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The Oxidation of 2-Thiopyrimidine and 2-Thiouracil by Ir(IV) Complexes

HENRY N. PO, CHANG-FAN LO, NIKOLA JONES and RICHARD W. LEE

Department of Chemistry, California State University, Long Beach, Calif. 90840, U.S.A.

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The kinetics of the oxidation of 2-thiopyrimidine (TP) by $IrCl_6^{2-}$ and $IrBr_6^{2-}$, and 2-thiouracil (TU) by $IrCl_6^{2-}$ follow a second-order rate law, first-order with respect to both the concentration of the oxidant and reductant. The second-order rate constants at 25.0 °C and at μ = 0.10 M *are: 3.30* M^{-1} *sec^{-1} for TP + $IrCl_6^{3-}$ at pH 2.10, 0.187* M^{-1} *sec^{-1} for TU + $IrCl_6^{2-}$ at pH 2.10, and 344* M^{-1} *sec^{-1} for TP + $IrBr_6^{2-}$ at pH 5.3. A pH-rate profile is observed to have nearly a constant rate at pH 2.1 to 3.5 and a rapid increase in rate from pH 3.5 to 5.5. This is accounted for by the equilibrium pKa of the thiols and by the higher reactivity of the mercaptide anions. The activation parameters calculated from the temperature dependence studies are:* $\Delta H^{\ddagger}$ *= 7.5 kcal/mole,* $\Delta S^{\ddagger}$ *= –31.0 e.u. for the TP + $IrCl_6^{2-}$, and* $\Delta H^{\ddagger}$ *= 10.1 kcal/mole,* $\Delta S^{\ddagger}$ *= –27.8 e.u. for the TU + $IrCl_6^{2-}$. A free radical mechanism is postulated to account for the above observed kinetics.*

Introduction

The metabolical and biological functions of thiols depend to a large extent on how the SH group can be protected from oxidation [1]. The kinetics and mechanisms of metal ions and complexes oxidation of several thiols such as thioureas [2], 2-mercaptoethanol [3], 2-mercaptosuccinic acid [4], thiomalic acid [5], 3-mercaptopropionic acid [6], and several alkyl-, benzyl-, and arylthiols [7] have been reported. In most instances thiyl radicals generation has been postulated as the rate determining step. Thiyl radicals have been trapped in known free radical addition reactions [8], and in radiolysis of alkanethiols [9].

In this study, we would like to present the results of a study on the oxidation of 2-thiopyrimidine (TP) and 2-thiouracil (TU) by one-electron oxidizing agents such as $IrCl_6^{2-}$ and $IrBr_6^{2-}$. The Ir(IV) complexes are selected because they are substitution inert and are also powerful oxidizing agents. Multielectron oxidation of series of substituted heterocyclic thioamides is presently being investigated [10].

Experimental Section

Chemicals

Potassium hexachloroiridate(IV) and potassium hexabromoiridate(IV) were obtained from McKay Chemical Company and were used without further purification. The 2-thiopyrimidine and 2-thiouracil were obtained from Aldrich Chemical Company and were recrystallized thrice from aqueous methanolic solutions. The purity of the thiols were checked spectrally with the Cary 14 recording spectrophotometer. Melting points were taken and compared with literature values. Triply distilled water was used in preparing the reacting solutions. Sodium perchlorate was prepared by neutralizing sodium carbonate with 70% perchloric acid solution. Stock solution of sodium perchlorate was then prepared and analyzed by gravimetric method.

Stoichiometry and Product Analysis

The stoichiometry of the reaction was obtained by measuring the absorbance changes of the reactants using the Cary Model 14 recording spectrophotometer. Corrections were made to account for the absorbance contribution of the disulfide products. With $[IrCl_6^{2-}]$ = 5.19 X 10^{-3} to 6.76 X 10^{-3} *M* and [TP] = 4.55 X 10^{-3} to 7.43 X 10^{-3} *M*, the average value of $\Delta[TP]/\Delta[IrCl_6^{2-}]$ = 0.99. Under slightly different concentrations of $IrBr_6^{2-}$, the stoichiometry ratio is 1:02. These values show that for both oxidants the stoichiometry for the reaction with 2-thiopyrimidine is 1:1. Similarly, one to one stoichiometry is obtained when the reductant is 2-thiouracil. Like the oxidation of thioureas [2], the ratio of $\Delta[IrX_6^{2-}]/\Delta[thiol]$ increases from one to four as the initial concentration ratio of IrX_6^{2-} to thiol increases. However, the one to one stoichiometry is assumed for the present kinetic reaction conditions where the thiol concentration is always in excess of the $[IrX_6^{2-}]$.

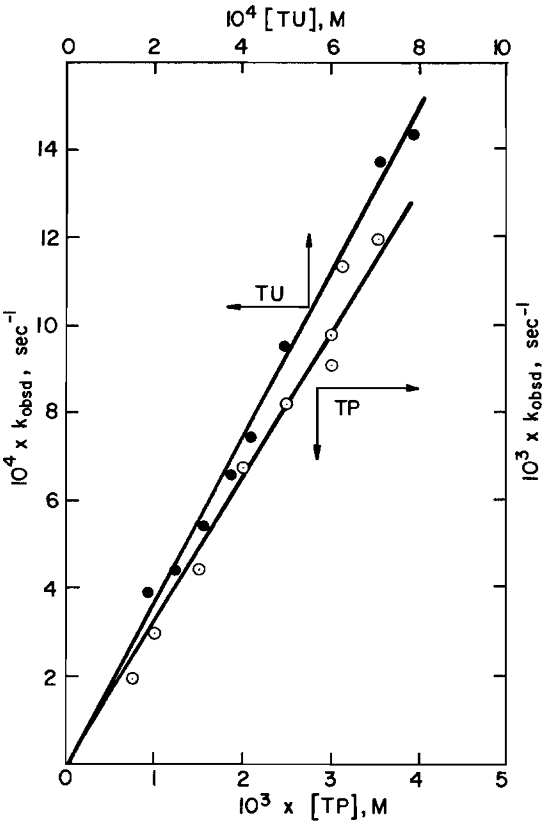

Fig. 1. k_{obsd} *versus* [Thiol]. Opened circles, $IrCl_6^{2-}$ +TP, pH = 2.10, μ = 0.10 *M*, at 25 °C; Filled circles, $IrCl_6^{2-}$ + TU, pH = 2.10, μ = 0.10 *M*, at 25.0 °C.

When excess 2-thiopyrimidine was reacted with $IrCl_6^{2-}$ at pH 5, the inorganic product identified was $IrCl_6^{3-}$ [11]. The organic product isolated by reacting 2 × 10^{-3} mol $IrCl_6^{2-}$ with 4 × 10^{-4} mol 2-thiopyrimidine in aqueous solution followed by ether extraction was identified to be the disulfide of TP. The melting point (139–140 °C), UV spectrum (λ_{max} = 237 nm), IR, and NMR spectral of the isolated product were compared with a synthesized disulfide and they matched completely [12]. Therefore the stoichiometric equation can be represented as follows

$$2\,IrCl_6^{2-} + 2TP \rightarrow 2\,IrCl_6^{3-} + (TP)_2 + 2\,H^+$$

The expected disulfide [13] of TU was not isolated, however, because of its similarity in stoichiometry with TP the reaction equation (*1*) is assumed.

Kinetic Procedure

A Cary Model 14 recording spectrophotometer was used to record the visible and UV spectra of the solutions as well as to monitor the reactions. The cell compartment of Cary 14 was thermostatted at 25.0 ± 0.5 °C. An Aminco-Morrow stopped-flow spectrophotometer was used to study the faster reactions. All the kinetics experiments were conducted under pseudo-first-order conditions with the concentrations of the thiols at least ten-fold in excess over IrX_6^{2-}. The disappearance of $IrCl_6^{2-}$ and $IrBr_6^{2-}$ were monitored at 488 and 585 nm. The values of k_{obsd} were calculated from plots of log(A_t – A_∞) *vs.* time. Fresh solutions at constant ionic strength of 0.10 *M* and constant pH were prepared for each kinetic run. Replicate kinetic measurements were made to ensure consistency in data.

TABLE I. Observed Rate Constants for the Oxidation of 2-Thiopyrimidine by $IrBr_6^{2-}$.

10^3[TP], *M*	k_{obsd}, sec^{-1}
0.86	0.34
1.36	0.47
1.59	0.55
1.72	0.66
2.11	0.75
2.52	0.87

[a] [$IrBr_6^{2-}$] = 4.3 × 10^{-5} *M*, pH 5.3, μ = 0.10 *M*, 25.0 °C.

Results and Discussion

Kinetics and Mechanism

The kinetics of the oxidation of TP and TU by the IrX_6^{2-} were carried out under pseudo-first-order conditions with the thiols always in excess. Reactions were also studied at constant ionic strength of 0.10 *M* and buffered solution to obtain constant pH. The dependence in IrX_6^{2-} concentration was determined with [TP] or [TU] at 3 × 10^{-3} *M* and [$IrCl_6^{2-}$] or [$IrBr_6^{2-}$] varied from 0.30 × 10^{-4} *M* to 2.90 × 10^{-4} *M*. Plots of log (A_t – A_∞) *vs.* time were linear for at least three half-lives, suggesting first-order in [IrX_6^{2-}] in all the three reactions between IrX_6^{2-} and the thiols. The average values of k_{obsd} for the three reactions studied; $IrCl_6^{2-}$ + TP, $IrBr_6^{2-}$ + TP, and $IrCl_6^{2-}$ + TU are 9.75 × 10^{-3} sec^{-1} (pH = 2.10), 8.89 × 10^{-1} sec^{-1} (pH = 5.3), and 7.55 × 10^{-4} sec^{-1} (pH = 2.10), respectively. A common rate law can be written to represent these three reactions.

$$-d\ln[IrX_6^{2-}]/dt = k_{obsd} \qquad (1)$$

The reductant dependence was studied with [IrX_6^{2-}] maintained constant at 5.0 × 10^{-5} *M* and [TP] or [TU] varied from ten to fifty-fold in excess. Figure 1 shows the linear plots of k_{obsd} versus [TP] or [TU] when the oxidant is $IrCl_6^{2-}$. The rate of oxidation of TU is at least ten to fifteen times slower than the oxidation of TP. Table I lists the data for the

TABLE II. Second Order Rate Constants as a Function of Temperatures and the Activation Parameters.

	TP + $IrCl_6^{2-}$	TU + $IrCl_6^{2-}$	TP + $IrBr_6^{2-}$
25.0 °C	3.30^a, M^{-1} sec^{-1}	0.187^a, M^{-1} sec^{-1}	344^b, M^{-1} sec^{-1}
30.0 °C	4.03	0.275	–
35.0 °C	4.73	0.351	–
40.0 °C	6.48	0.440	–
$\Delta H^{\ddagger}$, kcal/mol	7.5	10.1	–
$\Delta S^{\ddagger}$, e.u.	–31.0	–27.8	–
$\Delta G^{\ddagger}$, kcal/mol	16.7	18.4	–

[a] pH = 2.10 and μ = 0.10 *M*. [b] pH = 5.3 and μ = 0.10 *M*.

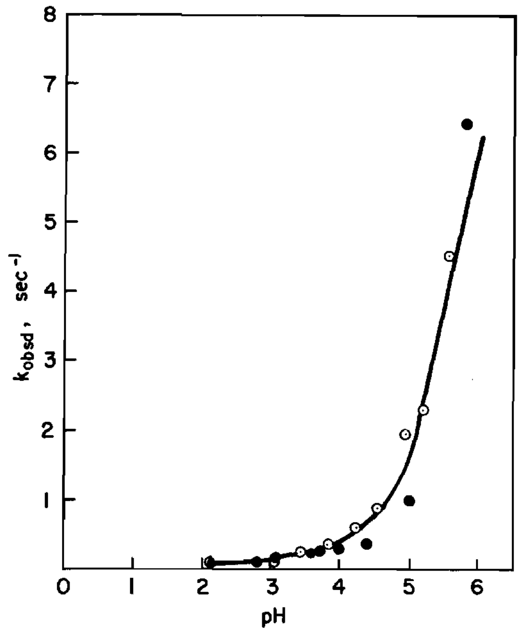

Fig. 2. pH-Rate profile. Opened circles, [$IrCl_6^{2-}$] = 3.13 × 10^{-5} *M*, [TP] = 1.43 × 10^{-3} *M*, μ = 0.1 *M*, at 25 °C; Filled circles, [$IrBr_6^{2-}$] = 6.67 × 10^{-5} *M*, [TP] = 3.57 × 10^{-3} *M*, μ = 0.1 *M*, at 25 °C.

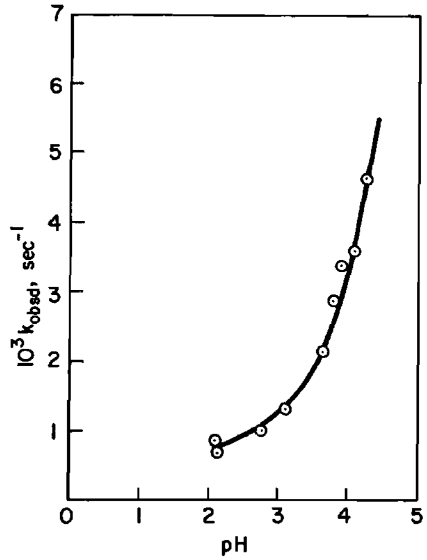

Fig. 3. pH-Rate Profile [$IrCl_6^{2-}$] = 1.31 × 10^{-4} *M*, [TU] = 2.81 × 10^{-3} *M*, μ = 0.1 *M*, at 25 °C.

$IrBr_6^{2-}$ oxidation of TP. A linear plot can also be obtained for this reaction. These results suggest that the kinetics is also first order in [Thiol]; that is,

$$-\mathrm{d}\ln[IrX_6^{2-}]/\mathrm{d}t = k^{11}[\mathrm{Thiol}] \qquad (2)$$

The second order rate constants can be calculated from the slopes of plots in Fig. 1 and are listed in Table II.

A mechanism that is common to all the three reactions and which conforms to the observed kinetics and stoichiometry can be postulated as follows

$$IrX_6^{2-} + RSH \rightarrow IrX_6^{3-} + RS\cdot + H^+$$

$$2RS\cdot \xrightarrow{\text{fast}} RSSR$$

where RSH represents either TP or TU in the reaction mechanism.

The rate determining step is the generation of thiyl radicals of the thiols by an outer-sphere one electron transfer in the oxidation of RSH by IrX_6^{2-}. Thiyl radicals of TP and TU have been shown in biological redox systems [14]. The rate of substitution of IrX_6^{2-} at around 10^{-5} sec^{-1} [11, 15] is much smaller than k^{11}. This suggests that an inner-sphere process is not likely to occur. It has been suggested by Brown and Higginson [16] that strong oxidants of substitution inert type will abstract an electron from the substrate to directly yield free radicals. The oxidation of 2,6-dimethylphenol by $IrCl_6^{2-}$ is another strong evidence of the free radical process [17].

pH Dependence

The pH dependence was carried out at 25.0 °C using acetate or phosphate buffers at high pH and appropriate amount of perchloric acid at low pH. The reactants' concentrations were kept constant for each series of pH runs. The pHs of the solutions were measured immediately after completion of the reactions. All three reactions show strong pH dependency above pH 4. A common pH-rate profile for the $IrCl_6^{2-}$ and $IrBr_6^{2-}$ oxidation of TP is shown in Fig. 2. The rate of reaction drops off significantly and tapered off asympotically below pH 4 but accelerates rapidly when solution becomes more basic. This pH-rate profile appears to resemble half of a sigmoidal pH-rate curve normally encountered in kinetics study when a substrate has an acid–base equilibrium in operation. The substrates that most likely to have this type of equilibrium are the TP and TU. The pH-rate profile of the TU + $IrCl_6^{2-}$ reaction is shown in Fig. 3. The reason for not following the reaction at pH higher than 6 is primarily because of the instability of IrX_6^{2-} in basic solution [18].

The uniqueness of the pH-rate profile plots of the $IrCl_6^{2-}$ and $IrBr_6^{2-}$ oxidation of TP indicates that a common reactive species from the reductant is present in both systems at the higher pH region. This is most likely the deprotonated mercaptide anion of 2-thiopyrimidine. The pKa's for TP and TU have been reported to be 7.14 [19] and 7.54 [20], respectively. Therefore RSH and RS^- are in equilibrium and both species react with the oxidants at high pH. A revised rate mechanism which would account for the pH dependence reaction profile is postulated below

$$RSH \rightleftharpoons RS^- + H^+ \qquad K$$

$$RSH + IrX_6^{2-} \xrightarrow{k_2} RS\cdot + IrX_6^{3-} + H^+$$

$$RS^- + IrX_6^{2-} \xrightarrow{k_3} RS\cdot + IrX_6^{3-}$$

$$2RS\cdot \rightarrow RSSR$$

The derived rate law for the above mechanism accounting for the pH dependency is therefore,

$$-d\ln[IrX_6^{2-}]/dt = \frac{k_3K + k_2[H^+]}{K + [H^+]}\,[RSH] \qquad (3)$$

where now the [RSH] represents the total concentration of the thiols. The second order rate constants k_2 and k_3 are for oxidation of RSH and RS^-, respectively.

The ratio for k_3/k_2 determined from the pH-rate date and eqn. (3) is 2×10^3. This supports the experimental results that the mercaptide anion is at least three order of magnitude more reactive than the neutral thiopyrimidine.

It is recognized that the tautomers of the heterocyclic thioamides can exist in aqueous solution and contribute perhaps to some extent some differences in reaction intermediates. Albert and Barlin [19] reported that the thioamides in aqueous solution favor the mercapto structures at equilibrium over the thio. However, because proton transfer is known to be very rapid, it becomes kinetically indistinguishable on which tautomer is the preferential reacting species in the mechanism.

Activation Parameter

The temperature dependence studies were carried out at four different temperatures ranging from 25.0 to 40.0 °C, and at constant pH and ionic strength. The $[IrX_6^{2-}]$ was kept at 5.0×10^{-5} *M* and the [Thiol] varied from 3.62×10^{-3} *M* to 6.35×10^{-3} *M*. The values for k_{II} are obtained from the slopes. of plots of k_{obsd} *vs.* [Thiol]. Since $IrBr_6^{2-}$ rate of reaction is very close to $IrCl_6^{2-}$, no temperature dependence study on this system was conducted. The $\Delta H^{\ddagger}$ difference between the oxidation of TP and TU by $IrCl_6^{2-}$ is the main reason why TU reacts at least ten to fifteen times slower than TP. This is in agreement with the expected electron withdrawing effect of the carbonyl oxygen on TU, reducing the electron density on the S atom which is the site of electron transfer.

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