International Journal on Recent Researches in Science, Engineering & Technology (IJRRSET)
A Journal Established in early 2000 as National journal and upgraded to International journal in 2013 and is in existence for the last 10 years. It is run by Retired Professors from NIT, Trichy. Journal Indexed in JIR, DIIF and SJIF.
Available online at: www.jrrset.com

ISSN (Print) : 2347-6729
ISSN (Online) : 2348-3105

Volume 5, Issue 7
November 2017.
JIR IF : 2.54
SJIF IF : 4.334
Cosmos: 5.395

Received on: 02.11.2017 Published on: 28.11.2017 Pages : 73-82

KINETICS AND THERMODYNAMICS PARAMETER OF INCLUSION COMPLEX

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Abstract

The kinetics and oxidation of histidine by PMS in the presence of β-cyclodextrin was studied in acetic acid -sodium acetate buffer medium at 308 K.The present paper deals with stability constant 321.7 LM^{-1} and validation method of LOD and LOQ are 0.927LM^{-1} and 2.81 LM^{-1} by plotting 1/A vs. [1/ β-CD] (Benesi-Hildebrand equation) using spectrophotometry. Host-guest hydrophobic interaction is through favorable pharmaceutical industry owing to their use as inclusion complex agent to increase the aqueous solubility of poor soluble. Kinetics studies shows that the rate of the reaction increases linearly, On the other hand the variation of PMS, sodium acetate, ionic strength and solvent polarity had negligible concern on the rate of the reaction .

KEY WORDS Histidine , peroxomonosulphate (PMS), β-cyclodextrin (β-CD), inclusion complex, kinetics, stability constant, validation method

Introduction

Histidine is one of the 22 proteinogenic amino acids. In terms of nutrition, Histidine is considered an essential amino acid in human infants. After reaching several years of age, humans begin to synthesize it, at which point it becomes a non-essential amino acid [1].Cyclodextrins with six to eight α-D-glucopyranose units are denoted as α- ß- and γ-cyclodextrins [2]. The kinetics of cleavage of phenyl phenyl acetates (PPA) and several para-substituted PPAs in basic aqueous sodium carbonate–bicarbonate buffer containing β-cyclodextrin (β-CD) [3]. The most important characteristics of CDs are the formation of inclusion complexes with various organic and inorganic guest molecules [4-7]. The inclusion complex of these host–guest systems occurs through various interactions, such as hydrogen bonding, van der Waals interaction, hydrophobic interactions and also electrostatic attraction [8]. The main driving force of complex formation is the release of enthalpy-rich water molecules from the cavity. Water molecules are displaced by more hydrophobic guest molecules present in the solution to attain an apolar–apolar association and decrease of cyclodextrin ring strain resulting in a more stable lower energy state [9]. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications, because inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions [10]. The lack of Histidine in the diet for a prolonged period resulted in decrease in albumin, transferrin and hemoglobin concentration occurred slowly over the Histidine depletion period [11]. Oxidation reactions of a-amino acids (AA) are one of the most relevant biochemical reactions because, such reactions serve as models for protein oxidations[12-14].

Materials and methods

β- Cyclodextrin was purchased from SD-Fine chemicals, India. histidine was obtained from Merck, India, and used as received. 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.

Kinetic Measurements.

The kinetics studies of 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). The reaction mixture was scanned in the ultraviolet and visible regions on a Perkin Elmer LS 25 UV spectrophotometer to unravel the intermediate formed during the course of the reaction. The absorption spectra were used to confirm the formation of inclusion complex.

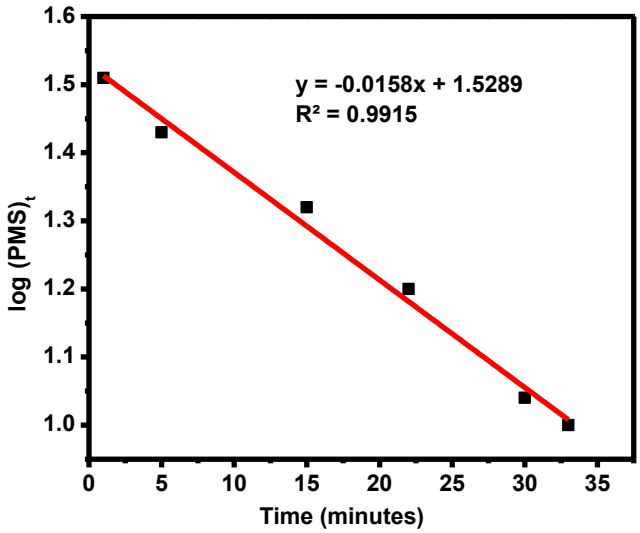
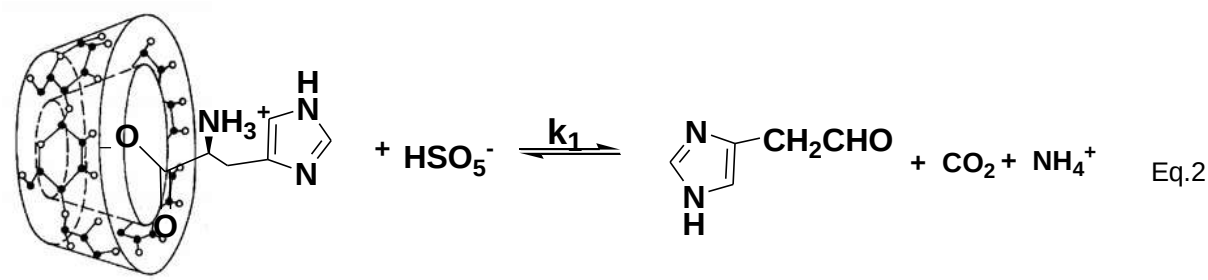


Fig. 1 Plot of log $[PMS]_t$ vs. time

$[H^+]$ = 5 x 10^{-1} M; [sodium acetate] = 8.5 x 10^{-2} M; [β-cyclodextrin] = 0.3g; [Drug] = 5x10^{-2}M; Temperature=308 K.

RESULTS

The stoichiometry of the oxidation of histidine was determined by adding the reaction mixtures containing a large excess of [PMS] 3.86 x 10^{-3} M, [β-cyclodextrin] 0.3 g over [histidine] 5 x 10^{-2} M having [pH] 3.6-5.2 until 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 and histidine: PMS was 1:1.



Eq.2

DISCUSSION

Effect of [amino acid] on k_{obs}

The reaction were carried out at various concentration of [Histidine] ranging from 0.025, 0.050, 0.075, 0.100 M keeping the other parameters [H^+], [sodium acetate], [β-cyclodextrin], [PMS] , temperature as constant. The values of k_{obs} Table (1) were independent of varying [Histidine]. This result indicated first order dependence of rate on [Histidine]. The k_{obs} increased with increase in [Histidine] Fig 2.

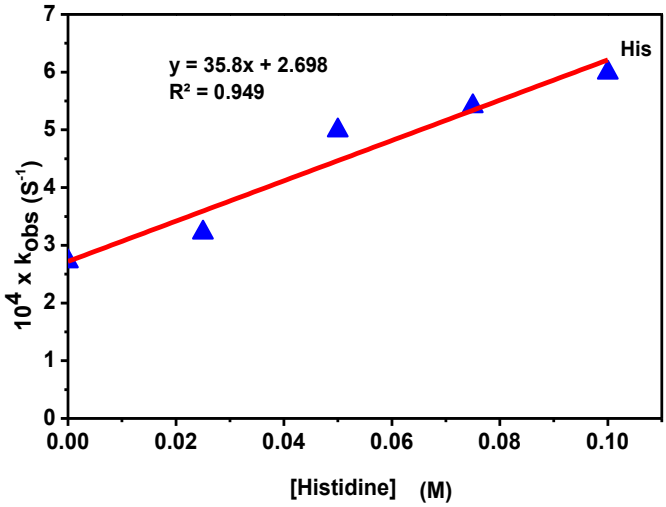


Fig. 2 Plot of k_{obs} vs [drug]

[H^+] = 5 x 10^{-1} M; [sodium acetate] = 8.5 x 10^{-2} M; [PMS] = 3.90 x 10^{-3} M; [β-cyclodextrin] = 0.3g; Temperature=308 K.

Effect of [β-cyclodextrin] on k_{obs}

The effect of [β-Cyclodextrin] was also investigated by varying concentrations ranging from 0.1, 0.2, 0.3, 0.5 g at constant other parameters. Table 1 the rate constant k_{obs} increased with increase in [β-cyclodextrin], indicating first order kinetics. Fig [3]

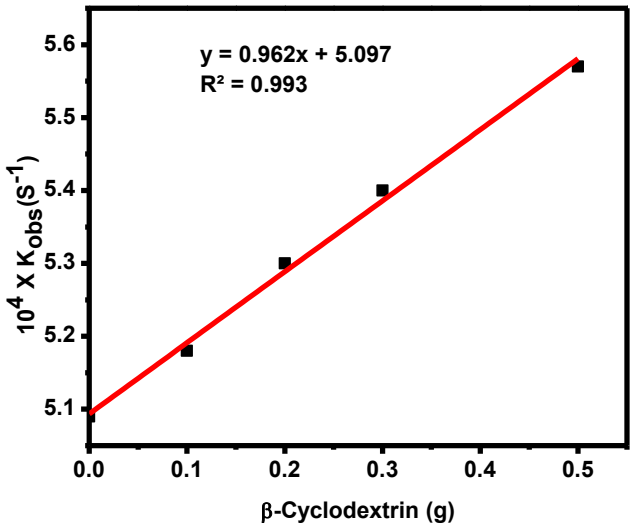


Fig. 3 Plot of k_{obs} vs [β-cyclodextrin]

$[H^+]$ = 5 x 10^{-1} M; [sodium acetate] = 8.5 x 10^{-2} M; [drug] = 5 x 10^{-2} ; [PMS] = 3.90 x 10^{-3} M; Temperature=308 K.

Effect of $[H^+]$

The effect of $[H^+]$ was also investigated by varying concentrations ranging from 0.79, 2.00, 5.00, 12.5 M^{-1} at constant other parameters. The k_{obs} values increased with increase in $[H^+]$ The plot of k_{obs} vs. $[H^+]$ gave straight lines Fig 4.

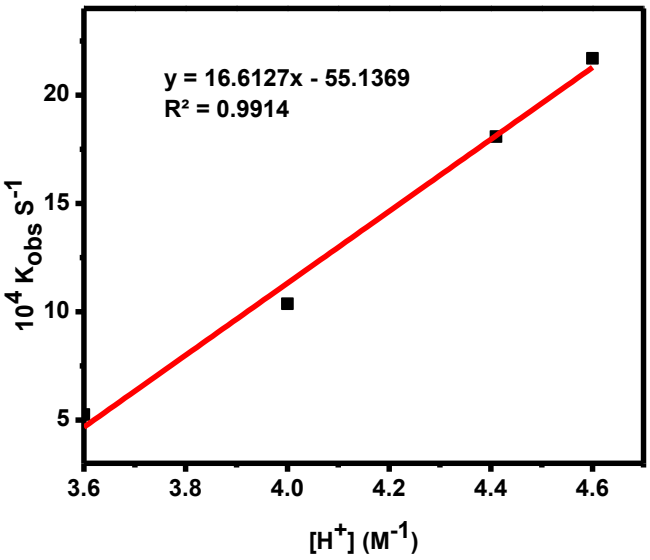


Fig. 4 Plot of k_{obs} vs. $[H^+]$ at 308 K

[drug] = 5 x 10^{-2} M; [sodium acetate] = 8.5 x 10^{-2} M: [β-cyclodextrin] = 0.3g; [PMS] = 3.90 x 10^{-3} M; Temperature=308K

Effect of temperature on k_{obs}

The rate of the reaction was studied by varying the temperature, viz., 303, 308, 314 and 318 K. and also by keeping other parameters at constant values. The k_{obs} increased with the increase in temperature (Table 1) .[15] The rate constant K_2 was calculated [16] Plot of log k_2 vs. 1/T Fig.5 was a straight line (Arrhenius plot) From the slope and intercept Fig. 5 thermodynamic parameters : ΔG^o, ΔH^o and ΔS^o values are -30.06 kJ mol^{-1}, 77.61 KJ mol^{-1}, 97.85J $K^{-1}mol^{-1}$respectively (Table 2). ΔG^o obtained are negative, which indicated that the inclusion process formed spontaneously at the experimental temperature. The positive ΔH^o together with positive ΔS^o suggested that the formation is an enthalpy controlled process.

Table 1: Effect of varying concentrations on the reaction rate at 308K

10^3 x [PMS] (mol dm^{-3})	10^2 x [drug] (mol dm^{-3})	10^2 x [sodium acetate] (mol dm^{-3})	pH± 0.1	β-cyclodextrine (gram)	10^4x k_{obs} (s^{-1})	Temperature (K)
1.93	5.00	8.50	4.0	0.3	5.20	308
3.86	5.00	8.50	4.0	0.3	5.28	308
5.79	5.00	8.50	4.0	0.3	5.28	308
7.72	5.00	8.50	4.0	0.3	5.28	308
3.86	0.025	8.50	4.0	0.3	3.22	308
3.86	0.0375	8.50	4.0	0.3	4.99	308
3.86	0.05	8.50	4.0	0.3	5.41	308
3.86	0.0625	8.50	4.0	0.3	5.99	308
3.86	5.00	2.13	4.0	0.3	5.04	308
3.86	5.00	4.25	4.0	0.3	5.04	308
3.86	5.00	6.38	4.0	0.3	5.04	308
3.86	5.00	10.63	4.0	0.3	5.04	308
3.86	5.00	8.50	3.6	0.3	10.28	308
3.86	5.00	8.50	4.0	0.3	10.40	308
3.86	5.00	8.50	4.4	0.3	13.43	308
3.86	5.00	8.50	4.8	0.3	15.40	308
3.86	5.00	8.50	4.0	0.1	5.14	308
3.86	5.00	8.50	4.0	0.2	5.18	308

3.86	5.00	8.50	4.0	0.3	5.41	308
3.86	5.00	8.50	4.0	0.5	5.57	308
3.86	5.00	8.50	4.0	0.3	5.02	303
3.86	5.00	8.50	4.0	0.3	10.28	308
3.86	5.00	8.50	4.0	0.3	12.09	314
3.86	5.00	8.50	4.0	0.3	19.88	318

Table 2: Kinetic and thermodynamic parameters for the oxidation of drug using β-cyclodextrin catalyst at 308 k

Drug	ΔH^0 KJ mol^{-1}	ΔS^0 J K $^{-1}$mol^{-1}	ΔG^0 kJ mol^{-1}
HISTIDINE	77.61	97.85	-30.06

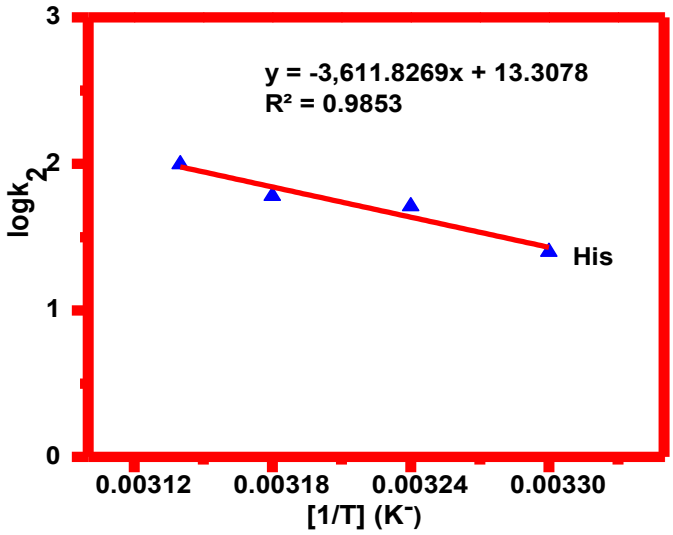


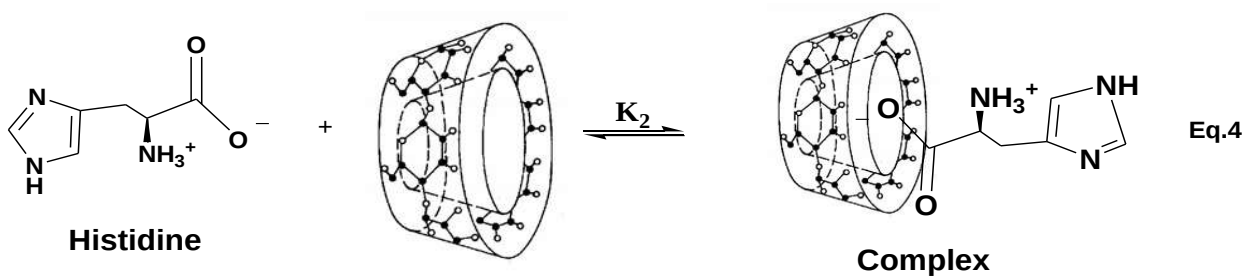
Fig. 5 Plot of log k_2 vs. 1/T (Arrhenius plot)

$[H^+]$ = 5 x 10^{-1} M; [sodium acetate] = 8.5 x 10^{-2} M: [β-cyclodextrin] = 0.3g; [drug] = 5 x 10^{-2} M ; [PMS] = 3.90 x 10^{-3} M

Thermodynamics values of the inclusion Complex

The ability of a cyclodextrin to form an inclusion complex with a guest molecule is a function of two key factors. The first is steric and depends on the relative size of the cyclodextrin to the size of the guest molecule or certain key functional groups within the guest. If the guest is the wrong size, it does not fit properly into the cyclodextrin cavity. The second critical factor is the thermodynamic

interactions between the different components of the system (cyclodextrin, guest, solvent). For a complex to form there must be a favorable net energetic driving force that pulls the guest into the cyclodextrin. . Hydrophobic interaction involves favorable positive entropy together with a slightly positive enthalpy change (Table 1), whereas the other forces involve negative ΔH^0 and ΔS^0 [17,18] Table 2



Absorption spectra

Absorption spectra were used to confirm the formation of inclusion complex. [19]. The concentrations of β-cyclodextrin is 500 mg and concentration of histidine is 50 mg. The inclusion complex had a decreased intensity at all points of wavelength due to the interaction of β-cyclodextrin and histidine (Fig.6). It is observed that, the absorbance value decreased with increasing β-cyclodextrin concentrations while the concentration of histidine remains the same. It indicates that the solubility of histidine increases upon forming the inclusion complex [20]. This theory can be proved if a linear relationship obtained from the reciprocal plot of 1/*A* *vs.* 1/[ß-Cyd] (Fig.7) based on the Hildebrand-Benesi Equation [21].

From the linear plot the stability constant was calculated 321.7 LM^{-1}. The stoichiometry ratio for the inclusion complex formation between histidine and β-cyclodextrin is 1:1. The LOD value and LOQ values for the inclusion complex are 0.927LM^{-1} and 2.81 LM^{-1}. (Table 3) In the absence of β-Cyclodextrin for the LOD and LOQ values 0.14 µg/mL and 0.042 µg/mL was reported [22]. In addition β-Cyclodextrin was added to the drug (histidine) was enhanced. The LOD values raised from 0.14 µg/mL to 0.927LM^{-1}. LOQ values raised from 2.81 LM^{-1} to 0.042 µg/mL. So it was pharmaceutical formulation with good accuracy of drug delivery.

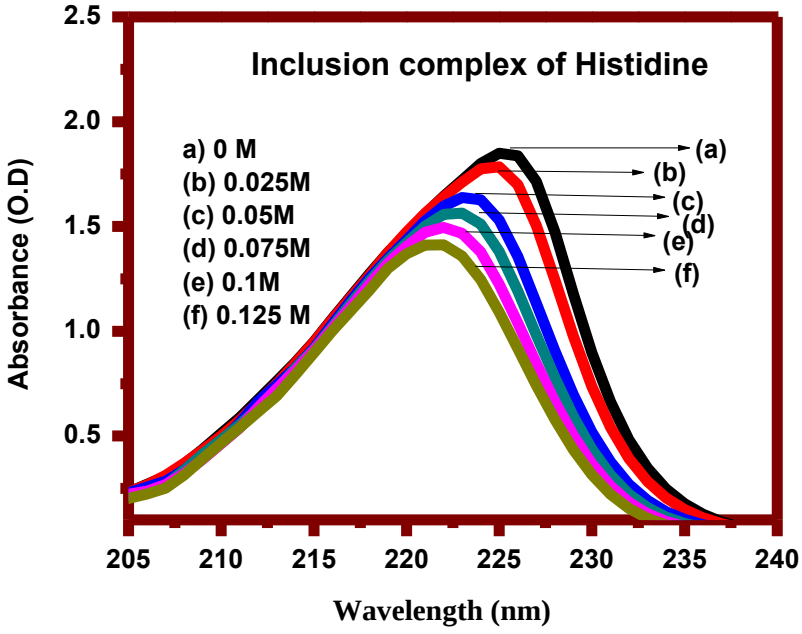


Figure 6 Absorption spectra of the inclusion complex of β-CD with [drug]
$[H^+]$ = 5 x 10^{-1} M; [sodium acetate] = 8.5 x 10^{-2} M;
[β-cyclodextrin] = 50mg

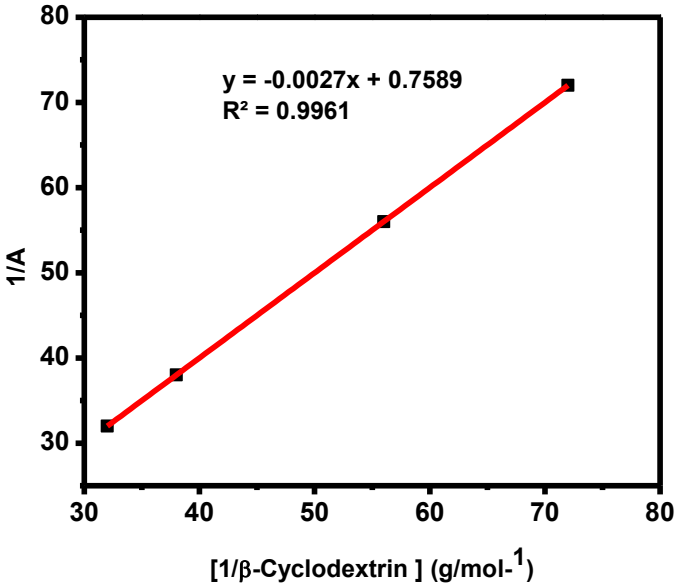


Fig. 7 Reciprocal plot for 1/A against 1/β–CD of drug inclusion complex

Table3: Detemination of Spectrophotometry

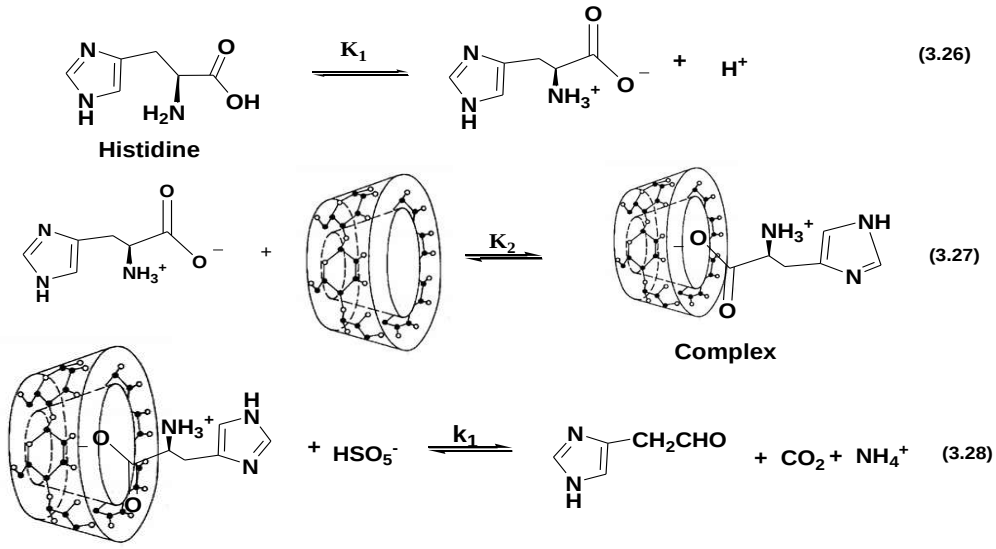
Histidine	Drug
Stability constant values	321.7 LM^{-1}
Linearity Equation	Y= -0.0027x + 0.7589 R^2= 0.9961
LOD	0.927LM^{-1}
LOQ	2.81 LM^{-1}

Conclusion

Kinetic results for the variation of histidine and β-cyclodextrin showed that the k_{obs} increased with increase in [histidine] and β- Cyclodextrin. Hydrophobic interaction essentially involves favorable positive entropy together with a slightly positive enthalpy change, whereas the other forces involve negative ΔH^0 and ΔS^0. As discussed above, ΔG^0 obtained are negative, which indicated that the inclusion process proceeded spontaneously at experimental temperature. ΔH^0 and ΔS^0 are 77.61 KJ

mol^{-1}97.85 J K $^{-1}$mol^{-1}suggested that guest-host is an enthalpy controlled process. Detailed mechanism was discussed scheme1

Scheme: 1



$$2HSO_5^- \xrightarrow{k_2} HSO_4^- + O_2 \quad (3.29)$$

$$-\frac{d[HSO_5^-]}{dt} = k_1[\text{Complex}]\,[HSO_5^-] + k_2[HSO_5^-] \quad (3.30)$$

$$= \frac{k_1K_1K_2[\text{Histidine}]\,[\beta\text{-CD}]\,[HSO_5^-]}{K_1 + [H^+]} + k_2[HSO_5^-] \quad (3.31)$$

$$k_{obs} = \frac{k_1K_1K_2[\text{Histidine}]\,[\beta\text{-CD}]}{K_1 + [H^+]} + k_2 \quad (3.32)$$

Since $K_1 << [H^+]$

$$\text{Hence} \quad k_{obs} = \frac{k_1K_1K_2[\text{Histidine}]\,[\beta\text{-CD}]}{[H^+]} + k_2 \quad (3.33)$$

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