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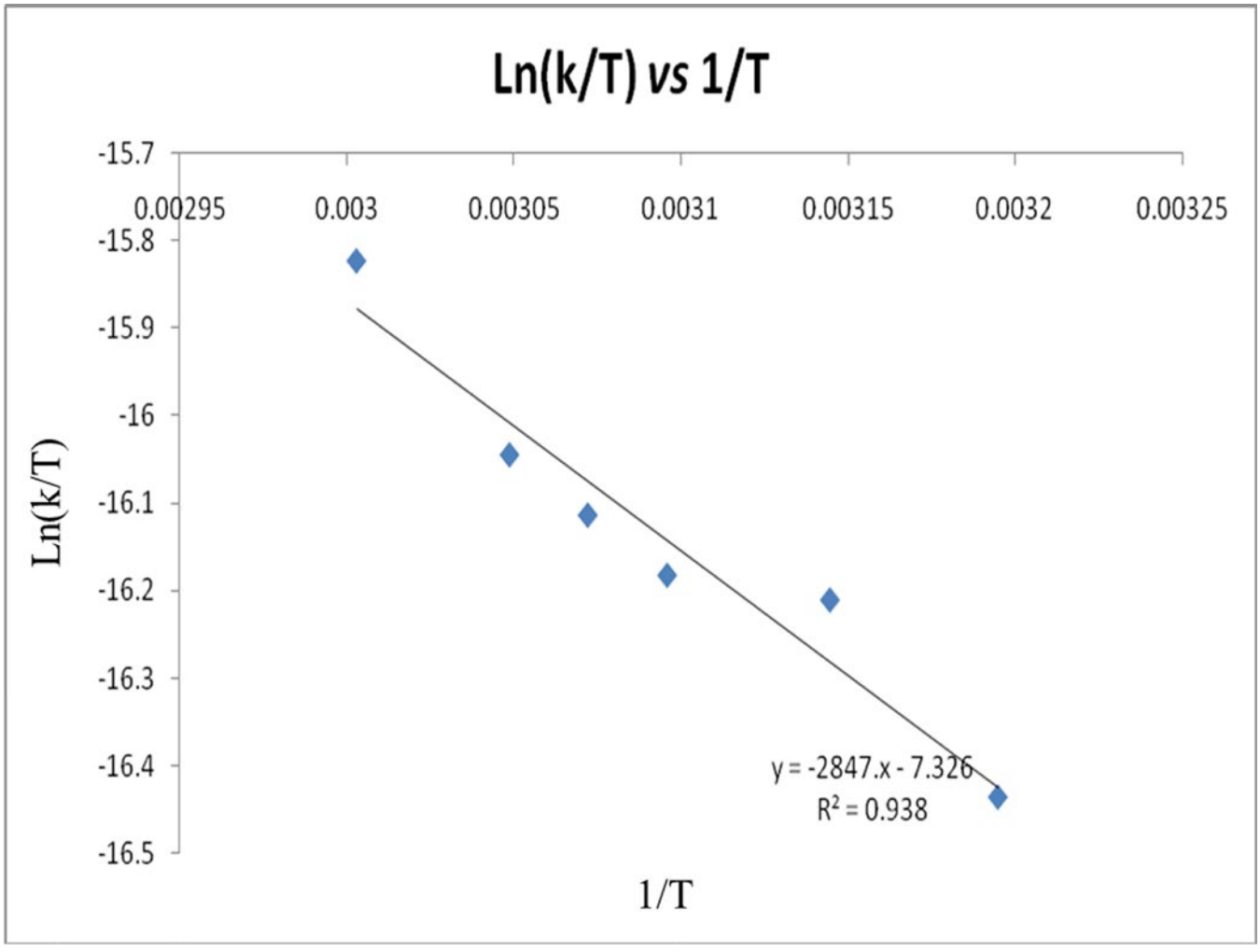

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Oxidation of glycylglycine by ferricyanide in acid medium: Kinetics and mechanism

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Abstract: The oxidative degradation of glycylglycine (GlyGly) to formic acid, ammonium ion, and carbon dioxide occurs when it reacts with ferricyanide in acid medium, which has been studied spectrophotometrically at 303 nm at constant temperature. Kinetic runs have been performed under a pseudo-first-order condition of $[GlyGly]_0$ >> $[ferricyanide]_0$. The experimental rate law obtained for the redox reaction is: rate = k^{I} $[Fe(CN)_6^{3-}]$ $[GlyGly]^x$ $[H^+]^y[Pd(II)]^0$, where x and y are fractional orders. Effects of ionic strength and dielectric constant are also investigated. Activation parameters have been evaluated using Arrhenius and Eyring plots. A probable mechanism has been proposed and the derived rate law is consistent with the kinetic data.

Subjects: Analytical Chemistry; Inorganic Chemistry; Natural Products; Physical Chemistry

Keywords: glycylglycine; ferricyanide; acid; oxidation; mechanism; rate

1. Introduction

Peptides and proteins are the most important chemical compounds found in the living organism. They perform impeccable roles as biomaterials in many biological, pharmaceutical, analytical, and

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ABOUT THE AUTHOR

Kishore Cholkar completed his BPharm in Pharmaceutical Sciences from Kakatiya University, Warangal, India and MS in Chemistry from Western Illinois University, USA. Dr. Cholkar received his Ph.D from University of Missouri Kansas City, USA. After completion of BPharm, he worked as an assistant quality controller in Novasyn Organic Pvt. Ltd., Hyderabad, India. Cholkar is a formulation scientist at Ricon Pharmaceuticals, New Jersey, USA. He was awarded several travel awards by School of Graduate Studies (SGS) and Interdisciplinary Doctoral Student Council (IDSC). Cholkar is an active member of American Association of Pharmaceutical Scientists (AAPS), Association of Research in Vision and Ophthalmology (ARVO), Pharmaceutical Sciences Graduate Student Association (PSGSA) and Ophthalmology group (OMICS). He received the First Best Poster Award from Ophthalmology group in 2014 at Ophthalmology-2014 Conference, Baltimore, USA. Cholkar authored/co-authored 20 peer-reviewed publications, six book chapters and presented his work (48 poster and one podium presentations) at several regional, national, and international conferences.

PUBLIC INTEREST STATEMENT

This paper reports the kinetic study of oxidative degradation of glycylglycine (GlyGly) to formic acid, ammonium ion, and carbon dioxide by the ferricyanide complex. Peptides and proteins are the most important chemical compounds found in the living organisms. GlyGly is used in preparing buffers and as a building block in the synthesis of more complex, biologically significant peptides and proteins. In view of the biochemical importance of GlyGly, we believe that the kinetic studies may throw some light on the oxidative mechanism of peptides in acid solutions. In the present study, the oxidative behavior of the title dipeptide with the ferricyanide oxidant is investigated to explore the redox chemistry and to determine the activation parameters, which along with orders of the reactants are required for understanding the reaction mechanism. These kinetic studies are sometimes helpful in the optimization of reaction parameters of organic syntheses, analytical conditions, and industrial production.

synthetic applications (*Biological buffers*, 2010; Iyengar & Mahadevappa, 1992). Glycylglycine (GlyGly) is the simplest and smallest of all dipeptides (DPs). Due to its low toxicity, GlyGly is useful as a buffer for biological systems with effective ranges of pH 2.5–3.8 and 7.5–8.9 (*Biological buffers,* 2010); however, it is only moderately stable for storage once dissolved (Smith & Smith, 1949). It is used in the synthesis of more complex peptides (Susan, 1989). Glycylglycine has also been found to be helpful in solubilizing recombinant proteins in *E. coli* (Ghosh et al., 2004). Glycylglycine is well known as a gamma glutamyl acceptor. It is also used as a metal-chelating agent. Extensive work on the kinetics of dipeptides with various metal ions and oxidants has been reported. It is oxidized by various oxidants such as manganese(III), chloramines-T, bromamine-T, and bromamine-B. Oxidative behavior of bromamine-B towards GlyGly was studied by Mahadevappa and co-workers (Iyengar & Mahadevappa, 1992). Rangappa et al. have reported the kinetics of three different DPs, Val–Gly, Ala–Pro, and Val-Pro, with N-bromosuccinimide (NBS) (Gowda, Kumara, Gowda, & Rangappa, 2006). The rate was found be first order each in [NBS], [amino acid or AA], and [DP]. No effect of $[H^+]$, reduction product [succinimide], and ionic strength was observed. They also studied the kinetics of Phe-Pro, Ile-Pro, and Leu-Pro with anodically generated manganese(III) (Kumara, Gowda, & Rangappa, 2002). The rate was first order with respect to both [Mn(III)] and [DP]. In a related work by them, the oxidation kinetics of dipeptides such as ValGly, AlaGly, and GlyGly by Mn(III) have been studied in the presence of sulfate ions in acid medium at 299 K. The dependence of the rate on both [Mn(III)] and [DP] was observed. Puttaswamy and co-workers have reported the kinetics N-haloamine oxidation of GlyGly using different platinum group metal ions as catalyst (Bera & De, 2004; Jagadeesh & Puttaswamya, 2008; Puttaswamy, Vaz, & Rajenahally Vgowda, 2008). The kinetics of the interaction of GlyGly with cis-$[Pt(en)(H_2O)_2](ClO_4)_2$ and cis-$[Pt(dmen)(H_2O)_2](ClO_4)_2$ have been studied spectrophotometrically as a function of [substrate complex], [GlyGly], and temperature at a particular pH (4.0), where the substrate complex exists predominantly as the diaqua species and GlyGly as the zwitterion (Bera & De, 2004; Jagadeesh & Puttaswamya, 2008). The reaction has been found to proceed through two consecutive steps. The first step involves the ligand-assisted anation, while the second step involves chelation where the second aqua ligand is displaced. The low enthalpy of activation and negative values of entropy of activation indicate an associative mode of activation for both steps. The kinetics of oxidation of GlyGly and other dipeptides (DPs) by chloramine-T (CAT) in NaOH medium was studied at 308 K (Cholkar, Kouassi, Ananda, Veeraiah, & Made Gowda, 2011). The reactions follow identical kinetics for all the dipeptides, showing first-order dependence each on [CAT] and [DP] and a fractional order on $[OH^-]$. The addition of the reduction product *p*-toluenesulfonamide or halide ions (Cl^- or Br^-) has no significant effect on the rate of reaction (Cholkar et al., 2011). The literature survey showed that there was no study reported on the kinetics of oxidation of GlyGly by any Fe(III) complex. Hence, we are herewith reporting the oxidative behavior of this dipeptide using ferricyanide as the oxidant in perchloric acid solutions.

2. Experimental

2.1. Materials

The dipeptide, glycylglycine (GlyGly), purchased from Eastman Kodak Co, USA was used as supplied (99.9% purity) to prepare stock aqueous solutions. Aqueous solutions of potassium ferricyanide (Fisher Scientific Co, USA) were prepared and standardized iodometrically. A stock solution of $PdCl_2$ was prepared in 0.100 M HCl. A concentrated solution of $NaClO_4$ (4.00 M) was prepared. All other chemicals used were of analytical grade. Triple-distilled water was used for preparing all aqueous solutions.

2.2. Instrumentation

Features of the UV/visible high-performance spectrophotometer (Shimadzu model 1601) used in the studies include: photometric, kinetic, spectrum scanning, multi-wavelength, and quantization capabilities. The spectrophotometer fitted with a thermostat and connected to a computer with appropriate kinetics software was used. The reaction was followed, under pseudo-first-order conditions, at 323 K by monitoring the ferricyanide absorbance with time at its λ_{max} of 303 nm.

2.3. Kinetic procedure

Kinetic runs for the reaction mixtures were conducted following the procedure reported earlier from our laboratory (Cholkar et al., 2011; Iyengar & Mahadevappa, 1992). In brief, kinetic reactions were conducted under pseudo-first-order conditions of higher concentrations of GlyGly maintained over that of ferricyanide. For each kinetic run, requisite amounts of solutions of GlyGly, $HClO_4$ (to maintain a constant acid strength), and $NaClO_4$ (to maintain a constant ionic strength) were mixed in a stoppered Pyrex glass tube. Sufficient water was added to maintain a constant total volume. The solution was thermostated for 600–900 s in a water bath set at a given temperature (323 K). The reaction was initiated by adding a measured volume of 0.100 M ferricyanide solution, which was also thermally equilibrated. Each aliquot of the reaction mixture was transferred into a quartz cuvette of 0.01 meter path length and placed in the temperature controlling unit of the spectrophotometer. The course of the reaction was monitored by measuring the solution absorbance at 303 nm at regular time intervals for three hours. First-order plots of ln (abs) vs. time were found to be linear (Figure 1). The slope of each plot gave the pseudo-first-order rate constant, k' or k_{obs}. Triplicate kinetic runs were performed for each experiment and the average k' value was calculated. Values of k' were reproducible within ± 3% error.

2.4. Reaction stoichiometry and product analysis

Reaction mixtures consisting of GlyGly, ferricyanide (10 times over GlyGly), and 0.250 M $NaClO_4$, in 0.100 M $HClO_4$ at 313 K were taken in stoppered Erlenmeyer flasks and allowed to stand for varying time periods for up to 172,800 s. A control experiment without GlyGly showed that ferricyanide concentration remained unchanged over the same period of time. Each reaction mixture was iodometrically titrated against a standardized thiosulfate solution. Results demonstrated that eight mols of the oxidant reacted with a mol of GlyGly generating formic acid, ammonium ion, CO_2, and ferrocyanide as end products. These products were identified by their conventional tests (Brown & Okamoto, 1958; Cholkar et al., 2011; Laidler & Eyring, 1939; Strecker, 1850).

2.5. Test for free radicals

Olefin monomer, acrylonitrile, or freshly prepared 10% acrylamide solution, under nitrogen atmosphere, was added to the GlyGly–ferricyanide reaction mixture in 0.1 M $HClO_4$, to initiate polymerization in the presence of free radicals formed *in situ.* Flasks were covered with aluminum foils and placed overnight in dark to prevent photochemical effects, if any. Absence of polymerization (turbidity) indicated that there were no free radicals formed *in situ*. Suitable control experiments in the absence of GlyGly or ferricyanide were also performed under the same experimental conditions.

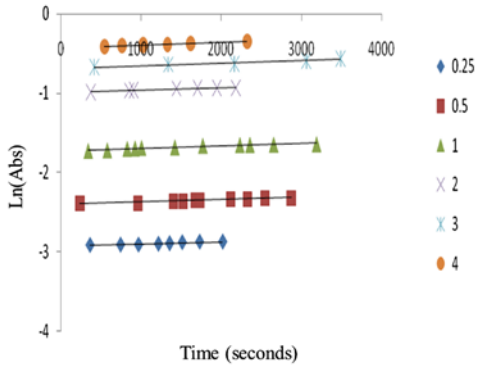

Figure 1. First-order plots for the oxidation of glycylglycine at varying concentrations of ferricyanide at 323 K.

Table 1. Effects of varying concentrations of $Fe(CN)_6^{3-}$, glycylglycine, $HClO_4$, and $NaClO_4$ on the reaction rate at 323 K

$[Fe(CN)_6^{3-}]_0$ (10^{-3} M)	$[Glycylglycine]_0$ (10^{-2} M)	$[HClO_4]$ (10^{-1} M)	$[NaClO_4]$ (M)	k′ (10^{-5} s^{-1})
0.250	2.00	1.00	0.250	2.99
0.500	2.00	1.00	0.250	3.10
1.00	2.00	1.00	0.250	3.05
2.00	2.00	1.00	0.250	3.20
3.00	2.00	1.00	0.250	3.27
4.00	2.00	1.00	0.250	3.28
1.00	1.00	1.00	0.250	1.84
1.00	2.00	1.00	0.250	3.05
1.00	3.00	1.00	0.250	3.10
1.00	4.00	1.00	0.250	3.34
1.00	5.00	1.00	0.250	3.94
1.00	8.00	1.00	0.250	4.89
1.00	2.00	1.00	0.050	3.23
1.00	2.00	1.00	0.100	3.12
1.00	2.00	1.00	0.250	3.05
1.00	2.00	1.00	0.500	3.23
1.00	2.00	1.00	0.750	3.21
1.00	2.00	0.050	0.250	1.43
1.00	2.00	0.100	0.250	3.05 (3.08)[a]
1.00	2.00	0.200	0.250	3.98 (3.09[b]; 3.90[c])
1.00	2.00	0.300	0.250	5.52
1.00	2.00	0.400	0.250	6.04
1.00	2.00	0.500	0.250	6.91

[a][Pd(II)]: 5.00×10^{-5} M; [MeOH].

[b]5%.

[c]25% (v/v).

3. Results and discussion

3.1. Reaction stoichiometry

The stoichiometry of one mol peptide to eight mols ferricyanide can be represented by Equation (1).

$$\underset{(SH^+ \text{or dipeptide})}{CH_2(^+NH_3)CONHCH_2COOH} + 8\underbrace{\left[Fe(CN)_6^{3-}\right]}_{(\text{oxidant})} + 5H_2O \rightarrow 2HCOOH + 8\left[Fe(CN)_6^{4-}\right] + \underset{7H^+ + 2NH_4^+ + 2CO_2}{} \quad (1)$$

Oxidation products, formic acid, ammonium ion, and CO_2, and the reduction product, ferrocyanide, were identified by conventional tests (Brown & Okamoto, 1958; Cholkar et al., 2011; Laidler & Eyring, 1939; Strecker, 1850).

3.2. Kinetics

Kinetic runs for the oxidation of GlyGly by ferricyanide were performed under pseudo-first-order conditions of $[GlyGly]_0$ >> $[ferricyanide]_0$ in $HClO_4$ at known acid concentration, ionic strength, and temperature.

The oxidation was studied at varying initial concentrations of ferricyanide (2.50×10^{-4}–4.00×10^{-3} M) with other conditions kept constant. Plots of ln (abs) vs. time were linear indicating a first-order dependence of the rate on [ferricyanide]. The constancy of the pseudo-first-order rate constants (k′ or k_{obs}) obtained at different initial [ferricyanide], as shown by the same slope for all plots (Figure 1), is a further evidence for the first-order dependence of the reaction rate (Table 1). Kinetic runs were carried out at different initial concentrations of GlyGly ranging from 1.00×10^{-2}–8.00×10^{-2} M, while keeping all other conditions constant (e.g. 0.100 M $HClO_4$, 1.00×10^{-3} M $[K_3Fe(CN)_6]$, 0.25 M $NaClO_4$, and 323 K). The reaction rate was found to increase with increase in $[GlyGly]_o$. A plot of ln k′ vs. ln $[GlyGly]_o$ was linear with a slope 0.438 indicating a fractional-order dependence of the rate on [GlyGly] (Figure 2). Similarly, kinetic runs were performed at varying concentrations of $NaClO_4$ (0.050–0.750 M) by maintaining other conditions constant including 0.100 M $HClO_4$, 1.00×10^{-3} M $K_3Fe(CN)_6$, and 2.00×10^{-2} M GlyGly. Results indicated that there was a small effect on the reaction rate with increased $[NaClO_4]$. Therefore, for further kinetic runs, $[NaClO_4]$ was fixed at 0.25 M.

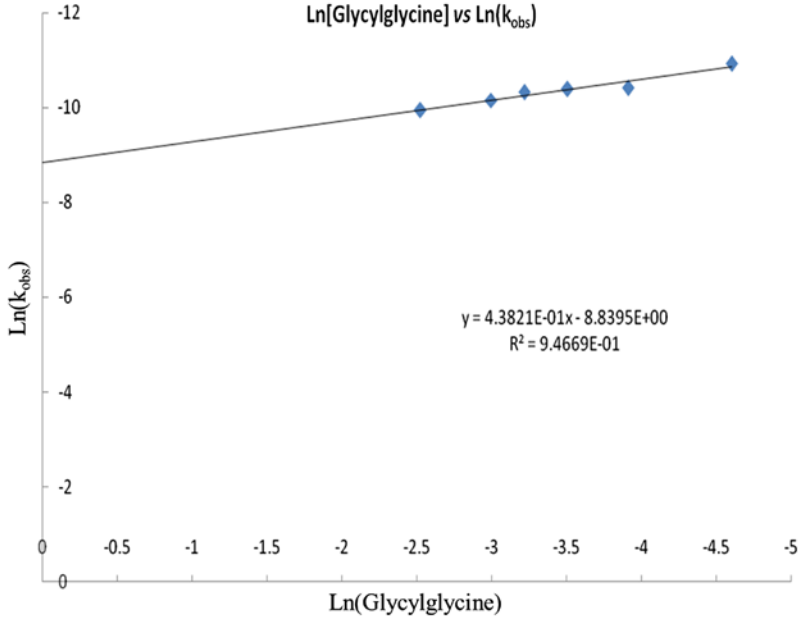

Figure 2. A ln–ln plot for the order of the reaction for glycylglycine.

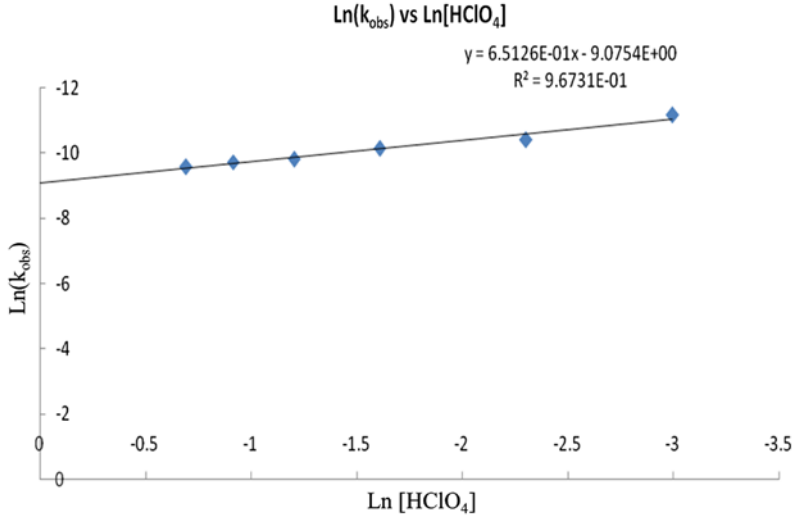

Figure 3. A plot of $ln(k_{obs})$ vs. $ln[HClO_4]$ for the order of acid.

Kinetic runs were carried out with 1.00×10^{-3} M $[K_3Fe(CN)_6]$, 2.00×10^{-2} M GlyGly, and 0.25 M $NaClO_4$ at different concentrations of perchloric acid (0.0500–0.500 M) at 323 K. A linear plot of ln k′ vs. ln $[HClO_4]$ gave a slope of 0.651 suggesting a fractional-order dependence on $[H^+]$ (Figure 3). Kinetic experiments were studied with varying concentrations of palladium(II) chloride used as catalyst. A range of 1.00×10^{-5}–6.00×10^{-5} M Pd(II) was employed for the kinetic runs while keeping all other conditions the same. The results indicated that the reaction rate was not significantly affected by the catalyst (Table 1). The effect of dielectric constant (D) was studied by varying the MeOH content in the reaction mixture (5–25% v/v). A reduction in D of the medium slightly enhanced the reaction rate (Table 1). Furthermore, the effect of temperature on the rate was investigated by determining the rate constants (k′) at different temperatures (313–333 K) (Table 2). Activation parameters, such as energy of activation (Ea), enthalpy of activation ($\Delta H^{\neq}$), entropy of activation ($\Delta S^{\neq}$), and Gibbs free energy of activation ($\Delta G^{\neq}$), were evaluated (Table 2) using the Arrhenius plot of ln k′ vs. 1/T and the Eyring plot of ln (k′/T) vs. 1/T (Figure 4) (Atwood, 1997).

3.3. Mechanism

The dissociation of peptides and amino acids depends on pH of the medium. In strongly basic and acidic solutions, the following equilibria exist for dipeptides such as glycylglycine (Smith & Smith, 1949):

$$\underset{(S',\text{anion})}{H_2NCH_2CONHCH_2COO^-} \overset{H^+}{\underset{OH^-}{\rightleftharpoons}} \underset{(S'',\text{Zwitterion})}{H_3\overset{+}{N}CH_2CONHCH_2COO^-} \overset{H^+}{\underset{OH^-}{\rightleftharpoons}} \underset{(SH^+,\text{cation})}{H_3\overset{+}{N}CH_2CONHCH_2COOH} \quad (2)$$

Table 2. Effect of temperature on the rate and activation parameters*

Temp (K)	k′ (10^{-5} s^{-1})	$\Delta G^{\neq}$ (kJ/mol)	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/Kmol)	E_a (kJ/mol)
313	2.21	66.4	23.6	−137	26.3
318	2.97	67.1			
323	3.05	67.8			
325.5	3.29	68.1			
328	3.55	68.4			
333	4.04	69.1			

Note: Activation parameters for the glycylglycine oxidation by ferricyanide: $[GlyGly]_0 = 2.00 \times 10^{-2}$ M, $[Fe(CN)_6^{3-}]_0 = 1.00 \times 10^{-3}$ M, $[HClO_4] = 1.00 \times 10^{-1}$ M, and $[NaClO_4] = 0.250$ M.

*Based on Arrhenius and Eyring plots (Atwood, 1997).

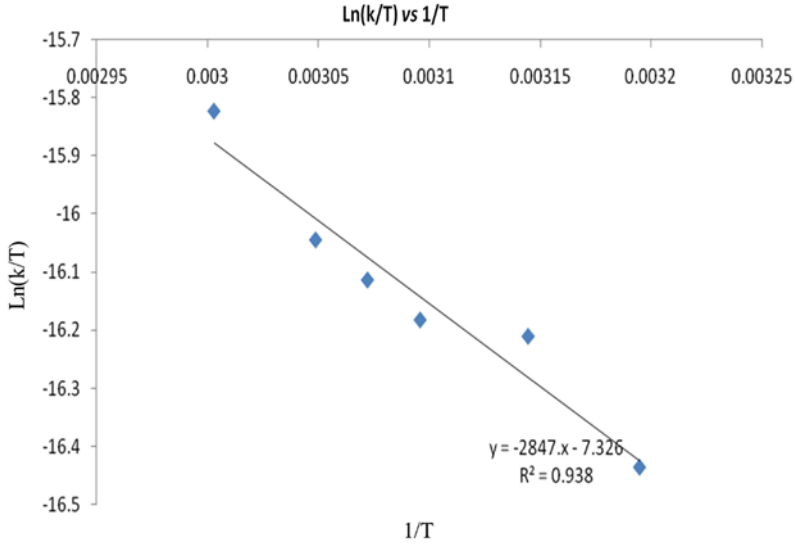

Figure 4. An Eyring plot of ln(k′/T) vs. 1/T.

Scheme 1. Mechanistic scheme for the oxidation of glycylglycine (S) by ferricyanide in acid medium.

$$S + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} SH^+ \qquad \text{(fast)} \quad \text{(i)}$$

$$SH^+ + Fe(III) \overset{K_2}{\rightleftharpoons} \underset{\text{(complex)}}{X} + H^+ \qquad \text{(fast)} \quad \text{(ii)}$$

$$\underset{\text{(complex)}}{X} + H_2O \xrightarrow{k_3} \underset{\text{(complex)}}{X'} + H^+ \qquad \text{(slow)} \quad \text{(iii)}$$

$$X' + Pd(II) \longrightarrow \underset{\text{complex}}{X''} \qquad \text{(fast)} \quad \text{(vi)}$$

$$X'' + 7Fe(III) \xrightarrow{H_2O} \text{---} \xrightarrow{H_2O} \text{products} \qquad \text{(fast)} \quad \text{(v)}$$

Here S stands for Glycylglycine while [Fe(III)] represents $[Fe(CN)_6^{3-}]$

In the present study in perchloric acid solutions, glycylglycine exists in the cationic SH^+ or $GlyGlyH^+$ form. Based on the preceding discussion of kinetic results, the following mechanism (Scheme 1) is proposed for the reaction:

3.4. Rate law derivation

From slow step (iii) of Scheme 1,

$$\text{Rate} = k_3[X][H_2O] \tag{3}$$

$$K_1 = \frac{[SH^+]}{[S][H^+]} \tag{4}$$

Application of the steady-state concept to the intermediate [X], leads to,

$$\frac{d[X]}{dt} = 0 = k_2[SH^+][Fe(III)] - k_{-2}[X][H^+] - k_3[X][H_2O] \tag{5}$$

$$\text{If}[Fe(III)]_t = [Fe(III)]_0 + [X] \text{ or } [Fe(III)] = [Fe(III)]_t - [X] \tag{6}$$

Substitution for $[Fe(III)]_0$ from Equation (6) in Equation (5), results in

$$k_2[SH^+][Fe(III)]_0 - k_2[SH^+][X] - k_{-2}[X][H^+] - k_3[X][H_2O] = 0$$

or

$$[X] = \frac{k_2[SH^+][Fe(III)]_0}{k_2[SH^+] + k_{-2}[H^+] + k_3[H_2O]} \tag{7}$$

By substituting for $[SH^+]$ from Equation (3) in Equation (7), we get,

$$[X] = \frac{K_1k_2[S][H^+][Fe(III)]_0}{K_1k_2[S][H^+] + k_{-2}[H^+] + k_3[H_2O]} \tag{8}$$

$$\text{Rate} = \frac{K_1K_2k_3[S][H^+][Fe(III)]_0[H_2O]}{K_1k_2[S][H^+] + k_{-2}[H^+] + k_3[H_2O]} \tag{9}$$

By dividing and multiplying Equation (9) with k_{-2}, we get

$$\text{Rate} = \frac{K_1K_2k_3[S][H^+][Fe(III)]_0[H_2O]}{K_1K_2[S][H^+] + [H^+] + (k_3/k_{-2})[H_2O]} \quad (10)$$

The derived rate law (10) is in good agreement with the experimental results such as a first-order dependence of the rate on [ferricyanide], fractional-order dependence each on [GlyGly], and [acid], and a zero order in [Pd(II)].

The proposed Scheme 1 and the derived rate law are also supported by the experimental observations discussed below. The variation of the ionic strength of the medium did not alter the rate, indicating that a neutral species is involved in the rate-determining step (slow step in Scheme 1). The reduction product, ferrocyanide, does not influence the rate, indicating that it is not involved in any pre-equilibrium step. In this study, the reaction rate increases with the increasing MeOH content (i.e. decreasing dielectric constant or D). The decrease in k′ with increasing D indicates that the transition state is less polar than the ground state. The effect of D on the reaction rate has been described in detail earlier in various monographs (Atwood, 1997; Dunbar & Heintz, 1997; Kendall & McKenzie, 1941/1929; Laidler & Eyring, 1939; Strecker, 1850). For the limiting case of zero angle of approach between two dipoles or an ion–dipole system, Amis (Carson, 1997) has shown that a plot of log k vs. 1/D gives a straight line with a negative slope for the reaction involving a negative ion and a dipole or between dipoles, while a positive slope is obtained for a positive ion–dipole interaction. The effect of varying permittivity on the rate observed in the present study can be explained by the Amis theory (Amis, 1966; Kendall & McKenzie, 1941/1929). By applying the Born concept, Laidler and co-workers (Laidler & Eyring, 1939) derived the following equation for a dipole–dipole interaction.

$$\text{Ln } k = \text{ln}k_0 + 3/8kT(2/D - 1)[\mu_A^2/r_A^3 + \mu_B^2/r_B^3 - \mu_{\neq}^2/r_{\neq}^3$$

where, k_0 is the rate constant in the medium of infinite D, μ is the dipole moment and "r" refers to the radii of the reactants and activated complex. It is seen that the rate should be greater in a medium of lower D, as observed in the present study, when $r^3 \neq > r^3_A + r^3_B$. On the other hand, $r^3 \neq \approx r^3_A + r^3_B$ implies the absence of dielectric constant effect on the rate signifying that the activated complex or transition state is not very different from the ground state.

Furthermore, the proposed mechanism is supported by the moderate values of energy of activation and other activation parameters (Atwood, 1997; Brown & Okamoto, 1958; Laidler & Eyring, 1939). The fairly positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the negative entropy of activation accounts for the formation of a compact associative transition state in which several degrees of freedom are lost.

4. Conclusions

The ferricyanide-GlyGly redox reaction has been investigated in perchloric acid solutions. The reaction stoichiometry involving the oxidative conversion of GlyGly to formic acid, ammonium ion, and CO_2, has been found to be 8:1 for ferricyanide:GlyGly. The reaction has the following experimental rate law: rate = $k^{\prime}$ $[Fe(CN)_6^{3-}]$ $[GlyGly]^{0.44}$ $[H^+]^{0.65}$ $[Pd(II)]^0$. The reduction product of the oxidant, ferrocyanide, does not influence the rate showing that it is not involved in any fast pre-equilibrium step. The variation in the ionic strength indicates the involvement of non-neutral reactants in the rate determining step of Scheme 1. The activation parameters, E_a, $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$, have been determined to understand whether the reaction is controlled by entropy or enthalpy. The negative $\Delta S^{\neq}$ value indicates the formation of a rigid transition state and the entropy-controlled reaction. A suitable mechanism in Scheme 1, consistent with the experimental observations, has been proposed and the rate law has been derived.

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