Kinetics and Mechanism of Sodium *N*-halo-*p*-toluenesulfonamides Oxidation of Diclofenac in Alkaline Medium

Puttaswamy and J. P. Shubha
Dept. of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore 560 001, India

DOI 10.1002/aic.11980

Diclofenac belongs to a class of drugs called nonsteroidal antiinflammatory drugs. The kinetics and mechanism of oxidation of diclofenac by sodium N-*halo*-p-*toluenesulfonamides viz., chloramine-T and bromamine-T in NaOH medium have been studied at 293 K. Under comparable experimental conditions, reactions with both the oxidants follow identical kinetics with a first-order dependence on each* $[\text{oxidant}]_o$ *and a fractional-order dependence on each* $[\text{diclofenac}]_o$ *and [NaOH]. Activation parameters have been computed.* N-*hydroxyldiclofenac is identified as the oxidation product of diclofenac. Michaelis-Menten type of mechanism has been suggested. The rate of oxidation of diclofenac is about four-fold faster with bromamine-T when compared with chloramine-T. This may be attributed to the difference in electrophilicities of* Cl^+ *and* Br^+ *ions and also the van der Waal's radii of chlorine and bromine. Plausible mechanism and related rate law have been designed for the observed kinetics.* © 2009 American Institute of Chemical Engineers *AIChE J,* 55: 3234–3240, 2009

Keywords: Diclofenac, chloramine-T, bromamine-T, oxidation-kinetics, alkaline medium

Introduction

The sodium salts of arylhalosulfonamides, generally known as organic haloamines, have attracted the attention of chemists as versatile redox titrants.[1] The diverse chemical behavior of organic haloamines is attributed in general to their ability to act as halonium cations, hypohalites, *N*-anions, which act both as bases and nucleophiles, and nitrenoids in limiting cases.[2] As a result, these compounds react with a wide range of functional groups and affect a variety of molecular changes. Organic haloamines are mild oxidants containing a strongly polarized *N*-linked halogen which is in +1 state. The subject has been extensively reviewed and well studied.[2–6] The important chlorine compound of this class is sodium *N*-chloro-*p*-toluenesulfonamide or chloramine-T (CAT), a byproduct in the manufacture of saccharin. This reagent has been exploited as an oxidant for a variety of substrates in both acidic and alkaline media.[1–11] The bromine analogue of CAT, bromamine-T (BAT), is gaining importance as a mild oxidant and is found to be a better oxidizing agent than the chloro derivative.[3–5,12–14] This reagent can be easily prepared by the bromination of CAT. Although BAT is a better oxidant compared with CAT, an extensive literature survey reveals that only sporadic references are available about the oxidative behavior of BAT from the kinetic and mechanistic points of view. This aroused our interest to perform the detailed kinetic study on the oxidation of diclofenac by the closely related reagents CAT and BAT in alkaline medium to explore the mechanistic aspects of these oxidations and, also, to asses their relative rates. The studies extended to the relevant kinetic features of CAT and BAT and to identify the reactive oxidizing species of these oxidants in aqueous alkaline medium.

Among the groups of pharmaceutical compounds of greatest environmental interest[15] are the nonsteroidal antiinflammatory drugs. Diclofenac, ([*o*-[(2,6-dichlorophenyl)amino]-phenyl] acetic acid), is a synthetic compound and therapeutically belongs to the group of nonsteroidal antiinflammatory

---

Correspondence concerning this article should be addressed to Puttaswamy at pswamy_chem@yahoo.com

drugs. It is one of the most commonly used pain killers and clinically largely used as sodium salt. It is a versatile drug having therapeutic nature, such as analgesic, antiarthritic, and antirheumatic.[16] In view of medicinal importance of this compound, a number of analytical methods[17,18] have been developed for its quantitative determination, and also, a very few oxidation[19] and degradation[20] investigations have been carried out. But surprisingly, to date, no oxidation study of this drug has been reported from its kinetic and mechanistic view points. Hence, there was a need for understanding the oxidation mechanism of this drug, so that the study could throw some light on the fate of the drug in the biological systems and the mode of action at molecular level. For these reasons, kinetics and mechanism of oxidation of diclofenac is a subject of interest and the current kinetic study gives an impetus, because the substrate diclofenac is a potent drug.

In the light of these considerations, we report herein, the hitherto unreported results on the oxidation kinetics and mechanistic aspects of diclofenac by CAT and BAT in NaOH medium. The principal aim of this research is to: (i) accumulate kinetic data, (ii) elucidate suitable mechanism, (iii) deduce relevant rate law, (iv) identify the oxidation products, (v) compute activation parameters, and (vi) assess relative reactivity and kinetic features of CAT and BAT toward diclofenac in NaOH medium.

Experimental Procedure

Materials

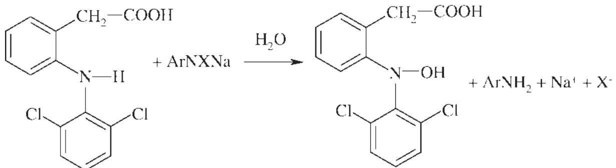
CAT (E. Merck) was purified by the method of Morris et al.[21] BAT was obtained[22] by the partial debromination of diBAT by 4 mol dm^{-3} NaOH. The purity of these reagents was assayed iodometrically to determine the active halogen content. Aqueous solution of these oxidants was standardized by the iodometric method and stored in brown bottles to prevent any of its photochemical deterioration. Pharmaceutical grade diclofenac (Johnson & Smith) was kindly provided by State Drug Control Unit, Bangalore, India, and of assigned purity of 98.7%. It was used as received, and aqueous solution of the compound was prepared fresh just before use. Solvent isotope studies were made with D$_2$O (99.4%) supplied by Bhabha Atomic Research Centre, Mumbai, India. Analytical grade chemicals and double distilled water was used throughout. The regression coefficient (r) was calculated using f_x-350TL scientific calculator.

Kinetic procedure

All the kinetic experiments were performed under pseudo first-order conditions of [substrate]$_o$ $\gg$ [oxidant]$_o$. In this study, the detailed kinetic experiments were performed at a standard temperature of 293 K. Reactions were studied in the temperature range of 283–313 K to evaluate activation parameters. For this purpose, a Raagaa Ultra Cold Chamber with digital temperature control (Thermostat, India) was used. The temperature was maintained constant with an accuracy of ±0.1°C. Reactions were performed in glass-stoppered pyrex boiling tubes, whose outer surfaces were coated black to eliminate any photochemical effects. For each run, requisite amounts of solutions of the substrate and NaOH, and water (to maintain a constant total volume) were introduced into the tube and thermostatted at 293 K until thermal equilibrium was attained (30 min). A measured amount of oxidant solution, also thermostatted at the same temperature, was added rapidly to the above mentioned mixture to initiate the reaction. The mixture was periodically shaken to ensure uniform concentration, and the progress of the reaction was monitored by an iodometric determination of oxidant in measured aliquots (5 ml each) of the reaction mixture at different time intervals. The reaction was followed for more than two half lives. The pseudofirst-order rate constants (k' s^{-1}), calculated from the linear plots of log [oxidant] vs. time, were reproducible within ±2–4%. The regression coefficient (r) for the linearity was performed using f_x-350TL scientific calculator.

Stoichiometry

Varying ratios of oxidant to diclofenac in presence of 0.5×10^{-3} mol dm^{-3} NaOH were equilibrated at 293 K for 24 h. The unreacted oxidant in the reaction mixture was determined by iodometric titration. This analysis showed that one mole of diclofenac consumed one mole of oxidant in both the cases, and the observed reaction stoichiometry is represented as follows:



(1)

Here, Ar = p-CH$_3$C$_6$H$_4$SO$_{2-}$ for CAT and BAT, with X = Cl or Br.

Product analysis

In the stoichiometric ratio, the reaction mixtures containing different concentrations of oxidant and substrate in 0.5×10^{-3} mol dm^{-3} NaOH, under stirred condition, was allowed to react for 24 h at 293 K. After completion of the reaction (monitored by thin layer chromatography), the reaction products were neutralized with acid and extracted with ether. The organic products were subjected to spot tests and chromatographic analysis, which revealed the formation of *N*-hydroxyldiclofenac as the oxidation product of diclofenac and *p*-toluenesulfonamide (PTS) as the reduction product of the oxidant. The presence of these two products was confirmed by Gas chromatography-mass spectrometry (GC-MS) analysis. GC-MS data was obtained on a 17A Shimadzu gas chromatograph with QP-5050A Shimadzu mass spectrometer. The mass spectrum showed a molecular ion peak at 311 amu (Figure 1), clearly confirming *N*-hydroxyldiclofenac. Further, it was noticed that there was no reaction between *N*-hydroxyldiclefenac and CAT or BAT under the present set of experimental conditions.

PTS was extracted with ethyl acetate and detected by paper chromatography.[6] Benzyl alcohol saturated with water was used as the solvent system, with 0.5% vanillin in 1% HCl solution in ethanol as spray reagent (R_f = 0.905). Further, the molecular ion peak of 171 amu (Figure 2) confirms

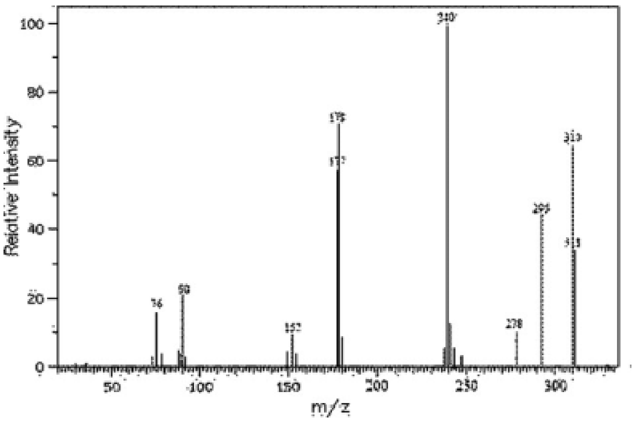


Figure 1. GC-Mass spectrum of N-hydroxyldiclofenac with its molecular ion peak at 311 amu.

PTS. All other peaks observed in GC-MS can be interpreted in accordance with the observed structure.

Table 1. Effect of Variation of Oxidant, Diclofenac, and NaOH Concentrations on the Reaction Rate at 293 K

10^4 [oxidant]$_o$ (mol dm^{-3})	10^3 [diclofenac]$_o$ (mol dm^{-3})	10^3 [NaOH] (mol dm^{-3})	10^4 k' (s^{-1}) CAT	BAT
0.5	2.0	0.5	2.41	8.02
1.0	2.0	0.5	2.33	7.82
1.8	2.0	0.5	2.36	7.90
3.6	2.0	0.5	2.30	7.88
5.0	2.0	0.5	2.37	7.86
1.8	0.5	0.5	1.37	3.48
1.8	1.0	0.5	1.74	5.72
1.8	2.0	0.5	2.36	7.90
1.8	4.0	0.5	3.13	10.6
1.8	8.0	0.5	4.38	15.9
1.8	2.0	0.1	0.95	3.73
1.8	2.0	0.2	1.53	5.17
1.8	2.0	0.5	2.36	7.90
1.8	2.0	1.0	3.64	11.2
1.8	2.0	2.0	5.28	15.2

[oxidant]$_o$ = 1.8×10^{-4} mol dm^{-3}; [diclofenac]$_o$ = 2.0×10^{-3} mol dm^{-3}; [NaOH] = 0.5×10^{-3} mol dm^{-3}.

Results and Discussion

The kinetics of oxidation of diclofenac by CAT and BAT (henceforth abbreviated as oxidant) have been investigated at several initial concentrations of the reactants, under pseudo first-order conditions of [substrate]$_o$ >> [oxidant]$_o$, in presence of NaOH at 293 K in both cases. Under the identical experimental conditions, the kinetic and mechanistic features for the oxidation of diclofenac with the closely related compounds CAT and BAT in NaOH medium are same. But the relative rates of oxidation of diclofenac by BAT are about four-fold faster than CAT.

Kinetic orders

Effect of Reactant Concentrations on the Reaction Rate. With the substrate in excess, at constant [diclofenac]$_o$, [NaOH], and temperature, plots of log [oxidant] vs. time were linear ($r > 0.9926$), indicating a first-order dependence of the reaction rate on [oxidant]$_o$. The pseudofirst-order rate constants (k' s^{-1}) remain unaltered with variation in [oxidant]$_o$, confirming the first-order dependence on [oxidant]$_o$ (Table 1). Under the same experimental conditions, the rate increases with increase in [diclofenac]$_o$ (Table 1) and plots of log k' vs. log [diclofenac] were linear ($r > 0.9957$) with slopes of 0.45 and 0.50 for CAT and BAT, indicating a fractional-order dependence of rate on [diclofenac]$_o$. Further, plots of k' vs. [diclofenac]$_o$ were linear ($r > 0.9851$) with an intercept, confirming a fractional-order dependence on [diclofenac]$_o$.

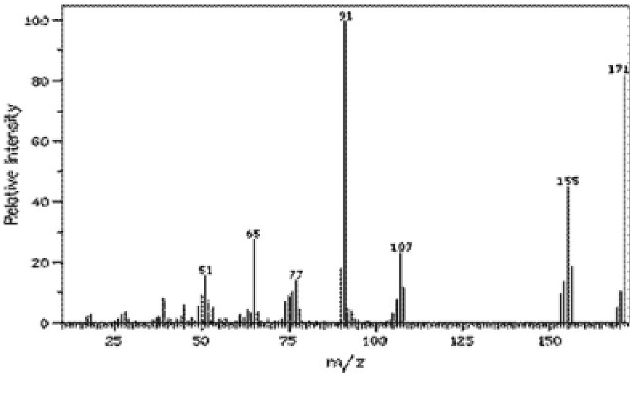


Figure 2. GC-Mass spectrum of PTS with its molecular ion peak at 171 amu.

Effect of NaOH and PTS Concentrations on the Reaction Rate. The rate of reaction increased with increase in [NaOH] (Table 1), and plots of log k' vs. log [NaOH] were linear ($r > 0.9986$) with slopes of 0.60 and 0.48 for CAT and BAT, showing a fractional-order dependence on [NaOH]. Addition of PTS ($ArNH_2$) to the reaction mixture (5.0×10^{-3} mol dm^{-3}) did not affect the rate significantly indicates that $ArNH_2$ is not involved in any step before the rate determining step of the proposed scheme.

Effect of Ionic Strength and Halide Ions on the Reaction Rate. Effect of ionic strength on the reaction rate was investigated in presence of 0.1 mol dm^{-3} sodium perchlorate, keeping all other experimental conditions constant. It was found that addition of $NaClO_4$ showed insignificant effect on the reaction rate, demonstrating the involvement of nonionic species in the rate determining step. Subsequently, the ionic strength of the reaction mixture was not fixed for kinetic runs. Further, addition of Br^- or Cl^- ions in the form of their sodium salts at the concentration of 5.0×10^{-3} mol dm^{-3} showed a negligible effect on the reaction rate, which suggests that no inter halogen or chlorine (or bromine) is formed and that there is a direct interaction of the oxidizing species with the substrate.

Effect of Dielectric Constant and Solvent Isotope on the Reaction Rate. Rate studies were carried out in water-MeOH mixtures having different compositions (0–30% v′v), thereby, varying the dielectric constant (D) of the medium, but the rates were not significantly altered in case of both the oxidants. Because the oxidation of diclofenac by CAT and BAT was accelerated by OH^- ions, the solvent isotope effect was studied in D_2O as the solvent medium for both the oxidants. The rate constants for CAT and BAT revealed that k' (H_2O) was equal to 2.36×10^{-4} s^{-1} and 7.90×10^{-4} s^{-1}, and k' (D_2O) was 3.86×10^{-4} s^{-1} and 10.4×10^{-4} s^{-1}, respectively. Thus,

Table 2. Temperature Dependence on the Reaction Rate and Activation Parameters for the Oxidation of Diclofenac by CAT and BAT in Alkaline Medium

Temperature (K)	$10^4\ k'$ (s^{-1}) ($10^4\ k_3\ s^{-1}$) CAT	$10^4\ k'$ (s^{-1}) ($10^4\ k_3\ s^{-1}$) BAT
283	1.37 (1.25)	3.59 (5.80)
288	1.74 (3.64)	4.90 (9.10)
293	2.36 (5.26)	7.90 (15.4)
303	3.13 (12.5)	14.7 (28.6)
313	4.38 (15.3)	29.0 (54.0)
E_a (kJ mol^{-1})	72.4 (62.1)	54.4 (48.3)
$\Delta H^{\neq}$ (kJ mol^{-1})	70.0 (59.6)	51.9 (45.8)
$\Delta G^{\neq}$ (kJ mol^{-1})	92.5 (90.6)	89.7 (88.3)
$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	−76.4 (−25.0)	−150 (−127)
Log A	12.4 (10.5)	8.93 (8.67)

Values in parentheses are the decomposition constants and activation parameters for the rate determining step.
$[\text{oxidant}]_o = 1.8 \times 10^{-4}$ mol dm^{-3}; $[\text{diclofenac}]_o = 2.0 \times 10^{-3}$ mol dm^{-3}; $[\text{NaOH}] = 0.5 \times 10^{-3}$ mol dm^{-3}.

the solvent isotope effect, $k'\ (H_2O)'k'\ (D_2O)$, was found to be 0.61 and 0.76 for CAT and BAT, respectively.

Effect of Temperature on the Reaction Rate. The reaction was studied at different temperatures (283–313 K), keeping other experimental conditions constant. From Arrhenius plots of log k' vs. 1/T ($r > 0.9934$), composite activation parameters (E_a, $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$, and log A) were computed for the oxidation of diclofenac by CAT and BAT. These data are summarized in Table 2.

Polymerization study

Alkene monomers, such as acrylonitrile, and freshly prepared 10% acryamide solution were added to the reaction mixture to initiate polymerization by free radicals formed in situ. The lack of polymerization indicated the absence of free radicals in the reaction mixture. This clearly ruled out the possibility of free radical mechanism. The controlled experiments were also performed under similar reaction conditions without oxidant.

Organic N*-haloamines*

Organic N-haloamines are sources of positive halogens, and these reagents have been exploited as oxidant for a variety of substrates in both acidic and alkaline media.[2–4] Because organic *N*-haloamines have similar chemical properties, it is expected that identical equilibria exist in aqueous acidic and basic solutions of these compounds.[23,24] CAT and BAT act as oxidizing agents in acidic and alkaline media,[2] with a two electron change per mole, giving PTS and NaCl or NaBr. The redox potential of CAT-PTS couple is pH dependent[25] and decreases with increase in pH of the medium (E_{redox}1.138 V, 1.778 V, 0.614 V, and 0.5 V at pH 0.65, 7.0, 9.7, and 12, respectively). In view of the homogeneity in properties of CAT and BAT, similar redox potential behavior can be expected for BAT as well. The nature of the active oxidizing species and mechanism depends on the nature of halogen atom, the groups attached to the nitrogen, and the reaction condition. The species responsible for such oxidizing character may be different depending on the pH of the medium.

Reactive species of CAT and BAT

CAT and BAT (ArNXNa) are moderately strong electrolytes[24] in aqueous solutions ($\text{ArNXNa} \rightleftharpoons \text{ArN}^-\text{X} + \text{Na}^+$), and depending on the pH of the medium, these reagents furnish different types of reactive species in solutions.[21,23–27] In alkaline solutions of CAT and BAT, dihaloamine ($ArNX_2$) does not exist, and the possible oxidizing species are ArNHX, HOX, and ArN^-X. Further, the following set of equilibria can be expected[23] in alkaline solutions of CAT and BAT:

$$\text{ArN}^-\text{X} + \text{H}_2\text{O} \rightleftharpoons \text{ArNH}_2 + \text{OX}^- \tag{2}$$

$$\text{ArN}^-\text{X} + \text{H}_2\text{O} \rightleftharpoons \text{ArNHX} + \text{OH}^- \tag{3}$$

$$\text{ArNHX} + \text{H}_2\text{O} \rightleftharpoons \text{ArNH}_2 + \text{HOX} \tag{4}$$

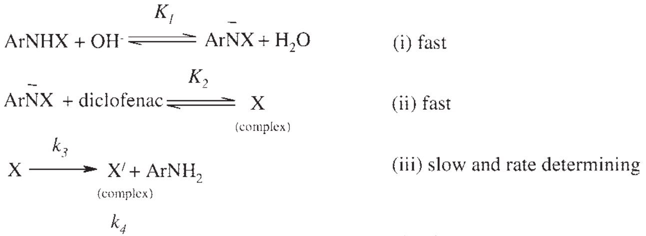
$$\text{ArNHX} + \text{OH}^- \rightleftharpoons \text{ArNH}_2 + \text{OX}^- \tag{5}$$

Equations 2, 4, and 5 suggest rate retardation with the addition of PTS ($ArNH_2$), whereas Eq. 3 predicts a decrease in rate by OH^- ions. Because these predictions are contrary to our experimental observations, it is likely that the anion, ArN^-X, itself acts as the reactive oxidant species in this work.

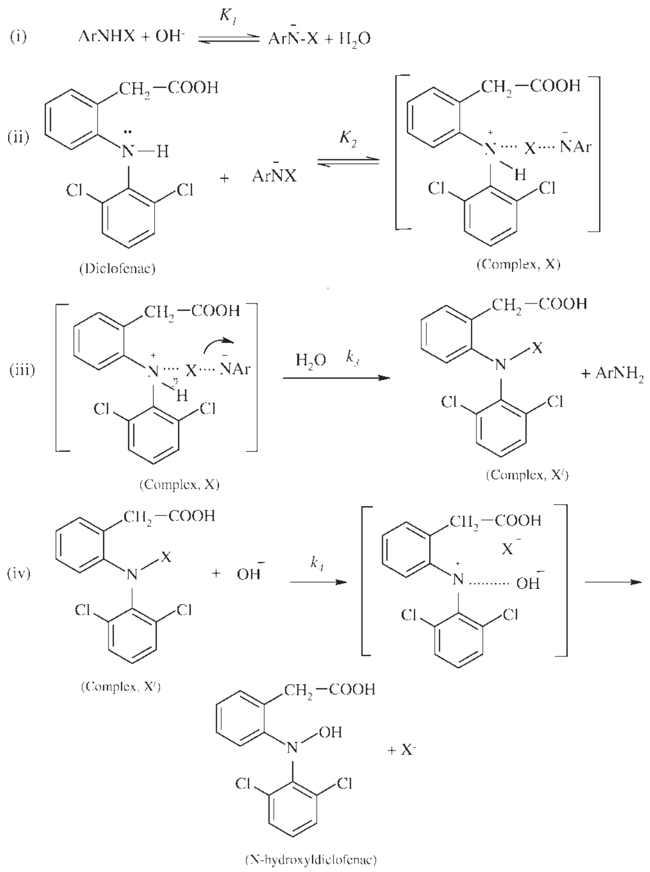
Reaction scheme

In these investigations, the acceleration of rate by OH^- ion indicates the formation of anion ArN^-X from the conjugate acid ArNHX in an OH^- accelerating step. In view of preceding discussion and the experimental facts, it is reasonable to assume an anion ArN^-X is the reactive oxidant species, which interacts with the substrate. In the light of these considerations, the oxidation mechanism for the oxidation of diclofenac by CAT and BAT in alkaline medium is formulated as given in Scheme 1.

A detailed mode of oxidation of diclofenac by CAT and BAT in alkaline medium is depicted in Scheme 2. In a fast initial equilibrium [step (i) of Scheme 1], the conjugate acid, ArNHX, in the alkali accelerating step generates the active oxidizing anionic species ArN^-X. In the next fast equilibrium [step (ii)], the lone pair of electrons on nitrogen of diclofenac attacks the positive halogen of ArN^-X, forming a transition state X. This transient species X in a slow′rate determining step [step (iii)] undergoes deprotonation to form a halo intermediate X′, with the elimination of $ArNH_2$. This transient species X′ interacts with the hydroxyl ion by



Scheme 1. A general reaction scheme for the oxidation of diclofenac by CAT and BAT in alkaline medium.



Scheme 2. A detailed mechanism involving the electron transfer during the oxidation of diclofenac by CAT and BAT in NaOH medium.

nucleophilic substitution, leading to the formation of *N*-hydroxyldiclofenac.

Kinetic modeling

If $[\text{oxidant}]_t$ is total effective concentration of oxidant, then

$$[\text{oxidant}]_t = [\text{ArNHX}] + [\text{ArN}^-\text{X}] + [\text{X}] \tag{6}$$

From steps (i) and (ii) of Scheme 1,

$$[\text{ArNHX}] = \frac{[\text{X}][\text{H}_2\text{O}]}{K_1K_2[\text{diclofenac}][\text{OH}^-]} \tag{7}$$

and

$$[\text{ArN}^-\text{HX}] = \frac{[\text{X}]}{K_2[\text{diclofenac}]} \tag{8}$$

By substituting for [ArNHX] and $[\text{ArN}^-\text{X}]$ from Eqs. 7 and 8, respectively, into Eq. 6 and solving for [X], we get

$$[\text{X}] = \frac{K_1K_2[\text{oxidant}]_t[\text{diclofenac}][\text{OH}^-]}{[\text{H}_2\text{O}] + K_1[\text{OH}^-] + K_1K_2[\text{diclofenac}][\text{OH}^-]} \tag{9}$$

From slow/rate determining step [step (iii)] of Scheme 1, we get

$$\text{Rate} = -[\text{oxidant}]_t/\text{dt} = \text{k}_3[\text{X}] \tag{10}$$

By substituting for [X] from Eq. 9 into Eq. 10, the following rate law is obtained.

$$\text{Rate} = \frac{K_1K_2k_3[\text{oxidant}]_t[\text{diclofenac}][\text{OH}^-]}{[\text{H}_2\text{O}] + K_1[\text{OH}^-] + K_1K_2[\text{diclofenac}][\text{OH}^-]} \tag{11}$$

Rate law (Eq. 11) is in accordance with the kinetic findings, wherein a first-order dependence of rate on $[\text{oxidant}]_o$ and fractional-order dependence on each of $[\text{diclofenac}]_o$ and $[\text{OH}^-]$ was observed. Because Rate $= k'$ $[\text{oxidant}]_t$, Eq. 11 can be transformed into Eqs. 12–14, as follows:

$$k' = \frac{\text{K}_1\text{K}_2\text{k}_3[\text{diclofenac}][\text{OH}^-]}{[\text{H}_2\text{O}] + K_1[\text{OH}^-] + K_1K_2[\text{diclofenac}][\text{OH}^-]} \tag{12}$$

$$\frac{1}{k'} = \frac{1}{[\text{diclofenac}]}\left\{\frac{[\text{H}_2\text{O}]}{K_1K_2k_3[\text{OH}^-]} + \frac{1}{K_2k_3}\right\} + \frac{1}{k_3} \tag{13}$$

$$\frac{1}{k'} = \frac{1}{[\text{OH}^-]}\left\{\frac{[\text{H}_2\text{O}]}{K_1K_2k_3[\text{diclofenac}]}\right\} + \left\{\frac{1}{K_2k_3[\text{diclofenac}]} + \frac{1}{k_3}\right\} \tag{14}$$

Above rate Eqs. 13 and 14 may be verified by plotting the graphs of $1/k'$ vs. 1/[diclofenac] and $1/k'$ vs. $1/[\text{OH}^-]$. A plot of $1/k'$ vs. 1/[diclofenac] ($r = 0.9936$; Figure 3) from Eq. 13 yields a slope $= [\text{H}_2\text{O}]/K_1\ K_2\ k_3\ [\text{OH}^-] + 1/K_2k_3$ and an intercept $= 1/k_3$. Similarly, a plot of $1/k'$ vs. $1/[\text{OH}^-]$ ($r = 0.9833$; Figure 4) from Eq. 14 gives a slope $= [\text{H}_2\text{O}]/K_1\ K_2\ k_3$ [diclofenac] and an intercept $= 1/K_2k_3$ [diclofenac] $+ 1/k_3$. From the slopes and intercepts of Eqs. 13 and 14, the values of the equilibrium constants, K_1 and K_2, and the decomposition constant k_3 were evaluated for the standard

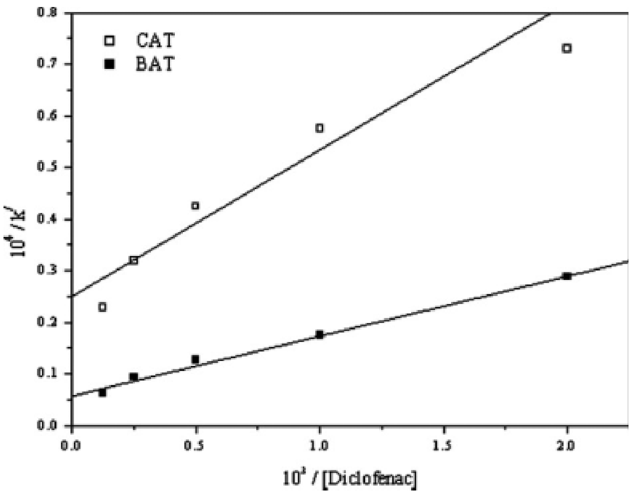


Figure 3. Double reciprocal plots of 1/*k*′ vs. 1/[diclofenac]. Experimental conditions are as in Table 1.

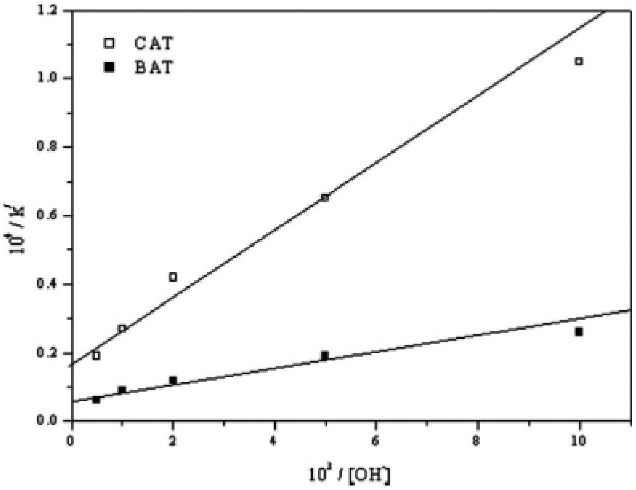


Figure 4. Double reciprocal plots of $1/k'$ vs. $1/[OH^-]$. Experimental conditions are as in Table 1.

run with the experimental conditions; $[\text{oxidant}]_o = 1.8 \times 10^{-4}$ mol dm^{-3}; $[\text{diclofenac}]_o = 2.0 \times 10^{-3}$ mol dm^{-3}; and $[NaOH] = 0.5 \times 10^{-3}$ mol dm^{-3} at 293 K for CAT and BAT. The values obtained are $K_1 = 7.07 \times 10^8$ and 19.5×10^8, $K_2 = 1.26 \times 10^{-2}$ and 46.0×10^{-2} dm^3 mol^{-1}, and $k_3 = 5.26 \times 10^{-4}$ and 15.4×10^{-4} s^{-1} for CAT and BAT, respectively. Further, the proposed mechanism and the derived rate law are supported by the following experimental findings.

Michaelis-Menten Kinetics. Because the rate was fractional-order in $[\text{diclofenac}]_o$, Michaelis–Menten type of kinetics[28] were adopted. The diclofenac was varied in the concentration range of 0.5×10^{-3} to 8.0×10^{-3} mol dm^{-3} at different temperatures (283–313 K), with all other experimental conditions being held constant. Based on Eq. 13, plots of $1/k'$ vs. 1/[diclofenac] were found to be linear ($r > 0.9851$). From the intercept of such a double reciprocal plot, the decomposition constant k_3 for the rate determining step were evaluated at different temperatures for both CAT and BAT. Further, activation parameters for the rate determining step [step (iii) of Scheme 1] were deduced using Arrhenius plots of log k_3 vs. 1/T. All these data are summarized in Table 2. The relative magnitudes of energy of activation and other thermodynamic parameters for the rate determining step, as well as the composite reaction, support the proposed reaction mechanism and the derived rate law.

Effect of Dielectric Constant. In these investigations, variation of dielectric constant of the medium does not affect the rate significantly. The effect of varying solvent composition and dielectric constant on the rate of reaction has been described in several studies.[29–33] For limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis[31] has shown that a plot of log k′ vs. 1/D gives a straight line, with a negative slope for a reaction between a negative ion and a dipole or between two dipoles, whereas a positive slope results for a positive ion-dipole interaction. The total absence of the effect of varying dielectric constant on the rate cannot be explained by the Amis theory.[31] Applying the Born equation, Laidler[32] has proposed the following equation for a dipole-dipole interaction:

$$\ln k' = \ln k_o + 3/8\,kT(2/D - 1)\left[\mu_A^2/r_A^3 + \mu_B^2/r_B^3 - \mu_{\neq}^2/r_{\neq}^3\right] \tag{15}$$

where k_o is the rate constant in a medium of infinite dielectric constant, μ represents the dipole moment, and r refers to the radii of the reactants and activated complex. It can be seen from Eq. 15 that the rates should be greater in a medium of lower dielectric constant when $r_{\neq}^3 = r_A^3 + r_B^3$, indicating that the extent of charge dispersal in the transition state is different. On the other hand, $r_{\neq}^3 \approx r_A^3 + r_B^3$ implies the absence of a dielectric effect of the solvent on the rate, as was observed in these investigations, signifying that the transition state is not very much different from the reactants with respect to the size and charge of the transition state and the reactants.

Effect of Solvent Isotope. The observed solvent isotope effect k' $(H_2O)/k'$ $(D_2O) < 1$ corroborates the proposed mechanism and the derived rate law. For a reaction involving a fast equilibrium H^+ or OH^- ion transfer, the rate increases in D_2O, because D_3O^+ and OD^- are a stronger acid and a stronger base, respectively, than H_3O^+ and OH^- ions.[34,35] According to the concept of solvent isotope effect, the expected increase of reaction rate in deuterium ions is about 2–3 times greater.[34] The increase of reaction rate with D_2O observed in these studies and the solvent isotope effect k' $(H_2O)/k'$ $(D_2O) < 1$ conform to the above theory. However, the magnitude of increase of rate in D_2O is small, which can be attributed to the fractional order dependence of rate on $[OH^-]$.

Relative reactivity of CAT and BAT

A comparison of the rates of reaction of CAT and BAT shows that the oxidation of diclofenac is about four-fold faster in BAT compared with that of CAT, under identical set of experimental conditions. This is endorsed by the relative magnitudes of activation energies (Table 2). This trend may be attributed to the difference in elctrophilicities of the halocations, Cl^+ and Br^+ ions, involved in the oxidation processes and is also related to the ease with which these species are generated in reactions. In these oxidation reactions, the electronegativity values of Br^+ and Cl^+ play a vital role. Bromine has the elctronegativity of 2.7, whereas chlorine has a higher value of 2.8. As the elcetronegativity increases, the electropositive nature decreases. Because the halo cations are the reactive species in these oxidation reactions, the electropositive nature is in the order: Br > Cl. Therefore, the reactivity of BAT is more, when compared with CAT. This trend may also be due to the moderate difference in the van der Waals's radii of bromine and chlorine. A similar behavior has been noted[4,5,12,14,36,37] in the oxidation of several other substrates using CAT and BAT. The facts furnished in this research and the literature reports[4,5,12,14,36,37] led to conclude that BAT is a stronger oxidant compared with CAT.

The proposed mechanism is also supported by the moderate values of energy of activation and other thermodynamic parameters. The energy of activation is highest for the slowest reaction and vice versa, indicating that the reaction is enthalpy controlled (Table 2). The positive values of $\Delta H^{\neq}$ and $\Delta G^{\neq}$ indicate that the transition state is highly solvated. The negative values of $\Delta S^{\neq}$ suggest the formation of a rigid associative transition state with a few degrees of freedom in both cases. Further, the comparable values of $\Delta G^{\neq}$ signify the same type of the reaction mechanism could be operative for the oxidation of diclofenac by CAT and BAT in alkaline medium. The values of frequency factor (A) specify the frequency of collisions and the orientation of reacting molecules. The ineffectiveness of the additions of PTS, neutral salts, and halide ions on the rate of the reaction are in agreement with the proposed mechanism and the derived rate law.

Conclusions

The kinetics of oxidation of diclofenac by CAT and BAT in NaOH medium follows the identical kinetics with a rate law—d[oxidant]/dt $= k$ [oxidant]$_o$ [diclofenac]$_o^x$ [OH$^-$]^y, where x and y are less than unity. *N*-hydroxyldiclofenac was identified as the oxidation product of diclofenac. Thermodynamic parameters and reaction constants were deduced. In the proposed mechanism, anion ArN$^-$X is assumed to be the reactive oxidant species, which interacts with the substrate. The relevant rate law has been designed. Under identical experimental conditions, the rate of oxidation of diclofenac is about four-fold faster with BAT when compared with CAT. This may be attributed to the difference in electrophilicities of Cl$^+$ and Br$^+$ ions and also the van der Waal's radii of chlorine and bromine.

Literature Cited

1. Jennings VJ. Analytical applications of chloramine-T. CRC *Critcal Rev Anal Chem*. 1974;3:407–419.
2. Campbell MM, Johnson G. Chloramine-T and related N-halogeno-N-metallo reagents. *Chem Rev*. 1978;78:65–79.
3. Banerji KK, Jayaram B, Mahadevappa DS. Mechanistic aspects of oxidation by N-metallo N-haloarylsulfonamides. *J Sci Ind Res*. 1987;46:65–76.
4. Kolvari E, Ghorbani-Choghamarani A, Salehi P, Shirini F, Zolfigol MA. Applications of N-halo reagents in organic synthesis. *J Iran Chem Soc*. 2007;4:126–174.
5. Rangappa KS. Oxidation of monosaccharides by N-metallo-N-haloarylsulfonamides: a review. *J Indian Chem Soc*. 2004;81:1025–1037.
6. Puttaswamy, Anuradha TM, Ramachandrappa R, Gowda NMM. Oxidation of isoniazid by N-haloarylsulfonamidates in alkaline medium: a kinetic and mechanistic study. *Int J Chem Kinet*. 2000; 32:221–230.
7. Agarwal MC, Upadhyay SK. Mechanistic investigations involving chloramine-T. *J Sci Ind Res*. 1990;49:13–18.
8. Ramachandra H, Rangappa KS, Mahadevappa DS, Gowda NMM. Oxidation of substituted phenathyl alcohols by sodium-N-chloro-p-toluenesulfonamide: a kinetic study. *Monatsh Chem*. 1996;127:241–255.
9. Kambo N, Upadhyay SK. Kinetics and mechanism of platinum (IV) catalyzed oxidation of some hexoses by alkaline chloramine-T. *Indian J Chem*. 2004;43A:1210–1215.
10. Puttaswamy, Jagadeesh RV. Mechanistic studies of oxidation of thiols to disulfides by sodium N-chloro-p-toluenesulfonamide in an alkaline medium: a mechanistic approach. *Ind Eng Chem Res*. 2006; 45:1563–1570.
11. Puttaswamy, Shubha JP. Ruthenium (III)-catalyzed and uncatalyzed kinetic studies on the oxidation of sulfanilic acid by chloramine-T in perchloric acid medium: a mechanistic approach. *Transition Met Chem*. 2008;33:1003–1011.
12. Naidu HMK, Yamuna B, Mahadevappa DS. Osmium (VIII) catalyzed reactions of allyl and crotyl alcohols with chloramine-T, chloramine-B, bromamine-T and bromamine-B: kinetics and mechanism of formation of halohydrins in alkaline medium. *Indian J Chem*. 1987;26A:114–117.
13. Rangappa KS, Ramachandra H, Mahadevappa DS, Gowda NMM. Osmium (VIII) catalyzed kinetics and mechanism of indoles oxidation with aryl-N-haloamines in alkaline medium. *Int J Chem Kinet*. 1996;28:265–274.
14. Puttaswamy, Jagadeesh RV. Chloraminometric and bromaminometric oxidation of sulfanilic acid in alkaline medium: a comparative kinetic and mechanistic study. *Int J Chem Kinet*. 2006;38: 48–56.
15. Williams DA, Lenke TL. *Foye's Principles of Medicinal Chemistry*. Philadelphia, PA: Lippincott Williams and Wilkins, 2005:751–790.
16. Bertram G Katzung. *Basic and Clinical Pharmacology*. San diego, CA: McGraw-Hill, 2006:574–576.
17. Castillo MA, Bruzzone L. Indirect fluorometric determination of diclofenac sodium. *Ana Sci*. 2006;22:431–433.
18. Roskar R, Kmetec V. Liquid chromatographic determination of diclofenac in human synovial fluid. *J Chromatogr B*. 2003;788:57–64.
19. Sein MM, Zedda M, Tuerk J, Schmidt TC, Golloch A, Sonntag CV. Oxidation of diclofenac with ozone in aqueous solution. *Environ Sci Technol*. 2008;42:6656–6662.
20. Perez-Estrada LA, Malato S, Gernjak W, Aguera A, Thurman EM, Ferrer I, Fernandez-Alba AR. Photo-fenton degradadation of diclofenac: identification of main intermediates and degradation pathway. *Environ Sci Technol*. 2005;39:8300–8306.
21. Morris JC, Salazar JA, Wineman MA. Equilibrium studies on chloro compounds: the ionization constant of N-chloro-p-tolunene sulfonamide. *J Am Chem Soc*. 1948;70:2036–2041.
22. Nair CGR, Lalithakumari R, Indrasenan P. Bromamine-T as a new oxidimetric titrant. *Talanta*. 1978;25:525–527.
23. Hardy FF, Johnston JP. The interactions of N-bromo-N-sodiobenzenesulfonamide (bromamine-B) with p-nitrophenoxide ion. *J Chem Soc Perkin Trans II*. 1973:742–750.
24. Bishop E, Jennings VJ. Titrimetric analysis with chloramine-T: the status of chloramine-T as a titrimetric reagent. *Talanta*. 1958;1:197–199.
25. Murthy ARV, Rao BS. Oxidation by chloramine-T. Part II. Redox potential of chloramine-T-sulfonamide systems. *Proc Indian Acad Sci*. 1952;35:69–72.
26. Pryde BG, Soper FD. The direct interchange of chlorine in the interaction of p-toluenesulfonamide and N-chloroacetanilide. *J Chem Soc*. 1931:1510–1512.
27. Higuchi T, Hasegawa T. Rate exchange of chlorine between dimethylchloramine and succinamide. *J Phys Chem*. 1965;69:796–799.
28. House JE. *Principles of Chemical Kinetics*. New York, NY: Academic Press, 2007:102–107.
29. Moelwyn-Hughes EA. *The kinetics of Reaction in Solutions*. Oxford, Clarender Press, 1947:374–381.
30. Frost AA, Pearson RG. *Kinetics and Mechanism*, New York, NY: Wiley, 1961:135–149.
31. Amis ES. Rates mechanisms and solvent. *Anal Chem*. 1955;27: 1672–1679.
32. Laidler KJ. *Chemical kinetics*. New Delhi: Tata Mc Graw-Hill, 1995:211–228.
33. Reichardt C. *Solvent and Solvent Effects in Organic Chemistry*. New York, NY: Wiley-Vctt, 2003:219–237.
34. Collins CJ, Bowman NS. *Isotope Effects in Chemical Reactions*. New York, NY: Van-Nostrand 1970:267.
35. Kohen A, Limbach HH. *Isotope Effects in Chemistry and Biology*. Florida: CRC Press, 2006:827–844.
36. Puttaswamy, Mahadevappa DS, Rangappa KS. Oxidation of indigo carmine by N-haloarenesulfonamidates: a kinetic study. *Bull Chem Soc Jpn*. 1989;62:3343–3348.
37. Puttaswamy, Jagadeesh RV. Ruthenium (III)-catalyzed mechanistic investigation of oxidation of an azo dye by sodium N-haloarenesulfonamidates: a comparative spectrophotometric kinetic study. *Appl Catal A Gen*. 2005;2923:259–271.

Manuscript received Jan. 27, 2009, and revision received May 11, 2009.