Journal of Molecular Catalysis A: Chemical 310 (2009) 24–33

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Kinetics and reactivities of ruthenium(III)- and osmium(VIII)-catalyzed oxidation of ornidazole with chloramine-T in acid and alkaline media: A mechanistic approach

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ARTICLE INFO

Article history:
Received 19 February 2009
Received in revised form 14 May 2009
Accepted 20 May 2009
Available online 27 May 2009

Keywords:
Ru(III) and Os(VIII) catalysis
Ornidazole oxidation
Chloramine-T

ABSTRACT

Ornidazole is an antiparasitic drug having a wide spectrum of activity. Literature survey has revealed that no attention has been paid towards the oxidation of ornidazole with any oxidant from the kinetic and mechanistic view point. Also no one has examined the role of platinum group metal ions as catalysts in the oxidation of this drug. Such studies are of much use in understanding the mechanistic profile of ornidazole in redox reactions and provide an insight into the interaction of metal ions with the substrate in biological systems. For these reasons, the Ru(III)- and Os(VIII)-catalyzed kinetics of oxidation of ornidazole with chloramine-T have been studied in HCl and NaOH media, respectively at 313 K. The oxidation products and kinetic patterns were found to be different in acid and alkaline media. Under comparable experimental conditions, in Ru(III)-catalyzed oxidation the rate law is $-d[CAT]/dt = k\ [CAT]_o[ornidazole]_o^x[H^+]^{-y}[Ru(III)]^z$ and it takes the form $-d[CAT]/dt = k\ [CAT]_o[ornidazole]_o^x[OH^-]^y[Os(VIII)][ArSO_2NH_2]^{-z}$ for Os(VIII)-catalyzed reaction, where x, y and z are less than unity. In acid medium, 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one and in alkaline medium, 1-hydroxy-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one were characterized as the oxidation products of ornidazole by GC–MS analysis. The reactions were studied at different temperatures and the overall activation parameters have been computed. The solvent isotope effect was studied using D_2O. Under identical set of experimental conditions, the kinetics of Ru(III) catalyzed oxidation of ornidazole by CAT in acid medium have been compared with uncatalyzed reactions. The relative rates revealed that the catalyzed reactions are about 5-fold faster whereas in Os(VIII) catalyzed reactions, it is around 9 times. The catalytic constant (K_C) has been calculated for both the catalysts at different temperatures and activation parameters with respect to each catalyst have been evaluated. The observed experimental results have been explained by plausible mechanisms. Related rate laws have been worked out.

1. Introduction

The diverse nature of the chemistry of N-haloamines is a consequence of their ability to act as sources of species, such as halonium cations, hypohalites and N-anions which act as bases, nucleophiles and nitrenoids [1–5]. They behave as mild oxidants and are suitable for the limited oxidation of several groups. Consequently, these reagents react with a wide variety of functional groups affecting an array of molecular transformations. Generally monohaloamines undergo two-electron change while dihaloamines are four-electron oxidants [1]. The reduction products are the respective sulfonamide and NaCl or HCl. The prominent member of this class of compounds, sodium N-chloro-4-methylbenzenesulfonamide, commonly known as chloramine-T (CAT; p-Me-$C_6H_4SO_2NClNa{\cdot}3H_2O$), is a by-product of saccharin manufacture. The redox potential of chloramine-T/p-toluenesulfonamide is pH dependent and decreases with an increase in the pH of the medium [6]. The nature of active oxidizing species of CAT depends on the pH of the medium and the reaction condition. Chloramine-T is a source of positive halogen and this reagent has been exploited as oxidant for a variety of substrates in both acidic and alkaline media [1,2,5,7–12]. Although a large number of various substrates have been oxidized by CAT, very few oxidation kinetic investigations of pharmaceuticals have been carried out with this reagent.

Antiparasitics are a class of medicines which are used for the treatment of infections caused by parasites, such as infectious protozoa and amoeba [13]. Nitroimidazole and its derivatives are the important antiparasitics. Ornidazole, chemically known as 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-ol, is well known amongst these compounds and is commonly used in the

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doi:10.1016/j.molcata.2009.05.015

treatment of amoebiasis, trichomoniasis, giardiasis and anaerobic infections [14]. Because of its excellent penetration into lipidic tissues, it is also used in abdominal and gynaecological surgery [14]. Because of its importance, several analytical procedures are reported in the literature [15–17] for the assay of this drug. After reviewing the literature, we found that there was no information available on the oxidation of ornidazole with any oxidant from its kinetic and mechanistic view point. Consequently, the mechanism and rate law for these redox systems were obscure. Hence the oxidation-kinetics of ornidazole is of importance, as it adds to the body of knowledge of redox chemistry. Such a kind of oxidation-kinetic study could throw some light on the fate of the drug in biological systems. Hence the present study is of significance as the substrate ornidazole is a potent drug.

The catalysis by platinum group metal ions in redox reactions is of recent interest and it plays an important role in understanding the mechanism of redox reactions. Subsequently, various platinum group metal catalysts have been used in the N-haloamine oxidation of various organic substrates [18,19]. In particular, ruthenium(III) chloride (Ru(III)) and osmium tetroxide (Os(VIII)) have been found to be highly efficient catalysts in acid and alkaline media, respectively. Further, some of these systems have proved suitable for kinetic analysis. The mechanisms of these catalysis are complicated due to the formation of different intermediate complexes, free radicals and differing oxidizing states of these catalysts [20,21]. Preliminary experimental results revealed that a micro-quantity of Ru(III) and Os(VIII) catalyses the oxidation of ornidazole with CAT in acid and alkaline media, respectively in order to realize the reaction mechanism and the rate law of the present redox systems. Such studies also provide an insight into the interaction of metal ions with the drug in biological systems.

Preliminary kinetic runs reveal that the reactions between ornidazole and CAT were found to be 'too slow' to be measured in neutral, acidic and alkaline media at ambient temperature. Alternatively it was found that Ru(III) and Os(VIII) are excellent catalysts for the facile oxidation of ornidazole by CAT in acid and alkaline media. Consequently, in order to explore the mechanism of ornidazole–CAT redox system in acid and alkaline media, Ru(III) and Os(VIII) catalysts were chosen in the present work. To our knowledge, this is the first report on the kinetics and mechanism of oxidation of ornidazole. Objectives of the present study are to (i) accumulate the kinetic data, (ii) elucidate plausible mechanisms, (iii) design kinetic rate laws (iv) ascertain the reactive species, (v) compare the relative rates in both the media, (vi) deduce thermodynamic parameters, (vii) characterize the products and (viii) find the catalytic efficiency of Ru(III) and Os(VIII).

2. Experimental

2.1. Materials

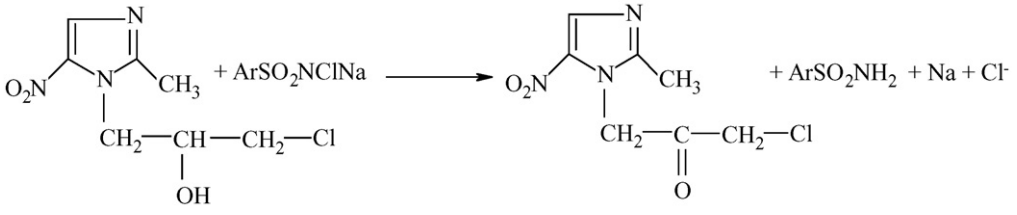
Chloramine-T (E-merk) was purified by the method of Morris et al. [22]. An aqueous solution of CAT was prepared, standardized by the iodometric method and preserved in brown bottles to prevent its any photochemical deterioration. Pharmaceutical grade ornidazole was kindly provided by Bio-Organics and Applied Materials Pvt. Ltd. Bangalore, India and of assigned purity of 99.8%. It was used as received and an aqueous solution of compound was prepared fresh, just before use. Solvent isotope studies were made with (D_2O, 99.4%) supplied by BARC, Mumbai, India. Analytical grade chemicals and double-distilled water were used throughout. Regression coefficient (r) was calculated using fx-350 TL scientific calculator.

2.2. Kinetic procedure

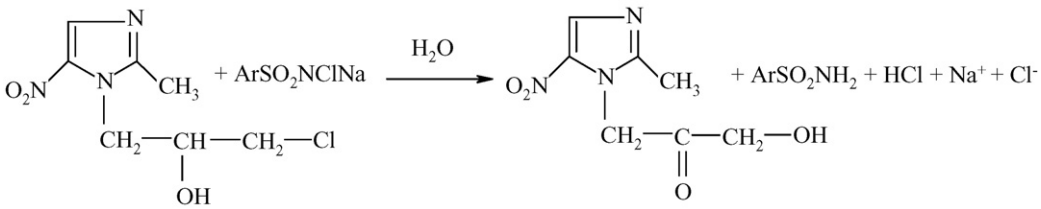
Reactions were carried out under pseudo first-order conditions with a known excess of $[substrate]_o$ over $[oxidant]_o$ at constant temperature of 313 K in glass stoppered pyrex boiling tubes coated black from outside to eliminate any photochemical deterioration. A Raaga digital proportional temperature controller (CH-61) was used to maintain the desired temperature with an accuracy of ±0.1 °C. Requisite amounts of solutions of substrate, HCl or NaOH, Ru(III) or Os(VIII) and enough water to keep the total volume constant (50 ml) for all kinetic runs were equilibriated at 313 K for about 30 min. A measured amount of CAT solution, also equilibriated at the same temperature was rapidly added to the reaction mixture which was periodically shaken for uniform concentration. The progress of the reaction was monitored by withdrawing measured aliquots (5 ml each) from the reaction mixture at regular time intervals and determined the unreacted CAT iodometrically. The course of the reaction was studied more than two half-lives. The pseudo first-order rate constants ($k^{/}$ s^{-1}) calculated from the linear plots of log [CAT] versus time were reproducible within ±5%.

2.3. Reaction stoichiometry

Varying ratios of CAT to ornidazole were equilibriated at 313 K for 24 h in presence of 2.0×10^{-3} HCl/NaOH mol dm^{-3} and 2.0×10^{-5} Ru(III)/Os(VIII) mol dm^{-3}. The unreacted oxidant was determined by iodometry and the analysis showed that one mole of ornidazole consumed per mole of CAT in both the media. Eqs. (1) and (2) represent the stoichiometric results in acid and alkaline media, respectively.



(1)



(2)

(Here Ar = p-$CH_3C_6H_4$-).

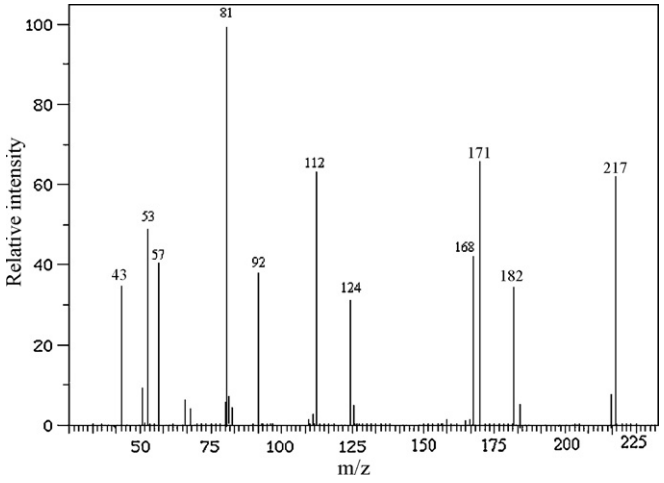


Fig. 1. GC-mass spectrum of 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one with its molecular ion peak at 217 amu.

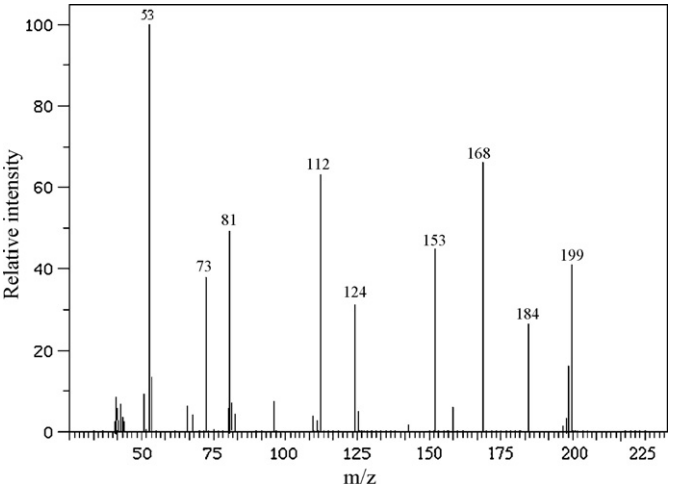


Fig. 2. GC-mass spectrum of 1-hydroxy-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one with its molecular ion peak at 199 amu.

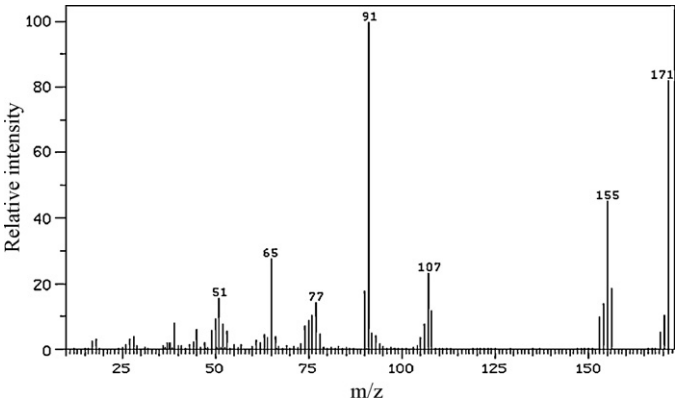


Fig. 3. GC-mass spectrum of p-toluenesulfonamide with its molecular ion peak 171 amu.

2.4. Product analysis

The ornidazole–CAT reaction mixture in the stoichiometric ratio in presence of HCl/NaOH and Ru(III)/Os(VIII) separately under stirred condition was allowed to progress for 24 h at 313 K. After completion of the reaction (monitored by TLC), the reaction products were neutralized with NaOH/HCl and extracted with ether. The organic products were subjected to spot tests and chromatographic analysis (TLC technique) which revealed the formation of 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one and 1-hydroxyl-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one as the oxidation products of ornidazole in acid and alkaline media, respectively. These oxidation products were separated by column chromatography and were confirmed by GC–MS analysis. The GC–MS data were obtained from 17A Shimadzu gas chromatograph with a QP-5050 Shimadzu mass spectrometer. The mass spectra showed a molecular ion peak at 217 amu (Fig. 1) and 199 amu (Fig. 2) clearly confirming 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one and 1-hydroxyl-3-(2-methyl-5-nitroimidazole-1-yl)propan-2-one, respectively. It was also noticed that there was no further oxidation of these products under prevailing kinetic conditions.

p-Toluenesulfonamide was extracted with ethyl acetate and detected by paper chromatography [11]. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl solution in ethanol as spray reagent (R_f = 0.905). Further, the molec-

Table 1
Effect of varying chloramine-T, ornidazole, HCl and Ru(III) concentrations on the reaction rate at 313 K.

$[CAT]_o$ ($\times 10^4$ mol dm^{-3})	$[ornidazole]_o$ ($\times 10^3$ mol dm^{-3})	[HCl] ($\times 10^3$ mol dm^{-3})	[Ru(III)] ($\times 10^5$ mol dm^{-3})	k' ($\times 10^4$ s^{-1})
0.2	1.0	2.0	2.0	4.27
0.4	1.0	2.0	2.0	4.30
0.6	1.0	2.0	2.0	4.39
1.0	1.0	2.0	2.0	4.35
2.0	1.0	2.0	2.0	4.31
0.6	0.2	2.0	2.0	2.92
0.6	0.5	2.0	2.0	3.51
0.6	1.0	2.0	2.0	4.39
0.6	2.0	2.0	2.0	5.76
0.6	4.0	2.0	2.0	7.93
0.6	1.0	0.5	2.0	6.82
0.6	1.0	1.0	2.0	5.34
0.6	1.0	2.0	2.0	4.39
0.6	1.0	4.0	2.0	3.22
0.6	1.0	6.0	2.0	2.56
0.6	1.0	2.0	0.5	2.64
0.6	1.0	2.0	1.0	3.53
0.6	1.0	2.0	2.0	4.39
0.6	1.0	2.0	4.0	7.94
0.6	1.0	2.0	5.0	9.12

Table 2
Effect of varying temperature and values of activation parameters for Ru(III) and Os(VIII) catalyzed oxidation of ornidazole by CAT in acid and alkaline media[a].

	$k^{/}$ ($\times 10^4$ s^{-1})	
	Acid	Alkaline
Temperature (K)		
298	1.52(0.21)	2.91(0.18)
303	1.92(0.48)	3.35(0.37)
308	3.41(0.57)	5.83(0.50)
313	4.39(1.02)	7.68(0.88)
318	5.76(1.64)	10.1(1.58)
E_a (kJ mol^{-1})	58.2(76.5)	45.0(84.2)
$\Delta H^{\#}$ (kJ mol^{-1})	55.7(74.0)	42.4(81.7)
$\Delta G^{\#}$ (kJ mol^{-1})	96.3(94.5)	94.8(93.8)
$\Delta S^{\#}$ (JK^{-1} mol^{-1})	−131(−66.2)	−170(−42.6)
log A	7.14(9.57)	7.60(13.2)

Values in parentheses refer to the oxidation of ornidazole by CAT in absence of catalysts. Experimental conditions for uncatalyzed reactions are same as above without Ru(III)/Os(VIII).

[a] Experimental conditions for catalyzed reactions: $[CAT]_o = 0.6 \times 10^{-4}$ mol dm^{-3}; $[ornidazole]_o = 1.0 \times 10^{-3}$ mol dm^{-3}; $[HCl]/[NaOH] = 2.0 \times 10^{-3}$ mol dm^{-3}; $[Ru(III)]/[Os(VIII)] = 2.0 \times 10^{-5}$ mol dm^{-3}.

ular ion peak of 171 amu (Fig. 3) confirms p-toluenesulfonamide. All other peaks observed in GC–MS can be interpreted in accordance with the observed structure.

3. Results and discussion

The kinetics of oxidation of ornidazole with CAT have been studied in HCl medium, catalyzed by Ru(III), and NaOH medium with Os(VIII) as catalyst at 313 K. In these two media, the products and kinetic patterns were found to be different. Since the detailed kinetic investigations have been carried out in acid and alkaline media and the observed kinetic data are different, for the sake of convenience the salient features obtained in these two media are discussed separately in the following. The detailed kinetic experiments were performed under pseudo first-order conditions of $[ornidazole]_o \gg [CAT]_o$ in both media.

3.1. Oxidation kinetic data in acid medium

With the [substrate] in excess, at constant $[ornidazole]_o$, [HCl], [Ru(III)] and temperature, the $[CAT]_o$ was varied. Plots of log [CAT] versus time were linear ($r > 0.9962$) indicating a first-order dependence of reaction rate on $[CAT]_o$. The values of pseudo first-order rate constants ($k^{/}$ s^{-1}) were unaltered with variation in $[CAT]_o$, confirming the first-order dependence on $[CAT]_o$ (Table 1). The rate increases with an increase in $[ornidazole]_o$ (Table 1) and a plot of log $k^{/}$ versus log [ornidazole] was linear ($r = 0.9867$) with a slope of 0.30, indicating a fractional-order dependence on $[ornidazole]_o$. Further, a plot of $k^{/}$ versus $[ornidazole]_o$ is a straight line ($r = 0.9940$) with a y-intercept, confirming a fractional-order dependence on $[ornidazole]_o$.

The reaction was studied with varying [HCl], keeping other experimental conditions constant, the rate of reaction decreased with the increase in [HCl] (Table 1). The plot of log $k^{/}$ versus log [HCl] was linear ($r = 0.9951$) with a negative slope of 0.41, showing an inverse fractional-order dependence of rate on [HCl]. The rate increased with increase in [Ru(III)] (Table 1) and a plot of log $k^{/}$ versus log [Ru(III)] was linear ($r = 0.9813$) with a slope of 0.56, indicating a fractional-order dependence on [Ru(III)]. At constant $[H^+] = 2.0 \times 10^{-3}$ mol dm^{-3} maintained with HCl, the addition of NaCl (5.0×10^{-3} mol dm^{-3}) did not affect the rate of the reaction. Hence, the dependence of rate on [HCl] confirms the effect of $[H^+]$ only. Similarly, addition of Br^- ions as of NaBr (5.0×10^{-3} mol dm^{-3}) had no effect on the rate. These results indicate that the halide ions play no role in the reaction sequence.

Addition of the reaction product, p-toluenesulfonamide (PTS), to the reaction mixture (0.5×10^{-3} to 4.0×10^{-3} mol dm^{-3}) did not affect the rate significantly, indicating PTS is not involved in any step prior to the rate limiting step. The effect of reaction rate on the ionic strength of the medium was studied in presence of 2.0 mol dm^{-3} $NaClO_4$ solution, keeping other experimental conditions constant. It was found that addition of $NaClO_4$ showed negligible effect on the reaction rate, indicating the involvement of non-ionic species in the rate limiting step. Hence, no attempts were made to keep the ionic strength of the medium constant for kinetic runs. As the oxidation of ornidazole by CAT was retarded by $[H^+]$, the solvent isotope effect was studied in D_2O as the solvent medium and reaction was further retarded with $k^{/} = 3.16 \times 10^{-4}$ s^{-1} in D_2O medium and 4.39×10^{-4} s^{-1} in H_2O, leading to a solvent isotope effect $k^{/}(H_2O)/k^{/}(D_2O) = 1.39$.

The effect of temperature on the reaction rate was studied by performing the kinetic runs in the range of 298–318 K, keeping other experimental conditions constant. From the linear Arrhenius plot of log $k^{/}$ versus $1/T$ ($r = 0.9864$), values of activation parameters (E_a, $\Delta H^{\#}$, $\Delta S^{\#}$, $\Delta G^{\#}$ and log A) for the overall reaction was computed. All these results are summarized in Table 2. Addition of

Table 3
Effect of varying chloramine-T, ornidazole, NaOH and Os(VIII) concentrations on the reaction rate at 313 K.

$[CAT]_o$ ($\times 10^4$ mol dm^{-3})	$[Ornidazole]_o$ ($\times 10^3$ mol dm^{-3})	[NaOH] ($\times 10^3$ mol dm^{-3})	[Os(VIII)] ($\times 10^5$ mol dm^{-3})	$k^{/}$ ($\times 10^4$ s^{-1})
0.2	1.0	2.0	2.0	7.60
0.4	1.0	2.0	2.0	7.59
0.6	1.0	2.0	2.0	7.68
1.0	1.0	2.0	2.0	7.65
2.0	1.0	2.0	2.0	7.57
0.6	0.2	2.0	2.0	3.98
0.6	0.5	2.0	2.0	5.97
0.6	1.0	2.0	2.0	7.68
0.6	2.0	2.0	2.0	10.8
0.6	4.0	2.0	2.0	16.0
0.6	1.0	0.5	2.0	3.84
0.6	1.0	1.0	2.0	5.12
0.6	1.0	2.0	2.0	7.68
0.6	1.0	4.0	2.0	10.7
0.6	1.0	6.0	2.0	17.0
0.6	1.0	2.0	0.5	1.84
0.6	1.0	2.0	1.0	4.13
0.6	1.0	2.0	2.0	7.68
0.6	1.0	2.0	4.0	15.7
0.6	1.0	2.0	5.0	19.8

the reaction mixture to the acrylamide monomer did not initiate polymerization, indicating the absence of any free radicals produced during the course of the reaction. The control experiments were also performed under similar reaction conditions without the oxidant.

3.2. Oxidation kinetic data in alkaline medium

Under the condition $[ornidazole]_o \gg [CAT]_o$, plots of log [CAT] versus time were linear ($r > 0.9819$) indicating a first-order dependence of reaction rate on $[CAT]_o$. The pseudo first-order rate constant (k^l s^{-1}) was independent of $[CAT]_o$, confirming the first-order dependence of rate on $[CAT]_o$ (Table 3). When $[ornidazole]_o$ was varied, keeping all other experimental conditions the same, the rate increased with increase in $[ornidazole]_o$ (Table 3), and a plot of log k^l versus log [ornidazole] was linear ($r = 0.9975$) with a slope of 0.43 indicating a fractional-order dependence on $[ornidazole]_o$. Further, a plot of k^l versus $[ornidazole]_o$ was linear ($r = 0.9923$) with a y-intercept, confirming a fractional-order dependence on $[ornidazole]_o$.

The rate of the reaction increased with increasing [NaOH] (Table 3) and the log–log plot of rate versus [NaOH] ($r = 0.9912$) showed that the order in [NaOH] was less than unity (0.73), indicating a fractional-order dependence of rate on [NaOH]. The reaction rate increases with increase in [Os(VIII)] (Table 3) and a plot of log k^l versus log [Os(VIII)] was linear ($r = 0.9956$) with a slope of unity, indicating a first-order dependence of rate on [Os(VIII)].

Addition PTS to the reaction mixture retards the rate and the rate constants at (0.5, 1.0, 2.0 and 4.0) $\times 10^{-3}$ [PTS] mol dm^{-3} were (6.62, 5.75, 5.13 and 4.17) $\times 10^{-4}$ s^{-1}, respectively. Further, a plot of log k^l versus log [PTS] was linear ($r = 0.9940$) with a negative slope of 0.24, indicating a negative fractional-order dependence of the rate on [PTS]. It also indicates that [PTS] is involved in a fast pre-equilibrium to the rate limiting step in the proposed scheme. Addition of Cl^- or Br^- ions in the form of NaCl or NaBr (5.0×10^{-2} mol dm^{-3}) had no pronounced effect on the reaction rate indicating that no interhalogen compound or free chlorine was formed. The reaction was not sensitive to change in ionic strength of the system in presence of 2.0 mol dm^{-3} $NaClO_4$, hence no attempt was made to keep it constant. Activation parameters were calculated (Table 2) by Arrhenius plot ($r = 0.9859$). Studies of rate in D_2O medium revealed that $k^l(H_2O) = 7.68 \times 10^{-4}$ s^{-1}, $k^l(D_2O) = 10.2 \times 10^{-4}$ s^{-1} giving solvent isotope effect $k^l(H_2O)/k^l(D_2O)$ of 0.75. Absence of free radicals in the reaction mixture has been demonstrated by acrylonitrile test.

3.3. Reactive species of CAT and ornidazole

Chloramine-T ($ArSO_2NClNa$) behaves as a strong electrolyte in aqueous solutions [23] and depending upon the pH of the medium, it furnishes [22–25] the following types of reactive species in solutions (Eqs. (3)–(9)):

$$ArSO_2NClNa \rightleftharpoons ArSO_2NCl^- + Na^+ \quad (3)$$

$$ArSO_2NCl^- + H_3O^+ \rightleftharpoons ArSO_2NHCl + H_2O \quad (4)$$

$$2ArsO_2NHCl^- \rightleftharpoons ArSO_2NH_2 + ArSO_2NCl_2 \quad (5)$$

$$ArSO_2NHCl + H_2O \rightleftharpoons ArSO_2NH_2 + HOCl \quad (6)$$

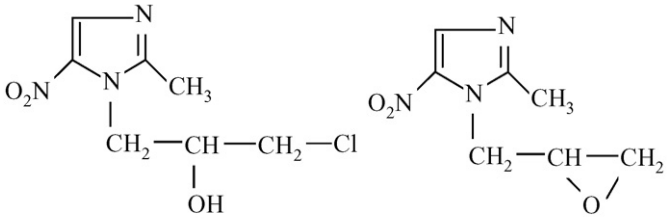
$$ArSO_2NCl_2 + H_2O \rightleftharpoons ArSO_2NHCl + HOCl \quad (7)$$

$$HOCl + H_2O \rightleftharpoons H_3O^+ + ClO^- \quad (8)$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+ \quad (9)$$

Chloramine-T dissociates according to the equilibrium (3) in aqueous solution. The anion picks up a proton in acid (Eq. (4)) to give the free acid, $ArSO_2NHCl$. It undergoes disproportionation [22] via reaction (5) giving rise to dichloramine-T and the parent amide. The free acid and dichloramine-T undergo hydrolysis (Eqs. (6) and (7)). Finally the hypohalous acid undergoes hydrolysis according to reaction (8). Possibly the hypohalous acid with a proton gives H_2OCl^+ species. Consequently, the possible oxidizing species in acidified CAT solutions are $ArSO_2NHCl$, $ArSO_2NCl_2$, HOCl and perhaps H_2OCl^+ and in alkaline CAT solutions they are $ArSO_2NHCl$, $ArSO_2NCl^-$, HOCl and ClO^-.

Valdes-Santurio et al. [26] have studied the decomposition of ornidazole as a function of pH and reported that the drug was stable below pH 6. At pH > 6, however, ornidazole rapidly decomposes to ornidazole epoxide. Bakshi et al. [27] also carried out the degradation studies on ornidazole in alkaline medium and reported that it decomposes to ornidazole epoxide. The structures of ornidazole (a) and ornidazole epoxide (b) are as shown below:



(a) ornidazole (b) ornidazole epoxide

Consequently, in the present investigations the substrate ornidazole itself involved in the oxidation reaction in acid medium whereas in alkaline medium, the reactive species of the substrate is in its epoxide form.

3.4. Reaction mechanism and rate law in acid medium

The possible oxidizing species in acidified CAT solutions are $ArSO_2NHCl$, $ArSO_2NCl_2$, HOCl and also perhaps H_2OCl^+. The probability of dichloramine-T as the reactive species is ruled out, since clean first-order plots are obtained for the disappearance of $[CAT]_o$. Added p-toluenesulfonamide does not retard the reaction indicating that the HOCl is not primarily involved in the rate limiting step. Further, Soper [28] reported that [HOCl] is very small and is independent of $[CAT]_o$. The predominant species of CAT is $ArSO_2NHCl$ under acidic conditions. Narayanan and Rao [29] and Subhashini et al. [30] have reported that $ArSO_2NHCl$ can further protonated as $ArSO_2NHCl + H^+ \rightleftharpoons ArSO_2NH_2Cl^+$ and the protonation constant for the reaction is found to be 1.02×10^2 at 25 °C. In the present case an inverse fractional dependence on $[H^+]$ suggests that deprotonation of $ArSO_2NH_2Cl^+$ results in the formation of $ArSO_2NHCl$, which is likely to be the active oxidizing species involved in the oxidation of ornidazole in acid medium.

The mechanism of catalysis is quite complicated due to the formation of different intermediate complexes, free radicals and different oxidizing states of Ru(III). Cady and Connick [31] and Connick and Fine [32] have investigated aqueous Ru(III) complex species using the ion exchange resins and UV-spectral studies. They found that the octahedral complex species $[RuCl_5(H_2O)]^{2-}$, $[RuCl_4(H_2O)_2]^-$, $[RuCl_3(H_2O)_3]$, $[RuCl_2(H_2O)_4]^+$ and $[RuCl(H_2O)_5]^{2+}$ may not exist in aqueous solution of Ru(III). Other studies [21,33,34] have shown in acidic solutions the following equations exist for Ru(III):

$$RuCl_3 \cdot xH_2O + 3HCl \rightarrow [RuCl_6]^{3-} + xH_2O + 3H^+ \quad (10)$$

$$[RuCl_6]^{3-} + H_2O \rightleftharpoons [RuCl_5(H_2O)]^{2-} + Cl^- \quad (11)$$

In the present study, the absence of chloride ion on the rate indicates that the equilibrium (11) does not play any role in the reaction and hence the complex ion, $[RuCl_5(H_2O)]^{2-}$, is assumed to be the reactive catalyst species.

$ArSO_2NH_2Cl^+ \overset{K_1}{\rightleftharpoons} ArSO_2NHCl + H^+$ (i) fast

$ArSO_2NHCl + Ru(III) \overset{K_2}{\rightleftharpoons} X$ (ii) fast

$X + ornidazole \overset{K_3}{\rightleftharpoons} X^I$ (iii) fast

$X^I \xrightarrow{k_4} X^{II} + ArSO_2NH_2 + Ru(III)$ (iv) slow and rate limiting

$X^{II} \xrightarrow{k_5} Products$ (v) fast

Scheme 1. A general reaction scheme for Ru(III) catalyzed oxidation of ornidazole by CAT in acid medium.

In the light of these considerations, a mechanism (Scheme 1) is proposed for the Ru(III) catalyzed oxidation of ornidazole by CAT in acid medium to account for the experimental observations.

The probable mode of this reaction scheme and structures of the complex intermediate species X, X^I and X^{II} are depicted in Scheme 2. In Scheme 2, in an initial equilibrium (step (i)) deprotonation of $ArSO_2NH_2Cl^+$ generates the conjugate free acid $ArSO_2NHCl$. In the next fast pre-equilibrium (step (ii)), the donor nitrogen atom of the oxidizing species coordinates to the metal centre of the active catalyst species gives an intermediate complex X. This intermediate complex X in the next fast step (step (iii)), forms another intermediate complex X^I with the substrate. In slow/rate limiting step (step (iv)), X^I disproportionates to form an another intermediate species X^{II} with the regeneration of the catalyst species and elimination of $ArSO_2NH_2$. This intermediate complex X^{II} in the last step (step (v)) yields final product with the loss of HCl.

$ArSO_2NHCl + OH^- \overset{K_6}{\rightleftharpoons} ArSO_2NH_2 + ClO^-$ (i) fast

$ClO^- + ornidazole \overset{K_7}{\rightleftharpoons} X^{III}$ (ii) fast

$X^{III} + Os(VIII) \xrightarrow{k_8} X^{IV}$ (iii) slow and rate limiting

$X^{IV} \xrightarrow{k_9} Products + Os(VIII)$ (iv) fast

Scheme 3. A general reaction scheme for Os(VIII) catalyzed oxidation of ornidazole by CAT in alkaline medium.

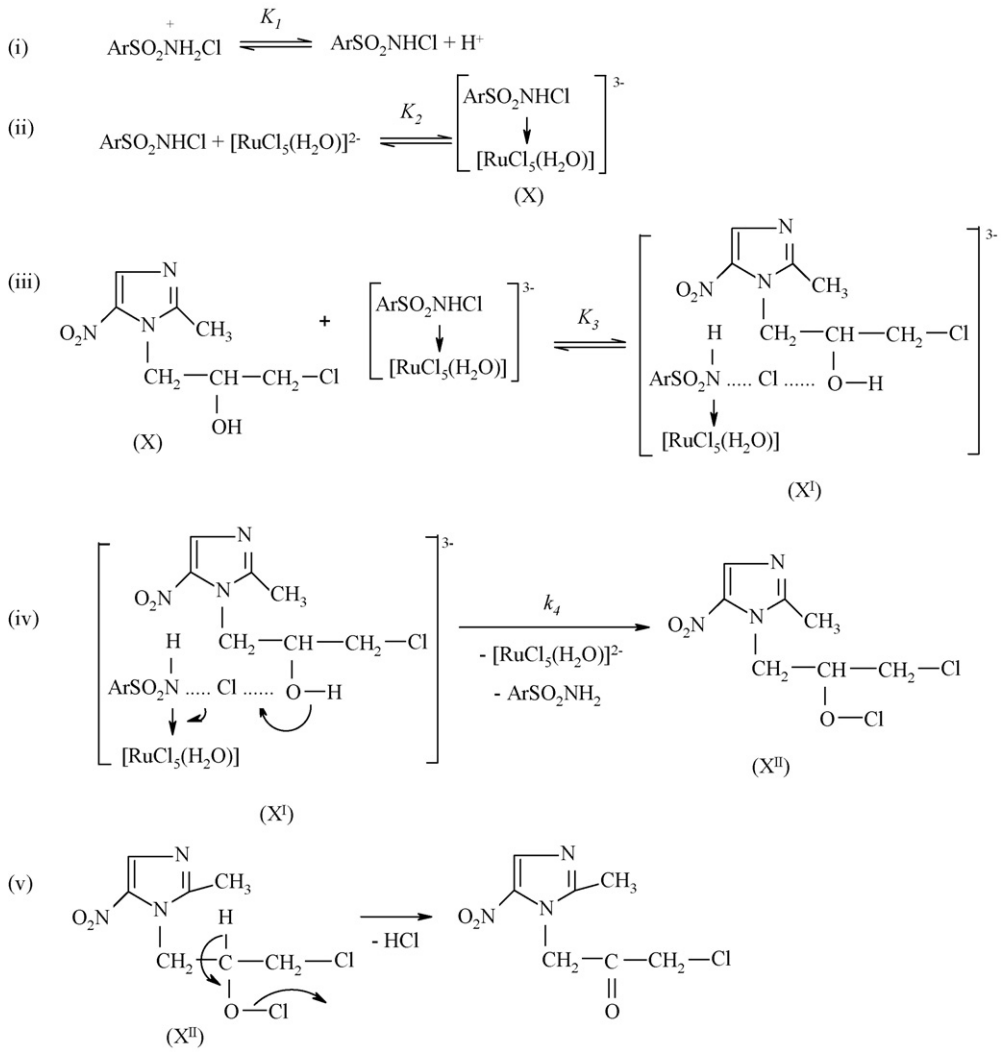
If $[CAT]_t$ is the total effective concentration of CAT, then

$$[CAT]_t = [ArSO_2NH_2Cl^+] + [ArSO_2NHCl] + [X] + [X^I] \quad (12)$$

From steps (i)–(iii) of Scheme 1,

$$[ArSO_2NH_2Cl^+] = \frac{[X^I][H^+]}{K_2K_2K_3[ornidazole][Ru(III)]} \quad (13)$$

$$[ArSO_2NHCl] = \frac{[X^I]}{K_2K_3[ornidazole][Ru(III)]} \quad (14)$$



Scheme 2. A detailed mechanistic interpretation for Ru(III) catalyzed oxidation of ornidazole by CAT in acid medium.

$$[X] = \frac{[X^I]}{K_3[\text{ornidazole}]} \quad (15)$$

By substituting for $[ArSO_2NH_2Cl^+]$, $[ArSO_2NHCl]$ and [X] from Eqs. (13), (14) and (15) into Eq. (12) and solving for $[X^I]$, one obtains

$$[X^I] = \frac{K_1K_2K_3[CAT]_t[\text{ornidazole}][Ru(III)]}{[H^+] + K_1 + K_1K_2[Ru(III)] + K_1K_2K_3[\text{ornidazole}][Ru(III)]} \quad (16)$$

From the slow and rate limiting step of Scheme 1,

$$\text{Rate} = \frac{-d[CAT]_t}{dt} = k_4[X^I] \quad (17)$$

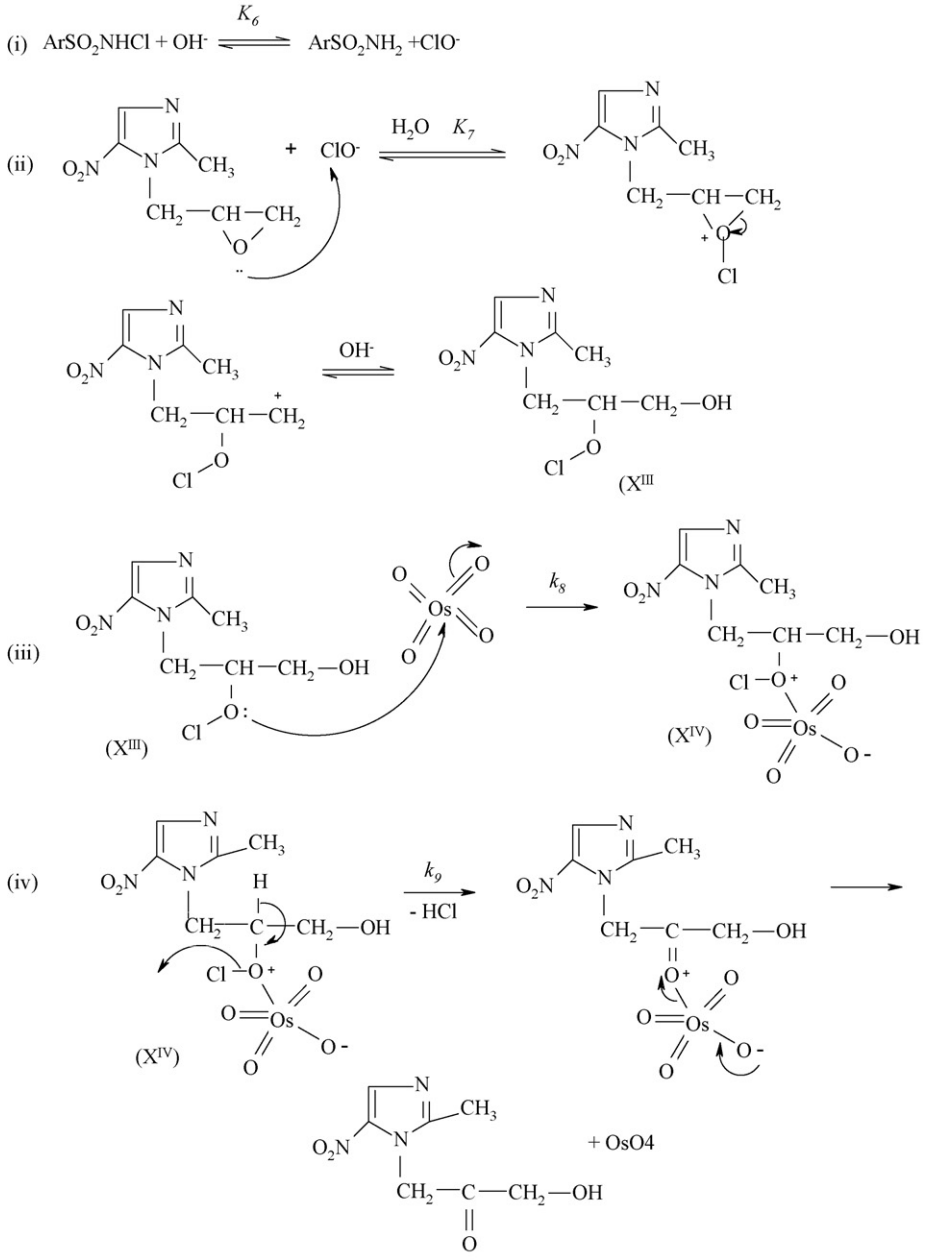
By substituting for $[X^I]$ from Eq. (16) into Eq. (17), the following rate law is obtained:

$$\frac{-d[CAT]}{dt} = \frac{K_1K_2K_3k_4[CAT]_t[\text{ornidazole}][Ru(III)]}{[H^+] + K_1 + K_1K_2[Ru(III)] + K_1K_2K_3[\text{ornidazole}][Ru(III)]} \quad (18)$$

This rate law is in complete agreement with the experimental results.

3.5. Reaction mechanism and rate law in alkaline medium

In alkaline solutions of CAT, $ArSO_2NCl_2$ and HOCl do not exist [35,36]. Hardy and Johnston [24] have indicated that there is a considerable concentration of $PhSO_2NHBr$ even in alkaline bromamine solutions. Because organic haloamines have similar chemical properties, we perhaps can extend the same argument to CAT also. Hence, it is likely that the predominant species in alkaline solutions of CAT are $ArSO_2NHCl$ and ClO^-. Further as the alkali increases, there is also an increase in the concentration of hypochlorite ion. In the present investigations, the rate is retarded by the reaction product, p-toluenesulfonamide ($ArSO_2NH_2$) indicating that it is involved in a pre-equilibrium step. A fractional-order dependence on $[OH^-]$ is observed. Hence $ArSO_2NHCl$ in the alkali accelerating step, gener-



Scheme 4. A detailed mechanistic interpretation for Os(VIII) catalyzed oxidation of ornidazole by CAT in alkaline medium.

ates ClO^- ion which is considered as the active species responsible for oxidizing ornidazole in the present case.

It has been shown that osmium has a stable + 8 oxidation state and exists as trans-octahedral complexes of $[OsO_4(OH)(H_2O)]^-$ and $[OsO_4(OH)_2]^{2-}$ in alkaline solutions according to the following equlibria [37–40]:

$$OsO_4 + OH^- + H_2O \rightleftharpoons [OsO_4(OH)(H_2O)]^- \quad (19)$$

$$[OsO_4(OH)(H_2O)]^- + OH^- \rightleftharpoons [OsO_4(OH)_2]^{2-} + H_2O \quad (20)$$

The complexes $[OsO_4(OH)(H_2O)]^-$ and $[OsO_4(OH)_2]^{2-}$ which can be reduced to $[OsO_2(OH)_4]^{2-}$ with octahedral geometries seem to be less likely to form species of higher coordination with the oxidant–substrate species. It is more reasonable to postulate OsO_4, which has tetrahedral geometry, is the active catalyst species that can effectively form a complex with the oxidant–substrate species in the present study. In view of the above facts and all the experimental data, the following mechanism (Scheme 3) may be suggested for Os(VIII) catalyzed oxidation of ornidazole by CAT in alkaline medium:

Structures of the complex intermediate species X^{III} and X^{IV} are shown in Scheme 4, where a detailed mechanistic interpretation of Os(VIII) catalyzed oxidation of ornidazole by CAT in alkaline medium is illustrated. In Scheme 4, in a fast initial equilibrium (step (i)), the conjugate acid $ArSO_2NHCl$ interacts with hydroxyl ion to give the reactive oxidizing species hypochlorite ion, ClO^-, with the elimination of p-tolunesulfonamide ($ArSO_2NH_2$). The negatively charged hypochlorite ion combines with the lone pair of electrons of the substrate forms an intermediate complex X^{III} in a fast equilibrium step (step (ii)). In the next slow/rate limiting step the intermediate complex X^{III} interacts with the metal centre of the active catalyst species forming a dipolar metal–substrate complex X^{IV}. This complex X^{IV} with the loss of HCl and the regeneration of catalyst yield the final product.The total effective concentration of CAT is

$$[CAT]_t = [ArSO_2NHCl] + [ClO^-] + [X^{III}] \quad (21)$$

From steps (i) and (ii) of Scheme 3,

$$[ArSO_2NHCl] = \frac{[X^{III}][ArSO_2NH_2]}{K_6K_7[\text{ornidazole}][OH^-]} \quad (22)$$

$$[ClO^-] = \frac{[X^{III}]}{K_7[\text{ornidazole}]} \quad (23)$$

By substituting for $[ArSO_2NHCl]$ and $[ClO^-]$ from Eqs. (22) and (23), into Eq. (21) and solving for $[X^{III}]$, we get

$$[X^{III}] = \frac{K_6K_7[CAT]_t[\text{ornidazole}][OH^-]}{[ArSO_2NH_2] + K_6[OH^-] + K_6K_7[\text{ornidazole}][OH^-]} \quad (24)$$

From slow/rate limiting step of Scheme 3

$$\text{Rate} = k_8[X^{III}][Os(VIII)] \quad (25)$$

By substituting for $[X^{III}]$ from Eq. (24) into Eq. (25), the following rate law is governed.

$$= \frac{-d[CAT]}{dt} = \frac{K_6K_7k_8[CAT]_t[\text{ornidazole}][OH^-][Os(VIII)]}{[ArSO_2NH_2] + K_6[OH^-] + K_6K_7[\text{ornidazole}][OH^-]} \quad (26)$$

Rate law (26) is in accordance with the experimental findings.

The proposed reaction schemes and derived rate laws agree well with all the following experimental results for both catalyzed reactions.

3.6. Solvent isotope effect

It is interesting to note that the rate in D_2O medium is slower in acid medium whereas it is faster in alkaline medium than that in H_2O. For a reaction involving a fast pre-equilibrium H^+ or OH^- ion transfer, the rate increases in D_2O medium since D_3O^+ and OD^- are a stronger acid and a stronger base, respectively than H_3O^+ and OH^- ions [41,42]. The reverse holds for reaction involving retardation by H^+ or OH^- ions. In the present case, the observed solvent isotope effect of $k^l(H_2O)/k^l(D_2O) > 1$ in acid medium and $k^l(H_2O)/k^l(D_2O) < 1$ in alkaline medium is due to the greater acidity of D_3O^+ compared to H_3O^+ and greater basicity of OD^- compared to OH^-, respectively. The magnitude, however, is small ($k^l(H_2O)/k^l(D_2O) = 1.39$ and 0.75 in acid and alkaline media) in both the cases compared to the expected value of 2–3 times greater [41], which can be attributed to the fractional-order dependence of rate on $[H^+]$ and $[OH^-]$ ions. Hence, the experimental rate observations are in conformity with the above concept [41] and the proposed mechanisms.

3.7. Comparison of Ru(III) and Os(VIII) catalyzed and uncatalyzed reactions

Under identical set of experimental conditions, the reactivity of CAT towards ornidazole in acid and alkaline media (in absence of Ru(III) and Os(VIII) catalysts) was compared with the Ru(III) and Os(VIII) catalyzed reactions. The relative rate constants and activation energies revealed that Ru(III) catalyzed reactions are about 5-fold whereas Os(VIII) catalyzed reactions are around 9-fold faster than uncatalyzed reactions. The activation parameters evaluated for the catalyzed and uncatalyzed reactions in both cases explain the catalytic effect on the reaction. The catalysts Ru(III) and Os(VIII) form complexes X and X^{IV} with the oxidant species and oxidant–substrate complex, respectively. These complexes make the reducing property of the substrate more effective than in the absence of catalysts. Further, the catalysts Ru(III) and Os(VIII) alters the reaction path by stabilizing the transition states, which in turn provides an alternative pathway having lower activation energies for the reaction. Thus, the observed rates of oxidation of ornidazole by CAT in acid and alkaline media catalyzed by Ru(III) and Os(VIII) catalysts justify the need of a catalyst for facile oxidation. Consequently, it can be concluded that Ru(III) and Os(VIII) are efficient catalysts for the facile oxidation of ornidazole by CAT in acid and alkaline media, respectively.

3.8. Catalytic activity of Ru(III) and Os(VIII)

The general equation relating for uncatalyzed and catalyzed reactions has been derived by Moelwyn and Hughes [43] and correlated as

$$k_1 = k_o + K_C[\text{catalyst}]^x \quad (27)$$

Here k_1 is the observed pseudo first-order rate constant in the presence of a catalyst, k_o is that for the uncatalyzed reaction, K_C is the catalytic constant and x is the order of the reaction with respect to catalyst. In the present case, x values for the standard runs were found to be 0.56 and 1.0 for Ru(III) and Os(VIII) catalysts. Then the value of K_C has been evaluated using the equation:

$$K_C = \frac{k_1 - k_o}{[\text{catalyst}]^x} \quad (28)$$

The values of K_C have been evaluated at different temperatures (298–318 K) and K_C was found to be vary with temperature. Further, plots of $\log K_C$ versus $1/T$ were linear (Fig. 4: $r > 0.9980$) and the values of energy of activation and other activation parameters for both the catalysts were computed. All these values are summarized in Table 4. Furthermore, for the standard run at 313 K, plots of k^l versus [Ru(III)] and k^l versus [Os(VIII)] were found to be linear ($r > 0.9862$) with an intercept equal to k_o. The values of k_o were found to be $1.50 \times 10^{-4}\ s^{-1}$ and $1.10 \times 10^{-4}\ s^{-1}$ for Ru(III)

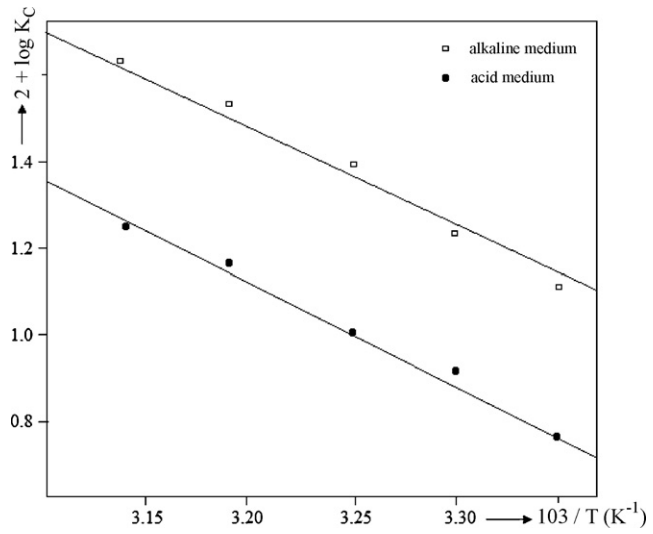


Fig. 4. Plots of log K_C versus 1/T. Experimental conditions are as in Table 4.

and Os(VIII), respectively. These values are fairly comparable with the rate constants determined experimentally for the uncatalyzed reactions at 313 K (Table 2). This signifies that both uncatalyzed and catalyzed reactions proceed in the parallel fashion.

From the inspection of rate constants and the values of energy of activation (Table 2), the relative reactivity of these catalysts during the oxidation of ornidazole by CAT in acid and alkaline media is Os(VIII) > Ru(III), under similar experimental conditions. It was also observed that the Ru(III) catalyzed reactions are 5-fold whereas Os(VIII) catalyzed reactions are 9-fold faster than the uncatalyzed reactions. The more reactivity of Os(VIII) can be explained based on the d electronic configuration of the metal ions. Osmium having d^0 electronic configuration has greater catalytic efficiency to oxidize the substrate compared to Ru(III) having d^5 electronic configuration. Thus the catalytic efficiency decreases as the number of electrons in the d-orbital increases. It is likely that during the course of the reaction the metal ion momentarily undergo reduction when the oxidant/oxidant–substrate complex is attached to the metal ions and after this the metal ion gets back to its original valence state as shown in Scheme 2 and 4. Hence, the observed catalytic trend is based on d electronic configuration of the metal ions, the reactivity decreases as the number of electrons increases in the d-orbital as d^0 (Os(VIII)) > d^5 (Ru(III)). Such a behaviour has also been reported in our earlier work [19,40,44].

The proposed reaction mechanisms are supported by the observed moderate values of energy of activation and other activation parameters. The fairly high positive values of the free energy of activation and of the enthalpy of activation support the formation of highly solvated transition state. The large negative entropy of activation suggests the formation of the compact activated complex with fewer degrees of freedom. Further, the experimental observations show that there is no effect of p-toluenesulfonamide in acid medium and ineffectiveness of halide ions and ionic strength on the reaction rate in both media also substantiates the proposed reaction mechanisms.

Table 4
Values of catalytic constant (K_C) at different temperatures and activation parameters calculated using K_C values[a].

	K_C	
	Acid	Alkaline
Temperature (K)		
298	0.06	13.7
303	0.08	17.4
308	0.10	26.7
313	0.14	34.0
318	0.18	42.5
E_a (kJ mol^{-1})	47.1	42.1
$\Delta H^{\#}$ (kJ mol^{-1})	44.5	39.6
$\Delta G^{\#}$ (kJ mol^{-1})	81.4	94.8
$\Delta S^{\#}$ (JK^{-1} mol^{-1})	−119	−93.0
log A	6.78	11.8

[a] Experimental conditions: $[CAT]_o = 0.6 \times 10^{-4}$ mol dm^{-3}; $[ornidazole]_o = 1.0 \times 10^{-3}$ mol dm^{-3}; $[HCl]/[NaOH] = 2.0 \times 10^{-3}$ mol dm^{-3}.

4. Conclusions

The kinetics of oxidation of ornidazole by CAT have been studied in HCl medium, catalyzed by Ru(III), and in NaOH medium with Os(VIII) as catalyst at 313 K. The oxidation products and kinetic features are different in acid and alkaline media. In acid medium the rate shows a first-order dependence on $[CAT]_o$ and less than unit order dependence on both $[ornidazole]_o$ and [Ru(III)]. The reaction rate is inversely dependent on $[H^+]$. In alkaline medium, the rate is first-order each in $[CAT]_o$ and $[Os(VIII)]_o$ and less than unit order dependence on each $[ornidazole]_o$ and $[OH^-]$. The rate is retarded with respect to $[ArSO_2NH_2]$ in alkaline medium. The Os(VIII) catalyzed reaction is faster than Ru(III) catalyzed reaction. Activation parameters for the catalyzed and uncatalyzed reactions, and also with respect to the catalysts have been evaluated. Plausible reaction mechanisms and related rate laws have been designed. It can also be concluded that Ru(III) and Os(VIII) act as efficient catalysts in the facile oxidation of ornidazole by CAT in acid and alkaline media.

Acknowledgement

The authors are thankful to Prof. M.A. Pasha of our department for helpful discussions.

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