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Kinetics and Mechanism of Oxidation of 2-Mercaptopyrimidine by a Tetraaza Macrocyclic–Silver(II) Complex

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Abstract

In buffered solutions the kinetics of the oxidation of 2-mercaptopyrimidine (MP) by $Ag(cyclam)^{2+}$ follows a second-order rate law. At $T = 25.0$ °C, $\mu = 0.10$ M, pH from 4.67 to 6.53, $[Ag(cyclam)^{2+}] = 0.89 \times 10^{-4}$ M and [MP] from 1.25×10^{-3} to 2.50×10^{-3} M, the second-order rate constants for the oxidation of MP and its anion are 5 and 145 $M^{-1} s^{-1}$, respectively. Rate–pH profile observed in the reaction can be accounted for by the acid–base equilibrium reaction of MP and the higher reactivity of the anion with the oxidant.

Introduction

Sulfhydryl (–SH) and disulfide (–SS–) groups are commonly found in biological compounds such as hormones, pharmacologically active polypeptides, enzymes, and other proteins [1, 2]. Since sulfur can have valences varying from −2 to +6, a variety of oxidation products can be made in addition to disulfides such that the oxidation of the sulfhydryl group becomes of interest. Biological oxidants such as flavins, cytochrome c, dehydroxylascorbate, quinones, amino acids and fumarate can oxidize sulfhydryl *in vivo* to disulfides [1].

Many inorganic oxidants such as hydrogen peroxide [3a, b], iodine [3c, d], potassium ferricyanide [3e, f], manganese(IV) oxide [3g, h], persulfate ion [3i], dioxygen and several transition metal complexes [4] have been used to study the kinetics and mechanisms of the oxidation of thiols, which include thioureas and heterocyclic thioamides. We also have used substitution-inert one-electron oxidizing agents such as hexachloroiridate(IV) [4] and tris(bipyridine)iron(III) [4] as oxidants and have reported the kinetics and mechanisms of the oxidation of several heterocyclic thioamides such as the 2-mercaptopyrimidine and its derivatives. These complexes are hexacoordinated and do not undergo reactions via the inner-sphere mechanism. Thus, we have used a square planar complex, silver(II)–cyclam, as an oxidant to investigate further the rate and mechanism of the oxidation of the 2-mercaptopyrimidine.

Experimental

Synthesis of Tetraaza Macrocyclic Silver(II) Perchlorate

The procedure for the synthesis of (1,4,8,11-tetraazacyclotetradecane)silver(II) perchlorate has been described by Barefield and Mocella [5]. The complex salt was prepared according to the procedure, recrystallized, and dissolved in water for spectral analysis using a Pye-Unicam Model SP8-100 UV–Vis recording spectrophotometer. The absorption maxima and their corresponding absorption coefficients determined for the complex from Beer–Lambert plots are 349 nm (6390 M^{-1} cm^{-1}) and 278 nm (3490 M^{-1} cm^{-1}). The complex was found to be stable in aqueous solution less than pH 7 for spectral and kinetic studies.

Chemicals

The reducing agent, 2-mercaptopyrimidine, was purchased from Aldrich Chemical Co. and was recrystallized from aqueous ethanol solution before being used. Sodium perchlorate was purchased from G.F. Smith Chemical Co. and was recrystallized from triple distilled water. Sodium acetate and sodium monohydrogen phosphate were from Mallinckrodt Chemicals and were used to prepare buffers for the kinetic experiments.

Kinetic Studies

The kinetics of the oxidation of 2-mercaptopyrimidine and (1,4,8,11-tetraazacyclotetradecane)silver(II) was monitored at 420 nm with a Dionex Model 110 Durrum stopped-flow instrument equipped with a thermostatted cell chamber. For simplicity, the reducing agent and the silver(II) complex will, henceforth, be denoted respectively as MP or RSH and $Ag(cyclam)^{2+}$ in the discussion. The kinetic was conducted under pseudo-first-order conditions with the concentration of MP in at least

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ten-fold excess over the oxidant concentration. The reaction temperature was maintained at 25.0 ± 0.1 °C by circulating thermostatted water from a Forma water bath. The reaction solution pH was maintained with acetate or phosphate buffer, and sodium perchlorate was added to adjust the ionic strength of each solution to 0.1 M. Acetate buffers were used for reactions below pH 5.2, phosphate buffers for those above pH 5.2. The pH of the reaction solution was measured using a Beckman digital pH meter.

Reactions were conducted with thermally equilibrated solutions prepared before the experiments. Excellent pseudo-first-order kinetic data were obtained with linearity exceeding three half-lives. The values of k_{obs} reported herein are averages of three runs.

Results and Discussion

Stoichiometry of the Reaction

The stoichiometry of the reaction was determined to be 1:1 with respect to [2-mercaptopyrimidine] and $[Ag(cyclam)^{2+}]$ based on the absorption change of the reacting species in solution. Listed in Table I are the absorption maxima of the reactants and products and their respective extinction coefficients. The solution used to determine the stoichiometry was initially 4.0×10^{-5} M in [MP] and 8.0×10^{-5} M in $[Ag(cyclam)^{2+}]$. By comparing the product spectrum of MP against the disulfide made separately by iodine oxidation of MP, the disulfide product was verified [3c, 6]. The absorption maximum of the disulfide and its extinction coefficient were found to be 237 nm and 18 150 M^{-1} cm^{-1}, respectively. From the increase in absorption of the reacted solution we have estimated the amount of disulfide to be 73% of the theoretical yield of 2.00×10^{-5} M. The lower value in yield could be attributed to further oxidation of the disulfide in solution. Therefore, the stoichiometry of the reaction can be written as

$$2RSH + 2Ag(cyclam)^{2+} \longrightarrow RSSR + 2Ag(cyclam)^{+} + 2H^{+} \quad (1)$$

TABLE I. UV–Vis Absorption Maxima and Extinction Coefficients[a] of MP, $Ag(cyclam)^{2+}$ and the Disulfide

	λ (nm)	ε (M^{-1} cm^{-1})
$Ag(cyclam)^{2+}$	349	6390
	278	3490
MP	346	2960
	281	21330
	214	9150
Disulfide	237	18150

[a]Extinction coefficients were determined from the slopes of Beer–Lambert plots.

Reaction Rate Order

The reaction rate orders with respect to $Ag(cyclam)^{2+}$ and MP concentrations were determined at 25 °C in buffered solutions of constant ionic strength (0.1 M). Linear plots of $\log(A_t - A_\infty)$ *versus* time over three half-lives were obtained. A_t and A_∞ are absorbances of $Ag(cyclam)^{2+}$ at reaction time, t, and at infinity time. Listed in Table II are the values of k_{obs} calculated from the slopes of these pseudo-first-order plots. The constancy of k_{obs} was also verified at pH 6.0 where the $[Ag(cyclam)^{2+}]$ was changed from 0.89×10^{-4} to 1.22×10^{-4} M. The values of k_{obs} at these two $Ag(cyclam)^{2+}$ concentrations agreed reasonably well, within 4.1% of the average k_{obs}.

At low pH, plots of k_{obs} *versus* [MP] are linear with zero intercepts suggesting first-order dependence

TABLE II. k_{obs} at Various pH and [MP]

pH	10^3 [MP] (M)	$10^2 k_{obs}$ (s^{-1})
4.67[a]	1.25	1.24
	1.50	1.62
	2.00	2.39
	2.25	2.62
	2.50	2.97
4.82[a]	1.25	1.64
	1.50	2.04
	1.75	2.33
	2.00	2.73
	2.25	3.02
	2.50	3.45
5.02[a]	1.25	1.75
	1.50	2.14
	1.75	2.62
	2.00	3.07
	2.25	3.28
	2.50	3.52
5.22[a]	1.25	1.96
	1.50	2.39
	1.75	2.80
	2.00	3.20
	2.25	3.68
	2.50	3.95
5.41[b]	1.25	1.86
	1.50	2.51
	1.75	3.02
	2.00	3.67
	2.25	4.31
	2.50	4.74
5.82[b]	1.25	2.57
	1.50	3.38
	1.75	3.64
	2.00	4.74
	2.25	5.60
	2.50	6.45

(continued)

TABLE II. *(continued)*

pH	10^3 [MP] (M)	$10^2 k_{obs}$ (s^{-1})
6.00^b	1.25	2.88
	1.50	3.48
	1.50	3.13^c
	1.75	3.73
	1.75	4.05^c
	2.00	5.40
	2.00	5.33^c
	2.25	7.33
	2.25	7.32^c
	2.50	9.57^c
	2.50	9.29^c
6.18^b	1.25	4.17
	1.50	5.87
	1.75	7.21
	2.00	9.02
	2.25	9.92
	2.50	12.7
6.36^b	1.25	5.09
	1.50	8.03
	1.75	9.60
	2.00	11.6
	2.25	14.8
	2.50	17.9
6.53^b	1.25	7.44
	1.50	10.8
	1.75	14.8
	2.00	18.6
	2.25	22.2

Reaction conditions: [Agcyclam^{2+}] = 0.89×10^{-4} M, μ = 0.10 M, T = 25.0 °C. ^{a}Acetate buffer. ^{b}Phosphate buffer. ^{c}[Ag(cyclam)$^{2+}$] = 1.22×10^{-4} M.

in [MP]. However, plots at higher pH are non-linear indicating H^+ dependence in the rate law. We have reported previously the oxidation of thiols by inorganic complexes to be pH dependent and have shown that this was due to the acid–base equilibria of the substrates in which the reactiveness of the anions was responsible [4]. Since the same rate–pH profiles were observed in the present study, the effect of the acid–base equilibrium reaction of the substrate should be taken into account in the rate law analysis. Therefore, another method was used to determine the reaction order of the thiol and its anion [7]. Calculations were done to fit the kinetic data listed in Table II and to determine the reaction order with respect to [RS$^-$]. Using the mathematical treatment described in ref. 7 we were able to determine the reaction rate order of the thiol anions. This treatment will be described in more detail in the mechanism section of the 'Discussion'.

pH Dependence

A kinetic pH–rate profile of the reaction is shown in Fig. 1, where k_{obs} of [MP] at 2.00×10^{-3} M is plotted *versus* pH. Similar pH dependence rate plots were obtained for reaction series at different MP concentrations. At pH below 5.5 the rate of oxidation changes slightly, however, the rate of reaction increases rapidly as the pH is increased higher than 5.5. This strong pH dependence is due to the acid–base equilibrium reaction of the RSH (eqn. (2)) as well as the oxidation of the RS$^-$ by Ag(cyclam)$^{+2}$.

$$\mathrm{RSH} \rightleftharpoons \mathrm{RS^-} + \mathrm{H^+} \qquad \mathrm{p}K_a = 7.14\ [8] \qquad (2)$$

Thus, the reaction rate law can be expected to have an inverse [H$^+$] dependence which is confirmed from the slope (0.967) of the steep portion of pH–rate plot in Fig. 1. Slopes of close to one were also obtained for the other pH–rate series listed in Table II. This reaction was not studied above pH 6.5 due to the instability of Ag(cyclam)$^{2+}$ in basic solution.

Reaction Mechanism

Based on the product analysis, the stoichiometry, the pH dependence, and the experimental rate order with respect to each reacting species a reaction mechanism is postulated below to accommodate all the experimental data and results.

$$\mathrm{RSH} \rightleftharpoons \mathrm{RS^-} + \mathrm{H^+}$$

$$\mathrm{RS^-} + \mathrm{Ag(cyclam)^{2+}} \xrightarrow[k_2]{} \mathrm{RS\cdot} + \mathrm{Ag(cyclam)^+}$$

$$\mathrm{RSH} + \mathrm{Ag(cyclam)^{2+}} \xrightarrow[k_2']{} \mathrm{RS\cdot} + \mathrm{Ag(cyclam)^+} + \mathrm{H^+}$$

$$2\mathrm{RS\cdot} \longrightarrow \mathrm{RSSR}$$

Since RS$^-$ has been reported as more reactive than RSH [4] at higher pH, a rate law (eqn. (3)) was derived under the following assumptions, [RS$^-$] < [RSH] and [H$^+$] > K_A.

$$-(\mathrm{d}\ln[\mathrm{Ag(cyclam)^{2+}}]/\mathrm{d}t)$$

$$= 2(k_2' + k_2K_A/[\mathrm{H^+}])[\mathrm{RSH}] \qquad (3)$$

The terms on the right hand side of eqn. (3) can be equated to the observed rate constant which allows the determination of k_2 and k_2' from plots of k_{obs}/[RSH] *versus* K_a/[H$^+$]. At 25 °C and 0.1 M ionic strength the values of k_2 and k_2' are $(1.45 \pm 0.50) \times 10^2$ and 5 ± 1 M^{-1} s^{-1}, respectively.

The values of the second order rate constants and the acidity constant were used to calculate k_{obs} at different pH values and MP concentrations using eqn. (3). The calculated k_{obs} values are in good agreement with the experimental k_{obs} with a correlation coefficient of 0.975 for all the experimental points.

The values of k_2 for the oxidation of MP by octahedral complexes such as $IrCl_6^{2-}$ and $Fe(bpy)_3^{3+}$ have been estimated to be around 10^4–10^5 M^{-1} s^{-1}, whereas the k_2 for the square planar complexes, Ag(cyclam)$^{2+}$, is 1.45×10^2 M^{-1} s^{-1}. The large differ-

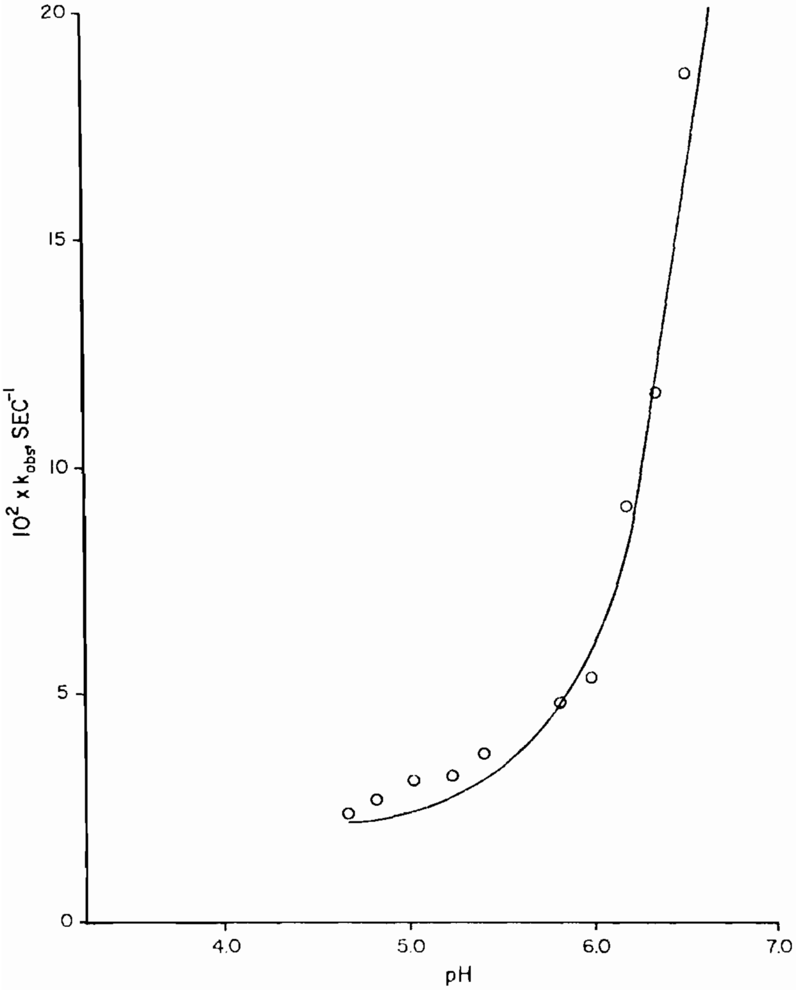

Fig. 1. k_{obs} *vs.* pH; [MP] = 2.00 x 10^{-3} M, [Ag(cyclam)$^{2+}$] = 0.89 x 10^{-4} M, T = 25 °C, and μ = 0.10 M. Solid line was calculated using eqn. (3).

ence in rate constants between these complexes suggests that perhaps different types of electron-transfer mechanisms are involved. Because of the vacant axial sites in Ag(cyclam)$^{2+}$, it is possible that a penta-coordinated species is involved in the electron-transfer reactions. Penta-coordinated intermediates have been postulated in other hypervalent silver systems studied by Kirschenbaum *et al.* in the oxidation of hydrogen peroxide [9], thiosulfate [10], and arsenite [11]. Similar penta-coordinated intermediates may be postulated in this study to account for the difference in rates between the octahedral and the square planar oxidizing agents.

Further studies are presently being carried out using other reductants and silver(II)cyclams to elucidate the redox mechanism.

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