Mechanism of the Oxidation of DL-Penicillamine and Glutathione by Chromium(VI) in Aqueous Solution

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The kinetics of the oxidation of DL-penicillamine (3-sulfanyl-D-valine) and glutathione (γ-glutamylcysteinylglycine) by potassium chromate has been studied at pH ≥ 7 under pseudo-first-order conditions of an excess of thiol, at $I = 0.50$ mol dm^{-3} ($NaClO_4$). The glutathione reaction is biphasic, while for penicillamine it is monophasic. The first stage of the oxidation of glutathione obeys the simple expression (i). The second stage of the same reaction is slower than the first by a factor of 10^4 and

$$k_{obs} = k_1[RSH] + k_{-1} \quad (i)$$

obeys the rate expression (ii). The biphasic nature is consistent with the formation and decay of a

$$\text{Rate} = \frac{(k_1k_2[RSH]^2 + k_1k_3[RSH])}{(k_{-1} + k_3 + k_2[RSH])}[Cr^{VI}]_T \quad (ii)$$

chromate–glutathione adduct. Parameter k_1/k_{-1} at 25.3 °C has been determined as 184 ± 4 dm^3 mol^{-1}. The second-order rate constant, k_2, for the decomposition of the intermediate is (1.07 ± 0.04) × 10^{-2} dm^3 mol^{-1} s^{-1}. The activation parameters were calculated as $\Delta H^{\ddagger} = 90 \pm 7$ kJ mol^{-1} and $\Delta S^{\ddagger} = 63 \pm 29$ J K^{-1} mol^{-1}. The oxidation of DL-penicillamine shows simple first-order kinetics with respect to [DL-penicillamine], and may also be represented by expression (ii). The second-order rate constant, k_1, obtained at 25.2 °C for the formation of a chromate–penicillamine intermediate is 0.23 ± 0.01 dm^3 mol^{-1} s^{-1}. The corresponding activation parameters are $\Delta H^{\ddagger} = 72 \pm 7$ kJ mol^{-1} and $\Delta S^{\ddagger} = -18 \pm 28$ J K^{-1} mol^{-1}. A common mechanism which is compatible with the kinetics of both reactions is proposed.

Glutathione (γ-glutamylcysteinylglycine) is a naturally occurring tripeptide found in living cells in fairly high concentrations,[1] and penicillamine (3-sulfonyl-D-valine) is a characteristic degradation product of the penicillin antibiotics.[2] Both are generally referred to as thiols and each reduce chromium(VI) to chromium(III) in aqueous acidic solution.[3–5] A feature of these reactions is the formation of distinct orange 1:1 sulfur-bonded intermediates, which subsequently undergo electron-transfer reactions.[4,6] Previously, it had been shown that 3 mol of thiol were oxidized by the chromium(VI) ion at acidic and neutral pH.[7–9]

The biological importance of sulfydryl compounds has led to the identification of low-molecular-weight cellular metabolites, including the ubiquitous glutathione, which are all considered to be detoxifying agents against chromate poisoning at or near conditions similar to those of the cellular environment.[7] Studies involving these metabolites are important since other vital sulfur-containing substrates and organelles, found within normal cells *in vivo*, can also interact with chromium(VI) species, thus damaging their structure and functional properties.[7]

The syntheses of numerous metal complexes including those of chromium(III) having L-cysteine, glutathione, penicillamine, L-histidine, *etc.* as ligands have been achieved.[8,10–15] These complexes have generated much interest, because of the potential use of these ligands in metal chelation therapy.[8,12–15]

Kinetic information has been published[7,9,16,17] on the oxidation of glutathione and penicillamine by chromium(VI) at neutral pH. Although more information is available on the glutathione–chromium(VI) reaction, consensus on aspects of the mechanism is lacking. Connett and Wetterhahn[9] found the glutathione reaction to be biphasic and reported an equilibrium constant for ester formation and a second-order rate constant for its decay to chromium(IV). These researchers also reported a second-order rate constant for formation of a penicillamine–chromium(VI) thioester. O'Brien and Ozolins[17] later obtained a squared dependence on glutathione concentration for the formation of chromium(V) species under different experimental conditions. The disappearance of the intermediate obeyed a simple first-order rate law. Recently, Bose *et al.*[5] presented evidence that it is not chromium(V) but chromium(IV) which is the dominant oxidation state produced during the oxidation of glutathione by the chromate ion.

We are primarily interested in oxidations of biologically related substrates by potentially toxic oxoanions at the body's physiological pH. In this paper a complete study of the kinetics and mechanism of oxidation of glutathione and also DL-penicillamine by the chromate ion is reported. The important temperature dependence and requisite activation parameters for both thiols, along with the pH variation for the glutathione reaction, which were previously unknown, are reported. In addition, an alternative explanation for the second-order glutathione dependence is suggested. Earlier studies on the glutathione–chromate reaction[9,17] were done *via* conventional spectrophotometry. It was observed that the first stage of the reaction was too fast to be studied by this method,[5,9] and we have confirmed this. The results from the previous studies may prove unreliable, and so we undertook properly to quantify this important stage of the reaction using the more effective stopped-flow technique. This study also supplies the appropriate kinetic information on that particular reaction, especially near the physiological pH chosen for these reactions.

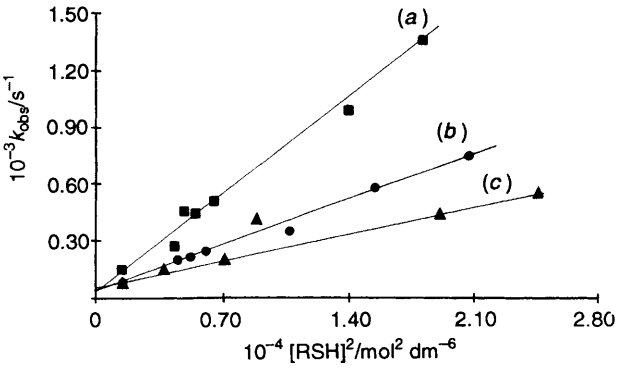

Fig. 1 Plots of k_{obs} *vs.* $[RSH]^2$ for the oxidation of glutathione by chromium(VI) ion. T = 35.0 (*a*), 30.0 (*b*) or 25.3 °C (*c*)

Experimental

Materials.—All chemicals were of the desired reagent grade and used as received. The purity of both thiols was determined spectrophotometrically.[18]

Analysis of Products.—Examination of final spectra from the reactions of both thiols with chromium(VI) at pH > 7 showed that the products were similar to known purple chromium(III) bis(chelates) of glutathione [UV/VIS: λ_{max}/nm 546 and 404 (ε 60.4 and 65.3 dm^3 mol^{-1} cm^{-1})] and penicillamine [λ_{max}/nm 550 and 412 (ε 71.7 and 77.6 dm^3 mol^{-1} cm^{-1})] which were synthesized by standard literature methods.[10-12]

Kinetics.—The kinetic studies were conducted *via* spectrophotometry and stopped-flow techniques.[19] The disappearance of the chromate peak was monitored at 370 nm as a function of time. All measurements were made under pseudo-first-order conditions of an excess of thiol and a constant ionic strength of 0.50 mol dm^{-3} ($NaClO_4$). The pH was maintained with Tris [tris(hydroxymethyl)methylamine]–HCl, and recorded as previously outlined.[19] Plots of $\ln(A_t - A_\infty)$ *vs.* time were linear for at least three half-lives. The rate constants for the slow second-stage oxidation of glutathione were obtained by fitting the time-based spectrophotometric data directly by a first-order rate equation in the kinetics module of the UV/VIS operating software. Those for the faster reaction were obtained from the analysis program RKDEM on the 386-AT computer connected to the stopped-flow assembly as described previously.[19]

Results and Discussion

Oxidation of Glutathione.—The reactions between glutathione and the chromium(VI) ion were studied under slightly basic conditions over the ranges 7.18 ⩽ pH ⩽ 8.40, 0.001 ⩽ [RSH] ⩽ 0.020 mol dm^{-3}, 25.3 ⩽ θ ⩽ 35.5 °C at ionic strength 0.50 mol dm^{-3} ($NaClO_4$). The first stage of the reaction was too fast to be studied by the conventional method and was investigated by the stopped-flow technique. The time-base for this first stage is very small compared to the second, hence both reactions could be studied independently. Rate constants increased with thiol concentration for both stages of the reaction (Table 1), but were unaffected in the absence of molecular oxygen. The experimental rate constants (second stage) seem to decrease as the pH is increased. Plots of k_{obs} *vs.* [RSH] for stages one and two showed that the first reaction is dependent on [glutathione], while the second is greater than first order with respect to [glutathione].

The kinetic profile indicates the formation of an intermediate followed by its slow decomposition. Earlier studies on the oxidation of glutathione by chromium(VI) revealed that the mechanism proceeds *via* the formation of a sulfur-linked chromate–glutathione ester intermediate.[6,7] Our results are consistent with formation of this chromate intermediate which

$$RSH + HOCrO_3^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RSCrO_3^- + H_2O \quad (K) \qquad (1)$$

$$RSH + RSCrO_3^- \xrightarrow{k_2} Cr^{IV} + RSSR \qquad (2)$$

$$RSCrO_3^- \xrightarrow{k_3} Cr^{V} + RS^{\bullet} \qquad (3)$$

$$H^+ + RSCrO_3^- \xrightarrow{k_4} Cr^{V} + RS^{\bullet} \qquad (4)$$

Scheme 1 RSH = DL-Penicillamine or glutathione

reacts further to produce intermediate oxidation states and disulfides or radicals as shown in Scheme 1. From equation (5)

$$k_{obs} = k_1[RSH]_T + k_{-1} \qquad (5)$$

for stage one a plot of k_{obs} *vs.* $[RSH]_T$ yields k_1 and k_{-1} as the slope and intercept respectively. The rate constant k_1 representing formation of the intermediate was found to be 13.8 ± 0.1 dm^3 mol^{-1} s^{-1}, while k_{-1}, its reversible decomposition, was (7.6 ± 0.2) × 10^{-2} s^{-1}. The equilibrium constant which can be calculated from the ratio, k_1/k_{-1}, was found to be 184 ± 4 dm^3 mol^{-1} (pH 7.80). At pH 2.70 the value of the equilibrium constant[5] was 400 dm^3 mol^{-1}, while in acidic perchlorate media[3] (0.01 ⩽ [H$^+$] ⩽ 0.1) the value increased to 1436 dm^3 mol^{-1}. The increase in the equilibrium constant with increasing [H$^+$] seems to support substitution at the chromate ion, which is known to be facile[6,9] at low pH.

Applying steady-state conditions to the formation of the intermediate in stage 2 of the reaction (Scheme 1), the overall expression obtained is (6). The k_4 path has been omitted based

$$k_{obs} = \frac{(k_1k_2[RSH]^2 + k_1k_3[RSH])}{(k_{-1} + k_3 + k_2[RSH])} \qquad (6)$$

on a fairly low value of (25 ± 4) × 10^{-2} mol^2 dm^{-6} s^{-1} obtained in acidic perchlorate media,[3] and because an acid-catalysed path is likely to be insignificant at neutral to basic pH. Now under similar conditions,[3] the k_3 pathway was found to be dependent on [H$^+$]^2, and this path may be negligible at pH > 7. Other researchers[9] in fact found that, at pH 7.4, $k_3 \ll k_2[RSH]$, so it is assumed in this study that $k_{-1} > (k_3 + k_2[RSH])$ leading to the modified equation (7) and resulting in

$$k_{obs} = k_1k_2[RSH]^2/k_{-1} \qquad (7)$$

a composite rate constant k_1k_2/k_{-1}. Plots of k_{obs} *vs.* $[RSH]^2$ are shown in Fig. 1, where the solid lines were calculated from equation (7). Negative or small intercepts with large errors were obtained indicating that an additional step independent of the concentration of glutathione did not contribute in any significant way to the second stage. From the value of k_1k_2/k_{-1} at 25.3 °C which is 1.97 ± 0.07 dm^6 mol^{-2} s^{-1} (Table 2), and using K (k_1/k_{-1}), obtained from this work, then k_2 can be calculated as (1.07 ± 0.04) × 10^{-2} dm^3 mol^{-1} s^{-1}.

O'Brien and Ozolins[17] investigated this reaction at 650 nm under conditions of no buffer or ionic strength adjustments. They studied both the formation and subsequent decay of a chromium(V) species and found that the first reaction was second order, whereas the other was first order with respect to [glutathione]. The explanation they proffered for the observed second-order dependency in [glutathione] is a reaction involving two molecules of glutathione and the intermediate. This is shown in equation (8) and can be regarded as an

$$Cr^{VI}\text{–}SR + 2RSH \longrightarrow Cr^{IV} + RSSR + H^+ + RSH \qquad (8)$$

extension of equation (2). These authors alluded to the reaction in equation (8) as a type of general base mechanism, where the extra molecule of glutathione acts as the base.[16,20]

Table 1 Pseudo-first-order rate constants for the oxidation of thiols by chromium(VI). Effect of thiol concentration (Tris–HCl buffer); I = 0.50 mol dm^{-3} ($NaClO_4$); $[CrO_4^{2-}]_T = 2.0 \times 10^{-4}$ mol dm^{-3}

Glutathione (pH 7.50, Second stage)

25.3 °C		30.0 °C		35.5 °C	
10^3 [RSH]/mol dm^{-3}	$10^4 k_{obs}/s^{-1}$	10^3 [RSH]/mol dm^{-3}	$10^4 k_{obs}/s^{-1}$	10^3 [RSH]/mol dm^{-3}	$10^4 k_{obs}/s^{-1}$
3.83	0.90	3.77	0.92	3.90	1.46
6.10	1.51	6.67	2.05	6.50	2.66
8.39	1.87	7.19	2.18	7.00	4.51
13.8	4.35	7.74	2.43	7.38	4.42
15.7	5.50	10.3	3.45	8.00	5.11
		12.4	5.79	11.8	9.92
		14.4	7.53	13.4	13.6

First stage

10^3 [RSH]/mol dm^{-3}	k_{obs}/s^{-1}	pH	$10^4 k_{obs}/s^{-1}$
1.8	0.10	7.18	7.77*
3.9	0.13	7.40	8.65*
8.2	0.19	7.70	7.53*
11.0	0.23	8.02	3.72*
16.0	0.30	8.18	2.26*
20.0	0.35	8.40	0.83*

DL-Penicillamine (pH 7.60)

19.9 °C		25.2 °C		30.1 °C	
10^3 [RSH]/mol dm^{-3}	$10^3 k_{obs}/s^{-1}$	10^3 [RSH]/mol dm^{-3}	$10^3 k_{obs}/s^{-1}$	10^3 [RSH]/mol dm^{-3}	$10^3 k_{obs}/s^{-1}$
1.87	0.38	3.90	0.98	2.41	1.02
2.20	0.33	6.16	1.42	4.90	1.83
4.28	0.54	8.04	1.88	7.43	2.70
6.83	0.88	12.3	2.68	8.57	3.03
10.3	1.27	18.8	4.50	14.5	5.49
11.7	1.50			19.1	6.72
14.1	1.76				
17.5	2.19				

* [RSH] = 1.0×10^{-2} mol dm^{-3}.

Table 2 Rate constants and activation parameters for the oxidation of thiols by chromium(VI)

Glutathione

T/°C	(k_2k_1/k_{-1})/dm^6 mol^{-2} s^{-1}
25.3	1.97 ± 0.07
30.0	3.41 ± 0.16
35.5	7.17 ± 0.35

$\Delta H^{\ddagger}$ = 90 ± 7 kJ mol^{-1}, $\Delta S^{\ddagger}$ = 63 ± 29 J K^{-1} mol^{-1}

DL-Penicillamine

T/°C	k_1/dm^3 mol^{-1} s^{-1}
19.9	0.12 ± 0.01 (0.12 ± 0.01)*
25.2	0.23 ± 0.01 (0.24 ± 0.01)*
30.3	0.35 ± 0.02 (0.37 ± 0.03)*

$\Delta H^{\ddagger}$ = 72 ± 7 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −18 ± 28 J K^{-1} mol^{-1}

* Parameters in parentheses were derived from equation (6) by allowing the parameters to float in a non-linear regressional computer analysis.

This proposed model for a reaction second order with respect to [glutathione] might be regarded as a kinetic anomaly, since termolecular reactions in solution are extremely rare.[21] However, second-order ligand dependencies have previously been encountered in a number of systems, some of which also involve sulfur centres.[22] A recent study between $[Cu(dmphen)]^{2+}$ (dmphen = 2,9-dimethyl-1,10-phenanthroline) showed up to second-order behaviour[23] in [glutathione] ⩾ 1 mmol dm^{-3}.

Connett and Wetterhahn[9] also assumed that k_3, the unimolecular pathway, was negligible, and that a rapid equilibrium exists between the intermediate and reactants. The rate expression resulting from such considerations [equation (9)] is shown below.[9] Non-linear fits with this expression

$$k_{obs} = \frac{k_2K[RSH]^2}{1 + K[RSH]} \quad (9)$$

using data from our work gave consistently large errors in k_2 and K. The most meaningful value for k_2 (25.7 °C) was (4.5 ± 0.2) × 10^{-2} dm^3 mol^{-1} s^{-1}, whereas K was 112 ± 71 dm^3 mol^{-1} which is in fairly good agreement with the other values (1.07 ± 0.04 × 10^{-2} dm^3 mol^{-1} s^{-1} and 184 ± 4 dm^3 mol^{-1}) obtained *via* a different analysis. For the same reaction, first[9] at pH 7.4, k_2 approximates to 0.20 ± 0.03 dm^3 mol^{-1} s^{-1}, while a much higher value of 0.89 dm^3 mol^{-1} s^{-1} (pH 2.70) was reported.[5] At pH 1–2 a lower one[3] of (12.1 ± 0.4) × 10^{-2} dm^3 mol^{-1} s^{-1} was obtained. These values may be due to the different conditions employed in each study.

A smaller equilibrium constant was reported for the reaction by Connett and Wetterhahn[9] (≈20 dm^3 mol^{-1}), so using that information it might be possible to make the assumption that K[RSH] < 1, thus equation (9) may be approximated to one of the form (10) which could also explain our kinetic data. This

$$k_{obs} = k_2K[RSH]^2 \quad (10)$$

assumption was quickly discounted based on the larger value of K obtained in this work, since K[RSH] > 1 at [RSH] in excess of 0.005 mol dm^{-3}. Thus, the glutathione–chromium(VI)

Table 3 Summary of rate constants and activation parameters for the oxidation of various substrates by Cr^{VI} at pH ≥ 7 (25 °C)

Reaction	k/dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	Ref.
HA^- [a]	0.10 ± 0.02	105 ± 32	69 ± 133	19
b	59.4 ± 0.5	44 ± 3	−62 ± 11	19
Glutathione[c]	(1.07 ± 0.04) × 10^{-2}	90 ± 7	63 ± 29	This work
d	0.20 ± 0.03			9
e	0.7			10
DL-Penicillamine[f]	0.23 ± 0.01	72 ± 7	−18 ± 28	This work
g	0.35 ± 0.03			9
L-Cysteine[d]	0.64	55	−84	11

[a] $k = k_f$ for oxidation of ascorbate monoanion by CrO_4^{2-}. [b] $k = k_f$ for oxidation by $HCrO_4^-$. [c] $k = k_2$ (Scheme 1), activation parameters from composite rate constants. [d] $k = k_2$. [e] k In mol^2 dm^{-6} s^{-1} and no ionic strength (20 °C). [f] $k = k_1$ or k_2. [g] $k = k_1$.

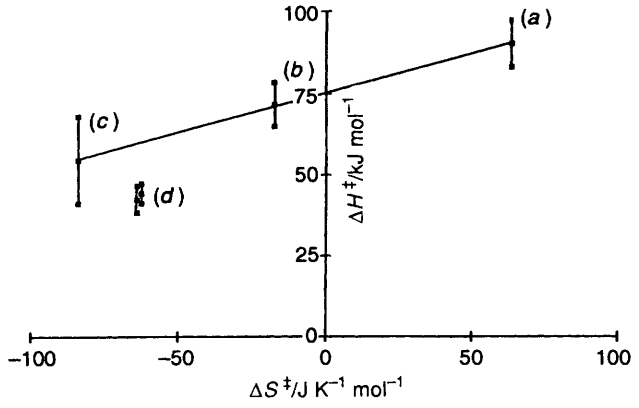

Fig. 2 Plot of $\Delta H^{\ddagger}$ *versus* $\Delta S^{\ddagger}$ for the oxidation of substrates by chromium(VI) ion: (*a*) glutathione, (*b*) DL-penicillamine, (*c*) L-cysteine and (*d*) L-ascorbic acid

intermediate complex might not maintain a rapid equilibrium with its reactants. The values for the electron transfers imply that the significant factor facilitating a more rapid reaction at lower pH is likely to be the rate of formation of the ester intermediate.

The $\Delta S^{\ddagger}$ (63 ± 29 J K^{-1} mol^{-1}) was determined from the composite rate parameters, so much significance is not attached to this value. However, it is possible that a dissociative mechanism is in operation. Any steric hindrance that may be caused by the bulky glutathione ligands should in fact decrease in the transition state if the mechanism is dissociative.[21] This large value is in contrast to the much lower one obtained in acidic perchlorate media. There the redox steps involving catalysis by protons, and the analogous k_2 path where a second molecule of glutathione reacts with the ester intermediate, both have negative entropies of activation[3] as shown in equations (11) and (12). A $\Delta H^{\ddagger}$ value of 90 ± 7 kJ mol^{-1} obtained from

$$Cr^{VI}\text{–}SR + RSH \xrightarrow{k_2} Cr^{IV}$$
$$\Delta S^{\ddagger} = -168 \pm 21 \text{ J K}^{-1} \text{ mol}^{-1} \quad (11)$$

$$RSCrO_3^- + 2H^+ \xrightarrow{k_3} Cr^{V}$$
$$\Delta S^{\ddagger} = -101 \pm 29 \text{ J K}^{-1} \text{ mol}^{-1} \quad (12)$$

this study (pH > 7), is three times larger than the corresponding value in acidic media[3] (29 ± 8 kJ mol^{-1}). These parameters must however be viewed with some caution as they were determined from composite rate constants, and the temperature dependence of K has not been really determined. Activation parameters for the oxidation of glutathione at neutral pH were not reported by the other workers.

The k_{obs} values seem independent of pH between 7 and 8, but show an overall decrease. Over the range (7.15 ≤ pH ≤ 8.40) where the kinetics was examined, both carboxyl groups of glutathione are ionized whereas the SH and NH_3^+ are largely unionized (pK_a = 8.93 and >9 respectively).[24] The data indicate, therefore, that both SH and NH_3^+ could be reactive. Under these experimental conditions where the predominant form of the chromate is CrO_4^{2-}, less than 2% exists as the $HCrO_4^-$ ion and this is quite reactive.[19] Changes in pH affect this concentration and may explain the small variation in the rate constants.

Oxidation of DL-*Penicillamine*.—The reaction between DL-penicillamine and the chromate ion was studied near neutral conditions over the ranges 0.002 ≤ [RSH] ≤ 0.020 mol dm^{-3}, 19.9 ≤ θ ≤ 30.3 °C, at ionic strength 0.50 mol dm^{-3} ($NaClO_4$). Unlike in the case of glutathione, plots of k_{obs} *vs.* [penicillamine] showed good linearity with small intercepts. This can be rationalized according to the mechanism given in Scheme 1, where it is assumed that the rate-determining step is the formation of the ester intermediate [equation (1)], from which expression (5) can be derived. Second-order rate constants determined directly from the slopes of these plots are shown in Table 2. The value of 0.32 dm^3 mol^{-1} s^{-1} for k_1 at pH 7.40 and 25 °C reported[9] by other authors is somewhat larger than the 0.23 dm^3 mol^{-1} s^{-1} from our data considering our error limits. The other parameter, k_{-1}, had large uncertainties or was negative.

Spectrally, repetitive scanning did not indicate the formation of a penicillamine–chromate intermediate. This does not rule out its existence, since there may be no build-up of this intermediate. So, alternatively, the steady-state approximation can be applied to the concentration of the intermediate, $RSCrO_3^-$ (as previously done) to give equation (6). However, k_3 might not be easily neglected, as co-ordinated penicillamine may be a better electron donor than glutathione, on account of the two electron-releasing methyl groups. Based on the small value of the intercepts, it is reasonable to assume that (k_{-1} + k_3) ≪ k_2[RSH], leading to equation (13) which is quite similar

$$k_{obs} = k_1[RSH] + (k_1k_3/k_2) \quad (13)$$

to (5). From this equation the ratio of slope to the intercept will give a value for the composite term k_3/k_2.

The value for k_1 obtained here is much smaller than that of 1.82 dm^3 mol^{-1} s^{-1} obtained for the acid-catalysed (k_f) path.[6] This may be due to the fact that the rate of substitution by penicillamine at the tetrahedral chromate centre is considerably decreased at higher pH, since k_f represents this pathway.[6] The activation parameters ($\Delta H^{\ddagger}$ = 25 ± 8 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −134 ± 50 J K^{-1} mol^{-1}) for the reaction under acidic conditions are different from those obtained for the reaction between chromium(VI) and penicillamine at pH > 7 studied in this work.

The rate constants and thermodynamic parameters for the oxidation of L-ascorbic acid and some thiols by chromium(VI) at pH ≤ 7 are summarized in Table 3. The plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$

shows that a similar mechanism is plausible for the oxidation of all the thiols (Fig. 2), except for ascorbate. Based on the standard redox potentials near physiological pH (ascorbate 0.07; cysteine −0.32; glutathione −0.24 V), glutathione should be a better reductant than L-ascorbic acid. From experimental observations, the standard redox potential seems not to be the most important factor determining the reducing properties of these substrates, supporting the view that these oxidations are influenced not by thermodynamic, but kinetic factors.

Electrostatic interaction between the reacting species as well as the steric hindrance inherently associated with each reductant are factors to be considered. The latter is more evident from the reactions of L-cysteine and DL-penicillamine. The two β-hydrogens of L-cysteine are substituted by two methyl groups in DL-penicillamine. This sterically hindered molecule results in lower rate constants than those obtained for the oxidation of cysteine.[11] Much lower rate constants were obtained for the oxidation of glutathione which is the bulkiest of the thiols. Thiols have been thought to be better chelators than ascorbate,[8] so the decrease in rate constants as the size of each substrate increases may be a measure of the extent of the associative nature of the reactions.

In acidic media the rate of oxidation of these four thiols is greater[3,6,19,25] than at pH > 7. The ability of substrates to donate a proton to the hydroxy group on the hydrogenchromate ion has always featured prominently in reactions of the chromate ion with acidic reagents.[4,26–35] This is generally believed to promote the formation of chromium(VI)-ester intermediates required for inner-sphere electron transfers.

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