Oxidation of mephenesin and guaifenesin with chloramine-B in hydrochloric acid medium: Design of kinetic model

Puttaswamy* & Anu Sukhdev
Department of Post-Graduate Studies in Chemistry, Central College, Bangalore University, Bangalore 560 001, India
Email: pswamy_chem@yahoo.com

Received 1 September 2008; revised and accepted 13 February 2009

Kinetics of oxidation of mephenesin and guaifenesin by sodium N-chlorobenzenesulfonamide (CAB) have been investigated in HCl medium at 303 K. The oxidation behaviour is similar for both the substrates. The rate shows a first order dependence on both \([\text{CAB}]_0\) and \([\text{HCl}]\), and is fractional in \([\text{substrate}]_0\). The orders individually in \([\text{H}^+]\) and \([\text{Cl}^-]\) are fractional. The variation of ionic strength and addition of the reduction product, benzenesulfonamide, has no significant effect on the reaction rate. The solvent isotope effect has been studied using D\(_2\)O, and the oxidation products have been identified. Composite activation parameters for the reaction have been determined from Arrhenius plots. Michaelis-Menten type of kinetics is observed and activation parameters for the rate limiting steps have also been computed. The proposed mechanism assumes the simultaneous catalysis by \([\text{H}^+]\) and \([\text{Cl}^-]\) ions. The reaction is found to be moderately faster in guaifenesin in comparison with mephenesin, which may be attributed to the involvement of methoxy and methyl groups of the substrate. The observed results have been explained by a plausible mechanism and the related rate law has been proposed.

**Keywords**: Kinetics, Reaction mechanisms, Oxidations, Propane diols, Mephenesin, Guaifenesin

**IPC Code**: Int. Cl. 8 CO7B33/00

The chemistry of N-haloamines has attracted the attention of many investigators on account of their diverse behaviour. The diverse nature of the chemistry of N-haloamines is due to their ability to act as sources of halonium cations, hypohalite species, and N-anions, which act both as bases and nucleophiles\(^1\). These compounds contain positive halogen and are mild oxidants. They interact with a wide range of functional groups, effecting a variety of molecular transformations. A prominent member of this class is chloramine-T (CAT) and this reagent has been exploited as analytical reagent and oxidizing agent for a variety of substrates in both acidic and alkaline medium\(^1\text{–}^9\). The other member of chloramines, chloramine-B (CAB, C\(_6\)H\(_5\)SO\(_2\)NClNa.1.5H\(_2\)O), is a stable compound and is found to be a better oxidizing agent than its analogue, CAT. However, there is less information in the literature on CAB, particularly with respect to the oxidation kinetics of pharmaceuticals\(^10\text{–}^15\). Preliminary experimental results revealed that the present oxidation reactions by CAB in HCl medium were facile. Therefore, CAB has been chosen as an oxidant in the present redox system.

Mephenesin (3-(2-methylphenoxy 1,2-propanediol), and guaifenesin also known as glyceryl guaiacolate (3-(2-methoxyphenoxy 1,2-propanediol), belong to a class of compounds known as propanediol derivatives. Mephenesin is an effective skeletal muscle relaxant and has mild sedative properties\(^16\). It is also useful in relief of tremors of Parkinsonism, acute alcoholism, anxiety and tension. Guaifenesin is used alone for its sedative action in anxiety and tension states\(^16\). It is most often used in combination with antihistamines, analgesics and vasoconstrictors in cough medicines for its expectorant action. One of the derivatives of guaifenesin is methocarbamol, which is widely used for the relief of skeletal muscle spasm.

It is noted that despite the importance of these two drugs, relatively little is known about their mode of action at the molecular level, and also their kinetic and mechanistic pathways of these drugs in redox systems. Except for the work of Shen et al.\(^17\text{,}^18\) on the kinetics and mechanism of oxidation of mephenesin and guaifenesin by bis (hydrogenperiodato) argentate(III) complex ion in alkaline medium, so far no kinetics and mechanistic
details are available on the oxidation of these drugs. Accordingly, it is of immense interest to follow the oxidation kinetics of these drugs with halogen +1 oxidant. The present kinetic study is of significance as the substrates mephenesin and guaifenesin are potent drugs. The present paper reports the kinetics of oxidation of mephenesin and guaifenesin by chloramine-B in acid medium with a view to investigating the mechanism of these drugs in solution and also assessing the relative rates of oxidation of these two drugs.

**Materials and Methods**

The purity of chloramine-B (Fluka, Switzerland) was checked iodometrically through its active chlorine content. An aqueous solution of the compound was prepared, standardized periodically by the iodometric method and preserved in brown bottles to prevent any photochemical deterioration. The substrates mephenesin (99.64% assay) and guaifenesin (99.61% assay) of analytical grade were gifted by Synthokem Lab Pvt. Ltd, Hyderabad, India and were used as received. Aqueous solutions of these substrates were prepared and employed. All other chemicals used were of AnalaR grade. Heavy water (D₂O 99.4%) was supplied by BARC, India. Doubly distilled water was used throughout the course of the reaction.

**Kinetic studies**

The kinetic runs were performed under pseudo-first order conditions with a large excess of substrate over oxidant at 303 K. The reaction was carried out in glass stoppered pyrex boiling tubes with outer surface coated black to eliminate photochemical effects. Appropriate amounts of the substrate, HCl solutions and water (to keep the total volume constant for all runs) were taken in the tube and thermostated at 303 K for thermal equilibrium. A measured amount of CAB solution, also thermostated at the same temperature, was rapidly added to the mixture in the boiling tube. The mixture was periodically shaken to ensure uniform concentration and the progress of the reaction was monitored by iodometric determination of unreacted CAB in a measured aliquot of the reaction mixture at different intervals of time. The course of the reaction was studied for more than two half-lives. The pseudo-first order rate constants (k′, s⁻¹), calculated from linear plots of log [CAB] versus time, were reproducible within 3-6%.

Varying ratios of CAB:substrate in the presence of 2.0 × 10⁻⁵ mol dm⁻³ were equilibrated at 303 K for 24 h. Determination of residual oxidant showed that one mole of CAB was consumed per mole of substrate. The stoichiometry obtained can be represented as:

\[
\begin{align*}
\text{OCH}_2\text{CH(OH)CH}_2\text{OH} + \text{PhSO}_2\text{NCINa} & \rightarrow \text{OCH}_2\text{CH(OH)CHO} + \text{PhSO}_2\text{NH}_2 + \text{Na}^+ + \text{Cl}^- \quad \text{...(1)}
\end{align*}
\]

Here R= -CH₃ for mephenesin and -OCH₃ for guaifenesin

The reaction mixture in the stoichiometric ratio under stirred condition was allowed to progress for 24 h at 303 K. After completion of the reaction, products were neutralized with NaOH and extracted with ether. The organic products were subjected to spot tests and chromatographic analysis. These oxidation products were separated by column chromatography on silica gel (60-120 mesh) using dichloromethane and pet. Ether (3:5 v/v) as the mobile phase. Analysis revealed the formation of the oxidation product of mephenesin to be 3-(2-methylphenoxy)2-hydroxy-1-propanal and 3-(2-methoxyphenoxy)2-hydroxy-1-propanal in the case of guaifenesin. The presence of the corresponding aldehyde products of these substrates in the reaction mixture was detected by their 2,4-DNP derivatives. These products were further confirmed by IR spectral analysis. IR spectrum was recorded on Nicolet (model impact 400D) FT-IR spectrum (KBr pellets, 3 cm⁻¹ resolution). IR spectral bands for the product of mephenesin were observed at 3424 cm⁻¹ (-OH), 1700 cm⁻¹ (-C=O) stretching and a band at 2785 cm⁻¹ for aldehydic C-H stretching. Similarly, IR spectral bands for the product of guaifenesin were observed at 3410 cm⁻¹ (-OH), 1690 cm⁻¹ and a band at 2820 cm⁻¹ for aldehydic C-H stretching. It was also noticed that there was no further oxidation of these products under the present set of experimental conditions. The reduction product of CAB, benzenesulfonamide was detected by TLC using petroleum ether, chloroform and 1-butanol (2:2:1 v/v) as the solvent, and iodine as the detecting agent (Rₖ = 0.88).
Results and Discussion

The oxidation of mephenesin (Meph.) and guaifenesin (Guaif.) (henceforth abbreviated as substrate) by CAB was kinetically investigated at different initial concentrations of the reactants in HCl medium at 303 K. The kinetic runs were carried out under pseudo-first order conditions with large excess of the substrate over oxidant. The same oxidation behaviour was observed for both the substrates.

With the substrate in excess, at constant [HCl] and [substrate]₀, plots of log[CAB] versus time were linear (r > 0.9897) in both the cases, indicating a first order dependence of rate on [CAB]₀. Values of pseudo-first order rate constants (k) are given in Table 1. These k values were unaffected by the variation in [CAB]₀, confirming the first order dependence on [CAB]₀. Under the same experimental conditions, an increase in [substrate]₀ increased the k’ value (Table 1). Plots of log k’ versus log [substrate] were linear (r > 0.9858) with slopes of 0.66 and 0.72 for mephenesin and guaifenesin, indicating a fractional order dependence of rate on [substrate]₀. Further, plots of k’ versus [substrate]₀ were linear (r > 0.9955) with y-intercepts, confirming the fractional order dependence on [substrate]₀.

The rate of reaction increased with increase in [HCl] (Table 2) and plots of log k’ versus log [HCl] were linear (r > 0.9984) with slopes of unity for both the drugs. To ascertain the true order with respect to [H⁺] and [Cl⁻], following kinetic runs were carried out. The effect of [H⁺] on rate was studied by adding HClO₄ at constant [Cl⁻] = 0.12 mol dm⁻³ using NaCl. A log-log plot of log k’ versus log [H⁺] gave straight lines (r > 0.9896) with fractional slopes of 0.69 and 0.64 for mephenesin and guaifenesin, respectively. At constant [H⁺] = 0.02 mol dm⁻³ maintained with HCl, the rate increased with addition of NaCl and the kinetic orders were found to be 0.35 and 0.38 respectively, for these substrates. These results clearly confirm the fractional orders with respect to H⁺ and Cl⁻ ions individually and the net order of unity on HCl concentration in both the cases (Table 2).

Addition of the reduction product of CAB, benzenesulfonamide (5.0 × 10⁻⁴ – 20.0 × 10⁻⁴ mol dm⁻³) had no effect on the rate, indicating that it is not involved in the pre-equilibrium with the oxidant. Variation of ionic strength of the medium by adding NaClO₄ (0.1-0.3 mol dm⁻³) did not influence the rate, indicating the involvement of non-ionic species in the rate limiting step. Hence, no attempt was made to keep ionic strength of the medium constant during kinetic runs. Solvent isotope studies were made using D₂O. For mephenesin, k’ was 2.75 × 10⁻⁴ s⁻¹ in D₂O and 2.0 × 10⁻⁴ s⁻¹ in H₂O, leading to a solvent isotope effect, k’ (H₂O)/k’ (D₂O), of 0.73 ± 0.05. The reaction rates were determined at different temperatures (298,

---

**Table 1** — Effect of varying reactant concentrations on the rate of reaction. ([HCl] = 2.0 × 10⁻² mol dm⁻³; T = 303 K)

<table>
<thead>
<tr>
<th>10⁴ [CAB]₀ (mol dm⁻³)</th>
<th>10⁴ [Substrate]₀ (mol dm⁻³)</th>
<th>10⁴ k’ (s⁻¹)</th>
<th>Meph.</th>
<th>Guaif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.0</td>
<td>1.98</td>
<td>2.58</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>2.01</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>2.06</td>
<td>2.65</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>1.0</td>
<td>2.04</td>
<td>2.55</td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>1.0</td>
<td>1.95</td>
<td>2.60</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>0.6</td>
<td>1.41</td>
<td>1.71</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>2.01</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
<td>3.16</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
<td>3.98</td>
<td>5.42</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>4.0</td>
<td>5.51</td>
<td>7.27</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>8.0</td>
<td>8.92</td>
<td>11.8</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** — Effect of varying [HCl], [H⁺] and [Cl⁻] on the rate of reaction.

([CAB]₀ = 1.0 × 10⁻⁴ mol dm⁻³; [Substrate]₀ = 1.0 × 10⁻³ mol dm⁻³; T = 303 K)

<table>
<thead>
<tr>
<th>10² [HCl] (mol dm⁻³)</th>
<th>10² k’ (s⁻¹)</th>
<th>10² [H⁺] (mol dm⁻³)</th>
<th>10² k’ (s⁻¹)</th>
<th>10² [Cl⁻] (mol dm⁻³)</th>
<th>10² k’ (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.12</td>
<td>1.34</td>
<td>1.0</td>
<td>4.24</td>
<td>5.35</td>
</tr>
<tr>
<td>2.0</td>
<td>2.01</td>
<td>2.63</td>
<td>2.0</td>
<td>5.39</td>
<td>6.24</td>
</tr>
<tr>
<td>4.0</td>
<td>4.39</td>
<td>5.42</td>
<td>4.0</td>
<td>6.84</td>
<td>7.44</td>
</tr>
<tr>
<td>5.0</td>
<td>5.48</td>
<td>6.99</td>
<td>6.0</td>
<td>8.78</td>
<td>10.2</td>
</tr>
<tr>
<td>8.0</td>
<td>8.6</td>
<td>10.6</td>
<td>10.0</td>
<td>11.2</td>
<td>12.6</td>
</tr>
<tr>
<td>10.0</td>
<td>10.9</td>
<td>13.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*At constant [Cl⁻] = 0.12 mol dm⁻³; *At constant [H⁺] = 0.02 mol dm⁻³.
The possible oxidizing species in acidified CAB solutions are thus PhSO$_2$NHCl, PhSO$_2$NCl$_2$ and HOCl. If PhSO$_2$NCl$_2$ were to be the reactive species, the rate law should predict a second order dependence of the rate on [CAB] as seen from Eq. (4), which is contrary to the experimental observations. Equation (6) indicates that the hydrolysis is slight, and if HOCl is involved, a first order retardation of rate by the added benzenesulphonamide (PhSO$_2$NH$_2$) is expected. Since no such effect is noticed, HOCl is ruled out as the oxidizing species. Further, it is well known that with aqueous haloamines solutions, the conjugate acid is a predominant species in acid solutions. Since organic haloamines have similar chemical properties, we can extend the same argument to CAB and PhSO$_2$NHCl can be assumed to be the oxidizing species under the experimental conditions employed.

Based on the above facts, the oxidation of mephenesin and guaifenesin by CAB in HCl medium is best explained by Scheme 1, which predicts simultaneous catalysis by H$^+$ and Cl$^-$ ions.

\[
\begin{align*}
\text{PhSO}_2\text{NHCl} + \text{H}^+ + \text{Cl}^- & \rightarrow \text{PhSO}_2\text{NCl}_2 \ldots \text{(i) fast} \\
\text{X} + \text{Substrate} & \rightarrow \text{X}' + \text{PhSO}_2\text{NH}_2 \ldots \text{(ii) fast} \\
\text{X}' & \rightarrow \text{products} \ldots \text{(iii) slow and rate limiting}
\end{align*}
\]

\textbf{Scheme 1}

In Scheme 1, X is the interhalogen intermediate species and X’ represents the complex intermediate species. A detailed mode of oxidation of mephenesin and guaifenesin is depicted in Scheme 2. Scheme 1 assumes the formation of a tight ion pair (X), which is an interhalogen intermediate species formed (step (ii)) from PhSO$_2$NHCl and H$^+$ and Cl$^-$. The former reacts with the substrate in an equilibrium step (step (ii)) to form the substrate – CAB complex (X’) with the elimination of PhSO$_2$NH$_2$. This complex decomposes in a rate limiting step (step (iii)) to give the final products.

The total effective concentration of CAB is [CAB]$_e$, then

\[ [\text{CAB}]_e = [\text{PhSO}_2\text{NHCl}] + [\text{X}] + [\text{X}'] \]
From step (i) of Scheme 1,

\[ K_j = \frac{[X]}{[PhSO_2NHCl][H^+][Cl^-]} \]

\[ [PhSO_2NHCl] = \frac{[X]}{K_j[H^+][Cl^-]} \]

From step (ii) of Scheme 1,

\[ K_2 = \frac{[X']}{{[X][substrate]}^{k2}} \]

\[ [X] = \frac{[X']}{K_2[substrate]} \]

By substituting for \([X]\) from Eq. (11) into Eq. (9), we get

\[ [PhSO_2NHCl] = \frac{[X']}{K_j K_2[substrate][H^+][Cl^-]} \]

By substituting for \([X]\) and \([PhSO_2NHCl]\) from Eq. (7), one obtains

\[ [CAB] = \frac{[X]}{K_j K_2[substrate][H^+][Cl^-]} + \frac{[X]}{K_2[substrate]} + [X'] \]

from which,

\[ [X'] = \frac{K_j K_2[CAB]_k[substrate][H^+][Cl^-]}{1 + K_j[H^+][Cl^-] + K_j K_2[substrate][H^+][Cl^-]} \]

From slow step (step (iii)) of Scheme 1,

\[ \text{Rate} = - \frac{d[CAB]}{dt} = k[X'] \]

By substituting for \([X']\) from Eq. (14) in Eq. (15), the following rate law is obtained

\[ \text{Rate} = \frac{K_j K_2 k_j [CAB]_k[substrate][H^+][Cl^-]}{1 + K_j[H^+][Cl^-] + K_j K_2[substrate][H^+][Cl^-]} \]
Rate law (16) is in accordance with the experimental results, wherein a first order dependence of rate on [CAB]₀, and fractional orders on each [substrate]₀, [H⁺] and [Cl⁻] was noticed.

Since rate = \( k' \) [CAT]₀, Eq. (16) can be transformed as:

\[
\frac{1}{k'} = \frac{K_1 K_2 k_3 [\text{substrate}] [H^+] [\text{Cl}^-]}{1 + K_1 [H^+] [\text{Cl}^-] + K_1 K_2 [\text{substrate}] [H^+] [\text{Cl}^-]} \\
\ldots (17)
\]

\[
\frac{1}{k'} = \frac{1}{[\text{substrate}]} \left\{ \frac{1}{K_1 K_2 k_3 [H^+] [\text{Cl}^-]} + \frac{1}{K_2 k_2 [H^+] [\text{Cl}^-]} \right\} + \frac{1}{k_3} \\
\ldots (18)
\]

From the intercepts of the linear double reciprocal plots of \( 1/k' \) versus \( 1/[\text{substrate}] \), decomposition constants \( (k_3) \) were calculated using Eq. (18) for both the substrates at 303 K. Since the rate was fractional in [substrate]₀, Michaelis-Menten type of kinetics were adopted to study the effect of [substrate]₀ on rate at different temperatures. From the plots of \( 1/k' \) versus \( 1/[\text{substrate}] \), (Fig. 1; \( r > 0.9849 \)) values of \( k_3 \) were calculated for both the substrates at different temperatures. The activation parameters for the rate limiting step were computed using Arrhenius plots of \( \log k_3 \) versus \( 1/T \) (\( r > 0.9823 \)). These results are summarized in Table 3.

The proposed mechanism is supported by an increase in rate in D₂O medium. For a reaction involving a fast equilibrium H⁺ or OH⁻ ion transfer, the rate increases in D₂O medium since D₂O⁺ and OD⁻ are a stronger acid and a stronger base respectively, than H⁺ and OH⁻ ions. In the present case, the observed solvent isotope effect of \( k'(\text{H}_2\text{O})/k' (\text{D}_2\text{O}) < 1 \) is due to the greater acidity of D₂O⁺ compared to H₂O⁺. However, the magnitude of acceleration is small (expected value is ~ 2 to 3 times greater) which can be attributed to the fractional order dependence of rate on [H⁺]. Hence, this observation supports the proposed mechanism.

The magnitudes of the reaction rates and activation energies indicate that the oxidation of guaifenesin is moderately faster when compared to that of mephenesin. The –CH₃ and –OCH₃ groups of mephenesin and guaifenesin are positive inductive in nature. In the case of guaifenesin the methoxy group increases the electron density on the reacting site by involving a lone pair of electrons on oxygen atom in resonance. Hence, the reactivity of guaifenesin towards CAB is moderately higher than that of mephenesin. The proposed mechanism is supported by the moderate values of energy of activation and other activation parameters. The fairly high positive values of \( \Delta G^\circ \) and \( \Delta H^\circ \) indicate that the transition state is highly solvated, while the negative \( \Delta S^\circ \) suggests that the transition state is fairly rigid with less degree of freedom. The constancy of rate constant on addition of neutral salt or reaction product (PhSO₂NH₂) is also in conformity with the proposed mechanism.

Conclusions
The kinetics of oxidation of mephenesin and guaifenesin by chloramine-B in HCl medium follows identical kinetics with a rate law, 

\[-d [\text{CAB}]/dt = k [\text{CAB}] [\text{substrate}]^x [H^+]^y [\text{Cl}^-]^z, \]

where \( x, y \) and \( z < 1 \). Michaelis-Menten kinetics is observed and activation parameters for the rate limiting step have been deduced. Oxidation products have been characterized. The rate of oxidation of guaifenesin is faster in comparison with mephenesin. The proposed mechanism assumes the simultaneous catalysis of H⁺ and Cl⁻ ions. Based on the experimental results, a kinetic model has been proposed.
Acknowledgement

Authors are gratefully acknowledge the gift of pure samples of mephenesin and guaifenesin from Ms Synthokem Labs Pvt. Ltd, Hyderabad, India.

References