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Kinetics and Mechanism of Oxidation of Metformin Hydrochloride by Hexamolybdocobaltate(III) in Acidic Medium

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The oxidation of metformin hydrochloride by Anderson-Evans type hexamolybdocobaltate(III) anion was investigated under pseudo-first-order condition in acidic medium at 298 K. The rate of reaction is accelerated by increase in the concentration of H^+ ion. The decrease in the reaction rate with increase in the concentration of the oxidant $[H_6CoMo_6O_{24}]^{3-}$ anion and added molybdate ion kinetically indicate existence of the prior equilibria between various forms of the oxidant. In present study, the oxidant exists in monomers $[H_6CoMo_6O_{24}]^{3-}$ anion, $[H_5CoMo_5O_{20}]^{2-}$ anion and dimer $[H_4Co_2Mo_{10}O_{38}]^{6-}$ forms between the pH 2 and 1. The active oxidant species is $[H_5CoMo_5O_{20}]^{2-}$ anion. Under experimental conditions, the reaction involves direct electron-transfer from metformin center to oxidant anion generating free radical in rate determining step. The fast hydrolysis of formed free radical in presence of second oxidant molecule leads to formation of carbonyl imino functional group in the oxidation product. The ionic strength and solvent polarity had no significant effect on the rate of reaction. FT-IR spectra of metformin and its oxidation product sample were recorded and analyzed. The FT-IR spectra show the change in frequency of the functional groups of oxidation product than that of the pure MET. The formation of oxidation product was confirmed by high performance liquid chromatography associated with electron impact mass spectroscopy (LC/EI-MS). Thermodynamic parameters are evaluated by temperature variation kinetic data and are in support of the proposed mechanism. The probable mechanism is proposed leading to complicated rate law as a result of involvement of prior equillibria between various forms of the oxidant.

Keywords: Anderson-Evans type, Metformin hydrochloride, Pseudo-first order, Kinetics, Monomer, Oxidation.

INTRODUCTION

Recent study focuses on electron-transfer processes for pharmaceutical and biological investigations. Heteropolyacids are widely reported to use as homogeneous and heterogeneous catalyst because of the higher thermal stability, stronger acidic nature and high oxidizing power. Polyoxometalates (POM) structure may be defined in general terms as the molecular metal oxide clusters formed through a condensation reaction of early transition metal-oxygen anions. Many POMs exhibit fast, reversible, multielectron redox transformations under mild conditions and considered as the most versatile and environmental friendly oxidizing agents [1]. POMs gain electron without large changes in their structure. It is reported that hetero POMs have considerably lower charge density and has central hetero metal ion securely caged by the polymetal ions, thus making them best candidates for the investigation of outer-sphere electron transfer reaction. The oxidation of organic compounds generally proceeds with low rates and they require rather drastic conditions. Many POMs show faster reversible multi-electron redox reactions under mild circumstances. Due to the discrete structure, POMs resemble it's enzymes in their activities specifically the oxidative transformations [2-5].

Metformin hydrochloride (MET; *N,N*-dimethyl imidocarbonimidic diamide hydrochloride) comprises the biguinide group. Pharmaceutically, metformin is reported as effective oral antihyperglycemic agent prescribed to treat type II diabetes mellitus [6], particularly in over-weighed and/or obese people and individuals with abnormal kidney functions [7]. Metformin hydrochloride is a biguanide, which belongs to a class of insulin sensitizer, helps in lowering both basal and postprandial plasma glucoses. It normalizes plasma glucose concentration without

any stimulation of insulin production. The primary action of metformin hydrochloride is to inhibit the production of hepatic glucose and to increase the sensitivity of insulin. As a result, metformin hydrochloride can help the body to respond better to its own insulin and decrease blood sugar level [8].

Despite being one of the most prescribed pharmaceuticals in the market, very few references are found on oxidation of metformin hydrochloride by different oxidizing agents [9-13]. Kinetic study of oxidation of metformin was reported earlier at drastic conditions like high temperature [10-12] or high concentration of NaOH [13]. Radical-induced oxidation of metformin [10] by water gamma radiolysis was also reported earlier. Kinetic oxidation of metformin in basic medium was also carried out by using oxidants like chloramines-B and bromamine-T [12,13].

Literature survey reveals that researchers working mainly on Keggin or Dawson type POM species. Due to thermodynamically stable structural arrangements, they characteristically maintain their identities in aqueous and non-aqueous solution as well as in ionic crystals. These properties make POM attractive as good oxidizing agent. In comparison with Keggin and Dawson types of salts, 6-molybdocobaltate(III) salts are substitution inert and compact. It belongs to Anderson-Evans structure and contains six non-ionizable protons. The kinetics of oxidation of numerous pharmaceutically important organic substrates such as L-cystine [14], pyridoxine [15], semicarbazide [16], guaifenesin [17], atenolol [18], levo-salbutamol [19], dichlophenac sodium [20], pyridoxine [21] and paracetamol [22] had been reported earlier. To the best of our knowledge, very limited study is available on kinetic and mechanistic study of oxidation by 6-molybdocobaltate(III) [22-26] as compared with Keggin and Dawson type of salts.

There was a need for understanding the oxidation mechanism of metformin hydrochloride so that the study could throw some light on the fate of this pharmaceutically active organic compound in biological system and also the behaviour of hexamolybdocobaltate(III) towards metformin hydrochloride in the presence of perchloric acid medium. In the view of above fact, present study reports the kinetics and mechanistic study of the oxidation of metformin hydrochloride by hexamolybdocobaltate(III) ion in perchloric acid medium. The mechanistic pathway and kinetic modeling have been deduced for this redox system.

EXPERIMENTAL

Analytical grade chemicals and double distilled water were used throughout the experiment. Hexamolybdocobaltate(III) anion was produced by the reported procedure with the slight modification using cobalt(II) sulphate, ammonium heptamolybdate, potassium persulphate (all S.D. Fine, India) and H_2SO_4 (Thomas Baker). Metformin hydrochloride (98%) was purchased from Hi media while sodium carbonate and perchloric acid were purchased from Merck, India.

Metformin hydrochloride solution was freshly prepared each time in double distilled water. Ionic strength was maintained by using $NaClO_4$ and to vary hydrogen ion concentration perchloric acid (Thomas Baker) was used, while the dielectric constant effect was studied by using acetonitrile (Finar). The preparation of sodium perchlorate was done by neutralizing sodium carbonate solution by required amount of perchloric acid. The stock solution was diluted to the required concentration and then used.

Hexamolybdocobaltate(III) was prepared by the reported method [23] and standardized spectrophotometrically (at 602 nm, [$\varepsilon = 16.9\ dm^3\ mol^{-1}\ cm^{-1}$) using Systronic 119 UV-visible spectrophotometer. The pH of the reaction mixture was observed by using Equip-Tronics EQ-602 pH meter. Mass spectra analysis of the reactant and product was monitored by 6200 series TOF/6500. FT-IR determinations were performed using Bruker Model Alpha FTIR spectrophotometer over the frequency range 4000-400 cm^{-1}.

Preparation of hexamolybdocobaltate(III): The oxidation of Co^{II} with molybdate generates both blue-green $[H_6CoMo_6O_{24}]^{3-}$ (the monomer) and olive-green dimer $[H_4Co_2Mo_{10}O_{38}]^{6-}$. Careful processing needed to gain the authentic sample of all species by discriminating selection for the oxidizing agents, pH and temperature. The product assignment little depends on pH, with an increasing amount of monomer generated at low pH value, which agrees with previously reported instability of dimer towards hydrogen ion.

Ammonium hexamolybdocobaltate(III), $(NH_4)_3[H_6Co(MoO_4)_6]$ was prepared by the reported method [23]. Preparation method involves the addition of an aqueous solution of $CoSO_4$ (5.0 g) to a boiling solution of ammonium heptamolybdate (40 g), in a minimum amount of H_2O. The pH of the resulting solution was maintained at 2.0 using sulphuric acid solution followed by the slowly addition of hot red potassium persulphate (5.0 g) solution, where upon the colour of the solution changed to green. The mixture was boiled for a few minutes on a water bath and the resultant hot solution undergone filtration. The filtrate was concentrated on water bath. The blue-green shiny crystals were obtained after 3 days at the room temperature. These blue-green shiny crystals were recrystallized twice from hot water. The recrystallized complex was dried in an oven and used. Yield: 21 g (42%).

Characterization of hexamolybdocobaltate(III)

Atomic absorption analysis: The complex $[H_6CoMo_6O_{24}]^{3-}$ was analyzed by atomic absorption spectroscopy (AAS). For this analysis solution was prepared by dissolving 100 mg of recrystallized sample in 100 mL doubly distilled water. 5 mL of this stock solution was diluted to 100 mL. Further, this solution was used for AAS (make: Perkin-Elmer Analyst-300 instrument) analysis of cobalt and molybdenum. Complex shows found (calcd) %: Co 4.65 (4.70) and Mo 47.10 (46.55).

Spectrophotometric measurements: The prepared hexamolybdocobaltate(III) ion was also characterized spectrophotometrically. A solution of the complex in water was standardized spectrophotometrically by using Elico SL 177 UV-VIS spectrometer. The application of Beer's law under the reaction condition had been verified in the concentration range of 4.0×10^{-3} to 4.0×10^{-2} mol dm^{-3} of hexamolybdocobaltate(III) at λ = 602 nm. The molar extinction coefficient of hexamolybdocobaltate(III) ion was found to be 19.6 $dm^3\ mol^{-1}\ cm^{-1}$, which is

in agreement with the literature [25]. The data for Beer's plot for hexamolybdocobaltate(III) are reported and the corresponding plot is depicted. The rate constants were measured by plotting log a/(a-x) against time plots.

The FT-IR spectrum of 6-molybdocobaltate(III) was recorded on Bruker instrument in KBr. The stretching vibration frequency of metal-oxygen lies in the region 1100-400 cm^{-1}. The band at 641.76 cm^{-1} corresponds to NH_4^+ ion. The spectrum also exhibits a peak at 940 cm^{-1}, which is a characteristic of molybdate ion and the Mo-O-Co stretching vibration is observed at 1422 cm^{-1}. The broad peaks at 3181 and 1627 cm^{-1} indicates water associated with Anderson structure.

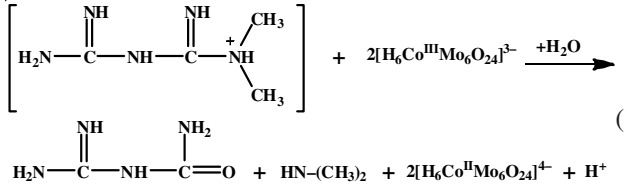
Dimer $[H_4Co_2Mo_{10}O_{38}]^{6-}$ and the monomer $[H_6Co^{III}Mo_6O_{24}]^{3-}$ anion absorbs at 599 nm and active species absorbs at 618 nm instead of 599 nm wavelength indicating $[H_5Co^{III}Mo_5O_{20}]^{2-}$ as the prominent oxidant species under the reaction conditions. In this study, the oxidant exists in the monomer $[H_6CoMo_6O_{24}]^{3-}$, $[H_5CoMo_5O_{24}]^{2-}$ anion and dimer $[H_4Co_2Mo_{10}O_{38}]^{6-}$ forms between the pH 2 and 1. The active oxidant species is $[H_5Co^{III}Mo_5O_{24}]^{2-}$ anion. A mixture of the blue-green monomer $[H_6CoMoO_{24}]^{-3}$ species and the olive green dimeric $[H_4Co_2Mo_{10}O_{38}]^{-6}$ can be produced in the oxidation of Co^{II} in presence of molybdate. The monomer percentage composition increased with the increase in $[H^+]$ ions [25].

Kinetic study: The oxidation of antidibetic drug, metformin hydrochloride by hexamolybdocobaltate(III) anion was carried under pseudo-first-order condition in perchloric acid medium at 298 K. The reactions could be monitored spectrophotometrically by following the decrease in absorbance of hexamolybdocobaltate(III) at 602 nm with time. UV-visible spectrophotometer connected to 1 cm quartz cells was used for absorbance measurements. All spectral measurements were performed using the blank solution as a reference. The pseudo-first-order rate constants were obtained from linear ($r > 0.986$) plots of log (absorbance) against time at various time intervals.

RESULTS AND DISCUSSION

Product analysis and stoichiometry: The reaction mixture containing known excess of the oxidant and metformin hydrochloride, 0.1 M of perchloric acid was mixed. The reaction mixture was allowed to stand for 48 h at constant temperature. The decrease in concentration of 6-molybdocobaltate(III) anion was analyzed spectrophotometrically at 602 nm wavelength. The stoichiometry was found to be two moles of 6-molybdocobaltate(III) anion per mole of substrate. The reaction mixture after 48 h was further processed for product analysis. The reaction mixture was neutralized with NaOH and the mass spectrum of the products was recorded.

Stoichiometric equation:



(1)

Test for free radical: The free radical involvement in the oxidation of metformin hydrochloride was studied by adding acrylonitrile in the reaction mixture. The formation of gel suggests free radicals may have been produced as intermediate under experimental conditions.

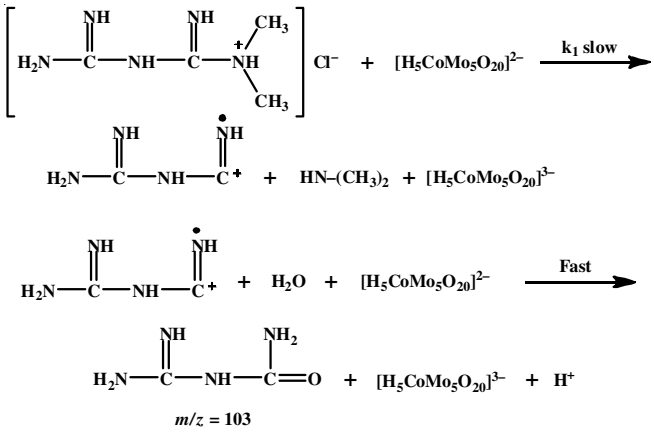
Chemically, metformin is hydrophilic base. However, it is usually present in oral dosage forms in its hydrochloric salt form [27]. The acid dissociation constant values (pK_a) of MET was found [28] to be 2.8 and 11.5. Due to such high value of its pK_a, MET hydrochloride is highly soluble in water and less soluble in lipids. Therefore, the acceleration of the reaction due to the increase in H^+ ion concentration is because of the prior protonation equilibria of oxidant 6-molybdocobaltate(III). On the other hand, the added molybdate ion decreases the reaction rate. The hexamolbdocobaltate(III) anion undergo dissociation in acidic medium by losing one of its molybdate unit to form $[H_5CoMo_5O_{20}]^{2-}$ ion which further dimerizes to give $[H_4Co_2Mo_{10}O_{38}]^{6-}$ ion. In acidic medium there will be equilibria between 6-molybdocobaltate ions $[H_6CoMo_6O_{24}]^{3-}$, $[H_5CoMo_5O_{20}]^{2-}$ and $[H_4Co_2Mo_{10}O_{38}]^{6-}$ as shown by eqns. 2 and 3.

$$[H_5CoMo_5O_{20}]^{2-} + H_2MoO_4 \underset{}{\overset{K_1}{\rightleftharpoons}} [H_6CoMo_6O_{24}]^{3-} + H^+ \quad (2)$$

$$2[H_5CoMo_5O_{20}]^{2-} \overset{K_2}{\rightleftharpoons} [H_4Co_2Mo_{10}O_{38}]^{4-} + 2H_2O + 2H^+ \quad (3)$$

Under experimental conditions, the reaction involves direct electron-transfer from metformin center to oxidant anion generating free radical in rate determining step. Then fast hydrolysis in presence of second oxidant molecule leads to formation of carbonyl imino functional group in the oxidation product. Since the reaction is accelerated by H^+ ion concentration and inhibited by the added molybdate ion, the active species of the oxidant is $[H_5CoMo_5O_{20}]^{2-}$ ion.

Probable reaction mechanism:



$$\text{Rate} = \frac{k_1[\text{metformin}][H_5CoMo_5O_{20}]^{2-}[H^+]^2}{([H^+]^2 + K_1[H_2MoO_4][H^+] + K_2[H_5CoMo_5O_{20}]^{2-})} \quad (4)$$

$$\frac{\text{Rate}}{[H_5CoMo_5O_{20}]^{2-}} = k_{obs} = \frac{k_1[\text{metformin}][H^+]^2}{([H^+]^2 + K_1[H_2MoO_4][H^+] + K_2[H_5CoMo_5O_{20}]^{2-})} \quad (5)$$

FTIR analysis: FT-IR spectra of metformin hydrochloride and its oxidation product sample are shown in Fig. 1. The key bands observed along with their assignment are summarized in Table-1. The FT-IR spectra show the change in frequency of the functional groups of oxidation product than that of the pure metformin.

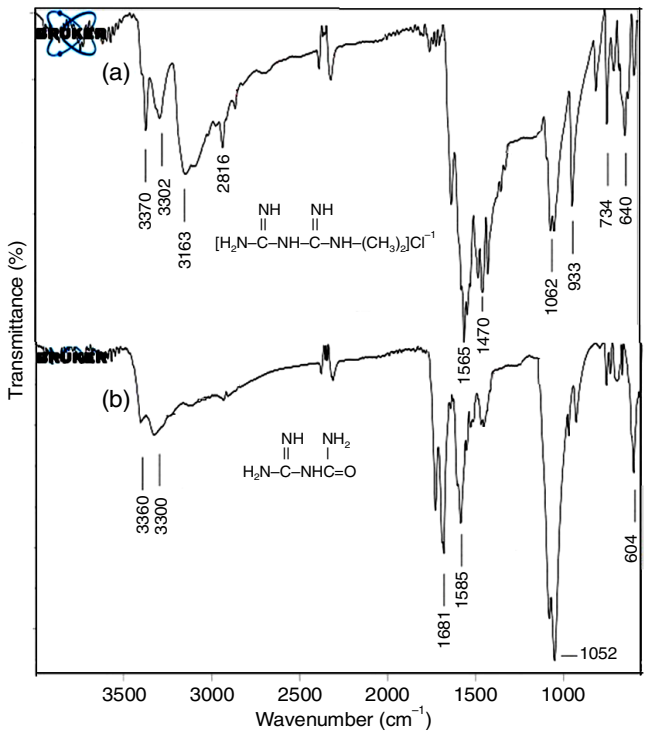


Fig. 1. FTIR spectra of metformin hydrochloride (substrate) and its oxidation product

TABLE-1
IR (cm^{-1}) ASSIGNMENT OF METFORMIN HYDROCHLORIDE (MET) [Ref. 29,30] AND ITS OXIDATION PRODUCT (GUANYL UREA)

Band assignment	MET	Oxidation product
N-H asym. *str.*	3370	3360
N-H sym. *str.*	3302	3300
C-H asym. *str.*	3173	Absent
-N-(CH$_3$)$_2$ *str.*	2816	Absent
-C=O amide *str.*	Absent	1681
C=N *str.*	1565	1585
CH$_3$ asym. def.	1470	Absent
C-N *str.*	1062	1052
C-H out-of-plane bending	933	Absent
-NH$_2$ wagg.	734, 640	604

LC/EI-MS analysis: The formation of oxidation product was further confirmed by HPLC associated with electron impact mass spectroscopy (LC/EI-MS). The mass spectrum reported the peaks at *m/z* are 45, 85, 103 and 130 (Fig. 2). Further oxidation of products formed does not occur under the present experimental conditions. The peak at *m/z* 130 corresponds to metformin remained unoxidized and sharp peak at *m/z* 103 corresponds to the product, guanyl urea.

Effect of oxidant and substrate concentration: The course of reaction was followed by measuring decrease in the absorbance of 6-molybdocobaltate(III) at 602 nm wavelength corresponding to maximum absorbance. Effect of variation of the substrate concentration was observed by increasing its concentration from 5.0×10^{-2} to 9.0×10^{-2} mol dm^{-3}. The value of rate constant remains constant as concentration of metformin hydrochloride increased and keeping concentration of 6-molybdocobaltate(III), perchloric acid and ionic strength constant. This indicates order in substrate to be unity (Table-2).

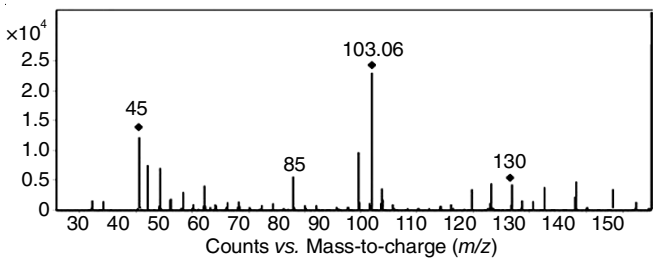


Fig. 2. Mass spectrum of oxidation product of metformin hydrochloride

TABLE-2
EFFECT OF [OXIDANT], [SUBSTRATE], [MoO_4^{2-}] AND [$HClO_4$] ON THE PSEUDO-FIRST-ORDER RATE CONSTANT (I = 0.3 mol dm^{-3}, T= 298 K)

10^2 [Substrate] (mol dm^{-3})	10^3 [Oxidant] (mol dm^{-3})	[$HClO_4$] (mol dm^{-3})	10^3[MoO_4^{2-}] (mol dm^{-3})	10^3 k_{obs} (s^{-1})
5.0	8.0	0.20	0.0	1.487
6.0	8.0	0.20	0.0	1.488
7.0	8.0	0.20	0.0	1.487
8.0	8.0	0.20	0.0	1.494
9.0	8.0	0.20	0.0	1.496
8.0	5.0	0.20	0.0	1.765
8.0	6.0	0.20	0.0	1.655
8.0	7.0	0.20	0.0	1.554
8.0	8.0	0.20	0.0	1.496
8.0	10.0	0.20	0.0	1.315
8.0	8.0	0.01	0.0	0.338
8.0	8.0	0.05	0.0	0.689
8.0	8.0	0.10	0.0	1.254
8.0	8.0	0.20	0.0	1.496
8.0	8.0	0.30	0.0	1.841
8.0	8.0	0.20	1.0	1.147
8.0	8.0	0.20	2.0	1.076
8.0	8.0	0.20	3.0	0.939
8.0	8.0	0.20	4.0	0.807

Effect of concentration of oxidant variation was observed by increasing its concentration from 5.0×10^{-3} to 1.0×10^{-2} mol dm^{-3} keeping concentration of metformin, [H^+] ion, ionic strength and temperature unvaried. The value of rate constants decreases with increase in concentration of oxidant (Table-2). The order with respect to oxidant concentration was depicted from slopes of linear plots of log k_{obs} *versus* log concentration of $[H_6CoMo_6O_{24}]^{3-}$. The order in oxidant concentration was found to be -0.51. Graph of log (k_{obs}) *versus* log [oxidant] was observed linear (Fig. 3).

Effect of $HClO_4$: Effect of concentration of H^+ ions of medium was observed to understand the nature of reactant species present in the solution. The effect of H^+ on the reaction was investigated by varying concentration of $HClO_4$ from 1.0

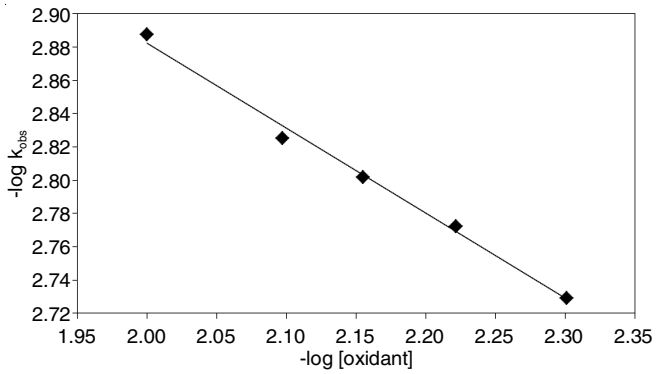


Fig. 3. Plot of log k_{obs} against log [oxidant]

$\times 10^{-2}$ to 0.3 mol dm^{-3} by keeping concentration of metformin, concentration of oxidant, ionic strength and temperature constant. It was observed that with increase in the concentration of H^+, there was prominent increase in the value of rate constants (Table-2). A plot of k_{obs} against H^+ ion concentration was linear, indicating first-order dependence on $[H^+]$ ion. The reaction order with respect to H^+ was found to be 0.5 from the plot (Fig. 4).

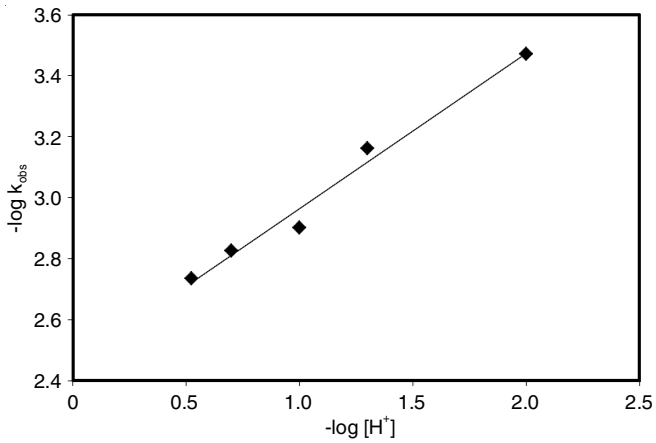


Fig. 4. Plot of log k_{obs} against log [H^+]

Effect of added molybdate ion concentration: The effect of added molybdate on the oxidation of metformin was studied by varying concentration of ammonium molybdate between the range 1.0×10^{-3} to 4.0×10^{-3} mol dm^{-3} keeping concentration of metformin, concentration of oxidant, concentration of H^+ ions and temperature constant. Increase in concentration of added molybdate decelerated the values of rate constant (Table-2). A plot of ($1/k_{obs}$) against [molybdate] was found to be linear.

Effect of ionic strength, solvent polarity and temperature: Sodium perchlorate and acetonitrile were used to vary the ionic strength and the solvent polarity respectively. The effect of ionic strength, solvent polarity and temperature were studied by keeping concentration of metformin, concentration of oxidant, concentration of H^+ ions constant at 8.0×10^{-2} mol dm^{-3}, 8.0×10^{-3} mol dm^{-3} and 0.2 mol dm^{-3}, respectively. The values of pseudo-first-order rate constants remains constant with increase in ionic strength and the solvent polarity under experimental conditions.

For variation in the ionic strength $NaClO_4$ was utilized. The values of pseudo-first-order rate constants do not change with increasing ionic strength from 0.2 to 2.0 mol/dm^3. For variation in solvent polarity, acetonitrile was used. The values of pseudo-first-order rate constants do not change with increasing concentration of acetonitrile under experimental conditions.

Effect of temperature on the reactions was observed by varying temperature between 15 to 40 ºC keeping constant concentration of substrate, oxidant, hydrogen ion and ionic strength constant. With increase in temperature, the value of pseudo-first-order rate constant of the reaction accelerated. The rate constants for oxidation of metformin at different temperatures were calculated. A graph of log k_{obs} *versus* 1/T was plotted. Activation energy and other parameters were calculated and are given in Table-3.

Anderson-Evans structure of 6-molybdocobaltate(III), $[H_6CoMo_6O_{24}]^{3-}$ anion consisting six non-ionizable protons is reported more compact than other Keggin-type 12-tungstocobaltate(III) [14]. In present study, the oxidant existed in the monomer $[H_6CoMo_6O_{24}]^{3-}$, $[H_5CoMo_5O_{20}]^{2-}$ anion and dimer $[H_4Co_2Mo_{10}O_{38}]^{6-}$ forms between the pH 2 and 1. The monomer form is having Anderson structure and dimer is having Evan-Showell type. During dimerization, one of the molybdate ion dissociates from each of the monomer and both the cobalt octahedral are joined to share an edge. From the structure of monomer, it can be noticed that the cobalt hetero ion is comparatively accessible for the approach of other reactants as it is surrounded by the six molybdate ions. On the other hand, the structure of dimer indicate that the cobalt center is buried in between molybdate units [31] thus limiting its access to the other reactants. Probably due to this reason, the active species in the oxidation reactions by Hexamolybdocobaltate(III) is the monomer while the dimer is inactive. The monomer belongs to D_{3d} symmetry while the dimer belongs to D_2 symmetry [31]. The oxidation of one-electron reductants by hexamolybdocobaltate(III) were found to exhibit outer-sphere mechanism.

The species $[H_6CoMo_6O_{24}]^{3-}$ is a strong acid, therefore in solution it exits as a free ion with three negative charges without any protonation even in acidic solution. Due to the discrete structure, POMs resemble enzymes in their activities specifi-

TABLE-3
EFFECT OF TEMPERATURE ON THE PSEUDO-FIRST-ORDER RATE CONSTANT
(10^3 [Oxidant] = 8.0 mol dm^{-3}, 10^2 [MET] = 8.0 mol dm^{-3}, [$HClO_4$] = 0.2 mol dm^{-3} AND I = 0.3 mol dm^{-3})

T (K)	10^3 k_{obs} (s^{-1})	E_a (kJ mol^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (J K^{-1} mol^{-1})	$\Delta G^{\#}$ (kJ mol^{-1})
288	5.34				
293	7.12				
298	8.08	31.56 ± 3	28.68 ± 3	-108 ± 5	60.95 ± 3
303	10.2				
313	15.6				

cally the oxidative transformations of some substrates. The cobalt ion in the structure of $[H_6CoMo_6O_{24}]^{3-}$ is surrounded by six octahedral molybdenum ions and the associated 24 oxide ion. Six proton attached to the oxide ion in the $[H_6Co^{III}Mo_6O_{24}]^{3-}$ are non-ionizable [32] and other three are strongly ionizable.

Conclusion

Oxidation of metformin by 6-molybdocobaltate(III) in acidic medium was found to first order and gradually decreased by increase in [oxidant]. The increase in concentration of H^+ ion increases the value of rate constants due to retarded rate of dimerization of active oxidant. As the reaction is accelerated by $[H^+]$ and inhibited by added molybdate and oxidant, the active species of the oxidant can be identified as the $[H_5CoMo_5O_{20}]^{2-}$ ion. The reaction involves direct electron transfer from metformin center to the oxidant anion generating free radicals in a rate determining step. The fast hydrolysis of formed free radical in presence of second oxidant molecule leads to formation of carbonyl imino functional group in the oxidation product. The stoichiometry of metformin oxidation was found to be two moles of hexamolybdocobaltate(III) anion per mole of metformin. There was no effect of ionic strength and change in solvent polarity on oxidation. The interaction between substrate and oxidant might be occurring through formation of a weak outer sphere complex. This observation, together with low and negative entropy of activation calculated by using Arrhenius plot supports the formation of such a weak complex between the reactants.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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