Kinetics and mechanism of oxidation of thioglycolic acid by hexachloroiridate(IV) †

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Oxidation of thioglycolic acid ($HSCH_2CO_2H$, TGA) by $[IrCl_6]^{2-}$ (Ir(IV)) in aqueous solution at 25 °C is highly susceptible to trace metal-ion catalysis. This catalysis can be effectively suppressed by bathophenanthroline-disulfonate (bathophen), allowing the direct oxidation to be studied. Although the corresponding disulfide is produced quantitatively in the absence of bathophen, a mixture of the disulfide and a species believed to be the sulfonate is produced in its presence. In both cases the Ir(IV) is reduced to $[IrCl_6]^{3-}$. The rate law when catalysis is suppressed is first order in both Ir(IV) and TGA. The pH dependence is complex, owing to the diprotic nature of TGA. At high pH there is a term corresponding to outer-sphere oxidation of $^-SCH_2CO_2^-$ with a rate constant of $(3.52 \pm 0.03) \times 10^6$ M^{-1} s^{-1} at $\mu = 0.1$ M. A self-exchange rate constant of 1×10^5 M^{-1} s^{-1} for the $^\bullet SCH_2CO_2^-/$ $^-SCH_2CO_2^-$ redox couple is derived from the Marcus cross relationship. In order to account for the product mixture, a mechanism is proposed in which RSO_3^- is produced in a series of steps originating with the oxidation of $RS^\bullet$ by $[IrCl_6]^{2-}$, while RSSR is produced by association of $RS^\bullet$ with TGA to generate $RSSR^{\bullet-}$ and oxidation of $RSSR^{\bullet-}$ by $[IrCl_6]^{2-}$.

Introduction

The oxidation of aliphatic thiols in aqueous solution is of great general importance, but it takes special significance in biochemistry where the oxidations of cysteine and glutathione have key physiological roles. There are diverse mechanisms for thiol oxidations,[1] but herein we are concerned with reactions in which the oxidant acts as a simple one-electron acceptor. When the oxidants are labile metal complexes, inner-sphere mechanisms usually arise as in, for example, the oxidation of thioglycolic acid by Fe^{3+}.[2] When "outer-sphere" oxidants are used a surprising result ensues: to our knowledge all published reports describe reactions that are either known to be catalyzed by metal-ion impurities or were not tested for such catalysis. The ubiquity of metal-ion catalysis implies that such catalysis must be assumed to occur unless proven otherwise.

As a typical aliphatic thiol we have selected thioglycolic acid (TGA) for detailed study because of its structural simplicity, its low vapor pressure, and its known one-electron redox potential.[3] Inner-sphere mechanisms were reported for the oxidations of TGA by $[Mn^{III}(cdta)]^-$ (H_4cdta = *trans*-cyclohexane-1,2-diaminetetraacetic acid),[4] two nickel(IV) oxime–imine complexes,[5] a nickel(III) oxime–imine complex,[6] $[V^V(HIDA)_2]^-$ (H_3HIDA = *N*-hydroxyiminodiacetic acid),[7] $[Fe(CN)_5NO]^{2-}$,[8] and Fe^{3+}.[2] Inner-sphere mechanisms may also be assumed for the oxidations by Np(VI),[9,10] Ce(IV),[9,11] Mo(VI) and Mo(V).[12] In the case of putative outer-sphere oxidants, the reaction of $[Fe(CN)_6]^{3-}$ was originally reported without mention of metal-ion catalysis,[13] but subsequent studies showed that such catalysis is so effective that no data could be obtained describing the direct electron-transfer reaction.[14,15] With $[Cr^{IV}(dien)(O_2)_2]$ the reaction is dominated by Fe^{III} catalysis.[16] Although this catalysis is inhibited by EDTA, it is unclear whether the residual rates are free of catalytic effects, for EDTA can form catalytically active complexes with the ions that it was intended to mask as shown by Bridgart and Wilson.[17] With $[Mo(CN)_8]^{3-}$ and $[Co^{III}O_4W_{12}O_{36}]^{5-}$ as oxidants, outer-sphere mechanisms were assumed, but no experiments were performed to test for metal-ion catalysis.[18,19] Overall, there are no convincing published examples of the direct outer-sphere oxidation of TGA.

In this, our initial report on the outer-sphere oxidation of thiols, we have selected $[IrCl_6]^{2-}$ as the oxidant. This choice was based on our prior experience with this reagent,[20–30] which is easily handled, generally acts as a one-electron oxidant, and often reacts as an outer-sphere oxidant. Of particular note are two studies in which we used this oxidant and were able to achieve complete suppression of trace metal-ion catalysis by use of appropriate chelating agents.[28,30] We now report that the direct electron-transfer reaction between TGA and $[IrCl_6]^{2-}$ can be studied by use of bathophenanthrolinedisulfonate as a chelating agent, that the reaction gives an unexpected mixture of products, and that the rate law identifies the thiolate as the reactive protonation state. The rates afford an opportunity to use Marcus theory in an evaluation of the self-exchange rate constant for the $^-SCH_2COO^-/^\bullet SCH_2COO^-$ couple, the first such report for a thiolate/thiyl system.

Experimental

Materials

Thioglycolic acid, sodium salt, $HSCH_2COONa$ (Aldrich), was purified by recrystallization using H_2O and EtOH as solvents. As this salt is freely soluble in water, and slightly soluble in ethanol, it was dissolved in water first, then precipitated by adding up to 90% absolute ethanol. The precipitate was dried in a vacuum oven overnight at 54 °C. Sodium hexachloro-iridate(IV), $Na_2IrCl_6 \cdot 6H_2O$ (Alfa), was used without further purification. Bathophenanthrolinedisulfonic acid, disodium salt hydrate, $Na_2[(O_3S)_2C_{24}H_{14}N_2] \cdot xH_2O$, (bathophen) was purchased from Acros. Sulfoacetic acid, HO_3SCH_2COOH (HO_3SR), 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt

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(DSS), and deuterium oxide (D$_2$O), 99.9 atom% D, were purchased from Aldrich. Dithiodiglycolic acid, C$_4$H$_6$O$_4$S$_2$ (RSSR), was purchased from Sigma. Certified grade anhydrous cupric sulfate (CuSO$_4$) was obtained from Fisher. All were used as supplied.

1 M HClO$_4$ solution was prepared by diluting perchloric acid 70% (Fisher, reagent grade) and standardized with trizma base (trizma = tris(hydroxymethyl)aminomethane). NaClO$_4$ (Fisher) was recrystallized from hot water. NaOAc (Fisher) was recrystallized from EtOH. The HOAc–NaOAc buffer was obtained by mixing HClO$_4$ and NaOAc. Sodium borate, Na$_2$B$_4$O$_7$·10H$_2$O, was purchased from Fisher, and reagent grade disodium phosphate Na$_2$HPO$_4$ was supplied by MCB; both were used as supplied.

Distilled deionized water was obtained from tap water by filtration through a Barnstead pretreatment cartridge and subsequent distillation in a Barnstead Fistreem all-glass still. All solutions were prepared with distilled deionized water and were permitted to contact only glass, Teflon, and platinum.

Methods

UV-vis spectra were recorded on Hewlett-Packard 8452A and 8453 diode array spectrophotometers with quartz cells of 1.00 cm path length. The spectrophotometers were equipped with thermostatted water baths to maintain the temperature at 25.0 ± 0.1 °C.

The kinetic studies were performed on a Hi-Tech Scientific model SF-51 stopped-flow apparatus equipped with an SU-40 spectrophotometer and a C-400 circulating water bath that maintained the temperature of the cell compartment at 25.0 ± 0.1 °C. An OLIS 4300 S system was used for data acquisition and analysis. Reactions were monitored at 489 nm, and the rate constants were obtained by fitting the data with OLIS-supplied first-order functions. Reported values of k_{obs} are the results of fits to single shots, and therefore do not have associated statistical uncertainties; from visual inspection of overlaid series of shots, reproducibility in k_{obs} is probably ±10%. A nonlinear-least-squares computer program was used to fit the overall rate law to the values of k_{obs}.[31]

^{1}H NMR spectra of reactant and product solutions were obtained with a Bruker AC 250 spectrometer. They were run in D$_2$O solution with all shifts reported (in ppm) downfield from DSS.

Stock solutions of Na$_2$IrCl$_6$ were bubbled with N$_2$ in an acid environment to prevent decomposition of the Na$_2$IrCl$_6$. Solutions of HSCH$_2$COOH were degassed with N$_2$ before reaction. All reactions were carried out under anaerobic conditions.

Results

Product identification

The products of the reduction of sodium hexachloroiridate(IV), Ir(IV), by thioglycolic acid (HSCH$_2$COOH) were determined by ^{1}H NMR spectroscopy and UV-vis spectrophotometry.

One set of experiments was performed under the conditions: [Ir(IV)]$_0$ = 0.2 mM; [TGA]$_0$ = 2 mM; [bathophen] = 1 mM; [NaOAc] = 0.1 M; [HClO$_4$] = 0.05 M. The product solution was colorless. After reaction, the solution was treated with chlorine gas (Cl$_2$) for 1 min to oxidize [IrCl$_6$]$^{3-}$ back to [IrCl$_6$]$^{2-}$. The color of the oxidized solution was the same as that of [IrCl$_6$]$^{2-}$, and the UV-vis spectrum of the oxidized solution showed a peak at 489 nm, identical in shape to that of an authentic sample of Na$_2$IrCl$_6$. An [IrCl$_6$]$^{2-}$ recovery of 92% was calculated by comparing the absorbance at 489 nm before and after the two reaction steps.

^{1}H NMR product spectra obtained under the conditions [TGA]$_0$ = 10 mM, [DSS] = 2 mM, [bathophen] = 1 mM, and [Ir(IV)]$_0$ = 2.2 mM~12.5 mM in D$_2$O solution, clearly reveal two

product resonances, one corresponding to dithiodiglycolic acid (RSSR) at 3.5 ppm, and the other, at 3.8 ppm, having the same chemical shift as that of sulfoacetate (RSO$_3^-$). One of these spectra, obtained with [Ir(IV)]$_0$ = 4 mM, is shown in Fig. 1. In this figure, the peaks at 0.00, 0.63, 1.76, and 2.9 ppm are due to the DSS standard, the peak at 4.8 ppm is due to HDO, the peak at 3.2 ppm is due to thioglycolic acid (TGA), and the peaks at 7.7, 8.0, and 9.2 ppm are due to bathophen. Confirmation of the product assignments was obtained by spiking the product solution with authentic samples of RSSR and HO$_3$SR, which led to increases in the peak heights of the corresponding products.
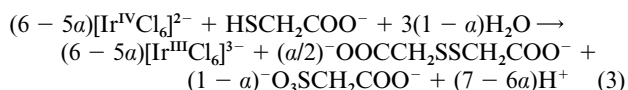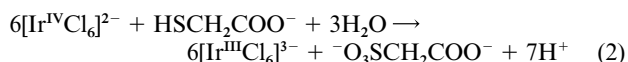
Stoichiometry

The stoichiometry of the reaction between TGA and [IrCl$_6$]$^{2-}$ depends qualitatively on the absence or presence of bathophen in the reaction mixture.

In the absence of bathophen a spectrophotometric titration was performed by the addition of small aliquots of Na$_2$IrCl$_6$ to a cuvette containing a sample of TGA in 0.10 M NaOAc–HOAc buffer (pH = 4.74 after the reaction). The cuvette was equipped with a stopcock to prevent the entry of O$_2$ from the air. Before the reaction commenced, the TGA (NaOAc) solution and the solvent (HClO$_4$) solution were degassed, then transfered to the cuvette bubbled with N$_2$. The solution of Ir(IV) was bubbled with N$_2$ and injected through the stopcock and into the cuvette using a syringe equipped with a Pt needle. Fig. 2 shows a plot of the absorbance at 489 nm as a function of the volume of Ir(IV) solution added. The absorbance at 489 nm is due to the Ir(IV) spectral absorbance peak ($\varepsilon_{489} = 3.8 \times 10^3$ M^{-1} cm^{-1}).[27] Before the end point is reached, the Ir(IV) is consumed completely. At the end point, there is an abrupt change in slope, with the absorbance rising as the excess Ir(IV) concentration increases. The end point corresponds to a consumption ratio of 0.93 for $n_{Ir(IV)}/n_{TGA}$, where n represents the number of moles of reactant. This consumption ratio, combined with the evidence for quantitative conversion of Ir(IV) to Ir(III) as described above, supports the description of the reaction by eqn. (1):

$$2[Ir^{IV}Cl_6]^{2-} + 2HSCH_2COO^- \longrightarrow$$
$$2[Ir^{III}Cl_6]^{3-} + {}^-OOCCH_2SSCH_2COO^- + 2H^+ \quad (1)$$
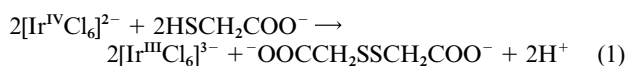
The above reaction was performed with no bathophen present. In this case, as is described below, metal ions adventitiously present catalyze the reaction. When bathophen is present, it combines with the metal ions as a chelate. The experiments below show that the products, mechanism, and stoichiometry of reactions with bathophen are all different from those of reactions without bathophen.

A similar spectrophotometric titration was performed with [bathophen] = 1 mM in 0.10 M NaOAc–HOAc buffer (pH = 4.41 after the reaction) as shown in Fig. 3. The end point corresponds to a consumption ratio of 5.0 for $n_{Ir(IV)}/n_{TGA}$. This consumption ratio, combined with the evidence for quantitative conversion of Ir(IV) to Ir(III) described above and the products of RSSR and RSO$_3^-$ determined by NMR spectroscopy, supports the description of the reaction as a linear combination of reactions 1 and 2 as given by eqn. (3) where a ranges from 0 to 1.

$$6[Ir^{IV}Cl_6]^{2-} + HSCH_2COO^- + 3H_2O \longrightarrow$$
$$6[Ir^{III}Cl_6]^{3-} + {}^-O_3SCH_2COO^- + 7H^+ \quad (2)$$

$$(6-5a)[Ir^{IV}Cl_6]^{2-} + HSCH_2COO^- + 3(1-a)H_2O \longrightarrow$$
$$(6-5a)[Ir^{III}Cl_6]^{3-} + (a/2){}^-OOCCH_2SSCH_2COO^- +$$
$$(1-a){}^-O_3SCH_2COO^- + (7-6a)H^+ \quad (3)$$

Eqn. (3) implies the following relationships: $n_{Ir(IV)}/n_{TGA} = 6 - 5a$, and $n_{RSO_3^-}/n_{RSSR} = (2/a) - 2$.

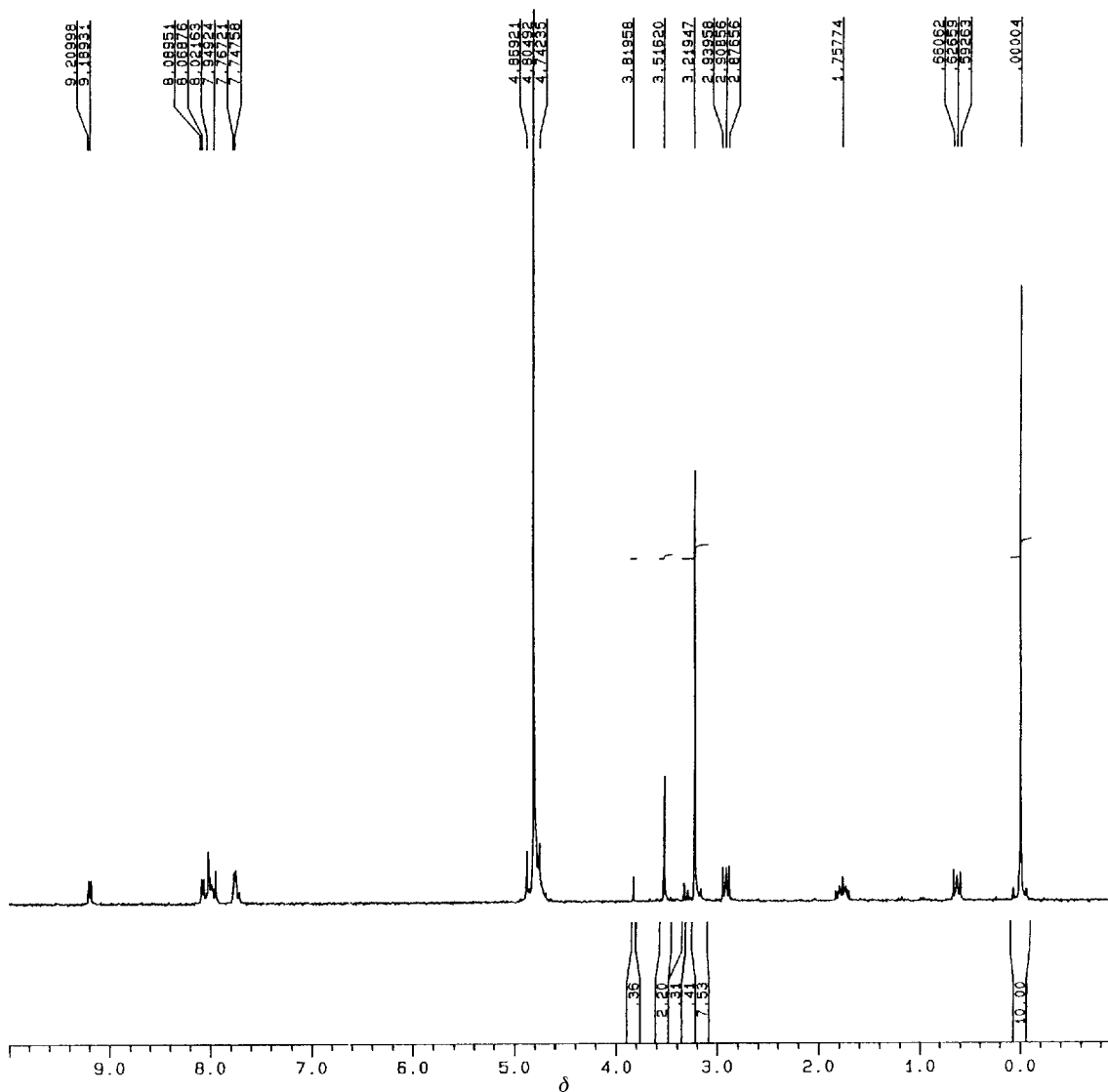**Fig. 1** ^{1}H NMR spectrum of products of the reaction between TGA and $[IrCl_6]^{2-}$ in D_2O with DSS and bathophen. $[TGA]_0 = 10$ mM, $[Ir(IV)]_0 = 4.0$ mM, $[DSS] = 2.1$ mM, and $[bathophen] = 1.1$ mM.

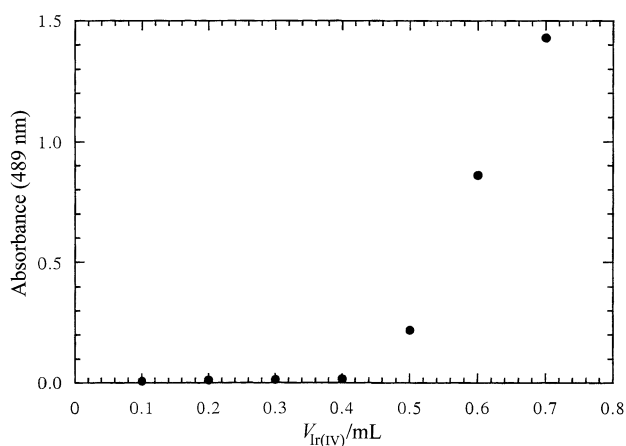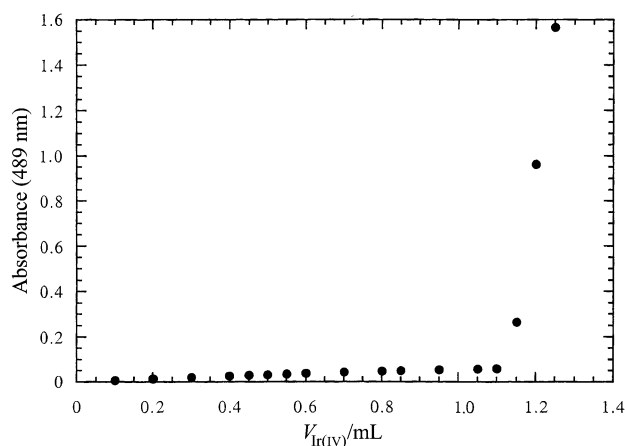**Fig. 2** Spectrophotometric titration of TGA with $[IrCl_6]^{2-}$ in the absence of bathophen. Absorbance on the left-hand ordinate at 489 nm is shown as a function of the volume of Ir(IV) solution added. pH = 4.74. $[TGA]_0 = 1.01$ mM, $n_0(TGA) = 2.53 \times 10^{-3}$ mmol, [Ir(IV) stock] = 5.03 mM, and intial volume of TGA solution = 2.5 mL.

Fig. 3 Spectrophotometric titration of TGA with $[IrCl_6]^{2-}$ in the presence of 1 mM bathophen. Absorbance on the ordinate at 489 nm is shown as a function of the volume of Ir(IV) solution added. pH = 4.41, $[TGA]_0 = 1.0$ mM, $n_0(TGA) = 2.5 \times 10^{-3}$ mmol, [Ir(IV) stock] = 11.0 mM, and initial volume of TGA solution = 2.5 mL.

Semiquantitative verification of the stoichiometry in eqn. (3) was obtained from peak integrals in the ^{1}H NMR spectra as given in Table 1. These results show that the product ratio $n_{RSO_3^-}/n_{RSSR}$ increases linearly as a function of $[Ir(IV)]_0$. The ratio of $n_{Ir(IV)}/n_{TGA}$ likewise increases from 2.04 to 3.86 as the initial

concentration of Ir(IV) increases. The parallel trend in these two quantities is in agreement with the requirements of eqn. (3). Precise agreement between these two measures of stoichiometry is not achieved because of the difficulty in determining accurate values for the consumption of TGA when only a small fraction

Table 1 ^{1}H NMR stoichiometry as a function of the initial concentration of $[IrCl_6]^{2-}$ ^{a}

$[Ir(IV)]_0$/M	$[TGA]_0$/M	$[TGA]_\infty$/M	$n_{Ir(IV)}/n_{TGA}$	$n_{RSO_3^-}/n_{RSSR}$
0.00216	0.0103	0.00924	2.04	0.88^b
0.0040	0.0101	0.00858	2.63	1.04
0.0080	0.0100	0.00793	3.86	1.32
0.0125	0.0101	0.00657	3.64	1.74

^{a} The reactions were performed in D_2O solvent. [DSS] = 0.002 M, and [bathophen] = 1.0 mM. [TGA] values were calculated by comparing the peaks with that of a known amount of TGA added after the reaction (internal standard method). $n_{RSO_3^-}/n_{RSSR} = 2(I(RSO_3^-)/I(RSSR))$ where $I(RSO_3^-)$ and $I(RSSR)$ are the integrals of the methylene proton resonances in RSO_3^- and RSSR. ^{b} pH = 4.7 for the product mixture in this experiment.

is consumed. These experiments were not buffered, so the changes in these ratios could be due to changing $[Ir(IV)]_0$ or changing pH.

Formation of RSO_3^- through pathways involving O_2 can be ruled out in the above experiments because the high yields of RSO_3^- obtained are incompatible with the low levels of O_2 that might have been present under the anaerobic conditions employed.

Kinetics

The kinetics of the reaction of TGA with $[IrCl_6]^{2-}$ were typically examined by use of stopped-flow spectrophotometry with a 10-fold or greater excess of TGA over $[Ir(IV)]_0$ at 25.0 °C, and monitored at 489 nm, which is the characteristic absorbance peak of $[IrCl_6]^{2-}$. Under these conditions, the kinetic traces displayed a pseudo first-order loss of absorbance, with the rate constants, k_{obs}, being defined by the equation:

$$-d[IrCl_6^{2-}]/dt = k_{obs}[IrCl_6^{2-}] \qquad (4)$$

A typical kinetic trace is shown in Fig. 4.
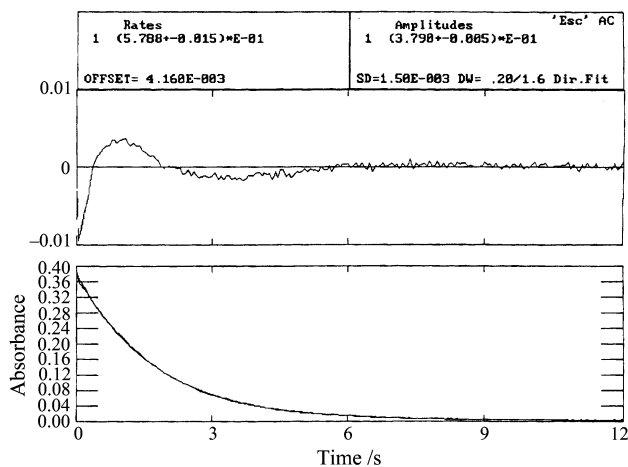

Fig. 4 Kinetic trace of the reaction of TGA with $[IrCl_6]^{2-}$ under conditions of [bathophen] = 1×10^{-3} M, $[TGA]_0 = 5 \times 10^{-3}$ M, $[Ir(IV)]_0 = 1 \times 10^{-4}$ M, HOAc–NaOAc buffer ($\mu = 0.1$ M), and pH = 4.49.

A series of experiments performed under the conditions $[TGA]_0 = 2 \times 10^{-4}$ M and $[Ir(IV)]_0 = 2 \times 10^{-5}$ M, with an NaOAc–HOAc buffer ($\mu = 0.1$ M, pH = 4.53~4.62), showed that $t_{1/2} = 0.0035$ s without any bathophen or Cu^{2+} added, $t_{1/2} < 2$ ms (less than the instrument dead-time) with [Cu^{2+}] = 2×10^{-6} M (no bathophen added), and $t_{1/2} = 6.9$ s with [bathophen] = 2×10^{-4} M (no Cu^{2+} added). These results show that Cu^{2+} can act as a catalyst at very low concentrations and that bathophen can inhibit the rates by as much as a factor of 2000.

Another series of experiments, under conditions of $[TGA]_0 = 5 \times 10^{-3}$ M and $[Ir(IV)]_0 = 1 \times 10^{-4}$ M, with an NaOAc–HOAc

buffer ($\mu = 0.1$ M, pH = 4.53~4.57), showed that the reaction at these higher concentrations of TGA and $[IrCl_6]^{2-}$ without bathophen is 10 times faster than the reaction with 0.1 mM bathophen. In the presence of 0.1 mM bathophen the catalytic effect of added Cu^{2+} up to 1×10^{-6} M was effectively suppressed.

In another test of the effectiveness of bathophen as a catalytic inhibitor a series of experiments was performed in which its concentration was varied between 0.1 and 1 mM, under conditions of [TGA] = 0.02 M and $[Ir(IV)]_0 = 1 \times 10^{-4}$ M, with an NaOAc–HOAc buffer ($\mu = 0.1$ M). The results, given in Table S1 (ESI) and plotted in Fig. 5, show that k_{obs} decreases to
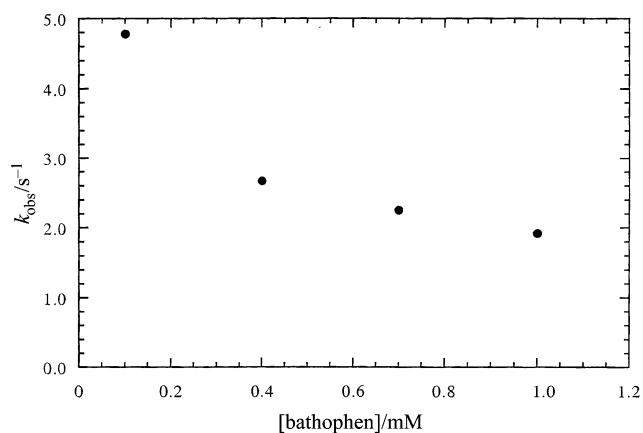
Fig. 5 Kinetics of the reaction of $[IrCl_6]^{2-}$ with TGA. Plot of k_{obs} as a function of [bathophen]. $[TGA]_0 = 0.020$ M, $[Ir(IV)]_0 = 1 \times 10^{-4}$ M, NaOAc–HOAc buffer ($\mu = 0.1$ M), and pH = 4.56~4.61.

a limiting value at high [bathophen]. Thus, at 1 mM bathophen, catalysis by impurity metal ions can be prevented at concentrations of $[TGA]_{tot}$ as high as 0.02 M. As all subsequent kinetic experiments were performed at low concentrations of $[TGA]_{tot}$ and $[IrCl_6^{2-}]_0$, it is reasonable to consider that the presence of 1 mM bathophen is generally sufficient to prevent catalysis by trace amounts of metal ions. All further kinetic experiments were performed accordingly.

Two types of experiments were conducted to probe whether the sulfur-containing products affected the kinetics of the oxidation of TGA. In the first of these TGA was the limiting reagent, the conditions being $[TGA]_0 = 5 \times 10^{-5}$ M, [bathophen] = 1×10^{-3} M, [NaOAc] = 0.10 M, [HClO$_4$] = 0.05 M, and $[Ir(IV)]_0 = 5 \times 10^{-4}$ M. As is shown in Fig. 6, these conditions lead to a biphasic loss of Ir(IV), with a rapid first step corre-
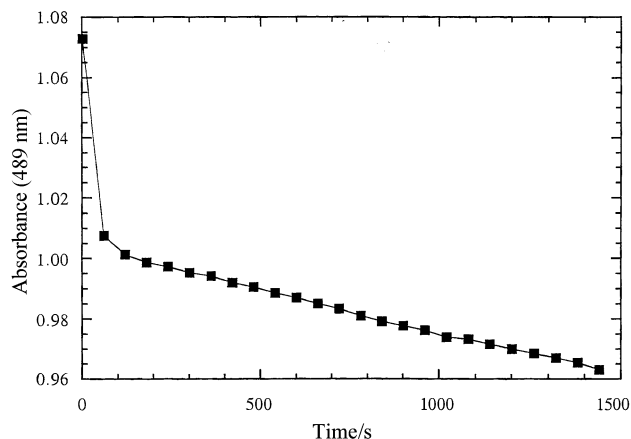
Fig. 6 Kinetic trace of the reaction of excess $[IrCl_6]^{2-}$ with TGA. Absorbance on the ordinate at 489 nm is shown as a function of time (s). $[TGA]_0 = 5 \times 10^{-5}$ M, $[Ir(IV)]_0 = 5 \times 10^{-4}$ M, [bathophen] = 1×10^{-3} M, [NaOAc] = 0.10 M, and [HClO$_4$] = 0.05 M. Note that because of the rapidity of the reaction of TGA with Ir(IV), most of the TGA is consumed prior to the initial absorbance reading.

sponding to the results obtained when Ir(IV) is the limiting reagent. The much slower second step is tentatively ascribed to the oxidation of the product, RSSR, by excess Ir(IV). In the second type of experiment this hypothesis was confirmed by directly examining the kinetics of reaction of RSSR with excess Ir(IV). The kinetic trace, displayed in Fig. 7, reveals that the
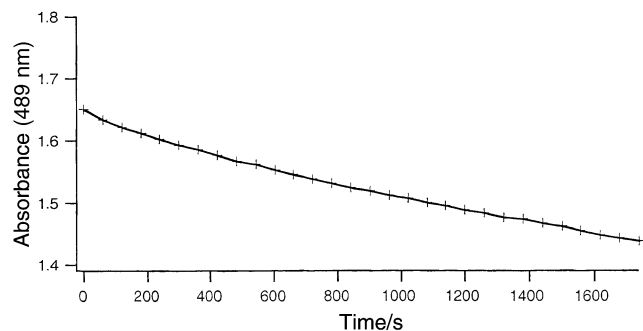

Fig. 7 Kinetic trace of the reaction of $[IrCl_6]^{2-}$ with RSSR. Absorbance on the ordinate at 489 nm is shown as a function of time (s). $[RSSR]_0 = 1.08 \times 10^{-4}$ M, $[Ir(IV)]_0 = 5.0 \times 10^{-4}$ M, $[bathophen] = 1.0 \times 10^{-3}$ M, $[NaOAc] = 0.10$ M, $[HClO_4] = 0.045$ M, and pH = 4.68.
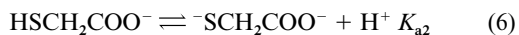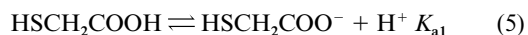
reaction of RSSR and Ir(IV) is quite slow, in agreement with the slow step in the biphasic reaction of TGA with excess Ir(IV). Thus, under typical conditions the reaction of Ir(IV) with excess TGA is unaffected by the slow reaction of Ir(IV) with the small amount of RSSR generated in the reaction.
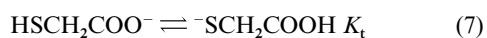
Ir(IV) dependence

In the oxidant dependence study, the kinetics were conducted under pseudo first-order conditions, where $[TGA] = 1 \times 10^{-2}$ M, $[bathophen] = 1 \times 10^{-3}$ M, and the initial concentration of Ir(IV) was varied from 1×10^{-5} to 1×10^{-4} M. The pH was controlled by an NaOAc–HOAc buffer (pH = 4.7). The ionic strength ($\mu = 0.11$ M) of the reacting solutions was adjusted by the addition of appropriate amounts of perchloric acid and sodium acetate solutions. Plots of $\ln(A_t - A)$ vs. time were linear over at least 5 half-lives, consistent with a first-order decrease in concentration of $[IrCl_6]^{2-}$, eqn. (4). As required by this rate expression, k_{obs} stays unchanged when $[Ir(IV)]_0$ is varied tenfold at constant reductant concentrations. The data are shown in Table S1 (ESI).

TGA dependence

When examining the dependence on reducing agent concentrations, preliminary experiments showed that the kinetics were sensitive to the pH and concentration of TGA. It is well-known that TGA engages in two rapid and reversible acid dissociation equilibria in water as shown in eqns. (5) and (6).

$$HSCH_2COOH \rightleftharpoons HSCH_2COO^- + H^+ \quad K_{a1} \quad (5)$$

$$HSCH_2COO^- \rightleftharpoons {}^-SCH_2COO^- + H^+ \quad K_{a2} \quad (6)$$

Literature values for these two equilibrium quotients at 25 °C and $\mu = 0.1$ M are $pK_{a1} = 3.48$ and $pK_{a2} = 10.11$.[32] Tautomerization between $HSCH_2COO^-$ and $^-SCH_2COOH$ as shown in eqn. (7) undoubtedly occurs also, although it has not been reported:

$$HSCH_2COO^- \rightleftharpoons {}^-SCH_2COOH \quad K_t \quad (7)$$

Consequently, all data are reported in terms of $[TGA]_{tot}$, which is the sum of the concentrations of these four protonation states.

The dependence on reductant concentration was studied with $[Ir(IV)]_0 = 1 \times 10^{-4}$ M, $[bathophen] = 1 \times 10^{-3}$ M, and

an NaOAc–HOAc buffer (pH = 4.5~4.6), at an ionic strength ($\mu = 0.10$ M) maintained by the NaOAc–HOAc buffer. The concentration of TGA was varied from 1×10^{-3} to 2×10^{-2} M. The kinetic data are shown in Table S1 (ESI). The rate dependence with respect to TGA concentration is first order, as shown by the linear plot of k_{obs} vs. $[TGA]_{tot}$ in Fig. S1 (ESI). The observed rate law can therefore be expressed as:

$$-d[IrCl_6^{2-}]/dt = k[IrCl_6^{2-}][TGA]_{tot} \quad (8)$$

The value of k obtained from the slope of the linear plot in Fig. S1 for the oxidation of TGA is 113 M^{-1} s^{-1} at pH 4.6.

pH dependence

The effect of pH on the rate of reaction was studied using various buffers as follows: an acetate buffer between pH 3.7 and 5.6, a phosphate buffer between pH 5.5 and 7.52, a TGA buffer between pH 3.18 and 3.97, and a borate buffer between pH 8.6 and 9.3. Between pH 2.5 and 3.21, no buffer was used and high levels of bathophen were used, up to 5 mM, due to the tendency of bathophen at low pH to combine with a proton to form Hbathophen$^+$, thus reducing the [bathophen].

The pH-dependent kinetic data are given in Table S1 (ESI). As is shown by the plot of $\log(k_{obs}/[TGA]_{tot})$ vs. pH (Fig. 8),
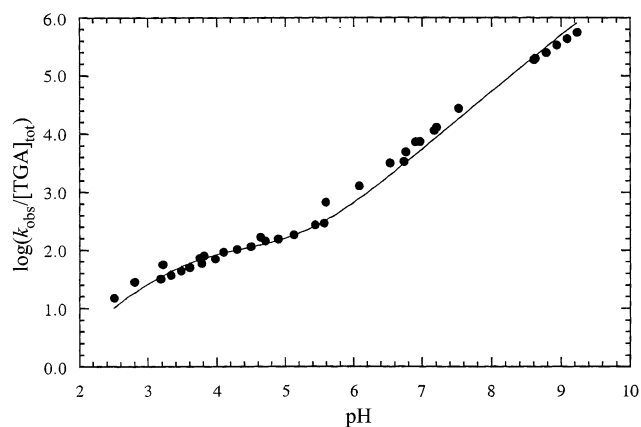

Fig. 8 Plot of $\log(k_{obs}/[TGA]_{tot})$ vs. pH for the reaction of $[IrCl_6]^{2-}$ with TGA. Data points are experimental values, and the solid line is the curve fit to eqn. (9). Conditions of experiments are as given in the text.

there is an irregular trend of increasing rates with increasing pH. The pH dependence of k_{obs} is complicated by the fact that TGA is a diprotic acid, leading to four potentially reactive states. As is suggested by the mechanism given below, the data were analyzed according to the relationship:

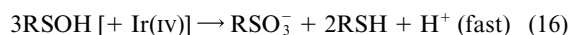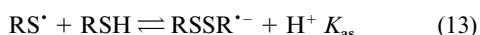$$k_{obs}([H^+] + K_{a1} + K_{a1}K_{a2}/[H^+])/[TGA]_{tot} = k' + k''/[H^+] \quad (9)$$

An excellent fit to eqn. (9) for all the kinetic data was achieved by a nonlinear-least-squares analysis, holding K_{a1} and K_{a2} at their literature values. The fit is shown in Fig. 8 (displayed as a solid line). The following results were obtained: $k' = (3.5 \pm 0.2) \times 10^{-2}$ s^{-1} and $k'' = (1.81 \pm 0.1) \times 10^{-7}$ M s^{-1}. The mild deviation of the points between pH 5.5 and 7.5 is likely due to the somewhat higher ionic strength employed with this phosphate buffer: higher ionic strengths are expected to increase the rates of reactions between anions.

Discussion

Proposed mechanism

As is described above, the oxidation of TGA with $[IrCl_6]^{2-}$ as the limiting reagent proceeds with consumption of Ir(IV) occurring in a single phase that leads to parallel production of RSSR

and RSO_3^-. A mechanism consistent with the observed stoichiometry and kinetics is shown in eqns. (10)–(16).

$$HSCH_2COO^- + [IrCl_6]^{2-} \longrightarrow$$
$$\qquad\qquad ^\bullet SCH_2COO^- + [IrCl_6]^{3-} + H^+ \quad k_b \quad (10)$$

$$^-SCH_2COOH + [IrCl_6]^{2-} \longrightarrow$$
$$\qquad\qquad ^\bullet SCH_2COOH + [IrCl_6]^{3-} \quad k_c \quad (11)$$

$$^-SCH_2COO^- + [IrCl_6]^{2-} \longrightarrow {}^\bullet SCH_2COO^- + [IrCl_6]^{3-} \quad k_d \quad (12)$$

$$RS^\bullet + RSH \rightleftharpoons RSSR^{\bullet-} + H^+ \quad K_{as} \quad (13)$$

$$RSSR^{\bullet-} + [IrCl_6]^{2-} \longrightarrow RSSR + [IrCl_6]^{3-} \quad k_2 \quad (14)$$

$$RS^\bullet + [IrCl_6]^{2-} + H_2O \longrightarrow RSOH + [IrCl_6]^{3-} + H^+ \quad k_3 \quad (15)$$

$$3RSOH\,[+\,Ir(IV)] \longrightarrow RSO_3^- + 2RSH + H^+ \quad (fast) \quad (16)$$
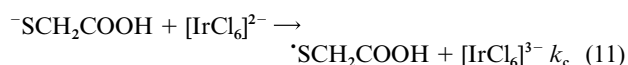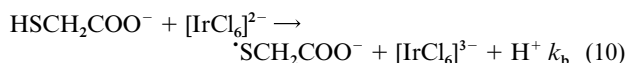
In steps 13–16 the exact states of protonation are unknown, and so we use R to represent either CH_2COOH or CH_2COO^-. RSOH is an unstable intermediate[33] often found in the literature of thiol oxidations.[1,34] RSO_3H is a strong acid (the pK_a of $MeSO_3H$ is -1.9),[35] and exists as RSO_3^- in solution. In reaction 16 we indicate the conversion of RSOH to RSO_3^- as a disproportionation which undoubtedly consists of several elementary steps. In view of the general opinion that sulfenic acids (RSOH) decompose to yield thiosulfinates and other species,[33] conversion to RSO_3^- may well entail the consumption of $[IrCl_6]^{2-}$. However, for convenience we omit this potential complication. Competition between reactions 14 and 15 as mediated by equilibrium 13 is the key mechanistic feature that leads to simultaneous production of RSSR and RSO_3^-. Reaction 14, the oxidation of $RSSR^{\bullet-}$, is entirely reasonable in view of the well-known chemistry of $RSSR^{\bullet-}$. On the other hand, the oxidation of $RS^\bullet$ in reaction 15 is more speculative. The reaction $RSOH + RSH \longrightarrow RSSR$ has been proposed in the literature,[34,36] but we omit this reaction, assuming either it does not occur or it is much slower than reaction 16.

By using the steady-state approximation for $[RS^\bullet]$ and $[RSSR^{\bullet-}]$ we obtain the following rate law:

$$-\frac{d[IrCl_6^{2-}]}{dt} = \qquad\qquad\qquad (17)$$
$$2\left\{\frac{k_b K_{a1}[H^+] + k_c K_t K_{a1}[H^+] + k_d K_{a1}K_{a2}}{[H^+]^2 + K_{a1}[H^+] + K_t K_{a1}[H^+] + K_{a1}K_{a2}}\right\}[TGA]_{tot}[IrCl_6^{2-}]$$

Given the typical pK_a values for thiols and carboxylic acids it is safe to assume that K_t is much less than unity, so eqn. (17) simplifies to:

$$-\frac{d[IrCl_6^{2-}]}{dt} = \qquad\qquad\qquad (18)$$
$$2\left\{\frac{(k_b + K_c K_t)K_{a1}[H^+] + k_d K_{a1}K_{a2}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}}\right\}[TGA]_{tot}[IrCl_6^{2-}]$$

In agreement with the empirical rate law 9, eqn. (18) shows that the rate of consumption of Ir(IV) is pseudo first-order with respect to $[IrCl_6^{2-}]$ and that the pseudo first-order rate constants are dependent on pH and $[TGA]_{tot}$. Compared with rate law 9, eqn. (18) identifies k' as $2K_{a1}(k_b + k_cK_t)$ and k'' as $2k_dK_{a1}K_{a2}$. By applying the literature values for K_{a1} and K_{a2} and the fitted values of k' and k'' we obtain the following results: $k_b + k_cK_t = 53 \pm 5$ and $k_d = (3.52 \pm 0.03) \times 10^6\ M^{-1}\ s^{-1}$. Although the values of k_b and k_c cannot be resolved, it is likely that the k_c term is dominant because it corresponds to oxidation of a thiolate,

which occurs unambiguously in reaction 12; in principle, direct oxidation of a thiol could occur unambiguously through reaction of $HSCH_2COOH$, but this reaction is undetected in our observed rate law and is clearly very slow. A similar influence of protonation on reactivity is seen in the oxidation of TGA by the two-electron oxidant $[Pt(CN)_4Cl_2]^{2-}$.[37]

The product ratio of $[RSO_3^-]/[RSSR]$ can be obtained from the following equations:

$$d[RSO_3^-]/dt = (1/3)k_3[RS^\bullet][IrCl_6^{2-}] \qquad (19)$$

$$d[RSSR]/dt = k_2[RSSR^{\bullet-}][IrCl_6^{2-}] \qquad (20)$$

and thus:

$$\frac{d[RSO_3^-]/dt}{d[RSSR]/dt} = \frac{k_3[H^+]}{3k_2 K_{as}[TGA]_{tot}} \qquad (21)$$

When the solutions are well buffered and $[TGA]_{tot} \gg [IrCl_6^{2-}]$, eqn. (21) leads to:

$$[RSO_3^-]_\infty/[RSSR]_\infty = k_3[H^+]/(3k_2 K_{as}[TGA]_{tot}) \qquad (22)$$

This result shows that the product ratio depends on pH and the TGA concentration. A hidden complexity is that k_2, k_3, and K_{as} are conditional constants since they refer to reactions of $RSSR^{\bullet-}$ and $RS^\bullet$, and both of these species can exist in various protonation states at their carboxylate groups.

The product ratios determined by ^1H NMR peak integration were performed with only a modest excess of [TGA] and were not buffered. As a consequence, both the pH and TGA concentration were not constant during the reactions, and the changes were more extreme for experiments at the higher initial Ir(IV) concentrations. From the stoichiometry given in eqn. (3) it is evident that acid is generated in the reaction. The net effect of the changing pH and TGA concentrations is that the product ratio is predicted to increase with increasing $[Ir(IV)]_0$, which is in agreement with the results in Table 1.

The K_{as} value for reaction 13 can be estimated by combining eqns. (23) and (6)

$$RS^\bullet + RS^- \rightleftharpoons RSSR^{\bullet-} \quad K'_{eq} \qquad (23)$$
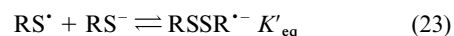
such that $K_{as} = K'_{eq}K_{a2}$. Although the value of K'_{eq} has not been reported for TGA, it is reasonable to assume that it is the same as for $HSCH_2CH_2COOH$ ($1.3 \times 10^3\ M^{-1}$).[38] With this assumption and the literature value for K_{a2} we obtain a value of 1.0×10^{-7} for K_{as} for TGA. Taken in combination with the product ratio $n_{RSO_3^-}/n_{RSSR}$ this estimate leads, via eqn. (22), to the ratio k_3/k_2. An NMR experiment under conditions $[TGA]_0 = 0.0103$ M, $[Ir(IV)]_0 = 0.00216$ M, [bathophen] = 1.0 mM, pH = 4.7, shows that $n_{RSO_3^-}/n_{RSSR} = 0.88$ and less than 10% of the TGA is consumed. As $[TGA]_{tot}$ and pH can be treated as constant in this experiment, eqn. (22) leads to a value 1.2×10^{-4} for k_3/k_2 at pH 4.7.

Marcus theory

Reaction 12 describes the simple one-electron oxidation of a thiolate uncomplicated by questions related to proton ambiguities, and our measurements provide a value of $3.5 \times 10^6\ M^{-1}\ s^{-1}$ for its rate constant (k_d). For more insight we write the reaction as follows:

$$^-SCH_2COO^- + [IrCl_6]^{2-} \rightleftharpoons$$
$$\qquad\qquad ^\bullet SCH_2COO^- + [IrCl_6]^{3-} \quad k_d,\,k_{-d},\,K_{et} \quad (24)$$
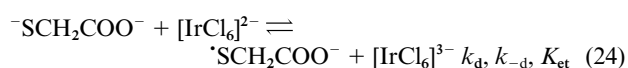
An estimate of the value of K_{et} can be obtained from the E° values of the component half reactions. There is a well-established value of 0.892 V for the reduction potential of

$[IrCl_6]^{2-}$ at $\mu = 0.1$ M.[39] The corresponding one-electron reduction potential of $^{\bullet}SCH_2COO^-$ ($E^{\circ} = 0.74$ V) was reported by Surdhar and Armstrong, who derived this result from pulse radiolysis measurements of redox equilibria.[3] These two reduction potentials lead to a calculated equilibrium constant K_{et} of 345. Given this moderately favorable driving force, the lack of evidence for reactive intermediates in this process, and the large rate constant k_d, it is not unreasonable to propose that reaction 24 has an outer-sphere mechanism.

The cross-relationship of Marcus theory is applicable to reaction 24 provided that it has an outer-sphere mechanism. We use the theory in the following form:[40]

$$k_{12} = (k_{11}k_{22}K_{12}f_{12})^{1/2}W_{12} \qquad (25)$$

$$\ln f_{12} = \frac{[\ln K_{12} + (w_{12} - w_{21})/RT]^2}{4\{\ln(k_{11}k_{22}/Z^2) + (w_{11} + w_{22})/RT\}} \qquad (26)$$

$$W_{12} = \exp[(-w_{12} - w_{21} + w_{11} + w_{22})/2RT] \qquad (27)$$

$$w_{ij} = 4.23 \times 10^3 \, Z_iZ_j/[r(1 + 0.328r(\mu)^{1/2})] \qquad (28)$$

In these equations, k_{12} represents the cross electron-transfer rate constant (k_d), k_{11} is the effective self-exchange rate constant for the $^{\bullet}SCH_2COO^-/^-SCH_2COO^-$ redox couple, and k_{22} is the self-exchange rate constant for the $[IrCl_6]^{2-}/[IrCl_6]^{3-}$ couple (2×10^5 M^{-1} s^{-1}).[41] K_{12} is the electron-transfer equilibrium constant (K_{et}). Z in eqn. (26) is the collision rate, for which a value of 1×10^{11} M^{-1} s^{-1} has been used. Z_i and Z_j in eqn. (28) are the ionic charges of the respective species, and R is the gas constant (kcal mol^{-1} K^{-1}). r is the center-to-center distance (Å) when the species are touching. Radii of 2.6 and 4.1 Å were used for $^-SCH_2COO^-$ and $[IrCl_6]^{2-}$, which were obtained from CPK models; these models show that $^-SCH_2COO^-$ is well approximated by a sphere. With these parameters, eqn. (25) was solved for the value of k_{11}, the effective thiyl/thiolate self-exchange rate constant. The value of k_{11} so obtained is 1.5×10^5 M^{-1} s^{-1}, which is the first reported k_{11} value for a thiyl/thiolate redox couple. A self-exchange rate constant as large as this is not unreasonable in view of the electronic structure of the thiyl radical, where the unpaired electron resides on the sulfur atom. This electronic structure leads to minimal changes in the C–S bond length accompanying electron transfer and a correspondingly small internal reorganization energy. Strong parallels are thus seen with the chemistry of $S_2O_3^{2-}$, where a k_{11} value of 2×10^5 M^{-1} s^{-1} was obtained for the $S_2O_3^-/S_2O_3^{2-}$ redox couple.[42]

Conclusions

Outer-sphere oxidation of aliphatic thiols is generally highly sensitive to trace metal-ion catalysis, and the present paper is the first to describe the outcome when this catalysis is thoroughly suppressed. We find that trace metal-ion catalysis in the oxidation of TGA by Ir(IV) not only accelerates the reaction dramatically but also alters the product distribution qualitatively. When such catalysis is adequately masked, the reaction proceeds by rate-limiting outer-sphere electron transfer from the thiolate forms of TGA to generate thiyl radicals. Association of RS$^{\bullet}$ with RSH controls the relative yields of RSSR and RSO$_3^-$. The rate law yields the rate constant for oxidation of $^-SCH_2COO^-$, from which the effective self-exchange rate constant for the $^-SCH_2COO^-/^{\bullet}SCH_2COO^-$ couple (1.5×10^5 M^{-1} s^{-1}) has been derived by use of Marcus theory.

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