Kinetics of Oxidation of Some Fluoroquinolones by Hexacyanoferrate (III) in Alkaline Medium

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ABSTRACT

Kinetics of osmium tetroxide catalyzed-oxidation of the studied fluoroquinolones by potassium hexacyanoferrate(III) in alkaline medium were studied. The rate was found to be independent on the concentration of hexacyanoferrate(III), and first order with respect to both fluoroquinolone and OsO_4. An empirical rate law was derived for the reaction, and the effect of various variables on the rate of reaction was studied. Thermodynamic parameters (E_a, ΔH^*, ΔS^*, ΔG^*) were also calculated.

Keywords- Fluoroquinolones, Potassium hexacyanoferrate(III), Osmium tetroxide, Oxidation, Kinetics.

1. INTRODUCTION

Fluoroquinolones are extremely useful for the treatment of a variety of infections, including urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexual transmitted diseases, prostatitis, community acquired pneumonia, acute bronchitis and sinusitis [1,2]. Recently a relatively new approach to the rational design of antitumor agents has been introduced based on some new quinolone molecules [3].

Quinolones are active against the DNA-gyrase enzyme, a type II topoisomerase. It is believed that DNA-gyrase introduces negative supercoils in DNA by wrapping the DNA around the enzyme [4]. Fluoroquinolones have been shown to be relatively resistant to microbial degradation [5,6]. However, other studies have reported extensive degradation of ciprofloxacin and enrofloxacin by certain fungi species [7]. Photodegradation of fluoroquinolones by direct UV photolysis or radical- mediated photolysis has been reported. Depending on the reaction conditions, more than ten photodegradation products including dealkyltaion, defluoronation and hydroxylation have been identified [8,9,10].

The use of oxidizing agents in attacking particular groups in simple and large molecules has received a great attention. Among these is potassium hexacyanoferrate(III) [11], a one electron oxidant with a redox potential of 0.36V. Although hexacyanoferrate (III) has some advantages that make it suitable for the oxidation of several organic substrates [12]. In particular, its stability over the entire pH scale and being a moderate oxidant, its reactions with some nitrogen containing compounds are not facile and require the presence of a catalyst [13]. Therefore, osmium tetroxide has been used widely for catalyzing such reactions [14,15]. In this communication, we aim at the elucidation the kinetics of osmium tetroxide catalyzed-oxidation of the studied fluoroquinolones by potassium hexacyanoferrate(III) in alkaline medium.

2. EXPERIMENTAL

2.1 Chemicals and Reagents

Potassium hexacyanoferrate (III) (Riedel-dehaen), osmium tetroxide, ciprofloxacin, norfloxacin, enrofloxacin, nalidixic acid and HCl were purchased from sigma and used as received. Stock solution of the drug (0.5M) was prepared by dissolving the desired amount of the drug and further dilution was performed using distilled water. The stock solution was kept in the refrigerator at 4.0^oC for not more than one week.

2.2 Instrumentation

UV-visible spectra were obtained using Shimadzu UV-VIS-NIR Scanning Spectrophotometer, model UV3101PC. The pH measurements were carried out using HANNA pH meter model HI 8424.

2.3 Methodology

Kinetics for the oxidation of the quinolones under study were followed spectrophotometrically by measuring the absorbance of potassium hexacyanoferrate (III) with the progress of time at 420 nm. The desired hydroxide ion concentration was achieved using standard sodium hydroxide solution. Sodium chloride solution was added to adjust the ionic strength of the reaction mixture to the required value. The required volumes of the drug, potassium hexacyanoferrate(III) and the required reagents were added to the reaction flask and mixed well. A portion of the reaction mixture was transferred to the measuring cell and the absorbance was recorded at appropriate intervals right after mixing.

3. RESULTS AND DISCUSSION

3.1 Kinetics of Oxidation of Quinolones by Hexacyanoferrate

The rate of oxidation of the flouroquinolones (fig. 1) namely: ciprofloxacin (CIP), norfloxacin (NOR), enrofloxacin (ENR) and nalidixic acid (NAL) by $K_3Fe(CN)_6$ was investigated by following the absorbance of $K_3Fe(CN)_6$ at 420 nm versus time. Alkaline hexacyanoferrate(III) showed almost no reaction with the studied quinolones in the absence of the catalyst.

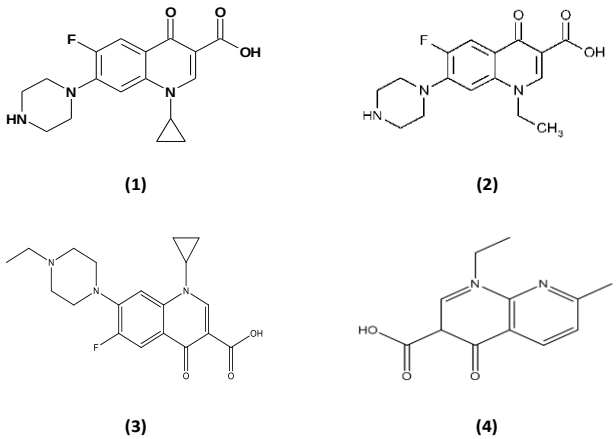

Fig. 1 The chemical Structure of: (1) Ciprofloxacin (2) Norfloxacin (3) Enrofloxacin (4) Nalidixic acid

The absorbance versus time plots were linear for the oxidation of the fluoroquinolones (CIP, NOR, and ENR) by $K_3Fe(CN)_6$ in alkaline medium catalyzed by osmium tetroxide, indicating that the order of reaction with respect to $K_3Fe(CN)_6$ is zero. Nalidixic acid showed no reaction with $K_3Fe(CN)_6$ even in the presence of the catalyst. This suggests that piperazine ring is the active site for oxidation of fluoroquinolones by hexacyanoferrate(III), which agrees with the results that we obtained using electrochemical oxidation methods.

The rate of reaction of fluoroquinolones with $K_3Fe\ (CN)_6$ was represented by the negative slope of the straight absorbance versus time lines obtained. The reproducibility of the pseudo-first-order rate constant (k) from replicate runs was within ± 3%. The dependence of the reaction rate on various parameters was investigated. These parameters included concentration of reactants, catalyst, hydroxide ion, potassium hexacyanoferrate(III) and other salts, as well as the temperature.

3.2 Dependence on reactants concentration

Kinetics were followed out at various initial concentrations of the desired reactant while keeping other parameters constant. The order of reaction with respect to each reactant is represented by the slope of the straight lines obtained from the plot of logarithms of the rates versus logarithms of the corresponding initial concentrations.

The dependence of the reaction rate on fluoroquinolone concentration is shown in fig. 2. It was found that the rate increases with increasing the initial concentration of the fluoroquinolone. The order of reaction with respect to the fluoroquinolone was found to be nearly unity (0.916 for CIP, 0.991 for NOR and 0.913 for ENR).

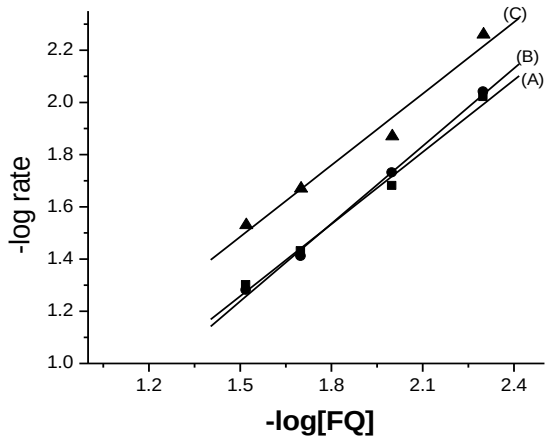

Fig. 2 Plots of –log [FQ] vs. –log rate for (A): CIP, (B): NOR, and (C): NER; where $[K_3Fe(CN)_6]$= 1x10^{-3}M, $[OsO_4]$= 1x10^{-5}M, $[OH^-]$= 0.1M, temperature= 25°C, μ= 0.15

Comparison of the reactivities of the fluoroquinolones points out to the inner nitrogen (N_1) of the piperazine ring to be the rate-limiting reactive site. For example, CIP and NOR differ only in the substituent (i.e. cyclopropyl versus ethyl) at the nitrogen atom of the aromatic heterocyclic ring. The fact that CIP and NOR have comparable reactivities suggests that the reaction center is unlikely associated with nitrogen atom of the heterocyclic ring. ENR differs from CIP only in its ethyl substituent at the outer nitrogen (N_6) of the piperazine ring.

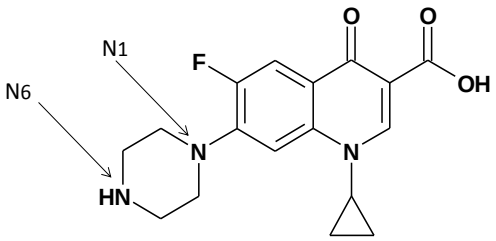

Fig. 3 The chemical structure shows the effect of the substituents at nitrogen (N_6) of the piperazine ring.

However, the rates of these two compounds are comparable (even a slower rate is observed for ENR). The rate of oxidation of aliphatic amines was found to follow the order; primary < secondary < tertiary owing to the increased basicity of nitrogen atom of the amine. Tertiary amines reacted at an average 4-fold faster rate than secondary amines [16]. If the rate-limiting step was associated with the outer nitrogen atom (N_6), then ENR (a tertiary amine) would react faster than CIP (a secondary amine)- a scenario that was clearly not observed in the experiments. s seen from fig. 4, the reactions followed zero-order dependence on potassium hexacyanoferrate (III) concentration.

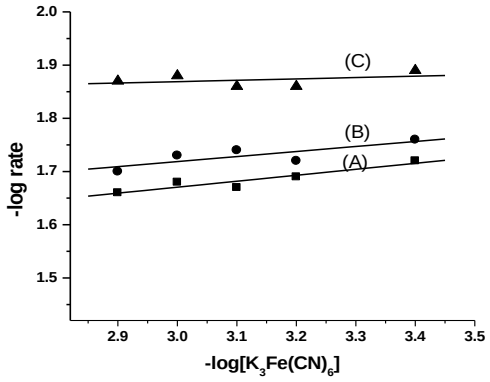

Fig. 4 Plots of –log rate vs. –log $[K_3Fe(CN)]$, [FQ]= 0.01M,$[OsO_4]$= 1x10^{-5}M, [OH-]= 0.1M, temperature = 25^{o}C, μ= 0.15.

The effect of osmium tetroxide on the reaction rate is shown in fig. 5. It was found that the rate of reaction is directly proportional to the concentration of OsO_4. The order of reaction with respect to OsO_4 was found to be about one for the studied FQ's. Species such as OsO_4, $[OsO_4(H_2O)_2]$, $[OsO_4(H_2O)(OH)]^-$ and $[OsO_4(OH)_2]^{2-}$ coexist in fast equilibria with each other, as different forms of Os(VIII), in basic medium. Since the present reaction medium is strongly basic, then the total [Os(VIII)] can be assumed as $[OsO_4(OH)_2]^{2-}$ [17].

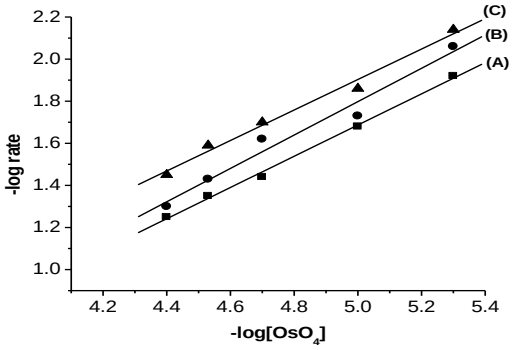

Fig. 5 Plots of –log rate vs. –log $[OsO_4]$; (A) Ciprofloxacin, (B) Norfloxacin, (C) Enrofloxacin; [FQ]= 0.01M, $[K_3Fe(CN)_6]$= 1x10^{-3}M, [OH^-]= 0.1M, temperature= 25°C, μ= 0.15.

Also, the dependence of the rate on initial hydroxide ion concentration was studied, and it was found that the rate increased slightly with increasing the hydroxide ion concentration in the reaction medium.

3.3 Effect of added salts

The reaction of FQ's with $K_3Fe(CN)_6$ in the presence of OsO_4 was carried out at different concentrations of potassium hexacyanoferrate(II). It was found that the rate decreases with increasing the concentration of $K_4Fe(CN)_6$ as shown in Table (1) for the three drugs.

Table 1: Effect of added $K_4Fe(CN)_6$ on reaction rate:[FQ] = 0.01M, [K3Fe(CN)6]= 1x10^{-3}M, [OsO_4]= 1x10^{-5} M, [OH^-]= 0.1 M temperature = 25 °C, μ= 0.15.

10^{-4} $[K_4Fe(CN)_6]$M	-log rate		
	CIP	NOR	ENR
0.0	1.68	1.73	1.86
5.0	1.75	1.81	1.89
10.0	1.80	1.88	1.91
15.0	1.85	1.92	1.95
20.0	1.88	1.95	1.98

Fig. 6 shows the effect of added of different concentrations of $K_4Fe(CN)_6$ for ciprofloxacin. This indicates that Fe $(CN)_6^{4-}$ is involved in a reversible step that could affect the rate determining step.

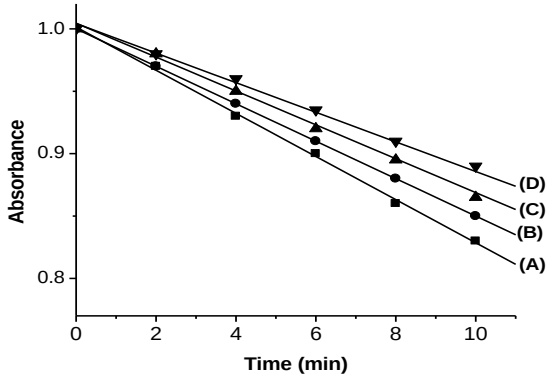

Fig. 6 Effect of added $K_4Fe(CN)_6$ at: (A) 0.5 mM, (B) 1.0 mM, (C) 1.5 mM, and (D) 2.0 mM on ciprofloxacin reaction rate; [CIP]=0.01M, $[K_3Fe(CN)_6]$=1x10^{-3}M, [OsO_4]=1x10^{-5}M, [OH^-] = 0.1M, temperature= 25 °C, μ= 0.15

Addition of different potassium salts to keep a constant ionic strength has no effect (within experimental error) on the reaction rates for the studied FQ's, as presented in Table (2) and showed in Fig. 7 for enrofloxacin.

Table 2: Effect of added salt on reaction rate; [FQ] =0.01M, $[K_3Fe(CN)_6]= 1x10^{-3}M$, $[OsO_4]= 1x10^{-5}M$, $[OH^-]= 0.1$, temperature = 25°C, μ = 0.15

Salt	-log rate		
	CIP	NOR	ENR
NaCl	1.68	1.73	1.86
NH_4Cl	1.85	1.86	1.95
KCl	1.69	1.75	1.88
KBr	1.70	1.71	1.82
KI	1.68	1.75	1.83

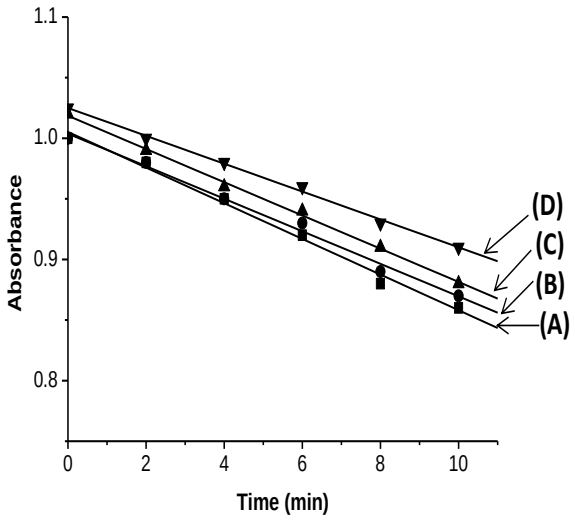

Fig. **7** Effect added of salt: (A) KI, (B) KBr, (C) KCl, (D) NH_4Cl on enrofloxacin reaction rate: [ENR]= 0.01M, $[K_3Fe(CN)_6]= 1x10^{-3}M$, $[OsO_4]= 1x10^{-5}M$, $[OH^-]= 0.1M$ temperature= 25°C, μ= 0.15

Addition of chlorides showed that sodium and potassium have no specific effect on the rate, whereas ammonium has. Being acidic, ammonium ion consumes some OH^- and thus affects the production of the assumed active form of the catalyst $[OsO_4 (OH)_2]^{2-}$. The resulting ammonia could also inhibit the reaction through the formation of a complex with Os(VIII), per say, $[OsO_4 (NH_3)_2]$.

3.4 Thermodynamic parameters

The activation parameters of the catalyzed reaction between the studied fluoroquinolones and $Fe(CN)_6^{3-}$ were calculated as tabulated in table (3) at different temperatures by using the experimental rate equation:

$$Rate = k[FQ][OsO_4] \quad (1)$$

Table 3: Activation parameters for the catalyzed oxidation of FQ's by potassium hexacyanoferrate(III) in alkaline medium

FQ	Ea(kJ)	ΔS*(J)	ΔH*(kJ)	ΔG*(kJ)
CIP	27.90	59.48	25.42	7.69
NOR	30.12	66.74	27.64	7.75
ENR	34.45	80.62	35.97	11.94

Whereas, the rate constants were calculated at these different temperatures as seen for an example for norfloxacin in table 4.

Table 4 Effect of temperature on norfloxacin reaction rate: [NOR] = 0.01M, $[K_3Fe(CN)_6]$ = $1x10^{-3}$M, $[OsO_4]$ = $1x10^{-5}$M, $[OH^-]$ = 0.1M, μ=0.15.

T(^oC)	10^3(1/T) (K^{-1})	10^2[Rate]	10^{-5} k	Lnk
15	3.47	1.31	1.31	11.76
20	3.41	1.64	1.64	11.90
25	3.36	1.85	1.85	12.11
30	3.30	2.39	2.39	12.35
37	3.22	3.11	3.11	12.64

The energy of activation was calculated according to Arrhenius equation:

$$K = A\, e^{-Ea/RT} \quad (2)$$

Where;
k: specific rate constant
A: frequency factor
E_a: energy of activation
R: gas constant
T: absolute temperature

The effect of temperature on reaction rate is plotted as lnk versus 1/T (Fig. 8) that shows linear with a slope of -Ea/RT, hence Ea is calculated.

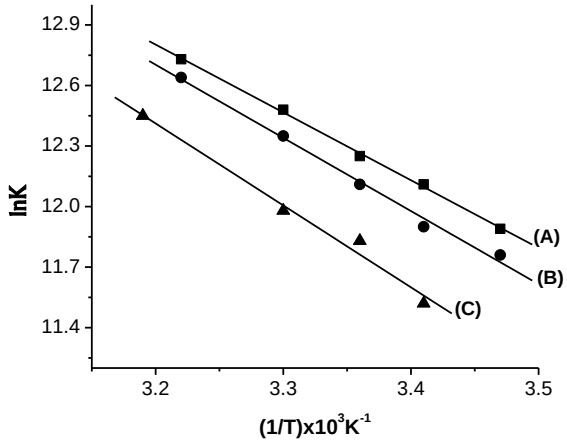

Fig. 8 Plot of ln k vs. 1/T, for: (A) 0.01M of CIP, (B) 0.01M of NOR, and (C) 0.01 M of ENR, $[K_3Fe(CN)_6]$= $1x10^{-3}$M, $[OsO_4]$= $1x10^{-5}$M, $[OH^-]$= 0.1M, μ= 0.15.

The entropy [ΔS*], the enthalpy [ΔH*] and the free energy [ΔG*] of activations were calculated from the following relations respectively [16]:

$$\log(k/T) = \mathrm{Log}(k_B/h) + \Delta S^*/4.57 - E_a/4.57T \quad (3)$$

Where k, T and E_a have the same significance as before. h: Plank's constant = $6.625X10^{-27}$ erg. Sec
k_B: Boltzman constant = $1.381X10^{-16}$ erg. Deg

$$\Delta H = Ea - RT \quad (4)$$

And

$$\Delta G = \Delta H - T\Delta S \quad (5)$$

The positive values of ΔS* indicates that the transition states are less ordered than the reactants. The constancy of ΔG* values indicates a common mechanism of oxidation for the FQ's studied.

4. CONCLUSIONS

The rate of oxidation of the studied fluoroquinolones is followed the order: ciprofloxacin > norfloxacin > Enrofloxacin, and the studied drugs followed zero-order kinetics with respect to $K_3Fe(CN)_6$, and the rate law was found experimentally to be; Rate= k[FQ][OsO_4]. Also, it is found that the oxidation for the studied compounds enhanced with increasing the concentration of hydroxide ion, and decreased with increasing the concentration of $K_4Fe(CN)_6$. However, the rate was not affected by the concentration of the added salts.

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