



Kinetic study and mechanistic elucidation for metformin oxidation by Mn(VII) in alkaline medium

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Abstract

The kinetics and oxidation of an anti-diabetic drug, metformin using permanganate in alkaline media was studied spectrophotometrically by keeping 0.01 mol dm⁻³ ionic strength. The oxidation among permanganate with metformin in NaOH media shows 1:6 stoichiometry (metformin: permanganate). The oxidation reaction is first order dependence in [permanganate ion] and less than unit order in MET and hydroxyl ion concentrations, respectively. When ionic strength of reaction medium is increased, the rate of the reaction also increased. The consequence of dielectric constant of the media and externally added products were also studied. A proper mechanism for oxidation was proposed. The main product of the title reaction was recognized using LC-MS technique. The various constants of the reaction concerned in various steps in the mechanism were computed. The activation constants and thermodynamic values are also evaluated by graphical method and discussed in detail.

Keywords: Oxidation, metformin, kinetics, permanganate.

Introduction

Diabetes, the faster growing disease in world, was categorized as insulin dependent or type 1 and does not depending on insulin or type 2. Metformin (N,N-dimethylbiguanide) (MET), is a biguanide prescribed and employed in treatment of type 2 diabetes¹ and is identified to raise glucose transfer crossways in the cell membrane in skeletal muscles. This drug was the main chosen drug for overweight patients² and MET also diminish the creation of advanced glycosylation end products³. According to International Diabetes Federation, one in ten people are living with diabetes. The statistical data says that, adults having diabetes are about 463 million worldwide and 700 million adults will have diabetes with in 2045, the prediction says. The diabetic people are more vulnerable to severe effect of corona virus. MET has common adverse effects such as diarrhea, nausea and abdominal pain and is not recommended for those with significant liver disease⁴.

Permanganate ion was used for the oxidation of various substrates and had broad range of relevance in organic synthesis also⁵⁻⁹, mainly in phase transfer catalysis which uses the solvents like benzene and methylene chloride⁷⁻⁹. The reaction medium which is used to carry out the reaction has much control on the oxidation mechanism of a substrate by permanganate ion¹⁰. In a strong alkaline medium, the established reduction product of MnO₄⁻ was MnO₄²⁻. Because of lack of mechanistic proof, it is not possible to differentiate among a direct one-electron reduction to Mn(VI) and a reaction wherein two electron step involved to form Mn(V) followed by

a fast reaction¹¹⁻¹³. In sight of the popularity and medicinal significance of MET and short of evidence about the oxidation reaction mechanism of MET by Mn(VII), it was needed to know the mechanism of oxidation this drug molecule. The present investigation may help to get some information of the drug in biological system. Therefore the title reaction was studied carefully in basic media using Mn(VII). The intention of the current study are (1) to obtain a suitable rate law for the oxidation reaction (2) to suggest a proper mechanism for the reaction (3) to recognize the species involved in the reaction, and (4) to know the products of oxidation of MET.

Materials and methods

Doubly distilled water and analytical grade chemicals were employed during the job. By dissolving proper amount of MET (Alfa Aser) was in doubly distilled, the stock solution water prepared from the stock solution the required amount of MET was used. The strength of prepared potassium permanganate (Nice Chem Ltd) solution was computed using oxalic acid¹⁴. As documented in literature¹⁵ the solution of potassium manganate was prepared. The potassium permanganate solution was boiled at about 100°C with KOH solution (8.0 mol dm⁻³) till color changed to green. The potassium manganate solid obtained on cooling the above content and using KOH solution it was recrystallized. Using this sample, potassium manganate stock solution was prepared using aqueous solution of KOH. To standardize the prepared solution, its absorbance was noted at 607 nm ($\epsilon = 1520 \pm 30 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$). The solutions of NaOH and NaClO₄ were prepared by doubly distilled water, and were

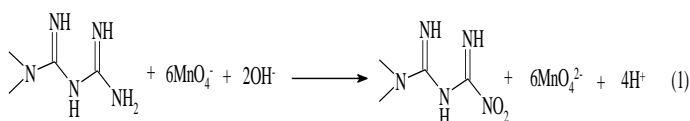
used to give the essential alkalinity and to retain the ionic strength, respectively. Stability studies conducted indicated that the alkali had no effect on the constancy of MET in absence of permanganate in the present experimental conditions.

A Bio UV-vis spectrophotometer (Varian CARY 50, Varian, Victoria-3170, Australia) connected to an accessory (peltier accessory for temperature control) was employed for the kinetic measurement. A Liquid Chromatography (Waters, Synapt G2, USA) connected to a mass spectrometer having EI ionization system was employed to identify product. A pH meter was utilized to measure pH.

At a temperature of $25 \pm 0.2^\circ\text{C}$ and maintaining pseudo-first-order conditions, the entire kinetic measurements were monitored by taking surplus quantity of MET over the quantity of permanganate by maintaining a steady ionic strength. All the solutions were thermostatted and the reaction was begun by adding permanganate and MET, which also has necessary amounts of NaClO_4 and NaOH for keeping necessary ionic strength and alkalinity, respectively. By measuring the reduction in optical density of Mn(VII) at its maximum optical density at 525nm, the path of this reaction was monitored. The validity of Beer's law at 525nm to Mn(VII) was checked, which gives $\epsilon = 2096 \pm 40 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ (lit. $\epsilon = 2200 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$). Using the graph of $\log_{10}(A_t - A_\infty)$ against time the rate constants of first order, k_{obs} were computed by appropriating the data to the formula $A_t = A_\infty + (A_0 - A_\infty) e^{-k_{obs}t}$, where A_t , A_0 , and A_∞ are absorbance of Mn(VII) at time t , 0, and ∞ , respectively. The obtained graphs were more or less straight line up to 80% completion of oxidation, and the error in k_{obs} values were about $\pm 5\%$ limit. While monitoring the title reaction, reaction mixture colour altered to blue from violet and later was green. A later obtained UV-Visible band of green solution is matching with that of MnO_4^{2-} . This was likely that, blue colour derived from the violet of Mn(VII) and the manganate shows green colour, without growing of hypomanganate {Mn(V)}. It was also observed while following the reaction that, the absorbance increases at 608nm and a decline in optical density at 525 nm, which indicated the transformation of Mn(VII) to Mn(VI).

Results and discussion

In presence of steady quantities of NaOH and sodium perchlorate, dissimilar sets of reaction blends having uneven proportions of Mn(VII) to MET were kept in a sealed vessel underneath an inert condition for 3 hours. After 3 hours, the left behind quantity of Mn(VII) was projected spectrophotometrically at 525nm. The outcome pointed out a stoichiometry of 1:6 as shown equation 1 below.



The reaction solution of permanganate and MET having necessary amount of NaOH was made to react for 32 hours at 25°C . Using hydrochloric acid solution, the product of the reaction was neutralized. Using ethyl acetate solvent, the aqueous layer present was extracted four times and this was used for thin layer chromatography. The main product of oxidation of MET, N-(N,N-dimethyl carbamimidoyl)-1-nitroformimidamide, was established by Liquid Chromatographic-Mass Spectroscopic analysis. A peak at 160.13amu corresponding to molecular ion as shown in Figure-1 confirms the existence of the product of the reaction, N-(N,N-dimethyl carbamimidoyl)-1-nitro formimidamide. It was observed that in the present reaction situation, N-(N,N-dimethyl carbamimidoyl)-1-nitro formimidamide was not undergoing further oxidation reaction.

By fluctuating the concentration of OH^- and MET and by maintaining all additional quantities and circumstances steady, the order of the reaction were computed by graphical method using the slopes of the graphs of $\log_{10} k_{obs}$ against \log (concentration).

At a fixed concentration of MET, $0.001 \text{ mol dm}^{-3}$ and OH^- , 0.04 mol dm^{-3} at a steady $10.0 \times 10^{-2} \text{ mol dm}^{-3}$ ionic strength, the oxidant quantity was fluctuated between 0.00002 to 0.000002 mol dm^{-3} . As seen from the Table-1, fairly constant values of k_{obs} points out that, the order in [Mn(VII)] was one. The graph of $\log_{10} [A_t - A_\infty]$ against time ($r^2 \geq 0.9852$) was linear to about 80% finishing of the oxidation reaction (Figure-2), points out that the oxidant order was one.

The influence of quantity of the substrate on title reaction has been examined by maintaining all other quantities and situations constant, the substrate quantity was assorted from 0.0004 to $0.00004 \text{ mol dm}^{-3}$ at 25°C . With increase in quantity of the substrate MET, the k_{obs} values also increased (Table-1). At these reaction environment and concentrations, the order in [MET] was computed to be less than unity. However, at elevated quantities of the substrate, the oxidation reaction was not dependent on [MET] and at lower quantities of MET, it was found that the reaction was first order in [MET].

The influence of hydroxyl ion concentration was evaluated by maintaining the oxidant, ionic strength and substrate quantity study. The rate of the reaction raised as alkali concentration was raised as in Table-1, and order with hydroxyl ion concentration was obtained as smaller than one. The order alters to zero order from first order with increasing concentrations of alkali.

The consequence of ionic strength on the title reaction was examined by altering the quantity of sodium perchlorate. The perchlorate was altered among 0.10 to 0.50 mol dm^{-3} by holding other situations and quantities steady. The study showed that the k_{obs} values increased as sodium perchlorate concentration increases. A graph of $\log k_{obs}$ against \sqrt{I} was straight line which shows slope as positive. Dielectric constant of the reaction

media has been altered using dissimilar quantities of tert-butyl alcohol and water. On declining the dielectric constant of the reaction media, there was reduction in reaction rate, and a graph of $\log k_{obs}$ against $1/D$ was straight line which has a negative slope (Figure-3).

It was found that the rate of the reaction did not altered significantly by product introduced at the beginning such as Mn(VI). The title reaction was followed in a sealed vessel containing nitrogen to study rate of reaction. Substantial deviation in observed results was not found in existence of air and under nitrogen. The control of carbonate on rate of reaction has been studied. It was observed that, reaction rates do not show any deviation by added carbonate. The rate law can be written based on the above experimental observations as

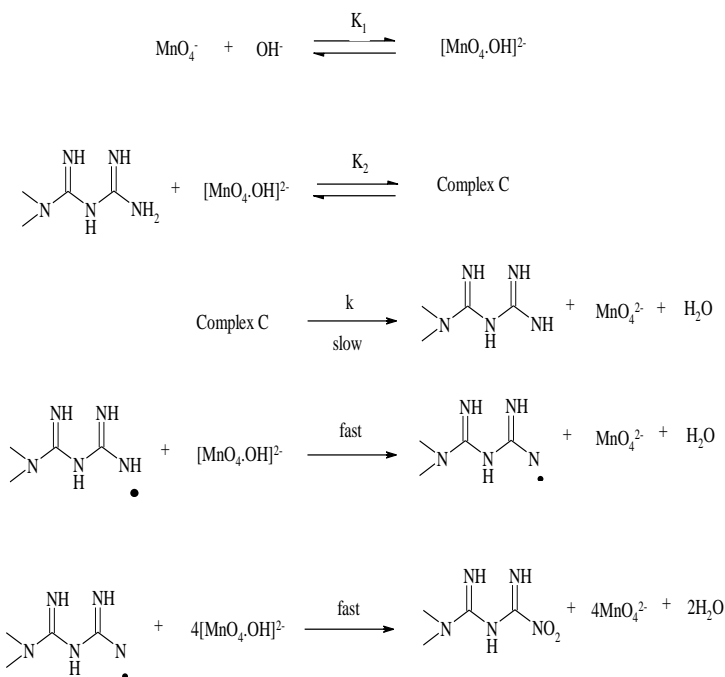
$$\text{Rate} = \frac{d[\text{MnO}_4^-]}{dt} = k_{obs}[\text{MnO}_4^-][\text{MET}]^{0.63}[\text{OH}^-]^{0.22}$$

To examine the free radicals involvement in the title reaction, a known amount of the monomer viz, acrylonitrile was introduced and kept aside for 2 hours in a sealed vessel with nitrogen. After stipulated time, a white precipitate was methanol was formed after adding methanol to the reaction mixture which indicates that involvement of free radicals in the reaction. However, the bare runs of alone oxidant or MET with the monomer did not showed any white precipitation using the environment employed earlier. But it was observed that the reaction rates decreased when acrylonitrile was added indicating that free radicals were present of in the reaction path as reported¹².

To know the control of temperature on the title oxidation reaction, the measurements were done on four dissimilar temperatures using unvarying extents of MnO_4^- , MET, NaOH and NaClO_4 . Using the intercepts of the graph of $1/k_{obs}$ against $1/[\text{MET}]$ ($r^2 \geq 0.995$), the rate constants, for the slow step in the Scheme-1 are computed at four dissimilar temperatures. Using the Arrhenius graph of $\log_{10} k$ against $1/T$, the activation energy was computed and from that value, the activation parameters were evaluated and were listed in Table-2.

In aqueous alkaline and acidic media, MnO_4^- is a powerful oxidant. Under the reaction condition employed in the title reaction, the reduction product Mn(VI) was steady and additional reduction was not anticipated, since the pH value is above 12¹⁵. Studies conducted above pH 12 using diode array rapid scan spectrophotometric studies had pointed out that, Mn(VII) was reduced to Mn(VI) and additional reduction did not take place. However, Mn(VI) was gradually reduced to Mn(IV) on extended time. It was noticed that, the colour changes from violet of Mn(VII) ion to dark green of Mn(VI) ion via blue of Mn(V). The reaction among MET and Mn(VII) in strong alkaline media has 1:6 stoichiometry with fractional order in [MET] and in [permanganate], first order and rate of

reaction enhances with increasing the quantity of alkali. Products added does not show any influence on rate of reaction.



Scheme-1: The probable mechanism for oxidation reaction.

The above mechanism was proposed for oxidation reaction of MET by the experimental observations and results that clarify all the orders observed experimentally. The results points out that, there is a combination of OH^- with permanganate in the preceding equilibrium step to form an alkaline permanganate species¹⁶⁻¹⁸ $[\text{MnO}_4.\text{OH}]^{2-}$. So formed permanganate species reacts with MET and gives Complex C. In a rate determining or slow step, the Complex C decays and gives a MET free radical, MnO_4^{2-} and a molecule of water, which is proceeded by successive quick steps to gave away the products of the reaction as proposed in Scheme-1.

By recording the UV-Vis spectra of permanganate (1.0×10^{-4} mol dm^{-3} , $[\text{OH}^-] = 0.04$ mol dm^{-3} and MET (1.0×10^{-3} mol dm^{-3}) and a blend of both, the creation of complex among the oxidant, Mn(VII) and substrate, MET was proved, which showed a shift of 6.0nm and this sort of complex formation was documented elsewhere¹⁸. With enhance in the amount of alkali, rate of reaction increases, which indicates the $[\text{MnO}_4.\text{OH}]^{2-}$ formation¹⁸. In agreement with well established principle of non-complimentary oxidation reactions which proceeds in a secession of one electron steps, an oxidant and a substrate would have a radical intermediate in the reaction as depicted in Scheme-1. The positive test for polymerization showed the presence of short lived free radical. The rate law can be written for the Scheme-1 as

$$\text{Rate} = \frac{d[\text{MnO}_4^-]}{dt} = k [\text{C}] \quad (2)$$

$$= kK_1K_2[\text{MET}]_f[\text{MnO}_4^-]_f[\text{OH}^-]_f \quad (3)$$

The total $[\text{MnO}_4^-]$ is given by

$$\begin{aligned} [\text{MnO}_4^-]_T &= [\text{MnO}_4^-]_f + [\text{MnO}_4 \cdot \text{OH}]^{2-} + [\text{C}] \\ &= [\text{MnO}_4^-]_f \{1 + K_1[\text{OH}^-] + K_1K_2[\text{MET}][\text{OH}^-]\} \end{aligned} \quad (4)$$

The terms $[\text{MnO}_4^-]_T$ and $[\text{MnO}_4^-]_f$ depict the MnO_4^- concentrations, and T and f are total and free concentrations, respectively. So, free $[\text{MnO}_4^-]$ can be written as

$$[\text{MnO}_4^-]_f = \frac{[\text{MnO}_4^-]_T}{1 + K_1[\text{OH}^-] + K_1K_2[\text{MET}][\text{OH}^-]} \quad (5)$$

Likewise $[\text{OH}^-]$ was calculated as

$$[\text{OH}^-]_f = \frac{[\text{OH}^-]_T}{1 + K_1[\text{MnO}_4^-] + K_1K_2[\text{MET}][\text{MnO}_4^-]}$$

But concentration of MnO_4^- and MET employed in this experiment were low, denominator in the beyond formula approximate to one. Hence,

$$[\text{OH}^-]_f = [\text{OH}^-]_T \quad (6)$$

$$\text{Likewise, } [\text{MET}]_f = [\text{MET}]_T \quad (7)$$

Equation 3 takes the form on putting values from equations 5, 6, and 7 after excluding T and f, we obtain

$$\text{Rate} = \frac{kK_1K_2[\text{MET}][\text{MnO}_4^-][\text{OH}^-]}{1 + K_1[\text{OH}^-] + K_1K_2[\text{MET}][\text{OH}^-]} \quad (8)$$

or

$$\frac{\text{Rate}}{[\text{MnO}_4^-]} = k_{\text{obs}} = \frac{kK_1K_2[\text{MET}][\text{OH}^-]}{1 + K_1[\text{OH}^-] + K_1K_2[\text{MET}][\text{OH}^-]} \quad (9)$$

The above equation (9) is making it clear about all the orders observed experimentally in diverse species involved in the reaction. This equation (9) was rearranged to equation (10), which was appropriate for the rate law verification.

$$\frac{1}{k_{\text{obs}}} = \frac{1}{kK_1K_2[\text{MET}][\text{OH}^-]} + \frac{1}{K_1K_2[\text{MET}]} + \frac{1}{k} \quad (10)$$

In accordance with the above equation, the graph of $1/k_{\text{obs}}$ against $1/[\text{MET}]$ ($r^2 \geq 0.9958$) and $1/k_{\text{obs}}$ against $1/[\text{OH}^-]$ ($r^2 \geq 0.9974$) has to be a straight line graph with intercept which validates the creation of $[\text{MnO}_4 \cdot \text{OH}]^{2-}$ - MET complex, the same was confirmed (Figure-4) at dissimilar temperatures. The k , K_1 , and K_2 values at 25°C were computed as $27.94 \times 10^{-2} \text{ s}^{-1}$, $1.09 \times 10^2 \text{ dm}^3 \text{ mol}^{-1}$, and $8.49 \times 10^2 \text{ dm}^3 \text{ mol}^{-1}$, respectively using slopes and intercepts of these graphs. The value of K_1 is in agreement with the reported data¹⁸. These values were used to compute the rate constants at dissimilar reaction situations employed using equation (9) and are used compare with experimentally examined statistics. Among them, there was a good matchup, supporting the proposed Scheme-1.

As depicted in Scheme-1, the reaction was among two species which were negatively charged was fortified, since reaction rate increases with raise in ionic strength of the media. In this study, the graph obtained has a negative slope as seen from Figure-3 that was further supporting the fact that negative ions were involved in the reaction as shown in the proposed Scheme-1.

We also computed quantities related to thermodynamic for the step first equilibrium as below. The $[\text{OH}^-]$ and $[\text{MET}]$ were varied (Table-1) at dissimilar temperatures. The values of K_1 and K_2 were computed at four dissimilar temperatures and using slopes and intercepts of graphs of $1/k_{\text{obs}}$ against $1/[\text{MET}]$ ($r^2 \geq 0.9958$) and $1/k_{\text{obs}}$ against $1/[\text{OH}^-]$ ($r^2 \geq 0.9974$), and are listed in Table-2. The obtained values of the heat of reaction, ΔH , entropy of the reaction, ΔS , and free energy of the reaction, ΔG , were computed from the van't Hoff's graph for deviation of K_1 with temperature; $\log K_1$ against $1/T$ ($r^2 \geq 0.9986$) and are listed in Table-3.

The values computed for the slow step are compared with latter values indicated that, these values are chiefly depict the limiting rate step support the reality that reaction was fast before the slow step and involve modest energy of activation²⁰. Similarly, at four dissimilar temperatures, the values of K_2 were computed and obtained quantities related to thermodynamic were listed in Table-3.

The obtained value of ΔS^\ddagger was negative which indicates that reactants are less ordered than the intermediate complex²¹. The modest ΔH^\ddagger and ΔS^\ddagger values were complimentary for a reaction which has an electron transfer.

Table-1: Influence of $[\text{MnO}_4^-]$, $[\text{MET}]$ and $[\text{OH}^-]$ on the oxidation of metformin by permanganate in alkaline medium at 25°C .

| $[\text{MnO}_4^-] \times 10^4$ (mol dm ⁻³) | $[\text{MET}] \times 10^3$ (mol dm ⁻³) | $[\text{OH}^-] \times 10^2$ (mol dm ⁻³) | $k_{obs} \times 10^2$ (s ⁻¹) | $k_{cal} \times 10^2$ (s ⁻¹) |
|---|---|--|---|---|
| 0.2 | 1.0 | 4.0 | 2.7 | 2.8 |
| 0.4 | 1.0 | 4.0 | 2.9 | 2.8 |
| 0.6 | 1.0 | 4.0 | 2.7 | 2.8 |
| 0.8 | 1.0 | 4.0 | 2.8 | 2.8 |
| 1.0 | 1.0 | 4.0 | 2.8 | 2.8 |
| 2.0 | 1.0 | 4.0 | 2.8 | 2.8 |
| 1.0 | 0.4 | 4.0 | 1.4 | 1.5 |
| 1.0 | 0.6 | 4.0 | 2.0 | 2.0 |
| 1.0 | 0.8 | 4.0 | 2.4 | 2.4 |
| 1.0 | 1.0 | 4.0 | 2.8 | 2.8 |
| 1.0 | 2.0 | 4.0 | 3.8 | 3.9 |
| 1.0 | 4.0 | 4.0 | 5.2 | 5.0 |
| 1.0 | 1.0 | 0.6 | 1.7 | 1.7 |
| 1.0 | 1.0 | 0.8 | 1.9 | 1.9 |
| 1.0 | 1.0 | 1.0 | 2.1 | 2.1 |
| 1.0 | 1.0 | 2.0 | 2.4 | 2.5 |
| 1.0 | 1.0 | 4.0 | 2.7 | 2.8 |
| 1.0 | 1.0 | 6.0 | 3.0 | 2.9 |

Table-2: The values of K_1 , K_2 , and k at dissimilar temperatures for the oxidation of metformin by Mn(VII) in alkaline media.

| Temp (K) | $K_1 \times 10^{-2}$ (dm ³ mol ⁻¹) | $K_2 \times 10^{-2}$ (dm ³ mol ⁻¹) | $k \times 10^2$ (s ⁻¹) |
|----------|---|---|------------------------------------|
| 288 | 1.22 | 9.48 | 15.02 |
| 293 | 1.15 | 8.68 | 21.32 |
| 298 | 1.09 | 8.49 | 27.94 |
| 303 | 1.03 | 8.27 | 40.92 |

Table-3: The activation parameters and thermodynamic quantities computed for the title reaction

| (a) Activation parameters | | | | |
|---|---|--|---|---------------------|
| E_a (kJ mol ⁻¹) | ΔH^\ddagger (kJ mol ⁻¹) | ΔS^\ddagger (J K ⁻¹ mol ⁻¹) | ΔG^\ddagger (kJ mol ⁻¹) | log ₁₀ A |
| 47 ± 2 | 45 ± 1 | -123 ± 2 | 81 ± 2 | 7 ± 1 |
| (b) Thermodynamic quantities | | | | |
| | values from K_1 | values from K_2 | | |
| ΔH (kJ mol ⁻¹) | -10.42 ± 1 | -8.73 ± 1 | | |
| ΔS (J K ⁻¹ mol ⁻¹) | -314.52 ± 5 | -308.86 ± 5 | | |
| ΔG_{298} (kJ mol ⁻¹) | 83.31 ± 3 | 83.31 ± 4 | | |

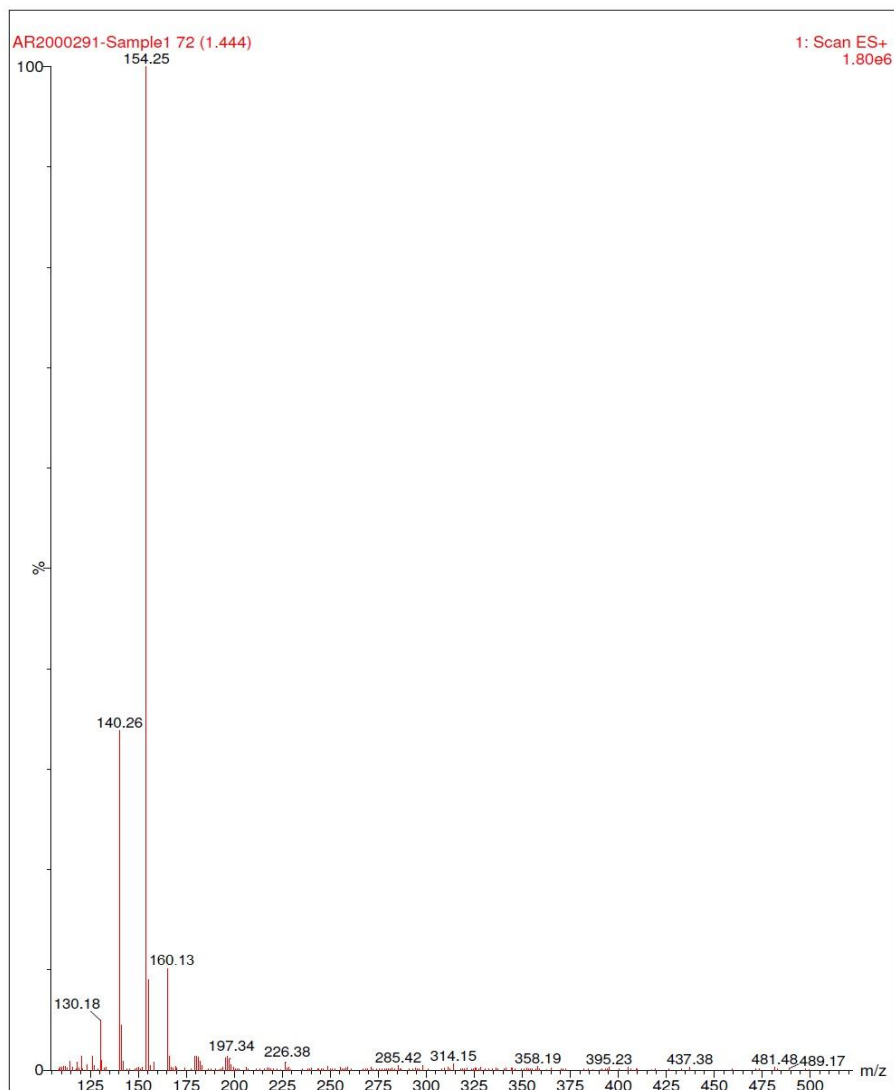


Figure-1: LC-MS spectra of N-(N,N-dimethyl carbamimidoyl)-1-nitro formimidamide (M+1) m/z at 160.13 amu.

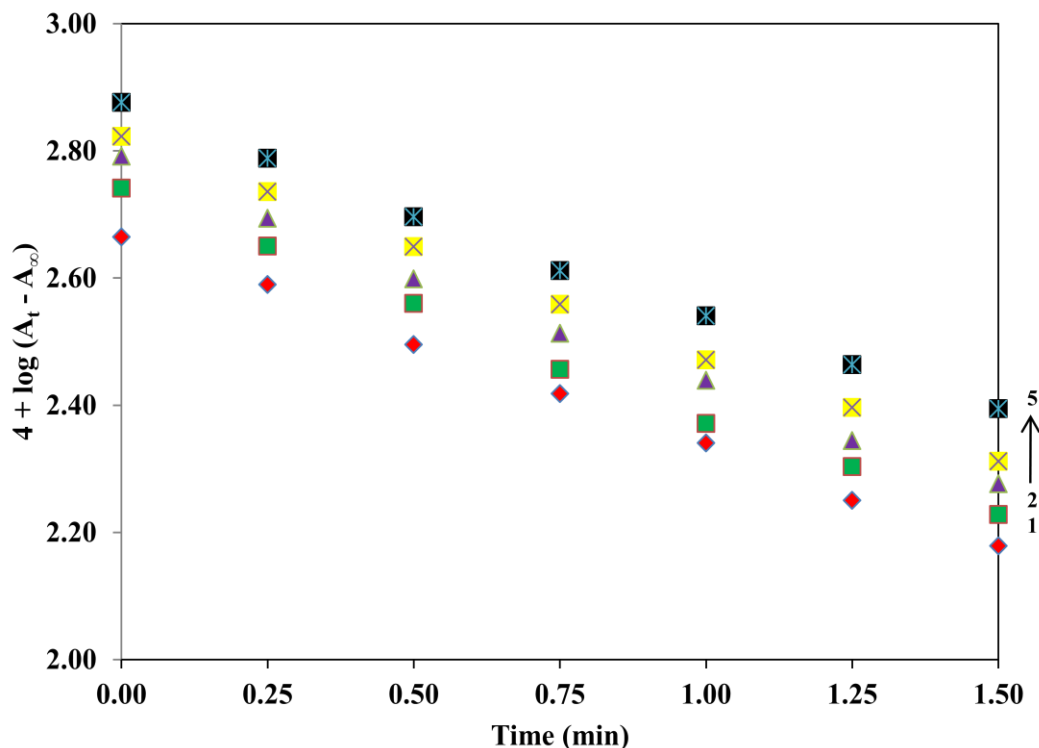


Figure-2: Graph showing first order dependence of [Mn(VII)] during the oxidation of metformin by Mn(VII) in alkaline media at 25°C $[MnO_4^-] \times 10^{-4}$ (mol dm⁻³): (1) 0.2, (2) 0.4, (3) 0.6, (4) 1.0, (5) 2.0, ([MET] = 1.0 × 10⁻³, [NaOH] = 0.04 and Ionic strength = 0.10 mol dm⁻³ respectively).

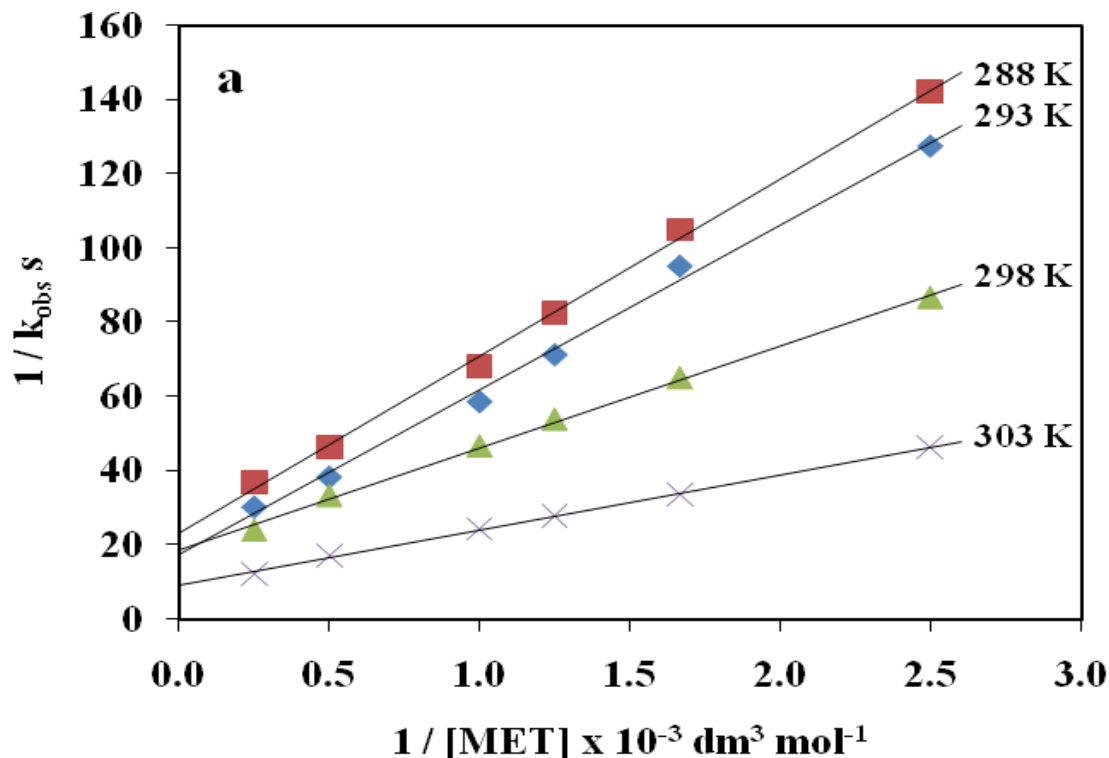


Figure-3: Influence of ionic strength and dielectric constant of the reaction media on the oxidation of metformin by Mn(VII) at 298 K.

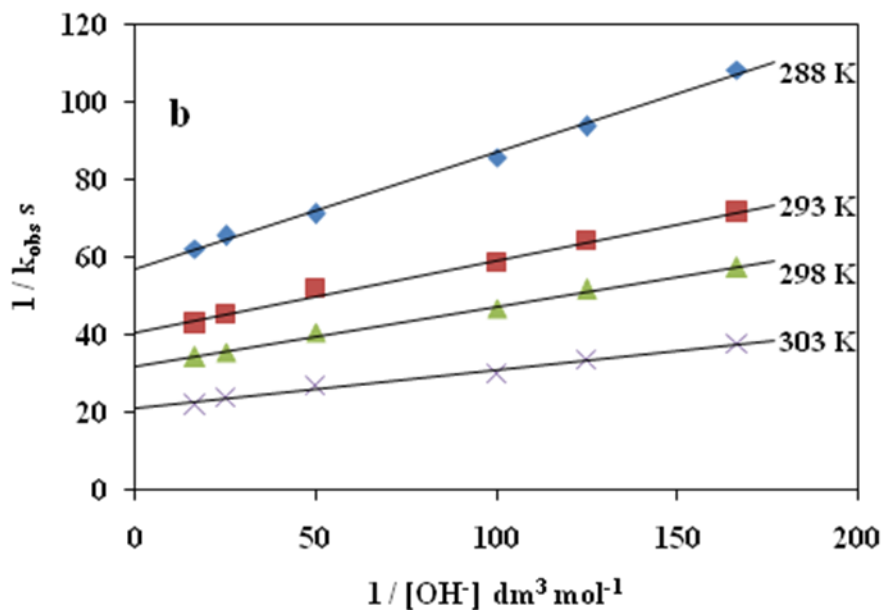


Figure-4: (a) Graphs of $1/k_{obs}$ versus $1/[MET]$ at four dissimilar temperatures (conditions as in Table-1). (b) Graphs of $1/k_{obs}$ versus $1/[OH^-]$ at four dissimilar temperatures (conditions as in Table-1).

Conclusion

The oxidation of antidiabetic drug metformin with Mn(VII) in alkaline media was analysed kinetically. In the title reaction, vital role was played by pH of the reaction environment. Since MnO_4^- , the oxidant species needs a pH more than 12, or else the system would be distressed and the further reaction yields Mn(IV) as the reduced product of the oxidant. The depiction of reaction mechanism of title reaction is reliable with all observations made including kinetic, mechanistic, product and spectral observations. The thermodynamic quantities were computed for all steps in the mechanism. For the slow step of the reaction, the activation parameters were evaluated.

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