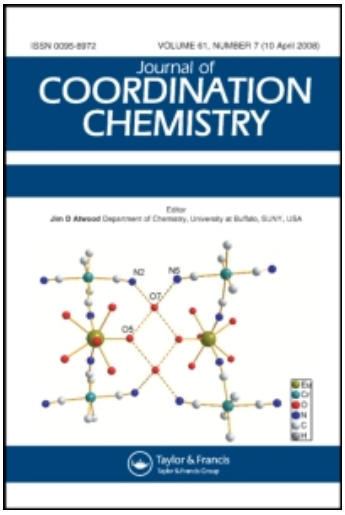

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Kinetics and mechanism of the oxidation of a heterocyclic thioamide by silver(II)-cyclam

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KINETICS AND MECHANISM OF THE OXIDATION OF A HETEROCYCLIC THIOAMIDE BY SILVER(II)-CYCLAM

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The kinetics of the oxidation of 4,6-dimethyl-2-mercaptopyrimidine (DMP) by $Ag(cyclam)^{2+}$ were studied in buffer solutions from pH 5.8 to 7.2 at constant ionic strength of 0.10 M ($NaClO_4$). The reaction is observed to be first-order with respect to [$Ag(cyclam)^{2+}$] and to [DMP]. However, the reaction rate is affected by the pH of the solution owing to the acid–base equilibrium of the thiol. The mechanism postulated to account for the kinetics includes an acid–base equilibrium and oxidation of thiol (RSH) and thiolate ion (RS^-) by $Ag(cyclam)^{2+}$ to $RS^{\bullet}$ radicals which undergo rapid dimerization to form disulfide (RSSR). From the postulated mechanism and the observed kinetics a rate expression was derived, and second-order rate constants and activation parameters were calculated. The pK_a values of the acid dissociation reaction of DMP were also determined at four temperatures using spectrophotometric methods, and thermodynamic parameters calculated from the K_a values.

Keywords: Kinetics and mechanism; Acid dissociation constants; Thermodynamics parameters; 4,6-Dimethyl-2-mercaptopyrimidine; Silver(II)-cyclam

INTRODUCTION

Sulfhydryl (–SH) and disulfide (–S–S–) groups are found in many biological compounds such as enzymes, hormones, polypeptides, proteins, and antibiotic drugs [1–7]. The oxidation of the –SH group is both chemically and biologically interesting, because sulfur has several oxidation states, from −2 to +6, that under different redox conditions produce different sulfur products such as disulfides (R–S–S–R), sulfenic acid (R–SOH), sulfinic acid (RSO_2H), and sulfonic acid (RSO_3H). Cysteine is a biochemical compound that forms all these sulfur products with common oxidizing agents [8]. An important biochemical reaction of –SH-containing compounds is their conversion to disulfides. Biological oxidants such as cytochrome *c*, flavins, quinones, dehydroxyascorbate, fumarate, and amino acids are known to oxidize *in vivo* –SH groups to disulfides [2]. With oxidizing agents such as hydrogen peroxide [9], ozone [10], iodine [11], metal complexes of Fe(III) [12,13], Cr(III) [14], Mo(IV) [15], Cu(II)

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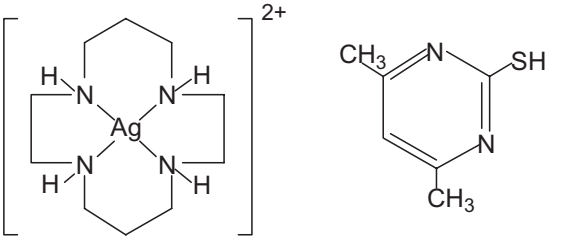

FIGURE 1 Silver(II)-cyclam and 4,6-dimethyl-2-mercaptopyrimidine.

[16], Ir(IV) [17,18], and 12-tungstocobaltate(III) [19], disulfides are formed. Several thiol compounds, such as 2-thiouracil and 2-mercaptopyrimidine and their derivatives, are used as drugs to treat hyperthyroidism; many studies have shown that they inhibit iodide organification in the thyroid gland [5,20].

Studies of the electrochemical oxidation pathways of –SH-containing biological compounds such as 2-thioxanthine [21], 6-thioguanine [22a], 6-mercaptopurine [22b], and xanthine-catalyzed electrochemical oxidation of 6-thioxanthine [23] have been reported. Other studies include the electrochemical oxidation of 2-mercaptopurine-*N*-oxide at a carbon electrode [24] and 2-mercaptobenzimidazole on a copper electrode [25] where both are dependent on the pH and involve free radical formation. All of these studies have shown that disulfides are the products. However, oxidation reactions of thiols with strong oxidizing agents, such as permanganate, chromate, and other metal ions, yield organic sulfonate products [26]. The oxidation of 2-mercaptopyrimidines and 2-thiouracils by substitution-inert octahedral complexes, tris(bipyridine)iron(III) and hexachloroiridate(IV), have been shown to be outer-sphere [17,18]. However, with square-planar complexes such as silver(II)-tetraaza macrocyclic complexes the electron-transfer mechanism is less certain [27–30]. We wish to report the kinetics and mechanism of the oxidation of 4,6-dimethyl-2-mercaptopyrimidine (DMP) by silver(II)-cyclam. Figure 1 shows the structures of the reactants.

EXPERIMENTAL

Materials

The thiol, 4,6-dimethyl-2-mercaptopyrimidine (DMP), and the ligand, 1,4,8,11-tetraazacyclotetradecane (cyclam), were purchased from Aldrich Chemical Co. Silver perchlorate was obtained from G. F. Smith Chemical Co. Analytical grade sodium acetate, sodium phosphate, sodium dihydrogen phosphate and sodium borate were from J. T. Baker, Inc. and were used to prepare buffer solutions of the desired pH for spectrophotometric and kinetic studies. For the pK_a series, the DMP was recrystallized by dissolving it in a solution of (1 : 1/v : v) ethanol and water at 60–70°C, then cooled, precipitated, and filtered. The recrystallized DMP was verified by melting point and FTIR analysis. For the spectral and kinetic studies, double-distilled water was used to prepare all solutions, including the buffer solutions. The complex, $[Ag(cyclam)](ClO_4)_2$, was synthesized according to published procedure [27,31].

Kinetics Studies

A Hi-Tech stopped-flow spectrophotometer equipped with an SU-40 spectrophotometer was used to collect kinetic data [32]. A refrigeration unit and a water circulator were used to circulate thermostatted water to keep the cell temperature constant throughout the reaction. A digital thermometer was used to record the cuvette temperature to within $\pm 0.1^{\circ}C$. The DMP solutions were prepared in buffers at the desired pH. Silver(II)-cyclam solutions at 0.10 M ionic strength ($NaClO_4$) were prepared fresh for each kinetic series. The reactions were followed at 430 nm where only silver(II)-cyclam absorbed. The kinetics were carried out under pseudo-first-order conditions with DMP concentrations at least 150 times in excess of that of the silver(II) complex. The reactant solutions were loaded into two glass micro syringes in the mixer chamber and allowed to equilibrate to the thermostatted temperature. The stopping syringe was set so that when 200 μL of solution was collected it would trigger data collection. The reacted solutions were collected and the pH measured with an Orion pH meter. The absorbance changes (the output voltage signals from the photomultiplier) were recorded as a function of time on an HP computer via an analog/digital converter. Sophisticated Hi-Tech kinetic software was used to analyze the data by fitting it with a single exponential, non-linear curve-fitting regression analysis procedure for first-order reactions. This procedure is based on the Gauss–Newton method and is enhanced with the Marquardt algorithm to ensure fit convergence [32]. The program calculates the rate constant, in this case the pseudo-first-order k_{obs}, and the percent error of the fit between the experimental and the theoretical kinetic curves. Typically, four kinetic runs were performed to obtain an average k_{obs} value with no more than 1% deviation.

UV–vis Spectral Measurements of DMP

For the acid dissociation constant study, the absorbance of DMP was measured as a function of pH at an ionic strength of 0.1 M (NaCl). The following reagents were used to prepare buffers of different pH values: acetate buffers (pH 4–5.2), phosphate buffers (pH 5.4–8.5 and 9.7–12), and borate buffers (pH 8.7–9.5). Absorption spectra were taken with a Shimadzu UV–vis spectrophotometer equipped with a refrigeration unit and a water circulator to maintain the temperature of the solution in the cuvette. Spectra were taken only after the solutions reached the desired temperature. An Orion Research model EA940 pH/ion analyzer with an automatic temperature compensation probe and a combination glass electrode with Ag/AgCl reference half-electrode was used for pH measurements.

RESULTS AND DISCUSSION

pK_a of 4,6-Dimethyl-2-mercaptopyrimidine

The acid dissociation constants of DMP at four temperatures were determined from the electronic absorption spectra as a function of pH. The buffers used were maintained at ionic strength 0.10 M with NaCl. Figure 2 shows the absorption spectra of DMP in three different buffers (pH 6.20, 8.70, and 11.08). Three isosbestic points, observed for this family of spectra, indicate that the thiol and its conjugate base are in equilibrium. The isosbestic points with their respective extinction coefficients, ε, and log ε are listed in Table I.

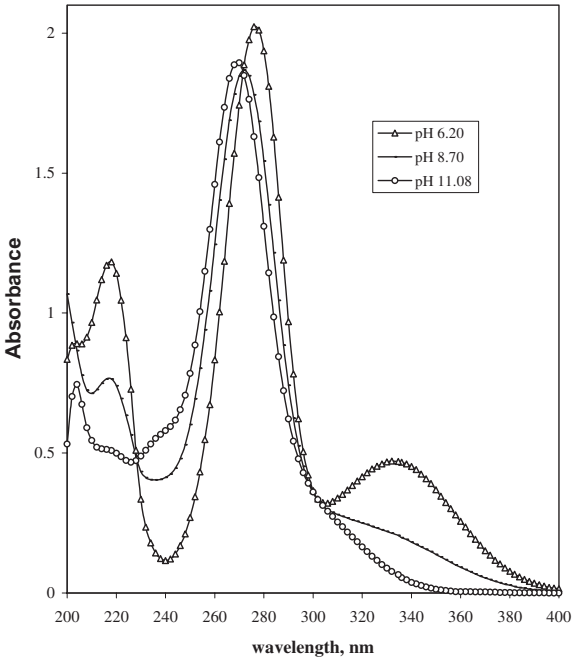

FIGURE 2 UV–vis spectra of DMP in various buffers. [DMP] = 1.00×10^{-4} M; 25°C.

TABLE I Isosbestic points of 4,6-dimethyl-2-mercaptopyrimidine

Isosbestic point (nm)	$\varepsilon(M^{-1}\,cm^{-1})$	*Log* ε
229	4 230	3.63
273	15 900	4.20
302	2 870	3.46

To determine the dissociation constants of DMP, the absorbances of the thiol in buffer solutions with pHs ranging from 5.81 to 12.82 were measured at 334 nm. More than 20 buffer solutions containing 2.50×10^{-4} M DMP were prepared and their absorbances recorded at 334 nm as a function of pH. From the K_a expression and the RSH balance, the equation for $[RS^-]_e$ [Eq. (3)] is obtained. From the Beer–Lambert relationship, the total absorbance due to RSH and RS^-, Eq. (4), is derived.

$$RSH + H_2O \rightleftharpoons RS^- + H_3O^+$$

$$K_a = \frac{[RS^-]_e[H_3O^+]}{[RSH]_e} \tag{1}$$

$$[RSH]_t = [RSH]_e + [RS^-]_e \tag{2}$$

$$[RS^-]_e = \frac{[RSH]_t(K_a/[H_3O^+])}{(1 + K_a[H_3O^+])} \tag{3}$$

$$A_t = \varepsilon_{RSH}[RSH]_t + (\varepsilon_{RS^-} - \varepsilon_{RSH})[RS^-]_e \tag{4}$$

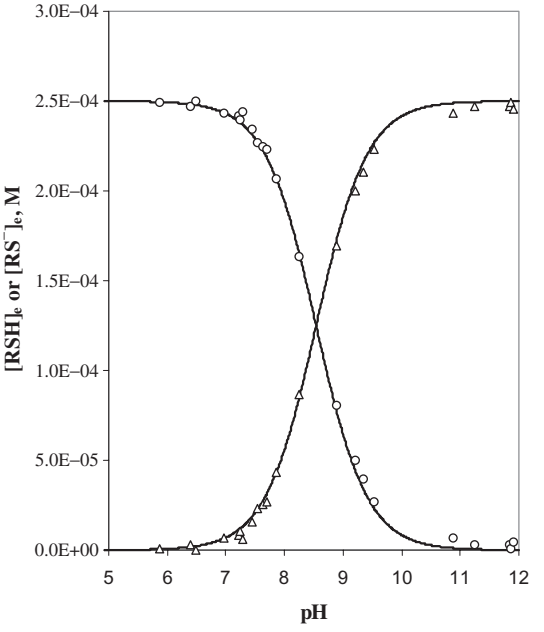

FIGURE 3 Plots of $[RSH]_e$ and $[RS^-]_e$ versus pH. Experimental points: $[RSH]_e$ (○) and $[RS^-]_e$ (△); Calculated curves (—). $[DMP] = 2.50 \times 10^{-4}$ M; $\mu = 0.10$ M; 25°C.

Equations (3) and (4) are used to calculate the total absorbance (A_t) and the equilibrium concentrations of RSH and RS^- as a function of $[H_3O^+]$. Using the total $[RSH]_t$ in solution and initial guess values of ε_{RS^-}, ε_{RSH}, and K_a the total absorbances for pH from 4 to 12 were calculated and compared with the experimental data. The initial guess values were then refined for subsequent iterations until excellent agreement between the calculated and the experimental A_t was reached. Figure 3 illustrates pH-dependent $[RSH]_e$ and $[RS^-]_e$ versus pH plots where the intersecting point is the pK_a value of DMP. In Fig. 3, the calculated lines are superimposed on the experimental points. The final value of K_a for DMP (at 25°C) calculated from curve-fitting is 2.88×10^{-9}, and the values of ε_{RSH} and ε_{RS^-} are 4000 and 510 $M^{-1}\,cm^{-1}$, respectively. Figure 4 is the absorbance versus pH sigmoidal plot that shows the theoretical fit of A_t on the experimental points. Similar curve-fitting procedures were carried out for absorbance versus pH at other temperatures; Table II lists all the K_a values.

From the temperature-dependent K_a values in Table II, thermodynamic parameters (ΔH° and ΔS°) for the acid dissociation equilibrium reaction of DMP were calculated from the slope and the intercept of $\ln K_a$ versus $1/T$ plot. The thermodynamic parameters at 298 K are expressed in Eq. (5) as

$$\Delta G^\circ = (45.6\,\text{kJ mol}^{-1}) - T(-9.92\,\text{J mol}^{-1}\,\text{K}^{-1}). \quad (5)$$

Stoichiometry of the Reaction

The stoichiometry of the reaction between DMP and $Ag(cyclam)^{2+}$ in aqueous solution was studied by following the absorbance change at 390 nm of five solutions of varying

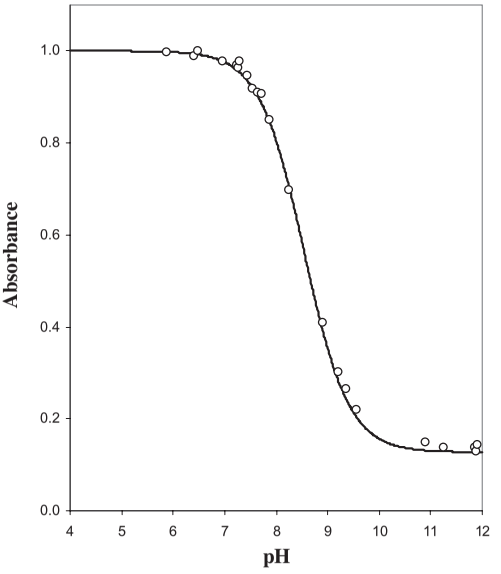

FIGURE 4 Absorbance versus pH plot. Experimental points (○); calculated curve (—). [DMP] = 2.50×10^{-4} M; $\mu = 0.10$ M; 25°C.

TABLE II Acid dissociation constants of DMP at various temperatures[a]

T (°C)	10^9 K_a	pK_a
20.0	2.30	8.64
25.0	2.88	8.54
30.0	4.70	8.33
35.0	5.37	8.27

[a] [DMP] = 2.50×10^{-4} M; $\mu = 0.10$ M.

initial concentration ratios of the reactants, $[Ag(cyclam)^{2+}]_i/[DMP]_i$. The reactions were allowed to proceed to completion, and the final absorbances recorded. The differences between the final and initial readings were obtained, and ratios of $\Delta[Ag(cyclam)^{2+}]_f/\Delta[DMP]_f$ calculated. An average value of 0.944 for $\Delta[Ag(cyclam)^{2+}]_f/\Delta[DMP]_f$ was obtained for the stoichiometry. Therefore, the stoichiometry for the reaction [Eq. (6)] is one mole of DMP to one mole of $Ag(cyclam)^{2+}$, which is expected because the same 1 : 1 ratio has been found in previous studies [27–30].

$$2Ag(cyclam)^{2+} + 2RSH = RSSR + 2Ag(cyclam)^{+} + 2H^{+}. \quad (6)$$

Moreover, we have electrochemically synthesized bis(4,6-dimethylpyrimidin-2-yl) disulfide and obtained its electronic absorption spectrum for comparison. In CH_3CN the disulfide has a λ_{max} at 240 nm with $\varepsilon = 16\,900\ M^{-1}\,cm^{-1}$.

Kinetics

The kinetics for oxidation of DMP by $Ag(cyclam)^{2+}$ in aqueous solution were investigated under pseudo-first-order conditions with [DMP] at least 150 times in

excess of $[Ag(cyclam)^{2+}]$. The observed rate law at constant pH and $\mu = 0.10\,M$ is

$$\frac{-d[Ag(cyclam)^{2+}}{dt} = k_{obs}[Ag(cyclam)^{2+}] \quad (7)$$

where k_{obs} is the pseudo-first-order rate constant, calculated using the non-linear curve-fitting software for first-order kinetics.

The rate dependence in [DMP] was determined by investigating the rate of reaction as a function of the reducing agent concentration at constant pH. The kinetics were investigated under the following conditions: $[Ag(cyclam)^{2+}] = 3.00 \times 10^{-5}\,M$, [DMP] from 4.30×10^{-3} to $1.00 \times 10^{-2}\,M$, and $pH = 6.47 \pm 0.08$. The rate of reaction was first-order with respect to [DMP] as shown by the linear plot of k_{obs} versus [DMP] in Fig. 5. For the pH dependence series, eight buffer solutions, pHs ranging from 5.76 to 7.21, were used. The concentrations of the reactants for this series were: $[Ag(cyclam)^{2+}] = 3.00 \times 10^{-5}\,M$ and $[DMP] = 5.13 \times 10^{-3}\,M$. Pseudo-first-order rate constants, k_{obs}, determined at four different temperatures as a function of pH were obtained.

All k_{obs} versus pH plots showed that at pH below 6.3 the reaction rates were slow, but above pH 6.3 the reaction rates became much faster. No kinetic runs were conducted above pH 7.2 because silver(II)-cyclam is unstable in basic solution. Similar pH-enhanced rate kinetics have been observed for the oxidation of 2-thiopyrimidines and 2-thiouracils by other transition metal complexes.

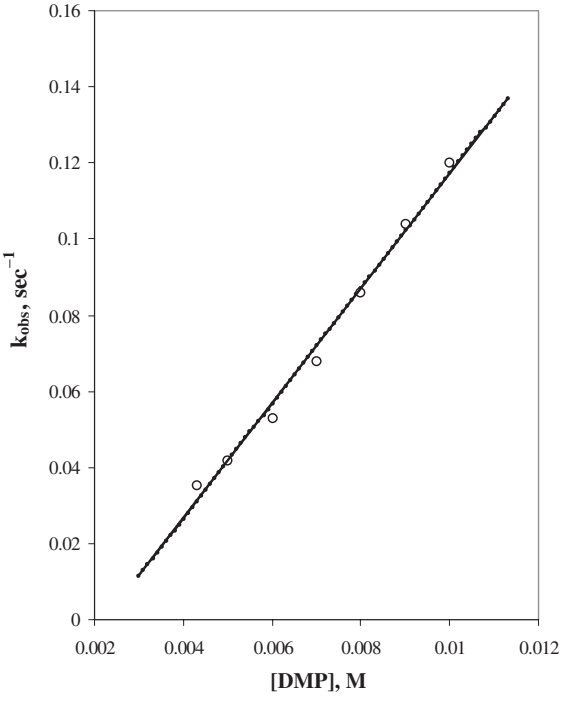

FIGURE 5 Plot of k_{obs} versus [DMP]. $[DMP] = (4.3\text{–}10.0) \times 10^{-4}\,M$; $[Ag(cyclam)^{2+}] = 3.00 \times 10^{-5}\,M$; $pH = 6.47 \pm 0.08$; $\mu = 0.10\,M$; 25°C.

Mechanism and the Derived Rate Expression

Figure 6 is the k_{obs} versus pH plot for the reaction at 25°C. From pH 5.8 to 6.3, the rate increases slowly, but the rate increases sharply at pH higher than 6.3. This type of kinetics behavior is usually associated with an acid–base equilibrium reaction of one of the reactants [33]. Based on the observed rate law and the reaction stoichiometry, a mechanism for the reaction to account for the rate–pH profile is postulated. The rate-determining step involves the formation of RS· free radicals from the oxidation of RS^-. The RS· radicals are also formed in the oxidation of RSH. The rate-terminating step is the rapid dimerization of the free radicals to disulfide. The reaction steps for the proposed mechanism are shown below.

$$RSH \overset{K_2}{\rightleftharpoons} RS^- + H^+$$

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

$$RSH + Ag(cyclam)^{2+} \xrightarrow{k_{2'}} RS\cdot + H^+ + Ag(cyclam)^+$$

$$2RS\cdot \rightarrow RSSR \quad \text{(fast)}$$

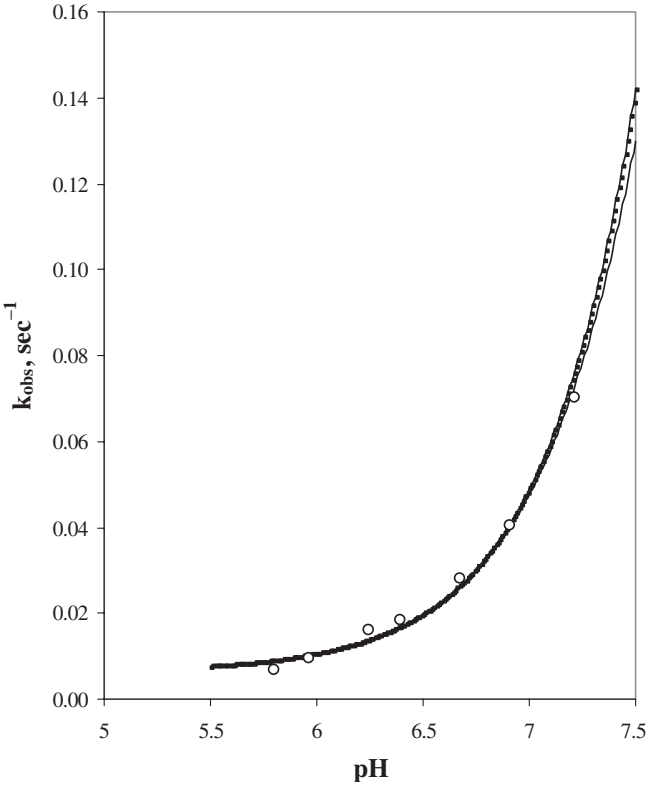

FIGURE 6 Theoretical fit of experimental k_{obs} as a function of pH at 25°C. Data points (○); lower curve – fitted with Eq. (9); upper curve – fitted with the denominator of Eq. (9) reduced to 1.

A rate expression, Eq. (8), was derived based on the proposed mechanism. Equations (7) and (8) when combined yield Eq. (9) which relates k_{obs} to K_a, k_2', k_2, and $[H^+]$.

$$\frac{-d[Ag(cyclam)^{2+}]}{dt} = \frac{2(k_2' + k_2 K_a/[H^+])}{(1 + K_a[H^+])} [RSH][Ag(cyclam)^{2+}] \quad (8)$$

$$k_{obs} = \frac{2(k_2' + k_2 K_a/[H^+])}{(1 + K_a/[H^+])} [RSH]. \quad (9)$$

Theoretical fit of k_{obs} versus $[H^+]$ or pH was carried out using the acid dissociation constant of DMP ($K_a = 2.88 \times 10^{-9}$) determined earlier at 25°C. The calculated fit of the experimental points was done by choosing an initial value for k_2' from the k_{obs} data at the low pH region. The concentration of [RSH] was assumed to be unchanged over the entire course of reaction since less than 5% is consumed when the reaction is complete. An initial k_2 value was used with k_2' and K_a in the curve-fitting. These initial values were adjusted in subsequent iterations until the best fit was obtained (Fig. 6). Two curve-fitting procedures were used in Fig. 6. The upper curve was calculated with the assumptions that $[H^+] \gg K_a$ and $[RSH] \gg [RS^-]$, which reduced the denominator in Eq. (9) to 1. The lower curve was calculated with no simplification of Eq. (9). It can be seen that in the high pH region, the two curves diverged and the lower curve appeared to be the better fit. At 25°C, the second-order rate constants, k_2' and k_2, are 0.60 and 145 $M^{-1} s^{-1}$, respectively. The same curve-fitting procedure was used to treat the temperature-dependent k_{obs}–pH kinetic data and the k_2 ($M^{-1} sec^{-1}$) values obtained are: 107 (20°C), 145 (25°C), 177 (30°C), and 199 (35°C).

We have recalculated k_2 for the oxidation of 2-mercaptopyrimidine (MP) by $Ag(cyclam)^{2+}$, $Ag(tmc)^{2+}$ and $Ag([15]aneN_4)^{2+}$ using Eq. (9) and the K_a values reported earlier [27,28]. Previously, k_2' and k_2 were obtained from the intercepts and slopes of plots of $k_{obs}/[RSH]$ versus $K_a/[H^+]$ with the following assumptions: $[RS^-] < [RSH]$ and $[H^+] > K_a$. These rate constants were used in activation parameters calculations.

Heterocyclic thioamides have tautomeric forms that can contribute to some differences in rates. However, Albert and Barlin [34] have reported that thioamides in aqueous solution favor the mercapto structure more than the thione at equilibrium. Because proton transfer is rapid between the tautomers, it becomes kinetically indistinguishable which tautomer is the reactive species in the kinetics.

Activation Parameters

The activation parameters for the k_2 path, the rate-determining step in the oxidation of RS^- by silver(II)-cyclam, are determined using the transition state equation [35]:

$$k_2 = (RT/Nh) \exp(\Delta S^{\ddagger}/R) \exp(-\Delta H^{\ddagger}/RT),$$

where N is Avogadro's number and h is Planck's constant. They are calculated from the slope and intercept of $\ln(k_2/T)$ versus $1/T$ plot, and they are: $\Delta H^{\ddagger} = 27.6$ kJ mol^{-1} and $\Delta S^{\ddagger} = -111$ J $mol^{-1} K^{-1}$. Activation parameters for other systems were also calculated for comparison with the DMP system. For the oxidation of MP, MMP, and DMP by $Ag(cyclam)^{2+}$, the $\Delta S^{\ddagger}$ values are −46, −83, and −111 J $mol^{-1} K^{-1}$, respectively. For

the series, the entropy of activation for the oxidation of the thiols by $Ag(cyclam)^{2+}$ follows the nucleophilic strengths of the thioamides. The $\Delta S^{\ddagger}$ values for oxidation of MMP and MP by $Ag(tmc)^{2+}$and $Ag([15]aneN_4)^{2+}$ are also negative (from -101 to $-115\,J\,mol^{-1}\,K^{-1}$) and are in close agreement with the DMP system. The entropy of activation shows that the oxidations of these mercaptopyrimidines by silver(II)-tetraaza macrocyclic complexes favor the inner-sphere mechanism. These silver(II) tetraaza macrocyclic complexes are square-planar [36–40], and RS^- could coordinate to an axial site to form pentacoordinated species. One can also compare the rates of oxidation of the thiols by octahedral complexes with the square-planar complexes using k_2/k_2' ratios. Table III lists these ratios for the oxidation reactions of several mercaptopyrimidines by octahedral and square-planar transition metal complexes. The k_2/k_2' ratios for outer-sphere oxidants such as hexachloroiridate(IV) and tris(bipyridine)iron(III) range from 10^4 to 10^5 and are two orders of magnitude larger than those of silver(II)-tetraaza macrocyclic complexes. This suggests that oxidation by square-planar complexes proceeds by a different electron-transfer mechanism. Kirschenbaum and co-workers have studied redox kinetics and mechanisms of a variety of substrates using the square-planar $Ag(OH)_4^-$ as oxidant [41–54] and reported transient pentacoordinated species in the oxidation of azide and thiosulfate ions [41,42]. Because of negative entropies of activation found in other systems such as the oxidation of hydrogen peroxide, thiourea, cyanide, thiocyanate, arsenite, sulfite, and hypophosphite ions by the same oxidant [43–49], they have proposed an inner sphere electron-transfer mechanism for these reactions. With biochemical and organic substrates such as triglycine and tetraglycine, ethylenediamine, *dl*-mandelate, edta, and *vic*-dioximates, transient pentacoordinated species formed in the replacement of the hydroxo ligand in $Ag(OH)_4^-$ [50–54]. More direct evidence is the reported observation of a silver(II)-ligand radical in reduction of a silver(III)-macrocyclic tetraaza complex [55]. Pentacoordinate species with thiol substrates have also been reported for other d^9 centers such as Cu(II) [56].

TABLE III Second-order rate constants for the oxidation of 2-mercaptopyrimidines by various transition metal complexes

Reaction	$k_2(M^{-1}\,s^{-1})$	k_2/k_2'	*Ref.*
$IrCl_6^{2-} + MP$	8×10^4	5×10^4	17
$IrCl_6^{2-} + MMP$	1×10^5	4×10^4	18
$IrCl_6^{2-} + DMP$	1×10^5	1×10^5	18
$IrCl_6^{2-} + TU$	2×10^3	2×10^4	17
$Fe(bpy)_3^{3+} + TU$	2×10^4	1×10^4	18
$Ag(cyclam)^{2+} + MP$	2.30×10^2	0.5×10^2	27, 28
$Ag(tmc)^{2+} + MP$	3.95×10^2	0.7×10^2	27, 28
$Ag([15]aneN_4)^{2+} + MP$	9.50×10^2	1.9×10^2	27, 28
$Ag(cyclam)^{2+} + MMP$	1.88×10^2	0.6×10^2	30
$Ag([15]aneN_4)^{2+} + MMP$	10.5×10^2	1.3×10^2	Unpublished results
$Ag(cyclam)^{2+} + DMP$	1.45×10^2	2.4×10^2	This work

MP = 2-mercaptopyrimidine; MMP = 4-methyl-2-mercaptopyrimidine; DMP = 4,6-dimethyl-2-mercaptopyrimidine; TU = 2-thiouracil.

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