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Effect of Cu(II) Ions Inclusion Complex- Kinetic and Thermodynamic Studies

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Abstract : The kinetics study of histidine in the form of inclusion complex with Cu (II) was studied with help of β-cyclodextrin in acetic acid -sodium acetate buffer medium at 308 K. Thermodynamic parameters: free energy of activation (ΔG^0) enthalpy of activation (ΔH^0) and entropy of activation (ΔS^0) was calculated by studying the reactions at 303K, 308 K and 318K respectively. The positive enthalpy values and positive entropy values are obtained due to hydrophobic interaction of host (β-cyclodextrin)-guest (histidine) inclusion complexes. The formation of inclusion complex was confirmed by UV-Visible absorption studies. The stability constant values of histidine are 194.3 L/mol. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.65 LM^{-1} and 1.96$LM^{-1.}$ ΔG° obtained are also negative. It indicated that the inclusion process proceeded spontaneously at experimental temperature.
Keywords : copper (II), histidine , peroxomonosulphate (PMS), β-cyclodextrin (β-CD) catalyst, inclusion complex, kinetics.

1.Introduction

There are numerous applications for cyclodextrins in the pharmaceuticals field. For example, the addition of β-cyclodextrin increases the water solubility of several poorly water-soluble substances. In some cases this results in improved bioavailability, increasing the pharmacolog- ical effect allowing a reduction in the dose of the drug administered. Inclusion complexes can also facilitate the handling of volatile products. This can lead to a different way of drug administering, e.g. in the form of tablets. Cyclodextrins are used to improve the stability of substances to increase their resistance to hydrolysis, oxidation, heat, light and metal salts. The inclusion of irritating products in cyclodextrins can also protect the gastric mucosa for the oral route, and reduce skin damage for the dermal route. Furthermore, cyclodextrins can be applied to reduce the effects of bitter or irritant

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tasting and bad smelling drugs [1-4]. The main interest in cyclodextrins lies in their ability to form inclusion complexes with several compounds [5–8].Cyclodextrin (CD) inclusion is a technique widely used in the pharmaceutical industry to enhance drug solubility [9–11]. In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability [12]. In addition, cyclodextrins can be used to several techniques are used to form cyclodextrin complexes The thermodynamic parameters for several series of drugs and other compounds have been determined and analyzed. Analysts have used this property of CDs, and a lot of methods based on the fluorescence inclusion complexes with CDs have been proposed for the determination of several pharmaceutical drugs, pesticides, and metal ions [13, 14].

2. EXPERIMENTAL METHODS

2.1 Materials and Reagents.

β- Cyclodextrin was purchased from SD-Fine chemicals, India. histidine was obtained from Merck, India, and used as received. **A** fresh solution of 2.5×10^{-3} mol dm^3 copper sulphate pentahydrate, (E Merck) was prepared by dissolving the appropriate amount of $CuSO_4.5H_2O$, PMS was obtained from Aldrich, USA, and the purity of the sample was found to be 98% when tested by iodometric estimation and hence used without further purification. PMS solution was freshly prepared every day, stored in a blackened vessel to prevent photodecomposition, and standardized iodometrically. Acetic acid (E Merck, India Ltd.) was distilled and a stock solution of 8N acetic acid was prepared and standardized using sodium hydroxide (E Merck, India Ltd.). 4N acetic acid was prepared from the stock solution and used to make the buffer solution.

2.2 Kinetic Measurements.

The kinetics studies of the catalytic effect of copper (II) with β– cyclodextrin on the oxidation of histidine by PMS, in acetic acid–sodium acetate buffered medium (pH 4.0) at 308K was studied under pseudo first order conditions i.e., [histidine] >> [PMS] at various time intervals. A known volume of PMS solution, thermostated at the desired temperature, was pipette out into the reaction mixture and simultaneously a timer was started. Consumption of PMS in this reaction mixture was monitored by iodometric method. The rate of the reaction followed first-order kinetics as shown (Fig.1).

2.3 Stoichiometry method of inclusion complex

The stoichiometry of the reactions was determined for the reaction mixtures containing a large excess of [PMS], [β-cyclodextrin] over [histidine], [Cu (II)]. Then the reaction mixture was kept for 48 h and the unconsumed PMS was estimated iodometrically. Corrections for the self-decomposition of PMS were made from the value obtained from the control experiments. The observed stoichiometry of the reaction in the mixture of β-cyclodextrin (Host) and histidine: : PMS was 1:1. Zwitterions arising from transfer of a proton from the carboxyl to the amino group (histidine). It exists as a dipolar ion in aqueous solutions. The dissociation of histidine depends on the pH of the medium. The pKa value was suggested that in acidic medium, histidine exist both in the protonated form and as zwitterions .

2.4 Product Analysis

The reaction mixture containing histidine in acetic acid-sodium acetate buffered medium (pH 4.0 ± 0.1), and a large excess of PMS and β-cyclodextrin with Cu (II) was taken in a blackened iodine flask and kept for 48 hours. After the completion of the reaction, the product present in the organic layer was separated, dried and FT-IR spectrum was taken.

2.5 FT-IR analysis

The product obtained in the oxidation of histidine with β-cyclodextrin by PMS in acetic acid-sodium acetate buffered medium was analysed by IR spectrometer.

2.6 UV Spectral Analysis

The reaction mixture was scanned in the ultraviolet and visible regions on Perkin Elmer LS 25 UV spectrophotometer for absorption studies. The absorption spectra were used to confirm the formation of inclusion complex.

3. RESULTS AND DISCUSSIONS

3.1 Effect of k_{obs} vs. [β-CD]

The rate constant k_{obs} increased with increase in [β-cyclodextrin] in addition to the catalyst we add Cu (II) ions Table 1 **.**The plots of k_{obs} vs. [β-cyclodextrin] were linear with positive intercepts in all the cases (Figure 2). This linear plot indicated that the formation of inclusion complex between β- cyclodextrin and drug. The same phenomenon has been observed by [16]. In addition to the catalyst we add Cu (II) ions which are responsible for greater importance in terms of the rate constant value.

3.2 Effect of [histidine] on k_{obs}

The rate constant increased with increase in [drug] Table 1.The plots of log k_{obs} vs. [drug] were linear, as shown (Fig.3). This result indicated first order dependence of rate on [drug]. The positive intercept obtained in the above plots revealed that the reaction proceeded in two steps: one dependent on [drug] and the other independent of [drug] [15].

3.3 EFFECT OF pH ON k_{obs}

The k_{obs} values increased with increase in pH values. The plot of k_{obs} vs. pH gave a straight line with a negative intercept. (Figure 4) The negative intercept obtained in the above plot revealed that the oxidation reaction proceeded in two steps - one dependent on the $[H^+]$ and the other independent of $[H^+]$ in presence of copper (II)) ions.[15]

3.4 EFFECT OF [COPPER (II)] ON k_{obs}

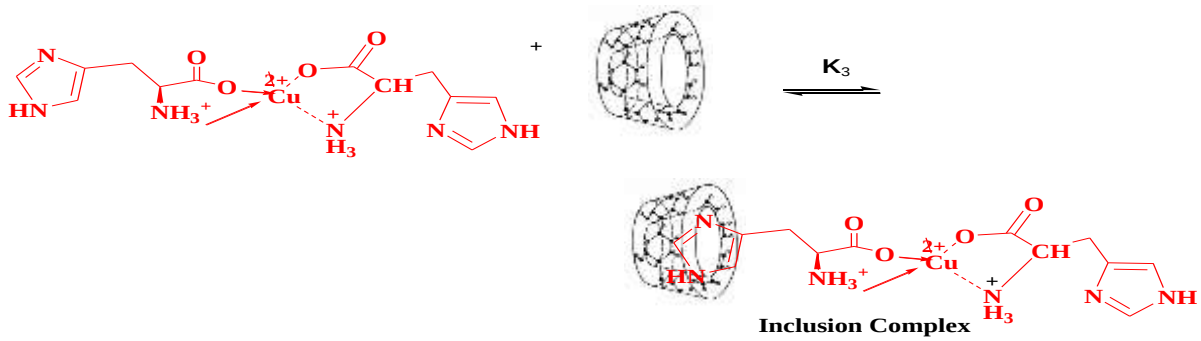
The rate of a reaction increased with increase in [copper (II)] ions. (Table 1). The plot of k_{obs} vs. copper (II) gave a straight line [16] with a positive intercept. (Figure5)

3.5 Effect of Temperature on k_{obs}

The rate of the reaction was studied by varying the temperature, viz., 303, 308, and 318 K. and also by keeping other parameters at constant values. The k_{obs} increased with the increase in temperature (Table 1) [16]. As heat stability of the complex varies from guest to guest, most complexes start to decompose at 50–60 C, while some complexes are stable at higher temperature.

3.6 Thermodynamics Values of the Inclusion Complex

The thermodynamic parameters (ΔH°, ΔS°, ΔG°**)** for the formation of inclusion complex were determined from the temperature dependence of the plot of log k_2 vs. 1/T (Arrhenius plot). (Figure 6) . The corresponding enthalpy and entropy values were obtained from the slope and intercept, respectively. ΔG^0 was obtained according to the equation: $\Delta G^0 = \Delta H^0 - T\Delta S^0$ .The results are shown in Table 2. The thermodynamic parameters: enthalpy changes (ΔH°*)* and entropy changes (ΔS°*)* of the binding reaction are important to confirm the force of hydrophobic interaction of drug with β-cyclodextrin. Hydrophobic interaction involves favorable positive entropy together with a slightly positive enthalpy change (Table.2). Upon complexation both positive enthalpic and positive entropic values are obtained, indicating that this inclusion is mainly entropically driven one. As discussed above, ΔG^0 obtained are negative (Table 2), which indicated that the inclusion process proceeded spontaneously at this experimental condition. The positive ΔH^0 together with positive ΔS^0 suggested that the inclusion process is an enthalpy controlled process in the case of the drug in the presence of copper (II) ions .



3.8 Determination of stability constant by Uv-visible spectral analysis

Absorption spectra were used to confirm the formation of inclusion complex between Histidine and β-cyclodextrin. The values of stability constant were calculated by varying and keeping the other parameters as constant. The concentrations of β- cyclodextrin and copper (II) ions have been assigned as 500 mg and concentrations of drug have been assigned as 50 mg. There was a linearly decrease in the absorbance with the successive addition of (0.5 ml, 1 ml, 1.5 ml, 2.0 ml) (Figure 7). There was also shift in the λ_{max} from 224 nm to 221 nm. The inclusion complex had decreased intensity at all points of wavelength due to the interaction of β-cyclodextrin and drug. It indicates that the solubility of drug increases upon forming the inclusion complex [24]. A very good linear relationship was obtained for 1/A vs. [1/ β-CD] (Figure 8). The stability constant value of drug was $194.3M^{-1}$ and the stoichiometry ratio for the inclusion complex formation between drug and β-cyclodextrin was 1:1 and also the LOD value and LOQ values for the inclusion complex are 0.65 LM^{-1} and $1.96LM^{-1}$. The least values are represented by very good accuracy methods.

3.7 FT-IR Spectral Analysis

The oxidation product of histidine was β-imidazolylacetaldehyde which showed the peak at 3434 cm^{-1} due to -NH stretching, 2924 and 2853 cm^{-1} due to CH stretching and 1635 cm^{-1} due to C=O stretching of carbonyl group (Figure 9).

4. CONCLUSION

The results of effect of β– cyclodextrin on the oxidation of drug by peroxomonosulphate (PMS) in the presence of copper (II) ions in acetic acid-sodium acetate buffered medium (pH 3.6-5.2) at 308 K were discussed. The rate constant k_{obs} remained constant with increase in [PMS], which revealed that the rate was first order in [PMS]. Kinetic results for the variation of drug showed that the k_{obs} increased with increase. The positive intercept obtained in the above plots revealed that the reaction proceeded by two pathways, one dependent on [drugs] and the other independent. Kinetic results for variation of β– cyclodextrin showed that the rate constant increased with increase in [β– cyclodextrin]. The plots of k_{obs} vs. [β-cyclodextrin] were linear with positive intercepts. This linear plot clearly indicated that the formation of inclusion complex between drug and β-cyclodextrin. In the pH variation, the k_{obs} values increased with increase in [pH] values. The plots of k_{obs} vs. $[H^+]$ gave straight lines. The variation of copper (II) ions showed that the k_{obs} increases with increase in [copper (II)] ions. The plots of k_{obs} vs. [copper (II)] ions were linear with a positive intercept in all the drug. The positive ΔH^0 together with positive ΔS^0 suggested that the inclusion process is an enthalpy controlled process in this case. The product analysis was carried out and the formations of inclusion complexes were confirmed by UV absorption studies. The stoichiometry ratios for the inclusion complex formation between drugs were determined. Detailed mechanism of copper (II) ions reaction was proposed. The products obtained were characterized by HPLC, FT-IR studied.

4.1 Selectivity

Host (β- cyclodextrin) – Guest (dosage) was found that no interference was introduced by any of them reactant. β- Cyclodextrin and Cu (II) acts as a catalyst to the reactive species is essential to propose the mechanism for kinetic studies.

4.2 Applications of the methods

In order to study the validity of the proposed method, the pharmaceutical dosage forms (histidine) was subjected to the analysis of their β- cyclodextrin content by the proposed method.

Indicate the high accuracy of the proposed method for the determination of the studied drug.

In addition to the catalyst we add Cu (II) ions which are responsible for greater importance in terms of the rate constant value, thermodynamic parameter and stability constant values for advantages of this method.

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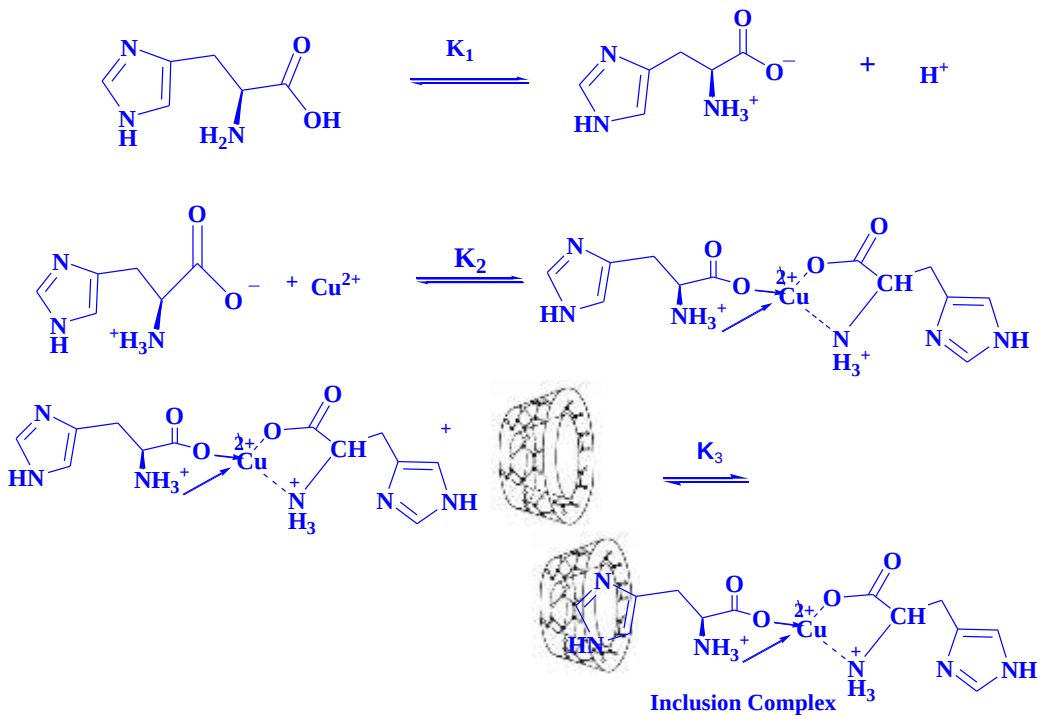
Scheme: 1



$$2HSO_5^- \xrightarrow{k_2} 2HSO_4^- + O_2$$

$$\frac{-d\,[HSO_5^-]}{dt} = k_1[complex]\,[HSO_5^-] + k_2\,[HSO_5^-]$$

$$k_{obs} = \frac{k_1K_1K_2K_3[Histidine]\,[Cu^{2+}]\,[\beta CD]}{K_1 + [H^+]} + k_2$$

Since $K_1 << [H^+]$

$$\text{Hence} \quad k_{obs} = \frac{k_1k_2K_1K_2K_3[Histidine]\,[Cu^{2+}]\,[\beta\text{–}CD]}{[H^+]}$$

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