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INTERACTION OF DL-PENICILLAMINE WITH DI-M-HYDROXOBIS(1,10-PHENANTHROLINE)DIPALLADIUM(II) ION IN AQUEOUS SOLUTION: KINETICS AND MECHANISM

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ABSTRACT

Kinetics of interaction between DL-penicillamine with the di-μ-hydroxobis(1,10-phenanthroline) dipalladium(II) ion complex has been studied spectrophotometrically as a function of $[Pd_2(1,10\text{-phen})_2(OH)_2]^{2+}$ concentration, where 1,10-phen = 1, 10-phenanthroline, [DL-penicillamine], pH and temperature. The reaction has been monitored at the λ_{max} 240 nm. of the substituted complex, where the spectral difference between the reactant and product is maximum. The reaction rate increases with an increase in DL-penicillamine concentration and it shows a linear dependence on the concentration of DL-penicillamine. The second order rate constants $10^2 k_2$ values are 69.99, 87.46, 133.93 and 159.19-dm^3 mol^{-1} s^{-1} at 20, 25, 30 and 35 ^{0}C respectively have been calculated from the slope of $k_{(obs)}$ versus [DL-penicillamine] plot. From the experimental findings an associative mechanism for the substitution reaction is proposed. The activation parameters ($\Delta H^{\neq}$ =45.39 $\pm$ 1.4 KJ/mol^{-1}, $\Delta S^{\neq}$ = -93.41 $\pm$ 2.3   JK^{-1}mol^{-1}) calculated from Eyring equation, support the proposition.

Key words: Kinetics and mechanism, hydroxo bridged palladium(II) complex, DL-penicillamine, 1,10-phenanthroline, associative mechanism.

INTRODUCTION

The physiological interaction of metal complexes such as cis-platin, carboplatin, nidaplatin etc. with the bioactive molecules, their function in vivo are very complex and the precise nature of such processes for most of the part are still unknown. The palladium(II) complexes are suitable compounds for the mechanistic studies on the action of platinum(II) antitumor drug, since they exhibit a 10^4-10^5 fold higher reactivity, whereas there structural and equilibrium behaviour are rather similar[1]. The kinetic and mechanistic studies on Pt(II) complexes has been extensively investigated during last two decades, owing to the antitumor activity of cisplatin and related compounds[2-6]. The discovery by Rosenberg et al.[7,8] that some platinum complexes exhibits carcinostatic properties, gave special impetus to this research. The antitumor drug cis-platin is well known but its toxicity has led to the search for second and third generation drugs with therapeutics activity comparable to that of cis-platin, but with reduces toxicity [9,10]. The actual mechanism of antitumor activity of platinum (II) complexes is still a matter of conjecture. The major cause of its toxicity is the formation of toxic hydrolysis products. In the cell, cis-platin is first hydrolyses to give $[Pt(NH_3)_2(OH_2)]^{2+}$ which is the effective drug. Complexes of other platinum group metals especially palladium(II), rhodium(III), iridium(III) and ruthenium(II) are also important for similar studies[11]. Again the interaction of Pt(II) complexes with sulfur containing bio-active molecules has been associated with negative phenomena, such as nephrotoxicity, neurotoxicity, gastrointestinal toxicity and ototoxicity [12,13]. It is well known that sulfur containing bioactive ligands may act as a drug reservoir for platination at DNA[14,15]. We have selected the $[Pd(1,10\text{-phen})(OH_2)_2]^{2+}$ complex, which exist as di-μ-hydroxobis(1,10-phenanthroline)dipalladium(II) ion, $[Pd_2(1,10\text{-phen})_2(OH)_2]^{2+}$ (**1**), at pH 6.5. It is analogues to the platinum(II) system for interaction study of sulfur containing bioactive molecules. $[Pd(1,10\text{-phen})(OH_2)_2]^{2+}$ complex at pH 6.5 exist as di-hydroxo bridged species[16-20] and bridged species

are less reactive than the monomeric. Similar types of kinetic interaction have been studied [21-23] on palladium(II) system by stopped follow spectrophotometer but it is studied by ordinary spectrophotometer. Again the importance of the work lies on the fact that the reaction has been studied in aqueous medium and we have selected aqua immine (1,10-phenanthroline) Pd(II) complex, which is better than chloro amine complexes (e.g. Cis-platin), since the hydrolysed side products of the chloro complex are toxic.

EXPERIMENTAL

The complex [Pd(1,10-phen)Cl$_2$] is prepared by following the synthetic method[18]. The diaqua complex [Pd(1,10-phen)(OH$_2$)$_2$]$^{2+}$ is prepared in solution by the method of Hay and Basak [24] by stirring the chloro complex with two mole equivalent of AgClO$_4$ and kept overnight (with careful protection from light). The precipitated AgCl was removed by filtration. The reactant complex ion di-μ-hydroxobis(1,10-phenanthroline)dipalladium(II) ion (complex **1**) was obtained in situ by adjusting the pH at 6.5 by adding NaOH/HClO$_4$. The reaction product of DL-penicillamine and complex(**1**) is prepared by mixing them in different ratios viz 1:1, 1:2, 1:3, 1:5 and 1:10 and thermosetting at 50 ^{0}C for few hours. The absorption spectra exhibited the same λ$_{max}$272nm. with almost same absorbance.

A pale yellow crystalline solid product is obtained by mixing two reactants, the complex and the ligand DL-penicillamine in 2:1 molar ratio at pH 6.5 by slow evaporation at room temperature. The i. r. spectrum of the product displays strong bands at 3628-3552 cm^{-1}, 3417 cm^{-1}, 3236 cm^{-1}, 1637-1617cm^{-1}1, 1430 cm^{-1}, 1089cm^{-1}, 627 cm^{-1} and 472 cm^{-1}. The asymmetric N-H out of plane bending frequency υ(asym) of amino acid occur at 1637 - 1617 cm^{-1}. At the same time, a broad spectrum appears at 1620-1590cm^{-1} due to overlapping of υ(asym) of N-H &COO$^-$, indicating that the COOH group is not a ligation site. No broad spectrum is appear at 3200-3150cm^{-1}, which indicate that –NH$_2$ group is not involve in the binding with Pd(II) in the product complex. The band at 1430cm^{-1} is assigned to υ(COO$^-$), the symmetric mode of vibration[25] A sharp peak at 472cm^{-1} appears due to Pd(II)-S-Pd(II) stretching frequency[26], whereas Pt(II)-S band appears at 524cm^{-1} [25]. The broad strong band appears at 1089cm^{-1} and 627 cm^{-1} is due to formation of perchlorate salt of the complex. A broad peak is observed at 3628-3552cm^{-1} for Pd(II) metal- metal bridged O-H str. frequency, which is not correspond to the OH group of COOH of DL-penicillamine because it remain as carboxilate(COO$^-$) at pH 6.5 and again a sharp band at 3236cm^{-1} due to N-H str. frequency. The i.r. spectrum suggests that the final product is DL-penicillamine's sulfur coordinated chelate and sulfur behaves as bridging ligand with both the Pd(II) bridged species. The composition of substituted complex in solution was determined by Job's method of continuous variation. The metal-ligand ratio is found to be 2:1(Figure -2). The *p*H of the solutions are adjusted with NaOH/HClO$_4$ and the measurements are carried out on a Systronics digital *p*H meter with an accuracy of $\pm$ 0.01. The other chemicals used are either AR grade or purified before use. The reactions are carried out at constant ionic strength (0.1M NaClO$_4$).

Kinetics

The kinetic studies are done on a Shimadzu UV 1601 spectrophotometer attached to a thermoelectric cell temperature controller (model TCC-240A, accuracy $\pm$ 0.1^o C). The development of a characteristic peak of the product complex(**2**) at 272 nm. is monitored with time at different temperatures and maximum difference is found with the complex(**1**) spectrum. The conventional mixing technique is followed and pseudo-first order conditions are employed throughout the kinetic study. The rate constants $k_{(obs)}$ are obtained from the plot of ln(A_∞ - A_o)/(A_∞ - A_t) versus time (*t*) due to linear fitting passing through origin, where A_o, A_t and A_∞ are absorbances at the outset, at time *t* and at infinite time (or after the completion of the reaction) respectively (Figure- 3). The reported rate data, represented as an average of duplicate runs, are reproducible to within $\pm$ 4%.
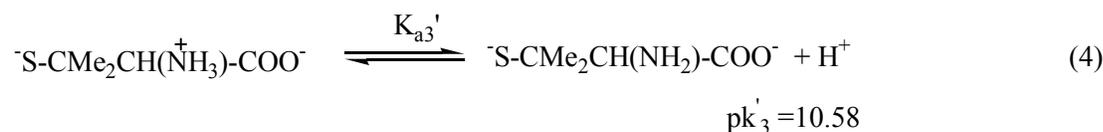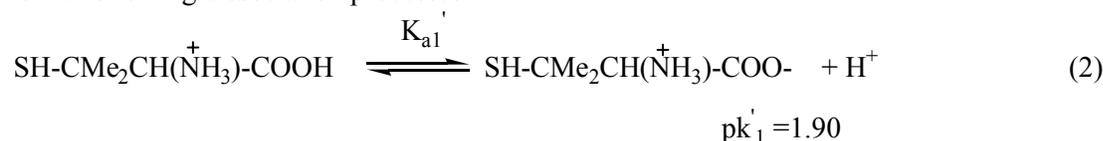
RESULTS AND DISCUSSION

Effect of [complex (1)] on the rate
At a fixed excess [DL-penicillamine] (4.135×10^{-3} mol dm^{-3}), pH 6.5, temperature 20° C and ionic strength (0.1 mol dm^{-3} NaClO$_4$) the reaction is found to be first order with respect to complex [(**1**)] i.e.,
$d[\mathbf{2}]/dt = k_{obs}$ [complex(**1**)]   (1)

Effect of pH
At fixed [complex(**1**)] (4.135×10^{-4} mol dm^{-3}), [Ligand] (4.135×10^{-3} mol dm^{-3}), temperature (20°C) and ionic strength (0.1 mol dm^{-3} NaClO$_4$) the $10^5 k_{obs}$ values are found to be 2.95 3.20, 4.10 and 4.30 s^{-1} at pH 5.5, 6.5, 7.0 and 7.4 respectively. The observation can be explained with the help of equillibria (2-5). The pKa'$_1$, pKa'$_2$ and pKa'$_3$ of DL-penicillamine [27] are 1.90, 7.88 and 10.58 respectively at 25 ^{O}C, which refer to the following dissociation processes.

$$SH\text{-}CMe_2CH(\overset{+}{N}H_3)\text{-}COOH \xrightleftharpoons{K_{a1}{}'} SH\text{-}CMe_2CH(\overset{+}{N}H_3)\text{-}COO\text{-} + H^+ \qquad (2)$$

$$pk'_1 = 1.90$$

$$SH\text{-}CMe_2CH(\overset{+}{N}H_3)\text{-}COO^- \xrightleftharpoons{K_{a2}{}'} {}^-S\text{-}CMe_2CH(\overset{+}{N}H_3)\text{-}COO^- + H^+ \qquad (3)$$

$$pk'_2 = 7.88$$

$${}^-S\text{-}CMe_2CH(\overset{+}{N}H_3)\text{-}COO^- \xrightleftharpoons{K_{a3}{}'} {}^-S\text{-}CMe_2CH(NH_2)\text{-}COO^- + H^+ \qquad (4)$$

$$pk'_3 = 10.58$$

Scheme.1

So that at pH 6.5 the major species involved in the kinetic process is the neutral form of DL-penicillamine. The pKa$_1$ of the complex is determined in laboratory by following the standard method [28] and found 6.05 at 25 ^{0}C. It is assume that at pH 6.5 the complex mainly exists as a dimeric [16-19, 23] species.

$$[Pd(1,10\text{-phen})(OH_2)_2]^{2+} \xrightarrow{K_{a1}} [Pd(1,10\text{-phen})(H_2O)(OH)] + H^+ \qquad (5)$$
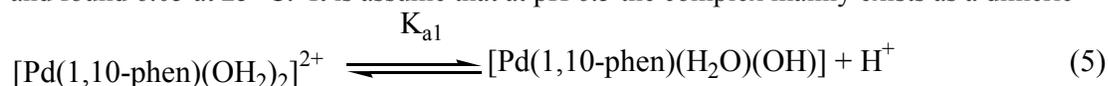
Pk$_{a1}$=6.05 at 25^{0}C
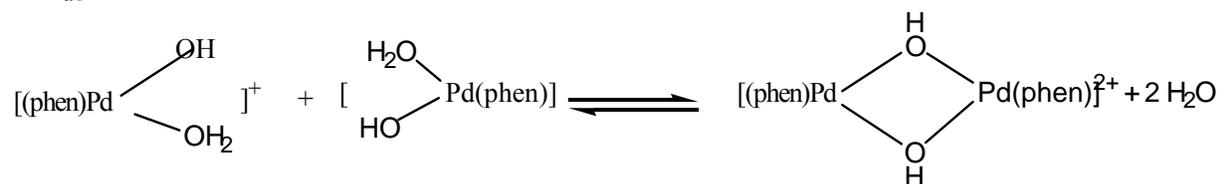
where phen = 1,10-phenanthroline

With an increase in pH the percentage of more reactive hydroxoaquapalladium(II) species in the solution is increased. The hydroxo species is more reactive due to the well known labialising effect of the –OH group via its π- bonding ability and strong electromeric effect. As a result the enhancement of rate with

the increase in pH can be accounted in the lower range. The effect of pH becomes insignificant due to the complex start to dimerise at pH 4.2 [18(b)], On the other hand the pKa_1', pKa_2' and pKa_3' of DL-penicillamine[27] are 1.90, 7.88 and 10.58 respectively at 25 ^{0}C. At pH 6.5 the amount of protonated form will be less and neutral molecule will be present in appreciable amount. With increase in pH from 6.0 to 7.4 the amount of deprotonated form increases and Zwitter-ionic form (Equilibrium 2) predominates which also partly account for the enhancement of the rate with increase in pH.

Effect of variation of [DL-penicillamine] on reaction rat*e*

At fixed [complex(**1**)] (4.135×10^{-4} mol dm^{-3}), at *p*H (6.5) and ionic strength (0.1 mol dm^{-3} NaClO$_4$) the effect of [DL-penicillamine] on the rate is studied in the $4.135 \times 10^{-3} - 12.4 \times 10^{-3}$ mol dm^{-3} range at 20, 25, 30 and 35 ^{0}C. The results are summarised in Table I. The $k_{(obs)}$ values increase linearly with increase in [DL-penicillamine]. The second order rate constants (k_2) are calculated from the slope of $k_{(obs)}$ versus [DL-penicillamine] plot (Figure- 4). The $10^2 k_2$ values are 69.99, 87.46, 133.93 and 159.19 dm^3 mol^{-1} s^{-1} at temperature 20, 25, 30, 35 ^{o}C respectively. It is assumed that at *p*H 6.5 the *cis*-hydroxoaqua(1,10-phen) palladium(II) forms a di-hydroxo bridged dimer[16-18,23] which takes part in the reaction and from the experimental observation of Job's method of continuous variation indicated as 2:1 metal-ligand ratio. The ligand DL-penicillamine then forms a bridge between the two palladium(II) centres. From the observations of Job's method of continuous variation, i.r. spectrum of the substituted product and thermodynamic parameters at *p*H 6.5 we may propose the mechanism of interaction in Scheme 2 as follow
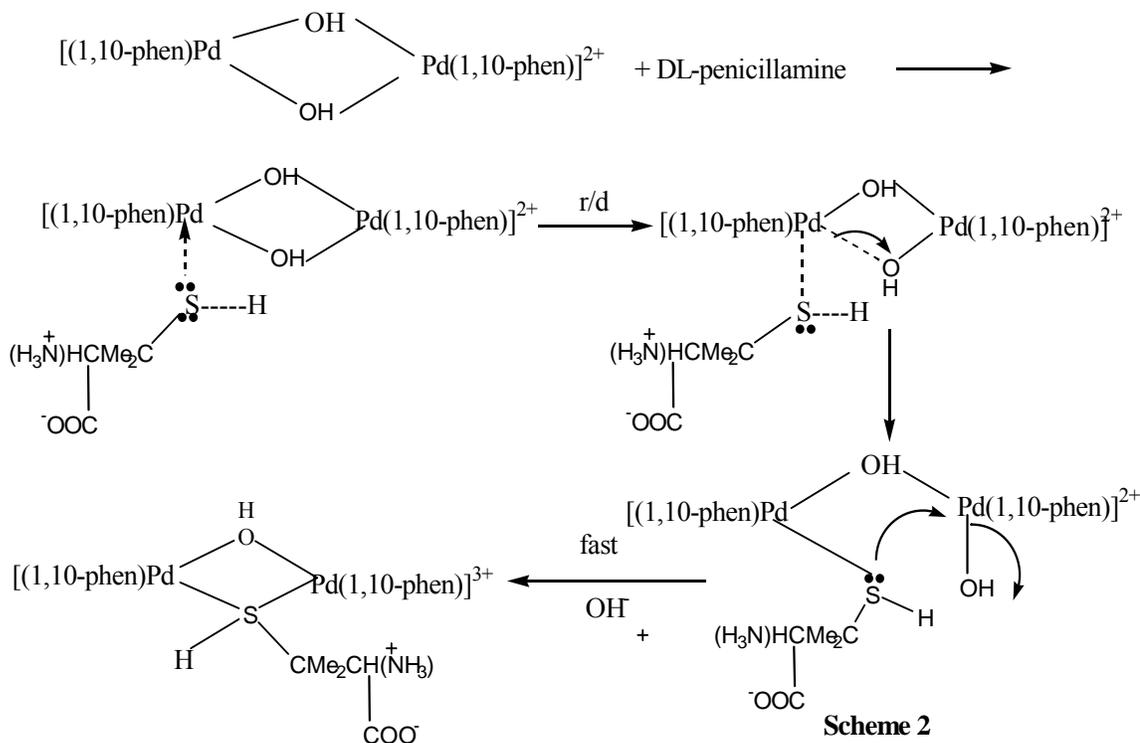
Scheme 2

The bonding mode of DL-penicillamine to the Pd (II) is not fully understood. But it is already noticed that the starting complex does not react well with azide (N$_3^-$), cytidine or thymidine. It reacts to a good extent with thioglycollic acid, L-cysteine, DL-methionine, L-glutathione and sulfur containing ligands. It is also supported from the soft nature of Pd(II). Thus for the ligand to behave as a bridging one with the hydroxo bridged complex the mono atom sulfur bridging [29,30] is the best fitting of substitution.

Effect of temperature on rate

The interaction reactions are studied at four different temperatures with different ligand concentrations. The second order anation rate constants ($10^2 k_2$) are 69.99, 87.46, 133.93 and 159.19 dm^3 mol^{-1}s^{-1} at 20, 25, 30 and 35 ^{o}C respectively. Activation parameters are computed from the Eyring plot and compared with literature data of the analogous systems (Table II). The low $\Delta H^{\neq}$ value, together with negative $\Delta S^{\neq}$ value, suggests ligand participation in the transition state and an associative mechanism is proposed for the interaction of DL-penicillamine with the complex (**1**). The participation of DL-penicillamine in the transition state results in a more compact state than that of the initial reactants and a negative $\Delta S^{\neq}$ is observed.

CONCLUSION

The Eyring plot of lnk_2h / K$_B$T versus 1/ T is linear, where K$_B$= Boltzmann constant (Figure- 5). The low $\Delta H^{\neq}$ value, together with negative $\Delta S^{\neq}$ value, suggests ligand participation in the transition state and an associative mechanism is proposed for the interaction of DL-penicillamine with the titled complex (**1**). The bonding mode of DL-penicillamine to the Pd(II) is not fully understood, But it is already noticed that the starting complex does not react well to azide (N_3^-), cytidine, or with thymidine. It reacts to a good extent with cysteine, DL-methionine, L-glutathione etc. sulfur containing bio-active molecules. It is also supported from the soft nature of Pd(II) toward the sulfur. Thus for the ligand to behave as a bridging one with the hydroxo bridged complex the mono atom Sulfur bridging is the best fitting among the other possibilities. After the completion of reaction, the pH of the solution increased which might be due to the bridged –OH group expulsion, consequently ring closure occur through sulfur bridging [29,30], again at this pH the thiol proton do not dissociate due to acidic medium. A sharp peak at 472 cm^{-1} appears due to Pd(II)-S-Pd(II) stretching frequency, alike the Pt(II)-S-Pt(II) stretching frequency at 524cm^{-1} [25]. The assumption of dimer formation of the starting complex may also be supported by the above fact, as the ligand remains neutral in this range. At very high pH (>6.0) the bridge opens and it forms di-hydroxo complex [20-23]. At higher range of pH >7.4 are not study due to formation of precipitate in the reaction cell. With an increase in pH the percentage of more reactive hydroxoaquapalladium(II) species in the solution is increased. The rate enhanced because hydroxo species is more reactive due to the well known labilsing effect of –OH group via its π- bonding ability and strong electromeric effect. The sulfur forms the associated complex in the r/d step, followed by opening of the bridged –OH group from the Pd(II) and simultaneously ring closure occur through sulfur bridging via OH$^-$ expulsion.

ACKNOWLEDGEMENTS

REFERENCES

1. T. Rau & R.Van Eldik , *in metal ion in Biological systems*, Vol. 32, edited by A. Sigel (Marcel Decker, New York) (1996).
2. *Cis-platin Chemistry and Biochemistry of a Leading Anti cancer Drug*, edited by B. Lippard, (Wiley-VCH, Zurich) (1999).
3. E. Wong & C.M. Giandomenico , *Chem. Rev*, **99**,2451(1999).
4. J. Reedijik , *Chem. Rev.*, *99*, 2499 (1999).
5. R.E. Jamieson &S.J. Lippard , *Chem. Rev.,* **99**, 2467(*1999).*
6. B.P. Esposito & Nijjar, *Coord . Chem. Rev.,* **232**, 137(2002).
7. B. Rosenberg, L.Van Camp and T. Kris , *Nature (London),* **205**, 698 (1965).
8. B. Rosenberg, L. Van Camp, J.E. Trosko and.V.H. Mansour, *Nature(London)* **222**, 365 (1969).
9. J.A. Broomhead, D.P. Fairlie, and M.W. Whitehouse, *Chem-Biol. Interact.*, **31**, 113 (1980).
10. A.S. Surrah, and M. Kettunen , *Curr. Med .Chem*, **13,** 1337-1357 (2006).
11. P. Kopt-Maier and H. Kopt , *Naturewissenschaften,* **73**, 239 (1986).

12. R.T. Door, *platinum and other metal coordination compound in cancer chemotherapy* edited by H.M. Pinedo & J.H. Schornagel, (plenum, NewYork), **131** (1996).
13. C. Rabik and M.E. Dolam, Cancer *Treat. Rev*, **33**, 9-23 (2007).
14. J. Reedijik, Chem.Rev., **99,** 2499 (1999).
15. S. Utku, F. Gumus, S. Gur and A. Ozkul, *T. J. Chem.,* **31**, 503-514 (2007).
16. G. Anderegg, H. Wanner , Inorg. Chim. Acta.*,* **113**, 101 (1986).
17. G. Alibrandi, M. Cusumano, A. Ginnetto & D. Minniti, *J. Chem. Soc,, Dalton Trans,* **375** (1989).
18. (a) S. Wimmer, P. Caston, F.L. Wimmer & N.P. Johnson, *J. Chem. Soc., Dalton Trans.*, **403** (1989).(b) EL. Ahmed, A. Sherif, M. Shoukry and R. Van Eldik, J. Chem. Soc, Dalton Trans*,* **1425 (**2003).
19. A. Adrian Rafael, A. Broker Grand, R.T. Tiekink Edward, A.Walmsley Judith, *Inorg. Chim. Acta*, **361**, 1261 (2008).
20. M. Shoukry and R. Van Eldik, *J. Chem. Soc., Dalton Trans,* **2673** *(1996)*
21. T.M. Buslacva & A.S. Simanova , *Russ. J .Coord. Chem. Rev.,* **25,** 151 (1999).
22. P. Banerjee, *Coord. Chem. Rev.,* **192**, 19 (1999).
23. M. Ray, S. Bhattacharyya & P. Banerjee, *J. Indian Chem. Soc.*, **76**, 151 (1999).
24. R.W. Hay &A.K. Basak, *J. Chem. Soc., Dalton Trans*, **1819** (1982).
25. P.S. Sengupta, R. Sinha, G.S. De, *Trans. Metal. Chem.,* **26,** 638 (2001).
26. S. Marchal , et al., *Polyhedron,* , **18**, 3675 (1999)
27. ' A.E. Martell and R.M. Smith, *Critical Stability Constants, 1, (Plenum press, NewYork),* **Vol.6,** 2nd suppl., p-21 (1989).
28. H. Hohmann & R Van Eldik, *Inorganica Chimica Acta*, **174,** 87-92 (1990).
29. L. Zhu & N.M. Kostic, *Inorg. Chem*, **31**, 3994 (1992).
30. L. Zhu & N.M. Kostic , *Inorg. Chim. Acta*, , **21**, 217 (1994).
31. G. Mahal & R. Van Eldik, *Inorg. Chem.,* **24**, 4165 (1985).
32. Y. Ducomnun , B. Hellqust ,L.I. Elding& A.E. Merbach , *Inorg. Chem.*, **26**, 1759 (1987).
33. L. Helm, L.I. Elding & A.E. Merbach, *Hel. Chim. Acta*, , **67**, 1453 (1984).

Table -1. $10^5 k_{(obs)}$ (s^{-1})values at different [DL-penicillamine] and at different temperatures. [1] = 4.135x10^{-4} mol dm^{-3}, pH= 6.5, ionic strength= 0.1 moldm^{-3} NaClO$_4$.

103[ligand] (moldm^{-3})	Temp(^{0}C)			
	20	25	30	35
4.135	3.2	4.1	5.9	7.21
6.20	4.11	5.32	8.12	9.86
8.27	5.91	7.63	10.98	13.11
10.34	6.94	8.46	13.64	16.55
12.40	8.96	11.34	16.92	20.01

Table -2. Activation parameters for analogous systems.

Systems	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	Ref.
[Pd$_2$(1,10-phen)$_2$(HO)$_2$]$^{+2}$/ DL-penicillamine	45.39 ±1.4	-93.41 ±2.3	This Work

$[Pd(Me_4dien)(OH_2)]^{2+}/$			
Cl^-	40.0	-49.0	[31]
Br^-	39.0	-47.0	
I^-	34.0	55.0	
N_3^-	32.0	-53.0	
$[Pd(Et_4dien)(OH_2)]^{2+}/$			
Cl^-	56.0	-45	[31]
HCO_3^-	68.0	-32	
$[Pd(OH_2)_4]^{2+}/$			
Me_2SO	58	-44	[32]
water exchange	49	-26	[33]

Fig.-1: Spectral difference between reactant and product (**1**) $[Pd_2 (1,10\text{-phen})_2(OH)_2]^{2+}$=4.135 x 10^{-4} mol dm^{-3}, (2) $[Pd_2(1,10\text{- phen})_2(OH)_2]^{2+}$ = 4.135 x 10^{-4} mol dm^{-3}, [DL-penicillamine] = 4.135 x 10^{-3} mol dm^{-3}, pH = 6.5, cell used 1cm.quartz
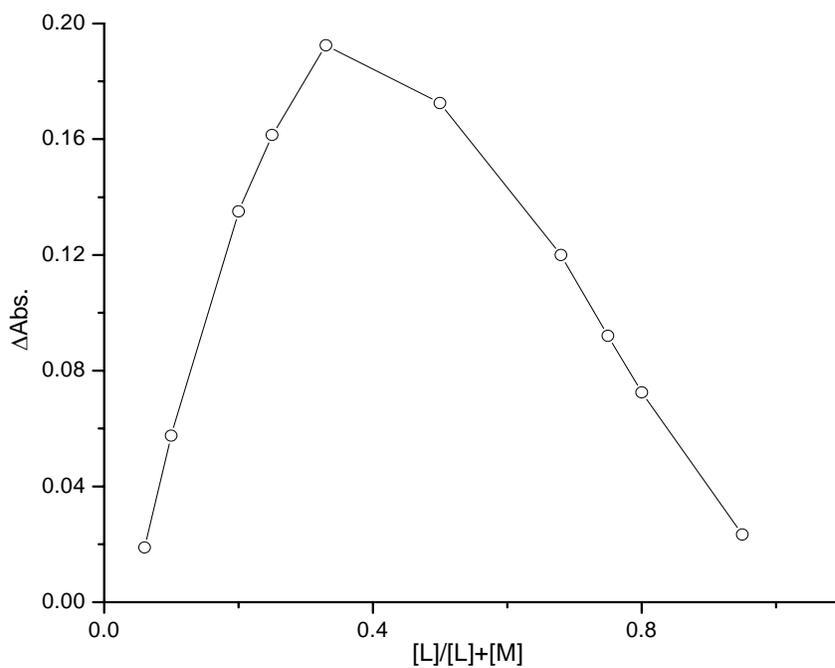
Fig.-2: Job's plot

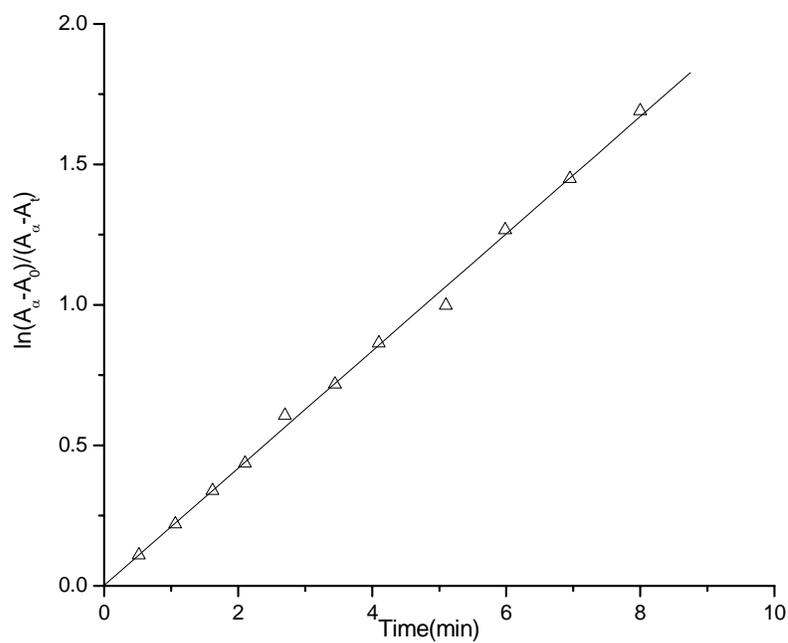

Fig.-3: Plot of $\ln(A_\infty - A_o)/(A_\infty - A_t)$ versus time, $[Pd_2(1,10\text{-phen})_2(OH)_2]^{2+}$ = 4.135x 10^{-4} mol dm^{-3}, [DL-penicillamine]= 4.135x10^{-3}moldm^{-3}, pH=6.5, temp.=25 ^{0}C
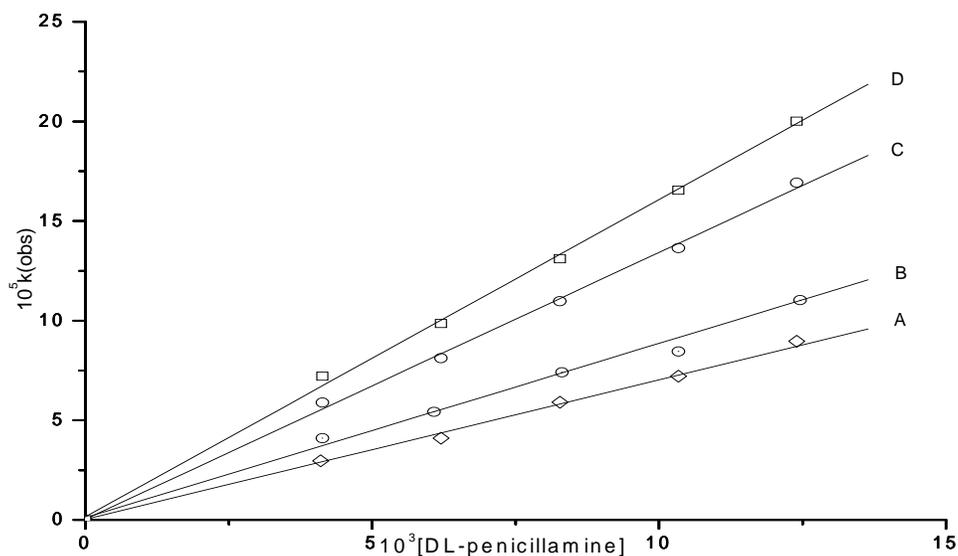
Fig.- 4: Plot of k(obs)) versus [DL-penicillamine] at different temperatures,
A=20 ^{0}C, B=25 ^{0}C, C=30 ^{0}C and D= 35 ^{0}C
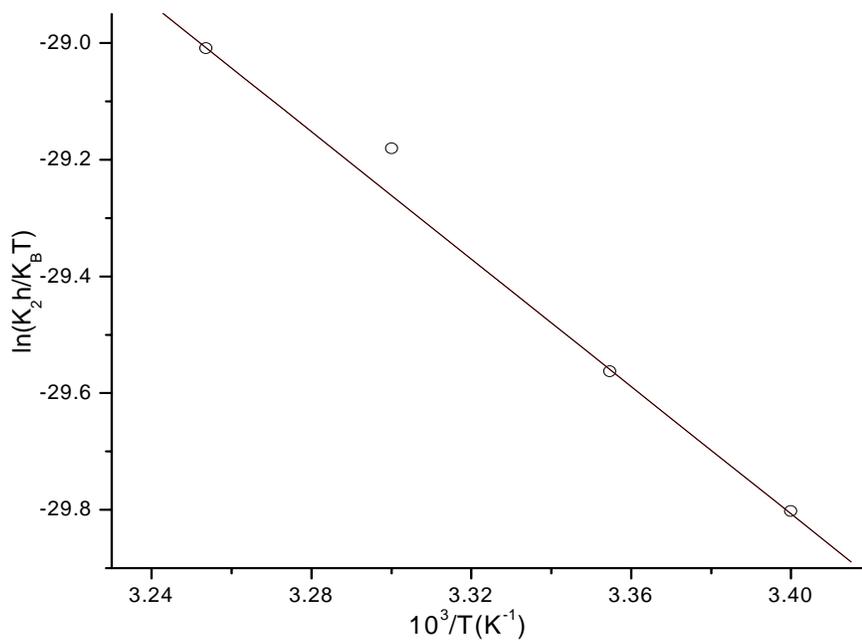
Fig.-5: Eyring plot of $\ln(K_2h/K_BT)$ versus 1/T