared spectrum of pyridoxal monohydrochloride, Figure 14, like the spectrum of neutral pyridoxal, has a strong peak at 1545 cm^{-1} and a medium peak at 1625 cm^{-1}. The peak at 1545 cm^{-1} indicates that the pyridine ring nitrogen is protonated. There is no carbonyl stretching peak, and hence the pyridoxal monohydrochloride might also exist as the hemiacetal form. The bands between 2100 and 2000 cm^{-1} in the spectrum of the neutral pyridoxal are absent in the spectrum of PLHCl.

There is no strong band between 1600 and 1500 cm^{-1} in the spectrum, Figure 15, of neutral pyridoxamine. This is an indication of the absence of a protonated pyridine ring nitrogen. There is a weak peak at 1620 cm^{-1} which could be assigned to a ring breathing frequency or the HNH bending mode. The weak peak at 2080 cm^{-1} shows the presence of a protonated amino group.[70] The broad band above 3000 cm^{-1} is due to NH and OH stretching vibration.

Figure 12. Infrared spectrum of pyridoxal.

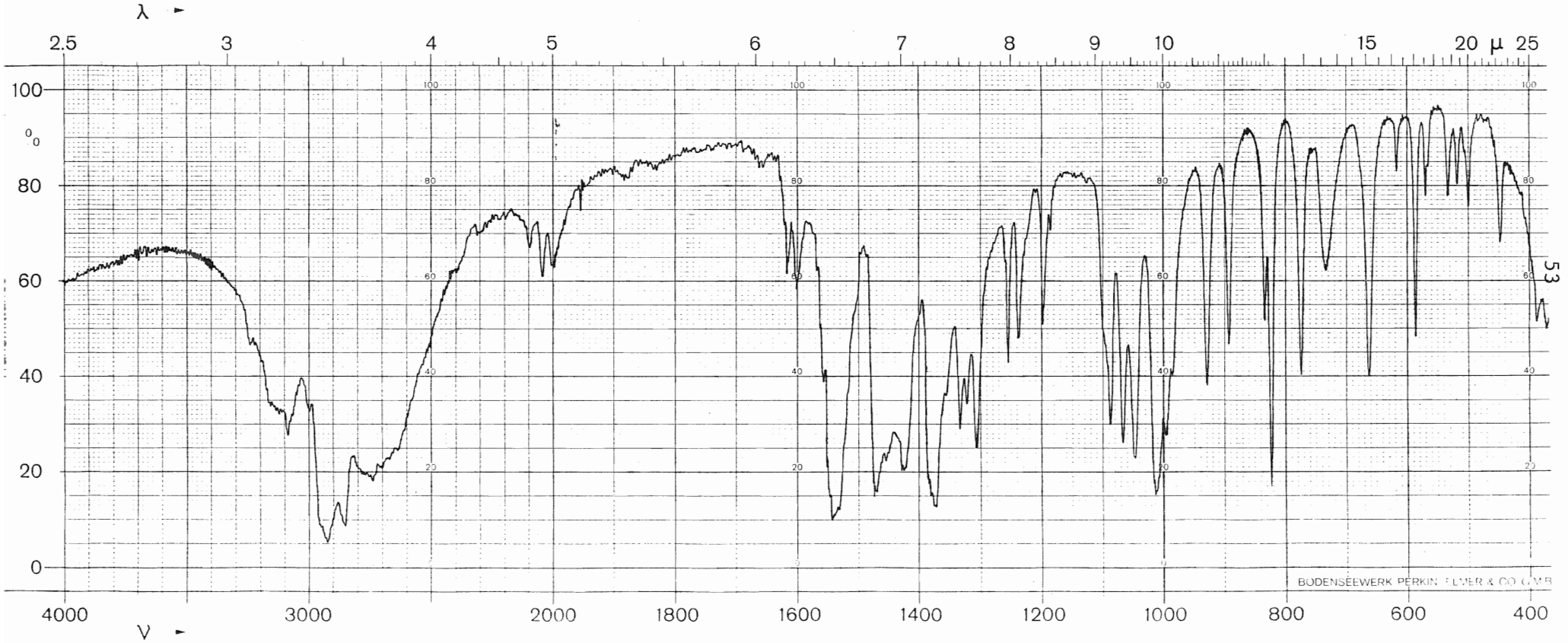


Figure 13. Structure of crystalline pyridoxal (free base).

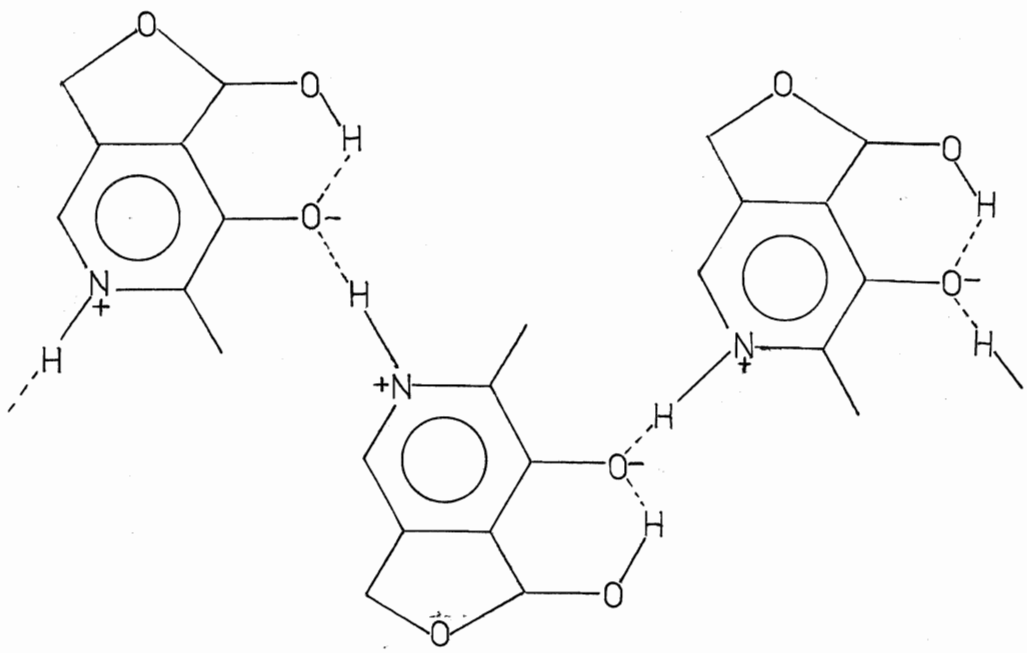


Figure 14. Infrared spectrum of pyridoxal monohydrochloride.

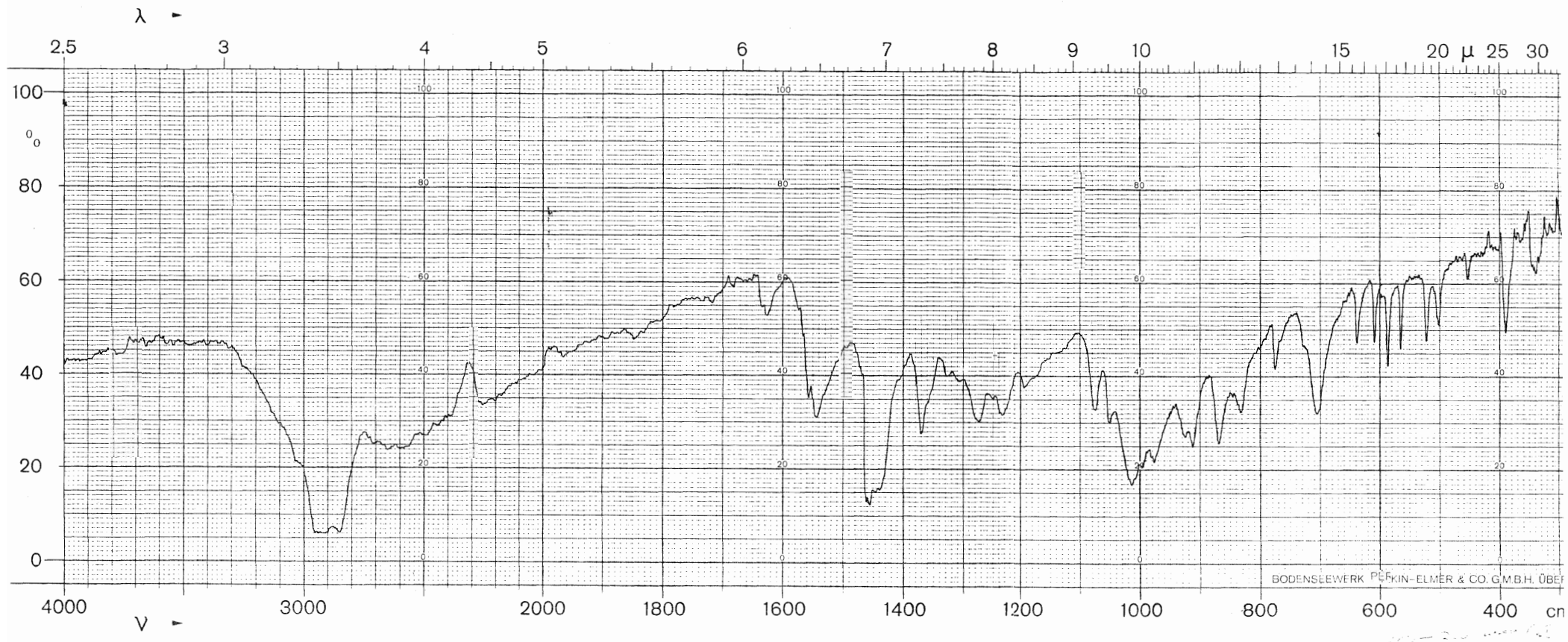


Figure 15. Infrared spectrum of $PM.2H_2O$.

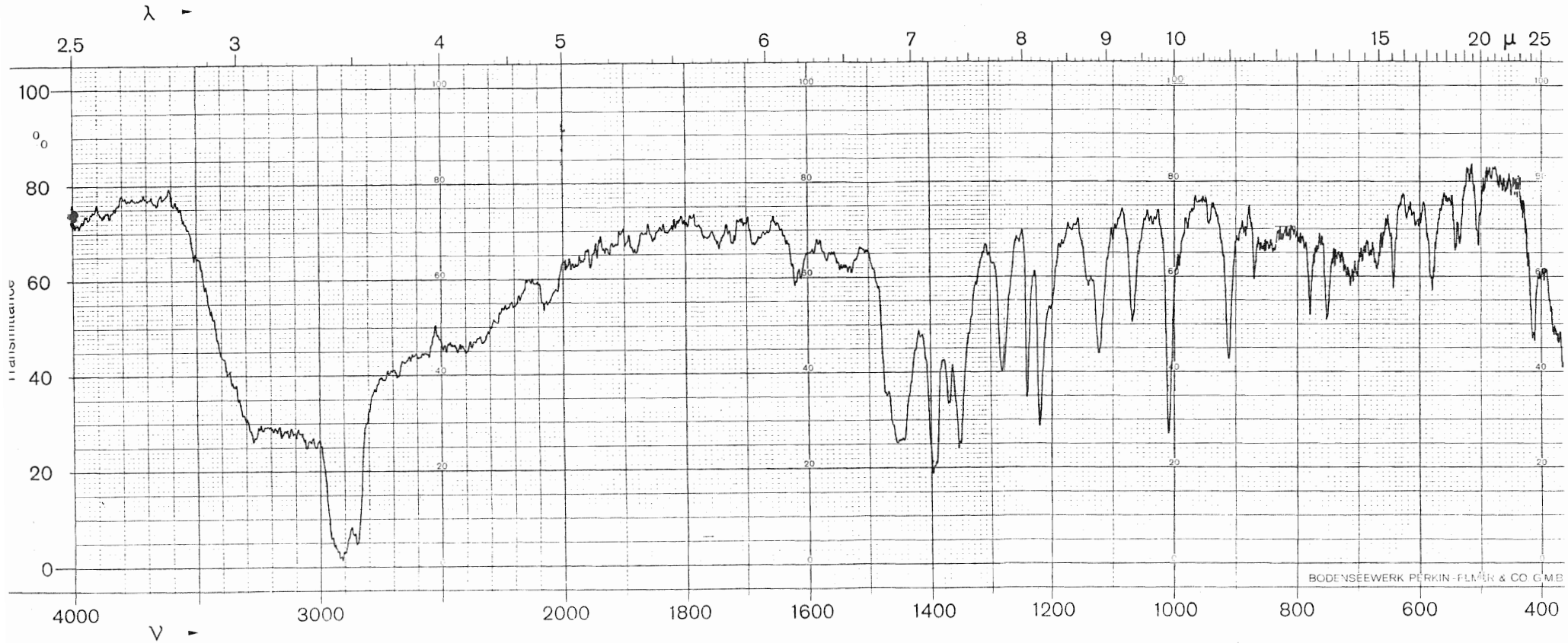


Figure 16 shows the infrared spectrum of pyridoxamine dihydrochloride. The spectrum exhibits a strong peak at 1535 cm^{-1} for a protonated pyridine nitrogen. There is a weak band at 1760 cm^{-1} which is also present in the spectrum of the neutral pyridoxamine, but it is hard to say which frequency this might be attributed to even though it has been observed that the weak peaks between 2200 and 1700 cm^{-1} could be due to the $-NH_3^+$ combination bands.

The spectrum of neutral pyridoxine, Figure 17, shows no strong peaks between 1600 cm^{-1} and 1500 cm^{-1}. An infrared study by Franklin and Richardson[25] shows that the weak peaks between 1600 and 1500 cm^{-1} in the spectra of neutral pyridoxine and pyridoxamine are essentially unchanged in the spectra of the deuterated compounds, and therefore cannot be attributed to the presence of a protonated pyridine nitrogen. The absence of a protonated pyridine nitrogen has been confirmed by single crystal x-ray studies.[23]

In contrast to the spectrum of neutral PN, the spectrum of pyridoxine monohydrochloride, Figure 18 shows strong peaks at 1540 cm^{-1} and 1620 cm^{-1}. The presence of a protonated pyridine ring nitrogen is obvious from the appearance of the peak at 1540 cm^{-1}. That the pyridine ring nitrogen is protonated is confirmed by the single crystal x-ray studies done by Hanic[71] and also neutron diffraction studies by Bacon and Plant.[61]

A peak at 405 cm^{-1} in the spectrum of pyridine has been assigned to the out-of-plane ring deformation. In neutral pyridoxamine, pyridoxine and pyridoxal, Figure 19, a strong peak occurs at 420 cm^{-1}, 415 cm^{-1} and

Figure 16. Infrared spectrum of pyridoxamine dihydrochloride.

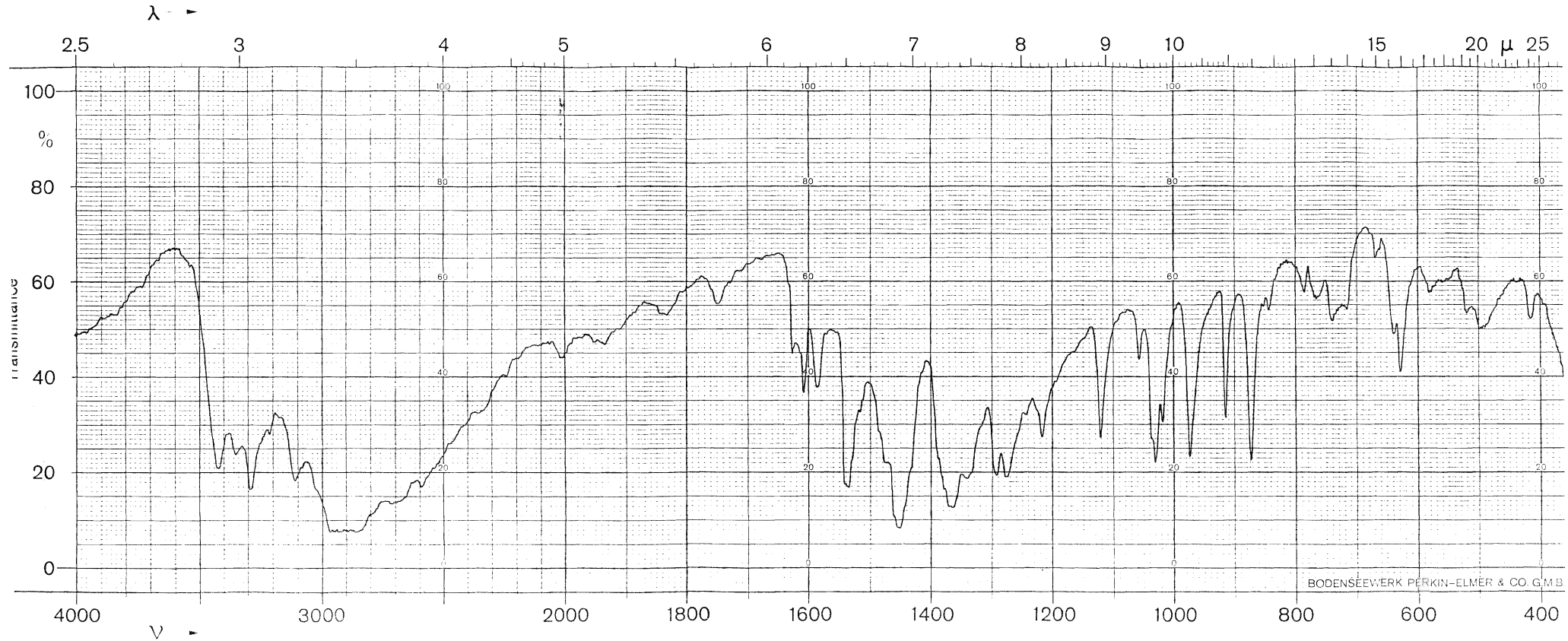


Figure 17. Infrared spectrum of neutral pyridoxine.

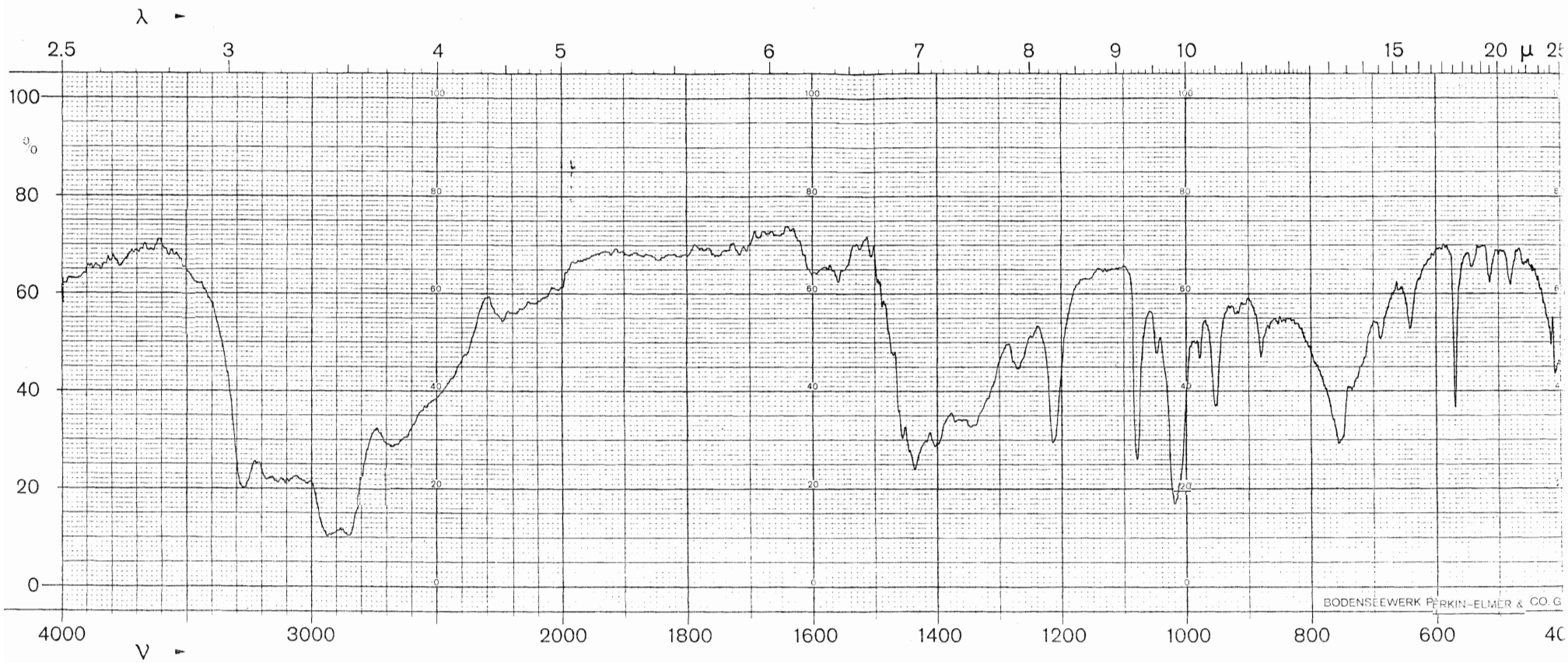
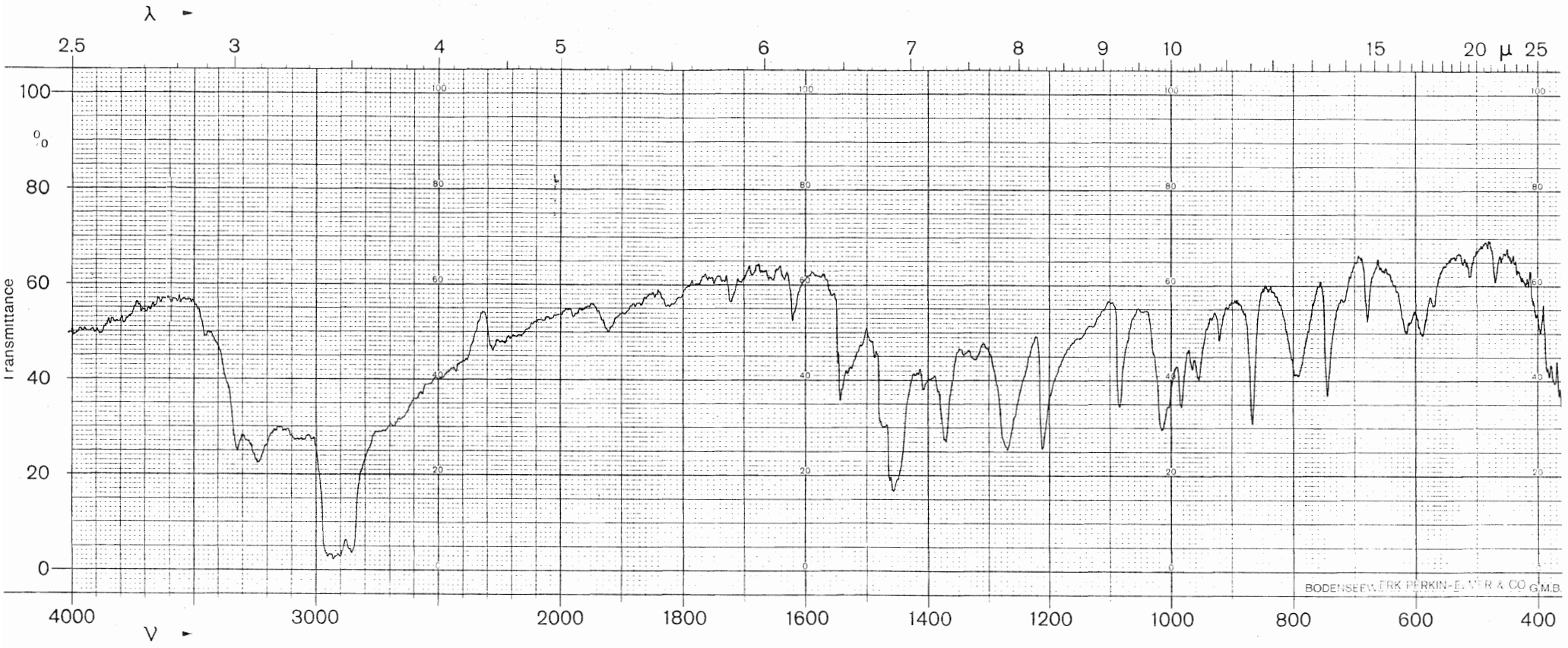


Figure 18. Infrared spectrum of pyridoxine monohydrochloride.



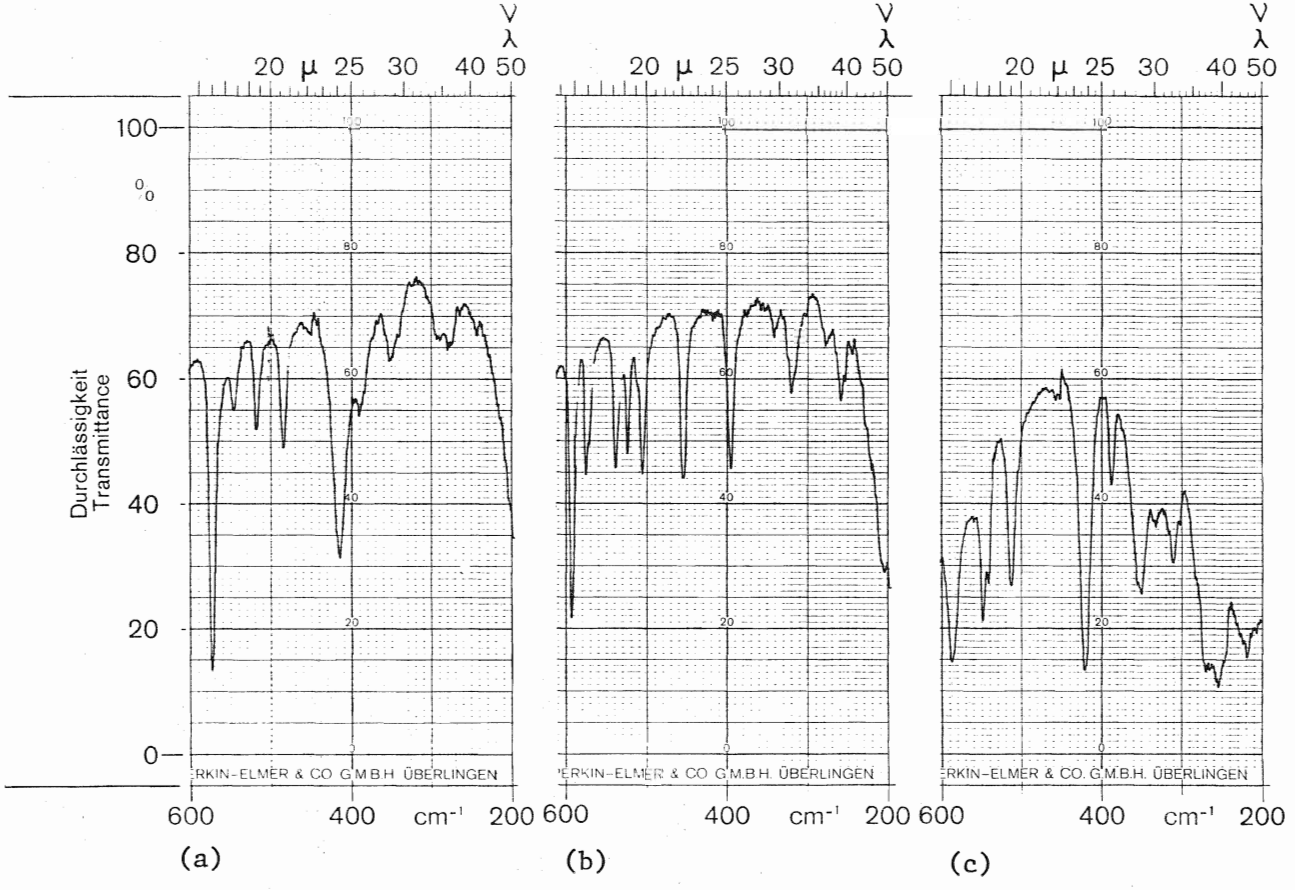


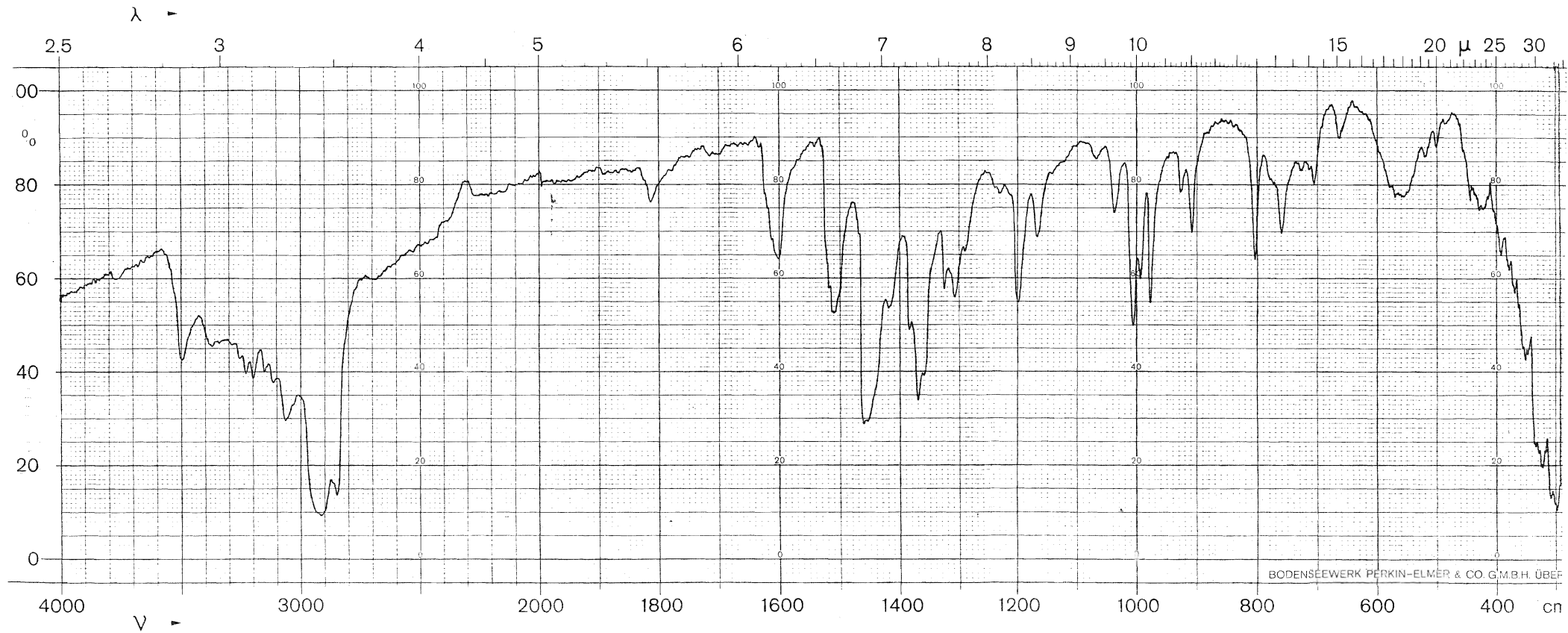
Figure 19. Ir (600-200 cm^{-1}) spectra of (a) pyridoxine, (b) pyridoxal and (c) pyridoxamine.

395 cm^{-1}, respectively. The peaks might correspond to the out-of-plane ring deformation bands for these compounds.

Infrared Spectra of the Complexes

$PtCl_2PM.H_2O$: The spectrum of $PtCl_2PM.H_2O$ is shown in Figure 20. The most noticeable feature is the appearance of a peak at about 1515 cm^{-1}. There is no similar peak in the spectrum of neutral pyridoxamine. The peak has been assigned to the vibration of the protonated pyridine ring nitrogen. The appearance of such a band in pyridoxamine complexes has also been observed in $Cu(PM)_2(NO_3)_2.H_2O$.[25] The band at 2080 cm^{-1} in the spectrum of neutral pyridoxamine (Fig. 15) which was assigned to the presence of a protonated amine group $-NH_3^+$ is absent in the spectrum of $PtCl_2PM.H_2O$ complex. The above two observations suggest that the proton on the amine group $-NH_3^+$ is lost to the pyridine ring nitrogen atom. In other words, complex formation involves a change in the tautomeric structure of pyridoxamine. The loss of the proton from the amine groups $-NH_3^+$ is reasonable since coordination of the amino group to the metal ion could occur only if the amino group is neutral, that is, in the $-NH_2$ form. Similar observation has been made by Farago et al.[49] With the $-NH_2$ coordinated the N-H stretching frequencies shift to lower values because the N-H bond order is reduced. There are a number of medium-weak peaks between 3500 and 3000 cm^{-1} in the spectrum of $PtCl_2PM.H_2O$. These peaks might be due to the N-H and O-H stretching frequencies. The band at 3500 cm^{-1} could be assigned to a stretching mode of lattice water. A

Figure 20. Infrared spectrum of $PtCl_2PM.H_2O$.



number of variations also occur in the region below 1500 cm^{-1}. The infrared spectrum of K_2PtCl_4 showed a Pt-Cl stretching frequency as a single very strong band at 322 cm^{-1}. Between 600 cm^{-1} and 200 cm^{-1} in the spectrum of $PtCl_2PM.H_2O$, Figure 21a, a Pt-Cl stretching frequency could be assigned to the sharp band at 342 cm^{-1}. There is a shoulder band at 334 cm^{-1} which indicates that the two chlorine atoms in $PtCl_2PM.H_2O$ are in the cis configuration. There are two peaks at 400 cm^{-1} and 445 cm^{-1} which could be assigned to Pt-O and Pt-N stretching vibrations, respectively. The spectrum of neutral pyridoxamine contains bands below the region 600 cm^{-1}, consequently the assignments are tentative and would be difficult to confirm without the use of isotope studies. The observations made in the preceding discussion of the infrared spectrum of $PtCl_2PM.H_2O$ agree well with the structure obtained by single crystal x-ray studies previously mentioned.

$PdCl_2PM$: Comparison of the spectrum of $PdCl_2PM$, Figure 22, with the spectrum of neutral pyridoxamine shows that the pyridine ring nitrogen is protonated as indicated by the strong band at 1540 cm^{-1}. As was observed in the spectrum of $PtCl_2PM.H_2O$ (Fig. 20), the $-NH_3^+$ band at 2080 cm^{-1} in the spectrum of neutral pyridoxamine is absent also in the spectrum of $PdCl_2PM$. This again means that the aminomethyl group is coordinated to the palladium through the nitrogen atom. Some peaks which are present in the spectrum of neutral pyridoxamine have been shifted or completely lost in the spectrum of $PdCl_2PM$ complex. There is a great variation between 600 cm^{-1} and 200 cm^{-1}. The peaks in the spectrum of $PdCl_2PM$, Figure 21b,

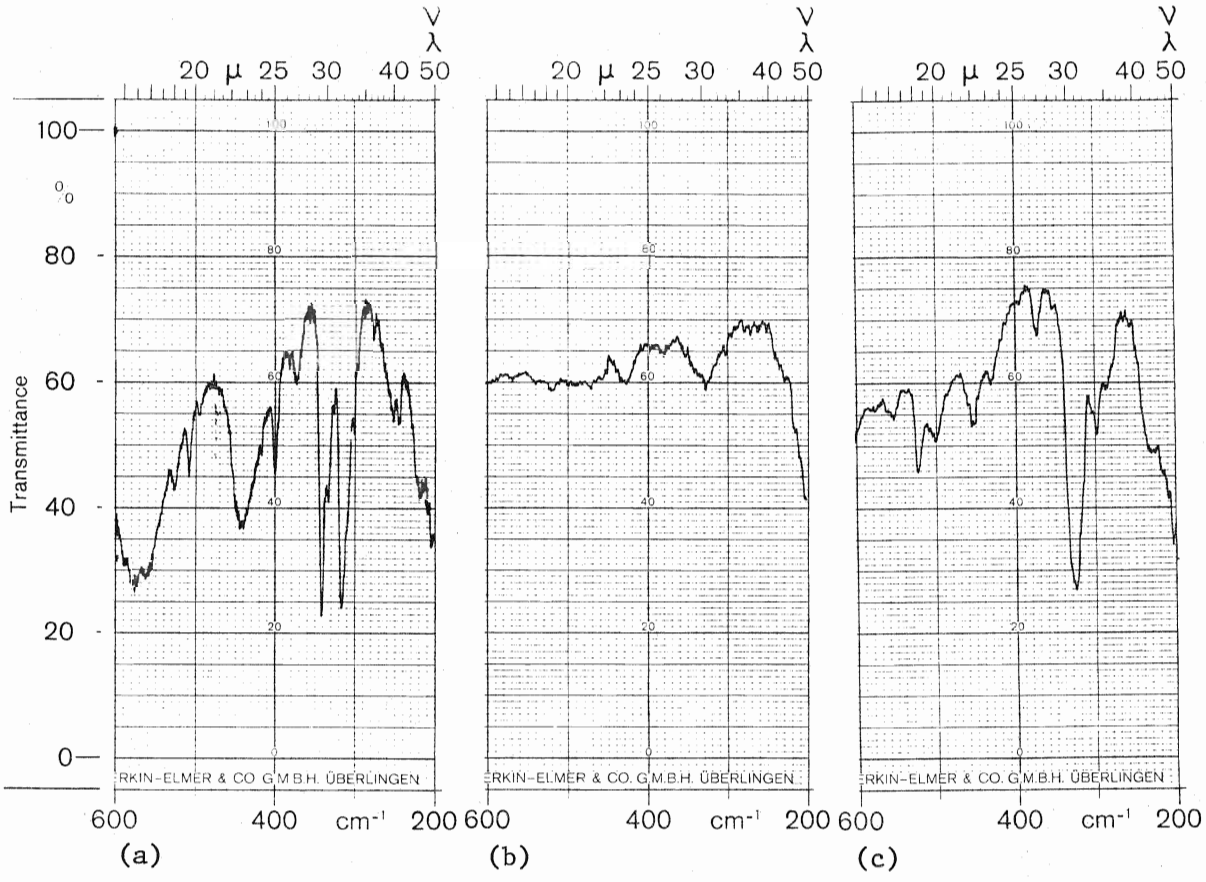
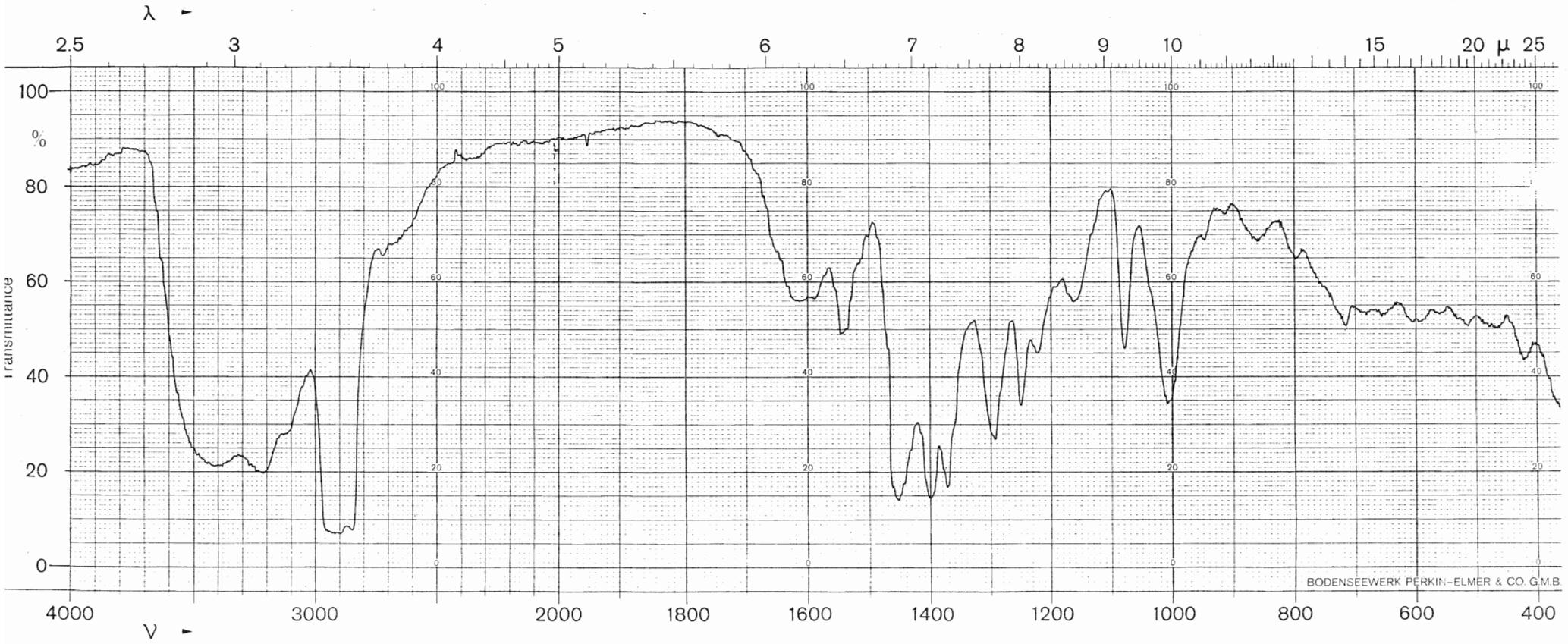


Figure 21. Ir (600-200 cm^{-1}) spectra of (a) $PtCl_2PM.H_2O$, (b) $PdCl_2PM$ and (c) $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$

Figure 22. Infrared spectrum of $PdCl_2PM$.



are very weak to absent. There is only a medium and broad peak at about 328 cm^{-1} which might be assigned to a Pd-Cl stretching frequency. Since the complex contains two chlorine atoms, four coordination of planar palladium complex could be achieved if pyridoxamine chelates to the palladium through the phenolate oxygen and amino nitrogen atoms. This is a well established observation in pyridoxamine complexes.

Chelation of the phenolate oxygen and the amino nitrogen atoms means that the two chlorine atoms are cis to each other. The occurrence of cis-Pd-Cl bonds in a complex is easily identified by the appearance of two absorption bands for the Pd-Cl bonds (sometimes it is a doublet and sometimes one is a shoulder of the other).[72] The broad nature of the Pd-Cl band at 328 cm^{-1} makes it difficult for the shoulder band to be observed. The Pd-Cl frequency in K_2PdCl_4 appears as a very strong band at 334 cm^{-1}. The large reduction in intensity and the shift of the band might clearly indicate that there is formation of a complex between Pd(II) and the pyridoxamine ligand. According to Kieft and Nakamoto,[73,74] the absorption bands for metal-nitrogen stretching vibration in complexes of amino acid derivatives with Pt(II) and Pd(II) have been assigned as weak-medium bands at 550 cm^{-1}, near 440 cm^{-1}, and in the region 585-510 cm^{-1}. However, the peaks at these regions in the spectrum of $PdCl_2PM$ are so weak that it is impossible to assign a Pd-N stretching frequency with certainty. For the same reason, no peaks can be assigned to the Pd-O vibration in $PdCl_2PM$. It is, however, reasonable to suggest that the structure of $PdCl_2PM$ is similar to that obtained for $PtCl_2PM.H_2O$ whose structure has been determined by single crystal x-ray studies.

$[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$: The cation $[PMH_2]^{2+}$ is a diprotonated pyridoxamine. The ir spectrum, Figure 23, shows a peak at 1560 cm^{-1} and a weak peak at 2040 cm^{-1}. The two peaks indicate that the pyridine ring nitrogen and the amino group are both protonated. There is no direct metal-ligand bonding and therefore Pd-N and Pd-O stretching vibrations are not expected in the spectrum of this compound. There is a Pd-Cl stretching frequency at 325 cm^{-1} in the spectrum, Figure 21c, of the complex. The structure of the compound could be envisaged as square planar $[PdCl_4]^{2-}$ anion hydrogen bonded by Cl...H to the $[PMH_2]^{2+}$ cation.

trans-$PdCl_2(PN)_2$: Unlike the spectrum of neutral pyridoxamine, Figure 17, the spectrum of trans-$PdCl_2(PN)_2$, Figure 24, contains a prominent peak at 1558 cm^{-1} which indicates that the pyridine ring nitrogen atom is coordinated. Gill et al.[62] have observed that when the pyridine ring nitrogen atom is coordinated to a metal, a weak band appears between 1235 cm^{-1} and 1250 cm^{-1}. The appearance of a medium peak at 1240 cm^{-1} in the spectrum of trans-$PdCl_2(PN)_2$, together with the peak at 1558 cm^{-1} shows that the pyridine nitrogen is coordinated to the metal. The metal chlorine stretching frequency appears at 345 cm^{-1} as a strong single peak, Figure 25a, which suggests a trans structure for the complex. Coates and Parkin[75] assigned a medium peak at 472 cm^{-1} for the Pd-N stretching in trans-$PdCl_2(pyridine)_2$. There are a number of bands between 400 cm^{-1} and 600 cm^{-1} in the spectrum of trans-$PdCl_2(PN)_2$, but since the spectrum of neutral pyridoxine contains bands in this range, it is difficult to assign a Pd-N stretching with certainty. The information from the infrared spectra tend to support the structure obtained by single crystal x-ray studies.

Figure 23. Infrared spectrum of $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$.

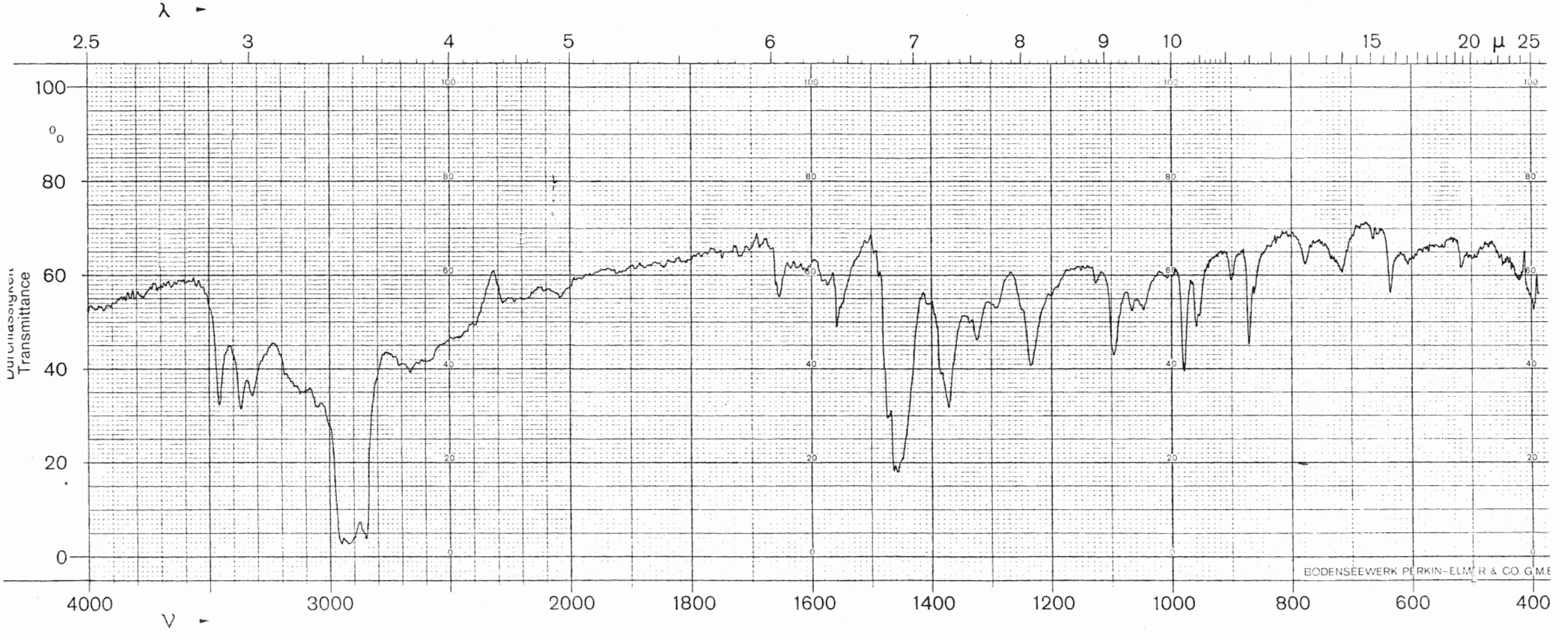
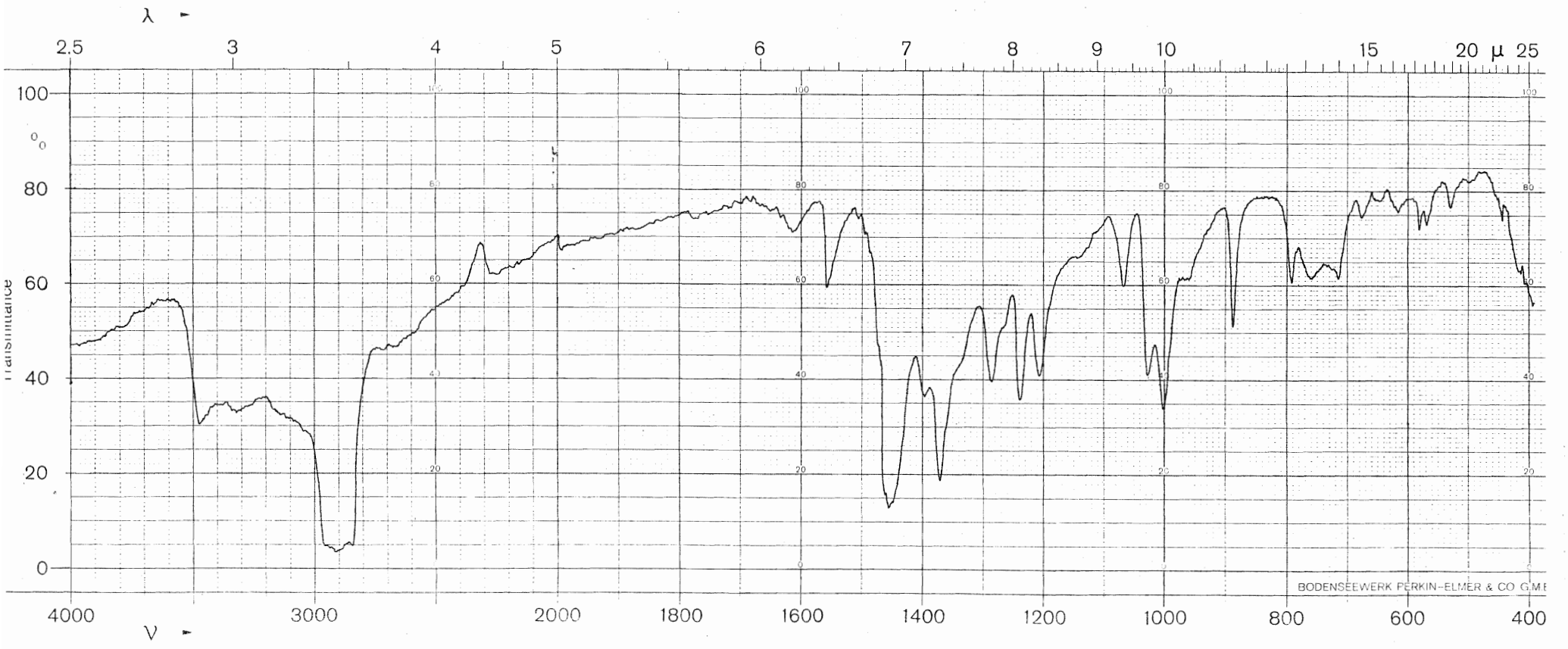


Figure 24. Infrared spectrum of <u>trans</u>-$PdCl_2(PN)_2$.



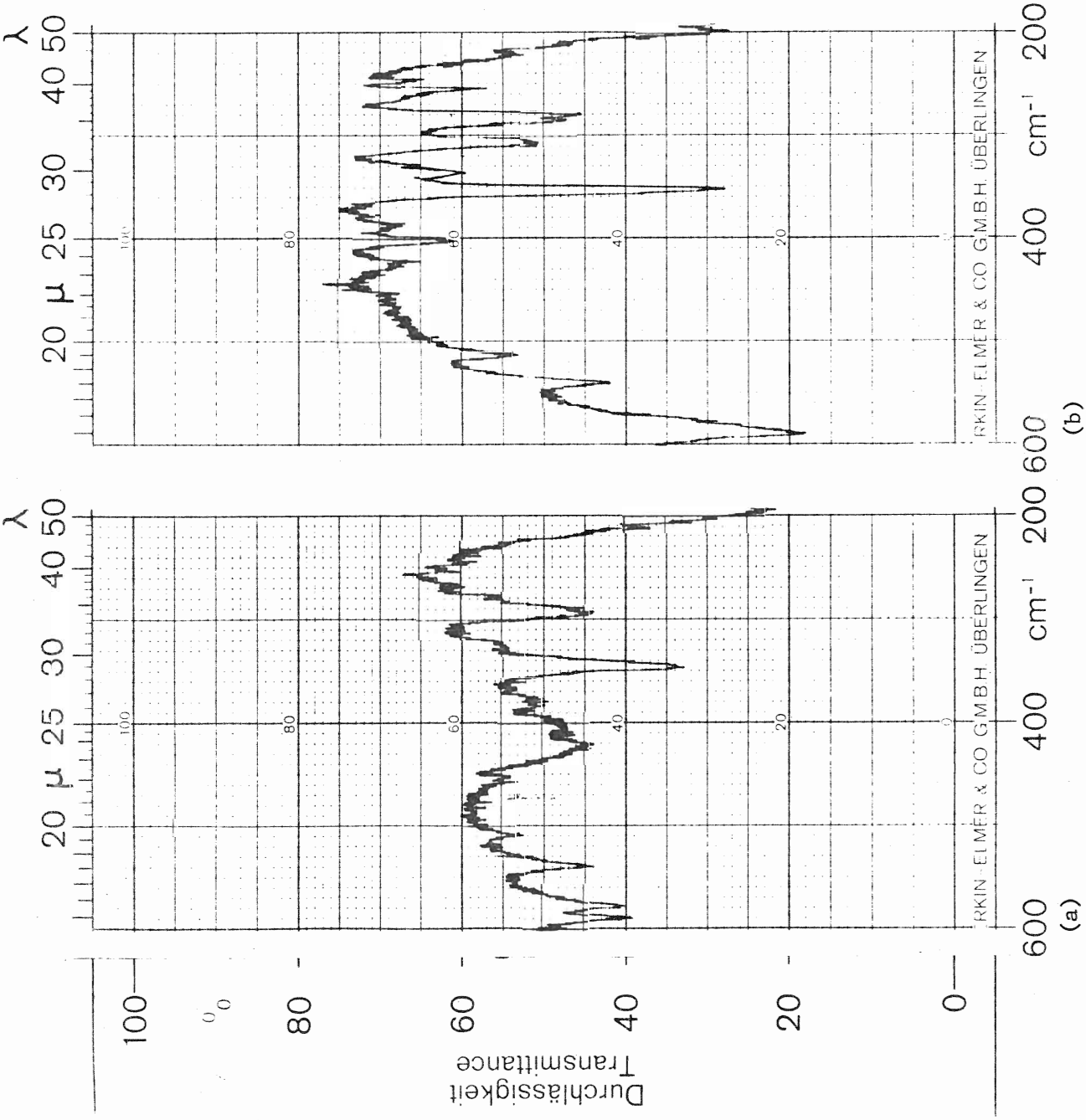


Figure 25. Ir (600-200 cm^{-1}) spectra of (a) trans-$PdCl_2(PN)_2$ and (b) cis-$PdCl_2(PN)_2$

cis-$PdCl_2(PN)_2$: The spectrum of cis-$PdCl_2(PN)_2$, Figure 26, exhibits peaks at 1562 cm^{-1} and 1245 cm^{-1} (compare with 1558 cm^{-1} and 1240 cm^{-1} respectively in trans-$PdCl_2(PN)_2$) indicating that the pyridine nitrogen is coordinated. The Pd-Cl stretching frequency occurs at 352 cm^{-1} with a shoulder band at 335 cm^{-1} (Fig. 25b), suggesting a cis Pd-Cl configuration.

cis-$PdCl_2(PL)_2$: The spectrum of cis-$PdCl_2(PL)_2$, Figure 27, compared with the spectrum of neutral PL, Figure 12, shows that there is a change in the region above 1400 cm^{-1}. The very strong peak at 1540 cm^{-1} in the spectrum of neutral PL is not present in the spectrum of the complex. Instead, there is a medium-weak peak at 1580 cm^{-1}. Since the pyridine nitrogen in neutral PL was protonated, the peak at 1580 cm^{-1} in the spectrum of cis-$PdCl_2(PL)_2$ might suggest that the pyridine nitrogen is coordinated to an element other than hydrogen. In other words, the pyridine nitrogen is coordinated to the metal. For cis-$PdCl_2(pyridine)_2$, Coates and Parkin[75] assigned a weak peak at 458 cm^{-1} and a medium peak at 446 cm^{-1} to the Pd-N stretching frequency. The spectrum of cis-$PdCl_2(PL)_2$, Figure 28a, contains a very weak band at about 458 cm^{-1} and probably a shoulder band at 455 cm^{-1}. These bands might correspond to the Pd-N stretching frequencies. There is no characteristic carbonyl stretching band. This indicates that the ligand is still in the hemiacetal form. The three bands at 2100-2000 cm^{-1} in the spectrum of neutral PL are absent in the spectrum of the complex. That is expected since on coordination to the metal through the pyridine nitrogen the dipolar nature of the ligand is destroyed. The peak at about 3410-3000 cm^{-1} in the spectrum of the complex might be assigned to the O-H

Figure 26. Infrared spectrum of <u>cis</u>-$PdCl_2(PN)_2$.

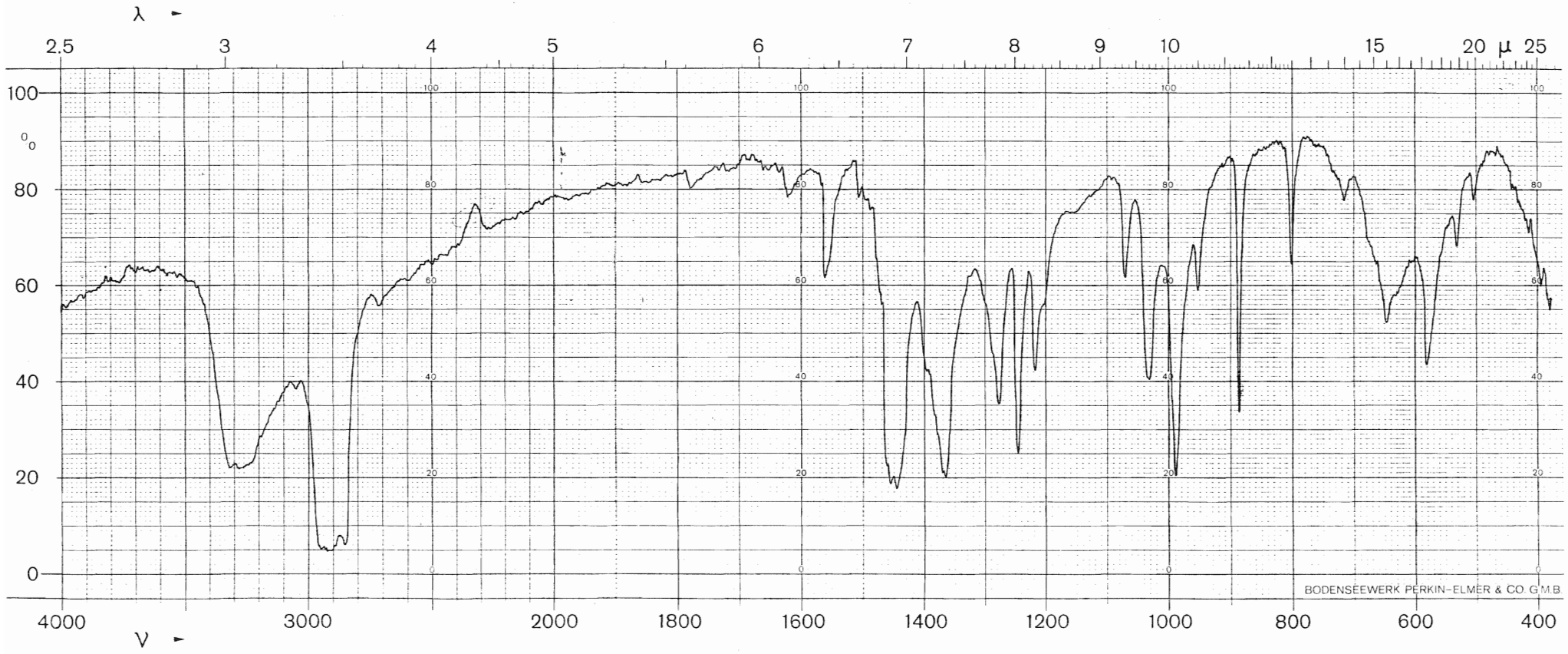


Figure 27. Infrared spectrum of cis-$PdCl_2(PL)_2$.

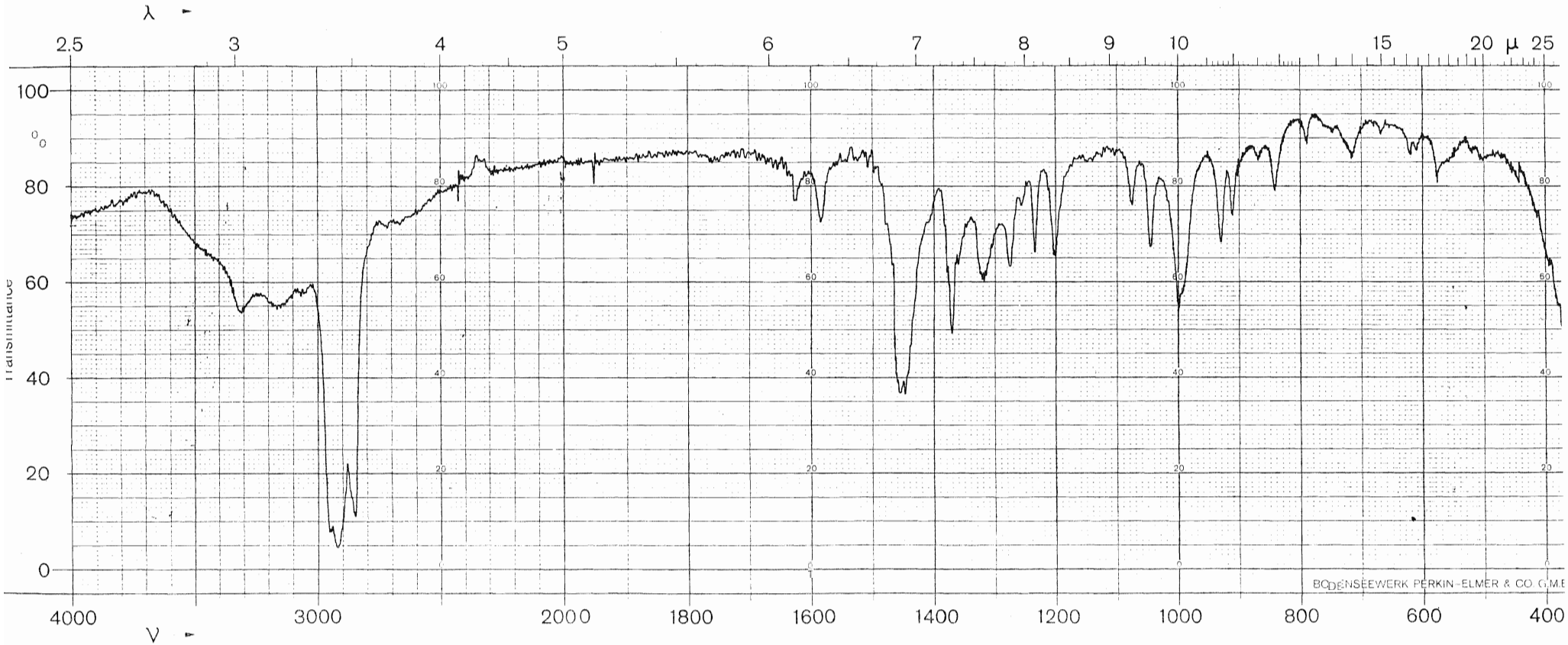
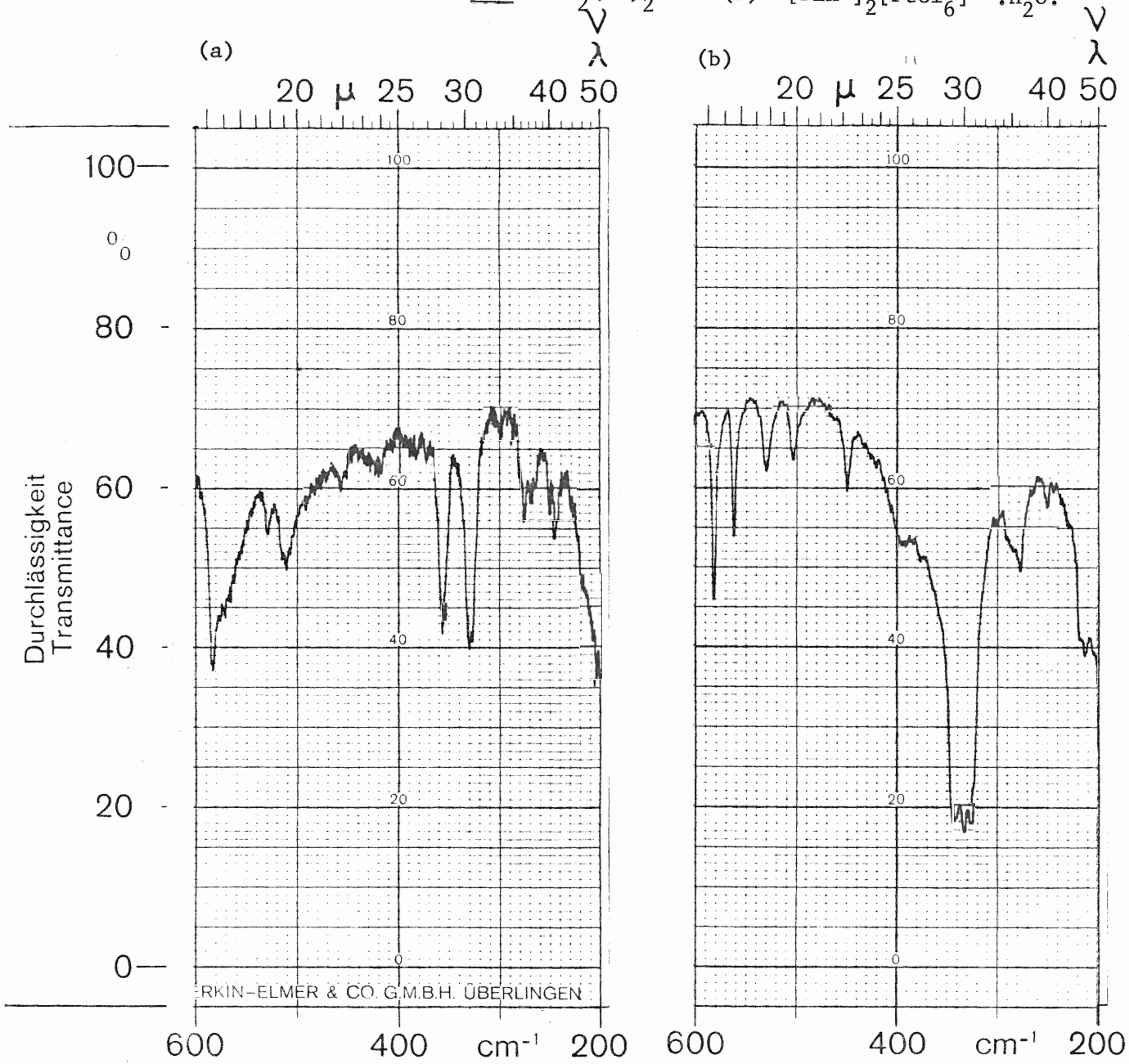


Figure 28. Ir (600-200 cm^{-1}) spectra of (a) cis-$PdCl_2(PL)_2$ and (b) $[PLH^+]_2[PtCl_6]^{2-}.H_2O$.



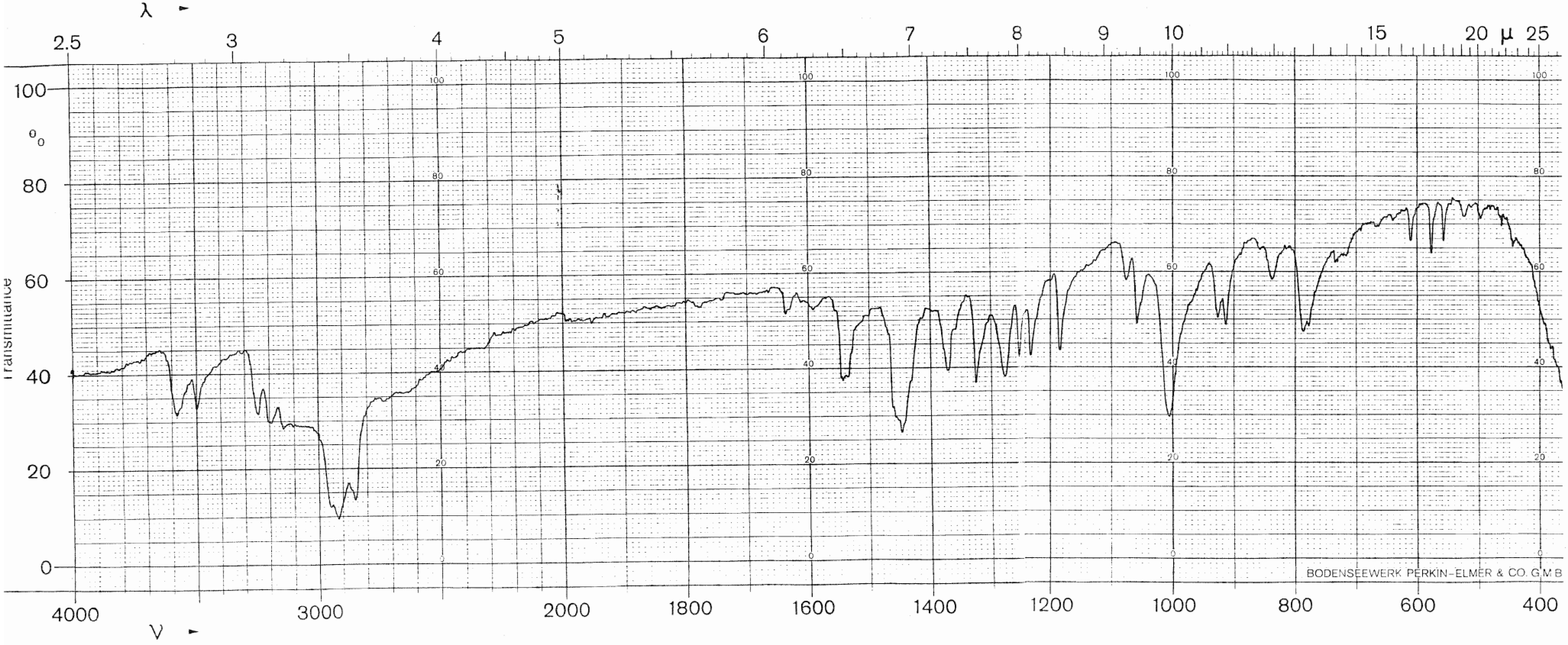
stretching frequency. The peaks below 1500 cm^{-1} shows changes both in intensity and in position as might be expected. There are two strong bands of about equal intensity at 330 cm^{-1} and 358 cm^{-1} (Fig. 28a). These might be assigned to the Pd-Cl stretching frequencies. The two peaks indicate a cis configuration. These bands compare well with those obtained by Coates and Parkin[25] who observed two strong bands at 342 cm^{-1} and 333 cm^{-1} for the cis-Pd-Cl stretching frequency in cis-$PdCl_2$(pyridine)$_2$.

$[PLH^+]_2[PtCl_6]^{2-}.H_2O$: The cation $[PLH^+]$ has the pyridine ring nitrogen protonated as was observed in the structure determined by single crystal x-ray studies. The peak at 1540 cm^{-1} in the spectrum of $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ Figure 29, indicates that the pyridine nitrogen is protonated as expected. The spectrum contains no carbonyl band, an indication that the $[PLH^+]$ cation is also in the hemiacetal form. This also is in agreement with the structure obtained by single crystal x-ray studies. There are bands between 3600 and 3100 cm^{-1} which might be assigned to O-H stretching frequencies. Much of the spectrum of $[PLH^+]_2[PtCl_6]^{2-}.H_2O$ between 1500 cm^{-1} and below resemble the spectrum of pyridoxal monohydrochloride. A strong band centered at 335 cm^{-1} in the spectrum of the complex, Figure 28b, might be assigned to the Pt-Cl stretching frequency.

Carbon-13 nuclear magnetic resonance spectra

The ligands pyridoxamine, pyridoxine and pyridoxal show eight peaks in their ^{13}C nmr spectra with ^1H decoupling. A complete assignment of the peaks have been done by a number of workers.[76,77,78,79] The carbon-13

Figure 29. Infrared spectrum of $[PLH^{+}]_2[PtCl_6]^{2-}.H_2O$.



chemical shifts have been found to have strong pH dependence because of protonation and deprotonation reactions. Table 7 shows the carbon-13 chemical shifts in ppm downfield from external Me_4Si, as obtained in DMSO-d_6 (that is in this work) and in D_2O. The spectrum of pyridoxal was difficult to obtain at neutral pH because of poor solubility in DMSO-d_6. There are slight variations in the positions of the peaks which might be due to difference in pH in D_2O and DMSO-d_6 at which the spectra were recorded. The effect of solute-solvent interaction[80] might also contribute to the difference in the positions of the peaks. However, the spectra obtained in DMSO-d_6 follow the general pattern as that obtained in D_2O. Since the spectra of the complexes were also recorded in DMSO-d_6, comparison of the spectra of the free ligands with those of the complexes could serve a good purpose of showing the effect of complexation on the chemical shifts of the ligands.

The spectra of pyridoxine, trans-$PdCl_2(PN)_2$ and cis-$PdCl_2(PN)_2$ are shown in Figures 30, 31 and 32 respectively. The trans-$PdCl_2(PN)_2$ complex shows a number of the peaks as doublets, notably the C(6), C(1), C(3) and C(5) atoms. The chemical shifts of the complexes are shown in Table 7. The double peaks suggest that the ligands are in slightly different environments.

The presence of the double peaks in the spectrum of trans-$PdCl_2(PN)_2$ might be attributed to (i) the partial isomerization of the complex to the cis configuration in solutions, (ii) the presence of uncoordinated ligand, (iii) rotation about the Pd-N bond when in solution, resulting in the two

Figure 30. C-13 nmr spectrum of pyridoxine

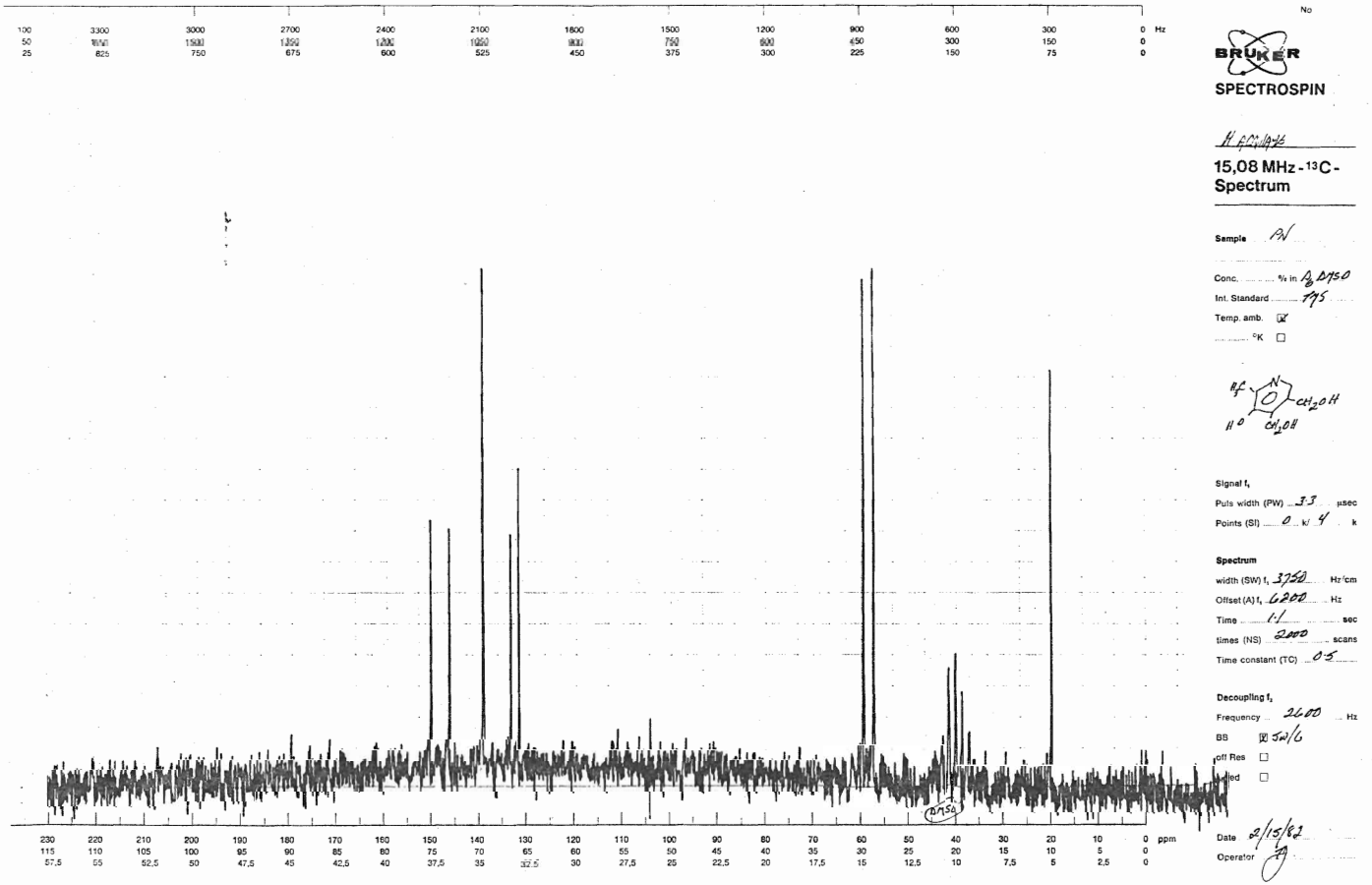


Figure 31. C-13 nmr spectrum of <u>trans</u>-$PdCl_2(PN)_2$

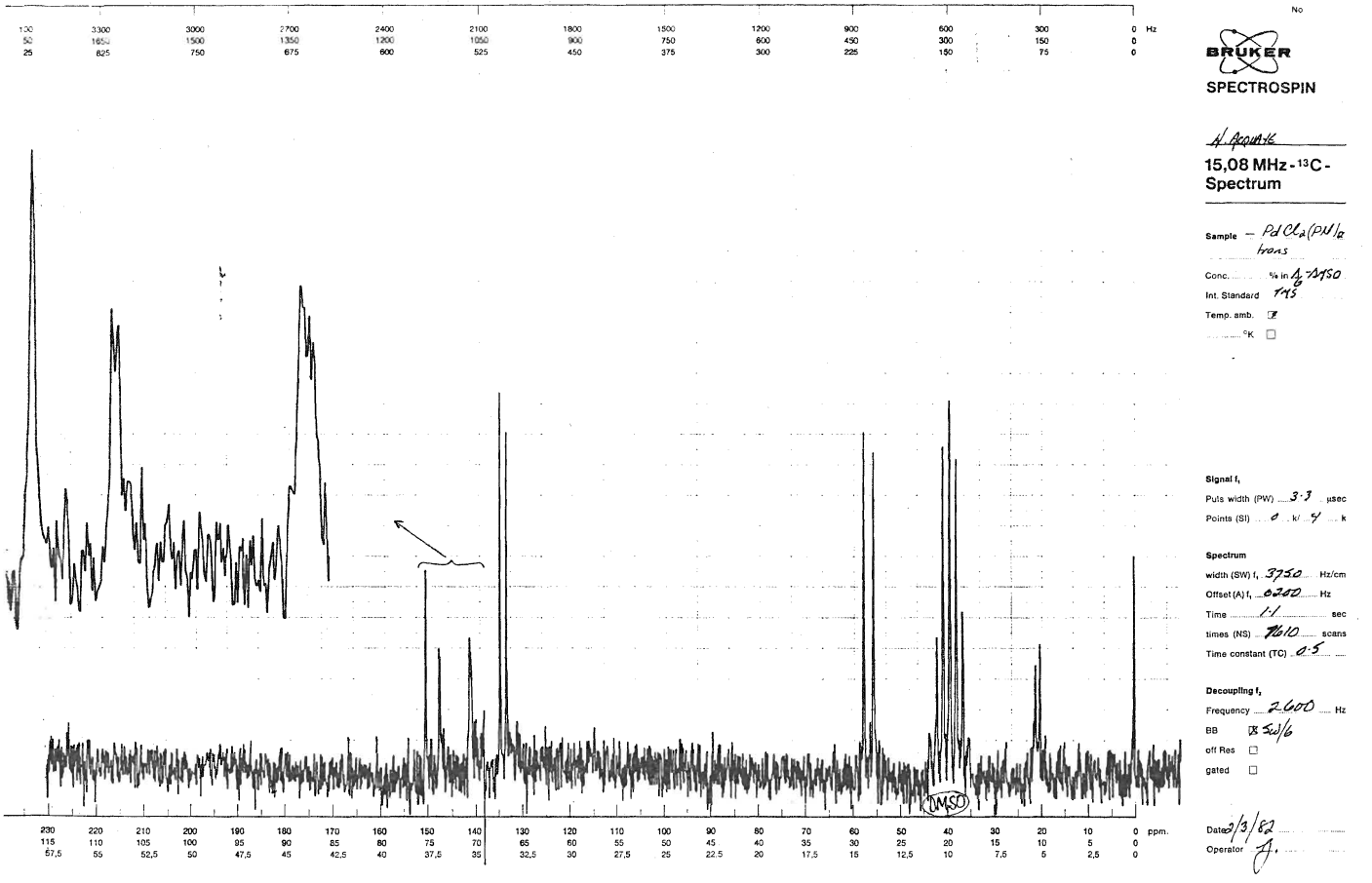


Figure 32. C-13 nmr spectrum of cis-$PdCl_2(PN)_2$

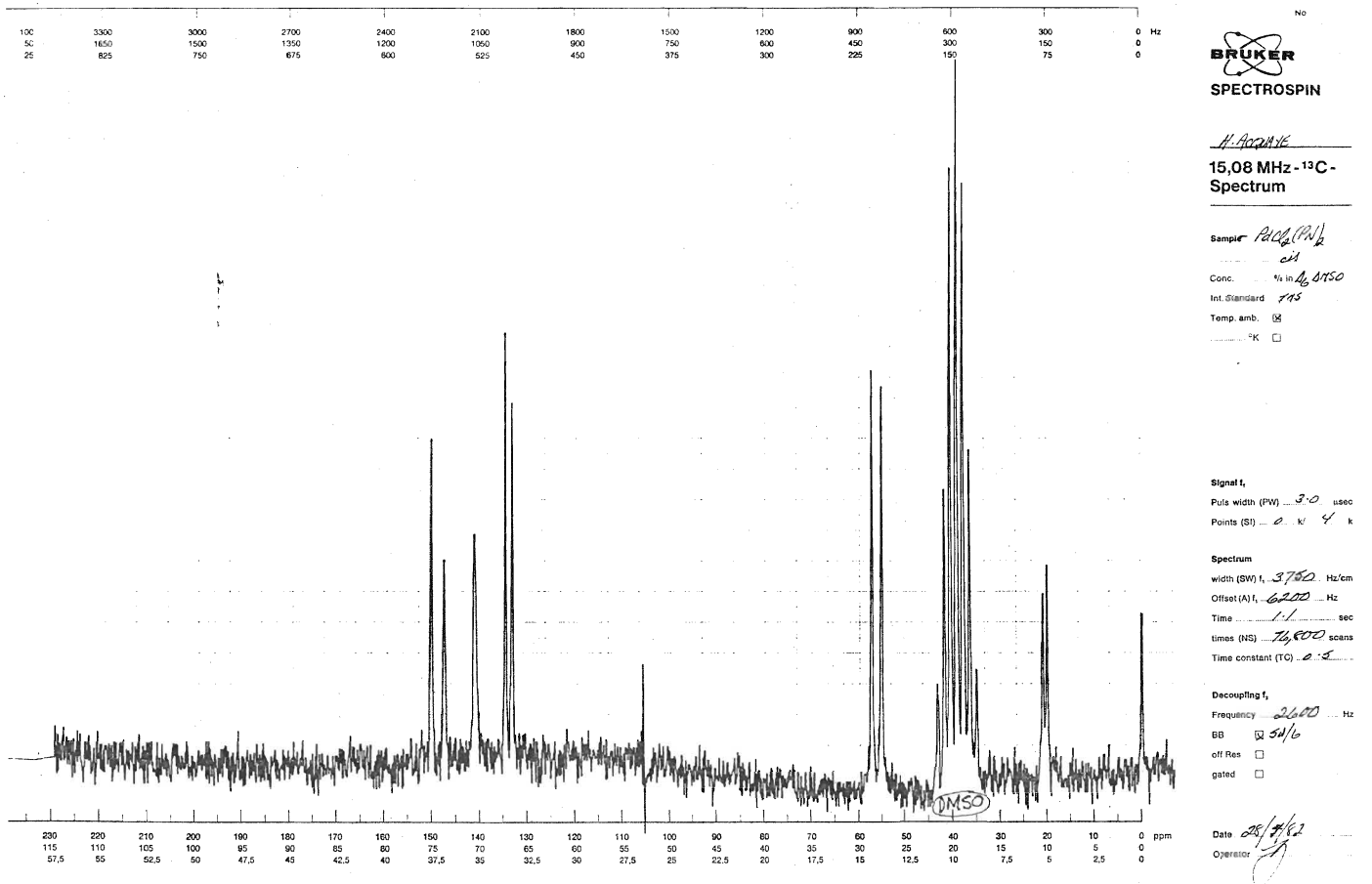


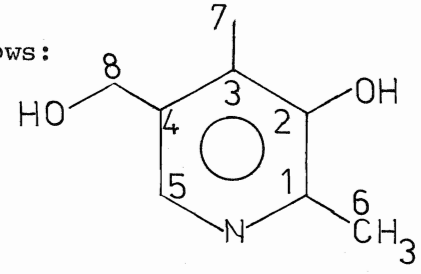
Table 7. C-13 chemical shifts (ppm) for the free ligands and complexes

		C(5)	C(4)	C(3)	C(2)	C(1)	C(6)	C(8)	C(7)
pyridoxine	DMSO-d_6	131.43	134.19	138.91	149.93	146.09	19.19	56.81	58.94
	D_2O pH 6.8	126.70	136.40	139.45	160.85	145.30	16.70	57.25	59.85
pyridoxamine	DMSO-d_6	129.03	132.13	137.43	153.32	145.43	18.56	58.98	36.70
	D_2O pH 7	124.65	137.00	133.50	164.05	146.10	16.50	60.30	37.85
pyridoxal	DMSO-d_6	128.08	136.36	137.15	146.58	144.45	18.04	70.68	99.90
	D_2O pH 12.5	127.30	134.95	131.80	162.20	153.35	19.70	67.65	100.70[a] 134.00
trans-$PdCl_2(PN)_2$	DMSO-d_6	133.53 133.72	135.12	141.51 141.20 141.19	150.76	148.02 147.78	21.30 20.33	55.81	57.94
cis-$PdCl_2(PN)_2$	DMSO-d_6	133.78	135.18	141.57	150.70	148.02	21.37 20.39	55.75	57.94
cis-$PdCl_2(PL)_2$	DMSO-d_6	135.73	136.21	147.17	148.26	148.02	21.00 20.15	68.65	98.23
$PdCl_2PM$	DMSO-d_6	132.99	134.14	135.60	160.38	148.14	19.54	58.73	--

Values in D_2O were those obtained by Lapper et al.[77]

[a] obtained at pH 6.2

C-atom numbering is as follows:



7 = CH_2OH, CHO, CH_2NH_2

ligands lying in different planes. Since evidence from the single crystal x-ray studies and the infrared spectrum indicate that the complex is in the trans configuration, the occurrence of the doublets of peaks might be due to an isomerization process in solution from the trans to the cis configuration. It is not understood why such rearrangement could take place. It is also expected that if the trans-$PdCl_2(PN)_2$ isomerised in solution to form the cis-$PdCl_2(PN)_2$, then the spectrum should be the same as that obtained for cis-$PdCl_2(PN)_2$. The two spectra are different. It is therefore unlikely that the isomerization does take place in solution, and therefore the occurrence of the double peaks could not be due to the presence of the cis isomer in solution. An uncoordinated ligand will be present if the solvent, that is, DMSO-d_6 displaces a pyridoxine ligand and is itself coordinated to the metal. Such an observation[51] has been made in solutions where in higher concentration, DMSO-d_6 competes with pyridoxine or pyridoxamine for Mn(II). However, if such displacement reaction occurs, then it is expected that the peak height of say the C(6) chemical shift should vary with time. Studies done by Prof. J. S. Hartman with the complex trans-$PdCl_2(PN)_2$ did not show any variation of the peak heights with time. It might perhaps be that the displacement reaction does occur immediately the DMSO-d_6 is added to the complex, and that the reaction goes to completion before the spectrum is recorded. If the free ligand does occur in solution, then it might be expected to have some of the chemical shifts being the same as for the shifts obtained in the absence of the metal. Since the chemical shifts of the complex are different from those of the

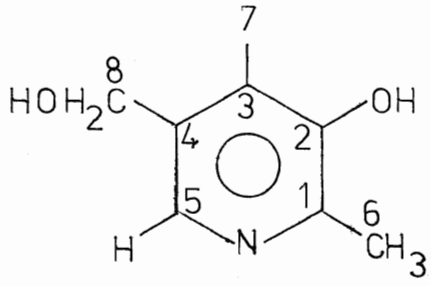
free ligand, it might be safe to say that the appearance of the double peaks is not due to the presence of a mixture of coordinated and uncoordinated ligands. In solution, the ligands might be free to rotate about the Pd-N bond. Such movements could result in a situation where the two pyridoxine ligands will be in slightly different planes with respect to each other. The two ligands will therefore have different chemical environments which could result in the appearance of the chemical shifts being in doublets.

The formation of a complex between the metal and the ligand is expected to induce some perturbation of the resonance conditions of the ligand nuclei. The differences between the ^{13}C chemical shifts of the complexes and the ligands are shown in Table 8. In trans-$PdCl_2(PN)_2$, the C(5), C(3), C(1) and C(6) atoms show the most sensitive influence of the metal. Their resonance peaks are shifted toward the higher frequencies, that is toward lower fields (= deshielding). This deshielding effect can be expected if the pyridine ring nitrogen is coordinated to the metal because charges on the nitrogen and its immediate neighbours will tend to be drawn toward the metal when complexation occurs. On the other hand, the C(4), C(2) and C(8) atoms should show little sensitivity since the metal atom is out of their immediate environment. Values for cis-$PdCl_2(PN)_2$ and cis-$PdCl_2(PL)_2$ could similarly be explained although the cis-$PdCl_2(PL)_2$ complex has larger values for the Ci atoms. The trend is, however, the same for the three complexes.

Table 8. ΔCi (ppm)

	C(5)	C(4)	C(3)	C(2)	C(1)	C(6)	C(8)	C(7)
trans-$PdCl_2(PN)_2$	2.10 2.29	0.93	2.60 2.29 2.28	0.83	1.93 1.69	2.11 1.14	-1.0	-1.0
cis-$PdCl_2(PN)_2$	2.35	0.99	2.66	0.77	1.93	2.17 1.20	-1.24	-1.0
cis-$PdCl_2(PL)_2$	7.65	-0.15	10.02	1.68	3.57	2.93 2.11	-2.03	-1.67
$PdCl_2PM$	3.96	2.01	-1.83	7.06	2.71	0.98	-0.25	

ΔCi = difference between the ^{13}C chemical shifts of Ci atom in the complex and the free ligand.



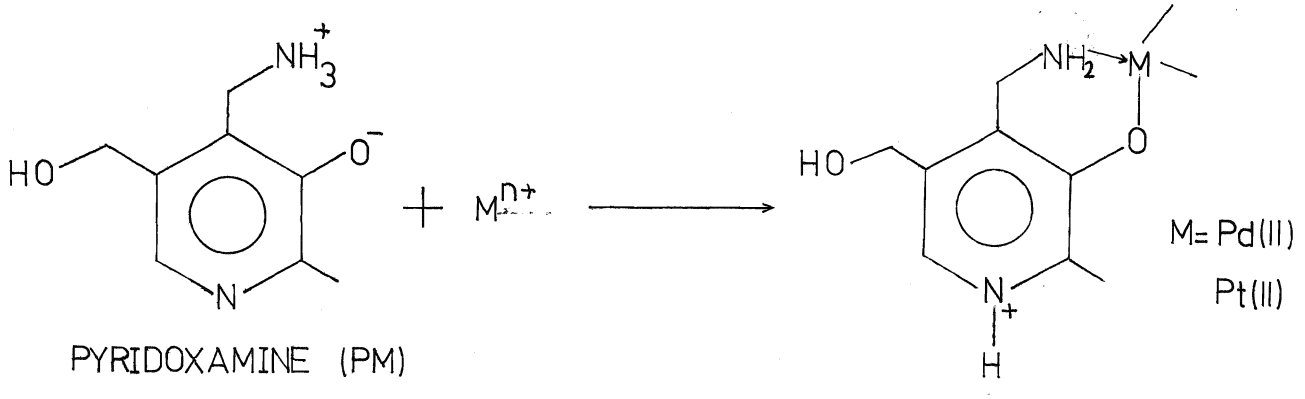
7 = CH_2OH, CHO, CH_2NH_2

In $PdCl_2PM$, the largest ΔCi value is for the C(2) atom. This is in contrast to values obtained for the pyridoxine and pyridoxal complexes where the C(2) atom showed little sensitivity. The large ΔCi value for the C(2) atom in $PdCl_2PM$ suggests that the phenolate oxygen is coordinated to the metal. The value for the C(7) atom could not be obtained because the peak occurs at the same position where the DMSO-d_6 peaks occur. It is, however, sufficient to conclude that in $PdCl_2PM$ the ligand chelates the metal atom through the phenolate oxygen and the amino nitrogen attached to the C(7) atom. The values for C(5) and C(1) for $PdCl_2PM$ can not be left unexplained. On chelation a proton is transferred from the amino nitrogen to the pyridine nitrogen. The protonation of the ring nitrogen will create a similar perturbation as occurred when the ring nitrogen coordinates to the metal. Thus, C(5) and C(1) atoms will be deshielded. The magnitude of the perturbation will, however, vary. Also, since the three ligands have different tautomeric forms in solution, coordination to the metal will not have the same magnitude of change in chemical shifts.

The ^{13}C nmr spectrum of $PtCl_2PM.H_2O$ could not be obtained. After about 36,000 scans, the peaks could hardly be seen. It was therefore neglected. The result is, however, not expected to be different from that of the $PdCl_2PM$ complex.

CONCLUSION

Palladium and platinum complexes of pyridoxamine, pyridoxine and pyridoxal have been prepared under various pH conditions. At neutral pH, palladium and platinum reacted with pyridoxamine to produce the compounds $PdCl_2PM$ and $PtCl_2PM.H_2O$ respectively. In these products, the metal is square planar and is chelated through the phenolate oxygen and the amino-methyl nitrogen of pyridoxamine. The square planar coordination is completed with the two chlorine atoms which are <u>cis</u> to each other. The resulting product has the pyridine ring nitrogen of pyridoxamine protonated.

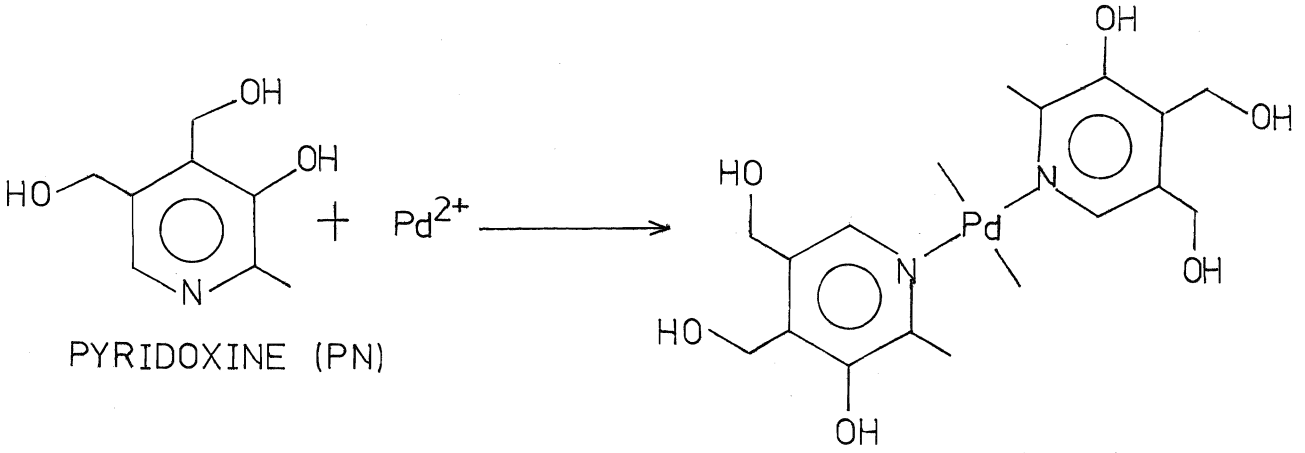


PYRIDOXAMINE (PM)

In acidic medium, pH = 2, palladium reacted with pyridoxamine to form the salt $[PMH_2]^{2+}[PdCl_4]^{2-}.H_2O$.

Pyridoxine reacted with palladium at neutral pH and in slightly acidic pH (pH = 6) to produce <u>trans</u>-$PdCl_2(PN)_2$ and <u>cis</u>-$PdCl_2(PN)_2$, respectively.

In both of these products, the pyridine nitrogen of pyridoxine is coordinated to the metal which is square planar.



PYRIDOXINE (PN)

trans-$PdCl_2(PN)_2$

With pyridoxal, palladium formed the complex cis-$PdCl_2(PL)_2$ at neutral pH. The compound is similar to cis-$PdCl_2(PN)_2$ in coordination. In acidic medium, the reaction of platinum with pyridoxal resulted in the formation of the salt $[PLH^+]_2[PtCl_6]^{2-}.2H_2O$.

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