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Kinetics and mechanism of the interaction of L - cysteine with diaquaethylenediamineplatinum(II) perchlorate in aqueous solution

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The kinetics of the interaction of L-cysteine with $[Pt(en)(H_2O)_2]^{2+}$ has been studied spectrophotometrically as a function of $[Pt(en)(H_2O)_2^{2+}]$, [L-cysteine], *p*H and temperature. The reaction has been monitored at 230 nm, where the spectral difference is maximum although the λ_{max} of the L-cysteine substituted product is at 213nm. The activation parameters have been evaluated from temperature coefficient of the reaction rates. The low value of $\Delta H^{\neq}$ (61.1 kJ mol^{-1}) and large negative value of $\Delta S^{\neq}$ (- 83 J K^{-1} mol^{-1}) indicate an associative mode of activation for the substitution process. The additional advantage of using aquaamine complexes as an amino acid binder is also discussed.

Synthesis of platinum metal complexes is of continued interest in view of their application as a tool for biotechnology or chemotherapeutic use in resemblance to *cis*-platin[1]. Due to the high toxicity of the *cis*-ddp (diamminedichloroplatinum(II)) the present research in the field spread among other platinum(II) complexes as well as other 4*d* and 5*d* metal ions. In this respect $[Pt(en)Cl_2]$ is well known for its less toxic effect than *cis*-platin[2]. It is reported that $[Pt(en)Cl_2]$ is hydrolysed in the cell to give corresponding aqua species that is activated with respect to the nucleophilic substitution, since water molecule is a good leaving group. As one would expect, the aqua species reacts much faster[3] in cell than the dichloro species and further the aqua variety is less toxic than the chloro species. It is generally accepted that DNA is the most important intracellular target to the inorganic metal complexes. However, DNA is not the only target. Binding to proteins and RNA also occurs as has been shown by many investigators[4-6]. In order to examine the reactivity of aquaamine complexes of Pd(II) and Pt(II) towards amino acids, nucleosides and nucleotides we have undertaken the present studies. In this paper we report the detailed kinetic investigation on the substitution of aqua molecules by L-cysteine in aqueous medium. The interest in the present work is related to the probability of using $[Pt(en)(H_2O)_2]^{2+}$ as amino acid binder. The work related to the activity of this complex as well as other pt(II) and Pd(II) aquaamine complexes using as binder of amino acids, DNA bases and DNA itself is under investigation .

Materials and Methods

The compound $[Pt(en)(H_2O)_2](ClO_4)_2$ (complex **1**) was prepared according to the literature method[7] and characterised spectroscopically[8] (λ_{max}=256nm) and by elemental analysis . The *p*H of the solution was so maintained that >90 % of the perchlorate salt is obtained as diaqua species. The product (substituted complex ; complex **2**) of the interaction reaction between complex **1** and L-cysteine was prepared by mixing them in different molar ratios viz. 1:5, 1:10, 1:20 and 1:30 and thermally equilibrating them at 60°C for 48 hours. In all the cases almost same absorbance at λ_{max} = 213 nm was obtained. The spectral difference is shown in Fig. 1. It was not possible to isolate the solid product but the composition in solution was determined by Job s method of continuous variation. The metal : ligand ratio was found to be 1:1. The *p*H of the solution was adjusted by adding NaOH / $HClO_4$ and the measurements were carried out with the help of a Systronics digital *p*H meter with an accuracy of $\pm$ 0.01 unit. Doubly distilled water was used to prepare all the solutions. All other chemicals used were of either AR grade or purified

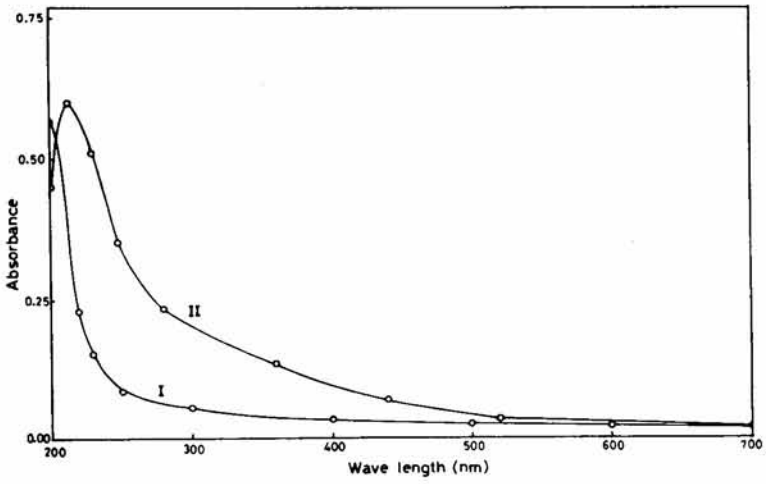


Fig 1 - Absorbance curves: I, $[Pt(en)(H_2O)_2^{2+}] = 0.75 \times 10^{-4}$ mol dm^{-3}; II, $[Pt(en)(H_2O)_2^{2+}] = 0.75 \times 10^{-4}$ mol dm^{-3} ([L- cysteine] = 1.5×10^{-3} mol dm^{-3}, *p*H = 4.0, cell used = 1 cm quartz)

before use The reactions were carried out at constant ionic strength .

Kinetics

Kinetic measurements were carried out on a Shimadzu Spectrophotometer (UV 2101 PC, equipped with a Shimadzu TB-85 thermobath (accuracy = ± 0.1 ° C). Absorption due to the ligand was subtracted by adding an equal amount of L-cysteine solution to both the sample and reference cells. The progress of the reaction was monitored by following the increase in absorbance at 230 nm, where the spectral difference was maximum. Conventional mixing technique was followed and pseudo-first order conditions were maintained throughout the course of the reaction. The rate constants were calculated from the plots of $\ln (A_\infty - A_0)/(A_\infty - A_t)$ against time, where A_0, A_t and A_∞ are the absorbances of the reaction mixture at the outset, at time t and at infinite time (or after the completion of the reaction) respectively. Rate data represented as an average of duplicate runs are reproducible within ± 4 %.

Results and Discussion

Effect of $[Pt(en)(H_2O)_2^{2+}]$ on the rate

At a fixed excess [L-cysteine] (3.0×10^{-3} mol dm^{-3}), *p*H = 4.0, T = 60° C and at constant ionic strength = 0.1 mol dm^{-3} $NaClO_4$ the reaction rate was found to first order with [complex **1**], i.e. ,

$$d[\text{complex } \mathbf{2}] / dt = k_{obs}[\text{complex } \mathbf{1}] \quad \ldots (1)$$

Effect of pH variation on rate

It was observed that in the 3.5 to 7.0 *p*H range the reaction rate increased initially and then slowed down at higher *p*H (after *p*H 5.5).Under the conditions $[Pt(en)(H_2O)_2^{2+}] = 1.5 \times 10^{-4}$ mol dm^{-3}, [L-cysteine] = 3×10^{-3} mol dm^{-3}, temp = 50°C and μ = 0.1 mol dm^{-3} $NaClO_4$, at *p*H. 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5 and 7.0, the $10^4 k_{obs}$ values are 0.977, 1.28, 1.45, 1.96, 2.19, 1.66, 1.02 0.952 s^{-1} respectively. The *p*H dependence of the reaction is associated with the substitution lability of various Pt(II)-en species, viz. $[Pt(en)(H_2O)_2]^{2+}$, $[Pt(en)(H_2O)(OH)]^+$ and $[Pt(en)(OH)_2]$. The characteristic *p*H dependence for this substitution is explained by equilibria 2 and 3:

$$[Pt(en)(H_2O)_2]^{2+} \overset{K_1}{\rightleftharpoons} [Pt(en)(H_2O)(OH)]^+ + H^+ \quad \ldots (2)$$
$$pK_1 = 5.8$$

$$[Pt(en)(H_2O)(OH)]^+ \overset{K_2}{\rightleftharpoons} [Pt(en)(OH)_2] + H^+ \quad \ldots (3)$$
$$pK_2 = 7.6$$

The acid dissociation equilibria of L-cysteine is :

$$HS\text{-}CH_2\text{-}CH(NH_3^+)\text{-}COOH \overset{K_1'}{\rightleftharpoons} HS\text{-}CH_2\text{-}CH(NH_3^+)\text{-}COO^- + H$$
$$pK_1' = 1.71^+ \quad \ldots (4)$$

$$HS\text{-}CH_2\text{-}CH(NH_3^+)\text{-}COO^- \overset{K_2'}{\rightleftharpoons} {}^-S\text{-}CH_2\text{-}CH(NH_3^+)\text{-}COO^- + H$$
$$pK_2' = 8.35^+ \quad \ldots (5)$$

$$^-S\text{-}CH_2\text{-}CH(NH_3^+)\text{-}COO^- \overset{K_3'}{\rightleftharpoons} {}^-S\text{-}CH_2\text{-}CH(NH_2)\text{-}COO^- + H^+$$
$$pK_3' = 10.78 \quad (6)$$

Within the *p*H range studied, The reaction pathways are :

$$[Pt(en)(H_2O)_2]^{2+} + cysH \xrightarrow{k_2\,(slow)} [Pt(en)(H_2O)cysH]^{2+} + H_2O \quad (7)$$

$$[Pt(en)(H_2O)(cysH)]^{2+} \xrightarrow{\text{fast, chelation}} [Pt(en)(cys)]^{+} + H_3O^{+} \quad \ldots\ldots (8)$$

$$[Pt(en)(H_2O)(OH)]^{+} + cysH \xrightarrow{k_3\,(slow)} [Pt(en)(cysH)(OH)]^{+} + H_2O \quad (9)$$

$$[Pt(en)(cysH)(OH)]^{+} \xrightarrow{\text{fast, chelation}} [Pt(en)(cys)]^{+} + H_2O \quad (10)$$

$$[Pt(en)(OH)_2] + cysH \xrightarrow{k_4\,(slow)} [Pt(en)(cysH)(OH)]^{+} + OH^{-} \quad (11)$$

$$[Pt(en)(cysH)(OH)]^{+} \xrightarrow{\text{fast, chelation}} [Pt(en)(cys)]^{+} + H_2O \quad (12)$$

In this *p*H range ligand mainly exists in the zwitterionic form and so it has no significant contribution to the variation of rate with *p*H. Job's method of continuous variation indicates the composition 1:1 for metal - ligand ratio of the product in solution. i.e., cysteine behaves as bidentate ligand . At low *p*H $[Pt(en)(H_2O)_2]^{2+}$ species is predominant and with increasing pH the percentage of the more labile $[Pt(en)(H_2O)(OH)]^{+}$ species (due to the labilising effect of -OH group) in solution increases and the significant contribution to the rate is solely due to reaction (9). But at higher *p*H the percentage of the dihydroxo species increases which is less labile than aquahydroxo species and a lower rate is observed Moreover, with increasing *p*H the net charge on the complex decreases which is not conducive for bimolecular attack by the ligand and as a consequence lowering in rate is observed.

Effect of [L-cysteine] on rate

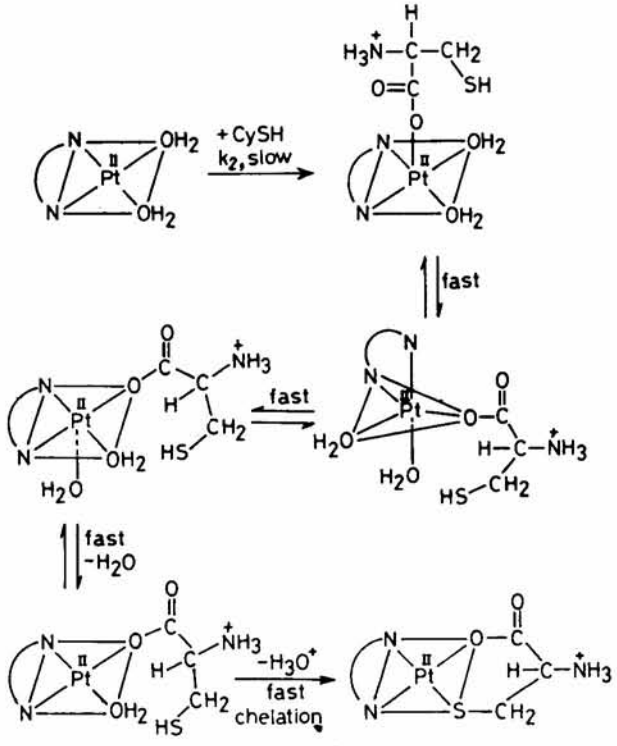
The concentration of L -cysteine was varied in the 1.5 x 10-^{3} to 6.0 x 10^{-3} range at fixed [complex 1] = 1.5 × 10^{-4} mol dm^{-3}, *p*H = 4.0 and ionic strength = 0.1 mol dm^{-3} $NaClO_4$ at temperatures 45, 50, 55 and 60^0 C . At each temperature the reaction rate was found to increase linearly with [ligand] and no limiting rate was observed in the studied range . The k_{obs} values with different [ligand] are collected in Table 1 . The second order rate constants (k_2) are calculated from the slope of k_{obs} versus [L] plot .

Temperature and reaction rate

Table 1 - $10^4 k_{obs}$ values with different [L-cysteine] at different temperatures

$[Pt(en)(H_2O)_2^{2+}] = 1.5 \times 10^{-4}$ mol dm^{-3}, *p*H = 4.0, μ = 0.1 mol dm^{-3} $NaClO_4$.

10^3[L-cysteine] (mol dm^{-3})	Temp. (° C)			
	45	50	55	60
1.5	0.416	0.695	1.0	1.44
2.25	0.66	0.96	1.39	1.94
3.0	0.86	1.28	1.63	2.60
3.75	1.10	1.53	2.36	3.47
4.5	1.30	2.00	2.92	3.92
6.0	1.76	2.56	3.07	5.36



Scheme 1

The reaction was studied at four different temperatures. The k_2 values obtained from the k_{obs} versus [L] plot are used to calculate Eyring $\Delta H^{\neq}$ and $\Delta S^{\neq}$. The $10^2 k_2$ values are 2.9, 4.2, 6.1 and 8.8 dm^3 mol^{-1} s^{-1} at s 45, 50, 55 and 60^0 C respectively. The $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values are 61.1 kJ mol^{-1} and -83.0 J K^{-1} mol^{-1}. The low $\Delta H^{\neq}$ value and large negative value of $\Delta S^{\neq}$ suggest the participation of incoming ligand in the activation step. Here the enthalpy change in bond breaking is partly compensated by new metal-ligand bond formation in the transition state. The large -ve value of $\Delta S^{\neq}$ indicates a more compact activated state in a bimolecular activation process.

The above observations indicate an associative mode of activation for the interaction reaction

between $[pt(en)(H_2O)_2]^{2+}$ and L-cysteine. The plausible mechanism is presented in Scheme 1.

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