INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

Research Article

SYNTHESIS AND CHARACTERIZATION OF A PROTON PUMP INHIBITOR WITH BIVALENT METAL IONS

Y. M. ISSA[A], W. H. HEGAZY[B] W. N. EL-SAYED[B], H. I. AHMED[B]

[a]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt
[b]Department of Chemistry, Faculty of Science, Suez University, Suez, Egypt
*Corresponding Author

Abstract

The synthesis and characterization of solid complexes for pantoprazole sodium sesquihydrate with Co(II) and Ni(II) metals in molar ratios M:L = 1:2 was studied. The complexes are stable solid and soluble only in DMF and DMSO. The metal complexes were characterized by elemental analysis, molar conductivity measurements, magnetic susceptibility, UV spectroscopy, IR, Mass spectra and analysis.

Keywords: Bivalent metal complex, Pantoprazole, proton pump inhibitor, thermal analysis.

1. Introduction

Pantoprazole sodium sesquihydrate is benzimidazole derivatives which have biological activity to inhibits gastric acid secretion[1]. Pantoprazole act as good ligand as it have several coordination mode[2,3]. Many drugs enhance its pharmacological and toxicological properties by their complexation with metal ions[4-9]. Ni(II) and Co(II) pantoprazole complexes was prepared and characterized by elemental analysis, IR, mass spectrometry, Electrical conductivity, magnetic suscebtibility, UV spectroscopy and thermal analysis.

2. Experimental

2.1 *Preparation of the complexes*

The complexes were prepared according to the procedure: (0.5 mmol) pantoprazole ligand is dissolved in 10 cm^3 H$_2$O then (0.25 mmol) of the dissolved bivalent metal in 10 cm^3 H$_2$O is added drop wise with stirring to the ligand solution. The formed precipitate was filtered, washed with hot water and dried. Synthesized solid complex was characterized by elemental analysis, IR, mass spectrometry, molar conductivity, magnetic susceptibility, UV spectroscopy and thermal analysis.

2.2 *Physical measurements*

The electronic absorption spectra were obtained by 10^{-5} M DMF solution in 1 cm quartz cell using Shimadzu-1601PC UV-Visible automatic recording spectrophotometer. The CHNS elemental analysis was estimated using Thermo Flash Eager 300. The infrared spectra were analyzed (KBr disc) in the 400-4000 cm^{-1} range using perkin Elmer 1650 FT-IR instrument. TG were obtained using a Shimazdu DTG – 60H in a dynamic air atmosphere (30 cm^3 min^{-1}) at a heating rate of 10 ^{o}C min^{-1}. The molar conductivity of the dissolved complexes were carried out at room temperature on freshly prepared 10^{-3} M DMF solutions using Jenco Model 1671 Dual Display Bench Top instrument pH/ORP (redox)/conductive. Magnetic susceptibility measurements were carried out using the modified Gouy method[10] on MSB-MK1 balance at room temperature using mercury(II) tetrathiocyanatecobaltate(II). The effective magnetic moment μ$_{eff}$, per metal atom was calculated from the expression μ$_{eff}$ =2.83 x.T B.M., where x is the molar susceptibility corrected using Pascal's constant for the diamagnetism of all atoms in the complexes. The mass spectra were done by AMD

Intectra Gmb HDP10. Data system EI/8 Kv spectrometer.

2.3 Kinetic parameters

In order to assess the influence of the structural properties of the ligand and the type of metal on thermal behavior of the complexes, the order n and the heat of activation E at the various decomposition stages were determined from TG and DTG thermograms using the Coats-Redfern equations in the following form[11]

$$\ln\left[\frac{1-(1-\alpha)^{1-n}}{(1-n)T^2}\right] = \ln\left(\frac{AR}{\beta E}\right)\left[1-\frac{2RT}{E}\right]-\left(\frac{E}{2.303RT}\right) \quad for\ n \neq 1 \tag{1}$$

$$\ln\left[-\frac{\ln(1-\alpha)}{T^2}\right] = \ln\left(\frac{AR}{\beta E}\right)\left[1-\frac{2RT}{E}\right]-\left(\frac{E}{2.303RT}\right) \quad for\ n = 1 \tag{2}$$

Where, is fraction of weight loss ,T is temperature (°K) , n is order of reaction , A is pre-exponential factor, R is molar gas constant , E_a is activation energy , is heating rate.

The correlation factor r is computed using the least squares method for equations (1) and (2). Linear curves were drawn for values equal 0.5, 1, 1.5, 2, 2.5

and 3. The value of n which gave the best linear plot was chosen as the order parameter for the decomposition stage of interest and the heat of activation was calculated from its slope.

The activation entropy S, the activation enthalpy H and the free energy of activation G were calculated using the following equations:

$$\Delta S = Rln(\frac{Ah}{KT}) \tag{3}$$

$$\Delta H = E - RT \tag{4}$$

$$\Delta G = \Delta H - T\Delta S \tag{5}$$

Where, K and h are the Boltzman's and plank's constants.

Results and Discussion

3.1 Elemental analysis
The results of elemental analysis of the solid complexes of pantoprazole are recorded in Table (1).

It is clear that the formula of the divalent Co and Ni complexes can be represented as $[ML_2(H_2O)_2].H_2O$.

Table.1: Analytical data and magnetic moments of the PNZ and its complexes

Compound	Chemical formula	% Found (calcd.)					eff. (298K) (B.M)
		C	H	N	S	M	
PNZ	$C_{16}H_{14}F_2N_3O_4S.Na.1.5H_2O$	43.2 (44.4)	3 (3.24)	9.4 (9.7)	6.5 (7.4)	--	--
Co-PNZ	$[Co(PNZ)_2(H_2O)_2].H_2O$	43.5 (43.75)	3.8 (3.87)	9.2 (9.57)	7.1 (7.29)	6.4 (6.7)	4.96
Ni-PNZ	$[Ni(PNZ)_2(H2O)_2].H_2O$	43 (43.76)	3.5 (3.87)	9.3 (9.57)	6.9 (7.29)	6.5 (6.68)	4

3.2 Molar conductivity measurements

The chelates were dissolved in DMF and the molar conductivities of 10^{-3} M of their solutions at 25±2 °C were measured. Table (2) shows the molar conductance values of the complexes. It is concluded from the results that the chelates have molar conductance values of 6-18.8 $^{-1}$cm^{2}mol^{-1} indicating that these chelates are non-electrolytes.

Table. 2: Physical data of the PNZ ligand and its complexes.

Compound	Chemical formula	M. Wt.	% Yeild	Color	($^{-1}$cm^{2}mol^{-1})	M.p.($^{\circ}$C)
PNZ	$C_{16}H_{14}F_2N_3O_4S.Na.1.5H_2O$	432.38		Off white		137
Co-PNZ	$[Co(PNZ)_2(H_2O)_2]H_2O$	877.66	64.9	pink	7.2	210
Ni-PNZ	$[Ni(PNZ)_2(H2O)_2]H_2O$	877.46	56	Faint green	9.8	180

3. 3 Magnetic susceptibility and electronic spectra measurements

The UV-Visible spectra of the ligand and its complexes were recorded in DMF at room temperature showed in (Figs. 1-3). The electronic spectrum of ligand showed only one intense band at 34246 cm^{-1}, which was assigned to n   * transition of the C=N chromophore. The electronic spectrum of the Co(II) complex gives two bands at 18484 and 20000 cm^{-1} wave number regions. These bands are assigned to the transitions $^4T_{1g}(F)$ $^4T_{2g}(F)$ and $^4T_{1g}(F)$ $^4T_{2g}(P)$, respectively, suggesting that there is an octahedral geometry around Co(II) ion, the band due to $^4T_{1g}(F)$ $^4A_{2g}(F)$ may be interfere with ligand band. The magnetic susceptibility measurements lie at 4.96 B.M. (normal range for octahedral Co(II) complexes is 4.3–5.2 B.M.), is an indicative of octahedral geometry[12]. The Ni(II) complex reported herein has a room temperature magnetic moment value of 4.00 B.M.; which indicates that, the complex of Ni(II) is six coordinate and probably octahedral[13,14]. The electronic spectrum displays two bands at 14492 cm^{-1}: $^3T_{1g}(F)$ $^3T_{2g}(F)$ and 20000 cm^{-1}: $^3T_{1g}(F)$ $^3T_{2g}(P)$. The band due to $^3T_{1g}(F)$ $^3A_{2g}(F)$ transition may attribute to ligand band.
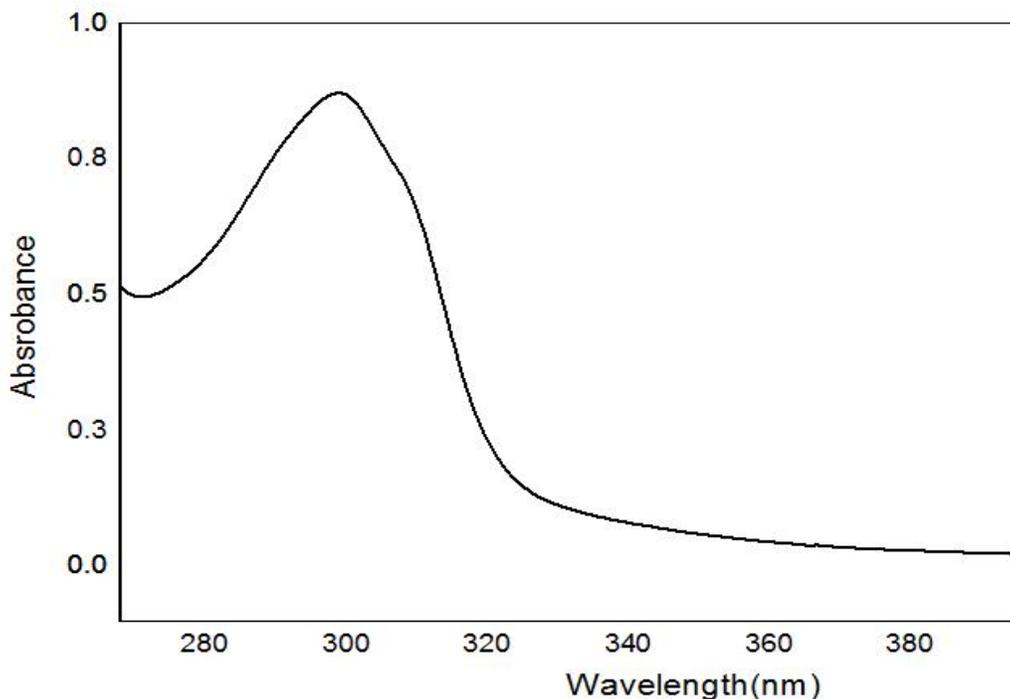
Fig. 1: UV spectroscopy of PNZ ligand.
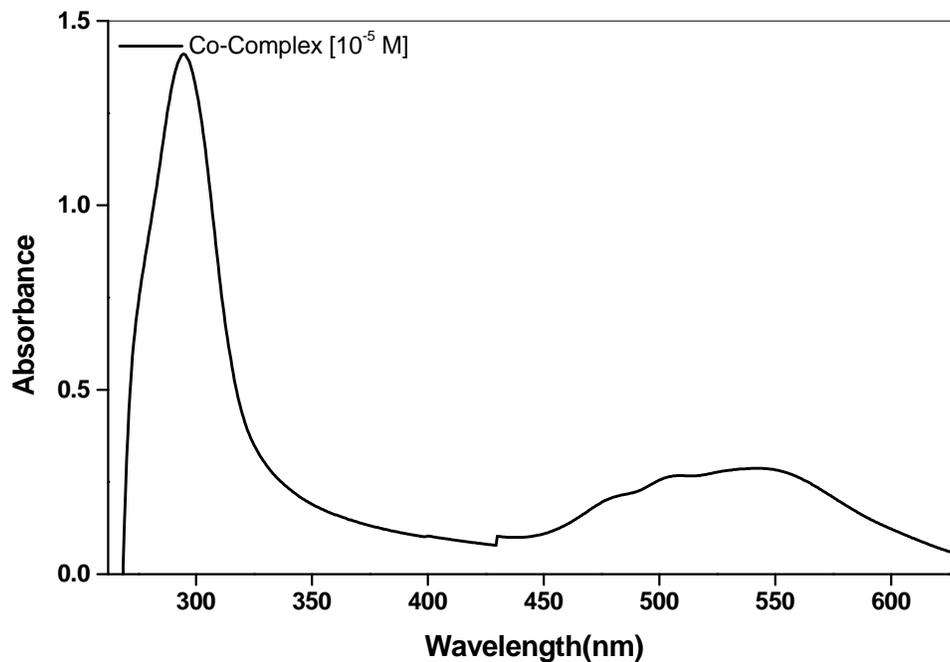
Fig. 2: UV spectroscopy of [Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex.
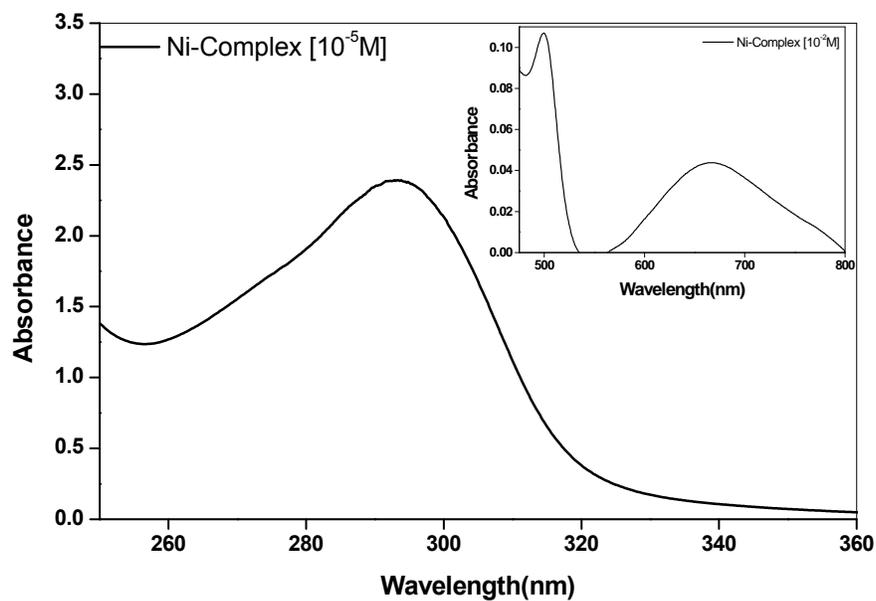
Fig. 3: UV spectroscopy of [Ni(PNZ)$_2$(H2O)$_2$].H$_2$O complex.

57

3. 4 IR spectra and mode of bonding

IR spectra for the ligand and its complexes shown in Table (3). In the free ligand, the band at 1373 cm^{-1} is assigned to (C-N) frequency as shown in Figs. (4-6); after complexation, this band is shifted to higher frequency in Ni(II) complex while in the case of Co(II) complex it appears to be shifted to lower frequency. Shifting of the (C-N) vibration is due to C-N M coordination[15]. Characteristic band at 3498 cm^{-1} is assigned to presence of water in the ligand structure; similarly presence of coordinated water is confirmed by the presence of band at 3372-3440 cm^{-1}[16]. Coordinated water molecule is also seen as a weak band at 815-820 cm^{-1} due to rocking mode while band at 450-630 cm^{-1} indicated the presence of water of crystallization[17]. In addition, IR spectrum of the ligand revealed a sharp band at 1035 cm^{-1} due to (S=O) of side chain, which is shifted to higher frequency after complexation in the two complexes, suggesting that oxygen atom of the side chain also contributes to the complexation. New bands appeared in the spectra of the complexes at 633-733 cm^{-1}, corresponding to O M and 410-540 cm^{-1} due to the N M vibrations which support the involvement of N and O atoms in complexation with metal ions under investigation[18]. Characteristic strong band at 1486 cm^{-1} is assignable to the stretching vibration of aromatic C=N group in benzimidazole ring that remained unchanged after complexation which confirmed the non-coordination of this group in complexes[19]. All this discussion indicates that the ligand is bidentate coordinating via O, N atoms.

Table. 3: IR spectral data of the PNZ and its complexes (cm^{-1})

Comp.	OH	CH$_3$	C=C	C=N	C-N	C-C	C-O	C-F	S=O	O-H	M-N	M-O	Water of crystallization (Rocking mode)
L	3498	3376 3190	1590	1486	1373	1298	1228 1166	1116	1035				
Co	3372	3213 2990	1590	1486	1366	1298	1234 1171	1121	1043	816	423	684	630
Ni	3427	3100 2957	1590	1482	1419	1300	1255 1170	1119	1058	820	453	633	553
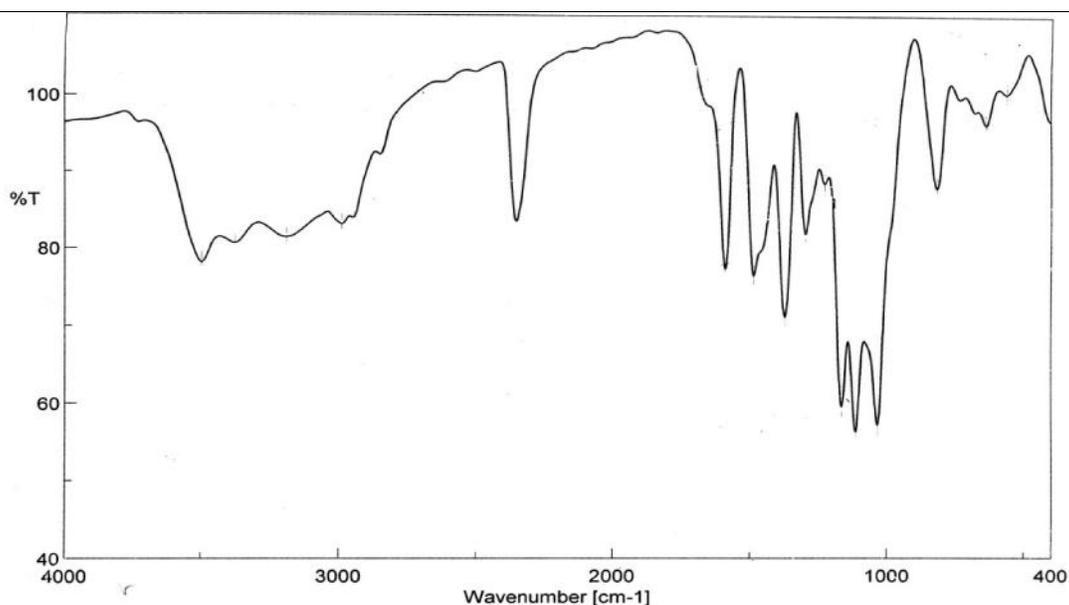
Fig. 4: IR spectra of the PNZ.
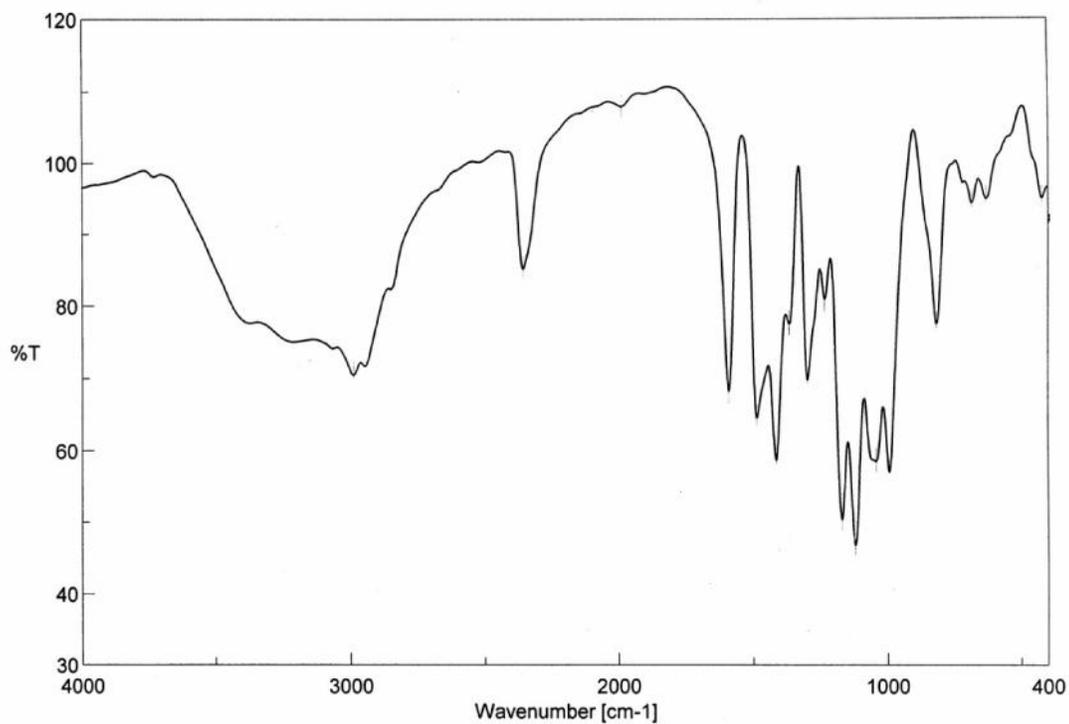
Fig. 5: IR spectra of the $[Co(PNZ)_2(H_2O)_2].H_2O$.
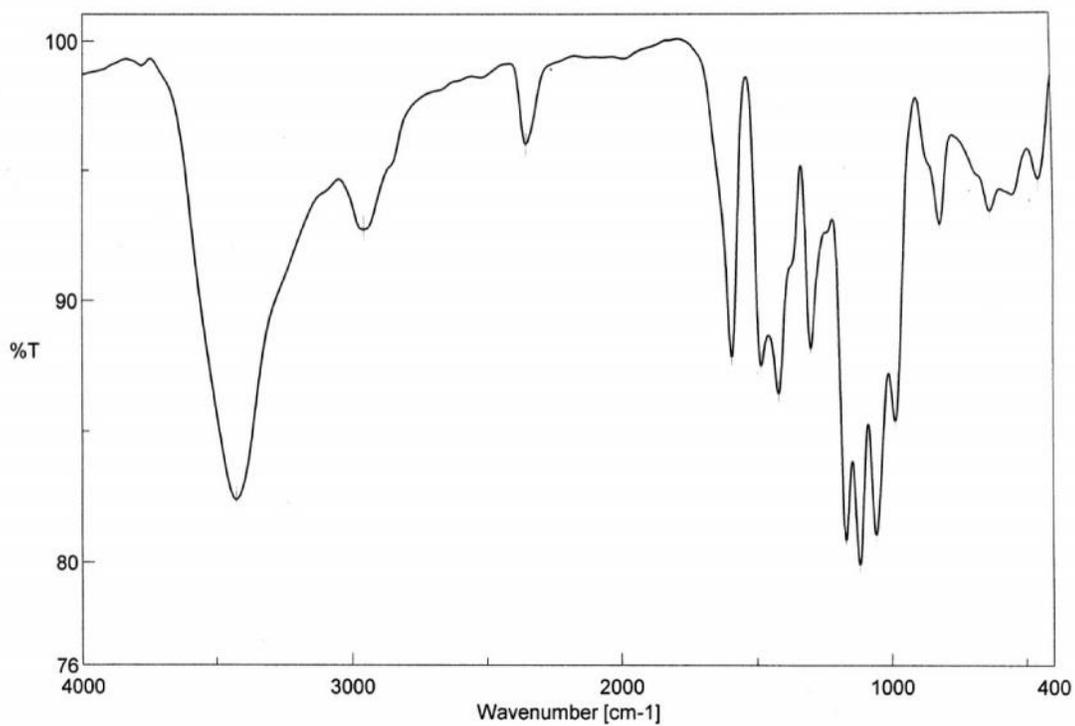
Fig. 6: IR spectra of the $[Ni(PNZ)_2(H2O)_2].H_2O$.

59

3. 5 Mass spectra

The mass spectral data shows in Figs. (7,8) did not show any of the required molecular ion peaks, but it could be deduced through studying of the assigned fragmentation peaks. The two complexes have the same fragmentation, which have the main fragments [a], [b], [c], [d], [e], [f] at m/z= 180(4.5), 116(8.5),

90(10.2), 78(14), 50(50.3) and 64(36.2) (as fragments of ligand), which confirm the proposed structure of complexes. This was also confirmed by the appearance of a peak at 179.5(7.9), 127(2.8), 291.5(5.1) and 321(5.6) for fragments [g], [h], [i] and [j] respectively. The most prominent peaks were assigned as shown in the following fragmentation (Scheme.1).
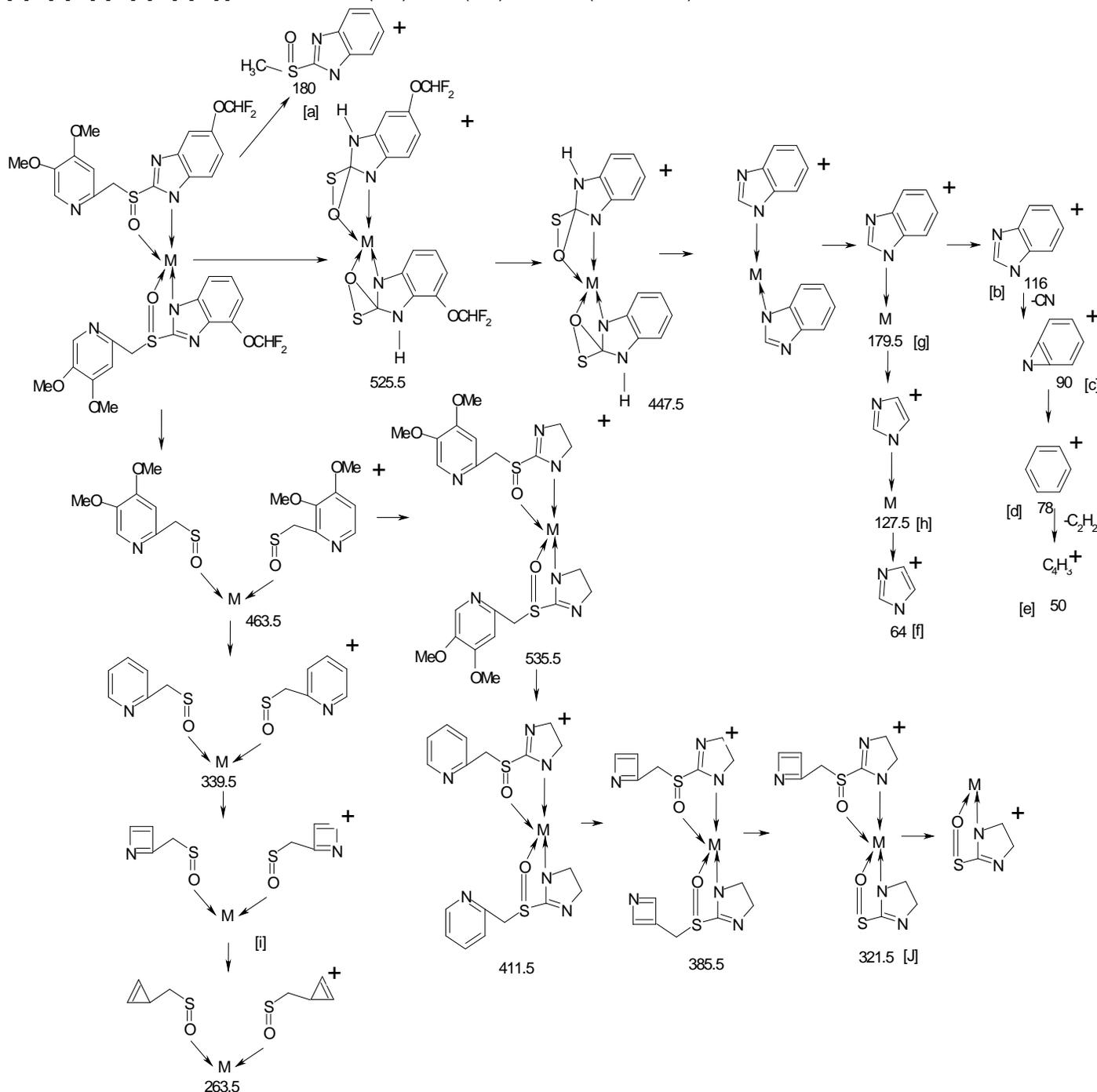
Scheme. 1 Fragmentation pattern for PNZ-complexes
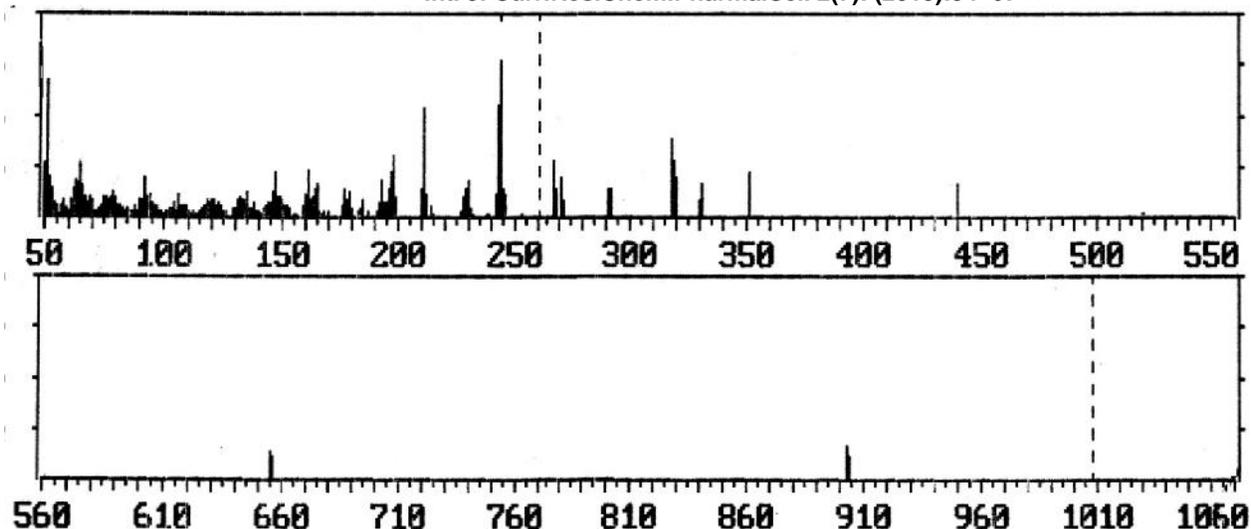
Fig. 7: Mass spectra of $[Co(PNZ)_2(H_2O)_2].H_2O$ complex.
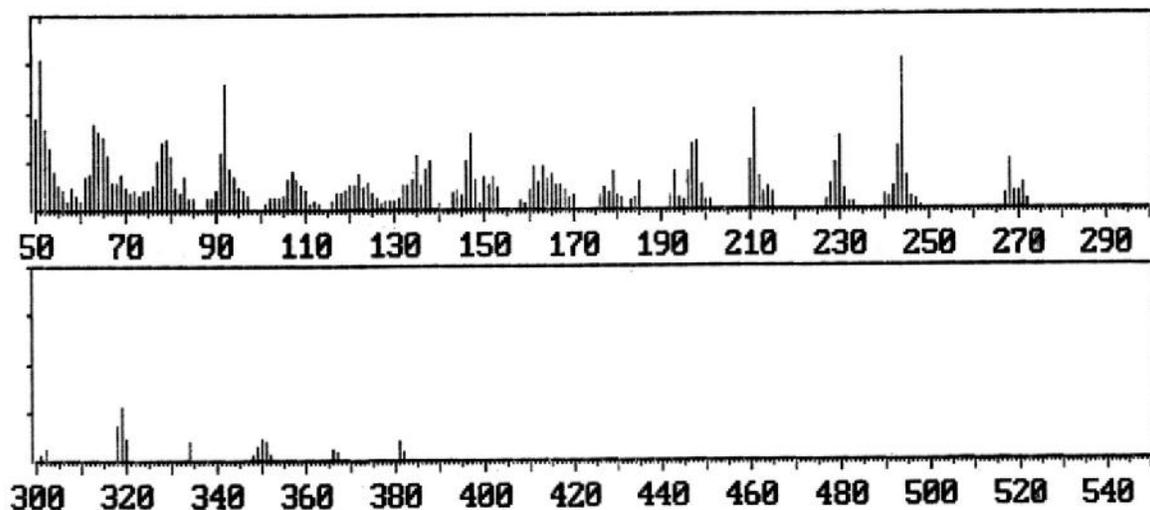
Fig. 8: Mass spectra of $[Ni(PNZ)_2(H_2O)_2].H_2O$ complex.

3.6 Thermal analysis

The thermal behavior of the PNZ-Complexes were characterized using TG/DTG method (Figs. 9,10). The decomposition stages, temperature ranges and decomposition products as well as the found and calculated weight loss are given in Table (4). The activation energies and kinetic parameters were calculated using Coats-Redfern equation[20] and the values are given in Table (5).

Thermal decomposition of cobalt complex takes place in four steps. The first stage starts at 59.4-163.4 °C range. This was accompanied with mass loss of 4.28 % (Calcd. 4.1 %) with maximum DTG at 135.9 °C which attributed to the volatilization of the hydrated water and one molecule of the coordinated water. The second decomposition stage takes place in the 164.7-302.59 °C range with maxima at 230.7 °C, which correspond to evolution of the coordinated water and partial decomposition of ligand. The third decomposition stage takes place at 303-461.3°C range with maximum DTG at 393.3 °C, which attributed to further decomposition of ligand with mass loss of 10.7 % (Calcd. 10.46 %). The final decomposition stage occurs in the range 462.4-799.7 °C with maxima at 509.4 °C. The final residue was calculated to be CoO.

61
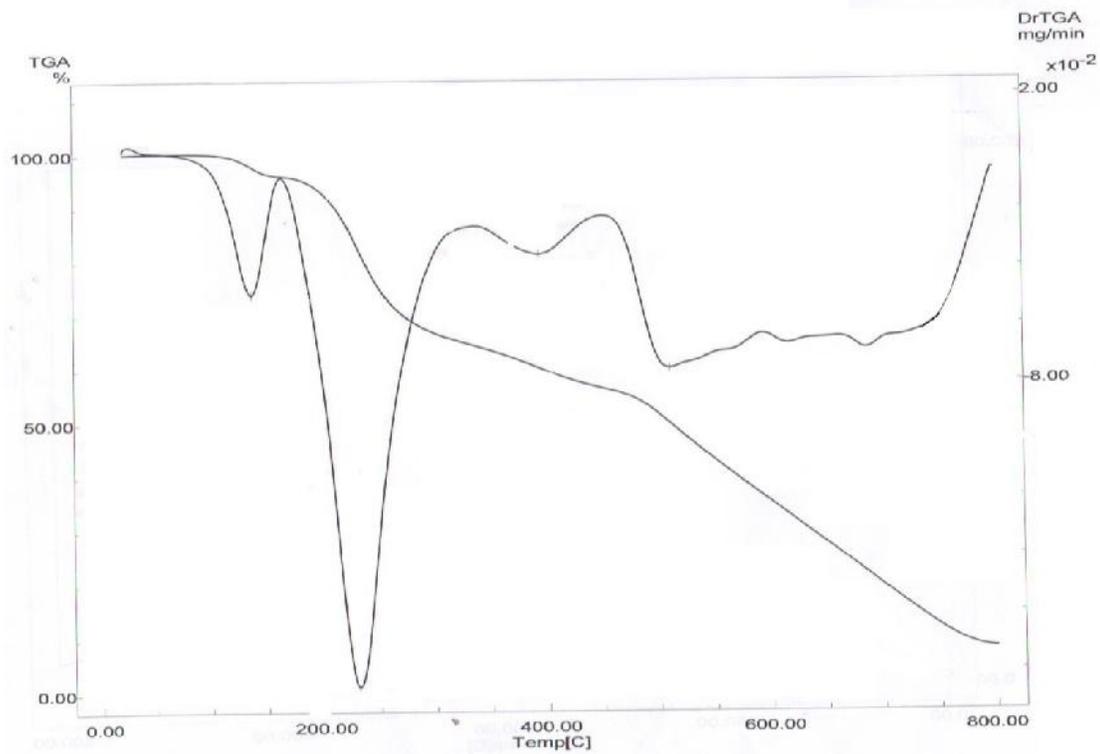
Fig. 9: TG and DTG of the [Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex.
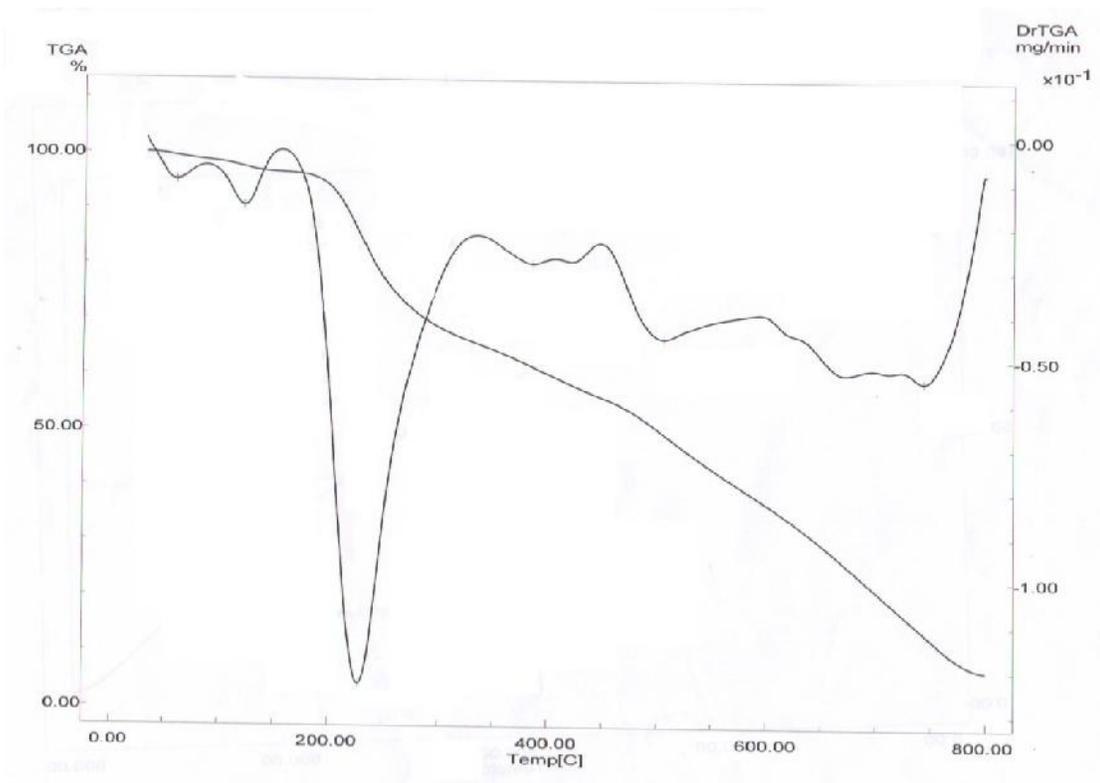
Fig. 10: TG and DTG of the [Ni(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex.

62

Table. 4: TG and DTG data of the PNZ and its complexes

Comp.	Temp. range °C	DTG °C	% Mass loss		Process	Product	Type % Residue
			Found	Calcd.			Found (Calcd.)
[Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O	59.44-163.84	135.93	4.277	4.1	Dehydration+Coor -dination sphere partial decomposition.	2H$_2$O	CoO
	164.73-302.59	230.72	29.49	29.06		H$_2$O+0.31L	7.909
	303.07-461.31	393.25	10.74	10.456	Coordination sphere partial decomposition. Ligand decomposition. Final decomposition.	0.12L	(8.5)
	462.35-799.68	509.4	47.55	47.9		0.55L	
[Ni(PNZ)$_2$(H$_2$O)$_2$].H$_2$O	32.97-154.59	59.86 121.62	3.4	4.1	Dehydration+Coor -dination sphere partial decomposition.	2H$_2$O	Ni
	155.12-425.21	228.15 385.9	38.527	38.66		H$_2$O+0.42L	6.89
	424.67-540.44	506.03	13.482	13.07	Coordination sphere partial decomposition. Ligand decomposition. Final decomposition.	0.15L	(6.689)
	541.38-799.4	743.6	37.57	37.48		0.43L	

Table. 5: Kinetic parameters for the first decomposition step of the PNZ-complexes

Comp.	Step	E	A	n	R	H	G	S
[[Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O	1	211.3417	2.75E+11	2	0.9983	207.1538	222.4114	-30.2898
	2	15.30354	19588.77	1	0.996	8.798671	142.4034	-170.763
[Ni(PNZ)$_2$(H$_2$O)$_2$].H$_2$O	1	243.9612	1.22E+17	3	0.9499	240.6803	209.1789	79.82724
	2	148.43	3.25E+08	3	0.9925	144.2634	187.4989	-86.2725
	3	51.3264	77.83389	1.5	0.9838	42.94922	263.439	-218.827

E, H, G, KJ/mol
S, J/mol.k
A , S^{-1}

The nickel complex decomposes in four steps. The first step occurs in the 32.9-154.6°C range with maximum at 59.9 and 121.6 °C corresponding to elimination of hydrated water and one molecule of coordinated water. The second step takes place in the 155-425 °C range associated with mass loss of 38.5 % (Calcd. 38.7 %) with maxima at 228 and 385.9 °C corresponding to loss of coordinated water and partial ligand decomposition. The following decomposition step occurs in the 424.7-540 °C range with maximum at 506 °C corresponding to ligand decomposition. The final decomposition takes place at 541-799 °C range with maxima at 743.6°C with the formation of Ni metal as final product.

From the TG curves, the order n, activation energy E, and pre-exponential factor A of the different thermal decomposition steps of the complexes have been elucidated by the method of Coats-Redfern[21]. Some examples of the linearization curves for the complexes, which were obtained, are presented in Figs. (11-15). The results of the kinetic studies of the TG/DTG curves are given in Table (4). The values of correlation coefficients of linearization curves of the complexes and their reaction orders are given in Table (5).The activation energy E and enthalpy of activation H of the Ni(II) and Co(II) complexes are expected to increase proportional to decrease in their radii[17]. The activation energy of the nickel complex is higher than that of cobalt one. The shorter the radius of metal ion, the easier the ligand approaches the central atom. As a result, metal-ligand interaction becomes stronger, the detachment of the link become s more difficult

and E values increase[18,19]. The negative values of the entropies in the decomposition reactions of the complexes Table (5) indicate that the reactions are slower than normal[20-22] and the activated complexes have more ordered structure than the reactants[23-24].
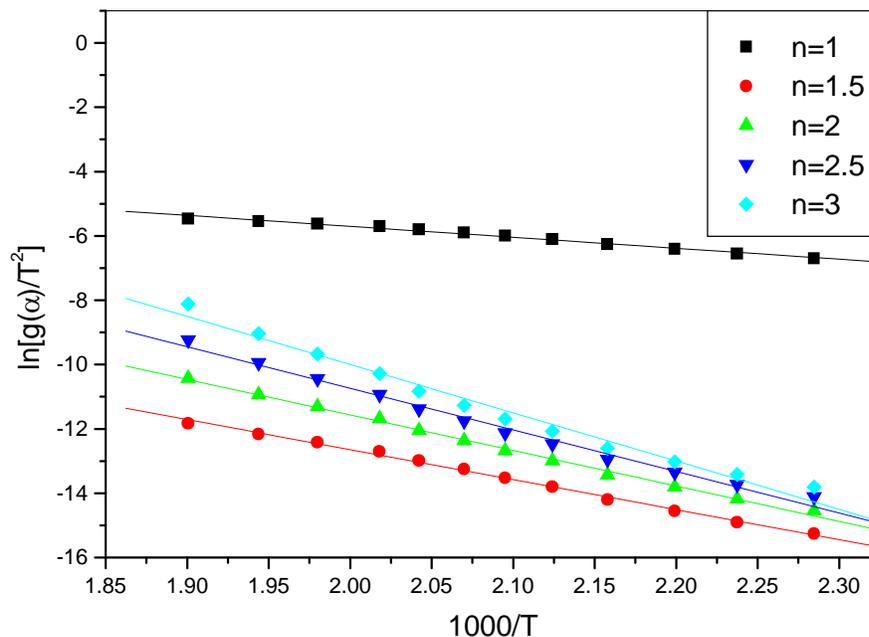
Fig. 11: Linearization curves of [Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex (first decomposition step).
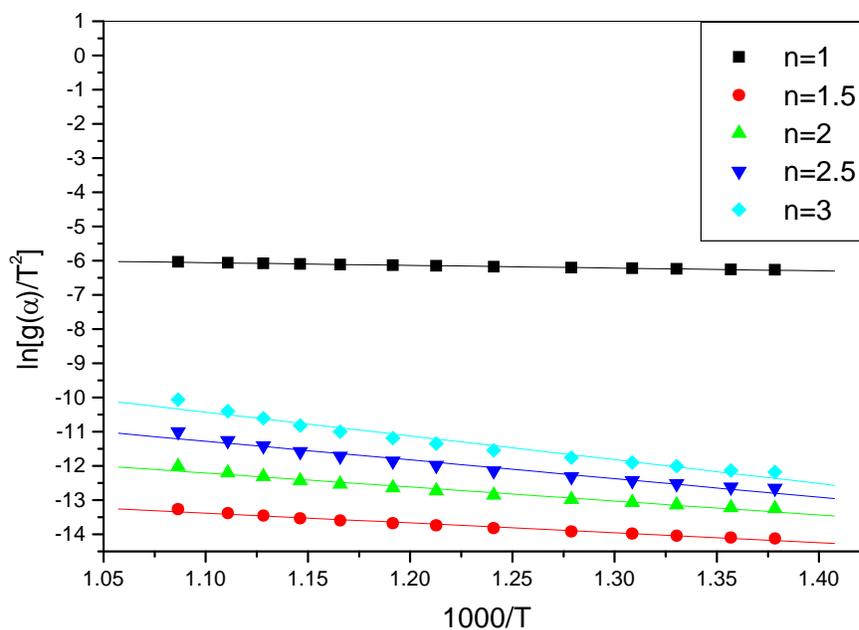
Fig. 12: Linearization curves of [Co(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex (second decomposition step).

64
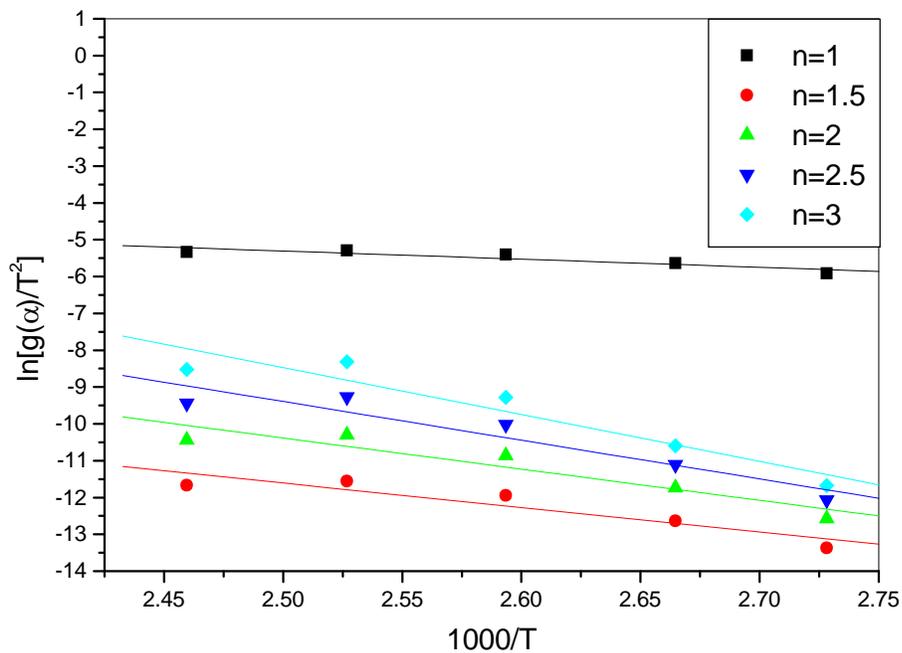
Fig. 13: Linearization curves of [Ni(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex (first decomposition step).
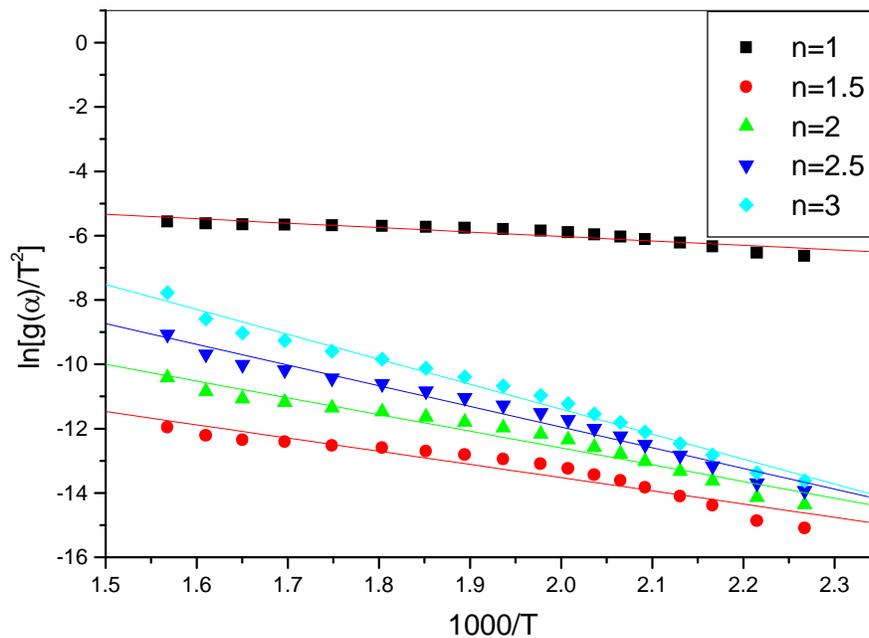
Fig. 14: Linearization curves of [Ni(PNZ)$_2$(H$_2$O)$_2$].H$_2$O complex (second decomposition step).
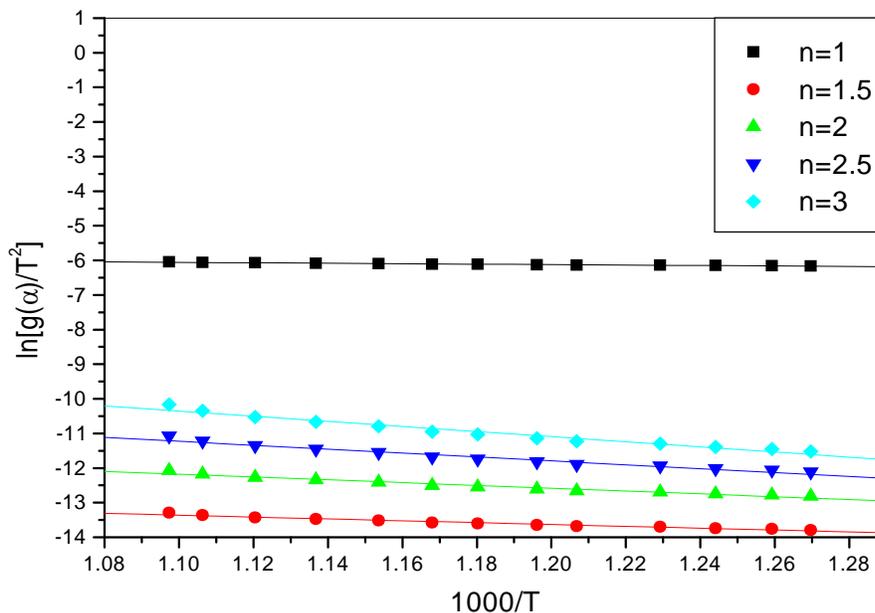
Fig. 15: Linearization curves of $[Ni(PNZ)_2(H_2O)_2].H_2O$ complex (third decomposition step).

Based on the above analytical data and physicochemical properties, the following structures are proposed in which the metal ion is coordinated through C-N, sulphonyl groups S=O, the coordinated water and the coordinated anion.

Conclusion

From elemental analysis it can be concluded that the formula of the Co^{2+} and Ni^{2+} complexes can be represented as $[ML_2(H_2O)_2]H_2O$, the molar conductance for the complexes were measured in DMF and showed that PNZ-complexes are non-electrolytes, from magnetic susceptibility and UV spectroscopy it's found that Co-PNZ and Ni-PNZ complexes are paramagnetic with octahedral geometry. IR spectra for ligand and its complexes showed that the pantoprazole act as bidentate ligand which form complexes with metals through C-N and S=O groups, also the spectra showed new peaks due to M-N and M-O which confirmed the involvement of N and O atoms in complexation with metal ions. The mass spectral data showed that Co-PNZ and Ni-PNZ, complexes formed with molar ratio M:L = 1:2. Thermal analysis showed the different decomposition stage of the metal complexes, which appear the presence of water of hydration in all complexes. The activation energies and kinetic parameters were calculated using Coats-Redfern equation. The activation energy E and enthalpy of activation H of the Co(II) and Ni(II)

complexes are expected to increase proportional to decrease in their radii.

References

1. P. O. Katz, L. B. Gerson, M. F. Vela, Am. J. Gastroenterology 2013, 108 (3), 308. doi:10.1038/ajg.2012.444.PMID 23419381

2. M. Suman, M. Jaishree, Der Pharmacia Sinica, 2011, 2 (4), 112.

3. M. Jaishree, M. Suman, S. Rashmi, UJPB 2013, 01 (03), 36.

4. J. Sheikha, H. Junejab, V. Ingleb, P. Alib, T. Ben Haddac, J. of Saudi Chem. Soc. 2013, 17 (3), 269.

5. D. H. Brown, A. J. Lewis, W. E. Smith, J. W. Teape, J. Med. Chem. 1980, 23, 729.

6. J. R. Anacona, G. Da Silva, J. Chil. Chem. Soc. 2005, 50 (2), 447.

7. M. M. Abd-Elzaher, W. H. Hegazy, A. E.-D M. Gaafar, App. Organomet. Chem. 2005, 19 (8), 911.

8. W. H. Hegazy, J. Molec. Str. 2014, 1075, 103.

9. W. H. Hegazy, Y. S. Al-Faiyz, Med. Chem. Res. 2014, 23 (1), 518.

10. B. N. Figgis, J. Lewis: in J. Lewis, R.G. Wilkins (Eds.), Magnetochemistry of complex compounds in Modern Coordination chemistry, Interscience, New York (1960).

11. A. W. Coats, J. P. Redfern, Nature 1964, 68, 201.

12. F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, Advanced Inorganic Chemistry, Sixth ed., Wiley, New York (1999).

13. M. K. Koley, S. C. Sivasubramanian, B. Varghese, P. T. Manoharan, A. P. Koley, Inorg. Chim. Acta 2008, 361, 1485.

14. G. G. Mohamed, N. E. A. El-Gamel, F. A. Nour El-Dien, Synth. React. Inorg. Met.-Org. Chem. 2001, 31, 347.

15. J. Kohout, M. Hvastijova, J. Kozisek, J. G. Diaz, M. Valko, L. Jager, I. Svoboda, Inorg. Chim. Acta 1999, 287, 186.

16. S. Y. Uçan, M. Uçan, B. Mercimek, Synth. React. Inorg. Met.-Org. Chem. 2005, 35, 417.

17. N. Sari, P. Gurkan, S. Arslan, Transit. Met. Chem. 2003, 28, 468.

18. B. S. Shyamala, P. V. A. Lakshmi, V. J. Raju, J. Sci. Res. 2010, 2, 525.

19. R. M. Silverstein, F. X. Webster, Spectrometric identification of organic compounds, Wiley India, Delhi, 2007, 102.

20. S. A. Sallam, Trans. Met. Chem. 2006, 31, 46.

21. H. S. Sangari, .S. Sodhi, Thermochim. Acta 1990, 171, 49.

22. E. Styczen, Z. Warnke, D. Wyrzykowski, Thermo Chim. Acta 2007, 454, 84.

23. V. Indria, G. Parameswaran, J. Therm. Anal. 1993, 39, 1417.

24. A. A. Frost, R. G. Pearson, Kinetics and Mechanism, Wiley, New York (1961).