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PHYSICAL CHEMISTRY | RESEARCH ARTICLE

Kinetics and mechanistic studies of oxidation of fluoroquionoline antibacterial agent norfloxacin by diperiodatocuprate(III) in aqueous alkaline medium

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Abstract: The kinetics of the oxidation of norfloxacin by diperiodatocuprate(III) in aqueous alkaline medium has been studied spectrophotometrically at 300 K and at constant ionic strength of 0.20 mol dm^{-3}. The oxidation products were identified by LC–ESI–MS technique and other spectral studies. The stoichiometry was found to be 1:2 ([NOR]:[DPC]. The active species of DPC is understood to be as monoperiodatocuprate(III). A suitable mechanism was proposed on the basis of experimental results. The reaction constants involved in the different steps of the reaction mechanism were calculated. The activation parameters with respect to the slow step of mechanism were determined and discussed.

Subjects: Engineering & Technology; Health and Social Care; Physical Sciences

Keywords: diperiodatocuprate(III); norfloxacin; oxidation; kinetics; mechanism

1. Introduction

In recent years, the study of highest oxidation state of transition metals has intrigued many researchers. Transition metals in a higher oxidation state can be stabilized by chelation with suitable polydentate ligands. Metal chelates such as diperiodatocuprate(III) (Reddy, Sethuram, & Navneeth Rao, 1984), diperiodatoargentate(III) (Kumar, Kumar, & Ramamurthy, 1999), and periodatonickelate(IV) (Shettar

Deepak S. Munavalli

ABOUT THE AUTHORS

The principal investigator and other authors have been actively engaged in the research of the area of mechanisms of uncatalyzed and catalyzed reactions.
Kinetic studies provide the most important type of evidence of the reaction mechanism. In the first part of the study, rate, order, stoichiometry, and the final products would be confirmed and estimated by known techniques, while the second part of the study will be made at varying temperatures. From this data, the different thermodynamic parameters will be calculated and the validity of the proposed reaction path will be confirmed. The presence and accumulation of fluoroquinolone antibiotics in aquatic environments, albeit at low concentrations, may pose threats to the ecosystem and human health by inducing increase and spread of bacterial drug resistance due to long-term exposure. This necessitates the development of various advanced oxidation processes for the transformation of fluoroquinolones in water.

PUBLIC INTEREST STATEMENT

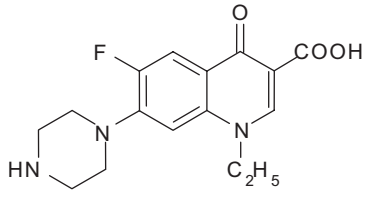
This paper reveals the kinetic study of oxidation of an antibacterial agent, norfloxacin, by diperiodatocuprate(III) complex as an oxidant. The extensive usage of fluoroquinolones may enter the environment via wastewater effluent and biosolids from sewage treatment plants and via manure and litters from food-producing animal husbandry. The presence and accumulation of fluoroquinolone antibiotics in aquatic environments, albeit at low concentrations, may pose threats to the ecosystem and human health by inducing increase and spread of bacterial drug resistance due to long-term exposure. This necessitates the development of various advanced oxidation processes for the transformation of fluoroquinolones in water. The present study also demonstrates with the title reaction in order to investigate the redox chemistry of DPC in alkaline media and to compute the thermodynamic quantities of various steps involved in the mechanism to those derived on the basis of kinetic and spectroscopic results.

& Nandibewoor, 2005) are good oxidants in a medium with an appropriate pH value. The oxidation reaction usually involves the copper(II)–copper(I) couple and such aspects are detailed in different reviews (Pierre, 2000; Solomon, Chen, Metz, Lee, & Palmer, 2001). It is used as an analytical reagent and is now well recognized. Copper(III) is involved in many biological electron transfer reactions (Peisach, Alsen, & Bloomberg, 1966). Periodate and tellurate complexes of copper(III) have been used in the estimation of various organic substrates. They have also been used in the differential titration of organic mixtures, in the estimation of chromium, calcium and magnesium from their ores, antimony, and arsenic and tin from their alloys (Sethuram, 2003). When the copper(III) periodate complex is oxidant and when multiple equilibria between different copper(III) species are involved, it would be interesting to know which of the species is the active oxidant.

Norfloxacin[1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid] is a synthetic, broad-spectrum, fluroquinoline antibacterial agent for oral administration. It has *in vitro* activity against many Gram-positive and Gram-negative bacteria. It also inhibits deoxyribonucleic acid synthesis, and is bactericidal (*Drug information 88*, 1988; Kastrup, 1988). Norfloxacin is a fluoroquinolone used in the treatment of several bacterial diseases, including urinary tract infections in humans (Lawrenson & Logie, 2001), enteritis in dogs (Bhaumik, 1997), and chronic respiratory disease in chickens (Sumano, Ocampo, Brumbaugh, & Lizarraga, 1998). A dextran-linked prodrug has been developed from norfloxacin for treating mycobacterium bovis infections (Domurado et al., 2005). Metabolism of norfloxacin via N-acetylation, oxidation, and breakdown of the piperazine ring has been reported for humans (Pauliukonis, Musson, & Bayne, 1984) and fungi (Parshikov et al., 2001). The drug and its formulations are listed in the US Pharmacopoeia (Mack, 1998) and *European Pharmacopoeia* (European Pharmacopoeia, 1997).

As a result of their extensive usage, fluoroquinolones may enter the environment via wastewater effluent and biosolids from sewage treatment plants and via manure and litters from food-producing animal husbandry. The presence and accumulation of fluoroquinolone antibiotics in aquatic environments, albeit at low concentrations, may pose threats to the ecosystem and human health by inducing increase and spread of bacterial drug resistance due to long-term exposure. This necessitates the development of various advanced oxidation processes for the transformation of fluoroquinolones in water.

The structure of norfloxacin is shown below which consists of piperazine and pyridine moieties.



In view of potential pharmaceutical importance of norfloxacin and lack of literature on the oxidation of this drug by any oxidant except in one case (Nanda, Mayanna, & Gowda, 1999) and the complexity of the reaction, a detailed study of the reaction becomes important. The present work is aimed at checking the reactivity of norfloxacin toward diperiodatocuprate(III) in an alkaline medium, at determining the redox chemistry of the diperiodatocuprate(III) in such media, and at arriving at a plausible mechanism.

2. Experimental

All chemicals used were of analytical grade. Double-distilled water was used throughout the work. The solution of norfloxacin (Bayer, AG) was prepared by dissolving known amount of compound in 6.0 cm^3 of 0.3 mol dm^{-3} NaOH (sd fine Chemicals) and further diluted to 100 cm^3 with double-distilled water. KNO_3 and KOH (sd fine Chemicals) were used to maintain the ionic strength and alkalinity of the reaction, respectively. A stock standard solution of periodate was prepared by dissolving a known weight

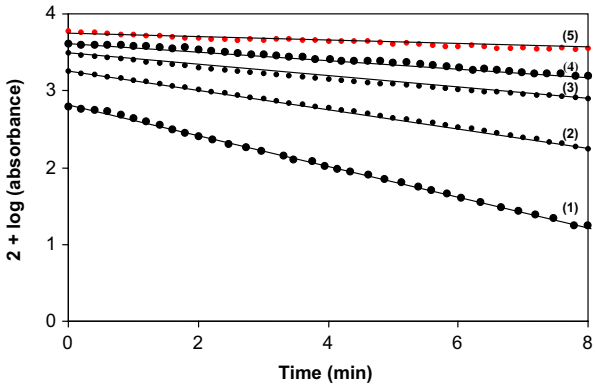


Figure 1. First-order plots for the oxidation of norfloxacin by DPC in an aqueous alkaline medium at 27°C.

Note: 10^5 [DPA] (mol dm^{-3}); (1) 1.0; (2) 3.0; (3) 5.0; (4) 7.0; (5) 10.0.

of KIO_4 (Riedel-de Haen) in hot water and used after keeping for 24 h. Its concentration was ascertained idometrically (Panigrahi & Misro, 1978) at neutral pH, which was maintained using phosphate buffer. The copper(III) periodate complex was prepared (Murthy, Sethuram, & Rao, 1981) and standardized by a standard procedure (Jeffery, Bassett, Mendham, & Denny, 1996).

2.1. Instruments used

For kinetic measurements: UV–vis spectrophotometer (Varian CARY 50 Bio). For product analysis: LC–ESI–MS technique**:** Hewlett Packard 1100 reverse phase high-performance liquid chromatography (HPLC) system with a phenomenes C-18 column, hp 1100 series diode array UV/Visible detector, and hp 1100 MSD Series mass analyzer. FTIR technique: Nicolet-5700 USA. ^{1}H NMR technique: Bruker 300 MHz.

2.2. Kinetics

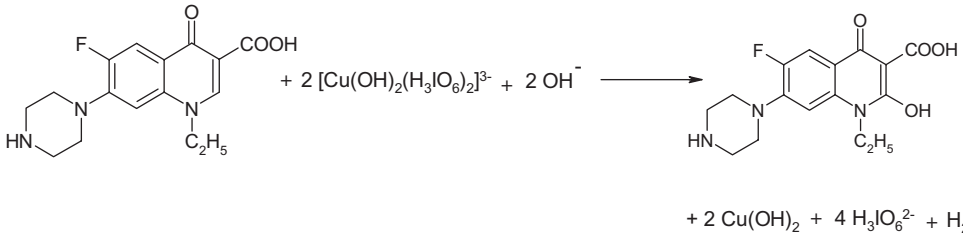
The oxidation of norfloxacin by DPC was followed under pseudo- first-order conditions where norfloxacin concentration was excess over DPC at 27.0 ± 0.1°C unless otherwise stated. The reaction was initiated by mixing the required quantities of previously thermostatted solutions of norfloxacin and DPC, which also contained definite quantities of KOH and KIO_4. The progress of reaction was followed by measuring the absorbance of unreacted DPC in the reaction mixture present in a 1-cm cell in a thermostatted compartment of a Varian CARY 50 Bio UV–vis. spectrophotometer at 415 nm. And extinction coefficient, ε, was found to be 6213 ± 100 dm^3 mol^{-1} cm^{-1}. The kinetic runs were followed and more than 75% completion of the reaction and good first kinetics were observed. The pseudo-first-order rate constants were determined from the slopes of log (absorbance) versus time plots (Figure 1) and are reproducible within ±5%. The effect of dissolved oxygen on the reaction was studied by preparing the reaction mixture and following the reaction in an atmosphere of nitrogen. No significant difference between the results was observed. However, fresh solutions were used during the experiments.

3. Results

3.1. Stoichiometry and product analysis

Different sets of concentrations of reaction mixtures at constant hydroxide ion and periodate ion concentrations were kept in a closed container under a nitrogen atmosphere at 27°C. After one hour, the DPC concentration was assayed by measuring the absorbance at 415 nm. The results indicated that one mole of norfloxacin reacts with two moles of DPC (1:2) as shown below. The main reaction product was identified as 1-ethyl-6-fluoro-2-hydroxy-4-oxo-7-piperazin-1-yl-1,4-hydroquinoline-3-carboxylic acid.

The oxidation product of norfloxacin, 1-ethyl-6-fluoro-2-hydroxy-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid was isolated with the help of TLC and other separation techniques and characterized by LC–ESI–MS, FTIR, and ^{1}H-NMR spectral studies. LC–ESI–MS analysis was carried out using a reverse phase HPLC system with phenomena's C-18 column, UV/Visible detector, and series mass analyzer. Twelve µL of acidified reaction mixture was injected. The mobile phase consisted of acetonitrile (eluent A) and methanol (containing 0.1% CH_3COOH) at a flow rate of 1 cm^3 min^{-1}. Gradient



elution was run to separate the substrate and reaction products. Gradient 0 min/95% A—15 min/35% A—25 min/35% A—30 min/95% A—35 min/35% A. LC–ESI–MS analysis of the reaction indicated the presence of a product with molecular ion of m/z 335 (yield 90%), corresponding to 1-ethyl-6-fluoro-2-hydroxy-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (Figure 2). The IR spectroscopy shows a peak at 1731 cm^{-1} and is due to acidic C=O stretching; the peak due to ketonic C=O stretching will appear at 1644 cm^{-1}; 3056 cm^{-1} is due to NH stretching of the piperzine moiety and the broad peak at 3424 cm^{-1} is due to OH stretching.

^{1}H-NMR (DMSO) shows singlet at 8.9 ppm due to acidic OH, NH of piperzine, and singlet of phenolic OH at 6.6 ppm, which disappears on D_2O exchange; this confirms the formation of product 1-ethyl-6-fluoro-2-hydroxy-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (Figure 3).

3.2. Reaction orders

The reaction orders were determined from the slope of log k_{obs} versus log (concentration) plots by varying the concentrations of norfloxacin and alkali in turn while keeping all other concentrations and conditions constant.

3.3. Effect of [diperiodatocuprate(III)]

At a constant concentration of norfloxacin, 5.0×10^{-4} mol dm^{-3}, alkali, 0.08 mol dm^{-3}, and at a constant ionic strength, 0.20 mol dm^{-3}, the DPC concentration was varied in the concentration range of 1.0×10^{-5}–1.0×10^{-4} mol dm^{-3}. The plot of log (absorbance) versus time was linear and almost parallel over three

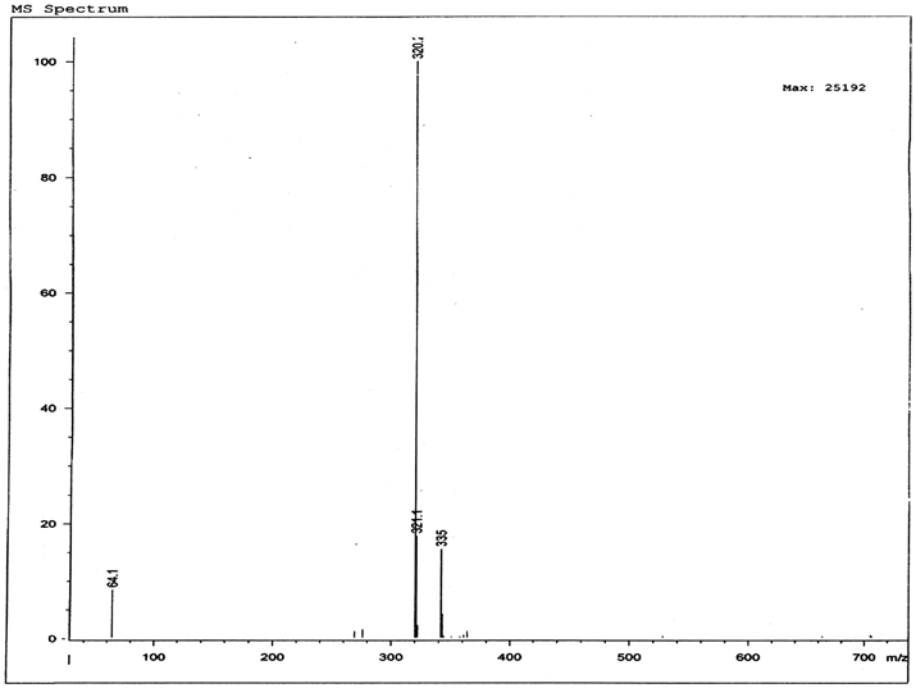


Figure 2. LC–ESI–MS spectra of the product of oxidation of norfloxacin by diperiodatocuprate(III).

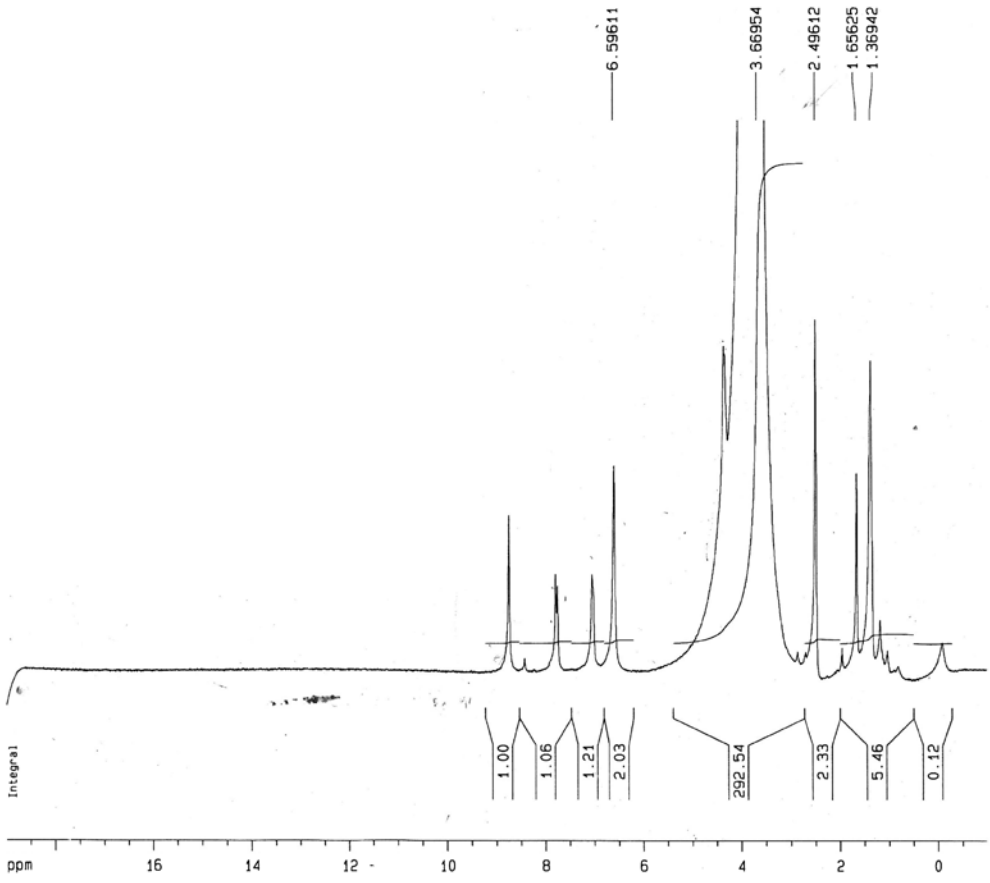


Figure 3. ^{1}H-NMR spectra of the product of oxidation of norfloxacin by diperiodatocuprate(III).

half-lives of the reaction for different initial concentrations of DPC (Figure 1), indicating the unit order with respect to DPC concentration. This was also confirmed by the constant values of pseudo-first-order rate constants, k_{obs}, for different DPC concentrations.

3.4. Effect of [norfloxacin]

The effect of norfloxacin concentration on the reaction was studied at constant concentrations of alkali and DPC and at a constant ionic strength of 0.20 mol dm^{-3} at 27°C. The substrate, norfloxacin, was varied in the range of 1.0×10^{-4}–1.0×10^{-3} mol dm^{-3}. The k_{obs} values increased with increase in the concentration of norfloxacin. The order with respect to norfloxacin concentration was found to be less than unity.

3.5. Effect of [alkali]

The effect of increase in concentration of alkali on the reaction was studied at constant concentrations of norfloxacin and DPC at a constant ionic strength of 0.2 mol dm^{-3} at 27°C. The pseudo-first-order rate constant, k_{obs}, was found to be increase with increase in alkali concentration (Table 1). The order with respect to OH^- ion concentration was found to be less than unity.

3.6. Effect of [periodate]

The effect of increase in concentration of periodate was studied by varying the periodate concentration from 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3}, keeping all other reactant concentrations constant. It was found that the added periodate had a retarding effect on the rate of reaction (Table 1). The order with respect to periodate concentration was found to be negative and less than unity.

Table 1. Effect of variation of [DPC], [NOR], [OH], and [IO^-] on oxidation of norfloxacin by DPC in an alkaline medium at 27°C, I = 0.20 mol dm^{-3}

10^5 [DPC]	104 [NOR]	[OH^-]	10^5 [IO_4^-]	k_{obs} × 10(s^{-1})	
				Found	Calc.
1.0	5.0	0.08	1.0	2.60	2.48
3.0	5.0	0.08	1.0	2.68	2.48
5.0	5.0	0.08	1.0	2.64	2.48
7.0	5.0	0.08	1.0	2.62	2.48
10.0	5.0	0.08	1.0	2.64	2.48
5.0	1.0	0.08	1.0	1.17	0.88
5.0	3.0	0.08	1.0	1.85	1.84
5.0	5.0	0.08	1.0	2.64	2.48
5.0	7.0	0.08	1.0	3.35	3.17
5.0	10.0	0.08	1.0	3.59	3.25
5.0	5.0	0.01	1.0	1.08	1.15
5.0	5.0	0.04	1.0	1.78	2.01
5.0	5.0	0.08	1.0	2.64	2.48
5.0	5.0	0.12	1.0	3.09	3.39
5.0	5.0	0.16	1.0	4.01	4.16
5.0	5.0	0.08	1.0	2.64	2.48
5.0	5.0	0.08	2.0	2.31	2.01
5.0	5.0	0.08	4.0	1.91	1.61
5.0	5.0	0.08	8.0	1.25	1.15
5.0	5.0	0.08	10.0	1.32	1.01

3.7. Effect of ionic strength and dielectric constant of the medium

The effect of ionic strength was studied by varying the KNO_3 concentration from 0.40 to 0.20 mol dm^{-3} at constant concentrations of DPC, norfloxacin, and alkali. It was found that increase in ionic strength had no effect on the rate of reaction. The effect of dielectric constant (D) was studied by varying the t-butanol–water content (v/v) in the reaction mixture, with all other conditions being maintained constant. The decrease in dielectric constant of the reaction medium has no effect on the rate of reaction.

3.8. Effect of initially added product

The Cu(II) ion concentration was varied from 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at constant concentrations of DPC, norfloxacin, alkali, and ionic strength. It was found that initially added Cu(II) ion had no effect on the rate of reaction.

3.9. Polymerization study

Under the reaction conditions used for kinetic measurements, a 100-cm^3 solution of norfloxacin contained 8% acrylonitrile mixed with a 100-cm^3 DPC in a three-neck flask; both solutions were flushed for 30 min with nitrogen gas before mixing. By stirring the reaction mixture for 3 h, under the protection of nitrogen gas, precipitation of polyacrylonitrile could be noticed. This observation implies the involvement of free radical in the reaction mixture.

3.10. Effect of temperature

The influence of temperature on the rate of reaction was studied at 17, 27, 37, and 47°C, under varying concentrations of norfloxacin, alkali, and periodate, keeping other conditions constant. The rate constant (k) of the slow step of Scheme 1 was obtained from the slopes and intercepts of $1/k_{obs}$ versus 1/[NOR], $1/k_{obs}$ versus 1/[OH^-], and $1/k_{obs}$ versus [$H_3IO_6^{2-}$] plots at four different temperatures. The

Table 2. Activation parameters for the oxidation of norfloxacin by DPC in an aqueous alkaline medium with respect to the slow step of Scheme 1

(A) Effect of temperature

Temperature (K)	10^3 k (s^{-1})
290	2.94 88
300	3.9055
310	4.6012
320	5.6012

(B) Activation parameters (Scheme 1)

Parameters	Values
Ea(kJ mol^{-1})	16.15 ± 0.05
$\Delta H^{\#}$ (kJ mol^{-1})	13.6 ± 2.0
$\Delta S^{\#}$ (JK^{-1} mol^{-1})	−246.0 ± 4.0
$\Delta G^{\#}$ (kJ mol^{-1})	88.7 ± 3.0
log A	0.40 ± 0.1

(C) Effect of temperature to calculate K_1, K_2, and K_3 for the oxidation of norfloxacin by diperiodatocuprate(III) in an aqueous alkaline medium

Temperature (K)	10^2 K_1 (dm^3 mol^{-1})	10^2 K_2 (mol dm^{-3})	$10^{-3}K_3$ (dm^3 mol^{-1})
290	3.5 ± 0.2	1.05 ± 0.03	3.2 ± 0.1
300	1.3 ± 0.4	1.90 ± 0.06	5.6 ± 0.3
310	0.5 ± 0.1	3.61 ± 0.03	9.2 ± 0.4
320	0.2 ± 0.1	5.58 ± 0.02	12.9 ± 0.5

(D) Thermodynamic quantities using K_1, K_2, and K_3

Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_3
ΔH (kJ mol^{-1})	−73.6 ± 0.6	43.7 ± 0.5	36.2 ± 0.7
ΔS (JK^{-1} mol^{-1})	−282 ± 4.0	113 ± 12.0	192 ± 15.0
ΔG (kJ mol^{-1})	12.3 ± 0.2	9.3 ± 0.9	−22.4 ± 0.8

values are given in Table 2. The activation parameters for the rate-determining step were obtained by the least square method of plot of log k_1 versus 1/T and are presented in Table 2.

4. Discussion

The water-soluble copper(III) periodate complex is reported (Reddy, Sethuram, & Navneeth, 1987) as $[Cu(HIO_6)_2(OH)_2]^{7-}$. However, in an aqueous alkaline medium and at a high pH range, as employed in the study, periodate is unlikely to exist as HIO_6^{4-} (as present in the complex), as is evident from its involvement in the multiple equilibria (Bailar, Emeleus, Nyholm, & Trotman Dikenson, 1975) (1)–(3) depending on the pH of the solution.

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \quad (1)$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+ \quad (2)$$

$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+ \quad (3)$$

Periodic acid exists as $H_5IO_6^-$ in an acid medium and as $H_4IO_6^-$ around pH 7. Thus, under the conditions employed in alkaline medium, the main species are expected to be $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. At higher concentrations, periodate also tends to dimerise (Sethuram, 2003). However, formation of this species is

negligible under conditions employed for kinetic study. Hence, at the pH employed in this study, the soluble copper(III) periodate complex exists as diperiodatocuprate (III), $[Cu(OH)_2(H_3IO_6)_2]^{3-}$, a conclusion also supported by the literature (Bal Reddy, Sethuram, & Navaneeth Rao, 1981).

The reaction between the diperiodatocuprate(III) complex and norfloaxacin in an alkaline medium has the stoichiometry 1:2 (norfloaxacin:DPC), with a first-order dependence on [DPC] and an apparent order of less than unity in [substrate] and [alkali], and negative fractional order dependence on the periodate. No effect of added products was observed. Based on the experimental results, a mechanism is proposed for which all the observed orders in each constituent such as [oxidant], [reductant], $[OH^-]$, and $[H_3IO_6]^{2-}$ may be well accommodated.

The result of increase in rate with increase in alkali concentration can be explained in terms of prevailing equilibrium of formation of $[Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-}$ from $[Cu(OH)_2(H_3IO_6)_2]^{3-}$ as

$$[Cu(OH)_2(H_3IO_6)_2]^{3-} + OH^- \overset{K_1}{\rightleftharpoons} [Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} + H_2O$$

Also, decrease in rate with increase with in $[H_3IO_6]^{2-}$ suggests the equilibrium of Cu(I) periodate complex to form monoperiodatocuprate(III) (MPC)

$$[Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} \overset{K_2}{\rightleftharpoons} [Cu(OH)_2(H_3IO_6)]^{-} + (H_2IO_6)^{3-}$$

Such type of equilibria has been noticed in the literature (Shetti & Nandibewoor, 2009). It may be expected that a lower periodate complex such as monoperiodatocuprate(III) (MPC) is more important in the reaction than the DPC. The inverse fractional order in $H_3IO_6^{2-}$ concentration might also be due to this reason. Therefore, MPC is the reactive form of the oxidant in the present study.

The fractional order with respect to norfloaxacin concentration indicates the formation of a complex between the norfloaxacin and the DPC species. Such a complex formation between the oxidant and norfloaxacin has also been observed in the literature (Hiremath, Kiran, & Nandibewoor, 2007). Then, this complex (C) breaks up in the slow step resulting in the formation of an intermediate free radical species of norfloaxacin. This intermediate species further reacts with another molecule of MPC species in a fast step to yield the products. On this basis, a general mechanism involving MPC is as follows:

$$Cu(HL)_2 + [OH^-] \rightleftharpoons CuL(HL) + H_2O$$

$$CuL(HL) \rightleftharpoons Cu(HL) + L$$

$$Cu(HL) + S \rightleftharpoons \text{Complex (C)}$$

$$\text{Complex (C)} \rightarrow S^* + Cu(II)$$

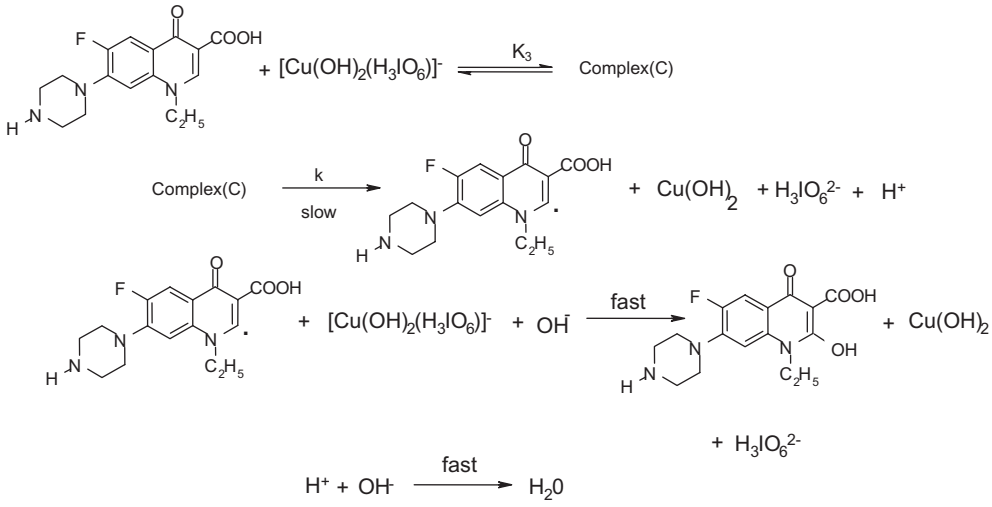
$$S^* + Cu(HL) \rightarrow \text{Products} + Cu(II)$$

So, the detailed mechanistic scheme for the oxidation of norfloaxacin by diperiodatocuprate(III) is as follows:

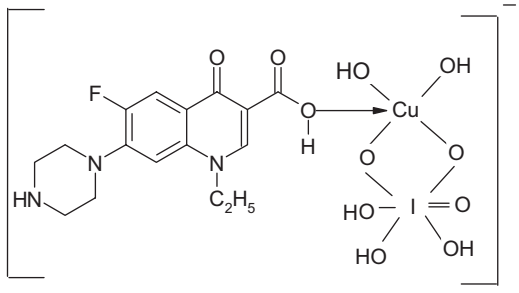
$$[Cu(OH)_2(H_3IO_6)_2]^{3-} + OH^- \overset{K_1}{\rightleftharpoons} [Cu(OH)_2(H_3IO_6)]^{-} + (H_2IO_6)^{4-} + H_2O$$

$$[Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} \overset{K_2}{\rightleftharpoons} [Cu(OH)_2(H_3IO_6)]^{-} + (H_2IO_6)^{3-}$$

Scheme 1. Mechanism for the oxidation of norfloxacin by alkaline diperiodato cuprate(III).



The probable structure of complex(C) is given below



Since Scheme 1 is in accordance with the generally well-accepted principle of non-complementary oxidations taking place in sequence of one-electron steps, the reaction between the substrate and oxidant would afford a radical intermediate. A free radical scavenging experiment revealed such a possibility (see infra). This type of radical intermediate has also been observed in the literature (Chougale, Hiremath, & Nandibewoor, 1997).

Spectroscopic evidence for the complex formation between the oxidant and substrate was obtained from UV–vis spectra of norfloaxacin (5.0×10^{-4}), DPC (5.0×10^{-5}) and [OH^-] (0.06 mol dm^{-3}), and mixture of both. A bathochromic shift of about 6 nm from 342 to 348 nm in the spectra of DPC was observed (Bal Reddy et al., 1981; Hiremath et al., 2007; Murthy et al., 1981; Shetti & Nandibewoor, 2009). However, the Michaelis–Menten plot also proved the complex formation between DPC and norfloaxacin, which explains the less than unit order dependence on [norfloaxacin]. From Scheme 1, the rate law (8) may be derived as follows:

$$\text{Rate} = -\frac{d[\text{DPC}]}{dt} = k[C] = \frac{kK_1K_2K_3[\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)]^-[\text{NOR}][\text{OH}^-]}{[\text{H}_3\text{IO}_6^{3-}]} \quad (4)$$

The total concentration of DPC, i.e. $[DPC]_t$, is given by,

$$[\text{DPC}]_t = [\text{DPC}]_f + [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^{4-} + [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)]^- + [\text{Complex(C)}]$$

$$[DPC]_t = [DPC]_f + K_1[DPC][OH^-] + \frac{K_1K_2[DPC][OH^-]}{[H_2IO_6^{3-}]} + \frac{K_1K_2[DPC][NOR][OH^-]}{[H_2IO_6^{3-}]}$$

$$[DPC]_t = [DPC]_f\left\{\frac{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + K_1K_2[DPC][NOR][OH^-]}{[H_2IO_6^{3-}]}\right\} \quad (5)$$

$$[DPC]_f = \frac{[DPC]_f[H_2IO_6^{3-}]}{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + K_1K_2[DPC][NOR][OH^-]}$$

where "t" and "f" refer to the total and free concentrations. Similarly, the total concentration of norfloaxacin is given by

$$[NOR]_t = [NOR]_f + [C]$$

$$[NOR]_t = [NOR]_f + \frac{K_1K_2K_3[DPC]^-[NOR][OH^-]}{[H_3IO_6^{3-}]}$$

$$[NOR]_t = \frac{[NOR]_f[H_3IO_6^{3-}] + K_1K_2K_3[DPC]^-[OH^-]}{[H_3IO_6^{3-}]}$$

$$[NOR]_f = \frac{[NOR]_t[H_3IO_6^{3-}]}{[H_3IO_6^{3-}] + K_1K_2K_3[DPC]^-[OH^-]}$$

In view of lower concentrations of DPC, OH^-, and $H_2IO_6^{3-}$ used,

$$[NOR]_f = [NOR]_t \quad (6)$$

Similarly,

$$[OH^-]_t = [OH^-]_f + [Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} + [Cu(OH)_2(H_3IO_6)]^- + [Complex(C)]$$

$$[OH]^-{}_t = [OH]_f + K_1[OH^-][Cu(OH)_2(H_3IO_6)_2]^- + \frac{K_1K_2[Cu(OH)_2(H_3IO_6)_2]^{3-}[OH^-]}{[H_2IO_6^{3-}]} + \frac{K_1K_2K_3[Cu(OH)_2(H_3IO_6)_2]^{3-}[NOR]}{[H_2IO_6^{3-}]} \quad (7)$$

In view of low concentration of DPC, NOR, and $H_2IO_6^{3-}$ used,

$$[OH^-]_f = [OH^-]_t$$

Substituting Equations 5, 6 and 7 in Equation 4 and omitting subscripts "t" and "f", we get,

$$\text{Rate} = -\frac{d[DPC]}{dt} = \frac{kK_1K_2K_3[DPC][NOR][OH^-]}{[H_2IO_6^{3-}] + K1[OH^-][H_2IO_6^{3-}] + K_1K_2[OH^-] + kK_1K_2[OH^-][NOR]}$$

or

$$k_{obs} = -\frac{\text{Rate}}{[DPC]} = \frac{kK_1K_2K_3[NOR][OH^-]}{[H_2IO_6^{3-}] + K1[OH^-][H_2IO_6^{3-}] + K_1K_2[OH^-] + kK_1K_2[OH^-][NOR]} \quad (8)$$

The rate law (8) can be rearranged to Equation 9, which is suitable for verification.

$$\frac{1}{k_{obs}} = \frac{[H_2IO_6^{3-}]}{kK_1K_2K_3[NOR][OH^-]} + \frac{[H_2IO_6^{3-}]}{kK_2K_3[NOR]} + \frac{1}{kK_3[NOR]} + \frac{1}{k} \quad (9)$$

According to Equation 9, the plots of $1/k_{obs}$ versus $1/[OH^-]$, $1/k_{obs}$ versus 1/[NOR], and $1/k_{obs}$ versus $[H_2IO_6^{3-}]$ should be linear and are found to be so (Figure 4). The slopes and intercepts of such plots

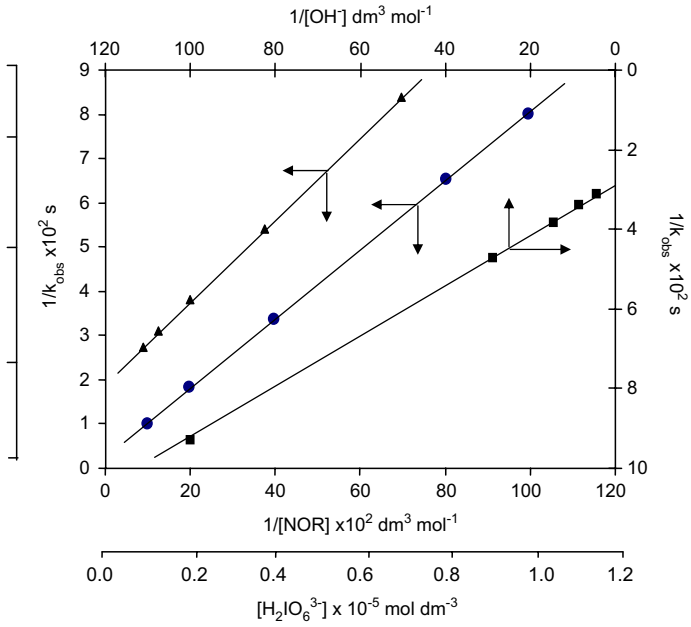


Figure 4. Verification of rate law (8) in the form of Equation 9 for the oxidation of norfloaxacin by diperiodatocuprate(III) in an aqueous alkaline medium at 27°C.

lead to the values of K_1, K_2, K_3, and k as (1.3 ± 0.4) × 10^{-2} mol dm^{-3}, (1.90 ± 0.06) × 10^{-2} mol dm^{-3}, (5.6 ± 0.3) × 10^3 dm^3 mol^{-1}, and (3.9 ± 0.2) × 10^{-3} s^{-1}, respectively. The equilibrium constant K_1 is far greater than K_2. This may be attributed to the greater tendency of DPC to undergo hydrolysis compared to the dissociation of the hydrolyzed species in an alkaline medium. The negligible small effect of ionic strength and dielectric constant of medium on the rate explains qualitatively the reaction between neutral and negatively charged ions, as seen in Scheme 1.

The thermodynamic quantities for the first, second, and third equilibrium steps of Scheme 1 can be evaluated as follows. The $[H_2IO_6^{3-}]$, [NOR], and $[OH^-]$ (as in Table 2) were varied at four different temperatures. The plots of $1/k_{obs}$ versus $1/[OH^-]$, $1/k_{obs}$ versus 1/[NOR], and $1/k_{obs}$ versus $[H_2IO_6^{3-}]$ should be linear (Figure 4). From the slopes and intercepts, the values of K_1 were calculated at different temperatures (Table 2). A van't Hoff plot was made for variation of K_1 with temperature (log K_1 versus 1/T) and the values of enthalpy of reaction, ΔH, entropy of reaction, ΔS, and free energy of reaction, ΔG, were calculated for the first equilibrium step. These values are given in Table 2. A comparison of the latter values with those obtained for the slow step of the reaction shows that these values mainly refer to the rate-limiting step, supporting the fact that the reaction before rate-determining step is fairly fast and involves low activation energy (Weissberger & Lewis, 1974). In the same manner, K_2 and K_3 values were calculated at different temperatures and their corresponding values of the thermodynamic quantities are given in the Table 2.

The values of $\Delta H^{\#}$ and $\Delta S^{\#}$ were both favorable for electron transfer processes. The negative value of $\Delta S^{\#}$ indicates that the complex(C) is more ordered than the reactants (Weissberger & Lewis, 1974). The value of $\Delta S^{\#}$ within the range for radical reaction has been ascribed (Walling, 1957) to the nature of electron pairing and unpairing processes and to the loss of degrees of freedom formerly available to the reactants upon the formation of rigid transition state. The observed modest enthalpy of activation and a relatively low value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation presumably occurs via inner-sphere mechanism. This conclusion is supported by the literature (Hiremath, Sirsalmath, & Nandibewoor, 2008).

5. Conclusion

Among various species of DPC in an alkaline medium, monoperiodatocuprate(III) (MPC) is considered as an active species for the title reaction. The results demonstrate that in carrying out this

reaction, the role of pH in the reaction medium is crucial. Rate constant of slow step and other equilibrium constants involved in the mechanism are evaluated and activation parameters with respect to slow step of reaction were computed.

Nomenclature and abbreviations

DPC diperiodatocuprate(III)
NF norfloxacin
ε molar absorption coefficient
kobs observed rate constant
k rate constant with respect to slow step of the mechanism
K_1 and K_2 equilibrium constants
ΔH change in enthalpy of reaction
ΔS change in entropy of reaction
ΔG change in free energy of reaction
$\Delta H^{\#}$ enthalpy of activation
$\Delta S^{\#}$ entropy of activation
$\Delta G^{\#}$ free energy of activation
D dielectric constant of the medium
I ionic strength of the medium
FT-IR Fourier transform infrared spectra
^{1}H NMR proton nuclear magnetic resonance
UV ultraviolet spectra
TLC thin layer chromatography
LC–ESI–MS liquid chromatography–electrospray ionization–mass spectrometry

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