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Synthesis and Characterization of Platinum(II) Mixed Ligand Complexes of Purines And N-Glycylglycine

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Abstract: Interaction of K_2PtCl_4 with N-glycylglycine and purine nucleobase resulted in ternary complexes. The complexes are characterized by chemical and thermal analyses, conductivity measurements, electronic, infrared, H^1 and C^{13} NMR spectral studies. Attempted synthesis of mixed ligand complexes of any of the pyrimidine bases was not successful. The results indicated that the complexes are of type $[\{Pt(glygly)\}_2Hnb]Cl_2 .H_2O$. In the complexes, the purine nucleobases act as neutral ligand and bridge the two platininum(II) centres through N1 and N7. The N-glycylglycine acts as tridentate ligand and satisfies the square planar geometry around platinum(II).

Keywords: Platinum(II) complexes, ternary, purines, NMR, thermal analyses.

INTRODUCTION

Compounds of the type cis–$[PtA_2G_2]^{2+}$, A= amine, A_2=chelating diammine, G=guanine, guanosine or guanosine phosphate have been investigated as the interactions may give an insight into an understanding of antitumour activity of plantinum compounds[1-6]. The complex cis-$[Pt(NH_3)_2(guo)_2]Cl_2$ which exhibits antitumour activity[7] has two guanosine ligands in head-to-tail fashion and the Pt(II) coordination is through N7 of the guanosine ligand. The other known cis-bis(nucleobase) complexes of platinum(II) are with cytosine bases[8], substituted purines[9], l-methyluracil[10], 1,3,9-trimethyxanthine[11].

The ^1H NMR studies on the interaction of Pt(II) with nucleic acid derivatives are useful mainly in elucidating the binding site of the nucleobases in the Pt(II) complexes. The ^1H NMR spectra of $[Pt(NH_3)_3(CH_3\text{-ade})]X_2$, X=Cl, ClO_4 and of trans-$[Pt(NH_3)_3(OH)_2(CH_3\text{-ade})]X_2$ indicated that N7 of CH_3-ade is coordinated to Pt(II) as evidenced by the coupling between H8 of the adenine ring and ^{195}Pt. The Pt(II) and Pt(IV) complexes can be differentiated on the basis of the magnitude of ^3J values of the complexes as Pt(II) complex is having higher values than Pt(IV) by a factor of about 1.57[12]. The ^1H NMR spectrum of cis-$[(NH_3)_2Pt(dcmp)_2]^{2-}$ shows resonances of H5 and H6 of cytosine consisting of four lines each of identical intensities. The absence of downfield shifts of the H5 and H6 resonances upon lowering of the pH proves that Pt(II) binding occurs via N3 positions of the cytosine moieties since there is no protonation possible any more at N3. In the free ligand $dcmp^{2-}$, the protonation at N3 causes considerable downfield shift of the H5 and H6 resonances. The ^{195}Pt resonance at - 2602 ppm indicates the presence of PtN_4chromophore[13]. The ^{31}P NMR signal at -0.33 ppm

excludes the participation of the phosphate groups in Pt(II) coordination. The observed doubling of the cytosine proton resonances is attributed to the existence of two diastereomers with head to tail oriented nucleobases. Here, reported are the synthesis of mixed ligand complexes of Pt(II) of type $[\{Pt(glygly)\}_2Hnb]Cl_2 .H_2O$ and their characterization.

EXPERIMENTAL

The complexes $[\{Pt(glygly)\}_2Hnb]Cl_2 .H_2O$, Hnb = ade, $C_6 H_5 CH_2$ –ade, hypoxan, Cl- gua, ado and Cl-guo are synthesized and characterized by chemical and thermal analyses, conductivity measurements, electronic, infrared, ^1H and ^{13}C NMR spectral studies.

Synthesis of Platinum(II) Mixed Ligand complexes

µ-(Adenine- N1,N7)bis(glycylglycinato)diplatinum(II)choridemonohydrate $[\{Pt(glygly)\}_2ade]Cl_2 .H_2O$

Potassium tetrachloroplatinate (1.0 mmol) is dissolved in an aqueous solution of Hglygly (1.0 mmol in 15ml of H_2O) and stirred for 2h. The colour changes from yellow to red is observed with a decrease in pH from 6 to 2. The pH of the solution is maintained at 5 using 0.1M KOH. The resultant solution is concentrated using rotary evaporator and adenine (1.0 mmol in 30 ml of H_2O) is added to the red coloured solution and stirred at room temperature for 24h. The resultant yellow precipitate is washed with hot water to remove any unreacted starting materials and then washed with acetone and air dried. The ternary complexes of the purines, namely,

µ-(N6- benzyladenine- N1,N7)bis(glycylglycinato)diplatinum(II)chloride monohydrate.

$[\{Pt(glygly)\}_2C_6 H_5 CH_2\text{-ade}]Cl_2 .H_2O$,

µ-(hypoxanthine- N1,N7)bis(glycylglycinato)diplatinum(II)chloride monohydrate.

$[\{Pt(glygly)\}_2hypoxan]Cl_2 .H_2O$,

µ-(guanine- N1,N7)bis(glycylglycinato)diplatinum(II)chloride monohydrate.

$[\{Pt(glygly)\}_2Cl\text{-gua}]Cl_2 .H_2O$,

µ-(adenosine- N1,N7)bis(glycylglycinato)diplatinum(II)chloride monohydrate.

$[\{Pt(glygly)\}_2ado]Cl_2 .H_2O$ and

µ-(6-chloroguanosine- N1,N7)bis(glycylglycinato)diplatinum(II)chloride monohydrate.

$[\{Pt(glygly)\}_2Cl\text{-guo}]Cl_2 .H_2O$

are prepared by following the above method using the respective purines. Yields range from 65-70%.
Attempted synthesis of mixed ligand complexes of any of the pyrimidine bases was not successful.

RESULTS AND DISCUSSSION

Plantium(II) Complexes of Purines and N-glycylglycine

The complexes are insoluble in water and in common organic solvents like acetone, alcohol, chloroform and benzene. The ade and hypoxan complexes are insoluble even in DMSO and DMF while the other complexes are soluble in these solvents. The results of chemical analyses and conductivity measurements of the complexes are given in Table 1. The complexes of Cl-gua, ado and Cl-guo show a molar conductance value around 105 $ohm^{-1} cm^2$. The value of molar conductance in the range 100-120 $ohm^{-1} cm^2$ in 10^{-3} M DMSO solution are characteristic of 1:2 electrolytes [14]. Thus, the conductance values in DMSO indicate that the complexes are 1:2 electrolytes. The magnetic measurements suggest that all the complexes are diamagnetic as expected for square planar platinum(II).

(a) Thermal analyses

Thermogravimetric and differential thermal analyses are carried out in order to understand the thermal behavior of the complexes. The thermoanalytical data are presented in Table 2. The TG curves of all the complexes show 3 stages of weight loss in the temperature ranges 70-85^{0}C, 110-125^{0}C and 160-410^{0}C. The first stage corresponds to the dehydration of the water of crystallization. It has been reported that the complexes containing chloride as one of the ligands on thermolysis lose chloride in the temperature range 160-215^{0}C [15-16]. The observed weight losses in the present chloro complexes are in good agreement with those of calculated weight losses due to the removal of chloride. Thus the second stage is attributed to the dehalogenation process. For example, in the complex [{Pt(glygly)}$_2$ade]Cl_2 .H_2O the observed weight losses of 2.9 and 7.9% in the first two stages agrees with the calculated values of 2.04 and 8.04% and corresponds to the dehydration and dehalogenation processes respectively. The DTA plots of these complexes exhibit endothermic effect around 80 and 120^0 C attributed to the dehydration and dehalogenation processes respectively. The third stage is due to the oxidative decomposition of ligands, Hglygly and purines. This process is characterized by broad exothermic peaks in the range 300-390^{0}C. In the complex [{Pt(glygly)}$_2$ade]Cl_2 .H_2O,the final residue of 9.8% of initial weight of the complex confirms the formation of metallic Pt. It has been observed that the nucleobase containing complexes (ade, C_6 H_5 CH_2-ade, hypoxan, Cl-gua) start decomposing around 210^{0}C while the nucleoside complexes (ado, Cl-guo) start decomposing around 160^{0}C. The lower stability of the nucleoside complexes than the nucleobase complexes is probably due to the presence of sugar moiety.

(b) Electronic spectral studies

The separation between different orbitals in the energy level diagram vary widely in square planer complexes depending on the nature of ligands[17], thereby making the assignment of transitions difficult. In addition, another specific problem in analyzing the electronic spectra of the square planar complexes arises due to high extinction coefficient of the d →d transitions. This mainly appears because of the proximity of d → d transitions to charge transfer bands arising due to ligands to metal charge transfer, commencing from 335 nm. Thus, the transition observed in the region around 345 nm in the ternary complexes is assigned to d → d transition of Pt(II), which suggests a square planar geometry around the metal. The molar absorption coefficients of d → d transition around 3000-4000 1 mol^{-1} cm^{-1} suggest that the transition is associated with ligand to platinum charge transfer [18]. The transition around 270 nm in all the ternary complexes is of ligand origin and is assigned to $\pi \rightarrow \pi^*$ of purines [19].

(**C) Infrared spectral studies**

The infrared spectral data of the complexes are tabulated in Table 3. The analysis of the spectra of the complexes with nucleosides and nucleobases is quite complicated because of the presence of two complex ligands (Hglygly and Hnb/Hns) which have absorptions in the overlapping regions and the possibility of the presence of combination bands. Therefore, the assignments could be made only for few select bands on comparison with the spectra of nucleobases which have already been dealt [20,21] in many reports.

Strong multiple bands in the region 3420 and 3330-3180 are assigned to υ_{OH} of water and υ_{NH} of nucleobases in the complexes. The band around 2900 cm^{-1} in complexes is assigned to υ_{CH} of the nucleobases. The strong band at 1665 cm^{-1} in the IR spectra of nucleobases (ade, C_6 H_5 CH_2-ade, ado Cl-guo) and complexes is assigned to δ_{NH2}[22]. The vibrational frequencies around 1600 and 1465 cm^{-1} are due to the pyrimidine moiety of purines (ade, C_6 H_5 CH_2-ade, and ado) and they appear around 1590, 1460 cm^{-1} in the complexes. The infrared frequencies due to the imidazole moiety in the spectra of ade, C_6 H_5 CH_2-ade and ado appear around 1420 1325 and 1305 cm^{-1}. In the complexes they are shifted to lower wave numbers around 1405, 1320 and 1305 cm^{-1}. The sharp and medium vibrational frequencies around 1600, 1549, 1453, 1400 and 1370 cm^{-1} In Cl-gua, Cl-guo and hypoxan are assigned to combinations of $\upsilon_{C=C}$ and $\upsilon_{C=N}$ of pyrimidine and imidazole fragments [23]. In the complexes of Cl-gua, Cl-guo and hypoxan, similar shifts to lower wave numbers are observed. Hence, the slight changes in both the pyrimidine and imidazone vibrations indicate the coordination of ring nitrogen atoms to Pt(II) [24] .

The infrared spectrum of Hglygly exhibited band at 1675 due to $\upsilon_{C=O.}$ The carboxylate group absorbs at 1700 cm^{-1} due to asymmetric carboxylate stretching. The strong absorption at 1665 cm^{-1} is due to δ_{NH2} group. The ligand Hglygly coordinates to metal ion either as a bidentate chelating through NH_2 and CO group forming a five-membered ring or as a tridentate through NH_2, CO and NH_2 forming two five-membered chelate rings[25]**.** In the complexes, it is observed that the frequencies of δ_{NH2} and $\upsilon_{asy(COO)}$ shifted to lower wave numbers by about

25 cm^{-1} probably indicating the tridenticity of Hglygly with the formation of two five-membered chelate rings with Pt(II). The assignments of metal ligands stretching frequencies are made by comparison with the spectra of free ligands and other Pt(II) metal complexes containing nitrogen and oxygen donor ligands in the region. Thus, the bands in the regions 550-480 cm^{-1} and 415-400 cm^{-1} are assigned to υ_{pt-N} and υ_{Pt-O} respectively[26,27].

(d) NMR spectral studies

The well resolved C^{13} NMR and ^1H NMR spectra of glycylglycine, nucleobases and their complexes in DMSO are reproduced in Fig 1 and 2. The spectral data are given in Table 4. The ^1H NMR spectrum of glycylglycine shows CH_2 resonances appearing as a singlet at 3.87 and 3.90 ppm. The COOH proton appears as a singlet at 11.10 ppm. A downfield shift of about 0.10 ppm and broadening of peaks are observed in CH_2 resonances of glycylglycine in the ternary complexes. The shift in the CH_2 resonances may be taken as an indication of coordination through the adjacent nitrogens and carboxylate oxygen. The absence of the peak at 11.10 ppm due to the carboxyl group in the complexes indicates the deprotonation of the carboxylic group and hence the coordination of oxygen to metal.

The spectrum of adenosine shows two singles at 7.74 and 7.94 ppm which are assigned to H2 and H8 protons respectivity[12]. The adenosine complex shows a downfield shift of H2 and H8 protons by 0.22 and 0.21 ppm respectively. Studies on metal complexes of purine and its derivatives indicate that a downfield shift of H8 arises due to the coordination through the adjacent nitrogen atoms N7 or N9. The presence of sugar moiety at N9 position ruled out the possibility of N9 coordination. Based on the observed resonances in the spectrum, it is proposed that adenosine is bridging the two Pt (II) atoms via N7 and N1 or N7 and N3 atoms. The ^1H NMR spectrum of free Cl-gua and Cl-guo exhibit singlets at 7.95 and 7.98 ppm respectively. A downfield shift of H8 proton by 0.15 and 0.22 ppm in the complexes and $[\{Pt(glygly)\}_2Cl\text{-}gua]Cl_2.H_2O$ and, $[\{Pt(glygly\}_2$ Cl-guo$]Cl_2.H_2O$ implies the coordination through N7 of Cl-gua and Cl-guo. The appearance of the signal around 12.0 ppm in the complex which is at the same position as in the free ligand ruled out the N9 coordination of 6 –chloroguanine and 6-chloroguanosine[13,28].

The C5 and C8 resonances of adenosine appear at 112.7 and 133.1 ppm respectively. In the complex, $[\{Pt(glygly\}_2$ ado$]Cl_2.H_2O$ these resonances show downfield shifts and appear at 116.8 and 137 ppm respectively which is consistent with N7 involvement in coordination. The C6 and C2 resonances of adenosine appear at 147.8 and 153.1 ppm respectively. Similarly, these resonances are seen in the downfield region of 151.8 and 156.9 ppm respectively suggesting the coordination of adjacent nitrogen,N1 to the metal. Further the C6 and C2 resonances of C1-gua appear at 154.1and148.1 ppm respectively. In the complex,$[\{Pt(glygly)\}_2Cl\text{-}gua]Cl_2.H_2O$ these resonances occur at 158.1 and 152.1 ppm respectively, suggesting the N1 coordination. Based on these results the following structure is proposed for the ternary complexes.

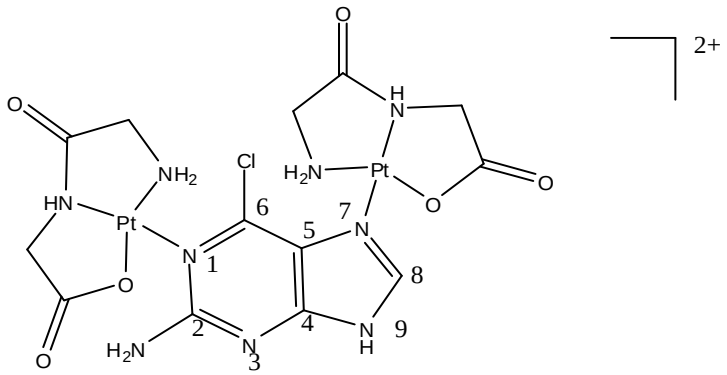


Table-1 Chemical Analysis and Conductivity Data of [{Pt(glygly}$_2$Hnb]Cl$_2$.H$_2$O

S.No	Complexes	C%		H%		N%		CI%		Pt%		Molar conductance ohm^{-1} cm^2
		Calc.	Found	Calc	Found	Calc.	Found	Calc.	Found	Calc.	Found	
1	[{Pt(glygly}$_2$ade]Cl$_2$.H$_2$O	17.71	17.30	2.40	2.51	15.82	16.70	8.04	8.91	44.26	45.00	-
2	[{Pt(glygly}$_2$C$_6$H$_5$CH$_2$ade]Cl$_2$.H$_2$O	21.01	21.64	2.28	3.18	10.09	10.39	7.30	7.92	40.75	40.69	-
3	[{Pt(glygly}$_2$hypoxan]Cl$_2$.H$_2$O	18.57	17.66	2.29	2.59	13.33	12.97	8.43	8.88	46.39	46.81	-
4	[{Pt(glygly}$_2$Cl-gua]Cl$_2$.H$_2$O	17.14	16.42	2.32	2.25	13.84	14.79	7.78	8.30	42.83	43.57	104
5	[{Pt(glygly}$_2$ado]Cl$_2$.H$_2$O	21.43	20.53	3.10	3.13	12.50	12.08	7.02	7.42	38.68	38.94	105
6	[{Pt(glygly}$_2$CL-guo]Cl$_2$.H$_2$O	20.71	20.53	2.80	2.81	12.08	12.02	6.79	6.47	37.37	36.81	100

*10^{-3} M in DMSO

Table-2.Thermoanalytical Data of [{Pt(glygly}$_2$Hnb]Cl$_2$.H$_2$O

S.NO	Complexes	Dehydration			Dehalogenation			Formation of Pt		
		Weight loss (%)		DTA peak (^{o}C)	Weight loss (%)		DTA peak (^{o}C)	Weight loss (%)		DTA peak (^{o}C)
		Found	Calc.		Found	Calc.		Found	Calc.	
1	[{Pt(glygly}$_2$ade]Cl$_2$.H$_2$O	2.9	2.04	-74	7.9	8.04	-120	90.2	89.92	+280 +310 +400
2	[{Pt(glygly}$_2$C$_6$H$_5$CH$_2$-ade]Cl$_2$.H$_2$O	2.3	1.85	-78	8.0	7.30	-116	90.1	90.85	+320 +405
3	[{Pt(glygly}$_2$hypoxan]Cl$_2$.H$_2$O	2.0	2.03	-80	9.1	8.03	-115	89.9	89.94	+320 +350 +400
4	[{Pt(glygly}$_2$Cl-gua]Cl$_2$.H$_2$O	2.1	1.96	-80	7.9	7.74	-120	90.2	90.30	+313 +396
5	[{Pt(glygly}$_2$ado]Cl$_2$.H$_2$O	2.2	1.78	-80	8.1	7.00	-118	90.0	91.22	+305 +380 +405
6	[{Pt(glygly}$_2$CL-guo]Cl$_2$.H$_2$O	2.0	1.72	-80	6.0	6.75	-120	91.3	91.53	+311 +375 +400

(-): endothern; (+): exothern

Table- 3. Principal IR and far IR Spectral Frequencies (cm) of [{Pt(glygly)}$_2$ Hnb]Cl $_2$.H_2O

S.No	Complexes	υ_{OH} (water)	V_{NH2}	υ_{CH}	υ(peptide)	δ_{NH2}(ade, peptide)	$\upsilon_{C=C}$,$\upsilon_{C=N}$ nucleobases	υ_{Pt-N}	υ_{Pt-O}
1.	[{Pt(glygly)}$_2$ade]Cl $_2$.H_2O	3420 S, br	3310 s 3180 s	3070 m	1675 s	1665 s 1640 m	1587 s 1460 m 1412 m 1326 w	495 w	405 w
2.	[{Pt(glygly)}$_2$ C_6 H_5 CH_2 .ade]Cl $_2$.H_2O	3400 s, br	3260 s 3200 s	3050 m	1672 sh	1645 sh	1580 s 1450 m 1412 m 1326 sh	495 w	410 vw
3.	[{Pt(glygly)}$_2$hypoxan] Cl $_2$.H_2O	3410 s, br	3260 s 3180 s	2900 m	1672 sh	1665 s 1640 sh	1580 s 1450 m 1410 m 1330 m	495 w	408 w
4.	[{Pt(glygly)}$_2$ Cl-gua]Cl $_2$.H_2O	3420 s	-	2920 m	1663 sh	1645 m	1597 s 1562 sh 1465 s 1335 m	500 m	415 m
5.	[{Pt(glygly)}$_2$ado]Cl $_2$.H_2O	3410 s	3270 s 3230 s	2920 m	1678 sh	1655 s 1640 sh	1580 1451 1406 1330	520 m	412 w
6.	[{Pt(glygly)}$_2$ Cl-guo]Cl $_2$.H_2O	3430 br	3330 s 3205 s	2990 m	1672 sh	1660 s 1643 sh	1587 m 1460 s 1415 m 1326 m	497 m	410 w

S – strong, br – board , m – medium, sh – shoulder, w – week, vw - weak

Table-4.Proton NMR Data of [{Pt(glygly}$_2$Hnb]Cl$_2$.H$_2$O

S.No.	Complexes	Purine protons (δ in ppm)		Hglgly protons (δ in ppm)
		H2	H8	CH2
1	[{Pt(glygly}$_2$Cl-gua]Cl$_2$.H$_2$O	-	8.10 (s)	3.95 (br,s) 4.10 (br,s)
2	[{Pt(glygly}$_2$ado]Cl$_2$.H$_2$O	7.96 (s)	8.10 (s)	3.97 (br,s) 4.10 (br,s)
3	[{Pt(glygly}$_2$CL-guo]Cl$_2$.H$_2$O	-	8.10 (s)	3.97 (br,s) 4.00 (br,s)

Standard – TMS; Solvent – d_6DMSO

Table-5. ^{13}C NMR Data of [{Pt(glygly}$_2$Hnb]Cl$_2$.H$_2$O

S.No	Complexes	Nucleobase Carbons (δ in ppm)										Hglgly carbons (δ in ppm)		
		C1	C4	C5	C6	C8	C1'	C2'	C3'	C4'	C5'	CH_2	CO	COOH
1	[{Pt(glygly}$_2$Cl-gua]Cl$_2$.H$_2$O	152.1	150.2	116.9	158.1	136.2	--	--	--	--	--	49.2	169.29	166.07
2	[{Pt(glygly}$_2$ado]Cl$_2$.H$_2$O	156.9	149.8	116.8	151.8	137.0	88.1	69.23	71.26	85.20	58.9	49.19	168.96	165.95

Standard – TMS – solvent – d_6 - DMSO

Figure 1. C^{13} NMR spectra

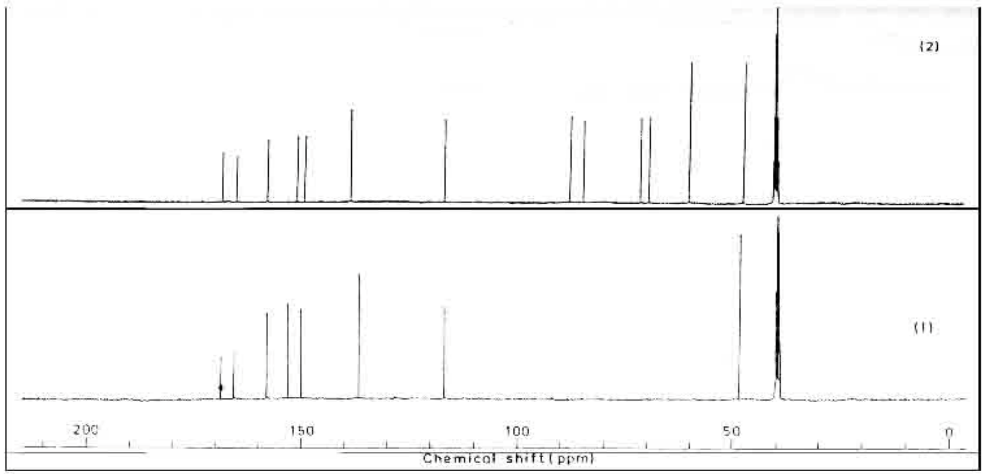
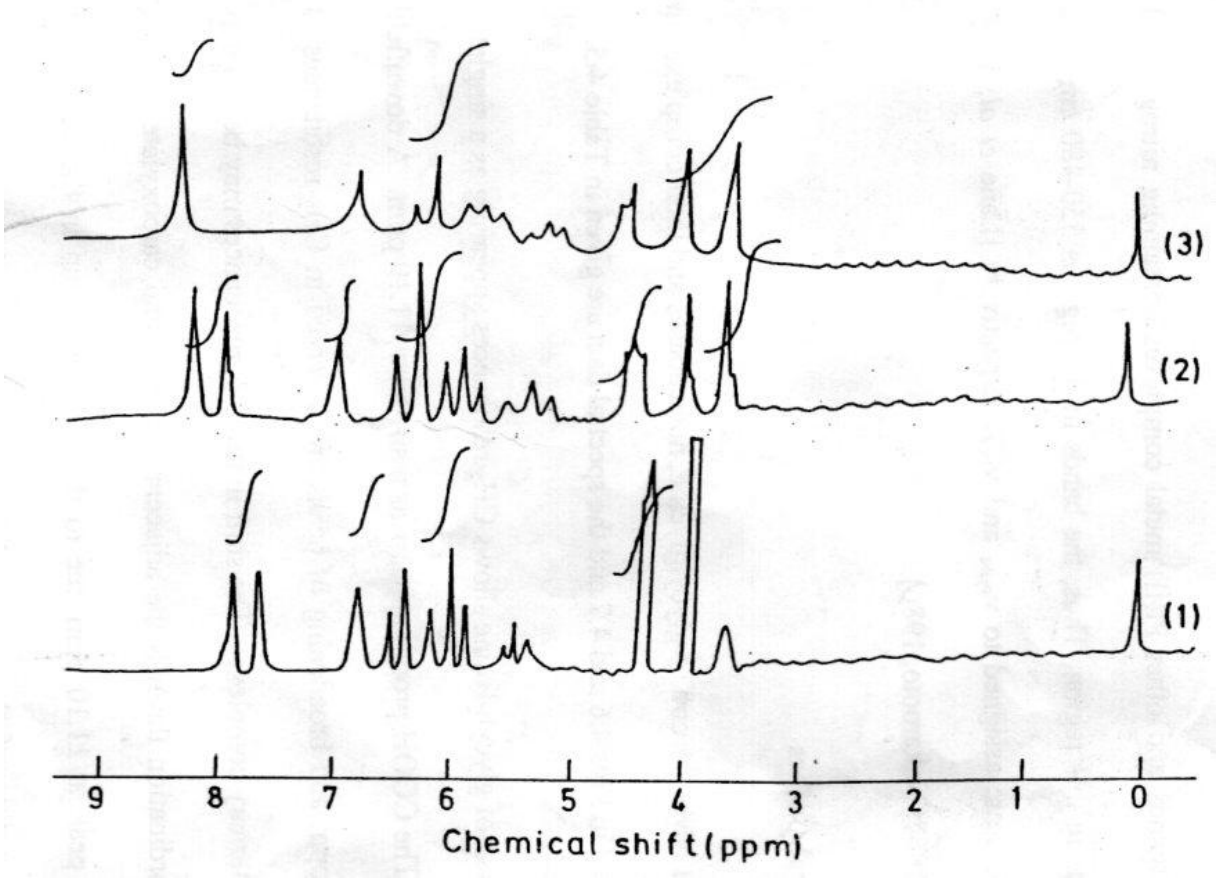


Figure.2 Proton NMR spectra



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