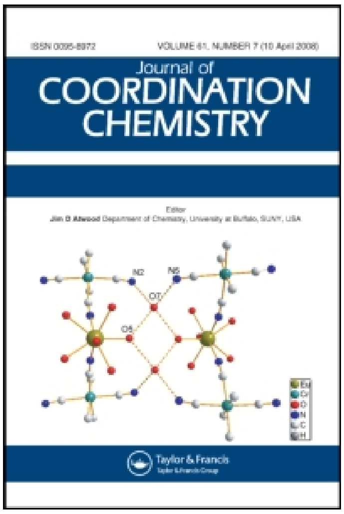

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KINETICS AND MECHANISM OF THE OXIDATION OF 4-METHYL-2-MERCAPTOPYRIMIDINE BY SILVER(II)-CYCLAM AND THE THERMODYNAMICS OF ITS ACID–BASE REACTION

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The kinetics of the oxidation of 4-methyl-2-mercaptopyrimidine (MMP) by $\mathrm{Ag(cyclam)}^{2+}$ was studied in buffer solutions from pH 5.68 to 7.33 at total ionic strength of 0.10 M ($\mathrm{NaClO_4}$). The reaction is first order with respect to each of the reactants, and is strongly influenced by the pH of the solution. The mechanism postulated to account for the kinetics and the pH behavior involves the acid–base reaction of MMP, the oxidation of RSH and $\mathrm{RS^-}$ to $\mathrm{RS^\bullet}$ and free radical dimerization to form RSSR. The reaction obeys the following rate law:

$$\frac{-\mathrm{d}\{[\mathrm{Ag(cyclam)}]^{2+}\}}{\mathrm{d}t} = \frac{2(k_2' + k_2K_\mathrm{a}/[\mathrm{H^+}])}{(1 + K_\mathrm{a}/[\mathrm{H^+}])}[\mathrm{RSH}]\{[\mathrm{Ag(cyclam)}]^{2+}\}$$

The second-order rate constants calculated for the oxidation of RSH (k_2') and $\mathrm{RS^-}$ (k_2) at 25°C are 3.3 and $188\,\mathrm{M^{-1}\,s^{-1}}$, respectively. The activation parameters for the k_2 path are $\Delta H^{\neq} = 33.6\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\neq} = -83.3\,\mathrm{J\,mol^{-1}\,K^{-1}}$. An inner-sphere electron-transfer mechanism, with the probable formation of a penta-coordinate species between silver(II)-cyclam and $\mathrm{RS^-}$, is postulated.

The acid–base reaction of MMP was investigated by UV–Vis spectroscopy from pH 4 to 12 at ionic strength of 0.10 M (NaCl) and at four temperatures. The pK_a values determined for MMP at 20°C, 25°C, 30°C and 35°C are 7.85, 7.73, 7.61 and 7.53, respectively. The thermodynamic parameters for the acid–base reaction of MMP at 298 K are $\Delta H^0 = 38.0\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^0 = -20.5\,\mathrm{J\,mol^{-1}\,K^{-1}}$.

Keywords: Kinetics; thermodynamics; 4-methyl-2-mercaptopyrimidine; silver(II)-cyclam

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INTRODUCTION

Sulfhydryl and disulfide groups are found in biological compounds such as hormones, enzymes, polypeptides, amino acids and proteins.[1-4] An important biochemical reaction of the sulfhydryl compounds is their conversion to disulfides by oxidation. Biological oxidants such as cytochrome c, flavins, quinones, dehydroxylascorbate, fumarate and amino acids are known to oxidize sulfhydryl groups *in vivo* to disulfides.[2] Several heterocyclic thioamides such as the 2-mercaptopyrimidines (MPs) and 2-thiouracils are known to have anti-hyperthyroidal activities and many studies have shown that these compounds act as inhibitors in the iodide organification process in the thyroid gland.[5]

Kinetics and mechanisms of the oxidation of organic compounds containing the –SH groups by various oxidizing agents including ozone,[6b] hydrogen peroxide,[6c] biochemical oxidants such as myeloperoxidase[6d] and many metal ions and metal complexes have been reported.[6-11] With mild oxidizing agents, disulfides are usually the products, but with strong oxidants such as permanganate ion,[6d] sulfonates are obtained. Studies of the electrochemical oxidation pathway of –SH containing biological compounds such as 6-thioguanine, 6-mercaptopurine and 6-thioxanthine have also been reported.[12-14] At moderate potentials, the thiol groups are oxidized and dimerized products are formed. The oxidation of 2-thiouracils and 2-mercaptopyrimidines with substitution-inert octahedral complexes such as hexachloroiridate(IV) and tris(bipyridine)iron(III) have been shown to proceed by an outer-sphere mechanism.[7,8] However, the inner-sphere mechanism for the oxidation of MPs with square-planar tetraaza macrocyclic complexes of silver(II) is less certain.[9-11] This study reports the kinetics and mechanism of the oxidation of 4-methyl-2-mercaptopyrimidine (MMP) by silver(II)-1,4,8,11-tetraazacyclotetradecane (silver(II)-cyclam). Figure 1 shows the structures of the reactants.

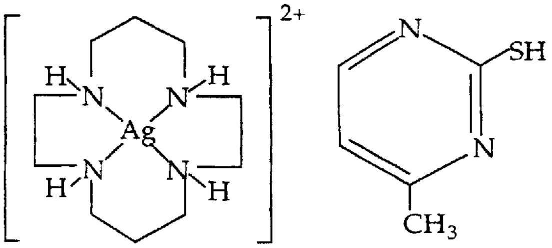

FIGURE 1 Structures of MMP and silver(II)-cyclam.

EXPERIMENTAL

Chemicals

The cyclam and MMP hydrochloride were obtained from Aldrich Chemical Co., and silver perchlorate and sodium perchlorate were from G.F. Smith Chemical Co. Absolute ethyl alcohol, acetone and anhydrous ether were reagent grade chemicals. Sodium acetate, sodium phosphate, sodium dihydrogen phosphate and sodium borate were all analytical grade chemicals from J.T. Baker Inc. The hydrochlorides of MMP were recrystallized further in 50% aqueous ethanol solution before use. Stock solutions of MMP were prepared and neutralized with 1 N sodium hydroxide. Aliquots were then diluted with proper amounts of buffers to prepare the reagent solutions for the thermodynamics and the kinetics experiments. Deionized-distilled water was used to prepare all solutions.

UV–Vis Spectrophotometry Measurements

In the absorbance–pH experiments, the following buffers were used: acetate buffers for pH 4–5.2, phosphate buffers for pH 5.4–8.5 and 9.7–12, and borate buffers for pH 8.7–9.5. Absorption spectra were taken with a Hewlett Packard model 8451A diode array spectrophotometer equipped with a thermostatted water circulator to keep the temperature of the solution in the cuvette constant. The average deviation in the temperature recorded by a BGR Industries digital thermometer was ±0.1°C. Spectra were taken only after the solutions had reached thermal equilibrium. An Orion Research model EA940 pH/ion analyzer equipped with an automatic temperature compensation probe and a Ag/AgCl combination reference electrode was used to monitor the pHs. The absorbance data for four temperatures (20°C, 25°C, 30°C and 35°C) were recorded as a function of pH, and more than twenty-five buffer solutions were used in each temperature series.

Synthesis of Silver(II)-Cyclam Perchlorate

The complex compound silver(II)-cyclam perchlorate ($\mathrm{Ag(cyclam)(ClO_4)_2}$) was prepared according to literature procedures with some modification.[10,15] Five mmol of the ligand and 10 mmol of silver perchlorate were mixed in 30 mL of water. The silver residue formed in the reaction was removed by vacuum filtration and the filtrate collected was cooled at 5°C overnight. The orange-colored crystals were separated and washed with cooled distilled water followed with 5 mL THF to remove any trace ligand. The crystals were then dried *in vacuo*. The silver(II)-cyclam perchlorate crystals were further recrystallized in warm distilled water before being used to make the reactant solutions for the kinetics experiments.

Kinetics Studies

The kinetics of the oxidation of MMP by $[Ag(cyclam)]^{2+}$ was studied using a Hi-Tech SF-51 stopped-flow spectrophotometer that was equipped with a SU-40 spectrophotometer unit. A refrigeration unit and a water circulator were used to keep the temperature of the mixer-cell assembly constant. Temperature of the thermostatted water in the mixer-cell unit was measured with a digital thermometer, and the average deviation was ±0.1°C. The MMP oxidation by silver(II)-cyclam was followed at 430 nm where only silver(II)-cyclam absorbed. The reactant solutions, at the same pH and ionic strength, were loaded into syringes in the mixer-cell unit. Both solutions were allowed to thermally equilibrate to the reaction temperature before mixing. The exit solutions from the stopped-flow were collected and their pH measured for each kinetics series. The output voltage signals from the photomultiplier unit were recorded with a Hewlett Packard model 300 computer *via* an analog/digital converter. The acquired data were then analyzed with the Unifit program using the single exponential non-linear curve-fitting regression analysis procedure. This procedure is based on the Gauss–Newton method and is enhanced with the Marquardt algorithm to ensure fit convergence.[16] *Pseudo*-first-order rate constants, k_{obs}, calculated by the program, were quite reproducible. Typically, four individual runs were performed to obtain the average k_{obs} values, and the average deviations were less than 1% with only a few higher than 2%.

RESULTS AND DISCUSSION

The pK_a of 4-Methyl-2-mercaptopyrimidine

The acid dissociation constants of MMP were determined from the UV–Vis absorption spectra in aqueous solutions as a function of pH. These solutions were buffered and maintained at an ionic strength of 0.10 M with NaCl. Figure 2 shows three absorption spectra of MMP at pH 5.50, 7.60,

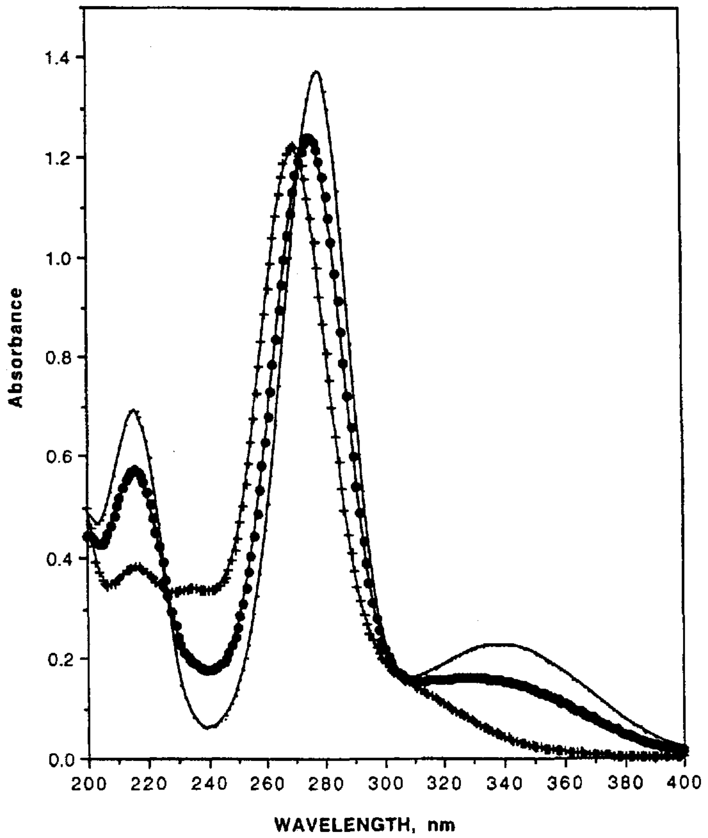

FIGURE 2 UV-Vis spectra of MMP at different pHs. pH 5.5 (line), 7.6 (circles), and 9 (+). $[\mathrm{MMP}] = 1.00 \times 10^{-4}$ M; $\mu = 0.10$ M; 25.0°C.

and 9.00. At pH 5.50, three absorption maxima were observed; a small peak at 339 nm, an intense peak at 278 nm and another small peak at 216 nm. The peaks at 339 and 216 nm gradually disappeared as the pH was increased, whereas the 278 nm peak became blue-shifted. The changes in spectra as a function of pH permit the calculation of [RSH] and $[\mathrm{RS}^-]$, and the K_a of MMP. In this investigation, more than twenty-five buffers (acetate, phosphate, and borate), with pH from 4.11 to 11.88, were used to prepare solutions containing 2.5×10^{-4} M MMP and 0.10 M NaCl. Table I lists the absorbance-pH data at $\lambda = 334$ nm collected for four temperatures. A theoretical fit of the absorbance-pH data was done using equations (3) and (4), which were derived from the acid-base reaction (equation (1)) and the

TABLE I Absorbances of MMP as a function of pH and temperature[a]

pH	*Abs* 20°C	pH	*Abs* 25°C	pH	*Abs* 30°C	pH	*Abs* 35°C
4.63	0.976	4.43	0.988	4.11	0.976	4.19	0.992
5.00	0.968	4.76	0.986	4.52	0.980	4.50	0.989
5.30	0.978	4.92	0.981	4.68	0.971	4.67	0.992
5.78	0.959	5.83	0.978	5.66	0.958	4.69	0.993
6.27	0.953	5.89	0.960	5.73	0.967	5.65	0.969
6.70	0.933	6.31	0.952	6.23	0.952	5.71	0.984
7.26	0.820	6.40	0.969	6.31	0.955	6.20	0.953
7.32	0.773	7.10	0.852	6.54	0.924	6.29	0.928
7.41	0.807	7.36	0.787	7.04	0.827	6.70	0.879
7.61	0.712	7.57	0.701	7.24	0.749	6.92	0.837
7.69	0.656	7.66	0.635	7.29	0.763	7.03	0.805
7.87	0.629	7.79	0.584	7.51	0.650	7.23	0.732
7.88	0.557	7.89	0.551	7.74	0.565	7.26	0.722
8.07	0.484	8.09	0.551	7.80	0.600	7.29	0.744
8.13	0.408	8.20	0.465	7.84	0.527	7.50	0.617
8.20	0.435	8.26	0.429	8.00	0.457	7.61	0.569
8.51	0.467	8.48	0.402	8.08	0.429	7.74	0.516
8.60	0.341	8.51	0.364	8.14	0.405	7.83	0.505
8.71	0.351	8.60	0.335	8.23	0.372	8.04	0.421
8.81	0.316	8.65	0.350	8.32	0.374	8.16	0.382
8.85	0.294	8.83	0.356	8.33	0.352	8.17	0.375
9.28	0.275	8.85	0.298	8.39	0.342	8.29	0.341
9.37	0.255	8.95	0.304	8.40	0.346	8.37	0.353
9.51	0.241	9.55	0.260	8.48	0.316	8.41	0.320
10.79	0.232	9.65	0.259	9.03	0.262	8.52	0.311
10.95	0.236	10.44	0.242	9.18	0.254	8.54	0.298
11.15	0.239	11.13	0.240	9.96	0.236	9.16	0.253
11.77	0.221	11.50	0.241	10.62	0.243	9.19	0.269
11.82	0.229			11.38	0.241	9.69	0.241
10.44	0.242					10.74	0.253
11.13	0.240					11.35	0.250
11.50	0.241						

[a] Measured at 334 nm in buffer solutions of 0.10 M ionic strength.

K_a expression (equation (2)):

$$RSH + H_2O \rightleftharpoons RS^- + H_3O^+ \tag{1}$$

$$K_a = \frac{[RS^-]_e[H_3O^+]}{[RSH]_e} \tag{2}$$

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

$$A_{tot} = \varepsilon_{RSH}[RSH]_i + (\varepsilon_{RS^-} - \varepsilon_{RSH})[RS^-]_e \tag{4}$$

In equations (3) and (4), A_{tot} is the total absorbance of RSH and RS^- in solution, whereas $[RSH]_i$ and $[RS^-]_e$ are the initial concentration of the thiol and the equilibrium concentration of the thiolate ion, respectively. The molar absorptivities of RSH and RS^- are represented by ε_{RSH} and ε_{RS^-}. Thus, theoretical values of A_{tot} were calculated as a function of $[H^+]$ (from pH 4 to 12) using the initial concentration of $[RSH]_i$ and the estimated values of ε_{RS^-}, ε_{RSH} and K_a. Iterative calculations were performed until superb agreement between theoretical and experimental A_{tot} was reached. Figure 3 shows the excellent match between the calculated curve and the data points at 25.0°C. The values of ε_{RSH} and ε_{RS^-} used in the curve fitting are 3930 ± 30 and $960 \pm 10\,M^{-1}cm^{-1}$, respectively. The final K_a at 25°C is 1.86×10^{-8}. In order to confirm the K_a value determined at 334 nm, a second series of absorbance–pH data was collected at $\lambda = 278$ nm. The MMP concentration used in this series was 1.00×10^{-4} M. Again, Figure 4

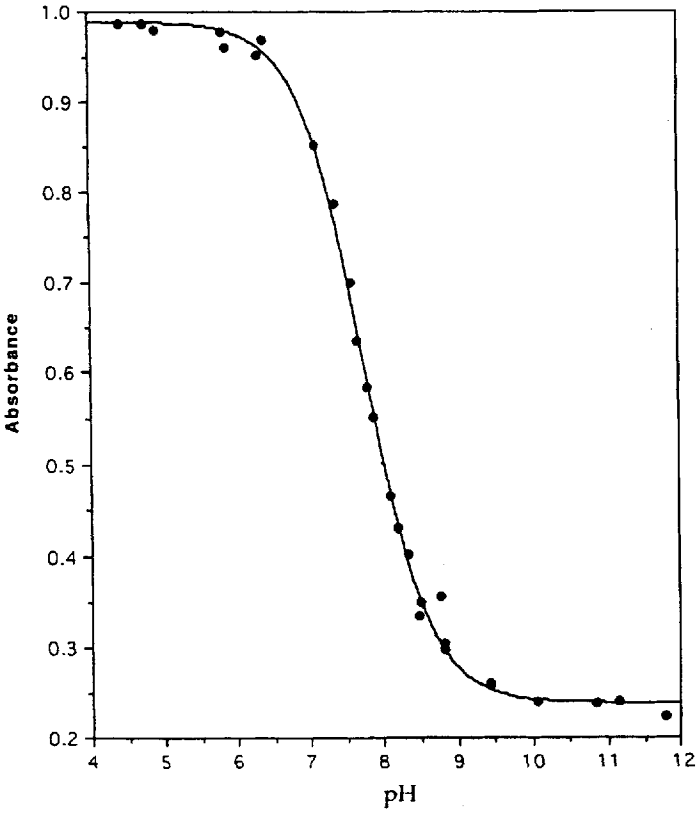

FIGURE 3 Absorbance of MMP at 334 nm as a function of pH. $[MMP] = 2.5 \times 10^{-4}$ M; $\mu = 0.10$ M; 25.0°C.

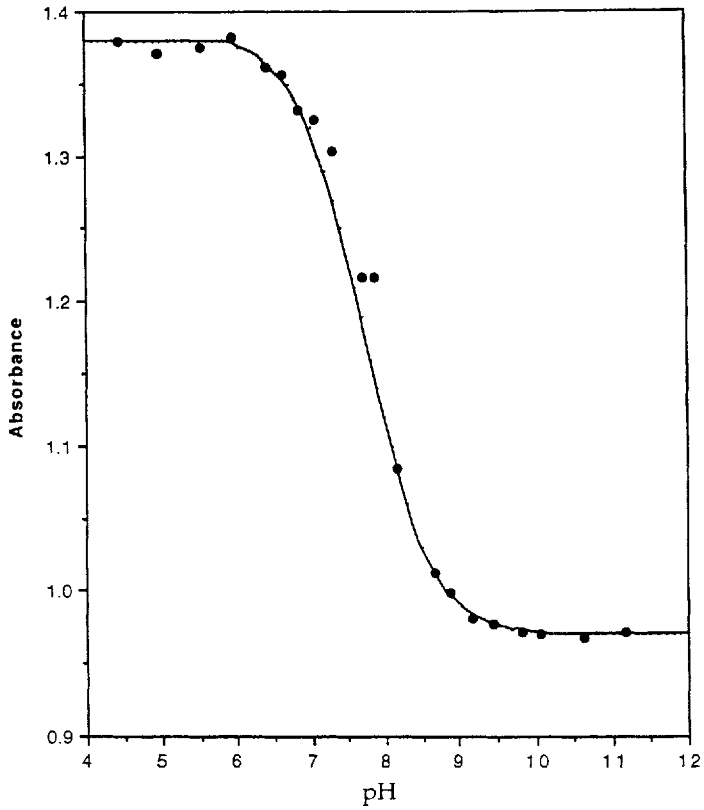

FIGURE 4 Absorbance of MMP at 278 nm as a function of pH. [MMP] = 1.0×10^{-4} M; $\mu = 0.10$ M; 25.0°C.

shows the excellent fit between the theoretical curve and the experimental points. The K_a calculated for this series is 1.80×10^{-8}; it is in very good agreement with the value obtained at 334 nm. The ε_{RSH} and ε_{RS^-} used in the 278 nm series are 9700 and 13,800 $M^{-1} cm^{-1}$, respectively. Another graphical method to treat the absorbance–pH data is to calculate the equilibrium concentration of RSH and RS^-. Figure 5 shows the two sigmoidal curves representing $[RSH]_e$ and $[RS^-]_e$ intersecting at pK_a 7.73, which is in good agreement with the data reported in the literature.[17] Table II lists all of the K_a and pK_a values calculated for the temperature data listed in Table I using a similar curve-fitting procedure.

Figure 6 shows the linear plot of $\ln K_a$ *vs.* $1/T$ for MMP. The thermodynamic parameters obtained from the slope and the intercept of Figure 6

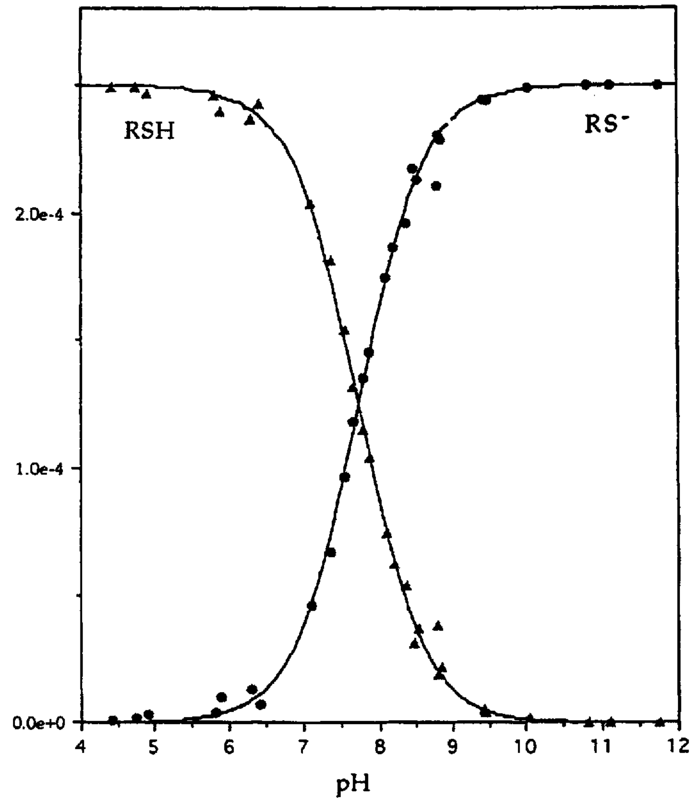

FIGURE 5 [RSH] and [RS$^-$] of MMP *vs.* pH. [MMP] = 2.5×10^{-4} M; $\mu = 0.10$ M; 25.0°C; absorbances measured at 334 nm.

TABLE II Acid dissociation constants of MMP at various temperatures

T, °C	$10^8 K_a$	pK_a
20.0	1.40	7.85
25.0	1.86[a]	7.73[a]
	1.80[b]	7.75[b]
30.0	2.45	7.61
35.0	2.95	7.53

[a] [MMP] = 2.5×10^{-4} M; $\mu = 0.10$ M; measured at 334 nm; [b] [MMP] = 1.0×10^{-4} M; $\mu = 0.10$ M; measured at 278 nm.

are $\Delta H^0 = 38.0\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^0 = -20.5\,\mathrm{J\,mol^{-1}\,K^{-1}}$. Equation (5) is the ΔG^0 expression relating ΔH^0 and ΔS^0 at 298 K:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 = (38.0\,\mathrm{kJ\,mol^{-1}}) - T(-20.5\,\mathrm{J\,mol^{-1}\,K^{-1}}). \qquad (5)$$

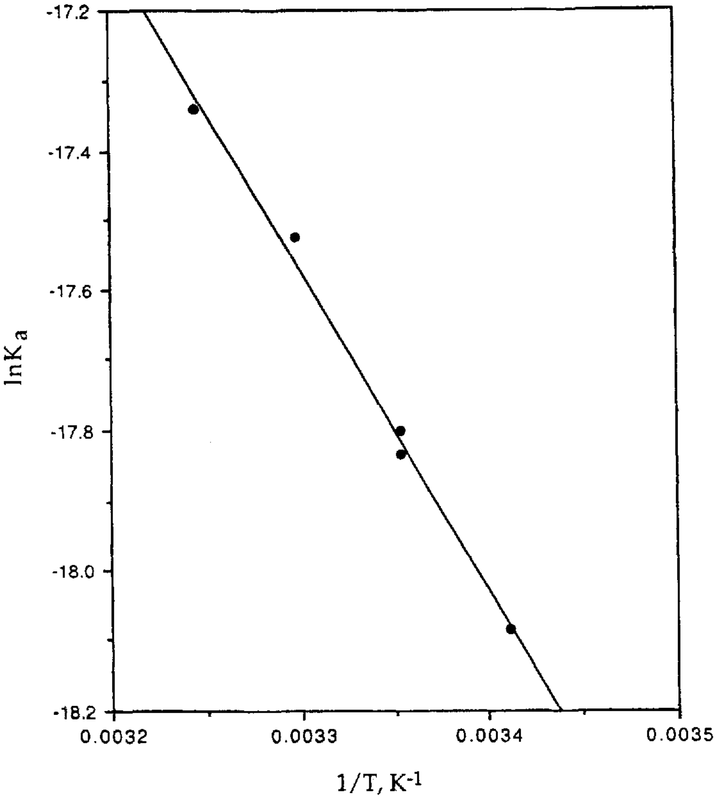

FIGURE 6 $\ln K_a$ *vs.* $1/T$ for the acid-base reaction of MMP. [MMP] $= 2.5 \times 10^{-4}$ M; $\mu = 0.10$ M; at 334 nm.

Stoichiometry

The stoichiometry of the reaction between MMP and $[\mathrm{Ag(cyclam)}]^{2+}$ in aqueous solution was investigated by UV–Vis spectroscopy. The absorption spectra of a solution initially containing 4.0×10^{-5} M MMP and 8.0×10^{-5} M silver(II)-cyclam were taken as a function of time. The following absorbances were recorded after several minutes: at 349 nm, $A = 0.355$; at 278 nm, $A = 0.333$; and at 238 nm, $A = 0.289$. The absorbance at 349 nm was determined to be that of $[\mathrm{Ag(cyclam)}]^{2+}$, whereas the 279 nm absorbance was from both $[\mathrm{Ag(cyclam)}]^{2+}$ and MMP. In order to obtain the spectrum of the disulfide, a synthetic sample was prepared by diiodine oxidation of MMP,[18] and it showed only one absorption peak at 238 nm. At this wavelength, neither $[\mathrm{Ag(cyclam)}]^{2+}$ nor MMP absorbed. Table III lists the

TABLE III Spectral properties of silver(II)-cyclam, MMP, and disulfide[a]

Compound	λ_{max}, nm	ε, $M^{-1}cm^{-1}$
$[Ag(cyclam)]^{2+}$	349	6390
	278	3490
MMP	339	2290[b]
	278	13,800
	216	6940
bis(4-methylpyrimidin-2-yl) disulfide[c]	238	17,500

[a]Measured in aqueous solution at 25°C. [b]Molar absorptivities were calculated directly with the Beer–Lambert equation from the absorbance at λ_{max} of 1.0×10^{-4} M MMP at pH 5.5. [c]Disulfide sample was prepared according to literature procedures.[18]

absorption maxima and the molar absorptivities of $[Ag(cyclam)]^{2+}$, MMP, and bis(4-methylpyrimidin-2-yl) disulfide that were used in the stoichiometry calculation. From the absorbances at 349 and 278 nm, 1.0×10^{-5} M MMP was found to remain unreacted; therefore, either 3.0×10^{-5} M MMP had reacted or 1.5×10^{-5} M disulfide was produced. This agreed well with the disulfide concentration of 1.65×10^{-5} M estimated from the absorption at 238 nm. Therefore, the stoichiometric ratio of MMP to $[Ag(cyclam)]^{2+}$ is one-to-one, consistent with previous reports.[7–11] Equation (6) shows the stoichiometry of the reaction:

$$2[Ag(cyclam)]^{2+} + 2RSH = RSSR + 2[Ag(cyclam)]^{+} + 2H^{+} \tag{6}$$

Kinetics

The kinetics of the oxidation of MMP by $[Ag(cyclam)]^{2+}$ in aqueous solution was investigated under *pseudo*-first-order conditions with [MMP] from twenty- to forty-fold in excess over $[Ag(cyclam)]^{2+}$. The observed rate law is

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

where k_{obs} is the *pseudo*-first-order rate constant.

The rate dependence in [MMP] was determined by investigating the rate of reaction as a function of the reductant concentration at constant pH. The kinetics were investigated under the following conditions: $[Ag(cyclam)]^{2+} = 4.50 \times 10^{-5}$ M and [MMP] varied from 1.00×10^{-3} to 2.00×10^{-3} M. Eight different phosphate buffers, with pH ranging from 5.69 to 7.33, were used in each MMP series. The rate results were analyzed using the Unifit single exponential non-linear curve-fitting program. Table IV lists the *pseudo*-first-order rate constants, k_{obs}, determined at 25.0°C. At low pH, the plots of

TABLE IV Observed rate constants ($10^2 k_{obs}$ (s^{-1})) as a function of MMP concentration and pH at 25.0°C

10^3 [MMP], M	pH = 5.69	pH = 5.88	pH = 6.12	pH = 6.5
1.00	0.93	1.21	1.64	2.39
1.25	1.22	1.58	2.19	2.93
1.50	1.52	1.97	2.79	3.76
1.75	1.82	2.40	3.56	5.19
2.00	2.14	2.75	4.19	2.80
10^3 [MMP], M	pH = 6.75	pH = 6.84	pH = 7.14	pH = 7.33
1.00	2.91	3.85	6.53	8.64
1.25	4.04	5.80	9.08	16.63
1.50	4.73	7.16	10.70	18.03
1.75	6.92	9.52	15.60	23.38
2.00	8.37	11.55	19.80	29.33

$[Ag(cyclam)]^{2+} = 4.5 \times 10^{-5}$ M and $\mu = 0.10$ M.

k_{obs} *vs.* MMP were linear, an indication that the rate order for MMP is one. However, these plots deviated from linearity at high pH. Similar types of rate–pH behavior have been observed previously in the oxidation of 2-thiopyrimidine and 2-thiouracil by hexachloroiridate(IV), tris(bipyridine)-iron(III) and silver(II)-macrocyclic complexes.[8–11] Because of the pH effects, a mechanism with [H$^+$] dependence in the rate law has to be considered to evaluate the rate constants.[19]

Mechanism and Derived Rate Law

As shown in Table V and Figure 7, the rate–pH plot of the data resembled a kinetics pH titration curve of one of the reacting substrates. From pH 5.69 to 6.5, the rate of reaction increased slowly, but after 6.5 the rate increased sharply. This type of kinetics behavior is usually associated with an acid–base equilibrium reaction of one of the reactants, in this case, the MMP. Based on the observed rate law, a mechanism for the reaction that would account for the stoichiometry and the rate–pH profile, was proposed. The reaction steps in the proposed mechanism are shown below:

$$\mathrm{RSH} \overset{K_a}{\rightleftharpoons} \mathrm{RS^-} + \mathrm{H^+} \tag{8}$$

$$\mathrm{RS^-} + [\mathrm{Ag(cyclam)}]^{2+} \xrightarrow{k_2} \mathrm{RS^\bullet} + [\mathrm{Ag(cyclam)}]^{+} \tag{9}$$

$$\mathrm{RSH} + [\mathrm{Ag(cyclam)}]^{2+} \xrightarrow{k_2'} \mathrm{RS^\bullet} + \mathrm{H^+} + [\mathrm{Ag(cyclam)}]^{+} \tag{10}$$

$$2\mathrm{RS^\bullet} \rightarrow \mathrm{RSSR} \quad \text{(fast)} \tag{11}$$

TABLE V Observed rate constants ($10^2 k_{obs}$ (s^{-1})) as a function of pH and temperature

T, °C	pH = 5.69	pH = 5.88	pH = 6.12	pH = 6.50
20.0	1.16	1.45	1.94	2.68
25.0	1.52	1.97	2.79	3.76
30.0	2.40	3.12	4.04	5.89
35.0	3.57	4.72	5.93	9.68
T, °C	pH = 6.75	pH = 6.84	pH = 7.14	pH = 7.33
20.0	3.09	4.65	6.95	11.63
25.0	4.73	7.16	10.70	18.03
30.0	6.89	11.23	16.00	25.88
35.0	10.43	16.48	24.60	36.78

$[Ag(cyclam)]^{2+} = 4.5 \times 10^{-5}$ M; [MMP] $= 1.5 \times 10^{-3}$ M; $\mu = 0.10$ M.

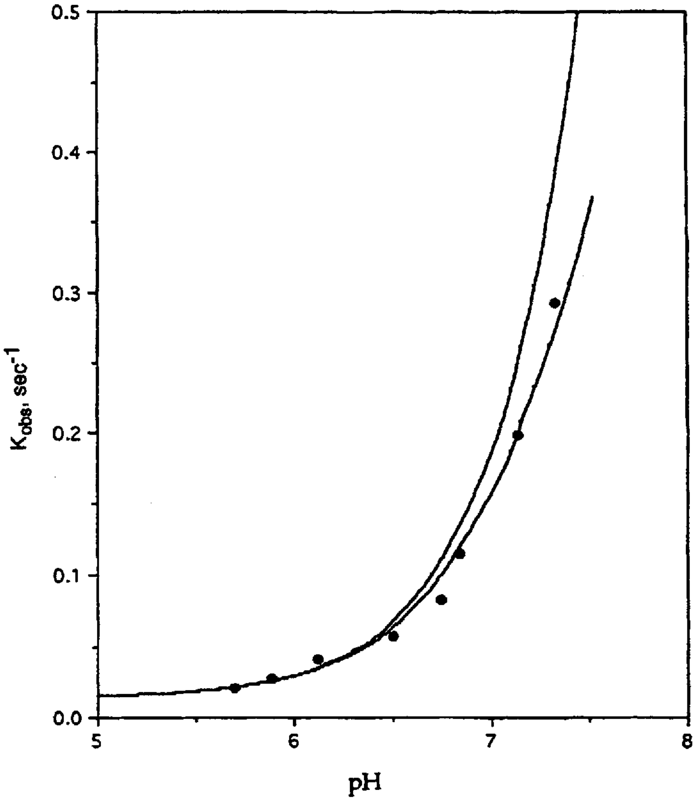

FIGURE 7 Theoretical fit of experimental k_{obs} as a function of pH at 25.0°C. Data points of [MMP] $= 2.00 \times 10^{-3}$ M (circles). Lower curve: fitted with equation (13). Upper curve: fitted with the denominator in equation (13) reduced to one.

The reaction mechanism consists of an acid–base equilibruim of MMP, which accounts for the inverse $[H^+]$ dependence. Both RSH and RS^- are oxidized to thiyl free radicals ($RS^\bullet$) by $[Ag(cyclam)]^{+2}$, and their respective rate constants are k_2' and k_2. Thiyl free radicals have been reported for thiopyrimidine and thiouracil in biochemical and in electrochemical studies.[20,21] The terminating step is the rapid dimerization of $RS^\bullet$ to the disulfide products. Based on the stoichiometry and the proposed mechanism, the rate expression, equation (12), was derived:

$$\frac{-d\{[Ag(cyclam)]^{2+}\}}{dt} = \frac{2(k_2' + k_2K_a/[H^+])}{(1 + K_a/[H^+])}[RSH]\{[Ag(cyclam)]^{2+}\} \quad (12)$$

Combining equations (7) and (12) yields equation (13), which relates k_{obs} to the equilibrium constant, the second-order rate constants and $[H^+]$:

$$k_{obs} = \frac{2(k_2' + k_2K_a/[H^+])}{(1 + K_a/[H^+])}[RSH] \quad (13)$$

A theoretical fit k_{obs} as a function of pH was carried out using the equilibrium constant of MMP ($K_a = 1.86 \times 10^{-8}$ at 25°C) determined earlier in the thermodynamic experiments. Theoretical calculation was done by carefully choosing the initial value for k_2' at the low pH region with the assumption that [RSH] remained constant. This assumption of constant [RSH] is reasonable since it is in excess; it is over 95% unreacted at the end of the reaction. An estimated value for k_2 was then selected and spreadsheet and graphic programs were used to calculate k_{obs} as a function of pH. The calculated and the experimental values of k_{obs} were plotted against pH for comparison in Figure 7. Careful adjustment of k_2' and k_2 produced an excellent fit of k_{obs} to the data points. This is the lower curve in Figure 7, on top of which the experimental points are superimposed. In previous studies,[9,10] the denominator in equation (13) was reduced to one with the following assumptions, $[H^+] \gg K_a$ and $[RSH] \gg [RS^-]$. Calculation based on the simplified equation is shown as the upper curve in Figure 7. This curve clearly fails to match the data points at high pH. The final k_2' and k_2 values obtained from the theoretical fit of equation (13) to the 25.0°C data are 3.3 ± 0.1 and $188 \pm 24\,M^{-1}\,s^{-1}$, respectively. Table VI lists all of the k_2 and k_2' values obtained for the temperature data using a similar curve-fitting procedure.

TABLE VI Second-order rate constants for the oxidation of RSH (k_2') and RS$^-$(k_2) by $[Ag(cyclam)]^{2+}$ [a]

T, °C	k_2', $M^{-1}s^{-1}$	k_2, $M^{-1}s^{-1}$
20.0	2.5	143
25.0	3.3	188
30.0	5.5	230
35.0	7.0	295

[a] The k_2 and k_2' are the final values used in the theoretical fits.

Activation Parameters

The activation parameters for the k_2 path, the oxidation of RS$^-$ by silver(II)-cyclam, are determined from the transition-state equation:[22]

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

Figure 8 shows a linear plot of $\ln(k_2/T)$ *vs.* $1/T$. The linear plot has a regression coefficient of 0.999, an indication of good correlation of the data. The activation parameters calculated are $\Delta H^{\neq} = 33.6\,\text{kJ mol}^{-1}$ and $\Delta S^{\neq} = -83.3\,\text{J mol}^{-1}\,\text{K}^{-1}$. Because silver(II) complexes are square-planar,[23-25] the axial positions are vacant and RS$^-$ can coordinate to silver to form penta-coordinate species. This is supported in part by the very negative $\Delta S^{\neq}$ obtained in the temperature study. This result augments those found in previous studies, the oxidation reactions of MP by $[Ag(cyclam)]^{2+}$, $[Ag([15]aneN_4)]^{2+}$ and $[Ag(tmc)]^{2+}$, where the values of $\Delta S^{\neq}$ are -42.6, -55.0 and $-83.3\,\text{J mol}^{-1}\,\text{K}^{-1}$, respectively.[9,10] The $\Delta S^{\neq}$ value for the k_2 path of MMP with $Ag(cyclam)^{2+}$ is twice as negative as when the substrate is MP. This difference is consistent with the fact that RS$^-$ of MMP is a better nucleophile and a better reducing agent than that of the corresponding ionized MP. Therefore, it is plausible that the oxidation of the RS$^-$ by the square-planar silver(II)-tetraaza macrocyclic complexes proceeds by an inner-sphere mechanism. Table VII lists the k_2 values and the k_2/k_2' ratios for the oxidation reactions of several mercaptopyrimidines by octahedral and square-planar transition metal complexes. The k_2/k_2' ratios for the outer-sphere oxidants, hexachloroiridate(IV) and tris(bipyridine)iron(III), vary from 10^4 to 10^5. They are two to three orders of magnitude larger than those of the silver(II)-macrocyclic complexes, suggesting that the square-planar complexes undergo electron transfer by a different mechanism. Inner-sphere electron-transfer reactions involving other square-planar

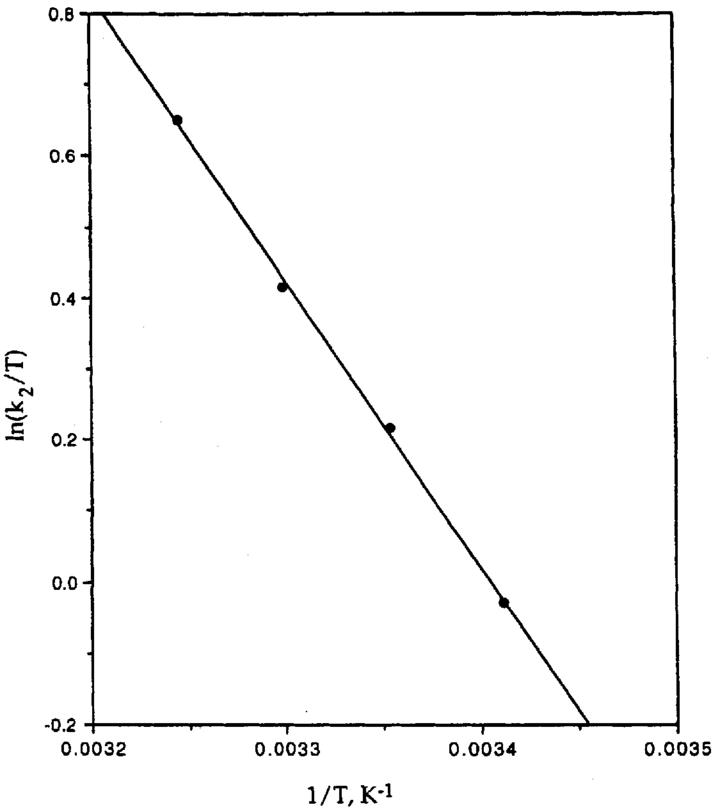

FIGURE 8 Activation energy plot of the k_2 path. $[\mathrm{Ag(cyclam)}]^{2+} = 4.5 \times 10^{-5}$ M; [MMP] = $(1.0\text{–}2.0) \times 10^{-3}$ M; $\mu = 0.10$ M; pH = 5.68–7.33.

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

Reaction	k_2, $\mathrm{M^{-1}\,s^{-1}}$	k_2/k_2'
$\mathrm{IrCl_6^{2-}}$ + MP[a]	8×10^4	5×10^4
$\mathrm{IrCl_6^{2-}}$ + MMP[b]	1×10^5	4×10^4
$\mathrm{IrCl_6^{2-}}$ + DMMP[b]	1×10^5	1×10^5
$\mathrm{IrCl_6^{2-}}$ + TU[a]	2×10^3	2×10^4
$[\mathrm{Fe(bpy)_3}]^{3+}$ + TU[b]	2×10^4	1×10^4
$[\mathrm{Ag(cyclam)}]^{2+}$ + MP[c]	1.5×10^2	30
$[\mathrm{Ag(tmc)}]^{2+}$ + MP[c]	3.5×10^2	44
$[\mathrm{Ag([15]aneN_4)}]^{2+}$ + MP[c]	8.0×10^2	110
$[\mathrm{Ag(cyclam)}]^{2+}$ + MMP[d]	1.9×10^2	57

MP = 2-mercaptopyrimidine; MMP = 4-methyl-2-mercaptopyrimidine; DMMP = 4,6-dimethyl-2-mercaptopyrimidine; TU = 2-thiouracil. [a]Ref. 7; [b]Ref. 8; [c]Refs. 9,10; [d]present work.

complexes have been extensively investigated by Kirschenbaum and co-workers,[26–39] who studied the redox kinetics and mechanisms of a large variety of substrates using square-planar $[Ag(OH)_4]^-$ as the oxidant. They have postulated transient penta-coordinated species for the oxidation of azide[26] and thiosulfate[27] ions. From the observed kinetics and the very negative entropies of activation, they also postulated that the oxidation reactions of hydrogen peroxide,[28] thiourea,[29] cyanide,[30] thiocyanate,[31] arsenite,[32] sulfite[33] and hypophosphite ions[34] proceed by an inner-sphere mechanism. Other substrates such as triglycine and tetraglycine,[35] ethylenediamine,[36] *dl*-mandelate,[37] edta ion[38] and several *vic*-dioximate[39] also formed complexes with $[Ag(OH)_4]^-$ after the replacement of hydroxide ligands. Moreover, transient penta-coordinated species are postulated in the mechanisms to account for the replacement of hydroxide ligands. Lastly, more direct evidence of an inner-sphere mechanism was the observation of a silver(II)-ligand radical in the reduction of a silver(III)-tetraaza macrocycle.[40]

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