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Palladium(II) Complex of the 5-Hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazone: Synthesis and Characterization

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Abstract

*The novel complex of 5-hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazone **(HPyEt)** with plalladium(II) have been prepared and characterized by elemental analysis, IR, ^{1}H-NMR, UV-visible spectroscopy and mass spectrometry (FAB). Coordination of the anionic thiosemicarbazone ligand is via the pyridyl nitrogen, imine nitrogen and thiolato sulfur atoms and the fourth coordination site being occupied by chloride ion in square planar geometry.*

Keywords: *Hydroxypyridine; thiosemicarbazone; palladium complex.*

Introduction

Thiosemicarbazones are very versatile ligands. They can coordinate to metals as neutral molecules or, after deprotonation, as anionic ligands, and can adopt a variety of different coordination modes[1]. Their antipathogenic and other biological activities *in vitro* depend on the N(4) substituent(s)[2]; the in *vivo activity* of those that are most active *in vitro* has been limited by their poor solubility in water. One agent of this series, 5- Hydroxy-2- carbaldehydethiosemicarbazone (5-HP), has been tested clinically and has shown carcinostatic potency in man. 5- Hydroxy-2- carbaldehydethiosemicarbazone (5-HP) is highly active intraperitioneally against leukemia L-1210, Ehrlich ascites carcinoma, and lymphoma L-5178 Y over a broad dose range[3]. The chemistry of the thiosemicarbazone has been an extremely active area of research primarily because of the beneficial biological (*viz.* antiviral, antibacterial, antitumor etc.) activities. The chelate palladium complex with salicylaldehyde N(4)-ethyl thiosemicarbazone in which ligand is bound to the metal in an O, N, S-tridentate coordination mode forming one six and one five-membered chelating ring and synthesis and crystal structure of a palladium with salicylaldehyde N(4)-hexamethyleneiminylthiosemicarbazone has been reported[4,5].

In earlier work, we investigated the palladium(II) Complexes of N(4)-ethylthiosemicarbazone of 3-Hydroxypyridine-2-carboxaldehyde and X-ray crystal structure has been solved[6].

Experimental Methods

Materials

4-Ethyl-3-thiosemicarbazide and 5-hydroxy-2-methyl pyridine were commercially available from Aldrich. Palladium chloride was purchased from BDH laboratory reagent Pvt. Limited, Mumbai while lithium chloride from Loba Chemie Pvt. Ltd., Mumbai. Activated MnO_2 was prepared by heating $MnCO_3$ at 300 ^{o}C for 12 hr. Gravity column chromatography separation were carried out using 60-120 mesh silica gels (Qualigenes Fine Chemicals). Thin layer chromatography plates 60 GF 254 0.2 mm, E.MerckDarmastadt, Germany were used for TLC to check the purity of the product. All the solvents

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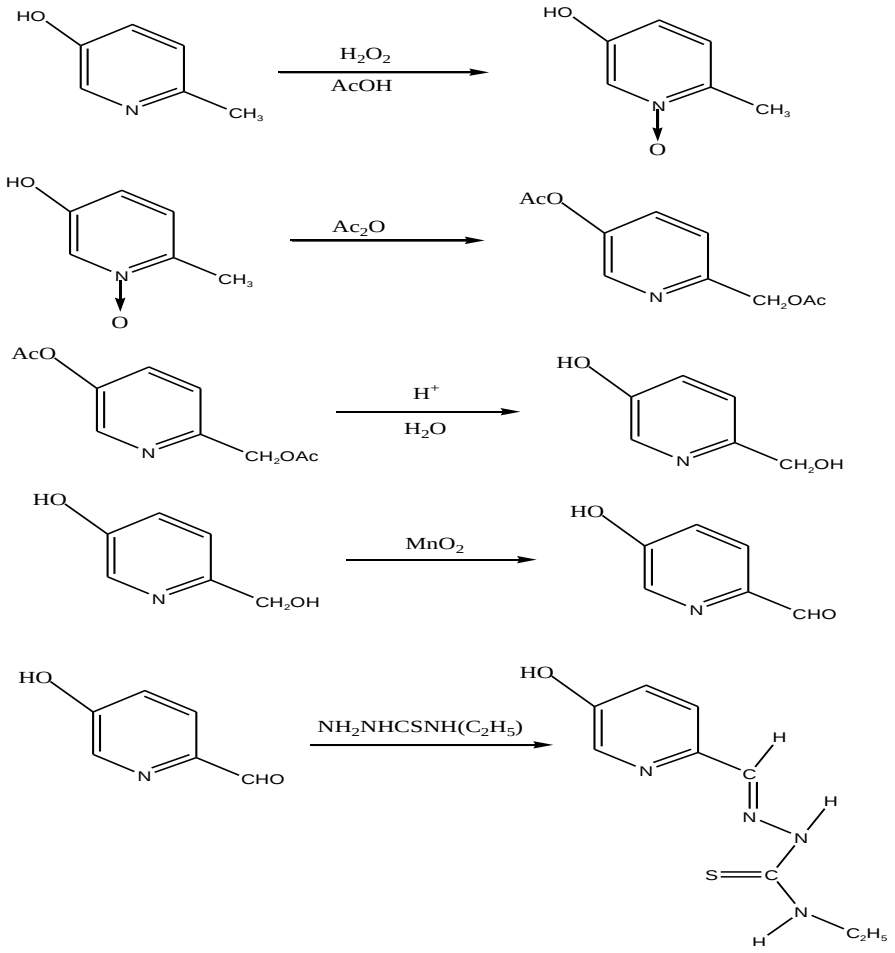
were purchased from Merck, Glaxo, BDH, Qualigens, and Ranbaxy chemical companies and used without further purification.

Measurements

Electronic spectra in DMF (5 X 10^{-5} mol/L) were recorded on Perkin Elmer Lambda 40 UV/VIS spectrometer at Drugs Administration Centre, Bijulibazar, Babarrmahal, Kathmandu. Elemental analysis (C, H, N), FAB mass spectra measurements and NMR (d_6-DMSO) spectra of complex were obtained from Central Drug Research Institute (CDRI), Lucknow, India. 2D-NMR of thiosemicarbazone was recorded in d_6-DMSO at RT on Nippon Denshi JEOL FT-500 NMR Spectrometer in Japan. The FAB mass spectra was recorded on a Jeol SX 102/Da-600 mass spectrometer/Data system using argon/xenon (60kV, 10mAO) as the FAB gas at CDRI. The accelerating voltage was 10kV and spectrum was recorded at room temperature. m-Nitrobenzyl alcohol was used as the matrix. IR spectra were recorded on Nexus FTIR spectrometer (Thermo Nicolet) at University of Padova (KBr). Analysis of palladium and chlorine were done by gravimetric and potentiometric techniques, respectively at Central Department of Chemistry, Tribhuvan university, kirtipur, Kathmandu.



Scheme I. Synthesis of 5-Hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazone.

Synthesis of 5-Hydroxypyridine-2-carbaldehyde N-ethylthiosemicarbazone

5-Hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazone was prepared by the method described by E. J. Blanz, Jr. et. al[7] *(scheme I)* and characterized by elemental analysis IR, UV-Vis, ^{1}H and 2D-NMR spectra. Yield: 84 %. Pale cream.M.P. 205^{o}C. UV/VIS (DMF, cm^{-1}): 30,487b*(1.96) IR: 3297m {ν(OH)}; 3257m { ν N(4)H}; 3208m { ν N(3)H}; 1592 w{ν(C=N)};1557s, 1532m{δ{N(4)H} + δ{N(3)H}; 1489s,1428m (Ring breath); 1225s {ν(C-O)}; 1101s {ν(N-N)}; 801m {ν(C=S)}. ^{1}H-NMR1: 11.44 {N(3)H};10.36 {C(5)OH}; 8.56{N(4)H}; 8.09 {C(6)H, C(7)H }; 8.00 {C(4)H}; 7.20 {C(3)H}; 1.12, 3.56 {N(4)C_2H_5}; ^{13}C-NMR:176.69 (C=S); 154.46 C(OH); 144.48 C(2);; 142.45 C(4); 137.32 C(6);122.73 C(3); 121.34 C(7); 38.30, 14.55 {N(4)C_2H_5}. Anal.calc. for $C_9H_{12}N_4OS$: C 48.20, H 5.39, N 24.98, ; found: C 47.86, H 5.17, N 24.29.
*b = Broad; m = Medium; w = Weak

Synthesis of chloro(5-hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazonato) palladium(II)

To lithium tetrachloropalladate (1.2 mmol), prepared in situ from $PdCl_2$ and LiCl, in MeOH (9 ml) was added a solution of ligand (1mmol) in MeOH (8 ml). The mixture was stirred for 24 h at room temperature, and then left standing in a refrigerator for 24 h. The resulting orange precipitate was filtered off, washed with cold MeOH and then with ether and dried at 50 ^{o}C for 12 hr and then at 95 $^\circ$C for 1.5 hr. Yield: 80%.Orange yellow. M.P. 241^{o}C. UV/VIS (DMF, cm^{-1}): 31,446s **( ),** 26315b **( ),** 21,276b **( )**. IR: 3032w [{ν(OH) + ν{N(4)H}]; 1600sb; {ν(C=N)}; 1600sb, 1567s{δ{N(4)H} + δ{N(3)H}; 1520m, 1489w, 1457m (Ring breath); 1210s{ν(C-O)}; 1152w {ν(N-N)}; 706m {ν(C=S)}. ^{1}H-NMR1**:** 8.12{N(4)H};7.88{C(6)H};8.01{C(7)H };7.62{C(4)H};7.48{C(3)H}; 3.23, 1.07{N(4)C_2H_5}.Anal. calc.for $C_9H_{11}ClN_4OPdS\cdot H_2O$: C 28.18; H 3.39; Cl 9.26; N 14.61; Pd 27.77; found: C 27.79; H 3.45; Cl 9.80; N14.21; Pd 28.34;

Results and discussion

IR Spectroscopy

The highest frequency band at 3297 cm^{-1}for thiosemicarbazone was assigned to ν (OH) stretch. The frequency at 3257 cm^{-1} was assigned to stretches of terminal N(4)H and the bands in 3208 cm^{-1} range was assigned to stretch of N(3)H. In the spectra of ligand, no ν(SH) band in the 2600-2500 cm^{-1} range was observed, in agreement with the presence of thione form[6].

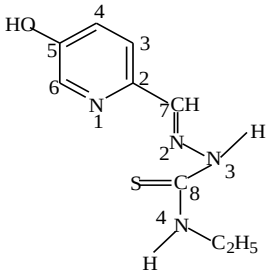


Figure 1.*5-Hydroxypyridine-2-carbaldehyde N4)-ethylthiosemicarbazone.*

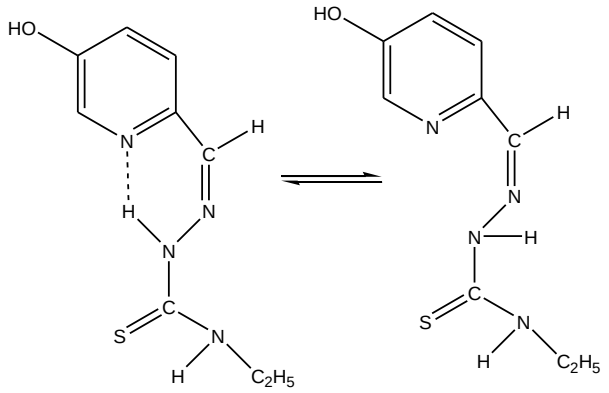
The strong band at 1592-1600 cm^{-1} in thiosemicarbazone attributed to ν(C=N) is shifted to higher frequency in the complex coupled with δ{N(4)H} and δ{N(3)H} to give broad band. Coordination of azomethine nitrogen of the deprotonated ligand is further supported by shift of ν(N-N) band to higher energy in the IR spectra of the complex compared to that in the ligand and absence of ν N(3)H stretch in the high frequency region. The breathing motion of the pyridine ring was shifted to a higher frequency

upon complexation and it was consistent with pyridine ring nitrogen coordination. The characteristic ν(C-O) stretch at 1225 cm^{-1} in the free thiosemicarbazone has been shifted insignificantly to lower frequency in the complex which clearly indicated that carbonyl oxygen has not been involved in coordination. Coordination of carbonyl oxygen leads to decreasing in ν(C-O) stretch by 70-80 cm^{-1}. Small shift in ν(C-O) stretch in the complex compare to that in free ligand was due to different strength of hydrogen bond in two. The ν(C=S) vibration in the free ligand at 801 cm^{-1} appears at lower frequency with reduced intensity in the complex at 706 cm^{-1}, suggesting coordination of sulfur in the deprotonated thiolate form[8,9,10].

NMR spectroscopy

Peak assignments are based on 2D-NMR data ($^1H,^1H$-COSY; $^1H,^{13}C$-HMQC; $^1H,^{13}C$-HMBC). For free thiosemicarbazone, N(3)H was found down field at 11.44 ppm due to its hydrogen bonding to the pyridine nitrogen. Existence of single strong resonance at such a down field for N(3)H reveals that it predominantly exist in the form of Z-isomer. Free ligand did not show any peak attributed to S-H proton indicating that it exist in thione form. The broad peak in the 10.39 ppm region was identified as C(5)OH signal and it was not detected in the complex may be because of excessive hydrogen bonding or exchange of –OH proton with the water molecule[6,11,12].

In the ^1H-NMR spectra of the complex, C(6)H in the free ligand (8.09 ppm) was shifted up field in the complex (7.88 ppm) upon coordination, in accord with an increased electron density at this site in the complex due to π-back bonding from Pd(II)[11]. Absence of the N(3)H signal in the complex, implies that anionic ligand was involved in coordination[9,11].



Z-Isomer E-Isomer

Figure 2.*Isomers of 5-Hydroxy-2-carbaldehyde N(4)-ethylthiosemicarbazone.*

On coordination of the sulphur and imine nitrogen atoms the electron density would be expected to be lost from the H-C=N function, as has been observed for many complexes of thiosemicarbazones. However, π-back bonding from the palladium(II) to the thiolate and imine functions occurs causing an up field shift. The shift of $N(4)C_2H_5$ proton resonance were not significant as the aldehyde hydrogen because of their greater distance from the coordinating thion sulphur[13].

^1H-NMR signals in the complex were essentially shifted upfield compare to that of free thiosemicarbazone and the affected proton resonance were C(6)H, C(7)H and S=C-N(4)H. These upfield shifts support coordination of the pyridinyl nitrogen, azomethine nitrogen and thionyl sulphur to Pd(II) forming two five membered chelate rings around Pd(II) centre which contribute to the stability of the complex a structural motive that seems to be stable both in the solid state and in DMSO solution[11,12].

Electronic Spectroscopy

N(4)-Ethylthiosemicarbazone have broad band at 30,487sb cm^{-1} (1.96)* associated with the n $\rightarrow\pi^*$ of the pyridine ring and TSC moiety (imine, thiomide) transition which has shifted at 31,446s cm^{-1} (1.10) in the complex. In the visible region of square planar complexes of Pd(II), three spin allowed $^1A_{1g}\rightarrow {}^1A_{2g}$, $<^1A_{1g}\rightarrow {}^1B_{1g}$, $<^1A_{1g}\rightarrow {}^1E_{1g}$, and three spin forbidden singlet-triplet d-d transitions from the three lower lying d levels to the empty d_x^2-y^2 orbitals are predicted. However, strong charge transfer transition for [Pd(PyEt)Cl].H_2O interfere and prevent the observation of all the expected bands. The band at 21,276sb cm^{-1} (0.37) was assignable to a combination of S→Pd(II) charge transfer, N(pyridinyl)→Pd(II) charge transfer and Pd(II) d→dbands. This band is also associated with spin-forbidden singlet–triplet transition which could have gained intensity through spin–orbit coupling. The band at 26,315sh cm^{-1} (0.82) was assignable to a combination of ligand-metal (L → M) and metal-ligand (M→L) charge transfer and d-d bands. A comparison of these bands with bands of free ligands revealed that there is decrease in intensity and increase in the frequency that is attributed to coordination of ligand[11,12,14,15].

*( ) = Absorbance; s = Strong, sb = strong broad, sh = Shoulder, b = Broad.

Mass spectrometry

The FAB mass spectrum of complex was recorded using m-nitrobenzyl alcohol (NBA) as the matrix. The spectrum of Pd(II) complex showed a number of informative fragment ions of different intensity confirming its molecular weight. The molecular ion peak was observed as $[M]^+$ (m/z = 383) and the major fragmentation pathway involved the cleavage of thioamide group giving highest mass fragment at m/z 369 (a) correspond to removal of –CH2 fraction from -N(4)C_2H_5. A peak at m/z 109 corresponds to the hydroxypicolinering fragment. The mass spectrum of the complex shows fragmentation patterns corresponding to succesive degradations of the molecule. A general splitting pathway followed by the complex is shown in *scheme 2*. The result presented here is interpreted in terms of simple bond cleavage and ligand losses[16,17]. A peak at *m/z* 367 corresponds to the fragment [$C_8H_7N_4OPdSCl.H_2O$] (b). Similarly, all the peaks at different *m/z* are shown in the *scheme II*.

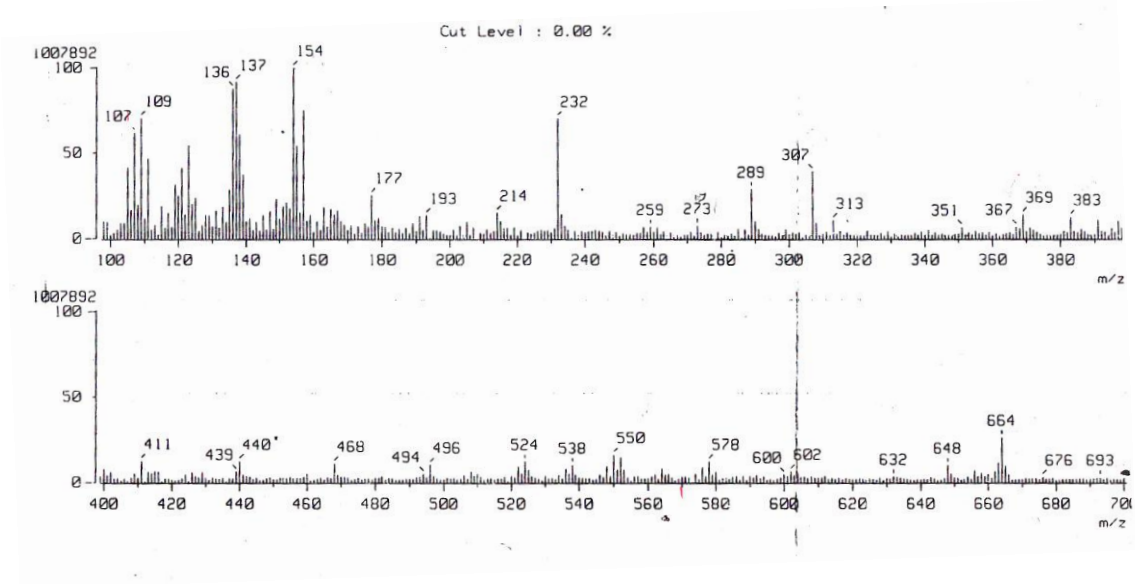
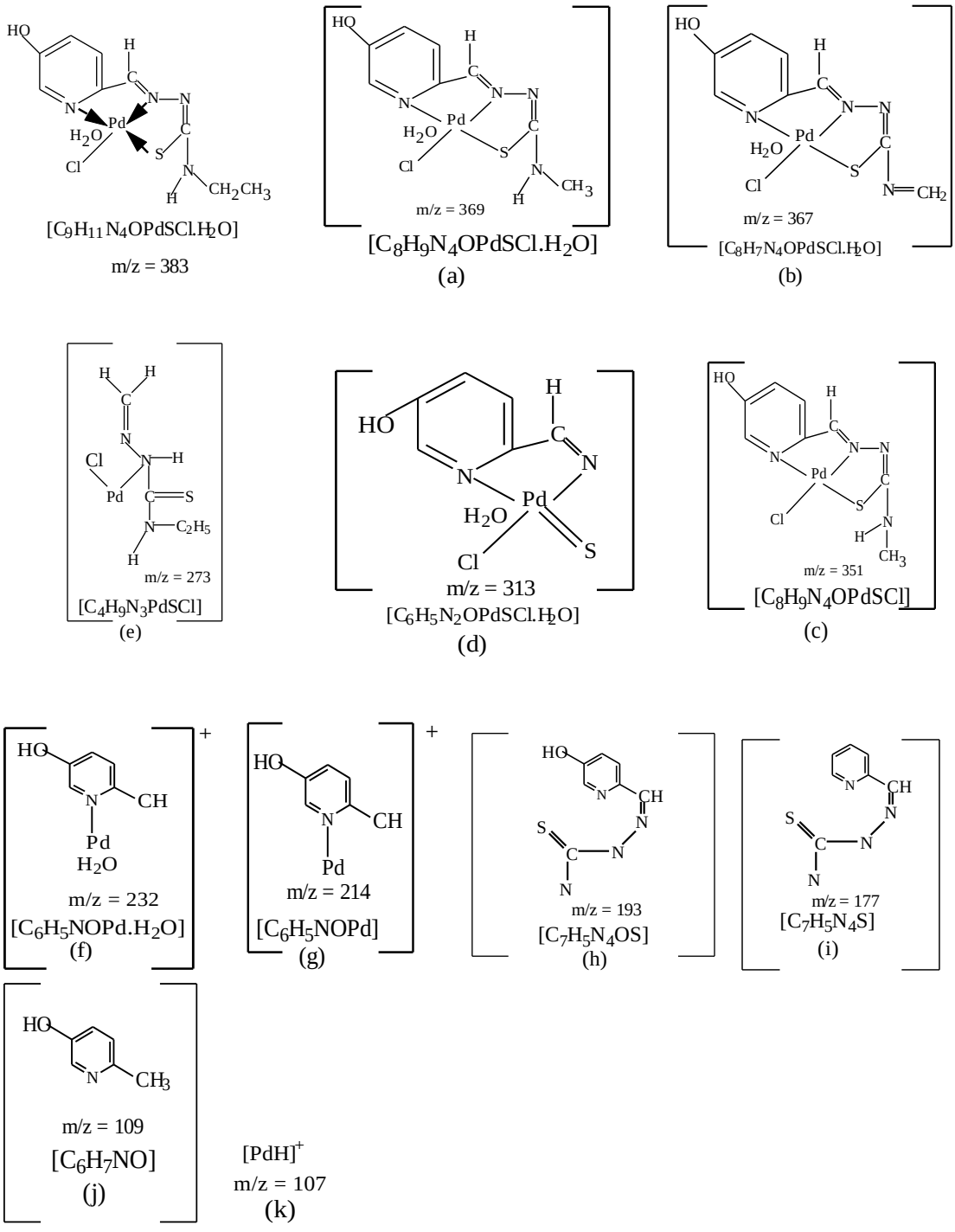


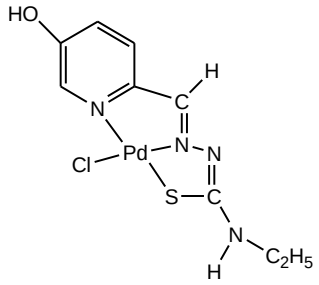
Fig. 3. Mass Spectra (FAB) of [Pd(PyEt)Cl].H_2O.



Scheme II. Proposed mass fragmentation pattern for complex [Pd(PyEt)Cl].H_2O.

Conclusions

5-Hydroxypyridine-2-carbaldehyde N(4)-ethylthiosemicarbazone was prepared and characterized by elemental analysis, IR, UV-Vis, and 2D-NMR spectra. From the reaction between lithium tetrachloropalladate prepared in situ from $PdCl_2$ and LiCl and 5-Hydroxy-2-carbaldehyde N(4)-ethylthiosemicarbazone, complex of stoichiometry 1:1 and general formula $[Pd(PyEt)Cl].H_2O$ was obtained. Palladium(II) complex $[Pd(PyEt)Cl].H_2O$ characterized by elemental analysis IR, ^{1}H-NMR, UV-visible spectroscopy and mass spectrometry (FAB) confirmed the expected palladium cation coordination by a chloride anion and thiosemicarbazonato anion; co-ordinated by pyridyl nitrogen, azomethine nitrogen and thionylsulphur The ligand was coordinated as a tridentate shown by NMR and IR spectroscopy. The overall geometry of the complex was square planar, based on composition, coordination number and mode of coordination. Hydroxy group was found non deprotonated and not involving in coordination with Pd(II) in the complex.



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