OXIDATION OF SKELETAL MUSCLE RELAXANT DRUGS: AN INTRODUCTION

Muscle relaxants are a group of drugs which affect skeletal muscle function and decreased the muscle tone. It may well be used to lighten symptoms such as muscle spasms, pain, and hyper reflexia. The term "muscle relaxant" is used to refer to two major therapeutic groups: neuromuscular blockers and spasmyotics [135]. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no central nervous system (CNS) activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis. Spasmyotics, also known as "centrally acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and also reduces spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmyotics are often grouped together as muscle relaxants, the term ‘muscle relaxant’ is commonly used to refer to spasmyotics only.

Mephenesin (3-(2-methylphenoxy-1,2-propanediol), and guaifenesin also known as glyceryl guaiacolate (3-(2-methoxyphenoxy-1,2-propanediol), belongs to a class of compounds known as propanediol derivatives comes under the group spasmyotics. Mephenesin is an effective skeletal muscle relaxant and has mild sedative properties. 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 [136]. 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. Because of the importance of mephenesin and guaifenesin drugs, several analytical methods were employed for determination of these drugs [137-139]. But, so far little work has been carried out on the oxidation-kinetics of these drugs by their mechanistic aspects and are cited below:

Oxidation of mephenesin by bis(hydrogenperiodato)argentate(III) complex anion, [Ag(HIO₆)₂]⁵⁻, has been studied in aqueous alkaline medium [140]. The major oxidation product of mephenesin has been identified as 3-(2-methylphenoxy)-2-ketone-1-propanol by
mass spectrometry. An overall second-order kinetics has been observed with first-order in [Ag(III)] and [mephenesin]. The effects of [OH⁻] and periodate concentration on the observed second-order rate constants have been analyzed, and accordingly an empirical expression has been deduced. Activation parameters have been calculated. Oxidation of guaifenesin [141] by a Ag(III) complex anion, [Ag(HIO₆)(OH⁻)]⁵⁻, was studied in aqueous alkaline medium by using spectrophotometry. The major oxidation product of guaifenesin was identified by mass spectrometry. The oxidation reaction exhibits an overall second-order kinetics: first-order with respect to both Ag(III) and guaifenesin concentrations. Variations of [OH⁻] and [IO₄⁻] had a significant influence on the reaction rates, where [IO₄⁻] represents the total concentration of periodate added externally. A mechanism involving the [Ag(HIO₆)(OH⁻)·(H₂O)]⁵⁻ as the reactive species of the oxidant was proposed.

Hence, inspite of 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. Therefore, it is of our immense interest to follow the oxidation-kinetics of these two drugs with halogen +1 oxidant. The present kinetic study gives an impetus, as the substrates mephenesin and guaifenesin are potent drugs. Consequently, the present research work reports the kinetics of oxidation of mephenesin and guaifenesin by chloramine-B in acid medium with a view to shed light on the mechanism of these drugs in solution and also assessing the relative rates of oxidation of these two drugs.
OXIDATION-KINETICS AND MECHANISM OF SKELETAL MUSCLE RELAXANTS WITH CHLORAMINE-B IN HYDROCHLORIC ACID MEDIUM

This chapter unfolds the study on the kinetics and mechanism of oxidation of two skeletal muscle relaxants namely, mepheneisin and guaifenesin with CAB in hydrochloric acid medium at 300 K. The materials and methods followed here have been cited in section 1.5 of Chapter 1.

**Stoichiometry:** Varying ratios of CAB to substrate in the presence of $2.0 \times 10^{-2}$ 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:

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

(Here $R = -\text{CH}_3$ for mepheneisin and $-\text{OCH}_3$ for guaifenesin)

**Product analysis:** 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 petroleum ether (3:5 $v/v$) as the mobile phase. This analysis revealed the formation of oxidation product of mepheneisin as 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 further confirmed by GC-mass spectral analysis. The mass spectra showed a
molecular ion peak at 180 and 196 amu clearly confirming 3-(2-methylphenoxy)2-hydroxy-1-
propanal 3-(2-methoxyphenoxy)2-hydroxy-1-propanal respectively (Figures 4.1 and 4.2). All
other peaks observed in GC-MS can be interpreted in accordance with the observed structure.
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
[142] by TLC using petroleum ether, chloroform and 1-butanol (2:2:1 v/v) as the solvent, and
iodine as the detecting agent \( R_f = 0.88 \). It was further confirmed by GC-MS analysis. The
molecular ion peak in the mass spectrum at 157 amu (Figure 4.3) confirms
benzenesulfonamide.

**Kinetic results:** With the substrate in excess, at constant [HCl] and [substrate]_0, plots of
log[CAB] versus time were linear \( (R^2 > 0.9897) \) in both the cases, indicating a first-order
dependence of rate on [CAB]_0. Values of pseudo-first-order rate constants \( (k' s^{-1}) \) are given in
Table 4.1. 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 4.1). Plots of log \( k' \) versus log [substrate] were linear
(Figure 4.4; \( R^2 > 0.9858 \)) 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 (Figure 4.5; \( R^2 > 0.9955 \)) with y-intercepts, confirming the fractional-order
dependence on [substrate]_0.

The rate of reaction increased with increase in [HCl] (Table 4.2) and plots of log \( k' \)
versus log [HCl] were linear (Figure 4.6; \( R^2 > 0.9984 \)) 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 \([Cl^-] = 0.12 \text{ mol dm}^{-3}\)
using NaCl. A log-log plot of log \( k' \) versus log \([H^+]\) gave straight lines (Figure 4.7; \( R^2 >
0.9896 \)) with fractional slopes of 0.69 and 0.64 for mephenesin and guaifenesin, respectively.
At constant \([H^+] = 0.02 \text{ mol dm}^{-3}, \) maintained with HCl, the rate increased with addition of
NaCl and the kinetic orders were found to be 0.35 and 0.38 for these substrates (Figure 4.8; \( R^2 >
0.9875 \)). These results clearly confirm the fractional-orders with respect to \(H^+\) and \(Cl^-\) ions

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individually and the net order of unity on HCl concentration in both the cases. These results are summarized in Table 4.2.

Addition of the reduction product of CAB, benzenesulfonamide (5.0 x 10^-4 – 20.0 x 10^-4 mol dm^-3) had no effect on the rate (values are not given), indicating that it is not involved in the pre-equilibrium with the oxidant. Variation of ionic strength of the medium by adding NaClO_4 (0.1-0.3 mol dm^-3) did not influence the rate (values are not reported), indicating the involvement of non-ionic species in the rate determining step. Hence, no attempt was made to keep ionic strength of the medium constant during kinetic runs. Solvent isotope studies were made using D_2O. For mephenesin, k' was 2.75 x 10^-4 s^-1 in D_2O and 2.0 x 10^-4 s^-1 in H_2O, leading to a solvent isotope effect, k' (H_2O) / k' (D_2O), of 0.73 ± 0.05. The reaction rates were determined at different temperatures (298, 303, 308 and 313 K), keeping the other experimental conditions the same. Based on the Arrhenius plots of log k' versus 1/T (Figure 4.9; R^2 > 0.9836), activation energy and other thermodynamic parameters were computed for overall reactions of mephenesin and guaifenesin (Table 4.3). Absence of free radicals in the reaction mixture was shown by the negative test with acrylamide, as no polymerization was initiated even after an hour.

**Discussion:** Chloramine-B (PhSO_2NCINa) is analogous to CAT in aqueous solution and similar equilibria exist in acidified solutions [8].

\[
\begin{align*}
\text{PhSO}_2\text{NCINa} & \rightleftharpoons \text{PhSO}_2\text{NCI}^- + \text{Na}^+ \quad (4.2) \\
\text{PhSO}_2\text{NCI}^- + \text{H}^+ & \rightleftharpoons \text{PhSO}_2\text{NHCl} \quad (4.3) \\
2\text{PhSO}_2\text{NHCl} & \rightleftharpoons \text{PhSO}_2\text{NH}_2 + \text{PhSO}_2\text{NCl}_2 \quad (4.4)
\end{align*}
\]

\[
K_d = 6.1 \times 10^{-2} \text{ at } 25^\circ\text{C}
\]

\[
\begin{align*}
\text{PhSO}_2\text{NCl}_2 + \text{H}_2\text{O} & \rightleftharpoons \text{PhSO}_2\text{NHCl} + \text{HOCl} \quad (4.5) \\
\text{PhSO}_2\text{NHCl} + \text{H}_2\text{O} & \rightleftharpoons \text{PhSO}_2\text{NH}_2 + \text{HOCl} \quad (4.6)
\end{align*}
\]

\[
K_h = 4.9 \times 10^{-8} \text{ at } 25^\circ\text{C}
\]
The possible oxidizing species in acidified CAB solutions are thus PhSO$_2$NHCl, PhSO$_2$NCl$_2$ and HOCI. 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]$_0$ as seen from Eq. (4.4), which is contrary to the experimental observations. Equation (4.6) indicates that the hydrolysis is slight, and if HOCI is involved, a first-order retardation of rate by the added benzenesulfonamide (PhSO$_2$NH$_2$) is expected. Since no such effect is noticed, HOCI 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 [8], we can extend the same argument to CAB and PhSO$_2$NHCl can be assumed as 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 4.1, which predicts simultaneous catalysis by H$^+$ and Cl$^-$ ions [142].

```
(i) \( \text{PhSO}_2\text{NHCl} + H^+ + Cl^- \xrightleftharpoons{K_1 \text{ fast}} \text{PhSO}_2\text{NH}_2\text{Cl} \xrightarrow{ \text{Cl}^- } \)

(ii) \[ \begin{array}{c}
\text{O} & \text{CH}_2 & \text{C} & \text{O} \\
\text{R} & \text{H} & \text{H} & \text{Cl}
\end{array} \] \quad \xrightarrow{K_2 \text{ fast}} \quad \begin{array}{c}
\text{O} & \text{CH}_2 & \text{C} & \text{O} & \text{Cl} \\
\text{R} & \text{H} & \text{H} & \text{Cl}
\end{array}

(iii) \[ \begin{array}{c}
\text{O} & \text{CH}_2 & \text{C} & \text{O} \\
\text{R} & \text{H} & \text{H} & \text{Cl}
\end{array} \] \quad \xrightarrow{k_2 \text{ slow and rds}} \quad \begin{array}{c}
\text{O} & \text{CH}_2 & \text{C} & \text{O} & \text{Cl} \\
\text{R} & \text{H} & \text{H} & \text{Cl}
\end{array}
\]

(Here R = -CH$_3$ for mephenesin and –OCH$_3$ for guaifenesin)

Scheme 4.1 A detailed reaction scheme for the oxidation of mephenesin and guaifenesin by CAB in HCl medium.
Scheme 4.1 assumes the formation of a tight ion pair (X), which is an interhalogen intermediate species formed (step (ii)) from PhSO₂NHCl 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 PhSO₂NH₂. This complex decomposes in a rate determining step (step (iii)) to the final products.

The total effective concentration of CAB is [CAB]₀, then

\[ [\text{CAB}]_0 = [\text{PhSO}_2\text{NHCl}] + [X] + [X'] \quad (4.7) \]

From step (i) of Scheme 4.1,

\[ K_f = \frac{[X]}{[\text{PhSO}_2\text{NHCl}] [H^+] [Cl^-]} \quad (4.8) \]

\[ [\text{PhSO}_2\text{NHCl}] = \frac{[X]}{K_f [H^+] [Cl^-]} \quad (4.9) \]

From step (ii) of Scheme 4.1,

\[ K_2 = \frac{[X']}{[X] \text{[substrate]}}, \quad (4.10) \]

\[ [X] = \frac{[X']}{K_2 \text{[substrate]}} \quad (4.11) \]

By substituting for [X] from Eq. (4.11) into Eq. (4.9), we get

\[ [\text{PhSO}_2\text{NHCl}] = \frac{[X']}{K_f K_2 \text{[substrate]} [H^+] [Cl^-]} \quad (4.12) \]

By substituting for [X] and [PhSO₂NHCl] into Eq. (4.7), one obtains

\[ [\text{CAB}]_0 = \frac{[X']}{K_f K_2 [\text{substrate}] [H^+] [Cl^-]} + \frac{[X']}{K_2 [\text{substrate}]} + [X'] \quad (4.13) \]
From which,

\[
[X'] = \frac{K_f K_2 [\text{CAB}]_i \text{[substrate]} [H^+] [Cl^-]}{1 + K_f [H^+] [Cl^-] + K_f K_2 \text{[substrate]} [H^+] [Cl^-]}
\]  

(4.14)

From slow step (step (iii)) of Scheme 4.1,

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

(4.15)

By substituting for \([X']\) from Eq. (4.14) into Eq. (4.15), the following rate law is obtained

\[
\text{Rate} = \frac{K_f K_2 k_3 [\text{CAB}]_i \text{[substrate]} [H^+] [Cl^-]}{1 + K_f [H^+] [Cl^-] + K_f K_2 \text{[substrate]} [H^+] [Cl^-]}
\]

(4.16)

Rate law (4.16) is in accordance with the experimental results, wherein a first-order dependence of rate on \([\text{CAB}]_o\), and fractional orders on each \([\text{substrate}]_o\), \([H^+]\) and \([Cl^-]\) was noticed.

Since rate = \(k' [\text{CAT}]_o\), Eq. (4.16) can be transformed as:

\[
1 / k' = \frac{K_f K_2 k_3 \text{[substrate]} [H^+] [Cl^-]}{1 + K_f [H^+] [Cl^-] + K_f K_2 \text{[substrate]} [H^+] [Cl^-]}
\]

(4.17)

\[
1 / k' = \frac{1}{[\text{substrate}]} \left\{ \frac{1}{K_f K_2 k_3 [H^+] [Cl^-]} + \frac{1}{K_2 k_3} \right\} + \frac{1}{k_3}
\]

(4.18)

From the intercepts of the linear double reciprocal plots of \(1 / k'\) versus \(1 / \text{[substrate]}\) decomposition constants \((k_i)\) were calculated using Eq. (4.18) for both the substrates at 303 K. Since the rate was fractional in \([\text{substrate}]_o\), Michaelis-Menten type of kinetics [102] were adopted to study the effect of \([\text{substrate}]_o\) on rate at different temperatures. From the plots of \(1 / k'\) versus \(1 / \text{[substrate]}\), (Figure 4.10; \(R^2 > 0.9849\)) values of \(k_3\) were calculated for both the substrates at different temperatures. The activation parameters for the rate-determining step
were computed using Arrhenius plots of log $k_3$ versus $1 / T$ (Figure 4.11; $R^2 > 0.9823$). These results are summarized in Table 4.3.

The proposed mechanism is supported by an increase in rate in D$_2$O medium. For a reaction involving a fast equilibrium H$^+$ or OH$^-$ ion transfer, the rate increases in D$_2$O medium since D$_3$O$^+$ and OD$^-$ are a stronger acid and a stronger base respectively, than H$^+$ and OH$^-$ ions [64, 65]. In the present case, the observed solvent isotope effect of $k' (H_2O) / k' (D_2O) < 1$ is due to the greater acidity of D$_3$O$^+$ compared to H$_3$O$. However, the magnitude of acceleration is small (expected value is ~ 2 to 3 times greater) which can be attributed to the fractional order dependence of rate on [H$^+$]. Hence, this observation supports the proposed mechanism.

The magnitudes of the reaction rates and activation energies indicate that the guaifenesin oxidation is moderately faster when compared to mephenesin. The –CH$_3$ and –OCH$_3$ groups of mephenesin and guaifenesin are positive inductive in nature. In case of guaifenesin the methoxy group increases the electron density on 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 $\Delta G^\ddagger$ and $\Delta H^\ddagger$ indicate that the transition state is highly solvated, while the negative $\Delta S^\ddagger$ 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 (PhSO$_2$NH$_2$) is also in conformity with the proposed mechanism.
Conclusion: The present study concludes that:

- The kinetics of oxidation of mephenesin and guaifenesin by CAB in HCl medium follows the identical kinetics with a rate law, \(-d [\text{CAB}] /dt = k [\text{CAB}] [\text{substrate}]^x [\text{H}^+]^y [\text{Cl}^-]^z\), where \(x, y, z < 1\).
- Michaelis-Menten kinetics is observed and activation parameters for the rate determining step have been deduced.
- 3-(2-methylphenoxy)2-hydroxy-1-propanal and 3-(2-methoxyphenoxy)2-hydroxy-1-propanal have been characterized as the oxidation products for mephenesin and guaifenesin, respectively.
- The rate of oxidation of guaifenesin is faster in comparison with mephenesin.
- The proposed mechanism assumes the simultaneous catalysis of \(\text{H}^+\) and \(\text{Cl}^-\) ions.
- Based on the experimental results, a kinetic model has been proposed.
Table 4.1 Effect of variation of \([\text{CAB}]_0\) and \([\text{substrate}]_0\) on the rate of reaction at 303 K.

<table>
<thead>
<tr>
<th>(10^4 [\text{CAB}]_0) (mol dm(^{-3}))</th>
<th>(10^3 [\text{substrate}]_0) (mol dm(^{-3}))</th>
<th>(10^4 k' (s^{-1})) mephensin</th>
<th>(10^4 k' (s^{-1})) guaifenesin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.0</td>
<td>1.98</td>
<td>2.58</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>2.01</td>
<td>2.63</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>2.06</td>
<td>2.65</td>
</tr>
<tr>
<td>4.0</td>
<td>1.0</td>
<td>2.04</td>
<td>2.55</td>
</tr>
<tr>
<td>6.0</td>
<td>1.0</td>
<td>1.95</td>
<td>2.60</td>
</tr>
<tr>
<td>1.0</td>
<td>0.6</td>
<td>1.41</td>
<td>1.71</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>2.01</td>
<td>2.63</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
<td>3.16</td>
<td>4.24</td>
</tr>
<tr>
<td>1.0</td>
<td>3.0</td>
<td>3.98</td>
<td>5.42</td>
</tr>
<tr>
<td>1.0</td>
<td>4.0</td>
<td>5.51</td>
<td>7.27</td>
</tr>
<tr>
<td>1.0</td>
<td>8.0</td>
<td>8.92</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*Experimental conditions \([\text{HCl}] = 2.0 \times 10^{-2} \text{ mol dm}^{-3}\).*
Table 4.2 Effect of variation of $[\text{HCl}]$, $[\text{H}^+]$ and $[\text{Cl}^-]$ on the rate of reaction at 303 K.

<table>
<thead>
<tr>
<th>$10^3[\text{HCl}]$ (mol dm$^{-3}$)</th>
<th>$10^4k$ (s$^{-1}$) mephenesin</th>
<th>$10^4k$ (s$^{-1}$) guaifenesin</th>
<th>$10^4k'$ (s$^{-1}$) mephenesin</th>
<th>$10^4k'$ (s$^{-1}$) guaifenesin</th>
<th>$10^4k$ (s$^{-1}$) mephenesin</th>
<th>$10^4k$ (s$^{-1}$) guaifenesin</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>
<td>1.0</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>
<td>2.0</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>
<td>4.0</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>
<td>6.0</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>
<td>10.0</td>
</tr>
<tr>
<td>10.0</td>
<td>10.9</td>
<td>13.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Experimental conditions: $[\text{CAB}]_o = 1.0 \times 10^{-4}$ mol dm$^{-3}$; $[\text{Substrate}]_o = 1.0 \times 10^{-5}$ mol dm$^{-3}$. 
### Table 4.3 Effect of variation of temperatures on the reaction rate and values of activation parameters.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>10^4 k' (s⁻¹) (10^4 k₃ (s⁻¹))</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mephenesin</td>
<td>guaifenesin</td>
</tr>
<tr>
<td>298</td>
<td>1.12 (6.3)</td>
<td>2.09 (8.3)</td>
</tr>
<tr>
<td>303</td>
<td>2.01 (10.0)</td>
<td>2.63 (12.5)</td>
</tr>
<tr>
<td>308</td>
<td>4.12 (19.6)</td>
<td>4.97 (25.0)</td>
</tr>
<tr>
<td>313</td>
<td>5.24 (28.6)</td>
<td>6.85 (33.3)</td>
</tr>
<tr>
<td>Eₐ (kJ mol⁻¹)</td>
<td>82.8 (71.8)</td>
<td>72.0 (63.9)</td>
</tr>
<tr>
<td>ΔH° (kJ mol⁻¹)</td>
<td>80.1±0.01 (65.9±0.03)</td>
<td>69.5±0.09 (61.3±0.01)</td>
</tr>
<tr>
<td>ΔG° (kJ mol⁻¹)</td>
<td>95.8±0.23 (92.3±0.13)</td>
<td>94.6±0.07 (91.3±0.10)</td>
</tr>
<tr>
<td>ΔS° (JK⁻¹ mol⁻¹)</td>
<td>-49.8±0.69 (-86.7±0.01)</td>
<td>-82.9±0.19 (-98.5±0.01)</td>
</tr>
<tr>
<td>log A</td>
<td>14.4 ±0.04</td>
<td>12.7 ±0.05</td>
</tr>
</tbody>
</table>

*Experimental conditions: [CAB]₀ = 1.0 x 10⁻⁷ mol dm⁻³; [Substrate]₀ = 1.0 x 10⁻³ mol dm⁻³; [HCl] = 2.0 x 10⁻² mol dm⁻³.*

*Values in parenthesis refer to rate-determining step.*
Figure 4.1 GC-Mass spectrum of 3-(2-methylphenoxy)2-hydroxy-1-propanal with a molecular ion peak at 180 amu.

Figure 4.2 GC-Mass spectrum of 3-(2-methoxyphenoxy)2-hydroxy-1-propanal with a molecular ion peak at 196 amu.
Figure 4.3 GC-Mass spectrum of benzenesulfonamide with its molecular ion peak at 157 amu.

Figure 4.4 Plots of log $k'$ versus log [substrate]
Figure 4.5 Plots of $k'$ versus [substrate]

Figure 4.6 Plots of $\log k'$ versus $\log [\text{HCl}]$
**Figure 4.7** Plots of log $k'$ versus log [H$^+$]

**Figure 4.8** Plots of log $k'$ versus log [Cl$^-$]
Figure 4.9 Plots of $\log k'$ versus $1/T$

Figure 4.10 Double reciprocal plots of $1/k'$ versus $1/\text{[Substrate]}$
Figure 4.11 Plots of log $k_3$ versus $1 / T$