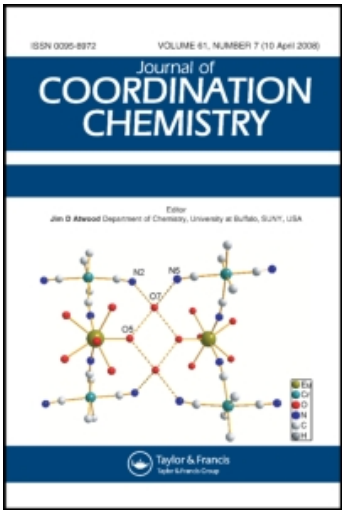

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Kinetics and mechanism of the interaction of DL-penicillamine with *cis*-diaqua(*cis*-1,2-diaminocyclohexane)platinum(II) perchlorate in aqueous medium

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First published on: 13 July 2010

To cite this Article Karmakar, Parnajyoti , Bera, Biplab K. , Barik, Kanai L. , Mukhopadhyay, Sudip K. and Ghosh, Alak K.(2010) 'Kinetics and mechanism of the interaction of DL-penicillamine with *cis*-diaqua(*cis*-1,2-diaminocyclohexane)platinum(II) perchlorate in aqueous medium', Journal of Coordination Chemistry, 63: 12, 2158 — 2171, First published on: 13 July 2010 (iFirst)
To link to this Article: DOI: 10.1080/00958972.2010.498910
URL: http://dx.doi.org/10.1080/00958972.2010.498910

Journal of Coordination Chemistry
Vol. 63, No. 12, 20 June 2010, 2158–2171

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Kinetics and mechanism of the interaction of DL-penicillamine with *cis*-diaqua(*cis*-1,2-diaminocyclohexane)platinum(II) perchlorate in aqueous medium

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(*Received 24 November 2009; in final form 17 March 2010*)

The kinetics of the interaction of DL-penicillamine with *cis*-[Pt(*cis*-dach)$(OH_2)_2]^{2+}$ has been studied spectrophotometrically as a function of [*cis*-[Pt(*cis*-dach)$(OH_2)_2]^{2+}$], [DL-penicillamine], and temperature at a particular pH (4.0), where the complex exists predominantly as the diaqua species and DL-penicillamine as a zwitterion. The substitution reaction proceeds via rapid outer sphere association, followed by two slow consecutive steps. The first is the conversion of title complex into an inner sphere complex and the second is the slower chelation step whereby another aqua ligand is replaced. The association equilibrium constant (K_E) for the outer sphere complex formation has been evaluated together with rate constant for two subsequent steps. The activation parameters for both steps have been evaluated using the Eyring equation: ($\Delta H_1^{\neq} = 36 \pm 4\,\mathrm{kJ\,mol^{-1}}$, $\Delta S_1^{\neq} = -175 \pm 12\,\mathrm{JK^{-1}\,mol^{-1}}$ and $\Delta H_2^{\neq} = 44 \pm 1\,\mathrm{kJ\,mol^{-1}}$, $\Delta S_2^{\neq} = -189 \pm 3\,\mathrm{JK^{-1}\,mol^{-1}}$). The low enthalpy of activation and large negative value of entropy of activation are consistent with an associative mode of activation for both consecutive steps. The kinetic study has been substantiated by conductivity measurement, product isolation, IR and ESI-MS spectroscopic analysis.

Keywords: Kinetics; Mechanism; Pt(II)

1. Introduction

Substitution on square planar platinum(II) complexes is of considerable interest in chemical and biomedical research. In particular, *cis* platin [1–7] and its structural analogs [8] are widely used in the treatment of specific cancers. It is now accepted that these platinum(II) complexes exercise their anti-tumor activity by inhibiting replication of cellular DNA [9, 10]. Nephrotoxicity and neurotoxicity coupled with drug resistance, which develops within patients after initial treatment have limited wider clinical application [11] of chloro derivatives of (*N*,*N*)-chelated Pt(II) complexes. Therefore, the

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Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online © 2010 Taylor & Francis
DOI: 10.1080/00958972.2010.498910

search for other drugs has continued and the aqua variety was found to be superior to some extent in this respect as the coordinated water molecule is a better leaving group than the chloro ligand in Pt(II) complexes [6]. In this context, the diaqua derivative of *cis*-[Pt(*cis*-dach)Cl_2], an effective anti-tumor compound with little nephrotoxicity, has cross resistance with DDP [12]. The hydroxobridged dimer and trimer of dach-Pt(II) complexes are active anticancer agents and less toxic than the monomer in contrast to NH_3 oligomers.

Pt(II) complexes can also interact with many other biomolecules, especially those containing sulfur for which Pt(II) has a very high affinity. Interaction of platinum(II) complexes with sulfur-containing biomolecules is responsible for a variety of biological effects, such as inactivation of Pt(II) complexes, development of cellular resistance to platinum, and toxic side effects, such as nephrotoxicity [13, 14]. The reactivity of aqua amine complexes of Pt(II) toward "S"-containing amino acids and "S"-containing substituted amino acids is thus of interest. In this article we have studied the kinetics of aqua-ligand substitutions of *cis*-$[Pt(cis\text{-dach})(OH_2)_2]^{2+}$ by DL-penicillamine (β,β'-dimethyl cysteine), a degradation product of β-lactum antibiotic, penicillin, and also a "S"-containing bioactive ligand.

2. Experimental

The reactant complex *cis*-$[Pt(cis\text{-dach})(OH_2)_2](ClO_4)_2$ (**1**) (dach = diaminocyclohexane) was prepared from *cis*-dichloro-(dach)platinum(II) by hydrolysis in the presence of two molar equivalents of silver perchlorate. The chloro compound spreads over the aqueous solution of silver perchlorate and the mixture was kept for 24 h and then filtered to remove AgCl. The diaqua complex was then characterized spectrophotometrically. The chloro complex *cis*-dichloro-(*cis*-dach)platinum(II) was prepared according to the literature method [15]. The pH of the solution was maintained at 4.0, so that perchlorate salt exists as diaqua species. The product of the reaction between **1** and DL-penicillamine was prepared by mixing the reagents at pH 4.0 in different molar ratios: namely 1 : 1, 1 : 2, 1 : 3, 1 : 4 and 1 : 5 and thermostating the mixture at 60°C for 48 h. The absorption spectra of the resulting solution were recorded and all were found to exhibit almost identical absorbance at 240 nm. The spectral differences between the product complex and the substrate complex are shown in figure 1.

The composition of the product in the reaction mixture was determined by Job's method of continuous variation (figure 2). The metal : ligand ratio was found to be 1 : 1.

Cis-$[Pt(cis\text{-dach})(OH_2)]^{2+}$ and DL-penicillamine were mixed in 1 : 1 molar ratio at pH 4.0 and a yellow product was obtained. The IR spectra of the yellow product in the KBr disc show strong bands at 3428 and 510 cm^{-1} together with prominent bands at 1711, 1627, and 1406 cm^{-1}. The asymmetric COO^- stretching frequency (ν_{asym}) of the amino acids occurs at 1580–1660 cm^{-1}, when the group is coordinated to metals, whereas a non-coordinated COO^- group has the $\nu_{asym}(COO^-)$ stretching at lower frequency [16]. The band at 1711 cm^{-1} is therefore due to the ν_{asym}(COOH) of the free carboxyl group. The band at 1627 cm^{-1} may be due to overlapping of the ν(asym)COO^- and δ NH_2 bending motion coordinated to platinum, indicating that the COOH group is not a ligation site. The presence of a strong –OH stretching band at 3428 cm^{-1} indicates the presence of free carboxyl (−COOH) group. The absence of weak absorption of

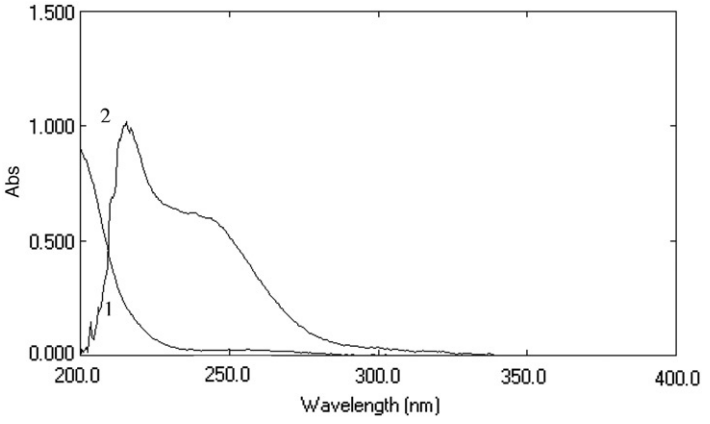

Figure 1. Spectral difference between **1** and the DL-penicillamine substituted product; (1) $[\mathbf{1}] = 2.00 \times 10^{-4}$ mol dm^{-3}; (2) $[\mathbf{1}] = 2.00 \times {}^{-}10^{-4}$ mol dm^{-3}; [DL-penicillamine] $= 8.00 \times 10^{-3}$ mol $^{-}$dm^{-3}, cell used = 1 cm quartz, pH = 4.0, and ionic strength = 0.1 mol dm^{-3} $NaClO_4$.

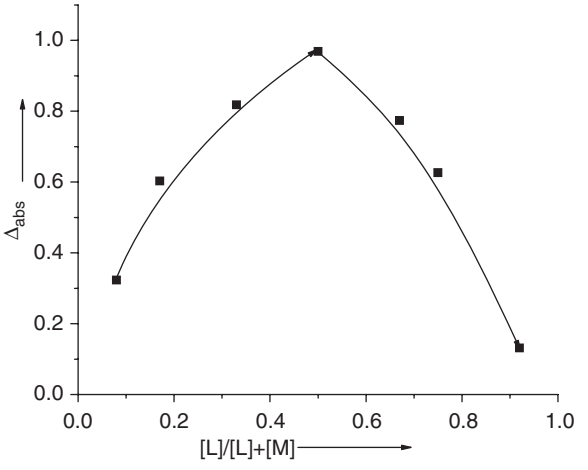

Figure 2. Job's plot for reaction between **1** and DL-penicillamine at pH = 4.0, and ionic strength = 0.1 mol dm^{-3} $NaClO_4$.

the −SH group at 2500 cm^{-1}, present in free DL-penicillamine, indicates formation of the Pt–S bond in the product [17]. The band at 510 cm^{-1} is also assigned to ν(Pt–N) [18]. The spectrum suggests that the final product is an S, N coordinated chelate and the DL-penicillamine is a bidentate ligand at the experimental pH. The observation is consistent with other studies [19–21] where (*N*,*N*)-platinum complexes bind to S-containing amino acids, substituted amino acids, and dipeptides through N and S.

The conductance measurement also reveals that bonding occurs through S and N of the DL-penicillamine ligand. During chelation, one proton is released from the −SH group of DL-penicillamine, which is supported by the increase in conductance with the reaction. Affinity of platinum(II) for sulfur is high providing the driving force for the deprotonation in the first step.

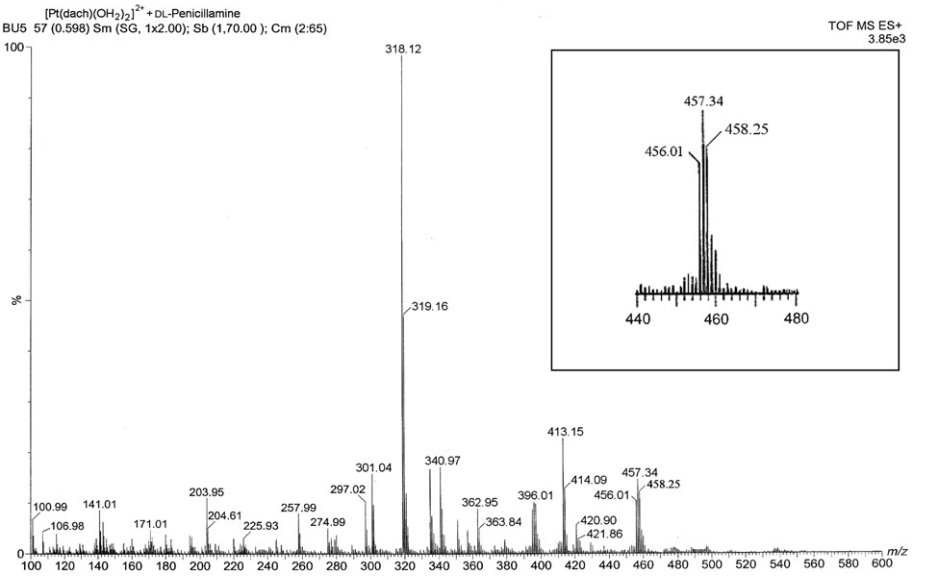

Figure 3. ESI-MS of the product for **1** and DL-penicillamine at pH 4.0 in aqueous medium and at ionic strength 0.1 mol dm^{-3} $NaClO_4$.

Aqueous solution of *cis*-[Pt(*cis*-dach)$(OH_2)_2]^{2+}$ and DL-penicillamine were mixed in a 1 : 1 molar ratio, and the mixture was thermostated at 60°C for 48 h and used for ESI-MS measurement. ESI-MS of the resulting solution are shown in figure 3. It is clear from this spectrum that the ion at *m*/*z* 457.34 (minor peak) has become the precursor ion species in the mixture solution and this is tentatively attributed to (DL-penicillamine + Pt + dach)$^+$; the relative abundance of isotope peaks match the expected values, i.e., *m*/*z* 456.01, *m*/*z* 457.34, and *m*/*z* 458.52. The fragment ion at *m*/*z* 413.15 corresponds to loss of 44 from the precursor ion and is thus attributed to the loss of CO_2, at the same time, the peak at 414.09 is the isotopic peak for the loss of CO_2. The fragment ion at *m*/*z* 318.12 has the maximum relative abundance as expected for $[Pt + 2\ NH_3 + S–CH\ (CH_3)–CH_2–NH_2]^+$ and peak at 319.16 is the isotopic peak for the same. The precursor ion and the fragmented products are shown schematically in figure 4.

We proposed that Pt(II) is likely to be coordinated to both sulfur and NH_2 considering the strong coordination ability of these functional groups [22–24]. Thus the structure proposed here for product ion species, deduced from ESI-MS, is generally consistent with those derived from other experimental methods. The pHs of the solution were adjusted by adding $NaOH/HClO_4$ and measurements were carried out with the help of a Sartorius Digital pH meter (model PB11) with an accuracy of ±0.01 units. Doubly distilled water was used to prepare all the solutions. All other chemicals were of AR grade. The reactions were carried out at constant ionic strength (0.1 mol dm^{-3} $NaClO_4$).

2.1. *Physical measurement*

All spectral scanning and kinetic measurements were done in a Shimadzu UV-Vis spectrophotometer (UV-2100). IR spectra (KBr disc, 4000–300 cm^{-1}) were measured in

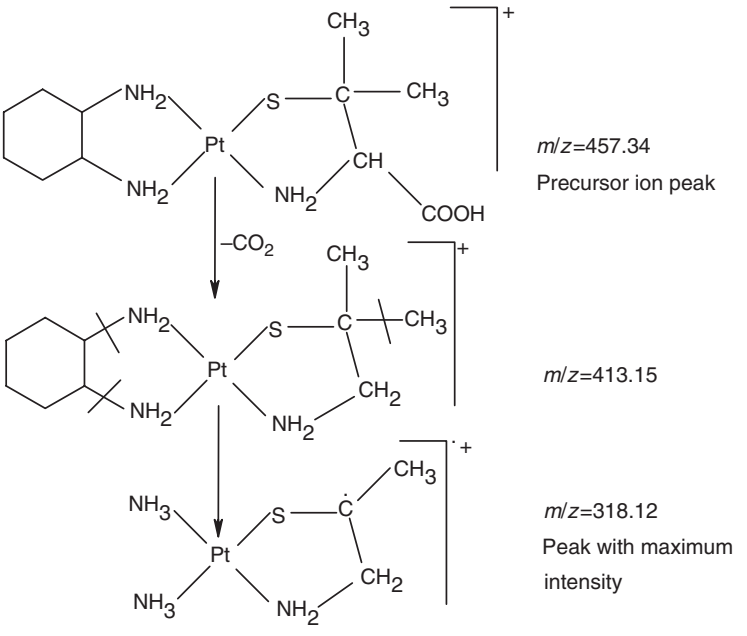

Figure 4. Plausible structures of the precursor ion and the fragmented ions matched with their m/z values obtained from the ESI-MS.

a Perkin-Elmer FTIR model RX1 infrared spectrophotometer. ESI-MS were recorded using a micromass Q-Tof micro™ mass spectrometer in +ve ion mode. Conductance measurements were carried out in a Systronics conductivity meter model 308 where the cell constant was calibrated with 0.01 mol L^{-1} KCl solution with water as solvent.

2.2. *Kinetic measurements*

Kinetic measurements were carried out on a Shimadzu spectrophotometer (UV-2100) equipped with a Shimadzu TB thermobath (accuracy ±0.1°C). The absorption due to DL-penicillamine was subtracted using 1 : 1 (molar ratio) ligand : water mixture in the reference cell. Following the increase in absorbance at 240 nm, the progress of the reaction was monitored. Conventional mixing technique was followed and pseudo-first order conditions with respect to metal ion concentration were maintained throughout the course of the reaction. The plot of $\ln(A_\infty - A_t)$ (where A_t and A_∞ are absorbances at the time and after completion of reaction) against time (t) (figure 5) is found to be nonlinear; it is curved initially and subsequently of constant slope indicating that the reaction involves two consecutive steps. From the limiting linear portion of $\ln(A_\infty - A_t)$ *versus* time (t) curves, $k_{2(\mathrm{obs})}$ were obtained. The $k_{1(\mathrm{obs})}$ values were obtained from the plot of $\ln \Delta$ *versus* time (t), where time (t) is small (figure 6). Origin software was used for computational work. Rate data, represented as an average of duplicate runs, are reproducible within ±4%.

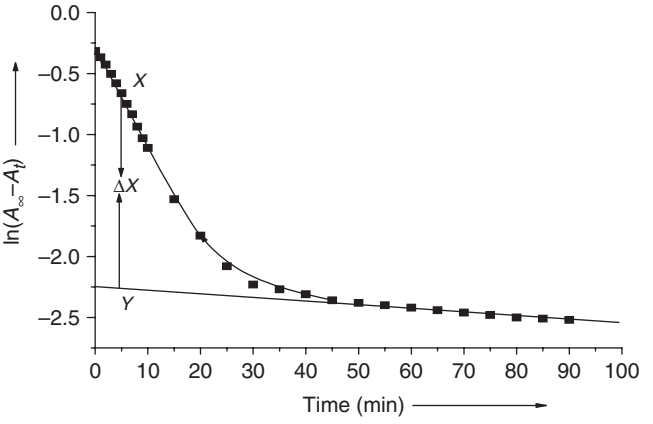

Figure 5. A typical kinetic plot of $\ln(A_\infty - A_t)$ *vs.* time (t). $[\mathbf{1}] = 2 \times 10^{-4}\,\mathrm{mol\,dm^{-3}}$; [DL-penicillamine] $= 4 \times 10^{-3}\,\mathrm{mol\,dm^{-3}}$; pH = 4.0; $\mu = 0.1\,\mathrm{mol\,dm^{-3}}$ $NaClO_4$ and temperature = 45°C.

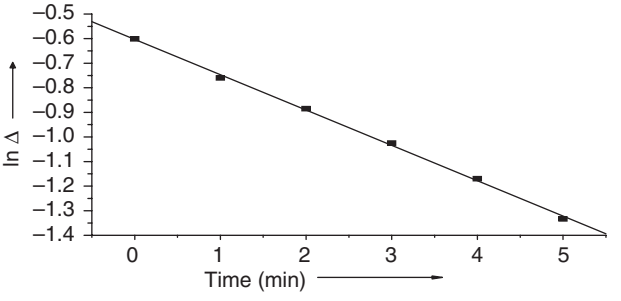

Figure 6. A typical kinetic plot of $\ln \Delta$ *vs.* time (t). $[\mathbf{1}] = 2.0 \times 10^{-4}\,\mathrm{mol\,dm^{-3}}$; [DL-penicillamine] $= 4.0 \times 10^{-3}\,\mathrm{mol\,dm^{-3}}$; pH = 4.0; $\mu = 0.1\,\mathrm{mol\,dm^{-3}}$ $NaClO_4$ and temperature = 45°C.

3. Results and discussion

The pK_1, pK_2, and pK_3 of DL-penicillamine [25] are 1.90, 7.88, and 10.58 at 25°C, respectively, which refer to the following dissociation processes (scheme 1):

$$HS-CMe_2-CH(NH_3^+)-COOH \rightleftharpoons HS-CMe_2-CH(NH_3^+)-COO^- + H^+ \quad pK_1 = 1.90$$
$$HS-CMe_2-CH(NH_3^+)-COO^- \rightleftharpoons {}^-S-CMe_2-CH(NH_3^+)-COO^- + H^+ \quad pK_2 = 7.88$$
$${}^-S-CMe_2-CH(NH_3^+)-COO^- \rightleftharpoons {}^-S-CMe_2-CH(NH_2)-COO^- + H^+ \quad pK_3 = 10.58$$

Scheme 1. Acid dissociation equilibria of the ligand DL-penicillamine.

At pH 4.0, the major species involved in the kinetic process is a zwitterionic form of DL-penicillamine. Since the pK_1 and pK_2 [26] for *cis*-(diaqua(*cis*-1,2-diaminocyclohexane)platinum(II) are 6.25 and 7.80, respectively, we assume that at pH 4.0, the reactant exists as the diaqua ion.

At constant temperature, constant pH (4.0) and fixed concentration of **1**, the $\ln(A_\infty - A_t)$ *versus* time plot for different ligand concentration is curved at the initial stage and subsequently of constant slope, indicating that the reaction involves a two-step consecutive process, the first step dependent on ligand concentration, whereas the second is independent of ligand concentration. In the first step, one aqua ligand was replaced from *cis*-[Pt(*cis*-dach)$(OH_2)_2]^{2+}$ by DL-penicillamine. The second is the slowest step, where another aqua ligand is substituted. This is the ring closure step. The rate constant for such process can be evaluated by assuming the following scheme:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C,$$

where A is the diaqua species (**1**) B the single substituted intermediate, and C the final product (**2**) [Pt(*cis*-dach)(DL-penicillamine)]$^+$. Formation of C from B is predominant after some time has elapsed.

3.1. *Calculation of k_1 for $A \rightarrow B$ step*

The rate constant $k_{1(\text{obs})}$ for the $A \rightarrow B$ step can be evaluated by the method of Weyh and Hamm [27] using the usual consecutive rate law;

$$(A_\infty - A_t) = a_1 \exp(-k_{1(\text{obs})}t) + a_2 \exp(-k_{2(\text{obs})}t), \quad (1)$$

whence

$$(A_\infty - A_t) - a_2 \exp(-k_{2(\text{obs})}t) = a_1 \exp(-k_{1(\text{obs})}t), \quad (2)$$

where a_1 and a_2 are constants depending on the rate constant and extinction coefficient. Values of $(A_\infty - A_t) - a_2 \exp(-k_{2(\text{obs})}\, t)$ are obtained from $X - Y$ at different time (t), so that

$$\Delta = a_1 \exp(-k_1(\text{obs})t)$$

or

$$\ln \Delta = \text{constant} - k_1(\text{obs})t, \quad (3)$$

where Δ is the difference of $\ln(A_\infty - A_t)$ values between the observed and extrapolated parts of the linear portion of $\ln(A_\infty - A_t)$ *versus* time (t) curve at any time (t). $k_{1(\text{obs})}$ is derived from the slope of $\ln \Delta$ *versus* time plot (correlation coefficient 0.998), when t is small (figure 6).

A similar procedure is applied for DL-penicillamine in the concentration range of 0.002–0.006 mol dm^{-3} at constant **1** of 0.0002 mol dm^{-3} at pH 4.0 and at 35°C, 40°C, 45°C, 50°C, and 55°C. The $k_{1(\text{obs})}$ values thus obtained are linearly dependent on the studied concentration range. The $k_{1(\text{obs})}$ values for different ligand concentrations at different temperatures are given in table 1. The ligand concentration dependence of $k_{1(\text{obs})}$ values can be explained in terms of rapid formation of an outer sphere association complex [6] between the reactant complex (**1**) and the sulfur end of zwitterionic form of DL-penicillamine in the $A \rightarrow B$ stage. The rate increases with increase in ligand concentration and reaches a limiting value (figure 7), which is probably due to completion of the outer sphere association complex formation.

Table 1. $10^3\,k_{1(obs)}$ (s^{-1}) values for different concentration of DL-penicillamine at different temperatures. [**1**] $= 2\times10^{-4}$ mol dm^{-3}, pH = 4.0, $\mu = 0.1$ mol dm^{-3} $NaClO_4$.

	10^3 [DL-Penicillamine] (mol dm^{-3})					
Temperature (°C)	2.00	3.00	4.00	5.00	6.00	8.00
35	0.62	0.85	1.06	1.21	1.34	1.57
40	0.93	1.26	1.57	1.81	1.96	2.29
45	1.48	1.94	2.40	2.69	2.91	3.40
50	1.97	2.62	3.01	3.39	3.65	4.05
55	3.27	4.09	4.74	5.26	5.58	6.13

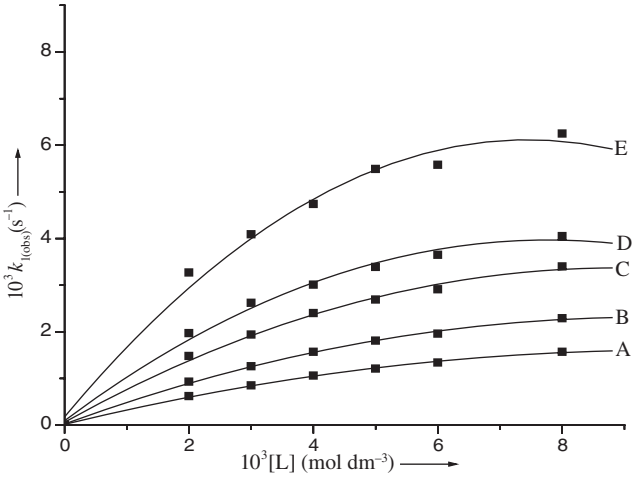

Figure 7. Plot of $k_{1(obs)}$ (s^{-1}) *vs.* [DL-penicillamine] at different temperatures; $A = 35°$, $B = 40°$, $C = 45°$, $D = 50°$, and $E = 55°$C; pH = 4.0 and ionic strength = 0.1 mol dm^{-3} $NaClO_4$.

Since the metal ion reacts with immediate environment, further change in ligand concentration beyond the saturation point will not affect the reaction rate and a gradual approach towards limiting rate is observed. At this stage, the interchange of the ligands from outer sphere to the inner sphere occurs. The following scheme can be proposed:

$$\underset{\text{A}}{\left[\text{Pt}(cis\text{-dach})(\text{H}_2\text{O})_2^{2+}\right]} + \text{L-LH} \overset{K_E}{\rightleftharpoons} \underset{\text{Outer sphere association complex}}{\left[\text{Pt}(cis\text{-dach})(\text{H}_2\text{O})_2^{2+}\right] + \text{L-LH}} \tag{4}$$

$$\left[\text{Pt}(cis\text{-dach})(\text{H}_2\text{O})_2^{2+}\right]\cdots\text{L-LH} \xrightarrow[\text{anation}]{K_1} \underset{\text{B}}{\left[\text{Pt}(cis\text{-dach})(\text{H}_2\text{O})(\text{L-L})^{+}\right]} + \text{H}_3\text{O}^{+} \tag{5}$$

$$\underset{\text{B}}{\left[\text{Pt}(cis\text{-dach})(\text{H}_2\text{O})(\text{L-L})^{+}\right]} \xrightarrow[\text{chelation}]{K_2} \underset{\text{C}}{\left[\text{Pt}(cis\text{-dach})(\text{L-L})^{+}\right]} + \text{H}_2\text{O}\,, \tag{6}$$

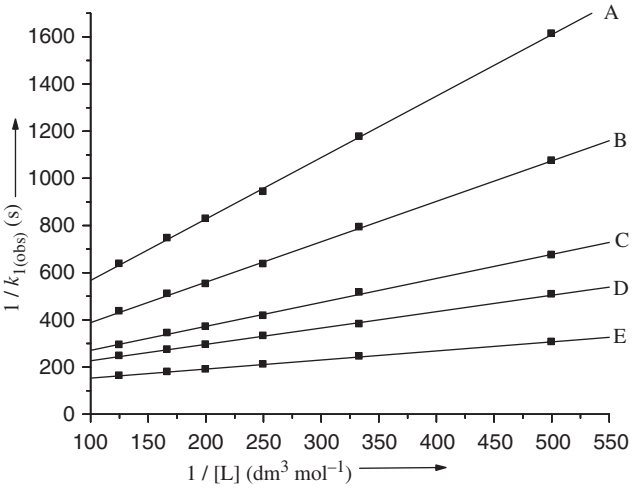

Figure 8. Plot of $1/k_{1(obs)}$ (s) *vs.* 1/[DL-penicillamine] at different temperatures; A = 35°, B = 40°, C = 45°, D = 50°, and E = 55°C; pH = 4.0; and ionic strength = 0.1 mol dm^{-3} $NaClO_4$.

where L-LH is the zwitterionic form of DL-penicillamine [HS−C(CH$_3$)$_2$−CH(NH$_3^+$)−COO$^-$]. Based on the above equations, a rate expression (10) can be derived for the A → B step:

$$\frac{dB}{dt} = \frac{k_1 K_E \left[\text{Pt}(cis\text{-dach})(H_2O)_2^{2+}\right]_{total}[\text{DL-penicillamine}]}{1 + K_E[\text{DL-penicillamine}]} \tag{7}$$

or

$$\frac{dB}{dt} = k_{1(obs)}\left[\text{Pt}(cis\text{-dach})(H_2O)_2^{2+}\right]_{total}, \tag{8}$$

where $\left[\text{Pt}(cis\text{-dach})(H_2O)_2^{2+}\right]_{total}$ is the concentration of the unreacted complex and [DL-penicillamine] the concentration of DL-penicillamine. Hence we can write:

$$k_{1(obs)} = \frac{k_1 K_E[\text{DL-penicillamine}]}{1 + K_E[\text{DL-penicillamine}]}, \tag{9}$$

where k_1 is the rate constant for conversion of outer sphere complex to inner sphere complex and K_E the outer sphere association equilibrium constant. Equation (9) can be rearranged:

$$\frac{1}{k_{1(obs)}} = \frac{1}{k_1} + \frac{1}{k_1 K_E[\text{DL-penicillamine}]}. \tag{10}$$

A plot of $1/k_{1(obs)}$ *versus* 1/[DL-penicillamine] should be linear with an intercept of $1/k_1$ and slope $1/k_1K_E$. This was found to be so at all the temperatures studied (figure 8); the k_1 and K_E values obtained from intercept and from slope to intercept ratio, respectively, are included in table 2.

Table 2. k_1, k_2, and K_E values for the substitution reaction.

Temperature (°C)	k_1 (s^{-1})	10^5 k_2 (s^{-1})	K_E ($dm^3\,mol^{-1}$)
35	3.26	2.56	117
40	4.59	3.37	127
45	5.89	4.54	167
50	6.35	6.32	227
55	8.75	7.77	297

3.2. *Calculation of k_2 for the B → C step*

The B → C step is the ring closure step in which the amino group of the substituted amino acid, DL-penicillamine, binds the metal center. Due to steric hindrance, this step is slow and independent of ligand concentration variation. At a particular temperature, the k_2 values were calculated from the limiting linear portion (where t is large) of the $\ln(A_\infty - A_t)$ *versus* time curve (figure 5). For different temperatures, k_2 values obtained directly from the limiting slope of $\ln(A_\infty - A_t)$ *versus* t are given in table 2.

3.3. *Effect of pH on reaction rate*

The reaction was studied at four different pH values. The k_{obs} values increase with increase in pH in the studied pH range. At a fixed 0.0002 mol dm^{-3} (**1**), 0.004 mol dm^{-3} [DL-penicillamine], and 0.1 mol dm^{-3} ionic strengths, the 10^3 $k_{1(obs)}$ values at 50°C in aqueous medium are 2.60, 2.86, 3.01, and 3.66 s^{-1} and 10^5 $k_{2(obs)}$ values are 4.61, 5.27, 6.32, and 7.66 s^{-1} at pH 2.8, 3.4, 4.0, and 4.6, respectively. The enhancement in the rate may be explained based on two acid dissociation equilibria of the ligand and the complex. In the studied pH range (2.8–4.6), with an increase in pH, the diaqua complex will be converted into hydroxoaqua complex. The reactivity of hydroxoaqua complex is usually higher than that of diaqua complex by the well-known labilizing effect of coordinated hydroxide. At the same time, with increase in pH deprotonation of the ligand occurs, which is also responsible for enhanced reactivity. Notwithstanding in the present kinetic runs, the substitution reactions were followed at a constant pH of 4.0 to avoid complication caused by adding an additional parameter of $[H^+]$ to the rate equation. At pH 4.0, **1** exists in the diaqua form.

3.4. *Effect of temperature on reaction rate*

The reaction was studied at five different temperatures for different ligand concentration and the anation rate constants for both A → B (k_1) and B → C (k_2) steps are given in table 2. The activation parameters calculated from Eyring plots (figures 9 and 10) are given in table 3 and compared with those for analogous systems involving substitution in square planar platinum(II) complexes.

4. Mechanism and conclusion

DL-Penicillamine exists as zwitterions at pH 4.0 (scheme 1). The sulfur end of DL-penicillamine is a soft donor and has large affinity for the soft Pt center. Thus in the

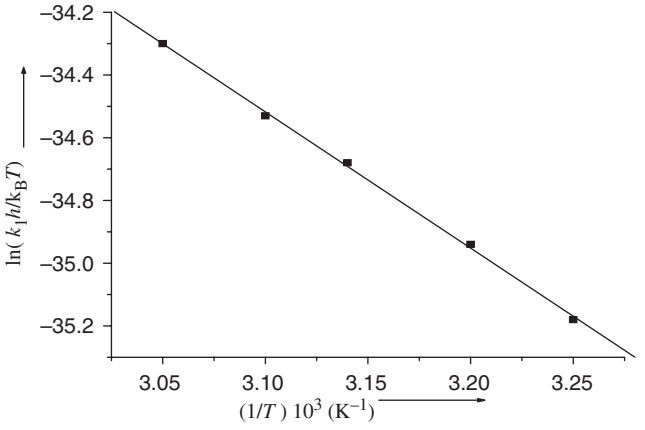

Figure 9. Eyring plot for k_1.

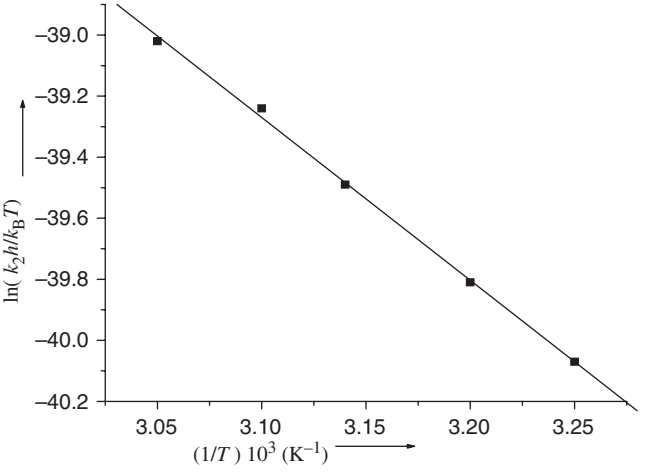

Figure 10. Eyring plot for k_2.

first stage, a rapid equilibrium is established, resulting in an outer sphere association complex between **1** and DL-penicillamine. Two *cis*- positions of platinum(II) ion are blocked by nitrogen ligands, and in view of the preference for square planar configuration it is unlikely that DL-penicillamine is a tridentate ligand in this complex formation. Job's method of continuous variation indicates 1 : 1 molar ratio and the IR spectrum of the solid product suggests that DL-penicillamine is bidentate with carboxyl group free. Finally ESI-MS provide a qualitative picture of the composition, i.e. the ligational sites are sulfur and nitrogen ends of DL-penicillamine. Thus the mechanism of substitution of aqua ligands in *cis*-diaqua(*cis*-1,2-diaminocyclohexane)platinum(II) ion can be explained in terms of rapid outer sphere association, followed by two consecutive steps, the first dependent on ligand concentration and the second chelation, i.e. ring closure step, which is slower than the first step and independent of ligand

Table 3. Activation parameters for analogous systems.

Systems	$\Delta H_1^{\neq}$ (kJ mol^{-1})	$\Delta S_1^{\neq}$ (JK^{-1} mol^{-1})	$\Delta H_2^{\neq}$ (kJ mol^{-1})	$\Delta S_2^{\neq}$ (JK^{-1} mol^{-1})	References
Cis-[Pt(en)$_2$(H$_2$O)$_2$]$^{2+}$					
DL-Methionine	15.6 ± 0.9	−230 ± 3	19.4 ± 1.2	−225.5 ± 4.0	[28]
Thiourea	61.9 ± 1.7	−71 ± 6	26.7 ± 0.8	−186.8 ± 2.7	[29]
Thiosemicarbazide	35.6 ± 0.8	−166 ± 3	44.5 ± 1.3	−182 ± 4	[30]
Cis-[Pt(*cis*-dach) (H$_2$O)$_2$]$^{2+}$					
Glutathione	32.9 ± 1.3	−187.2 ± 4.2	30.5 ± 0.1	−223.1 ± 0.3	[31]
Et$_2$DTC	66.8 ± 3.7	−81 ± 12	95.1 ± 2.8	−34.4 ± 9.1	[32]
DL-Penicillamine	36.1 ± 4.1	−175 ± 12	44.4 ± 1.1	−189 ± 3	[**]

**This study.

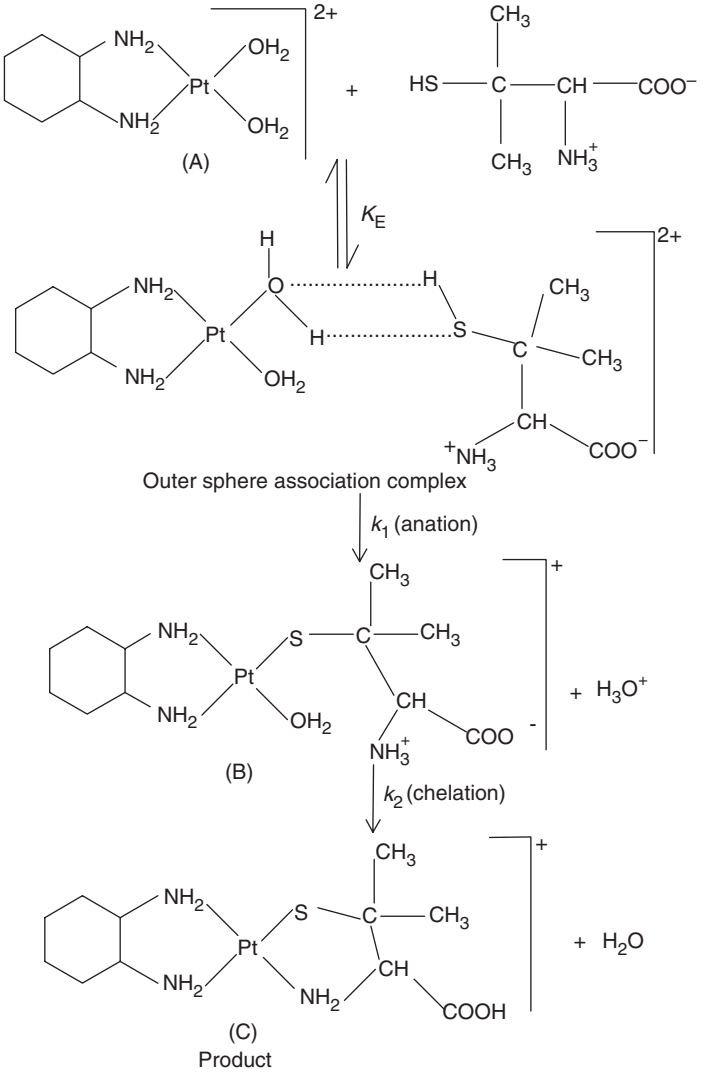

Figure 11. Plausible mechanism for the substitution of the aqua ligand from *cis*-[Pt(*cis*-dach)(H$_2$O)$_2$]$^{2+}$ by DL-penicillamine.

concentration (figure 11). The affinity for nitrogen of the amino group provides the driving force for the ring formation.

The activation parameters ($\Delta H_1^{\neq} = 36.1 \pm 4.1\,\text{kJ mol}^{-1}$, $\Delta S_1^{\neq} = -175 \pm 12\,\text{JK}^{-1}\,\text{mol}^{-1}$) for the first step and the second step ($\Delta H_2^{\neq} = 44.4 \pm 1.1\,\text{kJ mol}^{-1}$, $\Delta S_2^{\neq} = -189 \pm 3\,\text{JK}^{-1}\,\text{mol}^{-1}$) suggest an associative substitution. The enthalpy of activation ($\Delta H_1^{\neq}$ and $\Delta H_2^{\neq}$) values and negative ($\Delta S_1^{\neq}$ and $\Delta S_2^{\neq}$) values implies a good degree of ligand participation in the transition state. The positive enthalpy change for breaking the M–OH_2 bond is partially compensated by the formation of M–L bond in the transition state. The participation of DL-penicillamine in the transition state results in a more compact state and negative $\Delta S^{\neq}$. Further $\Delta S_2^{\neq}$ is less negative than $\Delta S_1^{\neq}$, suggesting that compactness has already been achieved in B and the transformation of B to C is only the replacement of another aqua ligand through chelation. Aqua ligand substitution on *cis*-[Pt(*cis*-dach) $(H_2O)_2]^{2+}$ with different sulfur donors gives different enthalpy of activation ($\Delta H^{\neq}$) and entropy of activation ($\Delta S^{\neq}$) depending on the ligand. For *cis*-[Pt(*cis*-dach) $(H_2O)_2]^{2+}$, the enthalpy of activation ($\Delta H_1^{\neq}$) values are 32.9, 66.8, and 36.1 kJ mol^{-1} for glutathione, Et_2DTC, and DL-penicillamine, respectively (table 3). Et_2DTC gives the highest enthalpy of activation due to its inability to form a hydrogen bond during substitution (outer sphere association) with leaving aqua ligand, whereas glutathione and DL-penicillamine, before deprotonation of –SH, are able to form a hydrogen bond which finally leads to Pt–S bond. DL-penicillamine has higher $\Delta H_1^{\neq}$ than glutathione as glutathione has higher pK_a for –S–H assisting glutathione to form outer sphere association compared to DL-penicillamine. Similarly the enthalpies of activation ($\Delta H_2^{\neq}$) values are 30.5, 95.1, and 44.4 kJ mol^{-1} for glutathione, Et_2DTC and DL-penicillamine, respectively (table 3).

Due to its great medical, biological, and biochemical importance, platinum chemistry attracts considerable interest. Kinetic and mechanistic aspects of the reaction of DL-penicillamine with **1** in aqueous medium extend the study of interaction platinum complexes with other biomolecules, providing new insights into this active research area.

References

[1] B. Rosenberg, L.Van Camp, J.E. Trosko, V.H. Mansour. *Nature*, **222**, 285 (1969).
[2] K. Hindmarsh, D.A. House, M.M. Turnbull. *Inorg. Chim. Acta*, **257**, 11 (1997).
[3] C.L. Baird, A.E. Griftitus, S. Baffic, P. Bryant, B. Wolf, J. Lutton, M. Beradini, G.M. Arvantis. *Inorg. Chim. Acta*, **256**, 253 (1997).
[4] C.F.G. Barnard. *Platinum Met. Rev.*, **30**, 116 (1986).
[5] J. Arpalahti, B. Lipert. *Inorg. Chem.*, **29**, 104 (1990).
[6] F. Basolo, R.G. Pearson. *Mechanism of Inorganic Reactions, A Study of Metal Complexes in Solution*, 2nd Edn, p. 36, Wiley, New York (1967).
[7] B. Lipert (Ed.). *Cisplatin – Chemistry and Biochemistry of Leading Anticancer Drug*, Wiley VCH, Weinheim (1999).
[8] P. Umapathy. *Coord. Chem. Rev.*, **95**, 129 (1989).
[9] J.J. Roberts, A.J. Thomson. *Prog. Nucl. Res. Mol. Biol.*, **22**, 71 (1979).
[10] J. Reedijk. *Pure Appl. Chem.*, **59**, 181 (1987).
[11] E. Wong, C.M. Giandomenico. *Adv. Inorg. Chem.*, **49**, 186 (2000).
[12] F. Legendre, V. Bas, J. Kozelka, J.C. Chottored. *Chem. Eur. J.*, **6**, 2002 (2000).
[13] E.L.M. Lempers, J. Reedijk. *Adv. Inorg. Chem.*, **37**, 175 (1992).
[14] R. Miao, G. Yong, Y. Miao, Y. Mei, J. Hong, C. Zhao, L. Zhu. *Rapid Commun. Mass Spectrom.*, **19**, 1031 (2005).
[15] A.R. Khokhar, I.H. Karkoff, M.P. Hacker, J.J. Mc Cormack. *Inorg. Chim. Acta*, **108**, 63 (1985).
[16] G. Pneumatikakis, N. Hadjiliadis. *J. Inorg. Nucl. Chem.*, **41**, 429 (1979).

[17] E.S. Raper. *Coord. Chem. Rev*., **61**, 115 (1985).
[18] J. Apralahti, P. Lehikoinen. *Inorg. Chim. Acta*, **159**, 115 (1989).
[19] J.E. Burgenson, N.M. Kostic. *Inorg. Chem*., **30**, 4299 (1990).
[20] P.S. Sengupta, R. Sinha, G.S. De. *Transition Met. Chem*., **26**, 638 (2001).
[21] S.K. Bera, S.K. Chandra, G.S. De. *Int. J. Chem. Kinet*., **35**, 252 (2003).
[22] T.G. Appelton. *Coord. Chem. Rev*., **313**, 166 (1997).
[23] X. Sun, C. Jin, Y. Mei, G. Yang, Z. Guo, L. Zhu. *Inorg. Chem*., **43**, 290 (2004).
[24] R.F. Coley, D.S. Martin Jr. *Inorg. Chim. Acta*, **7**, 573 (1973).
[25] A.E. Martel, R.M. Smith. *Critical Stability C.S.C*., Vol. I, Plenum Press, New York (1974).
[26] H.M. Irving, H.S. Rossotti. *J. Chem. Soc*., 2904 (1954).
[27] J.A. Weyh, R.E. Hamm. *Inorg. Chem*., **8**, 2298 (1969).
[28] S. Ghosh, P.S. Sengupta, G.S. De. *Transition Met. Chem*., **24**, 59 (1999).
[29] P.S. Sengupta, S. Ghosh, G.S. De. *Transition Met. Chem*., **25**, 279 (2000).
[30] S. Ghosh, P.S. Sengupta, G.S. De. *Indian J. Chem*., **38A**, 453 (2000).
[31] R. Sinha, A.K. Choudhury, G.S. De. *Indian J. Chem*., **42A**, 473 (2003).
[32] S.K. Mukhopadhyay. *Transition Met. Chem*., **33**, 739 (2008).