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Research Paper

Kinetics and mechanism of oxidation of cetirizine hydrochloride, an anti-allergy agent by Mn(VII) in acidic medium

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Abstract

The kinetics and mechanism of oxidation of cetirizine hydrochloride by Mn(VII) in acidic medium was studied spectrophotometrically. The electron transfer reaction between MnO_4^- and the drug have been studied over the range $2.0 \leq 10^3$ [cetirizine hydrochloride] ≤ 6.0, $2.5 \leq$ pH ≤ 4.5 and 295 K $\leq$ T $\leq$ 313 K in aqueous medium. The electron transfer reaction shows first order dependence in $[MnO_4^-]_T$ and [cetirizine hydrochloride]. The rate of the reaction was found to increase with increasing pH of the medium. The conjugate base of the reactant drug and MnO_4^- reacts to produce products. The activation parameters $\Delta H^{\neq}$ (kJ mol^{-1}) and $\Delta S^{\neq}$ (JK^{-1} mol^{-1}) for the electron transfer reaction was found to be 33.93 and -143.00. The product of the reaction was cetirizine N-oxide.

Keywords: *Cetirizine, Oxidation, Kinetics, Cetirizine N-Oxide, Spectrophotometer.*

1. Introduction

MnO_4^- is a strong oxidant with the standard redox potential (E^O) as 1.51 volt (Atkin et al.2012) for the MnO_4^-/Mn^{2+} couple. The oxidation state of Mn in the different manganese containing species may vary from +7 to +2 depending upon the nature of the Mn species and pH of the medium. Mn in +7 oxidation state is most potent oxidant in acidic medium. The electron transfer reaction of Mn(VII) in acidic medium has been extensively studied (Arrizabalaga et al.1996, Hassan et al.2009, Zaafarany.2010, Mohanty et al.2013)Large biological molecules such as nucleic acid (Simandanetet al.1998), proteins(Terashima etal.1999) ,thymine(Freeman et al.1975), Uracil(Freeman et al.1981), several amino acids(Mudalior et al.1983, Verma et al.1976, Perzez et al.1987, Zammar et al.1992, Timmanagoudar et al.1997, Timmanagoudar et al.1996) have already been studied. But the oxidation of various water soluble drugs with MnO_4^- has not been carried out. In this paper we present the redox reaction of an anti-allergic drug cetirizine hydrochloride by MnO_4^- . This study will show the path how the drug is oxidized under physiological conditions.

2. Experimental materials

The substrate cetirizine hydrochloride (CTZH) is of analytical grade of purity, was provided by local pharmaceutical company. It was used as received. Aqueous solution of cetirizine hydrochloride of desired strength was prepared in double distilled water freshly each time whenever required. Oxidant $KMnO_4^-$ (Merck) solution was prepared by standard procedure. It was standardized with standard Fe^{2+} solution (Vogel et al.1989). Fe^{2+} solution was standardized with the standard $Cr_2O_7^{2-}$ in acid medium (Mendham et al, 2011) All chemicals used were AnalaR grade of purity. Double distilled water was used throughout the work.

2.1. Kinetic measurements

The kinetics of oxidation of drug by MnO_4^- in acid medium was studied in temperature range 293K to 313K using Systronic 2202 UV-Vis spectrophotometer equipped with a thermostatic water bath for temperature control (accuracy = 0.1°C). The pH of the solution was measured using pre-standardized Elico (India) digital pH meter equipped with glass electrode. The kinetics of oxidation of drug was studied under pseudo-first order condition with [CTZH]: $[KMnO_4] > 10$: 1 at constant ionic strength I = 0.5 mol dm^{-3} ($NaClO_4$). The reaction was initiated by thoroughly mixing solutions of $[MnO_4^-]$, [CTZH] at definite pH. The progress of the reaction was monitored by following decrease of absorbance of $[MnO_4^-]$ at 525 nm. The pseudo-first order rate constant (k_{obs}) were evaluated from the slope of linear plots of ln $(A_t - A_\infty)$ vs t(s) from the relationship

$$\ln (A_t - A_\infty) = \ln (A_o - A_\infty) - k_{obs} \cdot t$$

Where A_o, at and A_∞ denote optical density of the reaction mixture at zero time, time't' and infinite time respectively. A_∞ Was measured after completion of the reaction. The correlation coefficient of plots used to determine k_{obs} were found to be 0.99 in most of the cases. Duplicate kinetic runs showed that the rate constants were reproducible within ±5%. All calculations were made on a PC using least square program.

2.2. Stoichiometry and identification of product

Different sets of the reaction mixture containing different amount of reactants $[MnO_4^-]$ > [CTZH] at constant pH and constant ionic strength I = 0.5 mol dm^{-3} were allowed to react for 3 h at 298 K in an inert atmosphere. The remaining MnO_4^- was analyzed spectrophotometrically. The result showed that two moles of MnO_4^- reacted with 5 moles of cetirizine hydrochloride.

$$5\ \text{CTZH} + 2\ MnO_4^- + 6\ H^+ \rightarrow 5\ \text{CTZH-N-Oxides} + 2\ Mn^{2+} + 3H_2O$$

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In order to get the reaction product 0.2 mol of $KMnO_4$ and 0.02 mol of CTZH were mixed at pH = 2, 298 K and kept for 5 h. Then it was concentrated by slow heating. The pasty mass was taken in watch glass and kept in a desiccators containing silica gel. After 48h, the crystalline product was formed and washed with ethanol and dried. The product was identified by FTIR as recorded in Perkin Elmer (UK) FTIR Spectrophotometer. FTIR spectra of the product given in Fig. 1(b) exhibits a broad peak at 3406 cm^{-1} and 3243 cm^{-1} corresponds to O-H stretching over lapping with C - H stretching of aromatic group. Two strong absorption bands at 1608 cm^{-1} and 1388 cm^{-1} corresponds to aliphatic N-O stretching and 713 cm^{-1} corresponds to monosubstituted benzene (Nakamato et al.1997). Comparing the FTIR spectra of cetirizine hydrochloride Fig. 1(a), the product was identified as cetirizine N-Oxide. Similar product was predicted by other author (Dyakonov et al, 2010) when cetirizine was oxidized by H_2O_2.

3. Results and discussion

When cetirizine hydrochloride (CTZH) was added to acidified ($HClO_4$) $KMnO_4$, the solution changed its color from violet to green. The spectra of green solution was identified as MnO_4^{2-} (Chimatadar et al.2003). It is evident from UV-Vis spectral scan as shown in Fig. 2. After a long interval (after 5h) the peak at 525 nm completely vanished and the solution becomes colorless due to formation of $[Mn(H_2O)_6]^{2+}$.

The kinetics of this redox reaction was followed at different concentration of oxidant, substrate and at different pH at λ_{max} = 525 nm and results tabulated in Table-1.

Effect of Substrate

When the cetirizine hydrochloride was changed from 2 x 10^{-3} to 6 x 10^{-3} mol dm^{-3} keeping all other conditions constant, the observed pseudo-first order rate constants. 10^3 k_{obs} (s^{-1}) varied from 0.793 to 1.18. Plot of k_{obs} versus [cetirizine hydrochloride] mol dm^{-3} was linear (Fig. 3) indicating first order dependence of rate with respect to cetirizine hydrochloride.

Effect of pH

The observed rate of oxidation also affected by pH of the medium (H^+ concentration). When pH varied from 2.5 to 4.5 keeping the entire conditions constant, the observed pseudo-first order rate constant 10^3k_{obs} (s^{-1}) changed from 0.795 to 0.95. Plot of 10^3k_{obs} (s^{-1}) versus pH was linear (Fig, 4). This indicates first order dependence of rate of oxidation as $[H^+]$ ion concentration.

Ionic strength effect

The effect of ionic strength was studied by varying I = 0.5 to 1.0 mol dm^{-3} ($NaClO_4$) keeping all other conditions remaining constant. The rate of pseudo-first order reaction was almost unchanged indicating rate of reaction is independent of ionic strength. This suggests that one of the reactant species is a neutral molecule (Amies et al.1996)

Free radical test

Addition of aqueous solution of acrylonitrile (6% v/v) to the reaction mixture did not initiate polymerization suggesting non-involvement of free radicals during oxidation.

Effect of temperature

The effect of temperature on reaction rate was studied by conducting kinetic runs at different temperatures (293K - 313 K) keeping all other experimental conditions constant. The rate of oxidation reaction increases with increase of temperature. At pH = 2.5 [CTZH] = 2 x 10^{-3} mol dm^{-3}, $[MnO_4^-]$ = 2 x 10^{-4} mol dm^{-3}, the observed pseudo-first order rate constant changed from 0.63 to 0.893 when temperature varied from 293K to 313K. From the linear Arrhenius plot of log k versus 1/T ($R^2 \approx 0.9$), the values of activation parameters $\Delta H^{\neq}$ (activation enthalpy) and $\Delta S^{\neq}$ (activation entropy) were calculated and tabulated in Table -2.

Mechanism of the reaction

The ionization equilibria of the drug cetirizine hydrochloride (AH_3) with their equilibrium constants were shown below. In acid medium AH_2^- is the predominant species.

K_1

$AH_3 \rightleftharpoons AH_2^- + H^+ \qquad pK_1 = 1.52$

K_2

$AH_2^- \rightleftharpoons AH^{2-} + H^+ \qquad pK_2 = 2.92$

K_3

$AH^{2-} \rightleftharpoons A^{3-} + H^+ \qquad pK_3 = 8.27$

The UV-Vis spectral scan Fig. 2 shows there is no shifting of λ_{max} = 525 nm during oxidation reaction indicating there is no intermediate complex formation suggesting outer sphere mechanism.

Based on the above experimental results the probable mechanism may be delineated as in Scheme-I.

AH_2^- is the predominant species in acid medium. In acid medium AH_2^- dissociates to $AH^{2-} + H^+$, where K_2 is the proton dissociation constant of AH_2^- species which is represented as

$$AH_2^- \rightleftharpoons AH^{2-} + H^+$$

$$K_2 = \frac{[AH^{2-}][H^+]}{[AH_2^-]}$$

$$[AH^{2-}] = K_2 \frac{[AH_2^-]}{[H^+]}$$

$$AH^{2-} + MnO_4^- \xrightarrow{k_{et}} \text{Products}$$

Slow

Scheme - I

From Scheme - I, the rate law can be derived as

$$\text{Rate} = k_{et}[AH^{2-}]_e[MnO_4^-]_T = \frac{k_{et} K_2 [AH_2^-]_e [MnO_4^-]_T}{[H^+]}$$

$$[AH_2^-]_T = [AH_2^-]_e + [AH^{2-}]_e = [AH_2^-]_e + K_2[AH_2^-]/[H^+]$$

$$= [AH_2^-]_e \left\{ \frac{[H^+] + K_2}{[H^+]} \right\}$$

$$[AH_2^-]_e = \frac{[H^+][AH_2^-]_T}{([H^+] + K_2)}$$

$$\text{Rate} = \frac{k_{et} K_2 [AH_2^-]_T [MnO_4^-]_T}{([H^+] + K_2)}$$

Since rate = kobs $[MnO_4^-]_T$

Comparing two rate equations

$$k_{obs} = \frac{k_{et} K_2 [AH_2^-]_T}{([H^+] + K_2)}$$

$[AH_2^-]_T = [AH_3]_T$ in the pH range 2.5 to 4.5 hence the rate law can be rewritten as

$$k_{obs} = \frac{k_{et} K_2 [AH_3]_T}{([H^+] + K_2)}$$

The rate law is consistent with experimental findings. From the above equation k_{et}, electron transfer reaction rate and K_2, the 2nd equilibrium constant can be calculated. The above equation can be rewritten as

$$\frac{k_{obs}}{[AH_3]_T} = k_2' = \frac{k_{et} K_2}{[[H^+] + K_2]}$$

Where is k_2' second order rate constant?

$$\frac{1}{k_2'} = \frac{[H^+] + K_2}{k_{et} K_2} = \frac{1}{k_{et}} + \frac{[H^+]}{k_{et} K_2}$$

$1/k_2'$ is plotted against $[H^+]$, the plot is linear, it produces intercept and slope.

Intercept (I) = $1/k_{et}$

Slope (S) = $1 / (k_{et}K_2)$

$I/S = K_2$ and $1/I = k_{et}$

Hence K_2 and k_{et} calculated from experimental results. Calculated K_2, pK_2 =2.33 at 298K is comparable with the reported data 2.93(Amies 1996) this results support the suggested mechanism. Electron transfer reaction rate (k_{et}) were calculated at 4 different

temperature (298 - 313 K) using these data on Eyring equation activation parameters were calculated and tabulated in Table 2 as

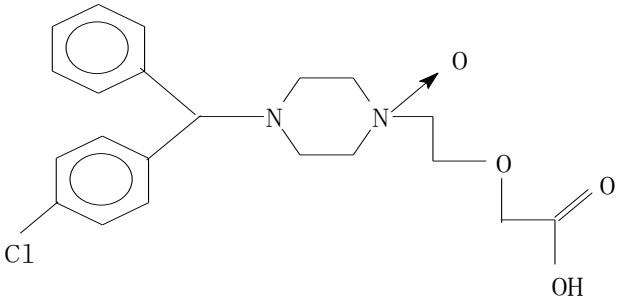
$\Delta H^{\neq}$ =33.93 k J mol^{-1}

$\Delta S^{\neq}$ =- 143.0 J K^{-1} mol^{-1}

The $\Delta H^{\neq}$ value was due to release of energy of solution change in the transition state. The negative value of $\Delta S^{\neq}$ indicate the loss of degree of freedom and formation of rigid transition state. The moderate value of activation parameters favours the electron transfer reaction between drug and MnO_4.

4. Conclusion

The kinetics of oxidation of cetirizine with MnO_4^- indicates that cetirizine is susceptible to oxidation in biological system. Sterically less hindered piperazine nitrogen undergoes oxidation forming cetirizine N-Oxide. It was supported by LCMS and ^1H NMR reported by others (Puttaswamy et al.2012) that oxidation product of cetirizine was cetirizine N-Oxide. So N-oxidation is the major pathway for cetirizine transformation. The reaction with respect to substrate and oxidant is first order but the overall electron transfer reaction is second order.



Cetirizine N-Oxide

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Table 1: Pseudo-first order rate constant (k_{obs} Sec^{-1}) of oxidation of Cetrizine Hydrochloride at different pH and different temperatures.

Concentration. (mol dm^{-3})	pH	10^3 k_{obs} (s^{-1})			
		293 K	298 K	308 K	313 K
0.002	2.5	0.631	0.717	0.795	0.893
	3.0	0.651	0.723	0.821	0.921
	3.5	0.748	0.754	0.869	0.949
	4.0	0.776	0.833	0.891	0.982
	4.5	0.81	0.951	0.982	1.07
0.003	2.5	0.673	0.833	0.891	1.05
	3.0	0.691	0.871	0.940	1.07
	3.5	0.805	0.949	0.998	1.09
	4.0	0.845	1.075	1.12	1.20
	4.5	0.96	1.102	1.18	1.31
0.004	2.5	0.721	0.898	0.978	1.08
	3.0	0.74	0.92	1.03	1.09
	3.5	0.830	1.07	1.11	1.176
	4.0	0.915	1.16	1.24	1.33
	4.5	1.06	1.26	1.30	1.46
0.005	2.5	0.801	0.902	1.03	1.14
	3.0	0.89	1.01	1.17	1.28
	3.5	0.901	1.13	1.25	1.32
	4.0	1.02	1.27	1.30	1.46
	4.5	1.10	1.37	1.43	1.62
0.006	2.5	0.908	0.992	1.18	1.66
	3.0	0.941	1.26	1.28	1.33
	3.5	1.075	1.30	1.32	1.41
	4.0	1.15	1.41	1.46	1.62
	4.5	1.21	1.45	1.48	1.66

Table 2: Electron transfer reaction rate constant and their activation parameters.

Temp. ^oA	293 K	298 K	308 K	313 K
k_{et} (dm^3 mol^{-1})	0.188	0.236	0.389	0.471
$\Delta H^{\neq}$ + 33.928 k J $\Delta S^{\neq}$ - 143.0 J K^{-1} mol^{-1}				

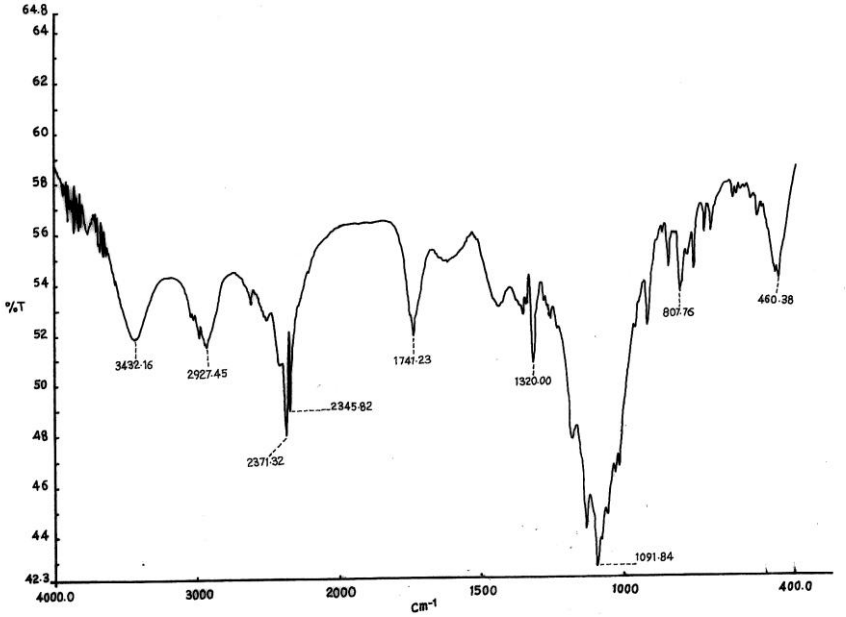

Fig. 1: (A) FTIR Spectra of Cetirizine Hydrochloride

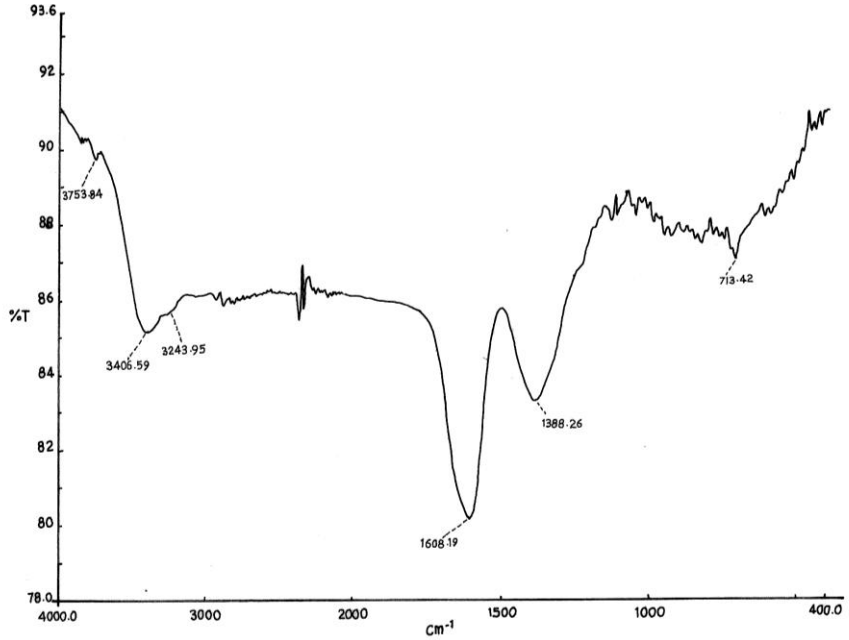

Fig. 1: (B) FTIR spectra of product (Cetirizine N-Oxide)

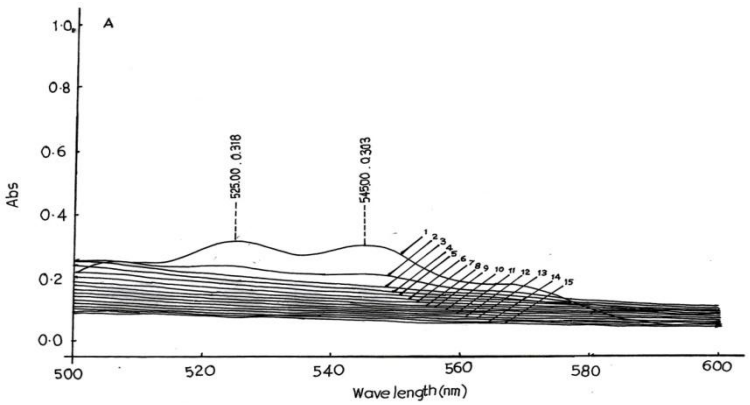

Fig. 2: UV-Vis spectral scan of the reaction mixture $[Mno_4^-]$ = 2 x10^{-4} mol dm^{-3}(1) with [CTZH] = 2 x10^{-3} mol dm^{-3} at 298K, I = 0.5 mol dm^{-3} immediately after mixing at different time interval curves (2-15), Δt =1 minute.

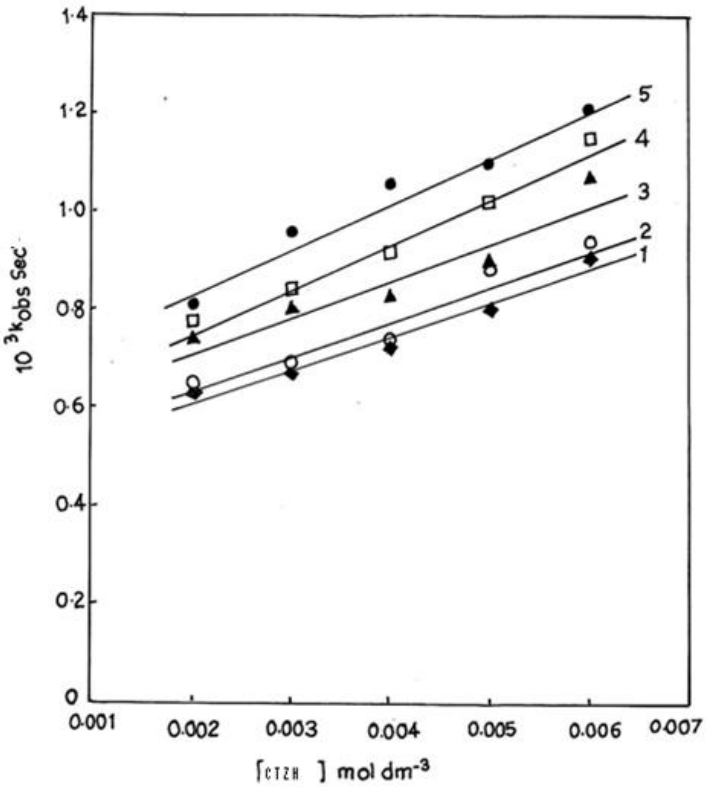

Fig. 3: Plot of k_{obs} versus mol dm^{-3} at 293 K, at pH =2.5 (1), 3.0 (2) 3.5 (3), 4.0 (4), 4.5 (5).

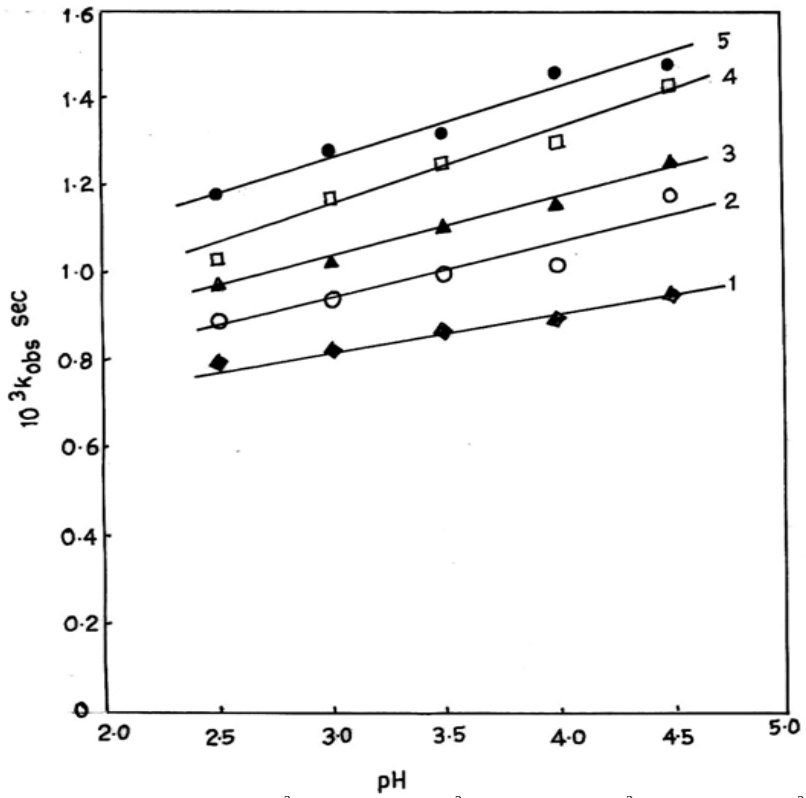

Fig. 4: Plot of k_{obs} versus pH at 298 K, [CTZH] = 0.002 mol dm^{-3} (1), 0.003 mol dm^{-3} (2), 0.004 mol dm^{-3} (3), 0.005 mol dm^{-3} (4), 0.006 mol dm^{-3} (5).

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