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ELECTRON TRANSFER REACTION BETWEEN PYRIDINIUM CHLOROCHROMATE (VI) AND METFORMIN, AN ANTIDIABETIC DRUG IN AQUEOUS ACID MEDIUM

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ABSTRACT

The electron transfer reaction of metformin with pyridinium chlorochromate (PCC) has been studied spectrophometrically over the range $2.0 \leq 10^3$[Metformin] ≤ 6.0, $0.05 \leq [H^+] \leq 0.20$, $293 \leq T \leq 313$ K and I = 0.3mol dm^{-3} ($NaClO_4$). The rate of the reaction is found to increase with increase in $[H^+]$ and [Metformin]. The activation parameters such as $\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$ for electron transfer reaction are found to be 11.55 ± 2.08 k J mol^{-1} and -212.3 ± 6.78 J K^{-1} mol^{-1} and 74.8 k J mol^{-1} respectively. Positive value of $\Delta G^{\neq}$ and positive value of $\Delta H^{\neq}$, indicate that transition state is highly solvated while negative value of $\Delta S^{\neq}$ suggests the formation of the compact activated complex. The oxidation product was isolated and identified as metformin N-Oxide which was supported by FTIR and Mass Spectral analysis.

KEYWORD: Kinetics and mechanism, electron transfer, pyridinum chlorochromate, metformin.

1. INTRODUCTION

The redox reaction of drugs in aqueous medium is a comparatively new area of research. Out of several reactions of drug under physiological conditions, oxidation is a major reaction. Hence study of redox reaction is important. Several redox reactions by chromium(VI) compounds have been reported such as oxidation of monosachhorides,[1] amino acids.[2] unsaturated acids,[3] aliphatic and aromatic alcohols,[4] phenols,[5] hetrocyclic compounds,[6] vitamin-C,[7] organic sulfur compounds,[8] peptides,[9] paracetamol.[10] However the oxidation

study of drug by Cr(VI) is very rare. We report here the oxidation of antidiabetic drug metformin by Cr(VI) complex, pyridinium chlorochromate (PCC) in acid medium.

Metformin is a biguanide anti-hyperglycemic agent,[11] having molecular formula $C_4H_{11}N_5.HCl$ and IUPAC name 3-(diaminomethylidene)-1,1-dimethyguanidine hydrochloride. It is used in the treatment of non-insulin dependent diabetes mellitus (NIDDH) or type-2 diabetes not responding to dietary modifiation. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose and increasing insulin mediated glucose up take.[12]

Interestingly this drug has two imino and one each of primary, secondary and tertiary amino centres in the molecular frame for donor sites and possible interaction with metal ions.

PCC is a mild oxidizing agent and is also used for quantitative detection of Cr(VI) in urine. When PCC with 5-diphenyl carbazide (DPC) is added to urine, immediately red colour appeared due to formation of chromium-DPC complex which shows a characteristic absorption peak and 544 nm and a shoulder at 575 nm.[13] This prompted us to study the interaction of PCC with metformin due to their biological relevance. We hope this study wil be helpful to understand the reaction of metformin in biological domain.

2. EXPERIMENTAL

2.1 Materials and reagents

Analytical grade chemicals were used. Pyridinium chlorochromate (PCC) was procured from Aldrich. Metformin was procured from local pharmaceutical firm. Ionic strength was maintained at I = 0.3 mol dm^{-3} by using freshly prepared $NaClO_4$ solution. Solution of different concentrations were prepared by proper dilution of the stock solution, fresh solutions were used for kinetic measurements. The strength of stock $NaClO_4$ solutions was estimated by a combined ion exchange alkali metric procedure. The resin Dowex 50W X8 (Na^+ form) was used for ion-exchange experiments. Fresh solutions were prepared using double distilled water in an all-quartz distillation apparatus containing $KMnO_4$ solution.

2.2. Kinetic measurements

The kinetics of the reaction between metformin and PCC in the aqueous acid medium was studied spectrophotometrically under pseudo-first order conditions with excess of metformin using temperature control SHIMAZU 1800 (German) UV-Vis Spectrophometer equipped

with a peltier system. The progress of the reaction was monitored by following decrease in absorbance at 360 nm with time using a convential mixing technique. A_∞ was measured after completion of the reaction (approximately after 24 hours of mixing) when the absorbance became almost constant.

The plot of ln (A_t - A_∞) versus t was found to be linear as indicated in the equation (1).

$$\ln (A_t - A_\infty) = \ln (A_o - A_\infty) - k_{obs}.t \quad (1)$$

where A_t and A_∞ are absorbance of the reaction mixture at time 't' and at equilibrium respectively. The correlation coefficient (R^2) of the plots used to determine k_{obs} were found to be 0.99 in most of the case. The redox reaction was followed for about 3 half lives. The reported data represent as an average of duplicate runs were reproducible to within ±3%.

2.3. Stoichiometry and product identification

The reaction mixture containing PCC and metformin in a molar ratio 1:10 was warmed at 318 K to complete the reaction. The unreacted chromium chromium(VI),[14] and product chromium(III) were estimated iodometrically.[15] From the above experimental study, it was observed that 2 moles of PCC reacted with 6 moles of metformin to generate metformin N-oxide and $Cr^{3+}_{(aq)}$. The stoichiometry of the above reaction is explained by equation (2).

$$6 \text{ Metformin} + 2 \text{ PCC} \longrightarrow \text{Metformin N-Oxide} + 2\ Cr(H_2O)_6^{3+} \quad (2)$$

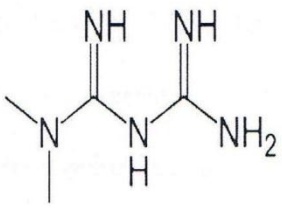
In order to get the reaction product PCC (0.2 mol) and metformin (0.6 mol) were mixed at $[H^+]$ = 0.2 mol dm^{-3}. The volume was made 50 ml. The reaction mixture was warmed for quick completion of the reaction. Metal ion was removed from the solution by using cation exchange resin Dowex 50W X8. The filtrate was evaporated slowly at lower temperature till it was reduced to ⅓ rd of total volume.

The solution was kept over night, a brown crystalline product was isolated and it was washed with diethylether and recrystallise and dried in desiccators. The yield of the product was 60%. The FTIR Spectra (Fig. 1 a, b) of the substrate and the product were recorded with a Perkin Elmer (UK) FTIR Spectrophotometer by using KBr pellet of the sample.

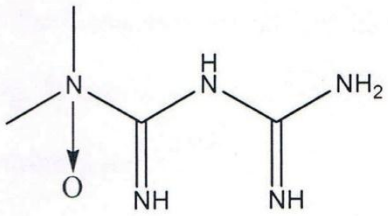
Fig. 1(a) and (b) are FTIR spectra for substrate and isolated product within the range 4000 - 400 cm^{-1}. Assignments of the infra-red spectral bands are based on literature.[16] The Fig. 1(b) shows a broad peak at 3425 cm^{-1} corresponding to the combination of bands such as

coordinated water, N-H stretching in primary amine and >C=NH stretching, 2917 cm^{-1} corresponds to C-H structure in CH_3 group, 1646 cm^{-1} corresponds to N-H bands and >C=N stretching of amino linkage. 1556 cm^{-1} corresponds to secondary N-H stretching, 1381 cm^{-1} is due to C-H bending in CH_3. A characteristic sharp peak at 976 cm^{-1} is due to N-Oxide stretching (aliphatic) which is not found in FTIR spectra of the substrate (Fig. 1a), 665 cm^{-1} is due to C-H out plan deformation (unsymmetrical). The 804 cm^{-1} peaks is due to N-H out plan bending compared with Fig. 1(a) which shows that metformin moiety remains unaffected during the reaction. Hence the product is metforminN-oxide. Similar product was reported by other authors for oxidation of metformin by Bromamin-T[17] and Chloramin- B[18]

Fig. 1(c) represent the mass spectrum of metformin and the product metformin N-oxide. It shows characteristics peaks at m/z 145, 129, 64, 60, 45, 30, 16. Molecular ion peak of metformin N-oxide corresponds to 145 amu and metformin ion corresponds to 129 amu, 60 amu corresponds to $(CH_3)_2NO^+$ and 30 corresponds to $CH_2{=}NH_2^+$ 45 corresponds to $C_2H_5NH_2^+$ where as 16 amu corresponds to NH_2^+. These peaks are in accordance with the proposed product metformin N-Oxide.



Metformin (Substrate)



metformin N-Oxide (Product)

3. RESULTS AND DISCUSSION

The electron transfer reaction between metformin and PCC has been studied over the range $2.0 \leq 10^3[\text{Metformin}] \leq 6.0$, $0.05 \leq [H^+] \leq 0.20$, $293 \leq T \leq 313$ K and I = 0.3mol dm^{-3}. The time dependent spectral scan (Fig. 2a) of the reaction mixture of metformin and PCC over the range $200 \leq \lambda(nm) \leq 400$ shows the decrease of λ_{max} at 360 nm. This indicates no formation of an intermediate species between metformin and PCC. After a long interval (approximately 24 hrs) the peak at 360 nm of the parent complex completely lost and two new peaks appeared at 410 nm and 656 nm (Fig. 2c) which corresponds to the spectrum of $Cr(H_2O)_6$.[19] The k_{obs} of the above reaction are listed in Table 1. The plot of k_{obs} versus

[Metformin] was linear (Fig. 3) for the temperature range studied. The pseudo first order rate constant 10^2 k_{obs} (s^{-1}) = 0.23±0.01 at 298 K was almost not affected by varying [PCC] in the range $2x10^{-3}$ to $6x10^{-3}$ mol dm^{-3} when [Metformin] = 0.005 mol dm^{-3}, $[H^+]$ = 0.05 mol dm^{-3} indicating the fact that the reaction is first order in $[PCC]_T$. The rate of the reaction was found to increase when $[H^+]$ was increased from 0.05 to 0.2 mol dm^{-3} for all the concentration range of metformin studied.

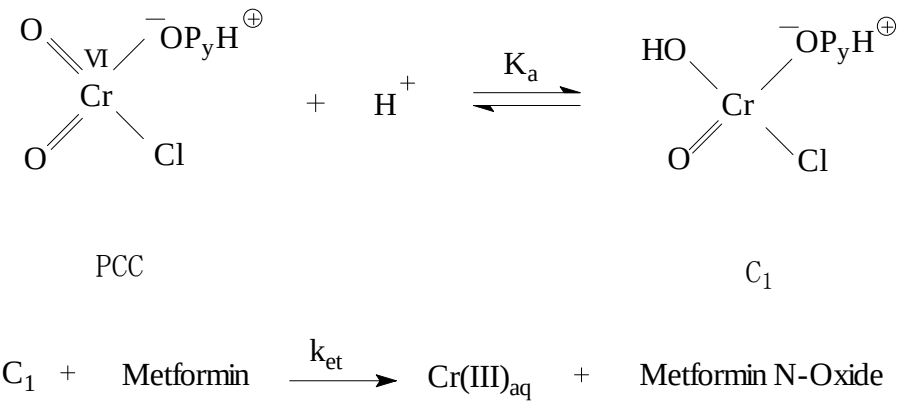
The effect of relative permittivity was studied at 303K by varying acetone 20% to 50% keeping PCC and metformin concentration constant . k_{obs} (s^{-1}) changed from 2.4 x 10^{-3} mol dm^{-3} to 7.05 x 10^{-3} mol dm^{-3} when the dielectric constant changes from 75 to 51. Plot of log k_{obs} versus D^{-1} is a straight line (Fig. 3) with a positive slope (R^2 = 0.98). This indicates ion dipolar interaction in the rate determining step.[20]

The reaction mixture was mixed with acrylonitrile monomer and kept for 2 hrs in an inert atmosphere. On dilution with methanol, white precipitate was not formed indicated the absence of free radical intervention in the reaction.

The effect of ionic strength was studied by varying sodium perchlorate concentration 0.3 to 0.6 mol dm^{-3} keeping all other conditions constant. Plot of log k_{obs} versus $I^{½}$ shows a parallel line,parallel to ionic strength axis (Fig. 4) indicating the reaction is independent of ionic strength.

The reaction rate was measured at four different temperatures from 293 K to 313 K with varying [Metformin] keeping other variables constant. The rate constants k_{obs} was found to increase with increasing temperature.

Basing on the above experimental facts, stoichiometry, identification of product, the probable mechanism may be delineated as in the Scheme I.



Scheme - I

The mechanism of the reaction C_1 with metformin to generate metformin N-Oxide is shown in Scheme II.

Since pK_a of metformin is 2.8, it will remain in undissociated form. The rate law for this electron transfer reaction can be derived in the following way.

$$\text{Rate} = k_{et}\,[C_1]_e\,[\text{Metformin}]_T \quad (3)$$

$$K_a = \frac{[C_1]_e}{[PCC]_e[H^+]_e} \quad (4)$$

$$[C_1]_e = K_a\,[PCC]_e\,[H^+]_e \quad (5)$$

Substitute the value of $[C_1]_e$ in equation (3),

$$\text{Rate} = k_{et}\,K_a\,[PCC]_e\,[H^+]_e \quad (6)$$

$$[PCC]_T = [PCC]_e + [C_1]_e$$

$$= [PCC]_e + K_a\,[PCC]_e\,[H^+]_e \quad (7)$$

$$[PCC]_e = \frac{[PCC]_T}{1+K_a[H^+]_e} \quad (8)$$

Substitute $[PCC]_e$ in equation (6),

$$\text{Rate} = \frac{k_{et}\,K_a\,[PCC]_T\,[H^+]_e\,[\text{Metformin}]_T}{1+K_a[H^+]_e} \quad (9)$$

$$\text{Rate} = k_{obs}\,[PCC]_T \quad (10)$$

Combine equation (9) and equation (10)

$$k_{obs} = \frac{k_{et}\,K_a\,[H^+]_e\,[\text{Metformin}]_T}{1+K_a[H^+]_e} \quad (11)$$

Since $K_a [H^+]_e \leq 1.0$

Equation (11) can be written as

$$k_{obs} = k_{et} K_a [H^+]_e [Metformin]_T \quad (12)$$

k_{obs} versus $[H^+]_T$ plots (Fig, 5) and k_{obs} versus $[Metformin]_T$ plots (Fig. 6) are linear. This supports the rate law indicated in equation (12).

$$\frac{k_{obs}}{[Metformin]_T} = k_{et} K_a [H^+] \quad (13)$$

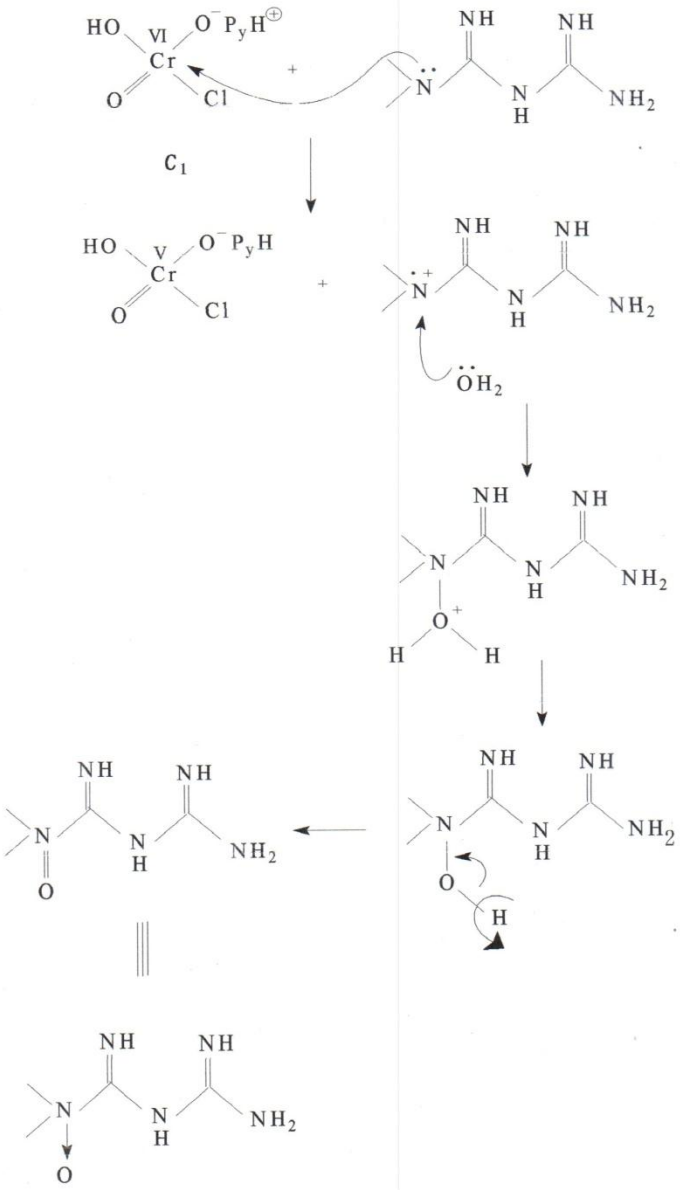
Plot of $\frac{k_{obs}}{[Metformin]_T}$ versus $[H^+]$ is linear (Fig. 7). The slope = $k_{et} K_a = k$

This is a composite rate constant (k). From the composite rate constant at four different temperatures 293 K to 313 K, activation parameters such a activation enthalpy ($\Delta H^{\neq}$), activation entropy ($\Delta S^{\neq}$) are calculated using Erying equation and tabulated in Table 2.

These values are $\Delta H^{\neq}$ = 11.54 $\pm$ 2.08 k J mol^{-1} and $\Delta S^{\neq}$ = -212.3 $\pm$6.78 J K^{-1} mol^{-1}

$\Delta G^{\neq}_{(298)}$ = 74.8 k J mol^{-1}.

The proposed mechanism is supported by the moderate value of energy of activation. Positive value of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, negative entropy of activation suggests the formation of the compact activated complex.



SCHEME II

Table - I: Pseudo first order rate constant (k_{obs} sec^{-1}) of oxidation of metformin hydrochloride at different acid concentration and different temperatures.

10^3 [Metformin] (mol dm^{-3})	10^3 k_{obs} (s^{-1})				
	[Acid]	293 K	298 K	308 K	313 K
2.0	0.05	1.02	1.10	1.15	1.20
	0.1	1.09	1.17	1.20	1.33
	0.15	1.16	1.23	1.28	1.36
	0.2	1.19	1.26	1.31	1.42
3.0	0.05	1.35	1.48	1.52	1.62
	0.1	1.44	1.51	1.58	1.65
	0.15	1.58	1.66	1.72	1.80
	0.2	1.60	1.69	1.75	1.84
4.0	0.05	1.71	1.80	1.87	1.98
	0.1	1.79	1.88	1.90	2.01
	0.15	1.89	1.97	2.06	2.24
	0.2	2.03	2.18	2.17	2.28
5.0	0.05	2.12	2.26	2.39	2.40
	0.1	2.25	2.41	2.51	2.55
	0.15	2.36	2.54	2.64	2.72
	0.2	2.45	2.62	2.76	2.80
6.0	0.05	2.56	2.78	2.85	2.48
	0.1	2.68	2.80	2.91	3.02
	0.15	2.76	2.95	3.10	3.29
	0.2	2.83	3.02	3.15	3.31

Table - II: Electron transfer reaction rate constant (k) at different temperature and their activation parameters.

Temp. A	293 K	298 K	308 K	313 K
10^3 k (mol^{-1} dm^3 s^{-1})	4.4	5.4	5.6	6.4

$\Delta H^{\neq}$ = 11.55± 2.08 K J mol^{-1}

$\Delta S^{\neq}$ = -212.3 ± 6.78 J K^{-1} mol^{-1}

$\Delta G^{\neq}_{298}$ = 74.8 K J mol^{-1}

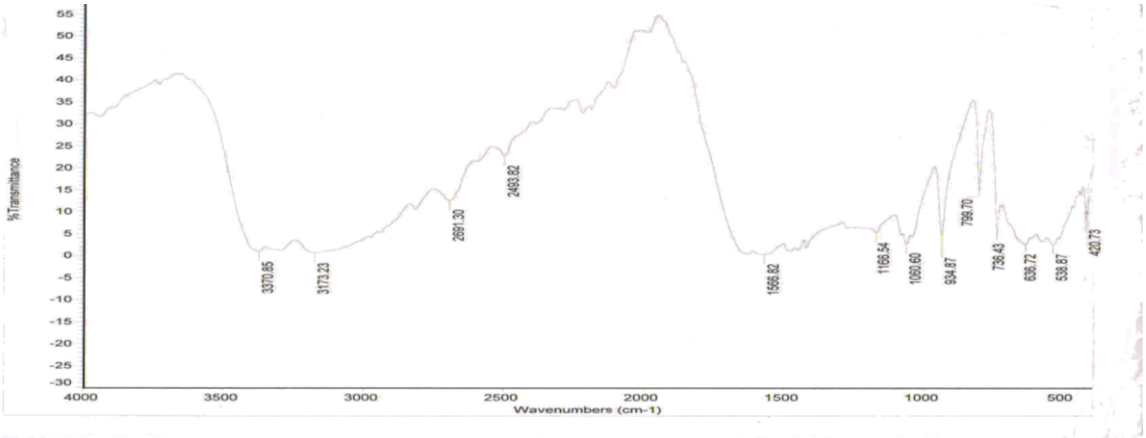


Fig. 1(a): FTIR Spectra of Metformin

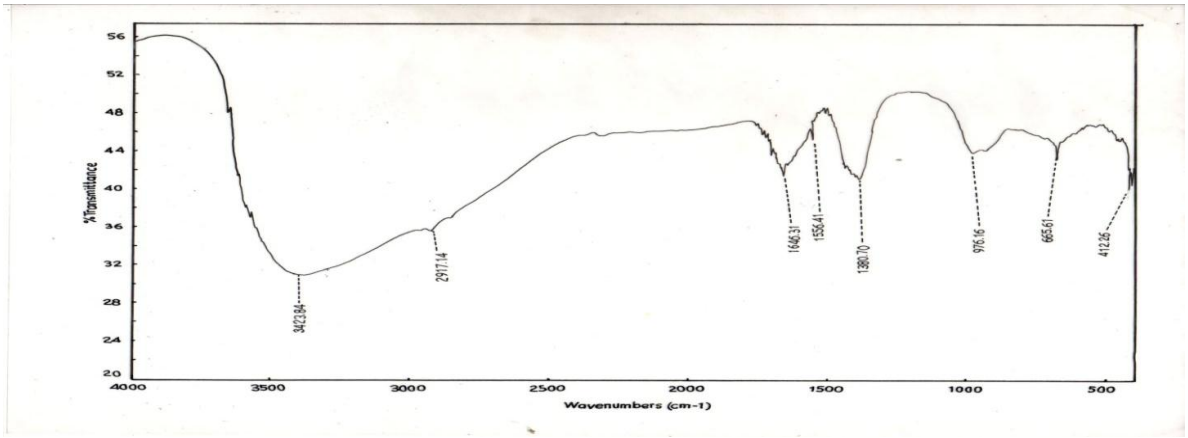


Fig. 1(b): FTIR Spectra of Metformin N-Oxide

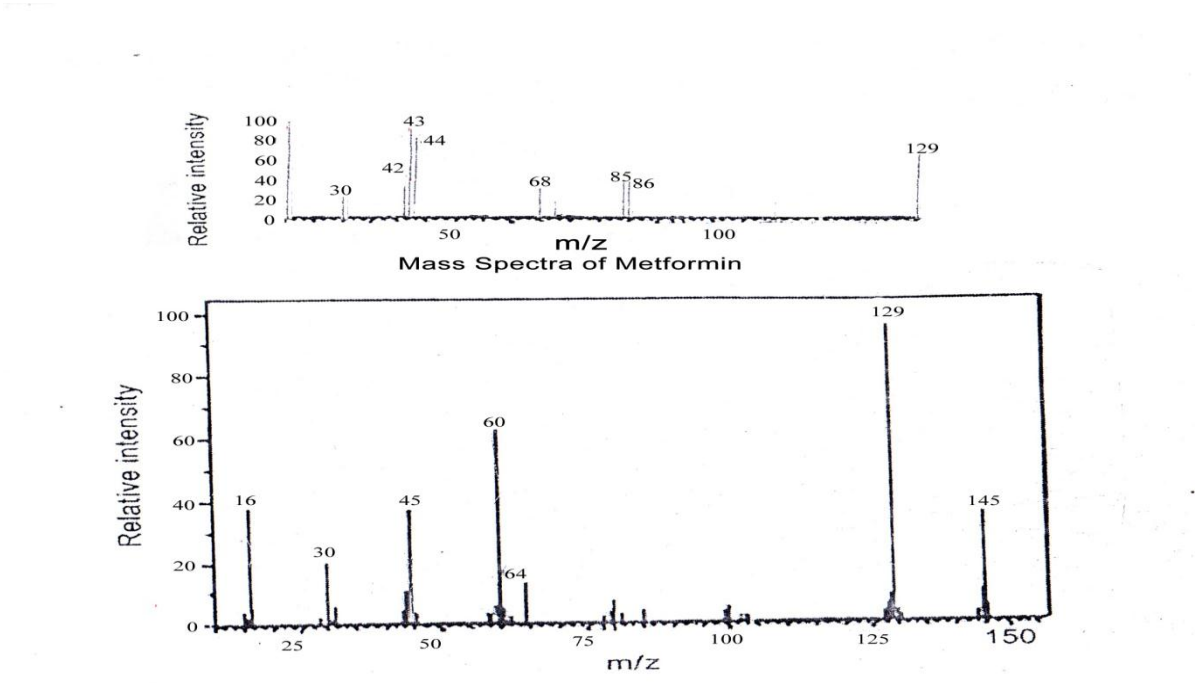


Fig 1 (c) Mass Spectra of Metformin N-oxide

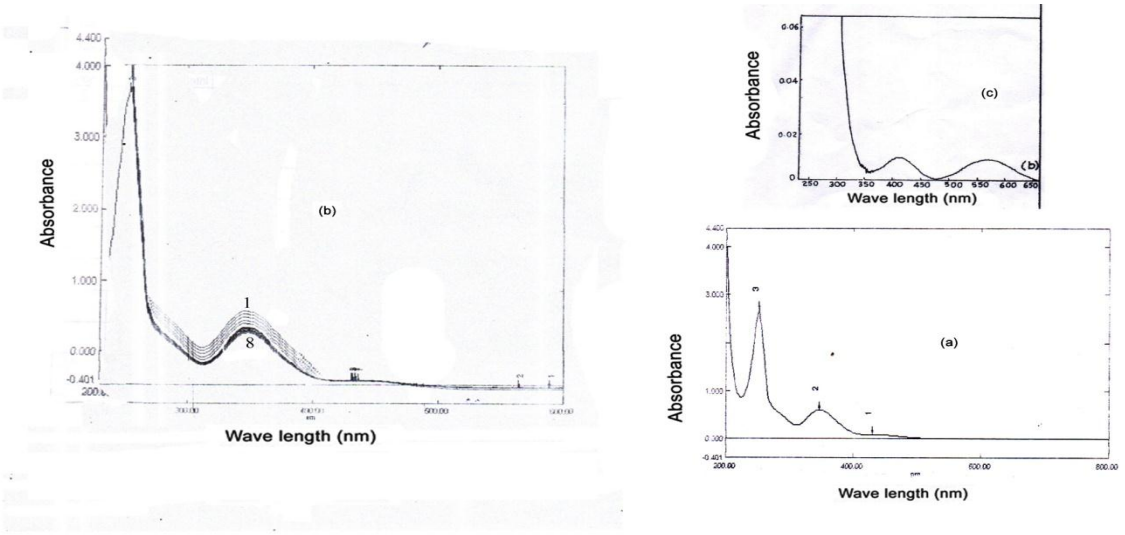


Fig. 2: UV-Visible Time Scan

a) [PCC] = 2 x 10^{-4} mol dm^{-3}

b) Time Scan mixture of [Metformin] = 4 x 10^{-3} mol dm^{-3} and [PCC] = 2 x 10^{-4} mol dm^{-3} and [H^+] = 0.1 mol dm^{-3} , I = 0.3 mol dm^{-3}, Curve 1 - 8, Δt = 2 seconds.

c) Spectra of the mixture after 24 hrs.

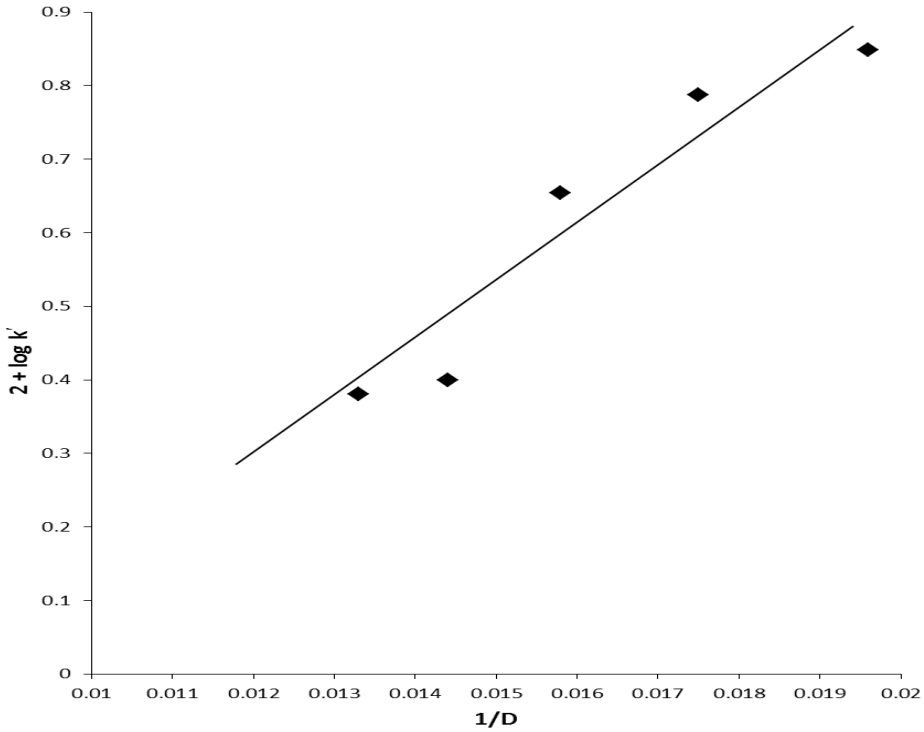


Fig. 3: Plot of 10^2 log k_{obs} (s^{-1}) versus 1/D at 298 K

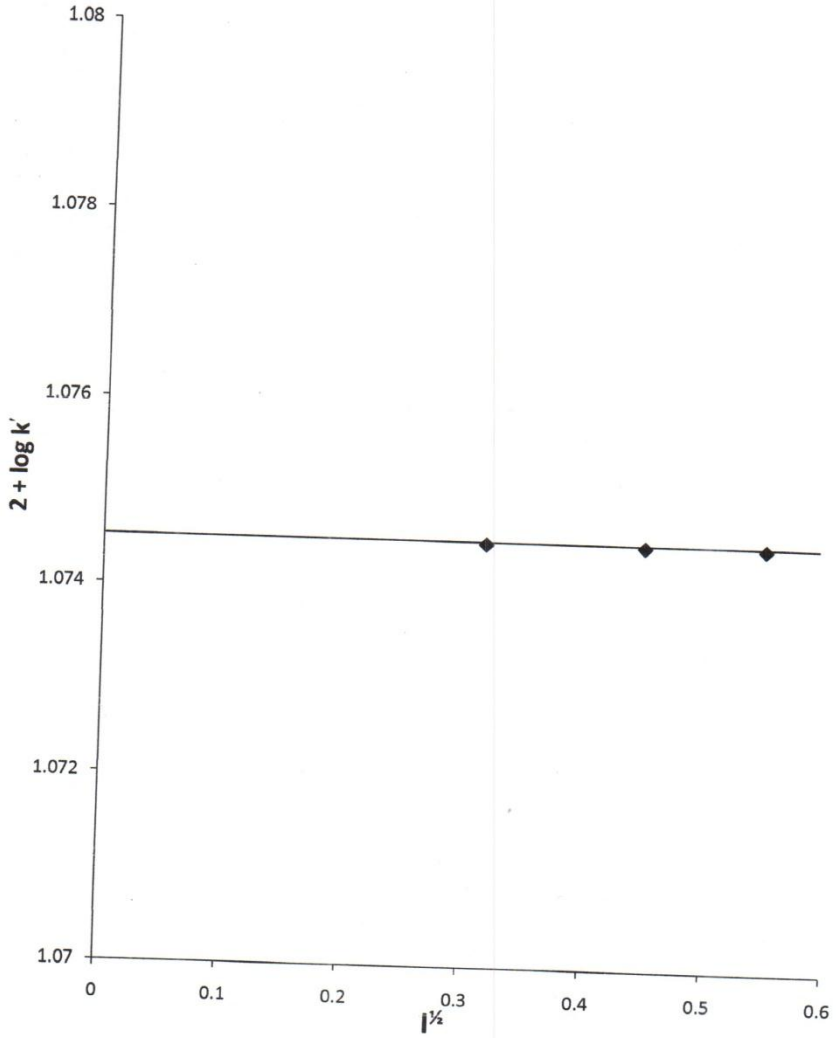


Fig. 4 : Plot of 10^2 log k_{obs} (s^{-1}) versus $I^{½}$ at 298 K

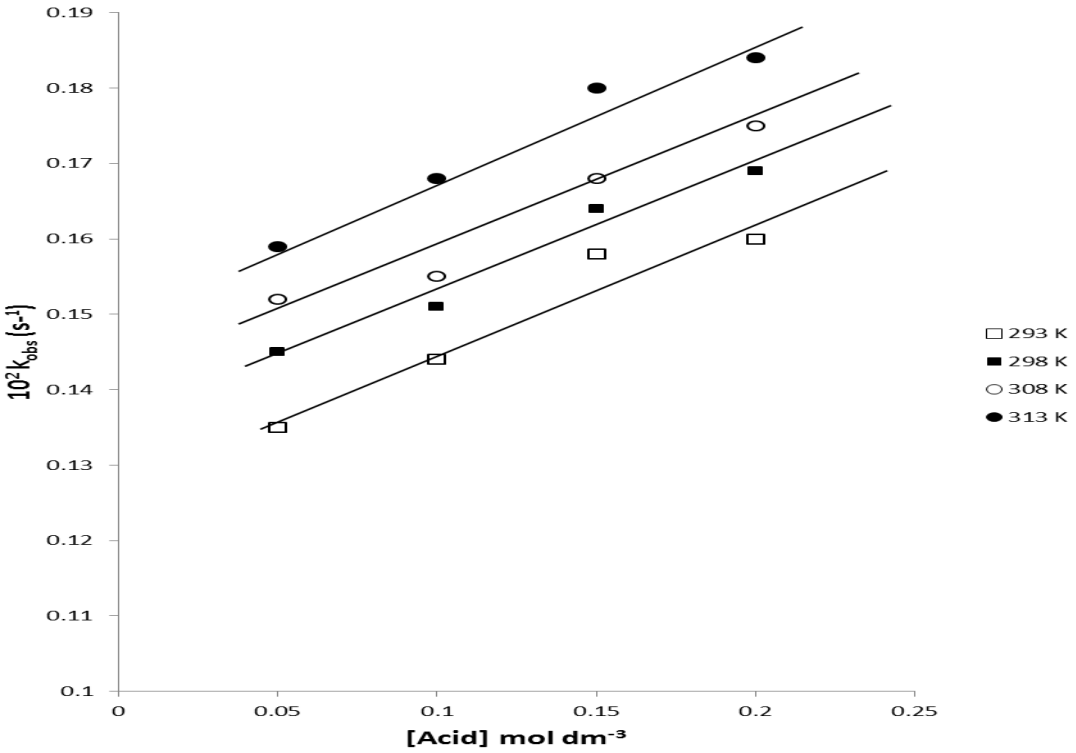


Fig. 5: Plot of 10^2 k_{obs} (s^{-1}) versus [H^+] (mol dm^{-3}) at (1) 293 K, (2) 298 K, (3) 308 K and (4) 313 K at [0.003] Metformin.

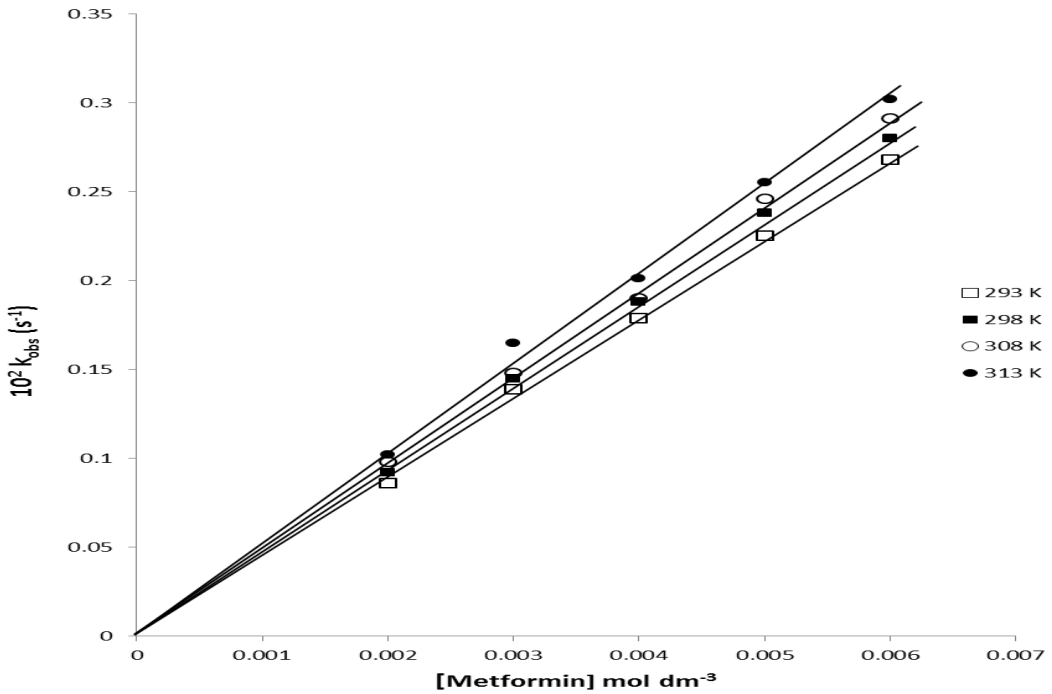


Fig. 6: Plot of 10^2 k_{obs} (s^{-1}) versus [Metformin] (mol dm^{-3}) at (1) 293 K, (2) 298 K, (3) 308 K and (4) 313 K at 0.1 Acid.

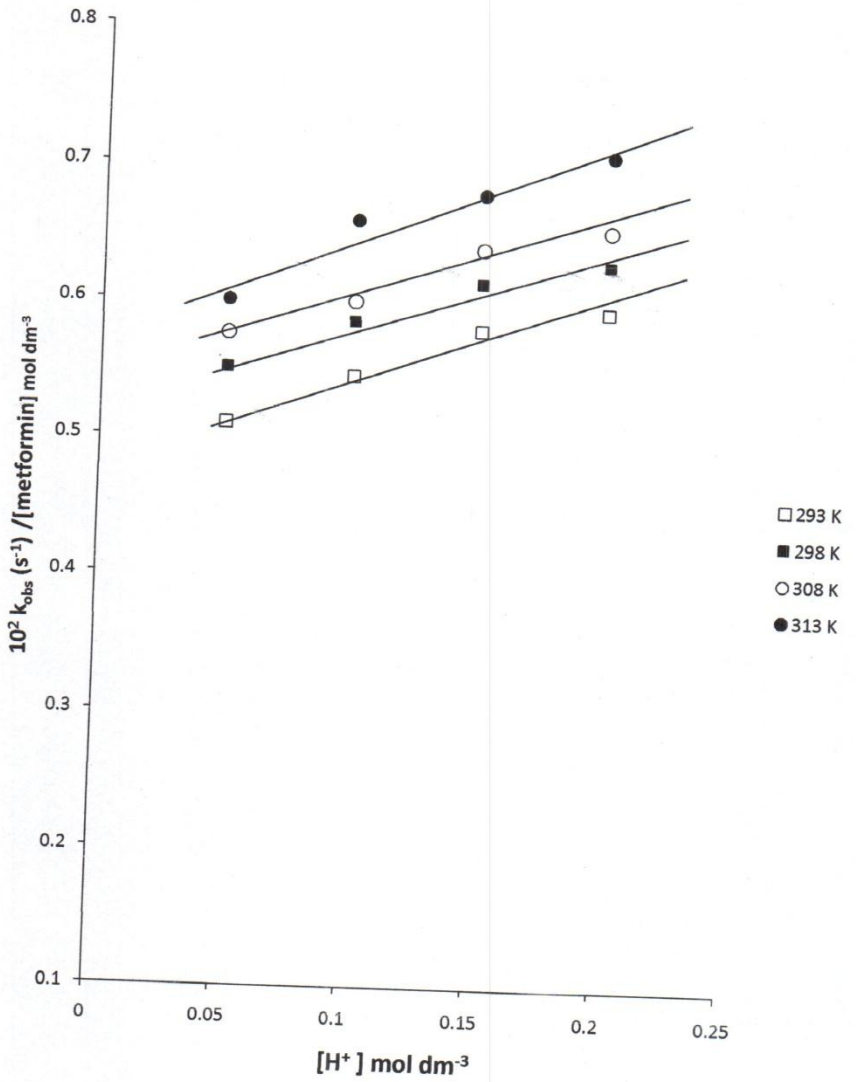


Fig. 7 : Plot of $10^2 k_{obs}$ (s^{-1})/[Metformin] mol dm^{-3} versus [H^+] mol dm^{-3} at (1) 293 K, (2) 298 K, (3) 308 K and (4) 313 K

4. CONCLUSION

The kinetics of oxidation of metformin by PCC in aqueous acid medium was studied in temperature range 293 K to 313 K. The stoichiometry of the reaction metformin and PCC was found to be 3:1. The reaction was first order with respect to metformin and first order with respect PCC. The product was isolated as Metformin N-Oxide. There is no evidence of direct coordination of metformin to Cr(IV)/III) centre (Fig.2a) suggesting an outer sphere mechanism.

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