Kinetics of Oxidation of L-Cysteine by Cobalt(III), Iron(III), and Chromium(III) Complexes of Salicylaldiminato Ligands

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Abstract
Kinetics of oxidation of L-cysteine by penta-coordinated Co(III), Fe(III), and Cr(III) complexes of salicylaldiminato ligands have been studied in aqueous solutions. Metal complexes of N-salicylidinecyclohexylamine, N-salicylidinisopropylaniline, N-salicylidinnaphthylamine, N-(4-sulfonitsalicylidine)cyclohexylamine, and N-(4-sulfonatesalicylidine)-2-isoprpylaniline were used in the studies. Measurements were run at constant temperature (25ºC), constant ionic strength (0.20 M), and constant pH (7.0) under pseudo-first order conditions, in which the concentration of cysteine is around two orders of magnitude greater than that of metal complex. The observed rate constant was determined by following the change in absorbance of reaction mixture at a predetermined wavelength with time. Results show that the rate of oxidation depends on steric factor and the electron withdrawing / releasing ability of the ligand bound to the metal ion. It also depends on the metal center. The Co(III) complexes were found to have the highest rates due to higher reduction potential of Co(III).

Keywords: Kinetics; Cysteine; Salicylaldiminato ligands; Co (III); Fe(III); Cr(III).

Introduction
Salen based complexes are fundamental class of compounds in coordination chemistry and they were introduced by Pfeiffer et al. in 1933[1]. Since then, they have been studied extensively and more than 2500 complexes have been synthesized and reported. Interest in salen type complexes intensified in 1990 when the groups of Jacobsen and Katsuki discovered the enanothioselective epoxidation of unfunctionalized alkenes using chiral Mn(salen) complexes as catalysts[2]. Since then, extremely wide variety of reactions catalyzed by salen complexes has been investigated. These include epoxidation of alkene[3], hydrolytic kinetic resolution of epoxides[4], intermolecular hydroamination of allenes[5], and vinyl polymerization of norbornene[6].

Oxidation of L-cysteine have been the subject of several studies in recent years, using various kinetics techniques and various transition metal complexes have been used[7-17].

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As an extension of our previous studies\cite{18-24} on both kinetics and catalytical application, to widen our knowledge about the oxidation of biologically important amino acids, we report the kinetics of oxidation of L-cysteine by a new series of bidentate nitrogen-oxygen ligands salen of five-coordinated cobalt(III), iron(III), and Cr(III) complexes synthesized in our laboratories (Figure 1). For each metal ion complex, observed rate and rate constant of reaction were determined. Effects on reaction's rates due to nature and type of auxiliary groups of ligands, the backbone structures of the complex and the nature of metal center are discussed.

![Figure 1: Structures for salen based complexes 1-9 used in the present study.](image)

**Experimental**

*Materials, analysis and synthesis of ligands and complexes:* L-cysteine (minimum assay 99%) was purchased from BDH Laboratory Supplies (England) and was used without further purification. CoCl$_2$.6H$_2$O, CrCl$_3$.6H$_2$O, and FeCl$_2$.6H$_2$O were purchased from (ACROS). Elemental analysis and Mass spectra (EI) measurements, for RSSR, were performed in our laboratories using a EURO EA 3000 and a Shimadzu-QP5050A,
respectively. Synthesis and characterizations of the ligands and their complexes with Co(III), Fe(III), and Cr(III) are mentioned in our recent publication\[19\].

**Kinetic measurements:** Freshly prepared aqueous solutions of the desired concentrations of the complex and L-cysteine were used for kinetic study. Measurements were carried out using a Diode Array Spectrophotometer model 8453E from HP Agilent Technologies. Reactions were monitored by following the change in absorbance of reaction mixture with time at a predetermined wavelength, which was determined by recording the absorption spectral curves for the metal complex (TMC) alone and for its mixture with cysteine (Cys) after completion of reaction. The wavelength of maximum absorbance difference ($\lambda_{mad}$) between the absorption of TMC and the mixture was selected. A list of $\lambda_{mad}$ for various complexes is shown in table 1. All reactions were studied under pseudo-first order condition, at which the concentrations of Cys [$10^{-2}$ – $10^{-1}$ mol dm$^{-3}$] chosen to be 1–2 orders of magnitude larger than those of TMC [$10^{-4}$ – $10^{-2}$ mol dm$^{-3}$]. Ionic strength of the solutions was kept constant at 0.20 mol dm$^{-3}$ using NaClO$_4$. Temperature of solution and its pH were both maintained constant at 25± 0.1°C and 7.0 ± 0.1, respectively.

**Table 1:** Observed rates, $k_{obs}$, for oxidation of L-cysteine by salen complexes of Co(III) and Fe (III), and Cr(III), in aqueous medium at 25°C, pH = 7.0 and ionic strength = 0.20 mol dm$^{-3}$.

<table>
<thead>
<tr>
<th>No.</th>
<th>Complex</th>
<th>Ligand</th>
<th>$\lambda_{mad}$ (nm)</th>
<th>$k_{obs}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co(SCHA)$_2$Cl]</td>
<td>SCHA</td>
<td>320</td>
<td>1.46 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>2</td>
<td>[Co(SIPA)$_2$Cl]</td>
<td>SIPA</td>
<td>326</td>
<td>3.86 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>3</td>
<td>[Co(SNA)$_2$Cl]</td>
<td>SNA</td>
<td>480</td>
<td>very slow</td>
</tr>
<tr>
<td>4</td>
<td>[Co(SSCHA)$_2$Cl]</td>
<td>SSCHA</td>
<td>450</td>
<td>7.22 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>5</td>
<td>[Co(SSIPA)$_2$Cl]</td>
<td>SSIPA</td>
<td>350</td>
<td>1.48 $\times$ 10$^{-2}$</td>
</tr>
<tr>
<td>6</td>
<td>[Fe(SCHA)$_2$Cl]</td>
<td>SCHA</td>
<td>500</td>
<td>3.03 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>7</td>
<td>[Fe(SIPA)$_2$Cl]</td>
<td>SIPA</td>
<td>460</td>
<td>6.62 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>8</td>
<td>[Fe(SNA)$_2$Cl]</td>
<td>SNA</td>
<td>504</td>
<td>very slow</td>
</tr>
<tr>
<td>9</td>
<td>[Cr(SIPA)$_2$Cl]</td>
<td>SIPA</td>
<td>310</td>
<td>2.10 $\times$ 10$^{-3}$</td>
</tr>
</tbody>
</table>

SCHA: N-salicylidinecyclohexylamine  
SIPA: N-salicylidinisopropylaniline  
SNA: N-salicylidinnaphthylamine,  
SSCHA: N-(4-sulfonitsalicylidine)cyclohexylamine  
SSIPA: N-(4-sulfonatesalicylidine)-2-isoprylaniline  
* Experimental errors are estimated to be 10%.
Results and Discussion

Oxidation of cysteine (RSH) leads to formation of cystine (RSSR), as shown below:\[1\]:

\[2 \text{RSH} \rightarrow \text{RSSR} + 2\text{H}^+ + 2\text{e}^-\]  \hspace{1cm} (1)

Estimation of residual oxidant suggested that two moles of cysteine consume two moles of transition metal complex (TMC), such that

\[2 [\text{M}^{III}(L-L)_{2}\text{Cl}] + 2 \text{RSH} \rightarrow 2 [\text{M}^{II}(L-L)_{2}] + \text{RSSR} + 2 \text{HCl}\]  \hspace{1cm} (2)

The rate of reaction is given by

\[
\text{Rate} = k [\text{Cys}]^a [\text{TMC}]^b
\]

Where \(k\) is the reaction rate constant and \((a)\) & \((b)\) are orders of reaction with respect to concentrations of Cys and TMC, respectively. In the present study, it was found that reaction rate depends on first power of concentration of both substrate and oxidant, i.e., \(a \approx b \approx 1\). This is in agreement with previous studies\[6,9,13-18\]. Since all M(III) complexes are one-electron oxidants, then, oxidation of cysteine is expected to give a radical intermediate, as shown below:

\[
\begin{align*}
\text{RSH} & \approx \text{RS}^- + \text{H}^+ \\
\text{RS}^- & \rightarrow \text{RS}^- \\
2\text{RS}^- & \rightarrow \text{RSSR}
\end{align*}
\]

(4)

Under pseudo-first order conditions in which \([\text{Cys}] \gg [\text{TMC}]\), the concentration of cysteine is essentially constant throughout the reaction. Reaction rate is then given by

\[
\frac{d[\text{TMC}]}{dt} = k_{\text{obs}} [\text{TMC}]^b
\]

\hspace{1cm} (5)

where \(k_{\text{obs}}\) is the observed rate constant of the reaction, given by

\[k_{\text{obs}} = k [\text{Cys}]^a\]  \hspace{1cm} (6)

Where \(k\) is the rate constant for reaction (2) above.

For a first-order dependence of reaction rate on [TMC], experimental absorbance-time data pairs were fit to the exponential function:

\[
\ln \left( \frac{A_t - A_\infty}{A_0 - A_\infty} \right) = -k_{\text{obs}} t
\]

or,

\[
\ln \left( \frac{A_t - A_\infty}{A_0 - A_\infty} \right) = -k_{\text{obs}} t
\]

(7)

Where \(A_t\) is the absorbance of TMC at a given time (t) through the reaction, \(A_0\) is its initial absorbance (t = 0) and \(A_\infty\) is the final absorbance of the reaction mixture at the end of the reaction, (t = \(\infty\)), at which there is no significant change in the absorbance of the mixture.

For all reactions studied, a plot of \(\ln [(A_t - A_\infty)/(A_0 - A_\infty)]\) versus time gave an increasing straight line with regression coefficient \(R^2 \geq 0.99\). From which the value of \(k_{\text{obs}} /\text{s}^{-1}\) was obtained. A plot of \(\ln k_{\text{obs}}\) versus \([\text{Cys}]\) gives the orders of reaction with respect to concentration of Cys (a), from the slope, and the rate constant, \(k /\text{dm}^3\text{mol}^{-1}\text{s}^{-1}\), from the intercept. Representative results of Abs. vs. time, and \(\ln \left( \frac{A_t - A_\infty}{A_0 - A_\infty} \right)\) vs. time are
shown in figure 2. Kinetics results for oxidation of L-cysteine by various salen complexes are shown in table 1.

![Figure 2:](image)

(a) Abs. vs. time for the oxidation of cysteine by [Co(SIPA)2Cl].

(b) \( \ln \left( \frac{A_t - A_\infty}{A_0 - A_\infty} \right) \) vs. time for the oxidation of cysteine by [Co(SIPA)2Cl].

Where \( A_t \), \( A_0 \) and \( A_\infty \) are defined in the text.

Different rates for different ligands and metal centers were obtained. The observed rate constant is found to depend strongly on the electronic factor of the ligand, regarding its electron withdrawing or releasing ability. It also depends on the size of the ligand and the nature of metal center. This dependence can be explained by reaction mechanism and geometric factor.

It is difficult to decide which oxidation mechanism is dominant. If ligand in the complex has extra lone pair(s) to form "links" with cysteine and/or if the geometry around the metal center have enough space for cysteine to bind to this ligand, then the reaction is more likely to proceed via an inner-sphere mechanism\[^6\]. In this case, a substitution reaction occurs that produces cysteine and TMC linked together. Then, a transfer of an electron in the oxidation process occurs followed by separation of the products. On the other hand, if the ligand has no extra lone pairs with which to form bonds to cysteine, or when there is a "closed" or crowded geometry around metal center, the ligands are tightly held and there is no change in the coordination sphere on the reaction. In this case, the reaction proceeds by outer-sphere electron transfer mechanism\[^25\].

Due to the availability of a vacant site of the penta coordinated complex for cysteine to approach, we believe that all reactions studied in the present work proceed via an inner-sphere mechanism. The ligand substitution occurs through an associative mechanism, which involves formation of an intermediate that includes removal of the chlorides in the TMC and forming RSSR. The reaction first proceeds by replacement of the chloride ion by a cysteine anion. This step is too fast to be measured on our instrument. A reductive elimination is then occurs to form the square planner M(II) complex and a white precipitate indicates the presence of cystine (RSSR), as shown in
Eqn. (2) above. This step is believed to be the rate-determining step. And its rate is what we intend to measure in the present work. The final products were isolated and characterized. The white precipitate was characterized by EA (calcd. C 29.99, H 5.03, N 11.66, S 26.69; found C 30.01, H 4.88, N 10.99, S 26.06), and mass spectroscopy (GC/MS (El, 70 eV): m/z (%) = 243 [M⁺], 76). This proves the formation of RSSR, which supports the suggested mechanisms for the reaction, as shown in figure 3.

![Figure 3: Suggested mechanism for oxidation of L-cysteine by salen complexes.](image)

RE refers to reductive elimination process.

For Schiff salen based complexes, with two donor atoms N and O, they exert different electronic effects on the transition metal complex. The phenolate oxygen is known to be a hard electron donor, which stabilizes the higher oxidation state of metal center, while the imine nitrogen is a soft electron donor that stabilizes the lower oxidation state of the metal. Therefore, the rate of electron transfer from Cys to M(III) should depend on the steric factor, nature of ligands regarding its electron withdrawing / donating ability and the nature of metal center.

Kinetic results show that the observed reaction rate constant among cobalt complexes increases in the order: \([\text{Co(SSIPA)}_2\text{Cl}] (5) \gtrsim [\text{Co(SSCHA)}_2\text{Cl}] (4) \gtrsim [\text{Co(SIPA)}_2\text{Cl}] (2) \gtrsim [\text{Co(SCHA)}_2\text{Cl}] (1) \gtrsim [\text{Co(SNA)}_2\text{Cl}] (3)\). The relative rates can be explained by both electronic and steric factors. Based on electronic factor, the stronger the electronic withdrawing ability of the ligand, the more stability it will provide to metal center. This will facilitate the reduction process of ion center and makes rate faster. The presence of strong electron withdrawing group (-SO₃) in (5) and (4) makes their observed reaction rates higher than the rest of the other Co(III) complexes. Also, the presence of an additional electron withdrawing phenyl group in (5), makes its rate faster than (4) which has an electron donating cyclohexyl group. Additionally, the presence of the bulky isopropyl group on the phenyl ring in (5) weakens the electronic donating ability of imine nitrogen towards the metal center²⁶ making it more susceptible to accept electrons from cysteine, hence, faster reaction. Therefore, in presence of an electron donating group attached to imine nitrogen in the ligand, the larger its size the weaker is the donating ability towards the metal center, hence, faster reaction rate with cysteine. This steric factor plays a more important role than the electronic factor for complexes (1), (2) and (3). The difference in the electronic factor for the three ligands is not large²⁵, however, their sizes differ much and increase in the
order: phenylisopropyl \( \rightarrow \) cyclohexyl \( \rightarrow \) naphthyl group. This explains the trend in reaction rate: \( (2) \) \( \rightarrow \) \( (1) \) \( \rightarrow \) \( (3) \). The same trend is observed for iron complexes. The observed reaction rate for Fe(III) complexes increases in the order: \([\text{Fe(SIPA)}_2\text{Cl}] (7) \) \( \rightarrow \) \([\text{Fe(SCHA)}_2\text{Cl}] (6) \) \( \rightarrow \) \([\text{Fe(SNA)}_2\text{Cl}] (8) \).

To check the effect of metal center on reaction rate, one needs to compare the overall rate constants \( (k / \text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}) \), which is independent of [TMC], for Co(III), Fe(III), and Cr(III) complexes having the same ligand. Complexes of these metal ions of SIPA were chosen. The rate constant was calculated using Eqn. (6) and found to increase in the order: \([\text{Co(SIPA)}_2\text{Cl}] (2) \) \( \rightarrow \) \([\text{Fe(SIPA)}_2\text{Cl}] (7) \) \( \rightarrow \) \([\text{Cr(SIPA)}_2\text{Cl}_2] (9) \). The rate constant for Co(III) complex \((4.90 \times 10^{-1} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1})\) is higher than that for Fe(III) complex \((6.73 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1})\), which is turn higher than that for Cr(III) complex \((3.11 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1})\). This trend has to do with the standard reduction potential of these metal ions. \( E^0[\text{Co}^{+3} \rightarrow \text{Co}^{+2}] = 1.8 \text{ V} \) \( \rightarrow \) \( E^0[\text{Fe}^{+3} \rightarrow \text{Fe}^{+2}] = 0.77 \text{ V} \) \( \rightarrow \) \( E^0[\text{Cr}^{+3} \rightarrow \text{Cr}^{+2}] = -0.41 \text{ V} \). Reduction of Cr(III) to the unstable Cr(II) has a negative reduction potential. This makes its reaction with cysteine the slowest.

**Conclusion**

Rates of oxidation of L-cysteine by Co (III), Fe(III) and Cr(III) complexes of various salen ligands were studied. The nature of substituent in ligands plays a role in determining reaction rates due to both electronic and steric factors. Factors which facilitate electron transfer making the oxidation process easier. Rates were found to be faster for complexes having an electron withdrawing groups in the ligands. In presence of an electron donating group, the bulkier the group the weaker is its donating ability towards the metal center and the faster is the reaction rate. Finally, reaction rates were found to depend on the nature of metal center, regarding its standard reduction potential. Among different metal centers having the same ligand, reaction rate increases as the standard reduction potential of the metal center increases.

**References**