Kinetic and mechanistic studies on the interaction of thiosemicarbazide with cis-diaquaethylenediamine platinum (II) ion

Shyamal Ghosh, Partha Sarathi Sengupta & Gauri Sankar De
Chemistry Department, The University of Burdwan 713 104, India

Received 23 November 1998; revised 3 March 1999

Kinetics of interaction of thiosemicarbazide with [Pt(en)(H₂O)₂]²⁺ has been studied spectrophotometrically as a function of [Pt(en)(H₂O)₂]²⁺, [thiosemicarbazide] and temperature at a particular pH(4.0) where the substrate complex exists predominantly as the diaqua species and the ligand thiosemicarbazide as a neutral molecule. The interaction reaction shows distinct two step consecutive process, the first step is the ligand assisted anation and the second step is the chelation step. The activation parameters for both the steps are evaluated (ΔH°' = 35.69 ± 0.80 kJ mol⁻¹, ΔS°' = -166± 2.54 JK⁻¹ mol⁻¹ and ΔH° = 44.54 ± 1.32 kJ mol⁻¹, ΔS° = -182 ± 4.18 JK⁻¹ mol⁻¹).

Nucleophilic substitution reactions on square planar platinum (II) complexes are interesting from both kinetic and bio-medical points of view. Cis-Platin, the well-known chemotherapeutic reagent having antitumor activity interacts specifically with DNA. When cis-platin is incubated with DNA, intrastand chelates are formed which perhaps hinders the replication of viral cells. Many investigators have made significant contribution in this field. Due to the major toxic effect of cis-platin [Pt(NH₃)₂Cl₂], aqua derivatives are now widely used, as one would expect the aqua species to react much faster in cell than the dichloro species. Further, the mechanistic understanding of the process is not well-developed and therefore it has been considered interesting to study the binding kinetics of diaquaethylenediamine platinum (II) ion with amino acids, nucleosides, nucleotides and other bioactive ligands like thiosemicarbazide which can provide some new insight to the biological activity of the platinum(II) complex.

The scope of this research work is immense, even if the mixed ligand complex reported here is not of itself applicable clinically, the mechanistic knowledge leads to the recognition of new targets for chemotherapeutic design of new drugs.

In this paper, we report the kinetics of aqua molecule substitution in [Pt(en)(H₂O)₂]²⁺ by thiosemicarbazide in aqueous medium.

Materials and Methods

The reactant complex, cis-[Pt(en)(H₂O)₂]²⁺ (complex 1) was prepared according to the literature method and characterised spectrally (λmax = 256 nm, ε= 200 cm⁻¹ M⁻¹) and by elemental analysis. The pH of the solution was so maintained (pH = 4.0) that > 90 % of the perchlorate salt was obtained as diaqua species. The product (substituted complex; complex 2) of the reaction was prepared in different molar ratios viz. 1:5, 1:10, 1:20 and 1:30 and kept in a thermostat at 55°C for 48 h. All the four solutions so prepared exhibited almost identical absorbances at λmax = 261 nm with a bathochromic shift of 4 nm to longer wave length for the stated concentration range indicating some type of metal - ligand association in the initial stage. The spectral differences are shown in Fig. 1. No solid product could be isolated. But the composition of the product in solution was determined by Job's method of continuous variation. The metal - ligand ratio was found to be 1:1. The pH of the solution was adjusted by adding NaOH/ HClO₄ and the measurements were carried out with the help of a systronic digital pH meter with an accuracy of ± 0.01 unit. Doubly distilled water was used to prepare all the solutions. All other chemicals used were of either AR grade or purified before use. The reactions were carried out at constant ionic strength (0.1 M NaClO₄).

Kinetics

Kinetic measurements were carried out on a Shimadzu Spectrophotometer (UV 2101 PC, equipped with a Shimadzu TB - 85 thermobath (accuracy = ± 0.1°C). The conventional mixing technique was followed and pseudo-first order conditions were employed throughout. The plot of log (Dₑ - Dₜ), where Dₜ and Dₖ...
Fig. 1 - Spectral difference between reactant and product,
[Pt(en)(H₂O)]²⁺ = 1.5 x 10⁻⁴ mol dm⁻³, [thiosemicarbazide] = 4.5 x 10⁻³ mol dm⁻³, pH = 4.0, temp = 55°C.

Fig. 2 - A typical plot of log (D₀ - Dₜ) versus time, [Pt(en)(H₂O)]²⁺ = 1.5 x 10⁻⁴ mol dm⁻³, [thiosemicarbazide] = 4.5 x 10⁻³ mol dm⁻³, pH = 4.0, temp = 35°C.

Table 1 - 10²kᵢ(obs) (s⁻¹) values at different temperatures and at fixed [complex] = 0.000075 mol dm⁻³ and at different [LH] (mol dm⁻³)

<table>
<thead>
<tr>
<th>10⁻²[LH] (mol dm⁻³)</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
</tr>
<tr>
<td>0.75</td>
<td>0.38</td>
</tr>
<tr>
<td>1.125</td>
<td>0.49</td>
</tr>
<tr>
<td>1.5</td>
<td>0.58</td>
</tr>
<tr>
<td>1.875</td>
<td>0.63</td>
</tr>
<tr>
<td>2.25</td>
<td>0.70</td>
</tr>
</tbody>
</table>

are absorbances at time t and at infinite time or after the completion of the reaction, against time is interestingly found to be non-linear; it is curved at the initial stage and subsequently of constant slope (Fig. 2). The method of Wyeh and Hamm was adopted to calculate rate constants for two consecutive steps. From the linear second portion kᵢ₂(obs) values were obtained. The kᵢ₁(obs) values were obtained from the plot of ln Δ versus t. A typical plot is shown in Fig. 3. Rate data, represented as an average of duplicate runs, are reproducible within ±4%.

Results and Discussion

The ionisation constants of protonated thiosemicarbazide is pK₁ = 2.0 at 25°C and pK₂ = 1.0, so that at pH 4 it is assumed to exist as the neutral molecule. Since the pK₁ and pK₂ values for cis-diaquaethylenediamine platinum(II) ion are 5.8 and 7.6 respectively, we can assume that at pH 4 the reactant exists as the diaqua ion.

At constant temperature, constant pH (4) and fixed concentration of complex (1) the log (D₀ - Dₜ) versus time (t) plot, for different ligand concentration is curved at the initial stage and subsequently of constant slope (Fig. 2). It indicates that the reaction is not a single step process, a two step consecutive process may be assumed, the first step is dependent and the second step is independent on ligand concentrations.

The rate constants for such process can be evaluated by assuming the following scheme A → B → C, where A is the diaqua species, B is the intermediate with monodentate LH and C is the final chelated [Pt(en)(LH)]²⁺. Formation of C from B is predominant after some time has elapsed.

Calculation of k₁ value for A → B step

The rate constant k₁(obs) for the A → B step can be evaluated by the method of Weyh and Hamm using the usual consecutive rate law.
GHOSH et al.: KINETICS OF INTERACTION OF THIOSEMICARBAZIDE WITH [Pt(en)H₂O]₂F⁺

Fig. 3 - A typical plot of ln Δ versus time, [Pt(en)(H₂O)₂]²⁺ = 1.5 x 10⁻⁴ mol dm⁻³, [thiosemicarbazide] = 4.5 x 10⁻³ mol dm⁻³, pH = 4.0, temp = 35°C.

\[ D_\infty - D_t = a_1 \exp(-k_{1_{obs}} t) + a_2 \exp(-k_{2_{obs}} t) \]  ... (1)

Whence

\[ (D_\infty - D_t) - a_2 \exp(-k_{2_{obs}} t) = a_1 \exp(-k_{1_{obs}} t) \]  ... (2)

where \( a_1 \) and \( a_2 \) are the constants dependent upon the rate constants and extinction coefficients.

Values of \( (D_\infty - D_t) - a_2 \exp(-k_{2_{obs}} t) \) are obtained from X - Y at different time \( t \), so that

\[ \Delta = a_1 \exp(-k_{1_{obs}} t) \]

or, \( \ln \Delta = \text{constant} - k_{1_{obs}} t \)  ... (3)

\( k_{1_{obs}} \) is derived from the slope of \( \ln \Delta \) versus \( t \), when \( t \) is small (Fig. 3).

A similar procedure is applied for each ligand concentrations in the 0.00075 to 0.00225 mol dm⁻³ range at constant complex (1) concentrations (0.000075 mol dm⁻³) at pH 4.0 and at different temperatures viz., 35, 40, 45 and 50°C respectively. The \( k_{1_{obs}} \) values thus obtained increase with the increase in ligand concentration. The \( k_{1_{obs}} \) values for ligand concentrations at different temperatures are given in Table 1.

The ligand concentration dependence of \( k_{1_{obs}} \) values can be explained in terms of rapid formation of outer sphere association complex between the reactant complex (1) and the sulphur atom of the thiosemicarbazide ligand in the A→B stage.

The mechanism proposed is given in Scheme 1

![Scheme 1](Image)

Table 2 - \( k_1 \) (dm⁻³ mol⁻¹ s⁻¹), \( K_E \) (dm⁻³ mol⁻¹) and \( k_2 \) (s⁻¹) values at different temperatures.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>( 10^4 k_1 )</th>
<th>( 10^8 K_E )</th>
<th>( k_2 ) (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>0.125</td>
<td>0.57</td>
<td>577</td>
</tr>
<tr>
<td>40</td>
<td>0.161</td>
<td>0.75</td>
<td>726</td>
</tr>
<tr>
<td>45</td>
<td>0.207</td>
<td>1.008</td>
<td>840</td>
</tr>
</tbody>
</table>

Fig. 4 - Plot of \( 1/k_{1_{obs}} \) versus \( 1/[L] \), A = 35°C, B = 40°C, C = 45°C, D = 50°C.
Table 3 - Activation parameters for analogous systems.

<table>
<thead>
<tr>
<th>Systems</th>
<th>( \Delta H^* )</th>
<th>( \Delta S^* )</th>
<th>( \Delta H^* )</th>
<th>( \Delta S^* )</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kJ mol(^{-1}))</td>
<td>(JK mol(^{-1}) mol(^{-1}))</td>
<td>(kJ mol(^{-1}))</td>
<td>(JK mol(^{-1}) mol(^{-1}))</td>
<td></td>
</tr>
<tr>
<td>Cis-Pt(NH(_3))(_2)(H(_2)O(_2))(^{2+}) / 5'-dGMPH(_2)</td>
<td>31.2±4.3</td>
<td>-117±15</td>
<td>60.8±5.3</td>
<td>-55±17.9</td>
<td>15</td>
</tr>
<tr>
<td>5'-GMPH(_2)</td>
<td>40.6±4.4</td>
<td>-106±16</td>
<td>62.8±1.5</td>
<td>-46.3±5.2</td>
<td>16</td>
</tr>
<tr>
<td>Cis - [Pt(en)(H(_2)O(_2))](^{2+}) / DL-Methionine</td>
<td>15.58±0.9</td>
<td>-230±3</td>
<td>19.43±1.2</td>
<td>-225±4</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>29.51±4.8</td>
<td>-188±15</td>
<td>48.99±1.0</td>
<td>-130±3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>63.7±1.6</td>
<td>-58±5</td>
<td>41.0±0.5</td>
<td>-197±1.5</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>61.95±1.7</td>
<td>-71±5.8</td>
<td>26.7±0.81</td>
<td>-186.8±2.7</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>35.69±0.80</td>
<td>-166±2.54</td>
<td>44.54±1.32</td>
<td>-182±4.18</td>
<td>this work</td>
</tr>
</tbody>
</table>

\[ \text{Scheme 2} \] — Plausible mechanism for the substitution of aqua ligands from [Pt(en)(H\(_2\)O\(_2\))]\(^{2+}\) by thiosemicarbazide

Based on Scheme 1 a rate expression can be derived for the A→B step.

\[
d[B]/dt = k_1 K_e [\text{Pt(en)(H}_2\text{O}_2)]^{2+}_{\text{rad}} [\text{thiosemi}] / (1 + K_e [\text{thiosemi}])
\]  

... (7)

or, \( \frac{d[B]}{dt} = k_1 [\text{Pt(en)(H}_2\text{O}_2)]^{2+}_{\text{rad}} \)  

... (8)

where \( [\text{Pt(en)(H}_2\text{O}_2)]^{2+}_{\text{rad}} \) is the concentration of the unreacted complex and we can write

\[
k_{\text{total}} = k_1 K_e [\text{thiosemi}] / (1 + K_e [\text{thiosemi}])
\]  

... (9)

where \( k_1 \) is the rate constant for the interchange of the outersphere complex to the innersphere complex, \( K_e \) is the outersphere association equilibrium constant. Equation (9) can be rearranged as

\[
1/k_{\text{total}} = 1/k_1 + 1/k_K_e [\text{thiosemi}]
\]  

... (10)
The plot of $1/k_{tobs}$ versus $1/[\text{thiosemi}]$ should be linear with an intercept of $1/k_1$ and slope of $1/k_2 K_E$. This was found to be so at all temperatures studied (Fig. 4). The $k_1$ and $K_E$ values obtained from the intercept and from slope to intercept ratios are given in Table 2.

**Calculation of $k_2$ values for the B $\rightarrow$ C step**

The B $\rightarrow$ C step is ring closure and is independent of ligand concentration. At a particular temperature the slope of $\log (D_n - D)$ versus time plot for different ligand concentrations was found constant in the region where the plot is linear (Fig. 2). For different temperatures the $k_2$ values, obtained directly from the limiting slope, are collected in Table 2.

Repeated attempts to isolate B failed. However, the experimental results show a similar curvature of $\log (D_n - D)$ versus time plot at different temperatures for varying ligand concentrations. The assumption of two consecutive steps for such a reaction and the computation of $k_1$ and $k_2$ values fit well with the experimental values.

**Temperature and reaction rate**

The reaction was studied at four different temperatures for different ligand concentrations and the results are listed in Tables 1 and 2. The activation parameters for both the steps,

$$k_1, k_2$$

A $\rightarrow$ B $\rightarrow$ C are evaluated from the linear Eyring plots. The activation parameters thus obtained are given in Table 3 along-with other analogous systems.

**Mechanism and conclusion**

The present investigation of aqua ligand substitution by thiosemicarbazide shows that in the first stage, a rapid equilibrium resulting outersphere association complex between complex (I) and thiosemicarbazide is favoured. It is an associative mode of activation or in other words an appreciable amount of ligand participation occurs in the transition state. The sulphur end of thiosemicarbazide is a soft donor centre and have large affinity to the soft acid Pt(II) centre. The second step is the ring closure which is slower than the first step and this step is ligand independent (Scheme 2).

**Acknowledgement**

The authors thank the UGC, New Delhi for providing financial assistance under DSA project in Chemistry and one of the author (SG) is thankful to the UGC, New Delhi for awarding a fellowship to him.

**References**