Kinetic and mechanistic studies on the interaction between azide and cis-diaqua-chloro-tris-(dimethyl sulfoxide)-ruthenium(II) complex in aqueous medium

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Received: 21st August, 2010 ; Accepted: 31st August, 2010

ABSTRACT

The kinetics of interaction between azide and cis-[RuCl(Me$_2$SO)$_3$(H$_2$O)$_2$]$^+$ have been studied spectrophotometrically as a function of [RuCl(Me$_2$SO)$_3$(H$_2$O)$_2$]$^+$, [azide] and temperature at a particular pH(5.0), where the substrate complex exists predominantly as a diaqua species (in aqueous solution) and azide as the monoanionic species. The reaction has been found to proceed via two distinct consecutive steps i.e., it shows a non-linear dependence on the concentration of azide: both processes are [ligand] dependant. The rate constants for the processes are: \( k_1 \sim 10^{-3} \text{s}^{-1} \) and \( k_2 \sim 10^{-5} \text{s}^{-1} \). The activation parameters were calculated from Eyring plots suggest an associative mechanism for the interaction process. From the temperature dependence of the outersphere association equilibrium constants, the thermodynamic parameters were also calculated, which gives a negative \( G^\circ \) value at all temperature studied, supporting the spontaneous formation of an outersphere association complex.

INTRODUCTION

A variety of displacement reactions of ruthenium(II), in which one unidentate ligand is replaced by another, have been reported in the literature. Anation studies on different substrates indicate both dissociative$^{1,2}$ as well as associative$^3$ mode of activation. No single mechanism is adequate to explain the variety of observations in ligand replacement reactions on ruthenium(II). On the other hand there is a steadily increasing interest in transition metal complexes other than the traditional Pt-based compounds for use as chemotherapeutic agents against cancer. Cis-platin$^4$ and carboplatin$^5$ are two well-known drugs for cancer chemotherapy, but certain tumours are resistant to two drugs. Also platinum complexes induce toxic effects such as nephrotoxicity and neurotoxicity. Complexes of other (4d) and (5d) metal ions, especially ruthenium, rhodium, iridium and palladium, have been reported to have antibacterial power$^{6,7}$. Complexes of these metal ions with nucleic acid constituents$^{8,9}$, di$^{10}$ and tri$^{11}$ peptides and other bioactive ligands$^{12-15}$ were studied. Mechanistic study on formation of these complexes by anation reaction may help to understand the mode of in vivo activities of these complexes. Especially ruthenium complexes are becoming more and more popular due to their well-developed synthetic chemistry and great flexibility to fine-tune properties by modification to the ligand sphere. Ruthenium(II) complexes are less toxic than cis-platin$^{16,17}$. A number of ruthenium compounds serve as bacterial mutagens which indicate that at least some ruthenium complexes are capable of damaging genetic materials$^{18-21}$. The studies on the bioactivities of ruthenium(II/III) complexes are still a developing area.
It was already established that [Ru(dmso)₄Cl₂] has anticancer and antitumor activity[22] but no study were done in aqueous medium. This is the first report where the kinetic study on [Ru(dmso)₄Cl₂] is done in aqueous medium. Sodium azide is a useful probe reagent, mutagen, and preservative. In hospitals and laboratories, it is a biocide; it is especially important in bulk reagents and stock solutions which may otherwise support bacterial growth where the sodium azide acts as a bacteriostatic by inhibiting cytochrome oxidase in gram-negative bacteria; gram-positive (pneumococci, lactobacilly) are resistant[23], a characteristic similar to antibiotic resistance. It is also used in agriculture for pest control. Azide inhibits cytochrome oxidase by binding irreversibly to the heme cofactor in a process similar to the action of carbon monoxide. Sodium azide particularly affects organs that undergo high rates of respiration, such as the heart and the brain.

With this background we planned to study the interaction of cis-[RuCl(Me₂SO)₃(H₂O)₂]⁺, the reactive species of [Ru(dmso)₄Cl₂] in aqueous medium, with different bioactive ligands e.g., azide, glycylglycine, glycyl-l-leucine, glycyl-l-valine etc. and with certain nucleocides and nucleotides. In the present work we have the kinetic and mechanistic details of the interaction of azide in the aqueous medium at pH 5.0 was examined. The importance of the work lies in the fact that in the aqueous medium the bonding mode of the substrate complex is very interesting and the reactivity of this complex in solution is promising.

**EXPERIMENTAL**

The reactant cis-[Ru(Me₂SO)₄Cl₂] was prepared and characterized according to the method reported by Evans et al.[24]. The substrate complex [RuCl(Me₂SO)₃(H₂O)₂]⁺ (1) was prepared in situ by dissolving the above reactant complex in the aqueous solution[25].
thermostated at 50°C for 48 hours and used for ESI mass spectra (Figure 3) of the resulting solution. It is clear from this spectrum that the precursor species in the mixture solution and this is tentatively attributed to [Ru + 3 dmso + 2 N$_3^-$ + Cl$^-$ + 2Na$^+$].

**Kinetic studies**

Kinetic measurements were carried out on a Shimadzu UV1601PC spectrophotometer attached to a thermoelectric cell temperature controller (model Shimadzu, TCA 240, accuracy ±0.1°C). The conventional mixing technique was followed and pseudo-first order conditions were employed throughout. The progress of the reaction was followed by measuring the increase in absorbance at 257 nm, where the spectral difference between the substrate and the product complex is maximum. The $k_{1\text{obs}}$ and $k_{2\text{obs}}$ values were calculated graphically (Figure 4 and 5) using the method of Weyh and Hamm$^{[29]}$. We did not use Origin or Excel softwares because where the first part is curved and second part is linear then Weyh and Hamm method gives good result. The rate data represented as an average of duplicate runs are reproducible within ±4%.

**RESULTS AND DISCUSSION**

The pKa value$^{[30]}$ of the azide is 4.59 at 25°C. Thus at pH=5.0 the ligand exists mainly as N$_3^-$. The interaction with the HN$_3$ may be neglected in comparison to interaction with N$_3^-$:

\[
\text{HN}_3 \xrightarrow{K_a} \text{N}_3^- + \text{H}^+; \text{pK}_a = 4.59 \text{ at } 25^\circ\text{C} \quad (1)
\]

| Table 1: $10^3 k_{1\text{obs}}$ values for different ligand concentrations at different temperatures |
|---|---|---|---|---|
| [Ligand] (mol dm$^{-3}$) | 35 | 40 | 45 | 50 |
| 1.0 | 0.74 | 1.21 | 1.62 | 1.97 |
| 2.0 | 1.70 | 2.19 | 3.06 | 3.75 |
| 3.0 | 2.36 | 2.95 | 3.77 | 4.47 |
| 4.0 | 2.82 | 3.50 | 4.23 | 5.23 |
| 5.0 | 2.98 | 3.79 | 4.63 | 5.37 |

| Table 2: $10^3 k_{2\text{obs}}$ values for different ligand concentrations at different temperatures |
|---|---|---|---|---|
| [Complex 1] = 1.0×10$^{-4}$ mol dm$^{-3}$, pH = 5.0 |
| [Ligand] (mol dm$^{-3}$) | 35 | 40 | 45 | 50 |
| 1.00 | 1.69 | 2.38 | 3.57 | 6.25 |
| 2.00 | 3.33 | 4.76 | 7.14 | 13.87 |
| 3.00 | 4.55 | 6.56 | 9.09 | 15.29 |
| 4.00 | 5.56 | 7.38 | 10.00 | 16.67 |
| 5.00 | 5.88 | 8.33 | 11.11 | 19.19 |

The ln(A$_{\infty}$-A$_t$) versus time, t plot indicates that the reaction is not a single step process, a two step consecutive process may be assumed, both steps are [ligand] dependent.

The rate constant for such process can be evaluated by assuming the following scheme.

\[
A \xrightarrow{k_1} B \xrightarrow{k_2} C
\]

A is the substrate complex, B is the intermediate with ligand azide and C is the final product complex [Ru(Me$_2$SO)$_3$(Cl)(L)$_2$].

**Calculation of $k_1$ value for A→B step**

The rate constant $k_{1\text{obs}}$ for A→B step can be evaluated by the method of Weyh and Hamm using the usual consecutive rate law:

\[
(A\rightarrow A_1) = a_1 \exp(-k_{1\text{obs}} t) + a_2 \exp(-k_{2\text{obs}} t)
\]

\[
(A\rightarrow A_2) = a_2 \exp(-k_{2\text{obs}} t)
\]

where $a_1$ and $a_2$ are rate constants dependent upon the rate constants and extinction coefficient. Values of $(A\rightarrow A_1) - a_2 \exp(-k_{2\text{obs}} t)$ are obtained from X-Y at different time t (Figure 4). So ln Δ = constant - $k_{1\text{obs}} t$. $k_{1\text{obs}}$ is derived from the slope of the ln Δ versus t (where t is small) (Figure 5). A similar procedure is applied for each ligand concentration in the 1.00×10$^{-3}$ mol dm$^{-3}$ to 5.00×10$^{-3}$ mol dm$^{-3}$ range, at constant [(1)] (1.0×10$^{-4}$ mol dm$^{-3}$).
Figure 2: Job's plot: \([\text{RuCl(Me}_2\text{SO)}(\text{H}_2\text{O})_2]^{2+}\) = 1.0 x 10^{-4} mol dm^{-3}, [azide] = 1.0 x 10^{-4} mol dm^{-3}, pH = 5.0

Figure 3: ESI mass spectrometry of azide substituted complex (complex 2)

Figure 4: A typical plot of ln \((\Delta \xi)\) versus time \(t\). [complex] = 1.0 x 10^{-4} mol dm^{-3}, [azide] = 5.0 x 10^{-3} mol dm^{-3}; pH = 5.0, Temp. = 40°C

Figure 5: A typical plot of ln \(|\Delta|\) versus time \(t\). [complex] = 1.0 x 10^{-4} mol dm^{-3}, [azide] = 5.0 x 10^{-3} mol dm^{-3}; pH = 5.0, Temp. = 40°C

Figure 6: Plot of \(k_{1,\text{obs}}\) versus [azide] at different temperatures. A = 35°C, B = 40°C, C = 45°C, and D = 50°C

Figure 7: Plot of \(1/k_{1,\text{obs}}\) versus \(1/[\text{azide}]\) at different temperatures, A = 35°C, B = 40°C, C = 45°C, and D = 50°C

The rate increases with increase in [ligand] and reaches a limiting value (Figure 6 & 7), which is probable due to the completion of the outer sphere asso-
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Figure 8: Plot of $k_{1\text{obs}}$ versus [azide] at different temperatures. A = 35, B = 40, C = 45, and D = 50°C

Figure 9: Plot of $1/k_{2\text{obs}}$ versus $1/[\text{azide}]$ at different temperatures. A = 35, B = 40, C = 45, and D = 50°C

Figure 10: Eyring plot ($\ln k_1h/k_B T$ versus $1/T$) for the step $A \rightarrow B$

Figure 11: Eyring plot ($\ln k_2h/k_B T$ versus $1/T$) for the step $B \rightarrow C$

TABLE 3: $10^3k_{1\text{obs}}$ and $K_{E1}$ values at different temperatures

<table>
<thead>
<tr>
<th>Temperatures (°C)</th>
<th>$10^3k_1$ (s$^{-1}$)</th>
<th>$K_{E1}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)</th>
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<tr>
<td>35</td>
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TABLE 4: $10^5k_{2\text{obs}}$ and $K_{E2}$ values at different temperatures

<table>
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<th>Temperatures (°C)</th>
<th>$10^5k_2$ (s$^{-1}$)</th>
<th>$K_{E2}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)</th>
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<tr>
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<td>50</td>
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</tbody>
</table>

Based on scheme 2 a rate expression can be derived for $A \rightarrow B$ step

$$\frac{d[B]}{dt} = \frac{k_1K_{E1}[A][\text{ligand}]}{(1 + K_{E1}[\text{ligand}])} \quad (1)$$

$$\frac{d[B]}{dt} = k_{1\text{obs}}[A]_T \quad (2)$$

$T$ stands for total concentration of Ru(II). Thus it can be written,

$$k_{1\text{obs}} = \frac{k_1K_{E1}[\text{ligand}]}{(1 + K_{E1}[\text{ligand}])} \quad (3)$$

association complex formation. Since the metal ion reacts with immediate environment, further change in [ligand] 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, i.e., azide attacks the Ru(II) atom of the substrate complex and forming intermediate. The outer sphere association complex is stabilised through H-bonding between the incoming azide ion and the coordinated water molecule$^{[31,32]}$. 

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An Indian Journal
where \( k_1 \) is the anation rate constant for the formation of intermediate (B) from the substrate complex, cis-[RuCl(Me_2SO)_3(H_2O)_2]^+ (A). \( K_{E1} \) is theoutersphere association equilibrium constant.

The equation can be written as

\[
\frac{1}{k_{1\text{(obs)}}} = \frac{1}{k_1} + \frac{1}{k_1 K_{E1}[\text{ligand}]} \quad (4)
\]

The plot of \( 1/k_{1\text{(obs)}} \) versus \( 1/[\text{ligand}] \) should be linear (Figure 6) with an intercept of \( 1/k_1 \) and slope \( 1/k_1 K_{E1} \).

The \( k_1 \) and \( K_{E1} \) values obtained from the intercept and from slope to intercept ratios are given in TABLE 3.

**Calculation of \( k_2 \) for step B → C step**

The rate constants were calculated from latter linear portions of the graphs and are collected in TABLE 4. This is again dependent on [Ligand] and shows a limiting value at higher concentration of the ligand (Figure 8). A new azide ligand attacks the ruthenium(II) center. The intermediate here also possibly stable through hydrogen bonding between coordinated H_2O and the approaching azide. The \( k_2 \) and \( K_{E2} \) for the B to C step is calculated similar to eq. (4) (Figure 9) and collected in TABLE 4.

**Effect of change in pH on the reaction rate**

The reaction was studied at five different pH values. The \( k_{1\text{(obs)}} \) values are found to increase with increase in pH in the pH range studied. The \( k_{1\text{(obs)}} \) values are collected in TABLE 5. The enhancement in rate may be due to the increase in percentage of more reactive ligand N_3 from HN_3 which is known from its pK_a values] with the increase of pH.

**Effect of temperature on the reaction rate**

Four different temperatures with varied ligand con-
centrations were chosen and the results are listed in TABLE 6. As there is no report in the literature, we could not compare our data with another system. The activation parameters for the step (1) → B and B → (2) are evaluated from the linear Eyring plots (Figure 10 and 11). As this study is first on this system, we could not compare with other reports.

The low ΔH≠ values are in support of the ligand participation in the transition state for both steps. The positive energy required for the bond breaking process is partly compensated for by the negative energy obtained from bond formation in the transition state and, hence, a low value of ΔH≠ is observed. The highly negative ΔS≠ values, on the other hand, suggest a more compact transition state than the starting complexes and this is also in support of the assumption of a ligand participated transition state. ΔH2≠ is higher than ΔH1≠ which is quite expected for the second step which is slower than the first step.

Mechanism and discussion

In the studied reaction condition i.e., at the pH 5.0, azide exists in the deprotonated form. The interaction of azide with the title ruthenium complex proceeds via two distinct consecutive substitution steps of aqua molecules (k₁ ~ 10⁻³ s⁻¹ and k₂ ~ 10⁻⁵ s⁻¹). Each step proceeds via an associative interchange activation. At the outset of each step outer sphere association complex results, which is stabilized through H-bonding and is followed by an interchange from the outer sphere to the inner sphere complex. The outer sphere association equilibrium constants, a measure of the extent of H-bonding for each step at different temperatures are evaluated. From the temperature dependence of the K_E1 and K_E2, the thermodynamic parameters are calculated

ΔH°₁ = 36.1 ± 4.0 kJ mol⁻¹, ΔS°₁ = 87 ± 12 J K⁻¹ mol⁻¹

and

ΔH°₂ = 30.8 ± 4.5 kJ mol⁻¹, ΔS°₂ = 108 ± 14 J K⁻¹ mol⁻¹.

ΔG° values, calculated for both steps at all temperature studied, have a negative magnitude which is once again in favor of the spontaneous formation of an outer sphere association complex. A plausible mechanism is shown in scheme 3.

ACKNOWLEDGEMENT

The authors thankfully acknowledge the assistance received from the University of Burdwan, Burdwan 713104, India. One of the authors (A. Mandal) is indebted to UGC, New Delhi, India for providing a fellowship to him. Authors are also indebted to Dr. P. Chattopadhyay, Reader, Department of Chemistry, The University of Burdwan, for his help to prepare the starting material.

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