

Kinetics of the Oxidation of *L*-Cysteine by *trans*- and *cis*-Cobalt(III) and Iron(III) Complexes

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Kinetics of oxidation of *L*-cysteine by pairs of *trans* and racemic *cis* isomers of cobalt(III) and iron(III) based transition metal complexes have been studied in aqueous solution. Kinetics measurements were run under *pseudo* first order conditions in which the concentration of cysteine is between one and two orders of magnitude greater than that of the isomers of the transition metal complex. The orders of the reaction with respect to both cysteine and the isomer were determined.

The observed rate constants and the overall rate constants of the oxidation process were measured. For all geometrical isomers, it was found that the rate constant of oxidation of *L*-cysteine by the *trans* isomer is between one to three orders of magnitude greater than that by the *cis* isomer. The difference in rates can be explained by a geometric factor around the metal ion center in the complex. The less crowded isomer (*trans*) makes electron transfer easier and hence facilitates the oxidation process which leads to a higher oxidation rate.

Key words: Co(III), Fe(III), Kinetics, Cysteine

Introduction

Geometric isomerisms are common among coordination compounds. They contain the same type and the same number of ligands, but arranged differently around the central transition metal ion in the complex. Study of isomers provides much of the experimental knowledge used to develop and defend coordination theory. For four-coordinated compounds, *trans* and *cis* isomers are common in square planar molecules. For the octahedral geometry of six-coordinated compounds, with monodentate ligands, several geometric isomerisms are possible. However, if some of the ligands are bidentates, the number of possible isomers is limited. In the present work, octahedral transition metal complexes of the type $[M(L-L)_2Cl_2]Cl$ (where *L-L* is a bidentate ligand) were selected for a kinetic study.

Several investigators have studied the effect of geometric isomerism on the reactivity of some isomers with various reagents. Using optical rotatory dispersion, IR and NMR spectroscopy, de Vekki *et al.* [1] studied the reaction of the optically active geometric isomers of the platinum(II) complex $(-)[Pt(Me-p-$

TolSO)(Py)Cl₂] with several nucleophilic reagents (Py, Ph₃PS, Ph₃P, Ph₃As, and MeSO). The effect of geometric isomerism in platinum complexes used as anti-tumor agents has been studied by Farrell *et al.* [2]. They found that the binuclear platinum complexes $[{trans-PtCl(NH_3)_2}]_2-\mu-\{NH_2(CH_2)_nNH_2\}(NO_3)_2$ ($n = 4, 6$) and $[{cis-PtCl(NH_3)_2}]_2-\mu-\{NH_2(CH_2)_nNH_2\}(NO_3)_2$ ($n = 4, 6$) exhibit anti-tumor activity comparable with cisplatin. Also, they found that, at 37 °C, the initial binding and reaction of the *cis* isomer was slower than that of the *trans* isomer. Toma *et al.* [3] reviewed linkage isomerization reactions from the aspect of kinetics and mechanisms involved, some focusing on selected cases of direct formation, as well as on electrochemical, photochemical, thermal and pH-induced generation of linkage isomers. The biodegradation kinetics of geometric isomers of model naphthenic acid in water has been studied by Peru *et al.* [4]. The rates of biodegradation of six model naphthanic acids by heterotrophic bacteria were compared. Specifically, they monitored by gas chromatography in surface water the biodegradation of *cis*- and *trans*-isomers of 4-methylcyclohexenylacetic acids, 4-methylcyclohexanyl-

carboxylic acids, and 3-methylcyclohexenylcarboxylic acids.

Oxidation of amino acids by a transition metal complex has been studied using different methods, including stopped-flow spectrophotometry, chemical analysis of products, and the use of radioactive and stable isotope tracers. Discussion of these methods, along with much of the data produced and interpretation of the results according to different pathways in this field, is given elsewhere [5]. Several investigators reported studies on the oxidation process of amino acids by various transition metal complexes [6–15]. Kinetics and mechanism of oxidation of *L*-methionine by a 1,10-phenanthroline iron(III) complex in perchloric acid medium have been studied by Vani *et al.* [6]. Sharma *et al.* [7] reported the reactivity of iron(V) and iron(VI) with both glycine and α -alanine, at pH 12.4 and 23–24 °C, using stopped-flow and pulse radiolysis techniques. Laloo *et al.* [8] studied the kinetics of the oxidation of three amino acids (lysine, arginine, and histidine) by alkaline hexacyanoferrate(III) at constant ionic strength over the temperature range 318–338 K. Jameson *et al.* [9, 10] reported anaerobic oxidation of cysteine to cystine by iron(III) in acidic solution using stopped-flow high-speed spectrophotometry. The oxidation of amino acids to aldehydes, in the presence of Os(VIII) as a catalyst, by alkaline hexacyanoferrate(III) has been reported by Mehrotra *et al.* [11].

From our laboratories, several papers have been published [12–15] on the oxidation of some amino acids by transition metal complexes. Of particular interest and relation to the present work, Abdel-Halim *et al.* [12] reported recently kinetic measurements of *L*-cysteine oxidation by chromium(III), manganese(III), iron(III), and cobalt(III) based transition metal complexes. The authors [13–15] also reported kinetic studies on the oxidation of *L*-cysteine and proline by some cobalt(III) and iron(III) based complexes containing various ligands such as CN, NO₂, acac, NH₃, urea, en, and 1,10-phenanthroline. They investigated the effect of the nature of the ligand in the transition metal complex on the rate of oxidation of cysteine. Previous studies on the coordination chemistry of heteroatom-containing ligands [16, 17], and their catalytic applications [18, 19], were also reported by these authors.

In the present work, kinetics of oxidation of *L*-cysteine by pairs of *trans* and racemic *cis* isomers of cobalt(III) and iron(III) based transition metal complexes have been studied in aqueous solution. For each

metal ion, the observed rates and the rate constants of oxidation processes is given. Correlation has been made between the rate of the oxidation process and the geometry around the metal ion (*cis* and *trans*).

Experimental Section

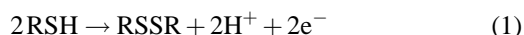
Materials: *L*-cysteine (minimum assay 99%) was purchased from BDH Laboratory Supplies (England) and was used without further purification. The cobalt(III) and iron(III) *trans*- and *cis*-pairs complexes: *trans*-[Co(en)₂Cl₂]Cl (**1**), *cis*-[Co(en)₂Cl₂]Cl (**2**) (en: 1,2-ethylenediamine), *trans*-[Co(bipy)₂Cl₂]Cl (**3**), *cis*-[Co(bipy)₂Cl₂]Cl (**4**) (bipy: 2,2'-bipyridine), *trans*-[Co(phen)₂Cl₂]Cl (**5**), *cis*-[Co(phen)₂Cl₂]Cl (**6**) (phen: 1,10-phenanthroline), *trans*-[Fe(en)₂Cl₂]Cl (**7**), *cis*-[Fe(en)₂Cl₂]Cl (**8**), *trans*-[Fe(bipy)₂Cl₂]Cl (**9**), *cis*-[Fe(bipy)₂Cl₂]Cl (**10**), *trans*-[Fe(phen)₂Cl₂]Cl (**11**), and *cis*-[Fe(phen)₂Cl₂]Cl (**12**), were prepared according to literature procedures [20] with some modification. The *trans*-isomers (**1**, **3**, **5**, **7**, **9**, and **11**) were prepared by the reaction of stoichiometric amounts of ligands with CoCl₂ · 6H₂O or FeCl₂ · 4H₂O in water. The resulting M(II) complexes were oxidized to M(III) complexes by the addition of a stoichiometric amount of H₂O₂. The product was then treated with excess HCl to form the desired dichloro species of the form [M(L-L)₂Cl₂]Cl. (L-L = 1,2-ethylenediamine, 2,2'-bipyridine, 1,10-phenanthroline; and M = Co, Fe). The product was filtered, washed with ethanol and diethylether, and dried. Slow evaporation of the filtrate for several days gave crystals of the corresponding racemic *cis*-isomers (**2**, **4**, **6**, **8**, **10**, and **12**). The geometry of each isomer was confirmed by its physical properties (melting point and color) and by its UV-vis spectrum: *trans*-[Co(en)₂Cl₂]Cl (**1**): Deep-green. – M. p. (dec) 229 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 608 nm (1.49). *cis*-[Co(en)₂Cl₂]Cl (**2**): Violet. – M. p. (dec) 221 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 536 nm (1.81). *trans*-[Co(bipy)₂Cl₂]Cl (**3**): Green. – M. p. (dec) 339 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 544 nm (1.75). *cis*-[Co(bipy)₂Cl₂]Cl (**4**): Deep-violet. – M. p. (dec) 292 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 518 nm (1.74). *trans*-[Co(phen)₂Cl₂]Cl (**5**): Green. – M. p. (dec) 250 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 465 nm (1.84). *cis*-[Co(phen)₂Cl₂]Cl (**6**): Gray. – M. p. (dec) 200 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 516 nm (1.97). *trans*-[Fe(en)₂Cl₂]Cl (**7**): Orange-red. – M. p. (dec) 231 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 368 nm (2.25). *cis*-[Fe(en)₂Cl₂]Cl (**8**): Pink. – M. p. (dec) 258 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 477 nm (0.98). *trans*-[Fe(bipy)₂Cl₂]Cl (**9**): Gray. – M. p. (dec) 300 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 557 nm (1.72). *cis*-[Fe(bipy)₂Cl₂]Cl (**10**): Orange. – M. p. 220 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 489 nm (1.20). *trans*-[Fe(phen)₂Cl₂]Cl (**11**): Purple. – M. p. (dec) 304 °C. – UV/vis (MeOH): λ_{\max} (lg ϵ) = 504 nm (2.71).

cis-[Fe(phen)₂Cl₂]Cl (**12**): Brown. – M. p. (dec) 215 °C. – UV/vis (H₂O): λ_{\max} (lg ϵ) = 507 nm (2.90).

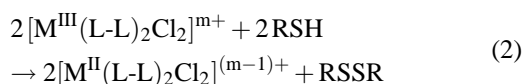
Kinetic measurements: Freshly prepared aqueous solutions of the desired concentrations of complexes and of *L*-cysteine were used for the kinetic measurements. The measurements were carried out using a Diode Array Spectrophotometer model 8453E from HP Agilent Technologies. The reactions were monitored by following the change in the absorbance of the *trans*- or the racemic *cis*-isomers of Co(III) and Fe(III) metal complex (MC) with time at a pre-determined wavelength. This wavelength was determined by recording the absorption spectral curves, for the MC and for its mixture with cysteine (Cys) after the completion of the reaction. The reaction progress and the reaction rate were monitored at the wavelength of *maximum absorbance difference* (λ_{mad}) between the absorption of MC and that of the mixture at the end of the reaction. A list of λ_{mad} for various complexes is shown in Table 1. All oxidation reactions were studied under *pseudo* first order conditions. The concentrations of Cys used [10^{-2} – 10^{-1} mol dm⁻³] were chosen to be 1-2 orders of magnitude larger than that of the MC [10^{-4} – 10^{-2} mol dm⁻³]. The ionic strength of the solutions was kept constant at 0.20 mol dm⁻³ using NaClO₄. The temperature of the solution and its pH were both maintained at 25 ± 0.1 °C and 7.0 ± 0.1 , respectively.

Results and Discussion

Oxidation of cysteine (RSH) leads to formation of cystine (RSSR), as shown below [21].



Estimation of residual oxidant suggested that 2 moles of cysteine consumed 2 moles of the MC, [M^{III}(L-L)₂Cl₂]^{m+}, where M is the transition metal, such that



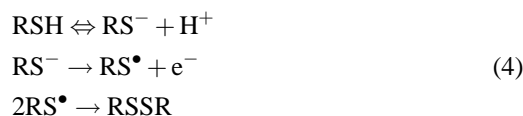
where m is the charge on the M(III)-L complex.

The rate of the reaction is given by

$$\text{Rate} = k[\text{Cys}]^a[\text{MC}]^b \quad (3)$$

where k is the reaction rate constant and a , b are the orders of the reaction with respect to the concentration of Cys and MC, respectively. It was found that the rate is, in general, dependent on the first power of both the concentrations of substrate and oxidant, *i. e.*, $a \approx$

$b \approx 1$, in agreement with previous studies [6, 8, 12 – 15]. Since M(III) complexes are all one-electron oxidants, the oxidation of cysteine would give a radical intermediate, and the following mechanism is proposed:



where the second step is the rate-determining step.

Under *pseudo* first order conditions, in which [Cys] \gg [MC], the concentration of the cysteine is essentially constant throughout the reaction. The reaction rate is then given by

$$\text{Rate} \approx -\frac{d[\text{MC}]}{dt} = k_{\text{obs}}[\text{MC}] \quad (5)$$

where k_{obs} is the observed rate for the reaction, given by

$$k_{\text{obs}} = k[\text{Cys}] \quad (6)$$

where k is the second-order rate constant for reaction (2) above.

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

$$A_t = (A_0 - A_\infty) \exp(-k_{\text{obs}}t) + A_\infty \quad (7)$$

where A_t is the absorbance of the MC at time t through the reaction, A_0 is the initial absorbance of the complex ($t = 0$) and A_∞ is the final absorbance of the reaction mixture at the end of the reaction ($t = \infty$).

The value of k_{obs} (in s⁻¹) can be obtained from a plot of $\ln(A_t)$ versus time. A plot of k_{obs} versus [Cys] gives the value of the second-order rate constant, k , in units of dm³ mol⁻¹s⁻¹. Kinetics results for the oxidation of cysteine by various *trans*- and *cis*-pairs are shown in Table 1.

Table 1 shows experimental results for various Co(III) and Fe(III) *trans*- and racemic *cis*-geometric pairs. For all complexes studied, the observed rate constant for the *trans*-isomer is found to be one to two orders of magnitude greater than that for the *cis*-isomer, while the second-order rate constant for the *trans*-reaction is two to three orders of magnitude greater than that of the racemic *cis*-isomer. This difference in rates can be explained by the reaction mechanism and geometric factors.

MC No.	Complex (MC)	Ligand	λ_{mad} (nm)	k_{obs} (s^{-1})	k^* ($\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$)
1	<i>trans</i> -[Co(en) ₂ Cl ₂]Cl	<i>trans</i> -en	400	1.22×10^{-3}	1.72×10^{-2}
2	<i>cis</i> -[Co(en) ₂ Cl ₂]Cl	<i>cis</i> -en	400	4.17×10^{-5}	5.32×10^{-5}
3	<i>trans</i> -[Co(bipy) ₂ Cl ₂]Cl	<i>trans</i> -bipy	400	7.43×10^{-2}	8.37×10^{-1}
4	<i>cis</i> -[Co(bipy) ₂ Cl ₂]Cl	<i>cis</i> -bipy	375	4.67×10^{-3}	2.11×10^{-2}
5	<i>trans</i> -[Co(phen) ₂ Cl ₂]Cl	<i>trans</i> -phen	400	2.99×10^{-3}	1.62×10^{-2}
6	<i>cis</i> -[Co(phen) ₂ Cl ₂]Cl	<i>cis</i> -phen	375	4.58×10^{-4}	7.32×10^{-4}
7	<i>trans</i> -[Fe(en) ₂ Cl ₂]Cl	<i>trans</i> -en	355	1.13×10^{-3}	1.46×10^{-2}
8	<i>cis</i> -[Fe(en) ₂ Cl ₂]Cl	<i>cis</i> -en	355	7.50×10^{-5}	1.85×10^{-4}
9	<i>trans</i> -[Fe(bipy) ₂ Cl ₂]Cl	<i>trans</i> -bipy	400	5.11×10^{-1}	9.88×10^{-1}
10	<i>cis</i> -[Fe(bipy) ₂ Cl ₂]Cl	<i>cis</i> -bipy	521	4.12×10^{-2}	3.44×10^{-2}
11	<i>trans</i> -[Fe(phen) ₂ Cl ₂]Cl	<i>trans</i> -phen	520	5.13×10^{-1}	9.74×10^{-1}
12	<i>cis</i> -[Fe(phen) ₂ Cl ₂]Cl	<i>cis</i> -phen	521	2.34×10^{-2}	2.87×10^{-1}

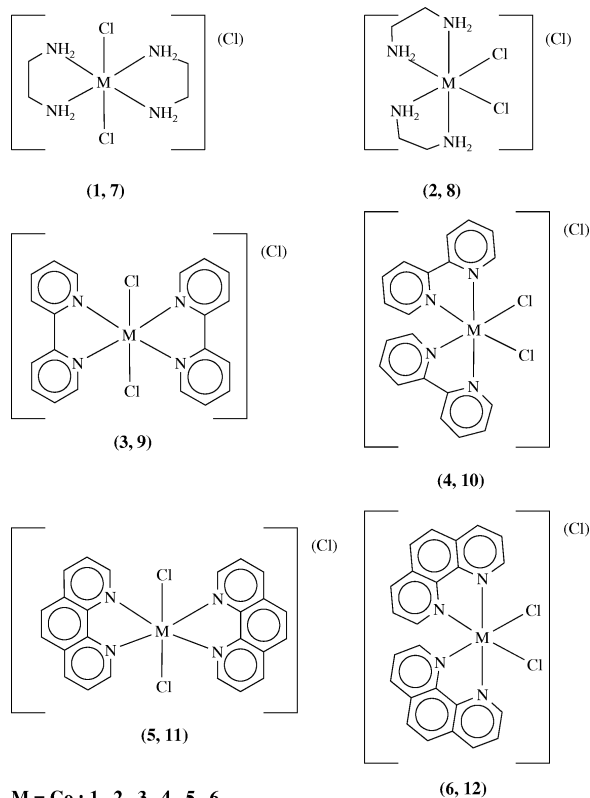
Table 1. Rates of oxidation of cysteine by various *trans*- and racemic *cis*-pairs of Co(III) and Fe(III) complexes in aqueous medium at 25 °C, pH = 7.0 and ionic strength = 0.20 mol dm⁻³.

* Experimental errors are estimated to be 20%.

Deciding *via* which mechanism the oxidation process of cysteine by a transition metal complex will proceed may be difficult. If the ligand in the complex has extra lone pair(s) with which to form “links” to cysteine and if the geometry around the metal center leaves enough space for cysteine to bind to this ligand, then the reaction is more likely to proceed *via* an inner-sphere mechanism. In this case, a substitution reaction that leaves cysteine and MC linked by the bridging ligand takes place, and the actual transfer of the electron is frequently accompanied by transfer of the ligand followed by separation of the products. However, when the ligands in the MC have *no extra* lone pairs with which to form bonds to cysteine, or when there is a “closed” or crowded geometry around metal center, then the ligands are tightly held and there is no change in the coordination sphere on reaction, the reaction proceeds by outer-sphere electron transfer [22].

Looking at ligands and structures of MC's studied in the present work (Fig. 1) reveals that they all have *closed* octahedral geometries that do not permit linking between cysteine and MC. Also, according to Taube [5], an inner-sphere redox reaction requires two metal centers, which is not the case in any of the MC's used. Therefore, we believe that *all* reactions studied in the present work proceed *via* an outer-sphere mechanism.

Since direct linkage between Cys and MC is not possible, then the rate of electron transfer from Cys to M(III) in the MC, according to (2) above, will depend on the closest distance the two reactants can approach each other. Obviously, the *trans*-isomer, which is less crowded than the *cis*-isomer, can provide a closer distance of approach from both sides (“top” and “bottom”) of the MC. This will lead to higher rates for *trans*-isomers than for *cis*-isomers. Table 1 clearly



M = Co : 1, 2, 3, 4, 5, 6

M = Fe : 7, 8, 9, 10, 11, 12

Fig. 1. Suggested structures for the complexes used in the present study.

shows that this is the case for all *trans*- and *cis*-isomers pairs studied.

The differences in rates due to the nature of the ligand [en, bipy and phen] and due to the metal center [Co(III) and Fe(III)] were discussed in our previously published work [12].

Conclusion

The rates of oxidation of *L*-cysteine by pairs of *trans*- and racemic *cis*-isomers of Co(III) and Fe(III) complexes with various ligands were studied. Rates

were found to be *one to three* orders of magnitudes higher for the *trans*-isomer. The differences are attributed to steric factors. The *less* crowded *trans*-isomers facilitate electron transfer making the oxidation process faster than the *cis*-isomers.

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- [1] D. A. de Vekki, V. N. Spevak, N. K. Skvortsov, Russ. J. Coord. Chem. **27**, 579 (2001).
 - [2] K. J. Mellish, Yun Qu, N. Scardale, N. Farrell, Nucl. Acid Res. **25**, 1265 (1997).
 - [3] H. E. Toma, R. C. Rocha, Craot. Chem Acta **74**, 499 (2001).
 - [4] J. V. Headley, S. Tanapat, G. Putz, K. M. Peru, Can. Water Resour. J. **27**, 25 (2001).
 - [5] T. J. Meyer, H. Taube, in: Comprehensive Coordination Chemistry, Vol. 1, Ch. 7.2, G. Wilkinson, R. D. Gillard, J. A. McCleverty (eds): Pergamon, Elmsford, N.Y (1987); H. Taube, Electron Transfer Reactions of Complex Ions in Solution, Academic Press, New York (1970); *idem*, Adv. Inorg. Chem. Radiochem. **1**, 1 (1959).
 - [6] P. Vani, K. Kishore, R. Rambabu, L. Dikshitulu, Proc. Indian Acad. Sci. (Chem. Sci.) **113**, 351 (2001).
 - [7] V. Sharma, H. Bielski, Inorg. Chem. **30**, 4306 (1991).
 - [8] D. Laloo, M. Mahanti, J. Chem. Soc., Dalton Trans. 311 (1990).
 - [9] R. Jameson, W. Linert, A. Tschinkowitz, V. Gutmann, J. Chem. Soc., Dalton Trans. 943 (1988).
 - [10] R. Jameson, W. Linert, A. Tschinkowitz, J. Chem. Soc., Dalton Trans. 2109 (1988).
 - [11] R. Mehrotra, R. Kapoor, and S. Vajpai, J. Chem. Soc., Dalton Trans. 999 (1984).
 - [12] H. M. Abdel-Halim, A. S. Abu-Surrah, S. E. Qaqish, Asian J. Chem. **18**, 947 (2006).
 - [13] H. M. Abdel-Halim, Intern. J. Chem. **11**, 131 (2001).
 - [14] H. M. Abdel-Halim, S. Salama, S. Al-Burtamani, Pak. J. Sci. Ind. Res. **41**, 71 (1998).
 - [15] H. M. Abdel-Halim, Y. Al-Lawatia, Asian J. Chem. **6**, 655 (1994).
 - [16] A. S. Abu-Surrah, U. Thewalt, B. Rieger, J. Organomet. Chem. **587**, 58 (1999).
 - [17] M. Kettunen, A. S. Abu-Surrah, H. M. Abdel-Halim, T. Repo, M. Leskelä, Polyhedron **23**, 1649 (2004).
 - [18] A. Abu-Surrah, B. Rieger, Topics in Catalysis **7**, 165 (1999).
 - [19] A. S. Abu-Surrah, K. Lappalainen, U. Piironen, P. Lehmus, T. Repo, M. Leskelä, J. Organomet. Chem. **648**, 55 (2002).
 - [20] J. Bailar, Inorg. Syn. **2**, 222 (1946).
 - [21] T. R. Ralph, M. L. Hitchman, J. P. Millington, F. C. Walsh, J. Electroanal. Chem. **375**, 1 (1994).
 - [22] See for example: G. L. Miessler, D. A. Tarr, Inorganic Chemistry, P. 398, Prentice-Hall, Inc., Engelwood Cliffs, New Jersey (1991), D. F. Shriver, P. W. Atkins, Inorganic Chemistry, 3rd Ed., ch. 14 Oxford Univ. Press, Oxford (1999).