Mechanism of Oxidation of \((p\)-Substituted\) Phenylthio)acetic Acids with \(N\)-Chlorosaccharin

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Received 28 June 2010; Accepted 18 August 2010

Abstract: The kinetics of oxidation of (phenylthio)acetic acid (PTAA) with \(N\)-chlorosaccharin (NCSA) have been studied potentiometrically in 80:20 (v/v) acetonitrile-water medium at 298 K. The reaction is first-order each with respect to PTAA and NCSA and shows a negative dependence on \([\text{H}^+]\). NCSA itself is shown to be the active oxidizing species. Effects of ionic strength variation, added saccharin, added acrylonitrile, added NaCl and solvent composition variation have been studied. Effect of substituents on the reaction rate has been analysed by employing various \((p\)-substituted phenylthio)acetic acids. The electron-releasing substituent in the phenyl ring of PTAA accelerates the reaction rate while the electron-withdrawing substituent retards the rate. The excellently linear Hammett plot yields a large negative \(\rho\) value, supporting the involvement of a chlorosulphonium ion intermediate in the rate-determining step.

Keywords: Potentiometry, \(N\)-Chlorosaccharin, (Phenylthio)acetic acid, Oxidation, Chlorosulphonium ion.

Introduction

\(N\)-halo compounds find increasingly vast usage\(^1\) as oxidant for the synthesis of a variety of organic compounds as they are the sources of positive halogen and the mechanism of these reactions depends on the nature of active oxidising species, which in turn depends on the nature of halogen atom, the groups attached to the nitrogen atom and the reaction conditions. The list of \(N\)-halo compounds being extensively used for kinetic studies includes \(N\)-chloro- and \(N\)-bromo-benzenesulphonamide\(^2,3\), \(N\)-bromo- and \(N\)-chloroacetamide\(^4\), \(N\)-chloro- and \(N\)-bromosuccinimide\(^5,8\), \(N\)-chloronicotinimide\(^9\), \(N\)-chloro- and \(N\)-bromo-benzenamide\(^10\), \(N\)-chloro- and \(N\)-bromosaccharin\(^11,12\), chloramines-T\(^13\), etc. Investigations on kinetics of oxidation of hydroxy acids\(^{11a}\), alcohols\(^{11b}\), aldehydes\(^{12a}\), amino acids\(^{76}\), thiosemicarbazides\(^{7c}\), alcohols\(^9\) and sulphides\(^{8a}\) with \(N\)-halo compounds are a bound in literature. However, no study involving (phenylthio)acetic acids and \(N\)-chlorosaccharin has been reported so far. Keeping these points in mind, we thought it fit to study the kinetics and mechanism of oxidation of \((p\)-substituted phenylthio)acetic acids \((p\)-X-C\(_6\)H\(_4\)SCH\(_2\)COOH; \(X = \text{H, OCH}_3, \text{CH}_3, \text{F, Cl and NO}_2\)) with NCSA. Hereunder, the results obtained in the present study are presented.
Experimental
The (phenylthio)acetic acids were prepared by known methods\textsuperscript{14} and were purified by repeated recrystallisation from aqueous ethanol. Doubly distilled water was used throughout the experiment, the second distillation being from permanganate. AR grade \textit{N}-chlorosaccharin (Aldrich), perchloric acid (E.Merck) and GR grade sodium perchlorate were used as received. Acetonitrile was purified\textsuperscript{15} by refluxing with \textit{P}_2\text{O}_5.

Kinetic measurements
The kinetic runs were carried out in 80\% acetonitrile - 20\% water (v/v) solvent mixture in acid medium, the acid strength being maintained by the addition of HClO\textsubscript{4} and the ionic strength by NaClO\textsubscript{4}. The kinetics were followed potentiometrically in a manner as described earlier\textsuperscript{16}. The emf of the cell was measured periodically using an Equip-Tronics potentiometer while the reaction mixture was magnetically stirred continuously. The temperature of the reaction mixture was maintained at the desired value to an accuracy of $\pm 0.1 \, ^\circ\text{C}$ by circulating thermostated water in the reaction vessel. The pseudo first-order rate constants ($k_{\text{obs}}$) were calculated from the slopes of $\text{ln}(E_t - E_\infty)$ versus time plots ($r > 0.990$) and the results were reproducible to an accuracy of $\pm 5\%$. The second-order rate constants ($k_2$) were obtained as $k_{\text{obs}}/[\text{PTAA}]$.

Product analysis
In a typical experiment, the reaction mixture containing 50 fold excess of PTAA over NCSA was kept overnight under stirring. The solvent was removed by distillation. The residue was then extracted with ether. The extract was dried over anhydrous sodium sulphate and the solvent evaporated. The residue was subjected to TLC analysis on a silica gel plate developed in a solvent system of \textit{n}-butanol-acetic acid-water (40-10-50\%, upper layer was used). The residue gave two spots, which were made visible by exposure to iodine; one corresponding to (phenylthio)acetic acid ($R_f = 0.84$) and the other to phenylsulphinylacetic acid ($R_f = 0.45$). Further, the IR spectra of the residue showed an intense absorption band at 1050 cm\textsuperscript{-1}/units characteristc of SO stretching frequency. The formation of corresponding phenylsulphinylacetic acid as the product was also confirmed with other (\textit{p}-substituted phenylthio)acetic acids also.

Stoichiometry
In a typical experiment, a reaction mixture containing 10 times excess of NCSA over PTAA was prepared and allowed to react overnight. Then the unreacted NCSA was estimated, which established a 1:1 stoichiometry between NCSA and PTAA, as represented in Scheme 1.

\begin{equation}
\text{PhSCH}_2\text{COOH} + \text{Cl}^+ + \text{H}^+ \rightarrow \text{PhSOCH}_2\text{COOH} + \text{HN}^+ + \text{Cl}^-
\end{equation}

Scheme 1

Results and Discussion
The kinetics of oxidation of PTAA by NCSA was carried out potentiometrically in 80:20 (v/v) acetonitrile-water mixture at 298 K in the presence of perchloric acid at constant ionic strength under pseudo first-order conditions ([PTAA] $>>$ [NCSA]). The ionic strength of the medium
was maintained by the addition of NaClO₄. The pseudo first-order rate constants, \( k_{obs} \) and the second-order rate constants, \( k_2 \) at different initial concentrations of NCSA, PTAA and H⁺ are presented in Table 1. At constant initial concentration of PTAA, \( k_{obs} \) values remain almost constant upon varying the initial concentration of NCSA; this coupled with the observation of linear \( \ln(E_t - E_\infty) versus \) time plots ensures that the order of the reaction in NCSA is one. Also, the rate data in Table 1 point out that \( k_{obs} \) value increases linearly in a first-order fashion with increase in the initial concentration of PTAA. Similar trend is observed in the \( k_{obs} \) and \( k_2 \) values for the oxidation of other (p-substituted phenylthio)acetic acids. The constancy of \( k_2 \) at varying initial concentrations of PTAA (Table 1) and the excellent linearity of the plot of log \( k_{obs} \) versus log \([PTAA]\) with unit slope (slope = 1.013 ± 0.003, \( r = 0.999 \)) point out that the reaction follows first-order kinetics with respect to [PTAA]. Also, the plot of \( 1/k_{obs} versus 1/[PTAA] \) is linear passing through origin (Figure 1; \( r = 0.999 \)), thus excluding a Michaelis-Menten type of mechanism.

Table 1. Pseudo-first-order and second-order rate constants for the oxidation of PTAA by NCSA in aqueous acetonitrile at 298 K \(^{a,b}\)

<table>
<thead>
<tr>
<th>([PTAA]_o), M</th>
<th>([NCSA]_o), M</th>
<th>([H^+]_o), M</th>
<th>(10^4 k_{obs} ), s⁻¹</th>
<th>(10^4 k_2), M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>1.4</td>
<td>5.23 ± 0.36</td>
<td>52.3 ± 3.6</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>1.4</td>
<td>10.6 ± 0.9</td>
<td>52.9 ± 4.3</td>
</tr>
<tr>
<td>4.0</td>
<td>1.0</td>
<td>1.4</td>
<td>21.2 ± 1.5</td>
<td>53.1 ± 3.8</td>
</tr>
<tr>
<td>7.0</td>
<td>1.0</td>
<td>1.4</td>
<td>37.4 ± 3.0</td>
<td>53.4 ± 4.3</td>
</tr>
<tr>
<td>10.0</td>
<td>1.0</td>
<td>1.4</td>
<td>54.1 ± 4.9</td>
<td>54.1 ± 4.9</td>
</tr>
<tr>
<td>2.0</td>
<td>0.4</td>
<td>1.4</td>
<td>10.1 ± 0.9</td>
<td>50.7 ± 4.7</td>
</tr>
<tr>
<td>2.0</td>
<td>0.7</td>
<td>1.4</td>
<td>10.3 ± 0.8</td>
<td>51.3 ± 4.1</td>
</tr>
<tr>
<td>2.0</td>
<td>1.3</td>
<td>1.4</td>
<td>10.4 ± 0.9</td>
<td>52.2 ± 4.4</td>
</tr>
<tr>
<td>2.0</td>
<td>1.6</td>
<td>1.4</td>
<td>10.6 ± 1.0</td>
<td>52.9 ± 5.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>0.2</td>
<td>15.9 ± 1.6</td>
<td>79.5 ± 8.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>0.6</td>
<td>13.9 ± 1.0</td>
<td>69.5 ± 5.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>11.9 ± 1.2</td>
<td>59.5 ± 6.0</td>
</tr>
<tr>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>8.37 ± 0.73</td>
<td>41.5 ± 3.7</td>
</tr>
</tbody>
</table>

\(^a\)As determined by a potentiometric technique following the disappearance of NCSA; the error quoted in \( k \) values is the 95% confidence limit of Student's t test \(^{17}\). \(^b\)General conditions: \([I]\) = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water. \(^c\)Estimated from pseudo first-order plots over 60% reaction. \(^d\)Individual \( k_2 \) values estimated as \( k_{obs}/[PTAA]_o \).

Figure 1. Double reciprocal plot for the oxidation of PTAA with NCSA
The $k_{\text{obs}}$ values measured at different initial concentrations of $H^+$ for the oxidation of PTAA (Table 1) reveal that the reaction rate decreases slightly with increase in the concentration of $H^+$. The plot of $k_2$ versus $[H^+]$ is linear ($r = 0.996$) with a negative slope (Figure 2), establishing the inhibitory role of $H^+$. The result obtained in the present study can be rationalized if NCSA itself is considered to be the oxidizing species. A similar conclusion has been arrived at in the oxidation of alkyl phenyl and diphenyl sulphides with NCS$^6$.

![Image](image.png)

**Figure 2.** Effect of $[H^+]$ in the oxidation of PTAA with NCSA.

The rate of the reaction is not significantly affected by the change in the ionic strength ($I$) of the medium (Table 2) brought about by the addition of sodium perchlorate, pointing out the participation of a neutral species as a reactant in the rate-determining step. The addition of saccharin has no effect on the rate of oxidation (Table 2), suggesting that the step in which saccharin is formed as one of the products is not reversible.

**Table 2.** Influence of ionic strength and saccharin on reaction rate for the oxidation of PTAA with NCSA$^a$

<table>
<thead>
<tr>
<th>$[I]$, M</th>
<th>$10^4k_{\text{obs}}, \text{s}^{-1}$</th>
<th>$10^4[\text{saccharin}], \text{M}$</th>
<th>$10^4k_{\text{obs}}, \text{s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.216</td>
<td>8.57 ± 0.76</td>
<td>0</td>
<td>10.6 ± 0.9</td>
</tr>
<tr>
<td>0.359</td>
<td>9.33 ± 0.88</td>
<td>1.0</td>
<td>10.3 ± 1.0</td>
</tr>
<tr>
<td>0.501</td>
<td>10.6 ± 0.9</td>
<td>3.0</td>
<td>10.5 ± 0.9</td>
</tr>
<tr>
<td>0.609</td>
<td>11.5 ± 1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$General conditions: $[\text{NCSA}] = 0.0001 \text{ M}$; $[\text{PTAA}] = 0.002 \text{ M}$; $[H^+] = 0.00014 \text{ M}$; $[I] = 0.501 \text{ M}$ unless otherwise stated; Solvent = 80:20 (v/v) acetonitrile-water

The involvement of free-radical intermediates during the reaction can be excluded as the rate constant is not affected by the addition of acrylonitrile (Table 3). The added NaCl has no effect on the rate of oxidation (Table 3), establishing that the course of the oxidation does not involve chloronium ion or molecular chlorine as active species. An increase in the water content of acetonitrile-water solvent system causes an increase in the rate of oxidation (Table 3). A plot of $\log k_{\text{obs}}$ versus $1/\varepsilon$ is linear (Figure 3; $r = 0.996$) with a negative slope indicating that the transition state is more polarized than the two reactants together in the initial state.
Table 3. Influence of added acrylonitrile (AN), NaCl and solvent composition on reaction rate for the oxidation of PTAA with NCSA

<table>
<thead>
<tr>
<th>[AN], M</th>
<th>$10^4 k_{obs}$, s$^{-1}$</th>
<th>[NaCl], M</th>
<th>$10^2 k_{obs}$, s$^{-1}$</th>
<th>% Water (v/v)$^b$</th>
<th>$10^2 k_{obs}$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.6 ± 0.9</td>
<td>0</td>
<td>10.6 ± 0.9</td>
<td>20</td>
<td>10.6 ± 0.9</td>
</tr>
<tr>
<td>0.003</td>
<td>10.6 ± 1.0</td>
<td>0.001</td>
<td>10.7 ± 0.9</td>
<td>30</td>
<td>26.5 ± 2.0</td>
</tr>
<tr>
<td>0.006</td>
<td>10.7 ± 1.0</td>
<td>0.002</td>
<td>10.5 ± 1.0</td>
<td>40</td>
<td>55.6 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td></td>
<td>10.8 ± 0.9</td>
<td>50</td>
<td>75.7 ± 6.9</td>
</tr>
</tbody>
</table>

$^a$General conditions: [NCSA] = 0.0001 M; [PTAA] = 0.002 M; [H$^+$] = 0.00014 M; [I] = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water unless otherwise stated; $^b$Rest was acetonitrile

Figure 3. Plot of log $k_{obs}$ versus $1/\epsilon$ for the oxidation of PTAA with NCSA

The effect of substituents at the 4-position of the phenyl ring of PTAA was also studied. The pseudo first-order and second-order rate constants for the oxidation of these ($p$-substituted phenylthio)acetic acids with NCSA at 298 K are collected Table 4. Electron-releasing substituents in the phenyl ring accelerate the rate, while electron-donating substituents produce the opposite effect. The log $k_2$ values show excellent correlation with $\sigma_p$ values (Figure 4; slope = -3.12 ± 0.08, r = 0.998). The negative value of $r$ indicates an accumulation of positive charge at the reaction sulphur centre, while the magnitude of $r$ value indicates the extent of charge development on the sulphur atom in the transition state of rate-determining step.

Table 4. Pseudo-first-order and second-order rate constants for the oxidation of thioacids, X-C$_6$H$_5$SCH$_2$COOH by NCSA

| X      | $10^4 k_{obs}$, s$^{-1}$ | $10^2 k_2$, M$^{-1}$s$^{-1}$ |
|--------|-----------------|-----------------|--------|-----------------|
| OMe    | 104 ± 9         | 52.0 ± 4.5      |
| Me     | 42.4 ± 2.8      | 21.2 ± 1.4      |
| H      | 10.6 ± 0.9      | 5.29 ± 0.43     |
| F      | 7.06 ± 0.54     | 3.53 ± 0.27     |
| Cl     | 2.16 ± 0.18     | 1.08 ± 0.09     |
| NO$_2$ | 0.05 ± 0.00     | 0.03 ± 0.00     |

$^a$General conditions: [NCSA]$_o$ = 0.0001 M; [Thioacid] = 0.002 M; [H$^+$]$_o$ = 0.00014 M; Ionic strength = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water mixture
Mechanism

In earlier studies with $N$-halo compounds in aqueous acid medium, $X^\bullet$, $X_2$, HOX, $H_2O^\bullet X$ and $>NXH^\bullet$ are discussed\textsuperscript{18} to be the probable reactive species. The observation that the reaction rate is not affected by added saccharin excludes the possibility of HOCl or $H_2O^\bullet Cl$ being the reactive species\textsuperscript{19,22}. The reaction rate is independent of the added NaCl concentration, which indicates that neither chloronium ion nor molecular chlorine is involved in the rate-determining step of the reaction\textsuperscript{19,23}. Also, the previous studies illustrate that a first-order dependence of rate of oxidation on $[H^\bullet]$ is attributed to the involvement of $H_2O^\bullet X$ active species\textsuperscript{19}, a zero-order dependence to the involvement of the HOX active species\textsuperscript{20} and a fractional-order dependence to the involvement of the $>NXH^\bullet$ active species\textsuperscript{6,21}. In the present investigation, therefore, the negative fractional-order dependence on $[H^\bullet]$ establishes the involvement of NCSA itself as reactive species. Based on these kinetic observations, the following mechanism (Scheme 2) has been proposed.

\[
\begin{align*}
\text{SCH}_2\text{COOH} + Cl^\bullet + H^\bullet & \quad \text{fast} \quad \text{SCH}_2\text{COOH} + Cl^\bullet + HCl \quad \text{H}^\bullet + Cl^- \\
\text{SCH}_2\text{COOH} + Cl^\bullet + H_2O & \quad \text{fast} \quad \text{SCH}_2\text{COOH} + Cl^\bullet + HCl \quad \text{H}^\bullet + Cl^\bullet + H^\bullet + Cl^- \\
\text{SCH}_2\text{COOH} + Cl^\bullet + H^\bullet & \quad \text{fast} \quad \text{SCH}_2\text{COOH} + Cl^\bullet + HCl \quad \text{H}^\bullet + Cl^- \\
\end{align*}
\]
The mechanism in Scheme 2 accounts for the decrease in rate of oxidation with increasing [H$^{+}$]. When the concentration of H$^{+}$ in the reaction solution is increased, more and more NCSA becomes inactive in the form of NCSAH$^{+}$ species (eq. 1), thereby causing a decrease in the rate of reaction. Similar conclusion has been arrived at in the studies of oxidation of acetophenone$^{24}$, aspirin$^{25}$ and $\alpha$-hydroxy acids$^{26}$ by NBP, amino acids by NBS$^{27}$, secondary amines by CAT$^{27}$ and L-tyrosine by BAB$^{28}$, where the N-halo reagent itself has been proposed as reactive oxidizing species.

The rate law can be expressed as

$$\text{Rate} = k_2 [\text{NCSA}] [\text{PTAA}]$$

(5)

The high $\rho$ value (-3.12) obtained in the present study provides support for the chlorosulphonium ion intermediate, (CH$_2$COOH)PhS$^+$Cl in the reaction. This conclusion is further supported by the fact that the present $\rho$ value is analogous to those reported for the oxidations of organic sulphides with NCS$^+$ (-3.33), NBA$^{29}$ (-2.37), NBB$^{30}$ (-3.18), CAT$^{31}$ (-4.25) and Br$_2^{18b}$ (-3.2), where the intermediacy of such halosulphonium ions has been proposed.

Conclusion

The NCSA oxidation of ($p$-substituted phenylthio)acetic acids follows a S$_N$2 type mechanism, in which NCSA itself is the oxidizing species. The proposed mechanism has been well substantiated by substituent effect studies.

Acknowledgment

NMIA thanks UGC, Hyderabad for financial assistance in the form of Minor Research Project. The authors thank the college management for providing the necessary facilities.

References

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