Kinetics of Oxidation of L-Cysteine by \( \text{trans-} \) and \( \text{cis-}\text{Co}^{\text{III}} \) and \( \text{Fe}^{\text{III}} \) Complexes based on \( \alpha-\) and \( \gamma\)-Diimine Schiff Base Ligands

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Abstract. Kinetics of oxidation of \( \text{L-cysteine by Co}^{\text{III}} \) and \( \text{Fe}^{\text{III}} \) complexes based on \( \alpha-\) and \( \gamma\)-dimine Schiff base ligands were studied in aqueous solution. Pairs of \( \text{trans-} \) and \( \text{cis-} \) isomers of the metal complexes were used in the studies. Kinetic measurements were performed at 25 °C and constant pH and ionic strength under pseudo-first-order condition, in which the concentration of cysteine was around two orders of magnitude greater than that of the metal complex. The observed rate constant was obtained by following the change in absorbance of the reaction mixture with time at a predetermined wavelength. The overall rate constant and order of the reaction with respect to cysteine and metal complex were determined. For both metal ions studied, the oxidation rate constant for the \( \text{trans} \) isomer was higher than that for the \( \text{cis} \) isomer. This was attributed to the contribution of the steric factor and the \( \text{trans} \) effect. The effects of substituents and the nature of the metal ion on the reaction rate are discussed.

Introduction

Kinetic studies of structural isomers of transition metal complexes provide important information on the influence of the arrangement (\( \text{cis-}/\text{trans}\)) on their reactivity. Kinetic studies of the reduction of isomers by various reducing agents provide much of the experimental knowledge used to develop coordination theory. Two types of structural isomers are common among transition metal complexes: tetra- and hexacoordinate. In the tetracoordinate compounds, \( \text{trans-} \) and \( \text{cis-} \) isomers exist mainly in square-planar arrangement. However, the octahedral hexacoordinate compounds have several possible structural isomers. If some ligands are bidendate, the number of possible isomers is limited, which facilitates identification of the metal complex. In the present work, octahedral transition metal complexes of the type [\( \text{M(L-L)}Cl_2\)] (where \( \text{L-L} \) is a bidentate ligand) were selected for kinetic studies.

Several research groups studied the effect of structural isomerism on the reactivity of transition metal complexes. Using optical rotatory dispersion, IR, and NMR spectroscopy, de Vekki et al. [1] studied the reaction of the optically active structural isomers of platinum(II) complex \( \text{cis-} \)–[\( \text{Pt} \text{(Me-p-ToSO)} \text{Cl}_2\)] \( \text{(ToSO} = \text{tolylsulfoxide)} \), with several nucleophilic reagents (\( \text{Py, Ph}_3\text{PS, Ph}_3\text{P, Ph}_3\text{As, and Me}_2\text{SO}) \). Farrell et al. [2] reported a study on the activity of platinum complexes as anti-tumor agents. For dinuclear platinum \( \text{cis-} \) and \( \text{trans-} \) \( \{\text{PtCl(NH}_3)_2\}_{\text{2-μ}}\text{-}[\text{NH}_2\text{(CH}_2)_2\text{NH}_2]\}(\text{NO}_3)_2 \) \( (n = 4, 6) \), they found that the initial binding and reaction rates of the \( \text{cis} \) isomer were slower than those of the \( \text{trans} \) isomer. Toma et al. [3] reviewed the kinetics and mechanisms involved in linkage isomerization reactions. The biodegradation kinetics of structural isomers of naphthenic acid in water was studied by Peru et al. [4]. Rates of biodegradation of \( \text{cis-} \) and \( \text{trans-} \) isomers of 4-methylecyclohexenylacetic acids, 4-methylecyclohexanecarboxylic acids, and 3-methylecyclohexenylcarboxylic acids by heterotrophic bacteria were compared.

Oxidation of amino acids by transition metal complexes were studied using different methods that include [5]: stopped-flow UV/Vis spectroscopy, chemical analysis of products, and the use of radioactive and stable isotope tracers. Several research groups reported studies on the oxidation of amino acids by transition metal complexes [6–17]. Olabe et al. [6] studied the reaction kinetics of ruthenium nitrosyl complexes with cysteine by UV/Vis spectroscopy using stopped-flow techniques. Vani et al. [7] reported on the kinetics and mechanism of the oxidation of \( \text{l-methionine by 1,10-phenanthroline \( \text{iron(III)} \) complex in perchloric acid. The reactivity of iron(V) and iron(VI) complexes with several amino acids using stopped-flow techniques and pulse radiolysis were studied by Sharma and Bielski [8]. Laloo and Mahanti [9] investigated the kinetics of oxidation of lysine, arginine, and histidine by alkaline hexacyanoferrate(III) in the temperature range 318–338 K. Anaerobic oxidation of cysteine to cystine by iron(III) complexes in acidic solution using stopped-flow techniques was reported by Jameson et al. [10, 11]. Mehrrotra et al. [12] studied the oxidation of amino acids to aldehydes by alkaline hexacyanoferrate(III) in the presence of OsVIII as a catalyst.

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Figure 1. Suggested structures for complexes 1–11 used in the present study.
Our investigations resulted in several papers dealing with the oxidation of amino acids by transition metal complexes [13–22]. Of particular interest and relevance to the present work, the authors have reported recently [13, 14] on the kinetics of oxidation of l-cysteine by trans- and cis-cobalt(III) and iron(III) complexes bearing ethylenediamine, bipyridine, and 1,10-phenanthroline ligands, as well as the oxidation of l-cysteine by chromium(III), manganese(III), iron(III), and cobalt(III) complexes. We additionally investigated the effect of the nature of ligand in a transition metal complex on the rate of oxidation of l-balt(III)complexes. We additionally investigated the effect of cysteine by chromium(III), manganese(III), iron(III), and co-complexes with various ligands such as CN, NO2, acetylacetone, NH3, urea, ethylenediamine, and phenanthroline [15–17]. Previous studies on the coordination chemistry of heteroatom-containing ligands [18, 19] and their catalytic applications [20, 21] were also reported by our research group.

In the present work, we report on the kinetics of oxidation of l-cysteine by new pairs of trans and racemic cis isomers of cobalt(III) and iron(III) complexes containing α- and γ-diimine bidentate nitrogen ligands (Figure 1). These transition metal complexes, which contain bidentate diimine ligands, were chosen because of their potential usage in a number of catalytic reactions including polymerization of alkenes, polymerization of polar monomers, enantioselective 1,3-dipolar cycloaddition reactions, and borylation of vinylarenes [22]. For each complex, a rate and rate constant of reaction was determined. Effects on reaction rates due to the metal ion, the arrangement around the metal ion, types of auxiliary ligands, and the backbone structures of the complex were discussed.

**Experimental Section**

**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. CoCl2·6H2O, and FeCl2·6H2O were purchased from ACROS. Elemental analysis and Mass spectra (EI) measurements, for RSSR, were performed in our laboratories with a EURO EA 3000 and a Shimadzu-QP5050A, respectively. The ligands and their Co(III) and Fe(III) complexes were synthesized according to reported procedures [22].

**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 with 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. The wavelength was determined by recording the absorption spectra for the transition metal complex (TMC) alone and for its mixture with cysteine (Cys) after completion of reaction. The wavelength of maximum absorbance difference (λmad), preferably in visible region of the spectra, between the absorption of TMC and the mixture was selected. A representative λ scan for reactants and products is shown in Figure 2 for oxidation of cysteine by cis-dichlorobis(N,N'-bis(cyclohexyl)-1,2-phenyldiimine)cobalt(III) chloride (6). A list of λmad for various complexes is shown in Table 1. All reactions were studied under pseudo-first order conditions, at which the concentrations of Cys (10−2–10−1 mol·dm−3) were 1–2 orders of magnitude larger than those of TMC (10−4–10−3 mol·dm−3). Ionic strength of the

![Figure 2. λ Scan for the products and for the reactants for the oxidation of cysteine by cis-dichlorobis(N,N'-bis(cyclohexyl)-1,2-phenyldiimine)cobalt(III) chloride (6).](image)

**Table 1. Rates of oxidation of l-cysteine by trans and cis of cobalt(III) and iron(III) complexes based on α- and γ-diimine Schiff base ligands in aqueous medium at 25 °C, pH = 7.0 and ionic strength = 0.20 mol·dm−3.**

<table>
<thead>
<tr>
<th>Family</th>
<th>No.</th>
<th>Complex (TMC)</th>
<th>λmax/nm</th>
<th>Ligand</th>
<th>k0 / dm3·mol−1·s−1</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-diimine</td>
<td>1</td>
<td>trans-[Co(BCHB)2Cl2]Cl</td>
<td>350</td>
<td>trans-BCHB</td>
<td>k1 = 1.9 × 10−1, k2 = 2.7 × 10−3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>cis-[Co(BCHB)2Cl2]Cl</td>
<td>480</td>
<td>cis-BCHB</td>
<td>1.2 × 10−3</td>
</tr>
<tr>
<td></td>
<td>3T, 3S</td>
<td>trans- and cis-[Co(BIPPP)2Cl2]Cl</td>
<td>419, 490</td>
<td>BIPPP</td>
<td>very fast</td>
</tr>
<tr>
<td></td>
<td>4T, 4S</td>
<td>trans- and cis-[Co(BIPPP)2Cl2]Cl</td>
<td>400, 511</td>
<td>BNB</td>
<td>very slow</td>
</tr>
<tr>
<td>γ-diimine</td>
<td>5</td>
<td>trans-[Co(BCHP)2Cl2]Cl</td>
<td>480</td>
<td>trans-BCHP</td>
<td>very fast</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>cis-[Co(BCHP)2Cl2]Cl</td>
<td>430</td>
<td>cis-BCHP</td>
<td>2.1 × 10−2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>trans-[Co(BIPPP)2Cl2]Cl</td>
<td>400</td>
<td>trans-BIPPBP</td>
<td>6.3 × 10−2, k2 = 9.1 × 10−2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>cis-[Co(BIPPP)2Cl2]Cl</td>
<td>400</td>
<td>cis-BIPPBP</td>
<td>4.2 × 10−2</td>
</tr>
<tr>
<td></td>
<td>9T, 9S</td>
<td>trans- and cis-[Co(BNPB)2Cl2]Cl</td>
<td>385, 500</td>
<td>BNP</td>
<td>very slow</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>cis-[Fe(BCHP)2Cl2]Cl</td>
<td>486</td>
<td>cis-BCHP</td>
<td>7.2 × 10−3</td>
</tr>
<tr>
<td></td>
<td>11T, 11S</td>
<td>trans- cis-[Fe(BNPB)2Cl2]Cl</td>
<td>400, 510</td>
<td>BNP</td>
<td>very slow</td>
</tr>
</tbody>
</table>

a) BCHB = N,N'-bis(cyclohexyl)-2,3-butandimidine; BIPPP = N,N'-bis(2-isopropylphenyl)-2,3-butandimidine; BNP = N,N'-bis(1-naphthyl)-2,3-butandimidine; BCHP = N,N'-bis(cyclohexyl)-1,2-phenyldiimidine; BIPPBP = N,N'-bis(2-isopropyl-phenyl)-1,2-phenyldiimidine; BNP = N,N'-bis(1-naphthyl)-1,2-phenyldiimidine. b) Experimental errors are estimated to be 10 %.
Oxidation of l-Cysteine by trans and cis CoIII and FeIII Complexes

Results and Discussion

Oxidation of Cys (RSH) leads to formation of cystine, RSSR

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

Estimation of residual oxidant indicates that two moles of Cys consume one mole of the transition metal complex (TMC), so that

\[ [M^{III}(L-L)Cl_2]^+ + 2RSH \rightarrow [M^{III}(L-L)Cl_2] + RSSR, \]  \hspace{1cm} (2)

where \([M^{III}(L-L)Cl_2]^+\) is the TMC, \(M\) is the transition metal, and \(L-L\) is the bidentate ligand. The rate of reaction is given by

\[ \text{Rate} = k [\text{Cys}]^a [\text{TMC}]^b \]  \hspace{1cm} (3)

where \(k\) is the reaction rate constant and \(a\) and \(b\) are orders of reaction with respect to the concentrations of Cys and TMC, respectively. Since all \(M^{III}\) complexes are one-electron oxidants, oxidation of cysteine gives a radical intermediate [23] as shown below:

\[ \text{RSSR} \rightarrow \text{RSS}^+ \]  \hspace{1cm} (4)

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

\[ \text{Rate} \approx \frac{d[\text{TMC}]}{dt} = k_{\text{obs}} [\text{TMC}]^b \]  \hspace{1cm} (5)

the observed rate for reaction is 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 fitted to the exponential function:

\[ (A_L - A_w) = (A_0 - A_w) \text{exp}(-k_{\text{obs}} t) \]  \hspace{1cm} (7)

where \(A_L\) is the absorbance of TMC at a given time \((t)\) through the reaction, \(A_0\) is its initial absorbance \((t = 0)\) and \(A_w\) is the absorbance of the mixture at the end of the reaction, i.e. when the absorbance no longer changes with time \((t = \infty)\).

Experimental results showed that a plot of \(\ln((A_L - A_w)/(A_0 - A_w))\) versus time gives a straight line, according to Equation (7). The value of \(k_{\text{obs}} \text{ s}^{-1}\) was obtained from the slope. Using Equation (6), a plot of \(\ln (k_{\text{obs}})\) versus \(\ln [\text{Cys}]\) is a straight line that gives both the order of reaction with respect to [Cys] (slope) and the reaction rate constant \(k \text{ dm}^{-3}\text{ mol}^{-1}\text{ s}^{-1}\) (intercept). For some reactions, two different rate constants were observed, which were called \(k_1\) and \(k_2\). Generally, it was found that the reaction rate depends on the concentration of both substrate and oxidant, i.e. \(a \approx b \approx 1\). This result is in agreement with previous studies [5, 8, 12–16]. Kinetic study results for the oxidation of l-cysteine by various trans and cis pairs are shown in Table 1. A brief look on this table shows that the rate constant \((k)\) for the trans isomer is higher than that for its corresponding cis isomer. For some trans isomers, \(k\) is two orders of magnitudes higher. This difference in rate can be explained by a combination of reaction mechanism and a structural factor.

It is difficult to decide which mechanism of oxidation is dominant. If a ligand in the complex has an extra lone pair(s) to form “links” with cysteine, and if the arrangement around the metal atom provides enough space for cysteine to bond to this ligand, the reaction is more likely to proceed by an inner-sphere mechanism. Additionally, according to Taube [5], the inner-sphere mechanism is more likely to occur if two metal atoms are present in the TMC. In this case, a substitution reaction occurs that leaves cysteine and TMC linked by a bridging ligand. In this case, transfer of an electron during oxidation is frequently accompanied by transfer of the ligand followed by separation of the products. On the other hand, if the ligand has no extra lone pairs to form bonds to cysteine, or when there is a “closed” or a crowded arrangement around the metal atom, the ligand is tightly held and there is no change in the coordination sphere of the reaction. In this case, the reaction proceeds by an outer-sphere electron transfer mechanism [24]. It appears that all reactions studied in the present work proceed by an inner-sphere mechanism, involving formation of an intermediate that includes replacement of the chlorides by RSSR. The rate of electron transfer from Cys to \(M^{III}\) should depend on the metal atom, the nature of the ligand (mainly its size), and the arrangement around the metal atom.

Table 1 shows that the reaction rate constants for trans-[Co(BCHB)2Cl2]Cl (1), trans-[Co(BIPPP)2Cl2]Cl (5), and trans-[Co(BIPP)2Cl2]Cl (7) are higher than their corresponding cis isomers 2, 6, and 8, respectively. The trans isomer, which is less crowded than the cis isomer, provides a shorter distance of approach for cysteine from TMC and from both top and bottom directions and leads thereby to higher rates for the trans isomers.

Different behavior is observed for trans and cis isomers. Two different rate constants \((k_1\) and \(k_2\)) were obtained for the reaction of the trans isomer but only one rate constant was found for the cis isomer. The reactions of both cis and trans isomers proceeded by replacement of the two Cl– by two RS– groups of Cys via pentacoordinate intermediates. However, for the trans isomer, replacement of one chloride ion yielded a structure, in which RSSR and chlorine are at trans to each other. Replacement of the second chlorine ion by another RS is influenced by the trans effect of the first RS. Therefore, two different rate constants were observed. On the other hand, replacement of the second chloride ion in the cis isomer is equivalent to replacement of the first chlorine ion since both are in trans positions to the other ligands bound to the metal. Hence, one rate is observed for oxidation of cysteine by the cis isomer. For both
isomers, the product undergoes a reductive elimination process (RE) that eliminates the two RS units to yield cysteine (RSSR), and an unstable M complex which immediately oxidizes to MII by O2 present in reaction mixture. The process can be summarized by the following steps:

\[
\]

**[M^{III}(L-L)(SR)]^{2+} + HCl**

\[
[M^{III}(L-L)(SR)]^{2+} + RSH \rightarrow [M^{III}(L-L)(SR)]^2+
\]

The difference in two rates for the trans isomers is due to two factors: the steric factor, caused by crowding in the octahedral arrangement and the trans effect, which arises from the ability of ligand to stabilize the transition state in the rate-limiting dissociation step. The -RS group has a stronger trans effect than chlorine due to its larger ability to act as a σ electron donor. For trans-dichlorobis(N,N'-bis(cyclohexyl)-2,3-butadiimine)cobalt(III) chloride (1), which has a large ligand, \( k_1 (1.9 \times 10^{-3} \text{s}^{-1}) \) is higher than \( k_2 (2.7 \times 10^{-3} \text{s}^{-1}) \) due to the steric factor associated with the first substitution of chlorine by cysteine. However, for trans-dichlorobis(N,N'-bis(2-isopropylphenyl)-1,2-phenyldiimine)cobalt(III) chloride (7), \( k_2 \) has a value of \( 9.1 \times 10^{-2} \text{s}^{-1} \) which is higher than \( k_1 (6.3 \times 10^{-3} \text{s}^{-1}) \) due to trans effect.

Table 1 also shows that the rate constant of cis-[Co(BIPP)2Cl]Cl (8) is higher than that of cis-[Co(BCHP)2Cl]Cl (2), which is in turn much higher than that of cis-[Co(BNP)2Cl]Cl (9S). The three isomers have the same structural backbone but with different substituents. Rates of cysteine oxidation by complexes based on 2-isopropylphenyl are faster than the rates for complexes with cyclohexyl substituents. Additionally, the reaction rates of complexes based on naphthyl groups (4T and 4S), (9T and 9S), and (11T and 11S) are very slow. This variety in rates is due to both steric and electronic factors. For 9S, the bulky naphthyl group hinders the cysteine anion from entering into the complex sphere (inactivating), whereas for compound 8, the 2-isopropylphenyl substituent provides both electronic donation from the alkyl group, and electronic withdrawing by the phenyl group. The electronic withdrawing influence is less important for complexes with cyclohexyl substituents (2), their reactions are slower than those of compound 8. A similar argument can be made about the different rates for other cis isomers. The rate constant of cis-[Co(BCHP)2Cl]Cl (5) is higher than that of cis-[Co(BCHP)2Cl]Cl (2) and the rate constant of oxidation of cysteine by compound 5, with phenylidineimine backbone, is higher than that of complex 2 with a butadiimine backbone. The electronic factor of the phenylidineimine, which has higher ability to act as an electron withdrawing group, increases the reductive potential for the metal ion making its reaction faster.

Finally, the effect of the metal ion on reaction rate was investigated. Rate constants for CoIII were higher than FeIII complexes with the same substituents. Table 1 shows that the rate of oxidation of cysteine by cis-[Co(BCHP)2Cl]Cl (6) is an order of magnitude larger than that of cis-[Fe(BCHP)2Cl]Cl (10). This can be attributed to the reduction potential of the ion. The standard reduction potential of Co3+ is +1.81 V, which is much higher than that of Fe3+ (+0.77 V). A higher E0 means stronger driving force for the reaction, which leads to higher reaction rates for CoIII than for FeIII complexes.

**Conclusions**

Rates of oxidation of L-cysteine by pairs of trans and cis CoIII and FeIII complexes based on α- and γ-dimine Schiff base ligands were studied. Higher rate constant for trans isomers were largely attributed to steric factor. The less crowded trans isomers facilitate electron transfer and thus increases the rate of oxidation. The nature of substituents in the ligands plays a role in determining reaction rates mainly through their size and electron donating ability. Additionally, reaction rates were found to depend on the metal ion. Oxidation rates of L-cysteine by CoIII complexes were higher than those by FeIII complexes due to the higher positive standard reduction potential of CoIII.

**References**

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