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Permanganate oxidative products of moxifloxacin, a fluoroquinolone drug: a mechanistic approach

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Abstract The kinetics of oxidation of moxifloxacin (MOX) was studied spectrophotometrically by a well-recognized analytical reagent, permanganate (Mn(VII), in aqueous alkaline medium at a constant ionic strength. The reaction was first order in [Mn(VII)] and less than unit order both in [MOX] and [alkali]. Retarding effect on rate of reaction was observed with an increase in ionic strength. The effect of dielectric constant of the medium was also studied. The multiple *m/z* values of ESI–MS spectra prove the existence of various oxidative products of MOX. The main product was identified as 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxo-pyrrolo[3,4-b] pyridin-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid. The other three oxidative products from MOX in the present study are similar to the oxidative products of other fluoroquinolones oxidations. However, the abnormally high values of *m/z* could be assigned to the permanganate complexes of the products, which are unusual in the non-metallic oxidation of MOX. A composite mechanism involving the monohydropermangante as the reactive species of the oxidant has been proposed. Activation parameters and thermodynamic parameters are calculated and the reaction constants involved in the different steps of the mechanisms are calculated.

Keywords Moxifloxacin · Oxidation · Kinetics · Thermodynamics · Mechanism

Introduction

Permanganate is a well-known oxidizing agent that oxidizes most of the substrates [1–15], particularly organic substrates, viz., alkenes, alcohols, aldehydes, ketones,

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carboxylic acids, poly-hydroxycarboxylic acids, sulfides, thiols, simple drugs, antibiotics, steroids, etc. Hence, it is used generally as an analytical reagent. Since permanganate is involved in five different oxidation [16] states, varying from +7 to +2, the mechanism of oxidation of such substrates has a fascination of multiple mechanisms. Nevertheless, it can be made a simple single equivalent oxidant (+7 to +6) in highly basic medium, bi-equivalent (+7 to +5) in moderately basic, tri-equivalent (+7 to +4) in neutral, and in acidic media as penta-equivalent oxidant (+7 to +2). Thus, its redox potential depends on pH of the media. In highly basic medium, its redox potential is +0.56 V, in slightly basic or in neutral +1.23 V, and in acid medium +1.51 V. Depending upon the resistance of substrates towards oxidation, pH of the reaction medium is maintained in permanganate oxidations. Sometimes permanganate is used as an oxidizing agent in alkaline medium [17, 18] to avoid the complexity in the mechanism of oxidation of drugs, particularly in kinetic studies to understand the reaction path of such biologically active molecules. Recently, permanganate has been successfully used for the in situ degradation of many organic contaminants [19, 20]. The study was undertaken to understand fully the kinetics and mechanism of oxidation of trichloroethylene, an important pollutant present in ground water [21]. Hence, in the present study permanganate is used as a single equivalent oxidant in establishing a reaction mechanism to understand the oxidative paths of a new antibiotic, moxifloxacin.

Fluoroquinolones (FQs) like lomefloxacin, norfloxacin, ofloxacin, enrofloxacin, ciprofloxacin etc., are a group of synthetic antibacterial agents that have been widely used in human and veterinary medicines. FQs have in vitro and in vivo activities against Gram-negative pathogens, Gram-positive cocci, aerobic intracellular bacteria, atypical organisms, and anaerobic bacteria [22]. Moxifloxacin (MOX) is a fourth-generation antibiotic of the class of fluoroquinolone, a modified form of ciprofloxacin and enrofloxacin. Chemically, it is 1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7- [(4aS, 7aS)-octahydro-6H-pyrrolo [3, 4-b] pyridin-6-yl]-4-oxo-3-quinoline carboxylic acid. It is a broad-spectrum antibiotic agent used in the treatment of bacterial infections (conjunctivitis) [23, 24]. The antimicrobial activity depends upon the inhibition of DNA gyrase (bacterial topoisomerase II) and topoisomerase IV, which regulate spatial arrangement of DNA in bacterial cells. These proteins can cut both strands of the nucleic acid and rejoin them. Inhibiting the activity of those enzymes by formation of irreversible complex drug/enzyme/DNA disables the DNA synthesis and leads to the bacterial cell death [25, 26]. In comparison with other fluoroquinolones, MOX presents a low profile of phototoxic and central nervous system excitatory effects. It has been found to be effective in acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, skin and skin-structure infections, and intra-abdominal infections including polymicrobial infections [27, 28].

Literature survey reveals [29] that many studies have been carried out on the stability of MOX in the presence of metal ions like Cu(II), Fe(II), Zn(II), or alimentary tract coating agent Al(III), which may result in some type of interaction during compound application in medical care. Acid hydrolysis of FQs with the presence of metal ions has been subjected to many studies, but MOX differs from the other FQs at positions 7 and 8 of the molecule, and this difference has an

influence on physicochemical properties and stability of the compound. Kinetic evaluation of decomposition of MOX at 90 and 110 °C showed that the decomposition of MOX in solutions in presence or in absence of metal ions follows first-order kinetics. The presence of metal ions in MOX solutions increases the rate of reaction and decreases the activation energy [29].

Due to the large usage, FQs could enter the environment via various routes including municipal and industrial wastewater effluent, wastewater sludge, manure from animal husbandry, and agricultural runoff. In recent years, studies from many parts of the world including North America, Europe, and China have reported frequent detection of FQs in surface water bodies at concentrations ranging from non-detectable to around 50 ng/l [30–35] and in municipal wastewater at concentrations as high as 700 ng/l in the influent and around 400 ng/l in the effluent [30, 36–40] for individual FQ compounds. The most commonly detected FQs include ciprofloxacin (CIP), norfloxacin (NOR), enrofloxacin (ENR), and ofloxacin (OFL). This new generation of FQ, moxifloxacin (MOX), may also be added up in the future. The presence of FQs in the aquatic environment, especially in surface water that will become the source of potable supply, merits particular concern because of potential health risks. FQs are potent antibiotics with low minimal inhibitory concentrations (MICs) against a wide range of bacterial species [41]. Effective removal of FQs by water treatment processes is important to minimize the possibility of antibiotic resistance development and other potential health risks that may be associated with FQ residues in drinking water.

Hence, the growing usage of antibacterial agents and the potent risks of fostering resistant pathogens and posing adverse effects on human health necessitate the better understanding of transformation of these compounds in aquatic environment.

Wang et al. [42] have made use of ClO_2 as an oxidant to understand the possible products of FQs [42]. Recently, Zhang et al. [43] used MnO_2 as a facilitating oxidant in FQs oxidations for the detection of their oxidative products. However, MOX was not used in their studies, neither in quantification nor in the kinetic studies of oxidative degradation. Although Hubicka et al. [44] studied the photochemical degradation of MOX, and Gouda et al. [45] used *N*-Bromosuccinimide, in the quantification of MOX and its products, no reaction paths have been established for its oxidative products either from its pure form or from its contaminants. Since permanganate has also been used for the treatment of surface water on par with ClO_2, the present study is undertaken for the evaluation of reaction paths of oxidation of MOX by alkaline permanganate.

Experimental

Materials

All chemicals used were of reagent grade and double-distilled water was used throughout the study. Stock solution of MOX is prepared by dissolving required quantity of sample; its purity was checked by its m. p (324–325 °C) [46] and TLC for single spot. It is known that MOX undergoes decarboxylation [29]. Though the

decarboxylation is slow and takes place in acidic medium, rate of decarboxylation was studied by measuring the kinetics runs with aqueous alkaline solution of MOX with different ageing solutions. It was found that there were no differences in kinetic results between fresh and aging solutions. However, fresh solutions were used in all kinetic runs to avoid the error if any were to arise.

The solution of Mn(VII) was made by dissolving the required quantity of $KMnO_4$ crystals in double-distilled water. It is known that $KMnO_4$ is not a primary standard solution, hence, it is standardized against sodium oxalate solution [47, 48]. Further, it is preserved in darkness to avoid degradation due to exposure to sun light. Potassium manganate Mn(VI) solution was prepared as described by Carrington and Symons [49] as follows; an aqueous solution of potassium permanganate was heated to boiling >100 °C in 8.0 mol dm^{-3} KOH solution. The green-colored solution of K_2MnO_4 formed is characterized by its visible spectrum. The solution was standardized spectrophotometrically at 608 nm (ε = 1,530 ± 20 dm^3 mol^{-1} cm^{-1}). This solution was used to study the product effect on rate of reaction. KOH and KNO_3 were used to provide the required alkalinity and to maintain the ionic strength, respectively.

Kinetic measurements

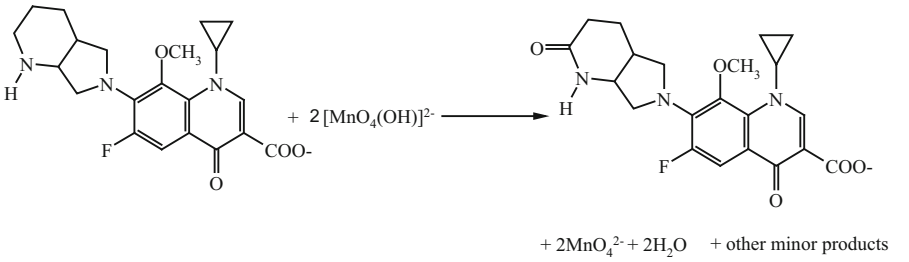
Kinetic measurements were carried out with [MOX] excess over [Mn(VII)] under pseudo-first-order condition, monitoring Mn(VII) consumption as absorption at its $\lambda_{max,}$ 526 nm in a 1-cm quartz cell of a thermostated compartment of Specord-200 plus spectrophotometer setup with a Peltier accessory to control temperature at 303 K as a function of time. Earlier it was verified that there is no interference from other reagents at this wavelength. The reaction was initiated by mixing previously thermostated solutions of Mn(VII) and MOX, which also contained the required quantities of KOH and KNO_3 to maintain required alkalinity and ionic strength, respectively. Application of Beer's law for permanganate at 526 nm had earlier been verified, giving ε, 2,170 ± 30 dm^3 mol^{-1} cm^{-1} (Lit. value = 2,200 dm^3 mol^{-1} cm^{-1}) [50]. First-order rate constants, k_{obs} were calculated by the plots log[Mn(VII)] versus time. In the course of measurements, the color of the solution changed from violet to green. The spectrum of green solution was identified to that of MnO_4^{2-} (Mn(VI)). The results were reproducible within ±3 %.

Product analysis

In order to identify the products formed in the reaction, known amounts of MOX and Mn(VII) with different percentage composition (mol/mol) were allowed to react completely at 303 K in 0.001 mol dm^{-3} KOH. After completion of the reaction and when [Mn(VII)] was in excess over MOX, the residual [Mn(VII)] in each case was analyzed spectrophotometrically at 526 nm. The reduction product, Mn(VI), was estimated by measuring its absorbance at 608 nm.

The oxidative product of MOX was identified as 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo[3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline-3- carboxylic acid. It was analyzed as follows: the reaction mixture after completing

the reaction was treated with 50 % methanol followed by acidification with HCl and 3 % acetonitrile and 1 % formic acid to make the solution in a positive-ion mode for the LC–ESI–MS analysis. The solution was subjected to LC–ESI–MS analysis at the rate of 5 μl/min with retention time 0.51–0.98 s in the applied voltage of 30 kV with a glass micro-syringe. The nitrogen gas was used as nebulizer. The LC–ESI–MS spectrum at positive electrode spray shows several peaks along with the unreacted MOX (Fig. 1). Based on the *m/z* values, each peak is assigned to the possible products as given in Scheme 2. Hence, it reveals that MOX on oxidation gives different products. The major product was identified as 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo[3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline -3-carboxylic acid. The stoichiometry for the main product can be written as:



(1)

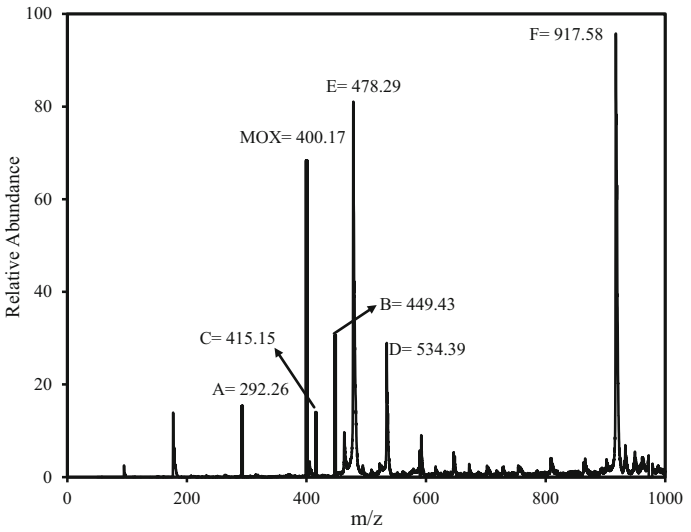


Fig. 1 LC-ESI–MS spectrum of the products resulted due to the oxidation of moxifloxacin by permanganate in aqueous alkaline medium

Results and discussion

Reaction order

The reaction orders were determined from the slopes of log k_{obs} versus log(concentration) plots varying the concentration of reductant and OH^- in turn while keeping others constant. Since the first-order plots were linear up to 90 %, the initial rate methods were not used for determining order of the reactants and other species.

Effect of [Mn(VII)] and [MOX]

The effect of [Mn(VII)] on the reaction rate was studied by varying the [Mn(VII)] from 4.0×10^{-5} to 6.0×10^{-4} mol dm^{-3} at constant concentrations of MOX, alkali, and ionic strength at a constant temperature (Table 1). It was observed that slope of the plot of log (conc.) versus time remained constant for most of the different [Mn(VII)] values. This was also confirmed from the linearity of plots of log(absorbance) versus time to about 90 % completion of the reaction. Hence, the order in [Mn(VII)] was considered as unity.

The effect of [MOX] on rate of reaction was studied at different temperatures in the concentration range, 8.0×10^{-4} to 8.0×10^{-3} mol dm^{-3} at all other reaction concentrations constant (Table 2). The k_{obs} values were increased with an increase in [MOX] in all the temperatures. The order in [MOX] from the plot of log k_{obs} versus log [MOX] was found to be positive fractional order of average 0.70 without much variation with temperature.

Effect of $[OH^-]$

The influence of $[OH^-]$ on rate of reaction was studied by varying [KOH] from 0.7×10^{-3} to 7.0×10^{-3} mol dm^{-3} by keeping all other reaction concentrations constant at temperature range from 303 to 318 K. It was observed that rates are increased with increase in $[OH^-]$ (Table 3). The first-order plots were linear for all the $[OH^-]$ in different temperatures and order from the plot of log k_{obs} versus log $[OH^-]$ was found to be positive fractional at a constant ionic strength of 0.007 mol dm^{-3}. In this case, the order with respect to $[OH^-]$ decreases from 0.61 to 0.39 for all the temperatures varied.

Effect of initially added product

The effect of initially added Mn(VI) on the rate of reaction was studied in the concentration range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at 303 K at constant [Mn(VII)] = 2.0×10^{-4}, [MOX] = 2.0×10^{-3}, $[OH^-] = 1.0 \times 10^{-3}$ and ionic strength = 7.0×10^{-3} mol dm^{-3}. The added product did not influence the rate of reaction.

Table 1 Effect of variation of $[MnO_4^-]$, [MOX], and $[OH^-]$ on oxidation of moxifloxacin by permanganate in aqueous alkaline medium at 303 K

$10^4 \times [MnO_4^-]$ (mol dm^{-3})	$10^3 \times$ [MOX] (mol dm^{-3})	$10^3 \times [OH^-]$ (mol dm^{-3})	$10^3 \times k_{obs}$ (s^{-1})	
			Exptl.[a]	Calc.[b]
0.4	2.0	1.0	3.99	–
0.6	2.0	1.0	3.99	–
1.0	2.0	1.0	4.30	–
2.0	2.0	1.0	4.58	–
4.0	2.0	1.0	4.44	–
6.0	2.0	1.0	4.50	–
2.0	0.8	1.0	2.64	1.96
2.0	1.0	1.0	3.04	2.41
2.0	2.0	1.0	4.58	4.44
2.0	4.0	1.0	7.85	7.67
2.0	6.0	1.0	10.7	10.1
2.0	8.0	1.0	13.4	12.1
2.0	2.0	0.7	3.73	3.33
2.0	2.0	0.9	4.14	4.09
2.0	2.0	1.0	4.58	4.44
2.0	2.0	2.0	6.08	7.29
2.0	2.0	3.0	7.53	9.28
2.0	2.0	4.0	9.00	10.7
2.0	2.0	5.0	11.8	11.9
2.0	2.0	6.0	14.0	12.7
2.0	2.0	7.0	16.3	13.5

$I = 0.007$/mol dm^{-3}

[a] Experimental

[b] Calculated: k_{obs} were calculated by using $k = 2.8 \times 10^{-2}$ s^{-1}, $K_1 = 77.2$ dm^3 mol^{-1} and $K_2 = 13.1 \times 10^2$ dm^3 mol^{-1} at 303 K in rate Eq. (11)

Effect of ionic strength and dielectric constant of the medium

The ionic strength of the reaction medium was varied between 0.2×10^{-2} and 2.0×10^{-2} mol dm^{-3} with potassium nitrate at constant concentrations of alkali, oxidant, and reductant at 303 K. It was found that as ionic strength increases, the rate of reaction decreases. A plot of log k_{obs} versus $\sqrt{I}$ was linear with negative slope -1.0 (Fig. 2).

Dielectric constant of the medium was varied by varying the percentage (v/v) of *t*-butyl alcohol/H_2O content in the reaction mixture. Its effect was studied on rate of reaction with all other conditions being constant. Since the D for various percentage compositions was not available in literature, they were computed from the values of the pure liquids as in earlier work [51]. In the reaction, k_{obs} values were increased with increasing the D (Fig. 2). Earlier, the reaction between *t*-butyl alcohol and oxidant was studied and it was observed that there are no reactions between solvent and oxidant.

Effect of temperature

The effect of temperature on the reaction rate was studied at various temperatures at constant concentrations of oxidant and reductant, with other reaction conditions being

Table 2 Effect of variation of [MOX] on oxidation of moxifloxacin by permanganate in aqueous alkaline medium at different temperatures

$10^3 \times$ [MOX] (mol dm^{-3})	$10^3 \times k_{obs}$ (s^{-1})				
	Exptl.[a]				Calc. for temp 303 K[b]
	303 K	308 K	313 K	318 K	
0.8	2.64	2.72	3.16	3.65	1.96
1.0	3.04	3.39	3.92	4.65	2.41
2.0	4.58	5.65	6.69	7.66	4.44
4.0	7.85	9.87	10.9	12.2	7.67
6.0	10.7	13.5	13.8	13.9	10.1
8.0	13.4	15.5	16.2	16.4	12.1
Order	0.70	0.78	0.73	0.69	0.70

$[MnO_4^-] = 2.0 \times 10^{-4}$; $[OH^-] = 0.001$; $I = 0.007$/mol dm^{-3}

[a] Experimental

[b] Calculated: k_{obs} were calculated by using, $k = 2.8 \times 10^{-2}$ s^{-1}, $K_1 = 77.2$ dm^3 mol^{-1} and $K_2 = 13.1 \times 10^2$ dm^3 mol^{-1} at 303 K in rate Eq. (11)

Table 3 Effect of variation of [OH$^-$] on oxidation of moxifloxacin by permanganate in alkaline medium at different temperatures

$10^3 \times$ [OH$^-$] (mol dm^{-3})	$10^3 \times k_{obs}$ (s^{-1})				
	Exptl.[a]				Calc. for temp 303 K[b]
	303 K	308 K	313 K	318 K	
0.7	3.73	5.55	8.19	11.2	3.33
0.9	4.14	5.71	8.26	11.9	4.09
1.0	4.58	5.94	8.65	12.2	4.44
2.0	6.08	8.69	11.8	13.5	7.29
3.0	7.53	11.6	13.4	16.7	9.28
4.0	9.00	12.8	15.3	17.5	10.7
5.0	11.8	13.5	16.2	19.1	11.9
6.0	14.0	15.2	16.9	20.0	12.7
7.0	16.3	15.8	17.2	20.6	13.5
Order	0.61	0.51	0.42	0.39	0.61

$[MnO_4^-] = 2.0 \times 10^{-4}$; $[MOX] = 2.0 \times 10^{-3}$; $I = 0.007$/mol dm^{-3}

[a] Experimental

[b] Calculated: k_{obs} were calculated by using, $k = 2.8 \times 10^{-2}$ s^{-1}, $K_1 = 77.2$ dm^3 mol^{-1} and $K_2 = 13.1 \times 10^2$ dm^3 mol^{-1} at 303 K in rate Eq. (11)

kept constant. The k_{obs} values increased with increasing temperature (Table 4). Since the reaction follows multistep mechanism, the reaction constants, viz., equilibrium constants and rate constant of the slow step are involved. In order to arrive at the values of such constants, the reaction was studied at various temperatures.

Therefore, the effect of temperature on the rate of reaction was studied at 303, 308, 313, and 318 K by varying [MOX] and [OH^-] in turn while others were kept constant at constant concentrations of [Mn(VII)] and ionic strength (Table 2, 3). From the slope of Arrhenius plot, log k_{obs} versus 1/T, the activation energy, Ea was calculated. Further, the other activation parameters, $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$ and log A (Table 5) were evaluated for overall reaction. On the hand, the rate constants (k) of the slow step of Scheme 1 were obtained from the intercept of $1/k_{obs}$ versus 1/[MOX] for the various temperatures. The values 'k' calculated for slow step remained almost constant with increase in temperature. Hence, activation parameters for the slow step are not calculated. This may be due to the involvement of two equilibria, which are also temperature-dependent steps (discussed elsewhere).

The equilibrium constants K_1 and K_2 of Scheme 1 were determined from the slopes and intercepts of the plots (Figs. 3, 4) of $1/k_{obs}$ versus 1/[MOX] and 1/[OH^-] for different temperatures (Table 6). From the van't Hoff plot, the thermodynamic parameters, ΔH, ΔS, and ΔG for the formation of monohydroxo permanganate, and complex between Mn(VII) and MOX anion were determined (Table 7).

Polymerization study

The intervention of free radicals in the reaction was examined as follows; the reaction mixture containing Mn(VII) and MOX with the concentration of 0.002 mol dm^{-3} each at constant concentrations of OH^- and ionic strength in which a known quantity of acrylonitrile scavenger has been initially added, was kept for 1 h. On dilution with methanol, a copious precipitation resulted. This indicates

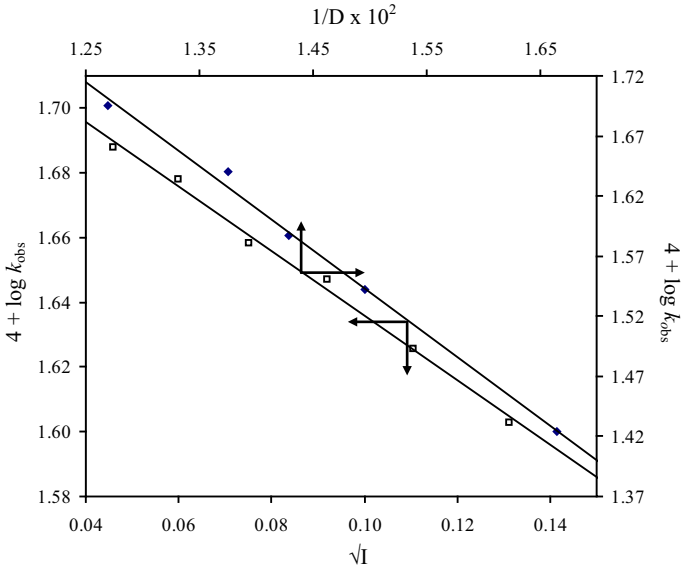


Fig. 2 Effect of ionic strength (I) and dielectric constant (D) on oxidation of moxifloxacin by permanganate in aqueous alkaline medium at 303 K

Table 4 Effect of temperature on the oxidation of moxifloxacin by permanganate in aqueous alkaline medium

Temperature (K)	$10^3 \times k_{obs}$ (overall reaction)	
	Exptl.[a]	Calc.[b]
303	4.58	4.44
308	5.63	5.87
313	7.10	7.71
318	9.32	9.59

$[MnO_4^-] = 2.0 \times 10^{-4}$; $[MOX] = 2.0 \times 10^{-3}$; $[OH^-] = 0.001$; $I = 0.007$/mol dm^{-3}

[a] Experimental

[b] Calculated: k_{obs} were calculated by using, $k = 2.8 \times 10^{-2}$ s^{-1}, $K_1 = 77.2$ dm^3 mol^{-1} and $K_2 = 13.1 \times 10^2$ dm^3 mol^{-1} at 303 K in rate Eq. (11)

that the reaction was routed through a free radical path. The experiment of either Mn(VII) or MOX with acrylonitrile alone did not induce polymerization under similar condition, as those induced with reaction mixture. It is also ascertained by the decrease in rate with initial addition of monomer.

The permanganate in alkaline medium exhibits various oxidation states, such as Mn(VII), Mn(V), and Mn(VI). During this study, the color of the solution changed from violet to blue and then to green. The spectrum of green solution was identical to that of MnO_4^{2-}. The concentration of MnO_4^- decreases at 526 nm and increases at 608 and 432 nm due to Mn(VI) which is one of the reduction products. No evidence of hypomanganate, MnO_4^{3-} with maxima located at 667 nm was seen in the present study. However, the reaction mixture turned to brown turbidity after keeping for 1 h, and development of pale yellow due to another oxidative product. This indicates that the manganate thus formed disproportionate to form permanganate and manganese dioxide as shown below:

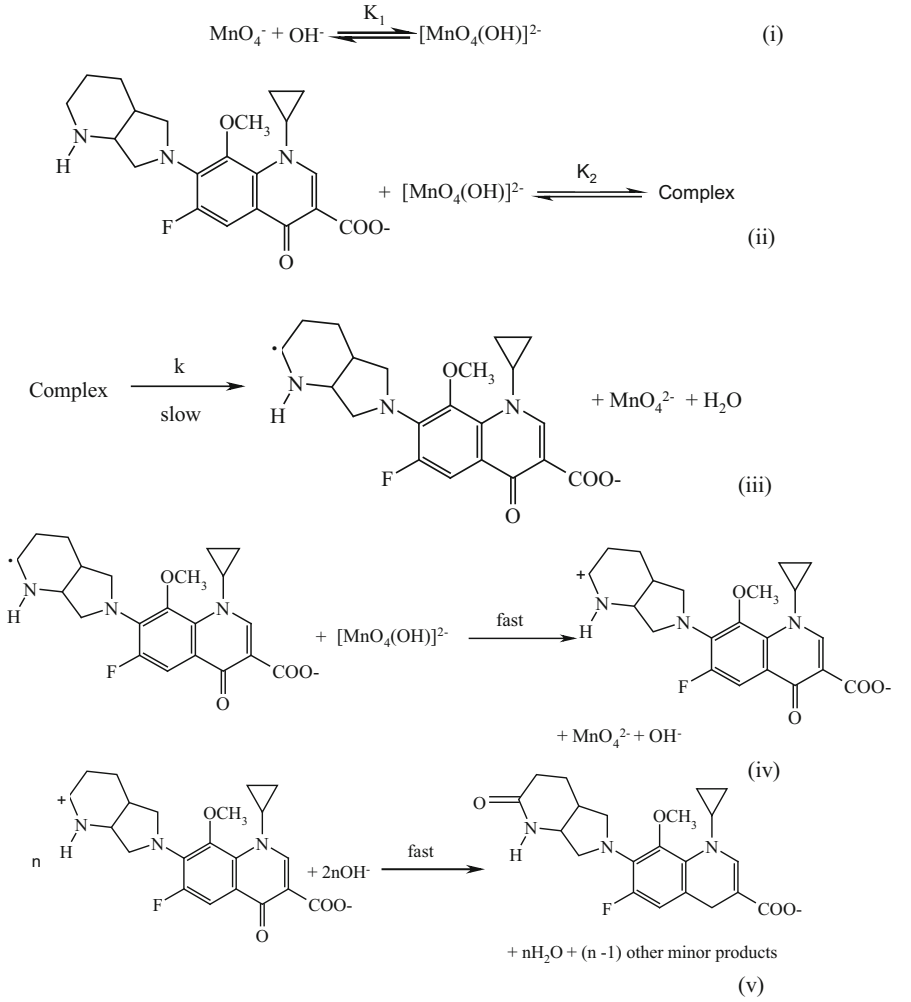
$$3MnO_4^{2-} + 2H_2O \rightarrow 2MnO_4^- + MnO_2 + OH^- \quad (2)$$

Potassium permanganate in alkali medium existed as MnO_4^- and $[MnO_4(OH)]^{2-}$, respectively, as given below:

$$MnO_4^- + OH^- \overset{K_1}{\rightleftharpoons} [MnO_4(OH)]^{2-} \quad (3)$$

Table 5 Activation parameters for the oxidation of moxifloxacin by permanganate in aqueous alkaline medium at 303 K

Activation parameters	Values (overall reaction)
E_a (kJ mol^{-1})	37.4 ± 1
$\Delta H^{\neq}$ (kJ mol^{-1})	34.9 ± 1
$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	−166 ± 4
$\Delta G^{\neq}$ (kJ mol^{-1})	85 ± 2
Log A	4.0 ± 0.1



Scheme 1 Mechanism of oxidation of moxifloxacin by permanganate in alkali

Equilibrium constant, (K_1) for the above step was reported to be as 70 $dm^3\ mol^{-1}$ [52]. In the present study, under the experimental condition and the alkali concentration used, the MnO_4^- is almost existed as $[MnO_4(OH)]^{2-}$, which is evidenced by the K_1 value (77.2 $dm^3\ mol^{-1}$). The reports of previous study of oxidation of ketorolac by permanganate in alkali supports the existence of equilibrium between Mn(VII) and OH^- (68.7 $dm^3\ mol^{-1}$).

The species of MnO_4^- in alkali depicted as $[MnO_4(OH)]^{2-}$ is acting as a single equivalent oxidant and it undergoes reduction up to manganate only (MnO_4^{2-}) as the alkali concentration was maintained well below 0.01 mol dm^{-3}. If its concentration exceeds 0.1 mol dm^{-3}, there was a possibility to undergo reduction up to Mn^{5+} and re-oxidation to Mn^{6+} in a fast step as shown below:

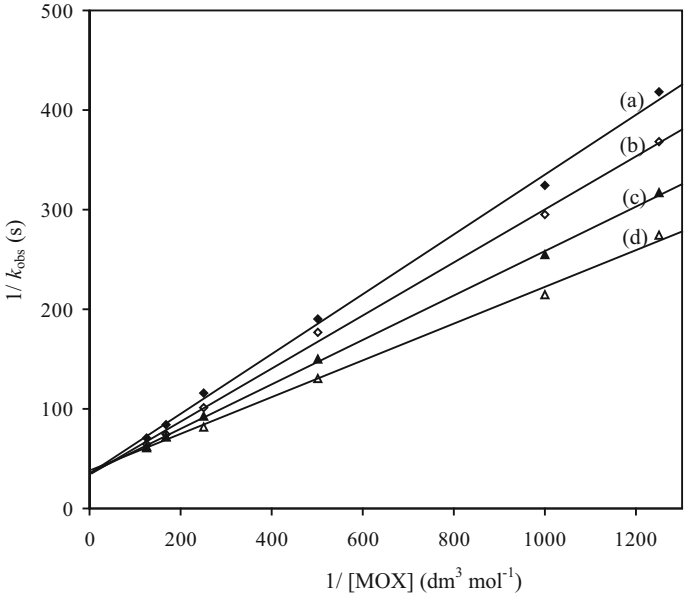


Fig. 3 Verification of rate law (11) and for calculation of k, K_1 and K_2 for the mechanism of oxidation of moxifloxacin by permanganate in aqueous alkaline medium at different temperatures (conditions as in Table 2). Temperature: *a* 303 K, *b* 308 K, *c* 313 K, *d* 318 K

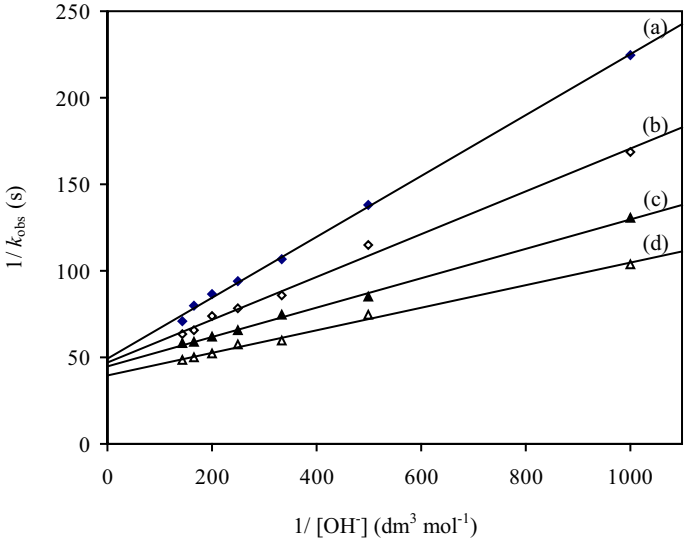


Fig. 4 Verification of rate law (11) and for calculation of k, K_1, and K_2 for the mechanism of oxidation of moxifloxacin by permanganate in aqueous alkaline medium at different temperatures (conditions as in Table 3). Temperature: *a* 303 K, *b* 308 K, *c* 313 K, *d* 318 K

Table 6 Rate constants and equilibrium constants involved in the mechanism of oxidation of moxifloxacin by permanganate in aqueous alkaline medium at different temperatures

Constants	Temperature (K)			
	303	308	313	318
$k \times 10^2$ (s^{-1})	3.54	2.84	1.95	2.42
K_1 (dm^3 mol^{-1})	77.2	95.4	110	130
$K_2 \times 10^{-2}$ (dm^3 mol^{-1})	13.1	16.6	23.0	32.0

Table 7 Thermodynamic parameters of various steps of mechanism of oxidation of moxifloxacin by permanganate in aqueous alkaline medium at 303 K

Equilibrium step	ΔH (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})	ΔG (kJ mol^{-1})
1.	28.0 ± 1	129 ± 2	−11.0 ± 1
2.	48.1 ± 1	219 ± 3	−18.1 ± 0.5

$$Mn^{7+} + 2e^- \rightarrow Mn^{5+} \quad (4)$$

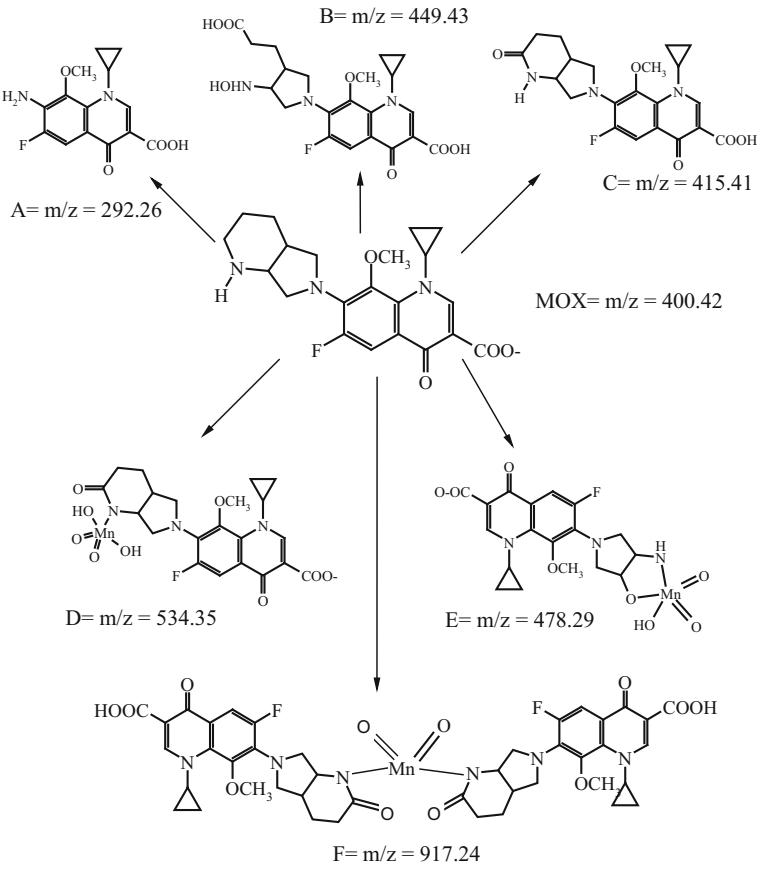
$$Mn^{5+} + Mn^{7+} \rightarrow Mn^{6+} \quad (5)$$

Such a possibility is ruled out due to the low concentration of OH^- used.

When MnO_4^- is a single equivalent oxidant at low [OH^-], the hydride ion (H^-) abstraction from the substrate is ruled out. It is possible [53] only when it is reduced to hypomanganate (Mn^{5+}) by the abstraction of two electrons in the form of H^-. Non-detection of peak at 667 nm due to hypomanganate and intervention of free radicals from the polymerization study also rules out such a possibility.

Polymerization test with OH^- in MnO_4^- but in absence of MOX fails to yield the precipitate. Nonetheless, the polymerization test was positive with MOX, even in the absence of OH^-. Hence, such possibility of generation of free radical from the OH^- may be ruled out. Thus, it may be concluded that the mechanism of oxidation of MOX by permanganate in alkali follows as per the Scheme 1.

The reaction between permanganate and MOX in alkaline medium has a stoichiometry of almost 2:1 for a major product, 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo [3,4-b] pyridine-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid, and a first-order dependency on the [Mn(VII)] and less than unit order dependence on both the concentration of alkali and MOX. Since the permanganate species is one electron oxidant in alkaline medium, a reaction between substrate and oxidant would afford a free radical intermediate evidenced by polymerization test. The initially added products had shown no effect on rate of reaction. The results imply that first the alkali present in the reaction mixture combines with permanganate ions to give a mono-hydroxo permanganate species, $[MnO_4(OH)]^{2-}$ in a prior equilibrium step (1), which is in accordance with literature [54], and also supported by experimentally observed order in [OH^-]. In the next equilibrium step, $[MnO_4(OH)]^{2-}$ formed immediately combines with MOX to form an intermediate complex (2). The fractional order with respect to MOX presumably



Scheme 2 Oxidative products of moxifloxacin as per LC–ESI–MS Spectra. [*A*] 7-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3- carboxylic acid. [*B*] 7-(3-(2-carboxyethyl)-4-hydroxylamine-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. [*C*] 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo[3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid. [*D*] 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo [3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid permanganate complex. [*E*] 7-(3-amino-4-hydroxypyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid permanganate complex. [*F*] Di-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo[3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid permanganate complex

resulted from the complex formation between oxidant and substrate prior to the slow step. However, the evidence for complex formation is obtained by kinetic studies, i.e., from the Michaelis–Menton plot ($1/k_{obs}$ versus 1/[MOX]). Further, the intermediate complex decomposes in a slow step (3) to form a free radical derived from MOX. Thus, the free radical formed reacts with another molecule of $[MnO_4(OH)]^{2-}$ in subsequent fast steps (4 and 5) to yield the product 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(octahydro-2-oxopyrrolo[3,4-b]pyridin-6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid, and other products as in Schemes 1 and 2.

The multiple *m/z* values of ESI–MS spectra prove the existence of different products (A, B, C, D, E, and F), resulted due to oxidation. Such values can be

assigned to the different possible products of MOX are as shown in Scheme 2. The oxidative products obtained (A, B, and C) from MOX in the present study are similar to the oxidative products of other FQs [42] and also the products of photochemical decomposition of MOX [44]. However, the abnormal high values of *m/z* can be assigned to the permanganate complexes of the products (D, E, and F), which are unusual in the non-metallic [42] oxidation of MOX. Nevertheless, the literature reveals that there is evidence for the formation of complex between Fe(III) and MOX [46]. Hence, formation of such complexes cannot be ruled out.

The rate law for the Scheme 1 can be derived as follows:

$$\begin{aligned} \text{Rate} &= -\frac{d[\text{MnO}_4^-]}{dt} = k[\text{Complex}] \\ \text{Rate} &= k\text{K}_2[\text{MnO}_4(\text{OH})]^{2-}\,[\text{MOX}]_\text{f} \\ \text{Rate} &= k\text{K}_1\text{K}_2[\text{MnO}_4^-]_\text{f}[\text{OH}^-]_\text{f}[\text{MOX}]_\text{f} \end{aligned} \tag{6}$$

However,

$$\begin{aligned} [\text{MnO}_4^-]_\text{T} &= [\text{MnO}_4^-]_\text{f} + [\text{MnO}_4(\text{OH})]^{2-} + [\text{Complex}] \\ &= [\text{MnO}_4^-]_\text{f} + \text{K}_1[\text{MnO}_4^-]_\text{f}[\text{OH}^-]_\text{f} + \text{K}_1\text{K}_2[\text{MnO}_4^-]_\text{f}[\text{OH}^-]_\text{f}\,[\text{MOX}]_\text{f} \\ &= [\text{MnO}_4^-]_\text{f}\{1 + \text{K}_1[\text{OH}^-]_\text{f} + \text{K}_1\text{K}_2[\text{MOX}]_\text{f}[\text{OH}^-]_\text{f}\} \end{aligned}$$

$$\begin{aligned} [\text{MnO}_4^-]_\text{f} &= \frac{[\text{MnO}_4^-]_\text{T}}{1 + \text{K}_1[\text{OH}^-]_\text{f} + \text{K}_1\text{K}_2[\text{MOX}]_\text{f}[\text{OH}^-]_\text{f}} \\ [\text{OH}^-]_\text{T} &= [\text{OH}^-]_\text{f} + [[\text{MnO}_4(\text{OH})]^{2-}] \\ &= [\text{OH}^-]_\text{f} + \text{K}_1[\text{MnO}_4^-]_\text{f}[\text{OH}^-]_\text{f} \\ &= [\text{OH}^-]_\text{f}\{1 + \text{K}_1[\text{MnO}_4^-]_\text{f}\} \\ [\text{OH}^-]_\text{f} &= \frac{[\text{OH}^-]_\text{T}}{1 + \text{K}_1[\text{MnO}_4^-]_\text{f}} \end{aligned} \tag{7}$$

At low concentration of [Mn(VII)], $[\text{OH}^-]_\text{f} = [\text{OH}^-]_\text{T}$

$$\begin{aligned} [\text{MOX}]_\text{T} &= [\text{MOX}]_\text{f} + [\text{Complex}] \\ &= [\text{MOX}]_\text{f} + \text{K}_1\text{K}_2[\text{MnO}_4^-]_\text{f}[\text{OH}^-]_\text{f}[\text{MOX}]_\text{f} \\ &= [\text{MOX}]_\text{f}\{1 + \text{K}_1\text{K}_2[\text{OH}^-]_\text{f}[\text{MnO}_4^-]_\text{f}\} \\ [\text{MOX}]_\text{f} &= \frac{[\text{MOX}]}{1 + \text{K}_1\text{K}_2[\text{OH}^-]_\text{f}[\text{MnO}_4^-]_\text{f}} \end{aligned} \tag{8}$$

The term $\text{K}_1\text{K}_2[\text{OH}^-]_\text{f}[\text{MnO}_4^-]_\text{f}$ can be neglected compared to 1 in the denominator as low concentration of MnO_4^- used. Therefore,

$$[\text{MOX}]_\text{f} = [\text{MOX}]_\text{T} \tag{9}$$

On substituting Eqs. (7), (8), and (9) in Eqs. (6), (10) results.

$$\text{Rate} = \frac{k\mathrm{K_1K_2}[\mathrm{MnO_4^-}]_\mathrm{T}[\mathrm{OH^-}]_\mathrm{T}[\mathrm{MOX}]_\mathrm{T}}{1 + \mathrm{K_1}[\mathrm{OH^-}]_\mathrm{f} + \mathrm{K_1K_2}[\mathrm{MOX}]_\mathrm{f}[\mathrm{OH^-}]_\mathrm{f}} \tag{10}$$

For verification of rate law, the subscripts 'T' and 'f' are omitted and hence Eq. (10) becomes Eq. (11) is rearranged into Eq. (12)

$$\frac{\text{Rate}}{[\mathrm{MnO_4^-}]} = k_\mathrm{obs} = \frac{k\mathrm{K_1K_2}[\mathrm{OH^-}][\mathrm{MOX}]}{1 + \mathrm{K_1}[\mathrm{OH^-}] + \mathrm{K_1K_2}[\mathrm{MOX}][\mathrm{OH^-}]} \tag{11}$$

$$\frac{1}{k_\mathrm{obs}} = \frac{1}{k\mathrm{K_1K_2}[\mathrm{OH^-}][\mathrm{MOX}]} + \frac{1}{k\mathrm{K_2}[\mathrm{MOX}]} + \frac{1}{k} \tag{12}$$

Rate law (11) can be rearranged in the form of Eq. (12) and is verified by plotting of $1/k_\mathrm{obs}$ versus $1/[\mathrm{OH^-}]$ and 1/[MOX] for all of which should be linear and are found so in Figs. 3, 4, and 5. From the slopes and intercepts of these plots, the values $k = 2.8 \times 10^{-2}$ s^{-1}, $\mathrm{K_1} = 77.2$ dm^3 mol^{-1}, and $\mathrm{K_2} = 13.1 \times 10^2$ dm^3 mol^{-1} for 303 K are calculated. The value of $\mathrm{K_1}$ obtained in this study is in close agreement with the literature [52] value (70 dm^3 mol^{-1}). Further, these values are used in rate law (11) at different experimental conditions to regenerate k_obs. The regenerated values are found to be in close agreement with those of experimental values (Table 1). This fortifies the mechanism of oxidation as shown in Scheme 1 and rate law (11).

The thermodynamic quantities for the equilibrium steps in Scheme 1 (Table 7) can be evaluated as follows; the $[\mathrm{OH^-}]$ and [MOX] were varied at four different temperatures and k, $\mathrm{K_1}$, and $\mathrm{K_2}$ values were determined (Figs. 3, 4) at each

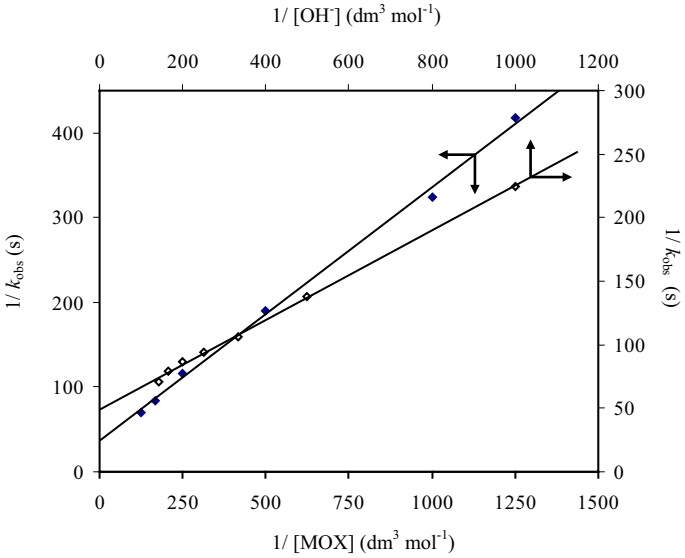


Fig. 5 Verification of rate law (11) for the oxidation of MOX by permanganate in aqueous alkaline medium for 303 K (conditions as in Table 1)

temperature (Table 6). The K_1 and K_2 values are found to be increased with increase in temperature. The van't Hoffs plots were made for the variation of K_1 and K_2 with temperature and the enthalpy of reaction (ΔH) was evaluated from its slope. The free energy change (ΔG) of the reaction was calculated from the relation between ΔG and equilibrium constant K_1; using ΔH and ΔG, the value of ΔS was determined. Similarly, ΔH, ΔS, and ΔG were calculated for K_2 for the equilibrium (2) (Table 7). The oxidation presumed to be occurred through a bridging nitrogen atom of piperazine ring. Thus, the inner sphere mechanism of oxidation of MOX by permanganate is expected. This is evidenced by the small value of frequency factor (4.0), activation energy 37.4 kJ mol^{-1}, and $\Delta S^{\neq}$ (-166 J K^{-1} mol^{-1}). Further, the large negative value of $\Delta S^{\neq}$ (-166 J K^{-1} mol^{-1}) indicates that the activated complex thus formed is more ordered than its reactants.

Since moxifloxacin has both COOH and NH_2 groups, it is an amphoteric molecule [55] having pKa_1 of 6.25 and pKa_2 of 9.29. At pH above or below of its isoelectric point (pH 8.0), the molecule will be charged, while at its isoelectric point it will be devoid of charge. Hence, the alkali maintained in the present study reveals that MOX may be existed in amphoteric form. The negative end of Mn(VII) through oxygen may be interacted with positive end of MOX at nitrogen of piperazine moiety. The interaction of these opposite charges might have been decreased in the rate of reaction with increase in ionic strength (-1.0). The study of variation of dielectric constant of the medium with different percentage composition of *t*-butyl alcohol and water on rate of reaction reveals that the rate increases with an increase in dielectric constant of the medium. It can be concluded that the activated complex may be more solvated at higher dielectric constant medium, supported by a negative slope in the plot of log k_{obs} versus $1/D$ (Fig. 2). Further, this activated complex may be more rigid than the reactants, evidenced by large negative value of $\Delta S^{\neq}$ (-166 J K^{-1} mol^{-1}) and large positive value of $\Delta G^{\neq}$ (85 kJ mol^{-1}).

The ΔH and ΔS values of equilibria (1) and (2) indicate that the formation of monohydroxo permanganate species and the formation of complex between oxidant and reductant are endothermic processes and formed by gain of degrees of freedom. Thus, such complexes may be highly reactive, evidenced by a large value of '*k*' (2.8×10^{-2} s^{-1}). The negative ΔG (Table 7) values for both the steps, (1) and (2), reveal the formation of monohydroxo permanganate species and complex are thermodynamically governed.

Conclusions

Kinetics of oxidation of MOX by Mn(VII) in alkali was followed by the intervention of free radical generated from MOX. The LC–ESI–MS studies reveal that there will be more than one oxidative product. Some major oxidative products are identified. Out of which three are of usual products, similar to FQs oxidations and the remaining are permanganate complexes. The main product was identified as 1-cyclopropyl -6-fluoro -1,4- dihydro -7- (octahydro -2- oxopyrrolo [3,4-b] pyridin -6-yl)-8-methoxy-4-oxoquinoline-3-carboxylic acid. The proposed mechanism involves multiple equilibria. The equilibrium constants are evaluated and compared

with the equilibrium constants of previous studies. The small value of log A indicated that the electron transfer takes place through inner-sphere mechanism. The thermodynamic parameters suggest that $[MnO_4(OH)]^{2-}$ and intermediate complex are thermodynamically governed.

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