Carbon–sulfur bond cleavage and reduction of thiols and dithioethers under oxidative conditions

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The reaction with hydrogen peroxide serves to cleave the carbon–sulfur bond and generate formally reduced products from certain thiols and dithioethers. The peroxide can be generated *in situ* from dioxygen using a supported palladium catalyst in the presence of a coreductant, either carbon monoxide or dihydrogen. The use of *in situ* generated oxidant provides a significant selectivity advantage compared to using a hydrogen peroxide solution. The reaction to form the reduced products is unique to compounds with a carboxylic group α to the carbon–sulfur bond.

Introduction

The oxidation of thiols and, in particular, 2-mercaptoacetic acid is by now well documented in the literature.[1-4] This is at least partially attributable to the pervasiveness of thiols in biological systems which exploit their easy oxidation.[5,6] For example, thiols serve as reductants in biological systems for enzymatic electron transfer reactions.[7] Furthermore, the interaction of 2-mercaptoacetic acid with vanadium has received attention for its potential therapeutic effect because by serving as a sacrificial reductant 2-mercaptoacetic acid prevents enzyme inactivation.[8]

In contrast to the above reports of thiol oxidations, we have recently observed an interesting result when 2-mercaptoacetic acid, 2,2′-dithiodiacetic acid, or analogous compounds are exposed to hydrogen peroxide. Rather than observing only oxidation products (glycolic, glyoxylic, and formic acids), these compounds are instead formally reduced to the respective methyl functionality, *e.g.*, 2-mercaptoacetic acid and its dimer forms primarily acetic acid (see Scheme 1). The reaction occurs in reasonable yield in aqueous solution and, when the peroxide is generated *in situ*, forms few other products. Hydrogen peroxide can be formed in this manner quite easily from dioxygen using supported metallic palladium and a sacrificial coreductant, carbon monoxide or hydrogen.[9,10] Herein, we report our results focusing on what circumstances enables this reaction to occur. It should be pointed out that this chemistry, if involving free radicals, occurs in the presence of dioxygen – which should serve to quench radicals resulting in oxygenated products.

Scheme 1
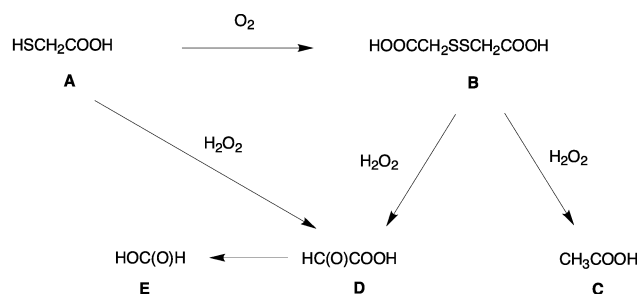
Results and discussion

Fig. 1 shows a representative ^1H NMR spectrum which qualitatively demonstrates that the major product is acetic acid (**C**) when either 2-mercaptoacetic acid (**A**) or 2,2′-dithiodiacetic acid (**B**) is exposed to the reaction conditions. Note that 2,2′-dithiodiacetic acid forms spontaneously and rapidly from the

oxidative coupling of 2-mercaptoacetic acid [eqn. (1)]. Table 1, entry 1, shows that oxidative dimerization of 2-mercaptoacetic acid proceeds exclusively to 2,2′-dithiodiacetic acid in the presence of dioxygen and carbon monoxide but in the absence of palladium. Under these conditions no acetic acid or further oxidation products are observed. As can be seen from Fig. 1, very little amounts of the oxidation products, glyoxylic (**D**) and formic (**E**) acids, are observed under the typical reaction conditions involving supported palladium catalyst in the presence of carbon monoxide and dioxygen. No glycolic acid ($HOCH_2$-COOH) was observed under these conditions. Table 1, entry 2 shows that acetic acid resists further oxidation under the reaction conditions, suggesting that the observed oxidation products are not derived from acetic acid.

$$2\ HSCH_2COOH \xrightarrow{O_2} HOOCCH_2SSCH_2COOH + H_2O \quad (1)$$

2,2′-Dithiodiacetic acid reacts faster with acetic acid compared to 2-mercaptoacetic acid (*cf.*, entries 3 and 4). It is also noteworthy that regardless of whether one uses 2-mercaptoacetic or 2,2′-dithiodiacetic acid as the starting material the amount of the oxidation products, glyoxylic and formic acid, remains nearly the same. This observation suggests that the oxidation products are formed *via* the same pathway regardless of starting material. In contrast, the observation that more acetic acid is formed when 2,2′-dithiodiacetic acid is the starting material suggests that the dimer is an intermediate in the formation of acetic acid from 2-mercaptoacetic acid. Scheme 1 summarizes these observations.

Glycolic acid ($HOCH_2COOH$) was not observed under typical reaction conditions. Using this as a substrate (1.5 mmol) led only to the formation of formic acid (0.071 mmol) with 0.98 mmol of the starting material remaining in the product mixture. It is notable that no glyoxylic acid is formed from this substrate, thereby eliminating the role of glycolic acid as an intermediate.
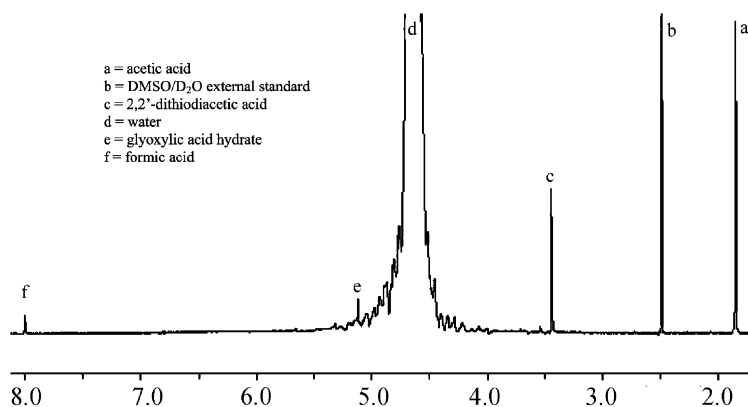
Our group[11,12] and others[9,10] have demonstrated that hydrogen peroxide can be effectively generated *in situ* from dioxygen using palladium catalyst and a coreductant. Several experiments were carried out to verify that this was the sole role of palladium in the present case. No reaction was observed in the absence of oxygen. Another coreductant, dihydrogen, can be used in place of carbon monoxide (Table 1, entry 5). In this case one observes a poorer mass balance and more formic acid than reactions involving carbon monoxide. This result is attributable to the significant increase in the rate of hydrogen peroxide formation from dihydrogen compared to carbon monoxide. As shown in Scheme 2, the formation of hydrogen peroxide starting with carbon monoxide is slower because a water gas shift reaction must precede H_2O_2 formation.[12] Finally, the direct use of

Table 1 Reaction products under typical oxidizing conditions[a]

Entry	Substrate	2,2′-Dithiodiacetic acid/mmol	Acetic acid/ mmol	Glyoxylic acid/ mmol	Formic acid/ mmol	Total[b]/ mmol
1[c]	2-Mercaptoacetic acid	0.60	0.0	0.0	0.0	1.2
2	Acetic acid	0.0	1.3	0.0	0.0	1.3
3	2-Mercaptoacetic acid	0.35	0.39	0.23	0.036	1.4
4	2,2′-Dithiodiacetic acid	0.22	0.59	0.30	0.013	1.3
5[d]	2,2′-Dithiodiacetic acid	0.24	0.40	0.004	0.22	1.1
6[e]	2,2′-Dithiodiacetic acid	0.020	0.34	—	1.1	1.5
7[f]	2,2′-Dithiodiacetic acid	0.19	0.55	0.03	0.32	1.3

[a] Reactions performed using 1.5 mmol thio units and 5% Pd/carbon in pH = 3 water. Results reported average at least 2 reactions (except 1 and 5). [b] Amount of 2,2′-dithiodiacetic acid doubled for total calculation. [c] Blank reaction with no Pd/carbon used. [d] Dihydrogen substituted for carbon monoxide. [e] Reactions performed in sealed glass vials with 0.2 mL of 50% hydrogen peroxide instead of Pd/CO/O$_2$ mixture at 70 °C. Other conditions were as above. [f] Conditions same as in entry 6, except the hydrogen peroxide was added by a syringe pump over a 4 h period (see Experimental).

a = acetic acid
b = DMSO/D$_2$O external standard
c = 2,2′-dithiodiacetic acid
d = water
e = glyoxylic acid hydrate
f = formic acid

Fig. 1 ^{1}H NMR spectrum in D$_2$O of a typical reaction of 2-mercaptoacetic acid or its dimer.
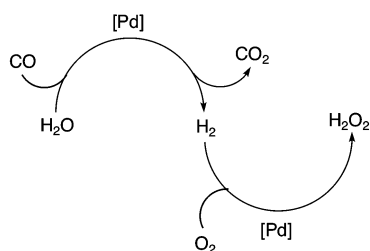
Scheme 2

hydrogen peroxide, even in the absence of palladium results in the formation of acetic acid (Table 1, entry 6). However, in this instance, the reaction is less selective for acetic acid, the principal product being formic acid. The difference appears to be due to the fact that the palladium-catalyzed system generates hydrogen peroxide in slow steady amounts which is utilized as it is formed. Consistent with this was the formation of significantly less formic acid and more acetic acid when the direct addition of hydrogen peroxide was carried out using a syringe pump over a 4 h period (Table 1, entry 7). The conclusion that can be derived from the above experiments is that palladium in the present system is acting exclusively as an *in situ* hydrogen peroxide generator and is not responsible for acetic acid formation.

The requirement of hydrogen peroxide suggests a radical mechanism for the formation of acetic acid from 2-mercapto-acetic acid and its dimer, and experiments were undertaken to examine this possibility. The first set of experiments was based on the literature assertion that the HOOCCH$_2$• species is particularly stable.[13] It follows that HOOCCH(CH$_3$)• should be more stable and that HOOCCH$_2$CH$_2$• should be less. Thus, 2-mercaptopropionic acid should form propionic acid under the reaction conditions but 3-mercaptopropionic acid should not. Indeed, as shown in Table 2, entry 1, 2-mercaptopropionic

acid yielded a significant amount of propionic acid along with some acetic acid. Independent experiments showed that the oxidative degradation of propionic acid to acetic acid is faster than that from acetic acid to formic acid. In contrast to 2-mer-captopropionic acid, the reaction of the 3,3′-dithiodipropionic acid gave no propionic acid (Table 2, entry 2). Note that in order to dissolve the higher thioacids, a mixture of heptafluoro-butyric acid and water, rather than pure water, was used for the reactions shown in Table 2. This resulted in lower yields compared to that observed in pure water (*cf.* Table 1, entry 4 *versus* Table 2, entry 3). While the above observations may be consistent with a radical mechanism, is not clear why the formation of acetic acid from 2-mercaptoacetic acid and its dimer is faster than the formation of propionic acid from 2-mercaptopropionic acid.

Attempting to carry out the reaction with other thiols and thioethers showed that the oxidative reduction was quite unique to compounds with a carboxylic group α to the carbon–sulfur bond. In the case of 2-mercaptoethanol and 1,2-dimercapto-ethane, no ethanol or ethane were observed, respectively. Likewise, thiodiacetic acid (containing –C–S–C– rather than –C–S–S–C– linkage) failed to produce acetic acid. Not surprisingly, these substrates were simply oxidized; a facile process for them in the presence of hydrogen peroxide.[14] The disodium salt of sulfoacetic acid (NaO$_3$SCH$_2$CO$_2$Na) was unreactive under the reaction conditions, thereby eliminating it as an intermediate to any of the products derived from 2-mercaptoacetic acid.

We turned to radical traps in order to probe for a radical mechanism. Unfortunately, the classical traps, carbon tetra-bromide and bromotrichloromethane, did not have sufficient solubility in water or fluorinated solvents. Thus, tribromoacetic acid was used in equimolar amounts to the substrate with the results listed in Table 3. As can be seen from entry 1 the reduction reaction is not observed upon the addition of tribromo-acetic acid. The expected radical-trapped species, bromoacetic acid, was also not observed in this reaction. This lead us to

Table 2 Reactions of higher thio acids[a]

Entry	Substrate	Propionic acid/mmol	Acetic acid/mmol	Glyoxylic acid/mmol	Formic acid/mmol
1	2-Mercaptopropionic acid	0.049	0.0045	—	0.011
2	3,3′-Dithiodipropionic acid	—	—	—	—
3	2,2′-Dithiodiacetic acid	—	0.15	0.21	0.20

[a] Reactions performed using 1.5 mmol thio units and 5% Pd/carbon in 3 mL of pH = 3 water and 3 mL of heptafluorobutyric acid.

Table 3 Results for 2,2′-dithiodiacetic acid in the presence of tribromoacetic acid[a]

Entry	2,2′-Dithiodiacetic acid/mmol	Acetic acid/mmol	Glyoxylic acid/mmol	Formic acid/mmol	Total/mmol[b]
1	0.58	0.0066	0.12	0.085	1.4
2[c]	0.049	0.16	0.046	0.65	1.4

[a] Reactions were performed with 5% Pd/carbon in 6 mL of pH = 3 water. 0.75 mmol 2,2′-dithiodiacetic acid was used along with 1.5 mmol tribromoacetic acid as substrate for 4 h. Results average two reactions. [b] Amount of 2,2′-dithiodiacetic acid doubled for total calculation. [c] Reactions performed in glass vials with 50% hydrogen peroxide instead of Pd/CO/O$_2$ mixture at 70 °C. Other conditions were as above.

a = acetic acid
b = 2,2'-dithiodiacetic acid
c = glyoxylic acid hydrate
d = formic acid
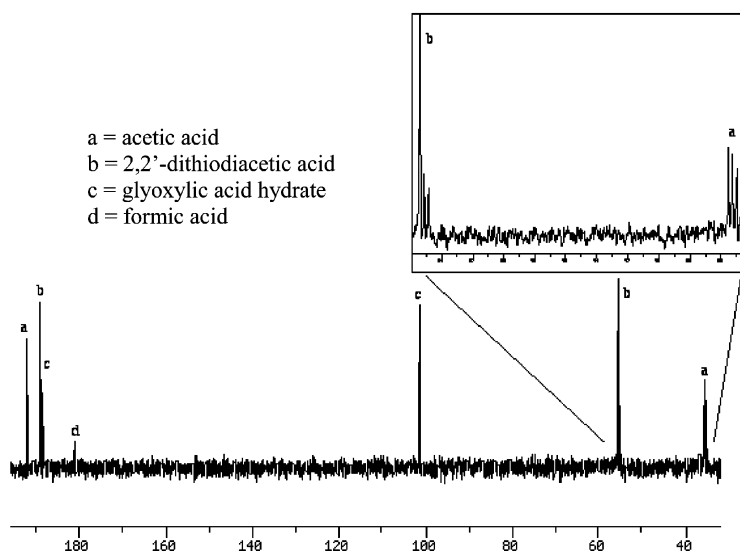
Fig. 2 ^{13}C {^{1}H} NMR spectrum of a reaction of 2,2′-dithiodiacetic acid carried out in D$_2$O with *in situ* generated hydrogen peroxide.

suspect that tribromoacetic acid was poisoning the palladium catalyst. Therefore, the experiment was repeated without palladium and with hydrogen peroxide added directly to the reaction mixture. As shown in Table 3 entry 2, 2,2′-dithiodiacetic acid was found to produce acetic acid even with the radical trap present. However, it is possible that tribromoacetic acid is not a sufficiently reactive trap. It should also be noted that a significant amount of bromoform was formed showing that radical decarboxylation of the trap was occurring. However, the bromoform was qualitatively not observed until the reaction had been going on for some period of time.

A final area of investigation involved the source of the hydrogen for the acetic acid formed. If it came from the solvent, then monodeutero (CH$_2$D–) acetic acid should be formed from the reaction of 2,2′-dithiodiacetic acid in deuterium oxide (acidified to pH = 3 with DCl). Indeed, this was observed as revealed by the presence of a triplet (due to ^{2}H coupling) in ^{1}H and ^{13}C NMR spectra of the product mixture (see Fig. 2). Interestingly, some deuteration of the starting material was also observed by NMR spectroscopy (Fig. 2). However, this was not observed when palladium was removed from the reaction mixture and D$_2$O$_2$ (formed from DCl and Na$_2$O$_2$) was directly added. Thus, one can conclude that the hydrogen on acetic acid does indeed come from the solvent, and that H/D exchange observed for the starting material arises from an unrelated palladium-catalyzed reaction. Note that control experiments show that the palladium-catalyzed H/D exchange does not occur for acetic acid.

An interesting issue is the mechanism by which a hydrogen atom from water is incorporated into the formed acetic acid. A comparison of homolytic bond energies clearly shows that HOOCCH$_2$• cannot abstract a hydrogen atom from water. Thus, while a radical mechanism for the carbon–sulfur bond-cleavage step appears to be intuitively reasonable, several of our observations are inconsistent with the intermediacy of a free radical, such as HOOCCH$_2$•.

Conclusion

We have observed the unusual carbon–sulfur bond cleavage and formal reduction of compounds with a carboxylic group α to the carbon–sulfur bond under oxidative conditions. Results indicate that the hydrogen on the acetic acid formed from 2-mercaptoacetic acid and its dimer originates from the solvent. The oxidation products are formed through an independent pathway not involving acetic acid. Though hydrogen peroxide is solely responsible for the observed reaction, a significant selectivity advantage is observed when H$_2$O$_2$ is generated *in situ* using a palladium catalyst.

Experimental

Caution: due care must be taken when dealing with gas mixtures under pressure. Special attention must be paid to gas flammability limits.[15]

Materials were purchased from commercially available sources in the highest purity available. 2-mercaptoacetic acid was azeotropically vacuum (<1 mm Hg) distilled from toluene. NMR spectra were recorded using a Bruker DPX-300 instrument. Spectra were reference to a calibrated, external DMSO/D_2O capillary for quantitative analysis. Compounds were positively identified by co-injection of authentic samples.

1.50 mmol of substrate (based on thio units; 2,2'-dithiodiacetic = 0.75 mmol) and 30.0 mg of 5% Pd on carbon were weighed into a glass reaction liner, and 6 ml of pH = 3.0 H_2O (acidified with HCl) and a small Teflon stir bar were added. The reaction was placed in a 300 ml stainless steel Parr autoclave sealed, flushed 4 times with CO, and charged to 100 psi with CO, to 1200 psi with N_2, and to 1300 psi with O_2 in that order. The contents were stirred at 75 °C for 24 h. Internal autoclave temperature was calibrated with an internal probe (for a 75 °C internal temperature, the autoclave was immersed *ca.* 2 cm into a 100 °C regulated oil bath). Following the reaction, the autoclave was cooled to 0 °C and then slowly vented. Prior to analysis catalyst and support were either allowed to settle or were centrifuged before sample decantation.

Two reactions that involved the direct addition of hydrogen peroxide were carried out. In the first (Table 1, entry 6), 1.50 mmol of substrate (based on thio units) in 6 mL pH = 3.0 H_2O (acidified with HCl) and 0.2 mL 50% H_2O_2 were stirred at 70 °C for 24 h. In the second (Table 1, entry 7), the substrate was dissolved in 5.2 mL of pH = 3 H_2O (acidified with HCl). 0.2 mL of 50% H_2O_2 was mixed with 0.6 mL of pH = 3 water and 0.8 mL of the peroxide/H_2O solution was then added to the substrate solution by a syringe pump over a 4 h period.

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