Investigation of electron-transfer reaction between alkaline hexacyanoferrate(III) and ranitidine hydrochloride – a histamine H₂ receptor antagonist, in the presence of homogenous ruthenium(III) catalyst

Laxmi N. Jattinagoudar, Sharanappa T. Nandibewoor and Shivamurti A. Chimatadar

P.G. Department of Studies in Chemistry, Karnatak University, Dharwad 580 003, India

(Received 22 February 2015; accepted 29 July 2015)

The ruthenium(III)-catalyzed electron-transfer reaction between hexacyanoferrate(III) and ranitidine hydrochloride is studied in alkaline medium at 25°C and at an ionic strength of 1.10 mol/dm³. The reaction stoichiometry is established and is found to be 1:4, that is, for the oxidation of one mole of ranitidine, four moles of hexacyanoferrate(III) are consumed. The reaction products were characterized by spectral studies such as IR, GC-MS, ¹H-NMR and ¹³C-NMR. The reaction rate shows a less than unit order in substrate and alkali and a first-order dependence in oxidant, [Fe(CN)₆]³⁻ and the catalyst, ruthenium(III) concentrations. The active species of ruthenium(III), [Ru(H₂O)₅OH]²⁺, forms an intermediate complex with the substrate. The attack of complex by hexacyanoferrate(III) in the rate determining step produces a radical cation, which is further oxidized in the subsequent step to form the oxidation product. The effect of the reaction environment on the rate constant upon adding varying concentrations of KNO₃ and t-butanol was studied. The initially added products did not have any significant effect on the reaction rate. A plausible mechanism is proposed based on the experimental results. The effect of varying temperature on the reaction rate was also studied. The activation parameters for the slow step and the thermodynamic quantities for the equilibrium steps were evaluated.

The mechanism of title reaction has been studied and one mole of ranitidine consumes four moles of [Fe(CN)₆]³⁻, as shown in the following equation:

\[
\text{H}_3\text{C}\text{-HN}\text{-CHNO}_2\text{N}\text{-CH}_3 + 4[\text{Fe(CN)}_6]^{3-} + 4\text{OH}^+ \xrightarrow{\text{Ru(III)}} \text{H}_3\text{C}\text{-HN}\text{-CHNO}_2\text{N}\text{-CH}_3 + 4[\text{Fe(CN)}_6]^{4-} + 3\text{H}_2\text{O}
\]

**Keywords:** ranitidine; hexacyanoferrate(III); ruthenium(III); kinetics; oxidation

*Corresponding author. Email: schimatadar@gmail.com

© 2015 Taylor & Francis
1. Introduction

Oxidation capacity depends upon the redox potential of the oxidant, for instance, the pH of the medium is governing the redox potential of $[\text{Fe(CN)}_6]^{3-}/[\text{Fe(CN)}_6]^{4-}$ couple in acid (+ 0.36 V) and basic medium (+ 0.40 V).\[1\] This indicates that hexacyanoferrate(III), $[\text{Fe(CN)}_6]^{3-}$, is a good oxidant in basic medium and it reduces to the stable product, hexacyanoferrate(II). In most of the oxidation reactions, $[\text{Fe(CN)}_6]^{3-}$ is mainly used as hydrogen atom abstractor.[2,3] and/or free radical generator.[4] Due to the unique properties of the cyanide ligand (strong $\sigma$-donor, good $\pi$-acceptor, and weak $\pi$-donor) and very high formation constants for both $[\text{Fe(CN)}_6]^{3-}$ and $[\text{Fe(CN)}_6]^{4-}$, the hexacyanoferrate(III) complex is often used in model mechanistic studies of ligand substitution and electron-transfer processes.[5] Moreover, its reactions with biological compounds are very interesting from a medicinal point of view. Unless a catalyst is employed these reactions are either extremely slow or do not proceed at all.

The ability of H$_2$-antagonists to block histamine-stimulated gastric secretion was of special clinical significance. Two H$_2$-receptor antagonists have been developed and used for the treatment of peptic ulcers. The first of these is metiamide and the other is cimetidine. Ranitidine (RNH) belongs to the pharmacologic and therapeutic classes of histamine H$_2$-receptor antagonist and antiulcer drug. Ranitidine is a newly developed H$_2$-receptor antagonist that lacks the imidazole ring common to histamine and these other two H$_2$-antagonist drugs.[6] The infection of Helicobacter pylori is a key factor in the occurrence and reoccurrence of peptic ulcer. Helicobacter pylori is a gram negative and microaerophilic organism which can wreck the mucosa, disturb the secretion of gastric acid, and induce inflammation.[7] Ranitidine is highly effective in the treatment of duodenal and stomach ulcers and Zollingen-Ellison syndrome. Ranitidine has been shown to be five to eight times more potent as an inhibitor of gastric secretion than other histamine H$_2$ receptor antagonists.[8] It is highly susceptible to oxidation and this property has been used for development of analytical methods for quality control.[9] It undergoes protonation in aqueous solutions with generation of different ionic forms depending on the pH of the solution.[10] Ranitidine undergoes degradation in the presence of oxidation agents [11,12] with production of mainly N- and S-oxides and desmethyl ranitidine.[13] It is believed that under the influence of high temperature and mild oxidative agent, only the S-oxide is generated.[12] Nitro ketene aminal group is optimum for activity. The skeletal formula of ranitidine is

![Skeletal formula of ranitidine](https://example.com/ranitidine.png)

Transition metal ions can function as homogenous catalysts because they can move between different oxidation states. The metal-catalyzed oxidation of organic substrates is a topic of great interest, especially for reactions in which the substrates are not easily oxidized by employing the oxidants. The redox potential of the couple, Ru(IV)/(Ru(III) in acetonitrile medium using saturated calomel electrode [14] is + 1.3 V.[1] Ruthenium(III) catalysis in redox reactions involves different degrees of complexity, due to the formation of different intermediate complexes, free radicals and different oxidation states of ruthenium. Ruthenium was chosen based on its unique characteristics as an extremely active catalyst for the oxidation reactions.
The literature survey reveals that kinetic studies on the oxidation of ranitidine were limited, using diperiodatocuprate(III) (DPC),[15] chloramines-T,[16] and KMnO₄ [17] as oxidants. To have a further insight into it, we have carried out the present work. The uncatalyzed reaction of ranitidine by [Fe(CN)₆]³⁻ in alkaline medium is slow, so ruthenium(III) in catalytic concentration is employed, as it allows the kinetics to be studied over a reasonable time. The understanding of mechanism of redox reaction is important, as it helps in the synthesis of specific reaction products. Hence in the present study, the reaction rates were measured, the empirical power-rate law equation from experimental results over a wide range of conditions is performed, and also the nature of the product resulting from the chemical reaction by employing [Fe(CN)₆]³⁻ is studied.

2. Results

2.1. Stoichiometry and product analysis

Five different sets of reaction mixtures with 1:2, 1:4, 1:3, 1:6, 1:5 of ranitidine : [Fe(CN)₆]³⁻ were allowed to react completely in the presence of 5.0 × 10⁻⁶ mol/dm³ of Ru(III) concentration at 25°C in 0.2 mol/dm³ OH⁻ and at an ionic strength of 1.10 mol/dm³ in a closed vessel for 8 h. The unreacted [Fe(CN)₆]³⁻ was obtained spectrophotometrically at 420 nm. The results confirmed that 1:4 reaction ratio as indicated in the following equation:

\[
\text{O} \quad \text{N-C} \quad \text{CHNO₂} \quad \text{N} \quad \text{CH₃} \\
\text{CHNO₂} \quad \text{O} \quad \text{N-C} \quad \text{CH₃} \\
\text{Ru(III)}
\]

\[
\text{H₃C}^- \quad \text{HN}^- \quad \text{HN}^- \quad \text{CHNO₂} \quad \text{N} \quad \text{CH₃} + 4 \text{[Fe(CN)₆]}^{3⁻} + 4 \text{OH}^-
\]

\[
\text{H₃C}^- \quad \text{HN}^- \quad \text{HN}^- \quad \text{CHNO₂} \quad \text{N} \quad \text{CH₃} \quad \text{O} \quad \text{N-C} \quad \text{CH₃} \quad \text{S} \quad \text{O} \\
\text{C₆} \quad \text{C₅} \quad \text{C₄} \quad \text{C₇} \quad \text{C₈}
\]

After the completion of the reaction, the reaction mixture was acidified using 10% hydrochloric acid in the cold condition then concentrated and extracted with ether. The formation of single oxidation product was confirmed by thin-layer chromatography. The obtained product was characterized by physicochemical spectral studies.

In the FT-IR spectrum (Figure 1) of N-((E)-2-((5-((dimethylamino)methyl)furan-2-yl)methyl)sulfinyl)vinyl)-N-methyl-2-nitroethene-1,1-diamine, the asymmetric and symmetric stretching of nitro group is found to be at 1577 and 1388 cm⁻¹, respectively. A band at 1041 cm⁻¹ is due to the stretching of S=O group. A band at 1617 cm⁻¹ is observed due to C=C stretching. Asymmetric and symmetric stretches of C–O–C gave bands at 1245 and 1015 cm⁻¹, respectively. A broad band for N–H and aliphatic C–H stretching was observed in the region 3219–2780 cm⁻¹.

The GC-MS spectrum (Figure 2) showed a molecular ion peak at 328 amu and a base peak at 44 amu, which is consistent with the product. The reduced product, [Fe(CN)₆]⁴⁻ is determined by titration in 1.0 mol/dm³ H₂SO₄ using N-phenylantranilic acid.[18]

The product was also confirmed by ¹H NMR and ¹³C NMR spectra. ¹H NMR spectrum was recorded on a BRUKER 400 MHz spectrometer using DMSO-d₆ as solvent and tetramethylsilane as internal reference. The methylene protons (C₆) adjacent to sulfoxide appeared as a doublet at 5.07 ppm. The vinylic protons of C₇ and C₈ resonated as doublets at 6.46 and 8.45 ppm, respectively (J = 14.8 Hz). The protons of C₅ and C₄ appeared as doublets at 6.28 and
6.27 ppm, respectively. The methyl groups of tertiary amine appeared at 2.31 ppm and that of C_{10} appeared at 6.09 ppm. The $^1H$ NMR spectrum is included as supporting information (SI figure 1).

In $^{13}$C NMR spectrum, the C_{8} and C_{7} carbon atoms resonated at 133 and 124 ppm, respectively. The C_{6} carbon appeared at 36 ppm. All the other $^{13}$C nuclei resonated at their expected regions. The $^{13}$C NMR spectrum is included as supporting information (SI figure 2).

### 2.2. Reaction orders

The reaction orders with respect to oxidant, substrate, alkali and catalyst were determined from the slopes of log $k_{obs}$ versus log (concentration) plots by varying one of these reactants at a time and keeping the concentrations of other reactants and conditions constant.
Table 1. Effect of variations of $[\text{Fe(CN)}_6]^{3-}$, $[\text{RNH}]$, $[\text{OH}^-]$ and $[\text{Ru(III)}]$ on the ruthenium(III)-catalyzed oxidation of ranitidine by $[\text{Fe(CN)}_6]^{3-}$ at 25°C and $I = 1.10 \text{ mol/dm}^3$.

| $[\text{HCF(III)}] \times 10^4$ (mol/dm$^3)$ | $[\text{RNH}] \times 10^3$ (mol/dm$^3)$ | $[\text{OH}^-]$ (mol/dm$^3)$ | $[\text{Ru(III)}] \times 10^6$ (mol/dm$^3)$ | $k_{\text{obs}} \times 10^3$ (s$^{-1}$) | $k_{\text{cal}} \times 10^3$ (s$^{-1}$) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 0.5                             | 5.0             | 0.2             | 5.0             | 2.03            | 2.05            |
| 1.0                             | 5.0             | 0.2             | 5.0             | 2.04            | 2.06            |
| 2.0                             | 5.0             | 0.2             | 5.0             | 2.09            | 2.11            |
| 3.0                             | 5.0             | 0.2             | 5.0             | 2.07            | 2.09            |
| 4.0                             | 5.0             | 0.2             | 5.0             | 2.03            | 2.05            |
| 5.0                             | 5.0             | 0.2             | 5.0             | 2.05            | 2.07            |
| 2.0                             | 0.5             | 0.2             | 5.0             | 0.41            | 0.41            |
| 2.0                             | 1.0             | 0.2             | 5.0             | 0.74            | 0.75            |
| 2.0                             | 2.0             | 0.2             | 5.0             | 1.29            | 1.25            |
| 2.0                             | 3.0             | 0.2             | 5.0             | 1.62            | 1.62            |
| 2.0                             | 4.0             | 0.2             | 5.0             | 1.84            | 1.89            |
| 2.0                             | 5.0             | 0.2             | 5.0             | 2.09            | 2.11            |
| 2.0                             | 5.0             | 0.05            | 5.0             | 1.29            | 1.29            |
| 2.0                             | 5.0             | 0.10            | 5.0             | 1.75            | 1.74            |
| 2.0                             | 5.0             | 0.20            | 5.0             | 2.09            | 2.11            |
| 2.0                             | 5.0             | 0.30            | 5.0             | 2.28            | 2.27            |
| 2.0                             | 5.0             | 0.40            | 5.0             | 2.36            | 2.36            |
| 2.0                             | 5.0             | 0.50            | 5.0             | 2.42            | 2.42            |
| 2.0                             | 5.0             | 0.2             | 1.0             | 0.44            | 0.42            |
| 2.0                             | 5.0             | 0.2             | 3.0             | 1.27            | 1.27            |
| 2.0                             | 5.0             | 0.2             | 5.0             | 2.09            | 2.11            |
| 2.0                             | 5.0             | 0.2             | 7.0             | 2.90            | 2.95            |
| 2.0                             | 5.0             | 0.2             | 9.0             | 3.75            | 3.79            |
| 2.0                             | 5.0             | 0.2             | 10.0            | 4.23            | 4.22            |

2.3. **Influence of varying concentrations of hexacyanoferrate(III)**

The rate constant, $k_{\text{obs}}$ was determined by varying the concentration of HCF(III) in the range $0.50 \times 10^{-4}$–$5.0 \times 10^{-4}$ mol/dm$^3$ as a function of time, while keeping all other reactant concentrations and conditions constant (Table 1). The non-variation of the pseudo-first-order rate constants at varying concentrations of $[\text{Fe(CN)}_6]^{3-}$ indicates that the order in $[\text{Fe(CN)}_6]^{3-}$ concentration is unity (Table 1). Further the linearity of the plot of log (absorbance) versus time also confirms the observed order in $[\text{Fe(CN)}_6]^{3-}$ concentration.

2.4. **Influence of varying concentrations of ranitidine**

The effect of ranitidine on the reaction rate was studied over a wide concentration range of $0.50 \times 10^{-3}$–$5.0 \times 10^{-3}$ mol/dm$^3$ while keeping all the reactant concentrations and conditions constant. It was observed that the rate constant, $k_{\text{obs}}$ increased with the increase in concentration of ranitidine. The slope of the plot of log $k_{\text{obs}}$ versus log $[\text{RNH}]$ shows less than unit order dependence in RNH concentration (0.705).

2.5. **Influence of varying concentrations of alkali**

The effect of alkali was studied by varying the concentrations of KOH, over a concentration range of 0.05–0.5 mol/dm$^3$ while keeping all the conditions and reactant concentrations constant. The increase in concentration of alkali increases the rate and the slope of the plot of log $k_{\text{obs}}$ versus log $[\text{OH}^-]$, shows less than unit order dependence in alkali concentration (0.341).
2.6. **Influence of varying concentrations of ruthenium(III)**

The effect of ruthenium(III) was studied by varying its concentration, over a range of $1.0 \times 10^{-6}$–$10.0 \times 10^{-6}$ mol/dm$^3$ while keeping all the conditions and reactant concentrations constant. As the ruthenium(III) concentration increases, the rate of reaction also increases. The order with respect to ruthenium(III) concentration was found to be unity.

2.7. **Influence of ionic strength and dielectric constant on the rate**

The effect of ionic strength was studied by varying KNO$_3$ in the concentration range of 0.1–1.0 mol/dm$^3$ while keeping all the conditions and reactant concentrations constant. The rate was found to decrease with the increase in the concentration of KNO$_3$. The plot of log $k_{obs}$ versus $I^{1/2}$ was linear with negative slope (Figure 3). The effect of dielectric constant was studied by varying the percentage of $t$-butanol-water (v/v) content in the reaction mixture with all the conditions and reactant concentrations being constant. It was found that there was no effect on the rate.

2.8. **Influence of added product**

The effect of initially added product, [Fe(CN)$_6$]$^{4-}$ was studied in the concentration range of $1.0 \times 10^{-4}$–$5.0 \times 10^{-4}$ mol/dm$^3$ while keeping all the conditions and reactant concentrations constant. It was found that the added product did not alter the rate of the reaction, thus having no significant effect.

2.9. **Polymerization study**

To test the intervention of free radicals, the reaction mixture was mixed with 2 cm$^3$ of acrylonitrile monomer and was kept at room temperature for 2 h under inert atmosphere. And upon dilution with methanol, a white precipitate of polymer was formed confirming the intervention of free radicals in the reaction. The blank experiments of either hexacyanoferrate(III) or ranitidine or ruthenium alone with acrylonitrile did not induce polymerization under the same condition as those induced with reaction mixtures. Initially added acrylonitrile decreases the rate which further supports the intervention of free radicals.
Influence of temperature

The reaction was studied in the temperature range of 15–45°C. The rate constants, $k$, of the slow step, at different temperatures were obtained from the intercept of the plot of $[\text{Ru(III)}]/k_{\text{obs}}$ versus $1/[\text{RNH}]$ (Figure 4). The values of the rate constants, $k$, increased with increasing temperature. The energy of activation, $E_a$ was evaluated from the slope of Arrhenius plot of $\log k$ versus $1/T$ (Figure 5) (Table 2). The other activation parameters, namely enthalpy of activation $\Delta H^\neq$, the entropy of activation $\Delta S^\neq$, and the free energy of activation $\Delta G^\neq$ were obtained by using the Eyring equation. The values of the equilibrium constants for the first equilibrium step, $K_1$ and second equilibrium step, $K_2$ of Scheme 1 are obtained from the slope and intercept of the plot of $[\text{Ru(III)}]/k_{\text{obs}}$ versus $1/[\text{OH}^-]$ (Figure 4). The van’t Hoff plots (Figure 6), $\log K_1$ versus $1/T$ and $\log K_2$ versus $1/T$ for first and second equilibrium steps were drawn and the corresponding values of enthalpy of reaction ($\Delta H$), entropy of reaction ($\Delta S$), and free energy of reaction ($\Delta G$) were calculated and are given in Table 2.

3. Discussion

In the present work, in the absence of ruthenium(III) the oxidation of ranitidine by $[\text{Fe(CN)}_6]^{3-}$ is not facile, while the reaction is smooth with a measurable speed in aqueous alkaline media in
Table 2. Activation parameters and thermodynamic quantities for the ruthenium(III)-catalyzed oxidation of RNH by HCF(III) in alkaline medium.

| Effect of temperature and activation parameters with respect to slow step of Scheme 1 | Temperature (K) | $k \times 10^{-2}$ (dm$^3$/mol/s) | Parameters | Values |
|---------------------------------|----------------|-------------------------------|------------|--------|
|                                  | 288            | 5.60                          | $E_a$ (kJ/mol) | 22 ± 1 |
|                                  | 298            | 7.76                          | $\Delta H^\circ$ (kJ/mol) | 20 ± 1 |
|                                  | 308            | 9.88                          | $\Delta S^\circ$ (J/K/mol) | −124 ± 3 |
|                                  | 318            | 13.60                         | $\Delta G^\circ$ (kJ/mol) | 57 ± 2 |
|                                  |                |                               | $\log A$  | 6.7 ± 0.2 |

| Effect of temperature on first and second equilibrium steps of Scheme 1 | Temperature (K) | $K_1$ (dm$^3$/mol) | $K_2 \times 10^{-2}$ (dm$^3$/mol) |
|---------------------------------------------------------------------|----------------|-------------------|----------------------------------|
|                                                                     | 288            | 4.09              | 5.43                             |
|                                                                     | 298            | 5.73              | 4.45                             |
|                                                                     | 308            | 7.59              | 4.38                             |
|                                                                     | 318            | 9.89              | 3.99                             |

| Thermodynamic quantities with respect to $K_1$ and $K_2$ | Values from $K_1$ | Values from $K_2$ |
|---------------------------------------------------------|-------------------|-------------------|
| $\Delta H$ (kJ/mol)                                     | 22.3              | −7.8              |
| $\Delta S$ (J/K/mol)                                    | 89.3              | 25.2              |
| $\Delta G$ (kJ/mol)                                     | −4.7              | −15.5             |

the presence of ruthenium(III). The concentrations of each of the reactants, namely [Fe(CN)$_6$]$^{3-}$, ranitidine, alkali, and ruthenium(III) are varied, while keeping the concentrations of other reactants constant, which exhibited that the reaction is first-order in concentrations of [Fe(CN)$_6$]$^{3-}$ and ruthenium(III) and less than unit order in RNH and alkali concentrations. The stoichiometry of the reaction between [Fe(CN)$_6$]$^{3-}$ and RNH in the alkaline medium, in the presence of micro amounts of ruthenium(III) is found to be 4:1. There is no effect of added products and also the possible effects of varying concentrations of ionic strength and dielectric constant are in accordance with the experimental results and are accommodated in the proposed mechanism as Scheme 1.

Ruthenium(III) is known to form different complexes with OH$^-$ ions, in alkaline medium. [Ru(H$_2$O)$_6$]$^{3+}$ has high crystal field stabilization energy (CFSE) compared to [Ru(H$_2$O)$_5$OH]$^{2+}$. The greater the CFSE of a species, the higher will be the activation energy needed for the reaction.
and hence the hydroxylated species of ruthenium \([\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}\) is presumed to be the reactive species of ruthenium(III). This species is well documented in the literature.\[19\]

Less than unit order and also the increase in the rate with an increase in concentration of OH\(^-\) indicates the presence of the highly stable trivalent hydroxylated species of ruthenium(III), \([\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}\) as reactive species, as shown in the first equilibrium step of Scheme 1 which is also in accordance with the earlier work.\[20\]

Inner-sphere electron-transfer reactions involve the formation of a bridged complex in which the two metal ions are connected by a bridging ligand that helps to promote the electron transfer. Often, but not always, the bridging ligand itself is transferred from one metal center to the other. In the sequence of steps, we note that, in the first equilibrium step, the labile hydroxo species of ruthenium, \([\text{Ru(H}_2\text{O})_6]^{3+}\) undergoes ligand replacement with the negatively charged less labile ligand, OH\(^-\) through a dissociative mechanism. During this process a coordination site on the metal is created and also there is a decrease in the overall charge on \([\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}\) species, which facilitates the attack by RNH molecule. There is less steric hindrance with the attack on \([\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}\) by RNH compared on \([\text{Ru(H}_2\text{O})_6]^{3+}\) which is also in this support. In the second equilibrium step, the formation of a complex(C) between the substrate, RNH, and catalyst, ruthenium(III) is supported by the observed less than unit order in RNH concentration. The substrate is most likely attached through the sulfur atom rather than through tertiary amino groups because the dipositively charged ruthenium ion in \([\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}\) is considered to be nearer to class “b” metal ions. And also the decrease in

---

Figure 6. Van’t Hoff plots for the ruthenium(III)-catalyzed oxidation of ranitidine by hexacyanoferrate(III) in alkaline medium: (a) Plot of log \(K_1\) versus 1/T for the first equilibrium and (b) Plot of log \(K_2\) versus 1/T for the second equilibrium step.
Scheme 1. A mechanism for ruthenium(III)-catalyzed oxidation of ranitidine by $[\text{Fe(CN)}_6]^{3-}$ in alkaline medium.

The overall charge on $[\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}$ due to the formation of hydroxyl species increases its tendency for complexation through sulfur which is also a class “b” base. Such a complexation has also been observed in earlier studies.[21,22] There is less scope for an effective electron transfer from sulfur to ruthenium(III) in the complex and an equilibrium in electron distribution may exist thus decreasing the rate of the reaction. In the slow step, $[\text{Fe(CN)}_6]^{3-}$ attaches
to ruthenium(III) in complex via cyanide bridge to form a radical cation derived from RNH. Such a type of cationic free radical has been reported in the literature.[23] There is a regeneration of the catalyst, ruthenium(III). Ruthenium(III) facilitates the electron transfer from RNH to $[\text{Fe(CN)}_6]^{3−}$, thus catalyzing the oxidation of RNH by $[\text{Fe(CN)}_6]^{3−}$. The radical cation reacts with another mole of $[\text{Fe(CN)}_6]^{3−}$ in the fast step to give ranitidine sulfoxide intermediate and reduced form of oxidant, $[\text{Fe(CN)}_6]^{4−}$. In the further fast step, the formed ranitidine sulfoxide intermediate reacts immediately with two moles of $[\text{Fe(CN)}_6]^{3−}$ and $\text{OH}^−$ ions to form the oxidation product, $\text{N-((E)-2-((5-((\text{dimethylamino)methyl)furan-2-yl)methylsulfinyl)vinyl)}-\text{N-methyl-2-nitroethene-1,1 diamine.}$

The results of the study suggest the formation of a complex between ranitidine and ruthenium(III). The spectral evidence for it was obtained from the UV–VIS spectra of ranitidine and a mixture of ruthenium(III) and ranitidine. A bathochromic shift of 5 nm from 341 to 346 nm is observed. Further kinetic support for the complex formation is obtained from the non-zero intercept of the plot of $[\text{Ru(III)}]/k_{\text{obs}}$ versus $1/[\text{RNH}]$. The probable structure of the complex formed between RNH and ruthenium(III) is as follows:

From Scheme 1, the following rate law (7) can be derived as follows:

$$\text{Rate} = k[\text{Fe(CN)}_6]^{3−} [\text{complex(C)}]$$
$$= kK_2[\text{Fe(CN)}_6]^{3−} [\text{RNH}] [\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}$$
$$= kK_1K_2[\text{Fe(CN)}_6]^{3−} [\text{RNH}] [\text{OH}^−] [\text{Ru(III)}]$$

(1)

The total concentration of RNH is given by, (subscripts t and f stand for total and free, respectively).

$$[\text{RNH}]_t = [\text{RNH}]_f + C$$
$$= [\text{RNH}]_f + K_2 [\text{RNH}]_f [\text{Ru(H}_2\text{O})_5\text{OH}]^{2+}$$
$$= [\text{RNH}]_f + K_1K_2[\text{RNH}]_f [\text{OH}^−]_f [\text{Ru(III)}]_f$$
$$= [\text{RNH}]_f [1 + K_1K_2[\text{OH}^−] [\text{Ru(III)}]]$$

Therefore, the free $[\text{RNH}]_f$ is given by,

$$[\text{RNH}]_f = \frac{[\text{RNH}]_t}{1 + K_1K_2[\text{OH}^−] [\text{Ru(III)}]}$$

(2)
Similarly,

\[
[\text{OH}^-]_t = [\text{OH}^-]_f + [\text{Ru(H}_2\text{O)}_5\text{OH}]^{2+}
\]

\[
= [\text{OH}^-]_f + K_1 [\text{OH}^-]_f [\text{Ru(III)}]_f
\]

\[
= [\text{OH}^-]_f (1 + K_1 [\text{Ru(III)}])
\]

\[
[\text{OH}^-]_t = \frac{[\text{OH}^-]_f}{1 + K_1 [\text{Ru(III)}]}
\] (3)

Similarly,

\[
[\text{Ru(III)}]_t = [\text{Ru(III)}]_f [\text{Ru(H}_2\text{O)}_5\text{OH}]^{2+} + C
\]

\[
= [\text{Ru(III)}]_f K_1 [\text{OH}^-]_f [\text{Ru(III)}]_f + K_2 [\text{RNH}]_f [\text{Ru(H}_2\text{O)}_5\text{OH}]^{2+}
\]

\[
= [\text{Ru(III)}]_f \{1 + K_1 [\text{OH}^-]_f + K_1 K_2 [\text{RNH}]_f [\text{OH}^-]_f\}
\]

Therefore,

\[
[\text{Ru(III)}]_t = \frac{[\text{Ru(III)}]_f}{1 + K_1 [\text{OH}^-]_f + K_1 K_2 [\text{RNH}]_f [\text{OH}^-]_f}
\] (4)

Substituting Equations (2)–(4) in Equation (1) and omitting the subscripts, we get

\[
\text{Rate} \ = \ -\frac{d[\text{Fe(CN)}_6]^{3-}}{dt} = \frac{kK_1 K_2 [\text{Fe(CN)}_6]^{3-} [\text{RNH}] [\text{OH}^-] [\text{Ru(III)}]}{(1 + K_1 K_2 [\text{OH}^-] [\text{Ru(III)}]) (1 + K_1 [\text{Ru(III)}]) (1 + K_1 [\text{OH}^-] + K_1 K_2 [\text{RNH}] [\text{OH}^-])}
\] (5)

or

\[
\text{Rate} \ \frac{[\text{Fe(CN)}_6]^{3-}}{[\text{Fe(CN)}_6]^{3-}} = k_{\text{obs}} = \frac{kK_1 K_2 [\text{RNH}] [\text{OH}^-] [\text{Ru(III)}]}{(1 + K_1 K_2 [\text{OH}^-] [\text{Ru(III)}]) (1 + K_1 [\text{Ru(III)}]) (1 + K_1 [\text{OH}^-] + K_1 K_2 [\text{RNH}] [\text{OH}^-])}
\] (6)

In view of low concentration of ruthenium(III) used, the terms \(1 + K_1 K_2 [\text{OH}^-] [\text{Ru(III)}]\) and \(1 + K_1 [\text{Ru(III)}]\) in the denominator of Equation (6) are approximately equal to unity. Therefore, Equation (6) can be written as the following equation, and we get

\[
\text{Rate} \ \frac{[\text{Fe(CN)}_6]^{3-}}{[\text{Fe(CN)}_6]^{3-}} = k_{\text{obs}} = \frac{kK_1 K_2 [\text{RNH}] [\text{OH}^-] [\text{Ru(III)}]}{1 + K_1 [\text{OH}^-] + K_1 K_2 [\text{RNH}] [\text{OH}^-]}
\] (7)

Furthermore, Equation (7) can be rearranged to the following equation, which is suitable for verification.

\[
\frac{[\text{Ru(III)}]}{k_{\text{obs}}} = \frac{1}{kK_1 K_2 [\text{RNH}] [\text{OH}^-]} + \frac{1}{kK_2 [\text{RNH}]} + \frac{1}{k}
\] (8)

The effect of ionic strength on the rate is understood on the basis of ionic species involved. The rate decreased with increasing ionic strength which implies that there is an involvement of opposite charges in the reaction which lead to a negative salt effect, as seen in Scheme 1. Amis
Journal of Sulfur Chemistry

has earlier described the effect of solvent on the rate of reaction.[24] The negligible effect of
dielectric constant on the rate of reaction indicates the involvement of a neutral species, as seen
in Scheme 1.

The positive values of $\Delta G^\ne$ and $\Delta H^\ne$ indicate that the transition state is highly solvated, while
negative value of entropy of activation ($\Delta S^\ne$) suggests the formation of an activated complex
with a reduction in the degree of freedom of molecules. The values of $\Delta H^\ne$ and $\Delta S^\ne$ were
both favorable for electron-transfer processes. The observed modest enthalpy of activation and
higher rate constant of the slow step indicate that the oxidation presumably occurs via an inner-
sphere mechanism. This conclusion is supported by earlier observations.[25] In Scheme 1, one
equivalent oxidant interacts with four equivalent substrate in accordance with the generally well-
accepted principle of non-complementary oxidations taking place in sequences of one-electron
steps. The possibility of electron transfer in non-complementary reaction is dependent on the
nature of both the oxidant and substrate.

The values of $\Delta H$, $\Delta S$, and $\Delta G$ were calculated for the first and second equilibrium steps
of the reaction and are given in Table 2. A comparison of enthalpy of reaction ($\Delta H$) of the first
equilibrium step with $\Delta H^\ne$ of the slow step indicates that the reaction before the rate determining
step is fairly slow and involves a high activation energy.[26]

4. Conclusions
The order in $[\text{Fe(CN)}_6]^{3-}$ and ruthenium(III) concentrations is unity, whereas the order in ran-
tidine and alkali concentrations is less than unity. The stoichiometry is found to be 1:4 in
reductant to oxidant. The reactive species of catalyst is $[\text{Ru(H}_2\text{O)}_5\text{OH}]^{2+}$, which is formed from
the $[\text{Ru(H}_2\text{O})_6]^{3+}$ through ligand replacement with OH$^-$ ion. A micro amount of ruthenium(III)
is sufficient to catalyze the reaction between $[\text{Fe(CN)}_6]^{3-}$ and ranitidine in alkaline medium.
The results obtained for the present study are essentially different from the earlier reports, as
ranitidine, has led to a different oxidation product. There is intervention of free radicals in the
reaction. The reaction proceeds through inner-sphere mechanism and also it is in accordance with
the non-complementary reaction. The mechanism is consistent with the experimental results. The
rate constant and activation parameters for the slow step are evaluated. Similarly, the equilibrium
constants and thermodynamic quantities for the equilibrium steps are also evaluated.

5. Experimental design

5.1. Materials and chemicals
All the chemicals were of analytical grade purity and were used as received. The stock solution of
the oxidant, hexacyanoferrate(III) was prepared by dissolving potassium hexacyanoferrate(III)
(SISCO-CHEM) in double-distilled water and the concentration was ascertained by iodometric
titration.[18] The stock solution (0.01 mol/dm$^3$) of Ranitidine hydrochloride (Sigma-Aldrich)
was prepared by accurately weighing required amount and dissolving it in double-distilled water.
The ruthenium(III) solution was prepared by dissolving a known amount of RuCl$_3$ (s. d. fine-
chem) in 0.20 mol/dm$^3$ of HCl. Mercury was added to the ruthenium(III) solution to reduce
any ruthenium(IV) formed during the preparation of the ruthenium(III) stock solution. The
ruthenium(III) solution was kept aside for 24 h and its concentration was assayed by EDTA
titration.[27] Potassium hydroxide (BDH) was used as the source of OH$^-$ to vary the alkali con-
centration in the reaction medium. Potassium nitrate (Nice) was used to provide the required
ionic strength. Hexacyanoferrate(II) solution was obtained by dissolving potassium hexacyano-
ferrate(II) (s. d. fine-chem) in water and standardizing with cerium(IV) solution. All the apparatus
were of pyrex glass and there was no reaction of alkali with the glass under the conditions
maintained.

5.2. **Instruments used**

Varian Cary 50 Bio UV–VIS spectrophotometer (Varian, Victoria, Australia) attached to a Peltier
accessory (temperature controlled) was used for recording kinetic and spectral data. For product
analysis, a Shimadzu 17A gas chromatograph with a Shimadzu QP-5050A mass spectrometer
using the electron impact (EI) ionization technique and a Nicolet 5700 FT-IR spectrometer
(Thermo Electron Corporation, Madison, WI) were used. A 400 MHz (BRUKER, Switzerland)
spectrometer was used for recording $^1$H NMR and $^{13}$C NMR spectra. Elico model LI120 pH
meter was used for pH measurement.

5.3. **Kinetic measurements**

All kinetic measurements using UV–VIS spectrophotometer were followed under pseudo-first-
order condition, where $[\text{RNH}] \ (5.0 \times 10^{-3}) > [\text{HCF(III)}] \ (2.0 \times 10^{-4})$ at 25°C ± 0.1°C and at
a constant ionic strength of 1.10 mol/dm$^3$ in the presence of micro amounts of ruthenium(III)
catalyst. The prepared stock solution of $[\text{Fe(CN)}_6]^{3-}$ was scanned in the range of 200–800
nm (blue-violet range) to determine the wavelength of maximum absorption and was found
to be 420 nm. There is no interference from other species present in the reaction mixture at
this wavelength. Thus, the kinetic studies were carried out at 420 nm. The extinction coeffi-
cient was determined at 420 nm for different concentrations of $[\text{Fe(CN)}_6]^{3-}$ and it is found to
be, $\varepsilon = 988 \pm 10$ dm$^3$/mol/cm. The total volume of the reaction mixture was always kept at
10 cm$^3$ and these volumes of solutions are allowed to attain thermal equilibrium by suspend-
ing them in a temperature-controlled water bath. Meanwhile, the instrument was set to auto
zero using water as solvent. The reaction was initiated by immediately adding the requisite

![Figure 7. Spectral changes during the ruthenium(III)-catalyzed oxidation of ranitidine by hexacyanoferrate(III) in alkali-line medium at 25°C; $[\text{Fe(CN)}_6]^{3-} = 2 \times 10^{-4}$, $[\text{RNH}] = 5 \times 10^{-3}$, $[\text{OH}^-] = 0.2$, $[\text{Ru(III)}] = 5 \times 10^{-6}$, $I = 1.10$
$\text{mol/dm}^3$ with scanning time interval of 1.0 min per scan.](image-url)
amount of pre-equilibrated solution of $[\text{Fe(CN)}_6]^{3-}$ to an equilibrated mixture of ranitidine, alkali, KNO$_3$ and ruthenium(III). The zero time of the reaction was noted when half of the $[\text{Fe(CN)}_6]^{3-}$ solution was added. The progress of the reaction was followed by measuring the absorbance of $[\text{Fe(CN)}_6]^{3-}$ solution at 420 nm in the quartz cuvettes of 1 cm length placed in the thermostated compartment of a Varian Cary 50 Bio UV–VIS spectrophotometer. The kinetics was followed for more than 75% completion of the reaction and good first-order kinetics was observed. The pseudo-first-order rate constant, $k_{obs}$ was obtained from the slope of the linear plot of log (absorbance) versus time. The first-order rate constants were reproducible within ±5% and the average of at least three independent kinetic runs. The spectral changes during the oxidation reaction for the standard condition at 25°C with scanning interval of 1 minute per scan is shown in Figure 7. It is evident that $[\text{Fe(CN)}_6]^{3-}$ decreases at 420 nm.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Supplemental data**

Supplemental data for this article can be accessed at 10.1080/17415993.2015.1078804.

**ORCID**

Shivamurti A. Chimatadar [http://orcid.org/0000-0001-5382-7317](http://orcid.org/0000-0001-5382-7317)

**References**

[1] Sharanabasamma K, Angadi MA, Tuwar SM. Kinetics and mechanism of ruthenium(III) catalyzed oxidation of L-proline by hexacyanoferrate(III) in aqueous alkali. TOCATJ. 2011;4:1–8.
[2] Martinez M, Pitarque M, Eldik RV. Outer-sphere redox reactions of $[\text{Co}^{III}(\text{NH}_3)_5(\text{H},\text{P},\text{O}_3)]^{(m-3)-}$ complexes. A temperature- and pressure-dependence kinetic study on the influence of the phosphorous oxoanions. J Chem Soc Dalton Trans. 1996:2665–2671.
[3] Kelson EP, Phengsy PP. Kinetic study of 2- propanol and benzyl alcohol oxidation by alkaline hexacyanoferrate (III) catalyzed by a terpyridyl ruthenium complex. Int J Chem Kinet. 2000;32:760–770.
[4] Sveha G. Vogel’s qualitative inorganic analysis. England: Longman; 1996.
[5] Ilkowska E, Eldik RV, Stochel G. Kinetics and mechanism of the reduction of hexacyanoferrate(III) by myoglobin in aqueous solution. J Biol Inorg Chem. 1997;2:603–610.
[6] Lebert PA, MacLeod SM, Mahon WA, Soldin SJ, Vandenbergh HM. Ranitidine kinetics and dynamics. I. Oral dose studies. Clin Pharmacol Ther. 1981;30:539–544.
[7] Li W, Tan F, Zhao K. Simultaneous determination of amoxicillin and ranitidine in rat plasma by high-performance liquid chromatography. J Pharm Biomed Anal. 2006;41:594–598.
[8] Campanero MA, Lopez-Ocariz A, Garcia-Quetglas E, Sadaba B, de la Maza A. Rapid determination of ranitidine in human plasma by high performance liquid chromatography. Chromatographia. 1998;47:391–395.
[9] Marcelino-Junior LH, Figueiredo-Filho LCS, Vieira HI, Fatibello-Filho O. Flow injection spectrophotometric system for ranitidine determination in pharmaceuticals using Cerium(IV) and Ferroin. Curr Anal Chem. 2009;5:213–218.
[10] Dumanovi D, Jurani I, Dovelovi D, Vasic VM, Jovanovic J. Protolytic constants of nizatidine, ranitidine and N,N′-dimethyl-2-nitro-1,1-ethenediamine; spectrophotometric and theoretical investigation. J Pharm Biomed Anal. 1997;15:1667–1678.
[11] Darwish IA, Hussein SA, Mahmoud AM, Hassan AI. Spectrophotometric determination of H$_2$-receptor antagonists via their oxidation with cerium(IV). Spectrochim. Acta, Part A. 2008;69:33–40.
[12] Amin AS, Ahmed IS, Dessouki HA, Gouda EA. Utility of oxidation–reduction reaction for the determination of ranitidine hydrochloride in pure form, in dosage forms and in the presence of its oxidative degradates. Spectrochim Acta, Part A. 2003;59:695–703.
[13] Chung WG, Park CS, Roh HK, Lee WK, Cha YN. Oxidation of ranitidine by isozymes of flavin-containing monooxygenase and cytochrome P450. Jpn J Pharmacol. 2000;84:213–220.
[14] Bhattacharyya D, Chakraborty S, Munshi P, Lahiri OK. Ruthenium(II/III) bipyridine complexes incorporating thiol-based imine functions synthesis, spectrosopic and redox properties. Polyhedron. 1999;18:2951–2959.
[15] Veeresh TM, Patil RK, Nandibewoor ST. Thermodynamic quantities for the oxidation of ranitidine by diperiodatocuprate(III) in aqueous alkaline medium. Transit Met Chem. 2008;33:981–988.

[16] Sukhdev A, Shubha JP, Puttaswamy. Kinetic and mechanistic investigation of S-oxidation of ranitidine hydrochloride with chloramine-T in acid and alkaline media. Prog React Kinet Mech. 2012;37:42–58.

[17] Gour S, Dobhal B, Farooqui M. A kinetics and mechanistic study of permanganic oxidation of ranitidine in acidic medium. Elixir Appl Chem. 2011;40:5568–5572.

[18] Jeffery GH, Bassett J, Mendham RC, Denney C. Vogel’s textbook of quantitative chemical analysis. Essex: ELBS Longman; 1996.

[19] Nandibewoor ST, Hiremath GA, Timmanagoudar PL. Ruthenium(III)-catalysed oxidation of thiocyanate by periodate in aqueous alkaline medium; autocatalysis in catalysis. Transit Met Chem. 2000;25:394–399.

[20] Balado AM, Galan BC, Martin FJP. Kinetic study of isobutyl alcohol oxidation reaction by alkaline hexacyanoferrate(III) using ruthenium(III) chloride as catalyst An Quim. 1992;88:170–174.

[21] Goel A, Sharma S. Mechanistic study of the oxidation of l-phenylalanine by hexacyanoferrate(III) catalyzed by iridium(III) in aqueous alkaline medium. Transit Met Chem. 2010;35:549–554.

[22] Rao BD, Partha Sarathi TVN, Annapurna N, Vani P. Mechanistic studies of ruthenium(III)-catalyzed oxidation of DL-methionine by hexacyanoferrate(III) in an alkaline medium. J Sulf Chem. 2011;32:263–272.

[23] Seetharamappa J, Motohashi N, Kovala-Demertz D. Application of phenothiazine derivatives and other compounds for the determination of metals in various samples. Curr Drug Targets. 2006;7:1107–1121.

[24] Amis ES. Solvent effects on reaction rates and mechanisms. New York: Academic Press; 1966.

[25] Hosahalli RV, Savanur AP, Nandibewoor ST, Chimatadar SA. Kinetics and mechanism of uncatalysed and ruthenium(III)-catalysed oxidation of D-panthenol by alkaline permanganate. Transit Met Chem. 2010;35:237–246.

[26] Rangappa KS, Raghavendra MP, Mahadevappa DS, Channegowda D. Sodium N-chlorobenzenesulfonamide as a selective oxidant for hexosamines in alkaline medium: a kinetic and mechanistic study. J Org Chem. 1998;63:531–536.

[27] Byadagi KS, Naik DV, Savanur AP, Nandibewoor ST, Chimatadar SA. Ruthenium(III) mediated oxidation of thiamine hydrochloride by cerium(IV) in perchloric acid medium: a kinetic and mechanistic approach. Reac Kinet Mech Cat. 2010;99:53–61.