Free Radical Mediated Oxidative Decarboxylation of L-Proline by Peroxomonosulphate in Neutral Medium-Catalytic Effect of Copper (II)

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Abstract: Kinetics and mechanism of copper (II) catalyzed and uncatalyzed oxidation of L-proline by peroxomonosulphate (PMS) in neutral medium (phosphate buffer, pH 6-8) was studied at 278K. The reaction proceeded through free radical pathway which was confirmed by the non oxidation of L-proline methyl ester by PMS at this condition. Variation of ionic strength had negligible effect on the rate of the reaction which ruled out the interaction between carboxylate group of L-proline with SO_5^{2-} of PMS. The initial step was the removal of CO_2 and formation of carbon free radical which on hydrolysis lead to the formation of the product 4-aminobutanal which was confirmed by IR and Mass spectral studies.
Keywords: L-Proline, PMS, copper (II) catalysis, free radical intermediate.

1. Introduction

Amino acids are one of the natural compounds which contribute an important role both as building blocks of proteins and as intermediates in metabolism. They are useful for the human nervous system, hormone production, and muscular structure aside from playing an important role in protein and enzyme synthesis. The unique structure of L-proline restricts the conformations that it can adopt within a peptide or protein, giving it a unique role in the secondary and tertiary structures of L-proline-containing proteins [1]. Proline is reported to be the world's smallest natural enzyme, and plays a binding role in collagen, which has high proline content [2]. From this biological point of view, L-proline, which is mostly present in the human body, also plays an important role in mimicking the biological reaction in our body because of their selectivity towards oxidants [3].

Peroxomonosulphate (PMS) is an inexpensive, eco-friendly oxidizing agent when compared with other oxidizing agents [4-8] due to its easy tendency to transfer oxygen. It is used to oxidize both inorganic [9], organic [10-12] and waste water [13-17]. Transition metal ion catalyzed oxidation of amino acids have been carried either in acetic medium [18-20] or alkaline medium [21, 22]. Copper complexes have occupied a major place in oxidation chemistry because of their abundance and relevance in biological chemistry [23,24].Hence, the present work is focused on the effect of Cu (II) in the oxidation of L-proline with PMS in neutral medium (phosphate buffer, pH 6-8) at 278K.

2. Experimental

2.1. Materials and methods

L-proline was obtained from Merck, India, and used as received. PMS was obtained from Aldrich, USA in the form of triple salt $2KHSO_5.KHSO_4.K_2SO_4$ (oxone) and the purity of the sample was found to be 98% when tested by iodometric estimation [25]. A fresh solution of PMS was prepared every time before starting the

experiments, doubly distilled water was used throughout this study. All other chemicals used in this study were of analar grade and used as received. The effect of copper (II) was observed even at concentration of 5×10^{-3} mol dm^{-3} and hence concentration of Cu (II) in the reaction mixture was kept at 5×10^{-3} mol dm^{-3}.

2.2. Instrumentation

For kinetic measurements, a Royal ultra cryostat (temperature control) was used. For product analysis, Jasco 6300 FT-IR spectrophotometer was used. The Mass spectral studies were carried out using 6890N Gas Chromatography Equipped with 5973N mass selective detector (Agilent make). The reaction mixture was scanned in the ultraviolet and visible regions on a Perkin Elmer LS 25 UV–visible spectrophotometer.

2.3. Measurement of Rate Constant

A known volume of PMS solution, thermostatted at the desired temperature (278K), was pipetted out into the reaction mixture of L-proline in the buffer and simultaneously a timer was started. Consumption of PMS in this reaction mixture was monitored by the iodometric method. The rate of the reaction was studied under pseudo first order condition, i.e., [L-proline] » [PMS]. The rate of the reaction followed first order kinetics as shown in (Fig. 1) and the rate constant k_{obs} was calculated from the linear plot of $\log[PMS]_t$ vs time according to Eq. 1

$$\log[PMS]_t = \log[PMS]_0 - kt/2.303 \qquad\qquad \text{--- (1)}$$

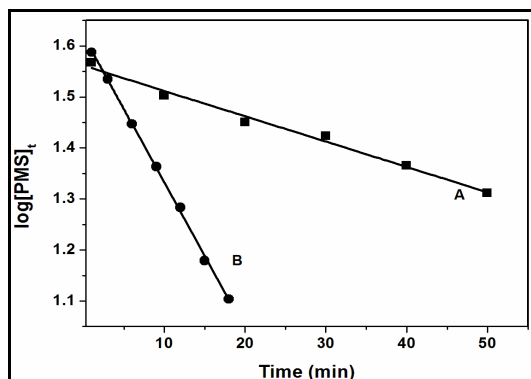The same methodology was adopted for the Cu (II) catalyzed oxidation as well.

Fig. 1 Plot of log $[PMS]_t$ vs time in the absence (A) and presence of (B) copper (II) ions at 278K [proline] = 5.0 x 10^{-2} mol dm^{-3}; [Cu (II)] = 2.5 x 10^{-3} mol dm^{-3}; pH = 7.0 ± 0.1; [PMS] = 4 x 10^{-3} mol dm^{-3}

2.4. Stoichiometry and product analysis

The stoichiometry of the reactions was determined for both copper (II) catalyzed and uncatalyzed reactions for the reaction mixtures containing a large excess of [PMS] over [L-proline]. Then the reaction mixture was allowed to stand for 48 h and the unconsumed PMS was estimated iodometrically. The observed stoichiometry of the reaction for both copper (II) catalyzed and uncatalyzed reaction was (L-proline: PMS = 1:2)
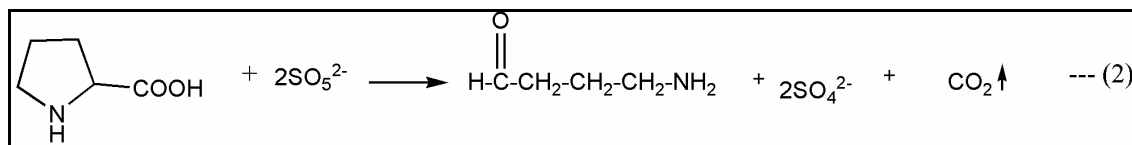
The reaction mixture was extracted with dichloromethane and the organic layer was given for IR spectral analysis. The product was 4-aminobutanal confirmed by the IR spectrum showing absorption bands at 3422 cm^{-1} due to –NH stretching, 2956 cm^{-1} due to CH stretching, and 1734 cm^{-1} due to aldehyde C=O stretching respectively (Fig. 2). GC-MS data showed a molecular ion peak at 88 m/z confirming 4-aminobutanal (Fig. 3)

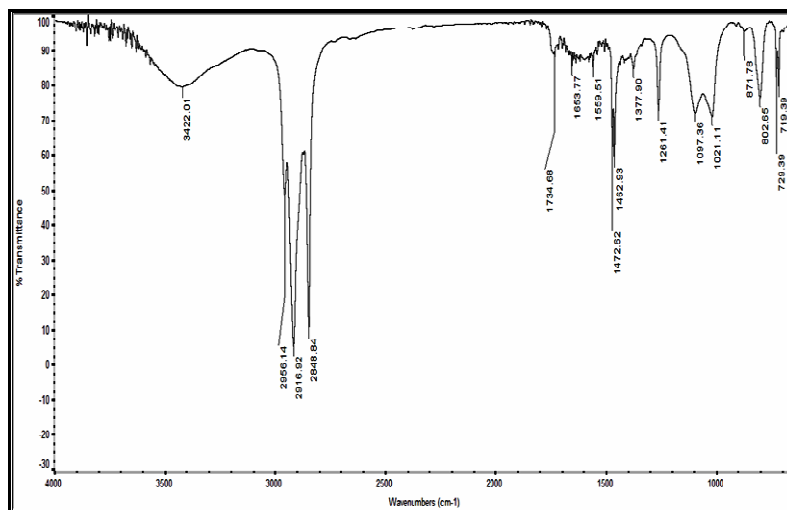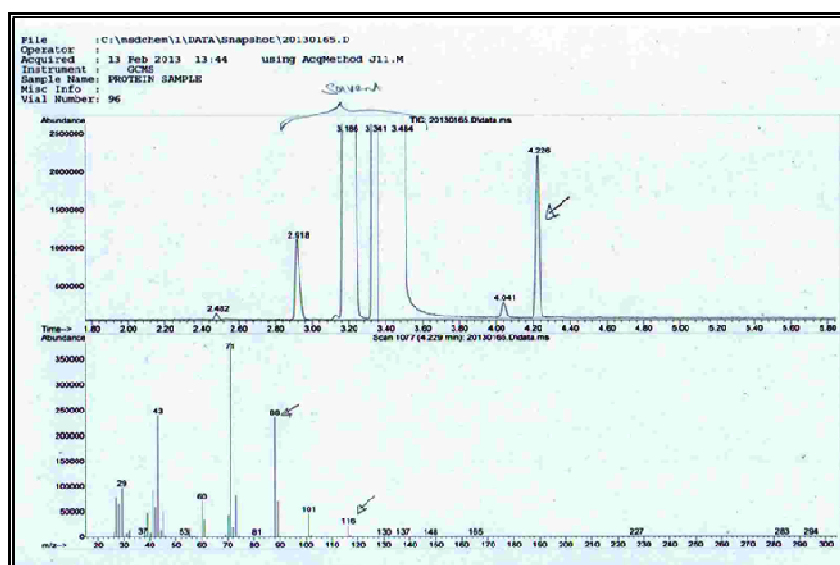**Fig. 2 FT-IR spectrum of 4-aminobutanal**

Fig. 3 GC Mass spectrum of 4-aminobutanal

3. Results and Discussion

Kinetics and mechanism of copper (II) catalyzed and uncatalyzed oxidation of L-proline by PMS in neutral medium was studied at 278 K. The rate of the reaction was monitored iodometrically by measuring the concentration of unreacted PMS as a function of time

3.1. Effect of [PMS] on k_{obs}

The values of k_{obs} were calculated for different concentrations of PMS by maintaining the other parameters at constant values. The results showed that the rate constant was unaffected with increase in [PMS] in the absence of copper (II).However the rate decreased with increase in [PMS] in the presence of copper (II) which might be due to the formation of an intermediate in equilibrium condition.

3.2. Effect of [L-proline] on k_{obs}

The values of k_{obs} were calculated for the reactions studied both in the presence and absence of copper (II) catalyst for different [L-proline], by keeping other parameters at constant values. The kinetic results showed that the rate constant increased with increase in [L-proline] (Table. 1) however the rate remained unchanged in the presence of the catalyst. Further, the plot of k_{obs} vs [L-proline] was linear, in the absence of copper (II).

3.3. Effect of pH on k_{obs}

In order to ascertain the effect of pH on the rate of the reaction, reactions in the presence and absence of copper (II) ions at different pH values were carried out. The rate constant (k_{obs}) values increased with increase in pH values in both cases. The plots of k_{obs} vs [H$^+$] were straight line with a high correlation coefficient

3.4. Effect of [copper (II)] on k_{obs}

The effect of [copper (II)] on the rate was studied by determining the values of k_{obs} at different [copper (II)], by keeping other parameters at predetermined values. The kinetic results showed that the rate increased with increase in [copper (II)] (Table 1), and the plot of k_{obs} vs [copper (II)] was linear (Fig. 4). The order of the reaction with respect to copper was more than one but less than 2 and the real order was fractional.

Table 1. Effect of k_{obs} for the oxidation of L-proline by PMS both in the absence and presence of Cu(II) in neutral medium at 278 K.

10^3[PMS] (mol dm^{-3})	10^2 [proline] (mol dm^{-3})	pH±0.1	$10^4 k_{obs}^a$ (s^{-1})	10^3 [Cu(II)] (mol dm^{-3})	$10^4 k_{obs}^b$ (s^{-1})
2.0	5.0	7.0	1.53	5.0	0.23
4.0	5.0	7.0	1.53	5.0	0.11
6.0	5.0	7.0	1.53	5.0	6.91
8.0	5.0	7.0	1.53	5.0	5.37
4.0	2.5	7.0	1.31	5.0	4.28
4.0	5.0	7.0	2.65	5.0	4.99
4.0	7.5	7.0	3.88	5.0	4.22
4.0	10.0	7.0	5.07	5.0	4.61
4.0	5.0	6.0	0.35	5.0	1.15
4.0	5.0	6.5	1.04	5.0	2.69
4.0	5.0	7.0	2.84	5.0	4.99
4.0	5.0	7.5	10.17	5.0	9.21
4.0	5.0	8.0	28.59	5.0	15.74
4.0	5.0	7.0	2.84	2.5	3.07
4.0	5.0	7.0	2.84	5.0	5.76
4.0	5.0	7.0	2.84	7.5	10.36
4.0	5.0	7.0	2.84	10.0	11.90
4.0	5.0	7.0	2.84	12.5	19.96

^{a}Without Cu(II). ^{b}With Cu(II).

3.5. Effect of Dielectric Constant on k_{obs}

The effect of the dielectric constant (ε) of the reaction mixture on the reaction rate was studied by using two different solvents, such as 2-methylpropan-2-ol (tert-butyl alcohol) and acetonitrile. The k_{obs} remained unaffected by the increase in composition of the solvents, ruling out the formation of more polar intermediate than the reactants.

3.6. Effect of Ionic Strength on k_{obs}

The effect of ionic strength on the reaction rate was studied by varying the ionic strength of the medium from 0.05 to 0.2 mol dm^{-3}, maintaining the other parameters at constant values. The increase in the ionic strength had negligible effect on the k_{obs} value. This ruled out the interaction between SO_5^{2-} of PMS and carboxylate group of L-proline. The negligible effect of ionic strength on the rate of the reaction revealed that L-proline is the active form and not the zwitter ionic form of L-proline

3.7. Test for Free Radical Intermediates

The reaction mixture initiated the polymerization of acrylonitrile when added to the reaction mixture in an inert atmosphere. On diluting the reaction mixture with methanol, a white precipitate was obtained which revealed the formation of the free radical intermediate. Moreover, with the addition of tertbutyl alcohol, the rate

of the reaction was not affected, which clearly indicated the absence of hydroxyl free radicals, since tertbutyl alcohol is an effective scavenger of hydroxyl free radicals.
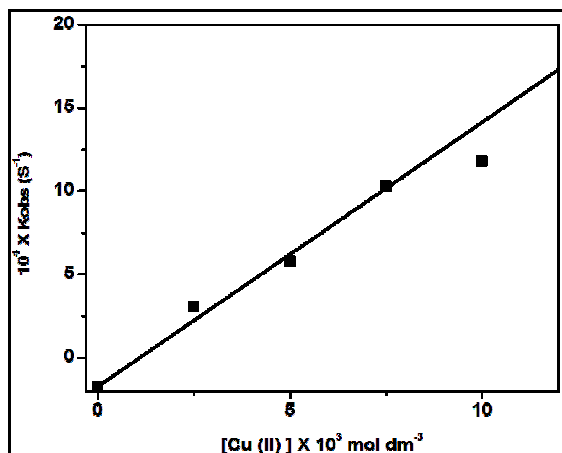

Fig. 4 Plot of k_{obs} vs [copper (II)]. [Proline] = 5.0 x 10^{-2} mol dm^{-3}; pH = 7.0 ± 0.1; [PMS] = 4 x 10^{-3} mol dm^{-3}

Figure 5A shows the UV−visible spectra of a mixture containing L-proline and PMS in phosphate buffered medium. Initially the λ_{max} observed at 205 nm was due to L-proline and scanning at different time intervals showed an increase in absorbance and also development of another band at 225 nm which might be due to forming imine intermediate. However, in the presence of copper (II), absorption maximum was observed at 242 nm (merger of the two peaks) only at low concentration of copper (II). At high concentration, copper (II) in water has λ_{max} at 810 nm, copper (II) with L-proline has λ_{max} at 636 nm, and copper (II) with L-proline and PMS in phosphate buffer has λ_{max} at 628 nm, which indicated (fig. 5B) a hypsochromic shift revealing the formation of copper (II) L-proline complex initially, followed by formation of complexes with PMS and copper phosphate-L-proline−PMS complex respectively.
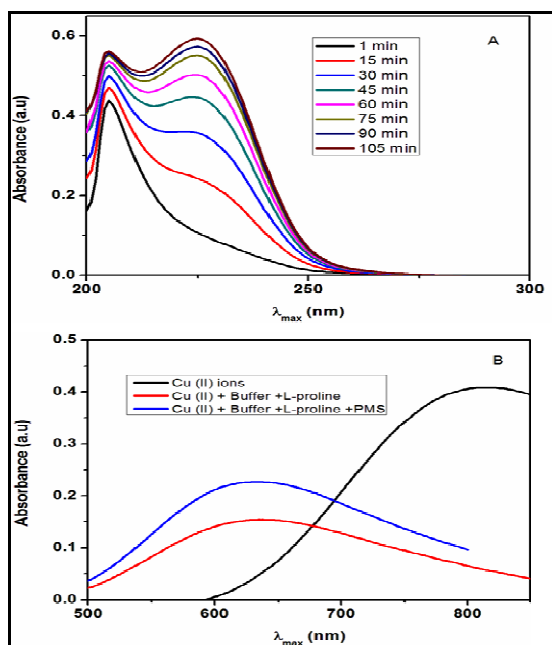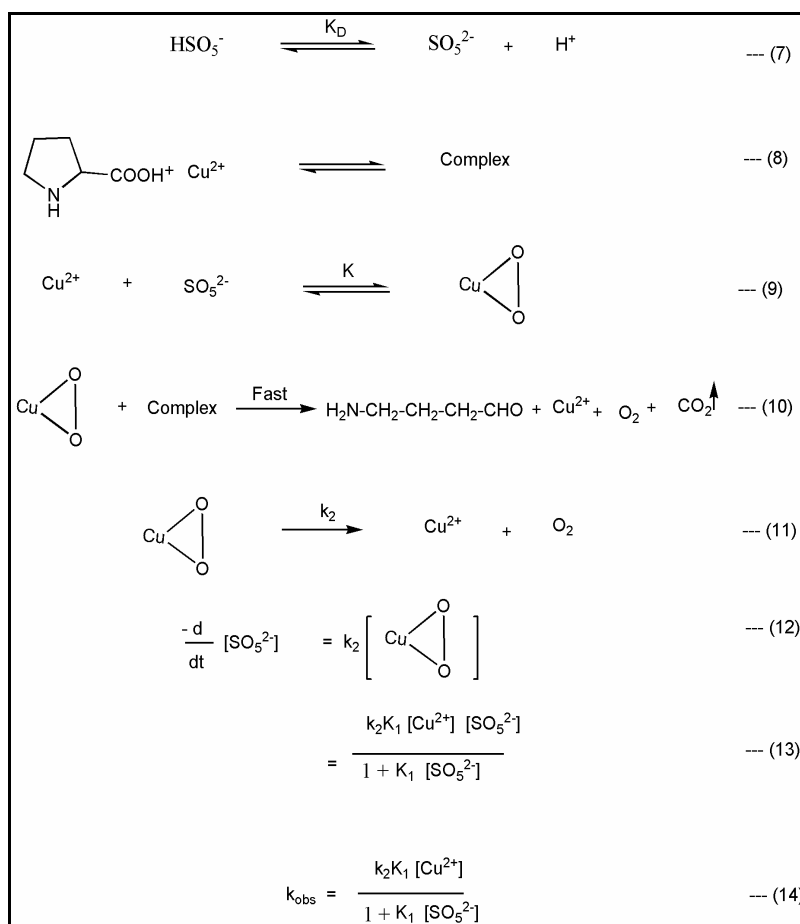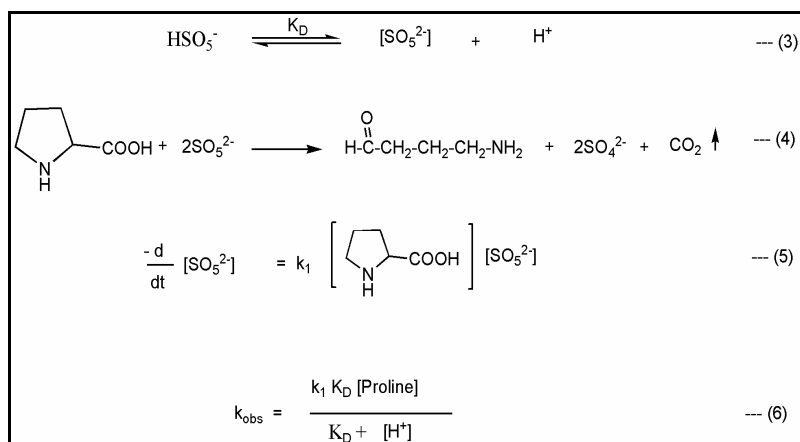

Fig. 5A. The absorption spectra of the reaction mixture in the absence of copper (II) ions in different time interval: [L-proline] = 5.0 x10^{-2} mol dm^{-3}; [Cu (II)] = 1.5 x 10^{-5} mol dm^{-3}; pH =7.0 ± 0.1; [PMS] = 4.0 x 10^{-3} mol dm^{-3}, B. Copper peak at high concentration

Based on the results obtained, the following reaction mechanism was proposed

$$HSO_5^- \underset{}{\overset{K_D}{\rightleftharpoons}} [SO_5^{2-}] + H^+ \qquad \text{--- (3)}$$

$$\text{(pyrrolidine)-COOH} + 2SO_5^{2-} \longrightarrow \overset{O}{\underset{}{H-C}}-CH_2-CH_2-CH_2-NH_2 + 2SO_4^{2-} + CO_2\uparrow \qquad \text{--- (4)}$$

$$\frac{-d}{dt}[SO_5^{2-}] = k_1 \left[\text{(pyrrolidine)-COOH} \right][SO_5^{2-}] \qquad \text{--- (5)}$$

$$k_{obs} = \frac{k_1 K_D [Proline]}{K_D + [H^+]} \qquad \text{--- (6)}$$

$$HSO_5^- \underset{}{\overset{K_D}{\rightleftharpoons}} SO_5^{2-} + H^+ \qquad \text{--- (7)}$$

$$\text{(pyrrolidine)-COOH} + Cu^{2+} \rightleftharpoons Complex \qquad \text{--- (8)}$$

$$Cu^{2+} + SO_5^{2-} \underset{}{\overset{K}{\rightleftharpoons}} Cu\overset{O}{\underset{O}{\diagdown}} \qquad \text{--- (9)}$$

$$Cu\overset{O}{\underset{O}{\diagdown}} + Complex \overset{Fast}{\longrightarrow} H_2N-CH_2-CH_2-CH_2-CHO + Cu^{2+} + O_2 + CO_2\uparrow \qquad \text{--- (10)}$$

$$Cu\overset{O}{\underset{O}{\diagdown}} \overset{k_2}{\longrightarrow} Cu^{2+} + O_2 \qquad \text{--- (11)}$$

$$\frac{-d}{dt}[SO_5^{2-}] = k_2 \left[Cu\overset{O}{\underset{O}{\diagdown}} \right] \qquad \text{--- (12)}$$

$$= \frac{k_2 K_1 [Cu^{2+}] [SO_5^{2-}]}{1 + K_1 [SO_5^{2-}]} \qquad \text{--- (13)}$$

$$k_{obs} = \frac{k_2 K_1 [Cu^{2+}]}{1 + K_1 [SO_5^{2-}]} \qquad \text{--- (14)}$$

5. Conclusion

The kinetics of the oxidation of L-proline by peroxomonosulfate in phosphate buffered medium (pH 6−8) in the presence and absence of copper (II) catalyst was studied. The formation of polar intermediate was ruled out since the solvent polarity did not affect the reaction rate significantly. The mechanism proposed involving the formation of carbon free radical intermediate. The free radical intermediate was confirmed by studying the oxidation of proline methyl ester which did not get hydrolysed/oxidized at this experimental condition. Electronic absorption studies confirmed the formation of copper (II) − L-proline −PMS complex. The product of the reaction was confirmed as 4-aminobutanal by IR and Mass spectral studies.

Acknowledgments

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