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# Iron(III)–Ethylenediaminetetraacetic Acid Mediated Oxidation of Thiols to Disulfides with Molecular Oxygen†

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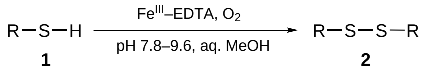
$Fe^{III}$–EDTA in aqueous methanol offers a simple environmentally acceptable synthetic tool for oxidizing thiols to the corresponding disulfides by molecular oxygen in excellent yields, under mild conditions and devoid of side reactions.

The conversion of thiols into the corresponding disulfides (oxidative S–S coupling) is an important reaction and many stoichiometric reagents have been reported to be effective oxidants for it, such as dichromates,[1] chlorochromates,[2] manganese dioxide,[3] diethyl azodicarboxylate,[4] halosilane–chromium trioxide,[5] nickel peroxide,[6] chromium peoxide,[7] diaryl telluroxides,[8] tetrabutylammonium cerium(IV) nitrate,[9] sodium perborate[10] and silver trifluoromethanesulfonate.[11] Owing to the growing environmental concerns surrounding the use of toxic and dangerous oxidants, oxidative catalytic transformations of organic compounds with molecular oxygen have become an area of continued research and development in recent years.[12] The catalytic oxidation of thiols present in petroleum fractions to disulfides with molecular oxygen under strongly alkaline conditions using metal phthalocyanines as catalysts has been extensively studied.[13] However, there are only a few reports on the synthesis of disulfides by catalytic oxidation of thiols using molecular oxygen as the primary oxidant, with basic alumina,[14] cobalt tetrasulfonatophthalocyanine,[15] intercalated $[MO^{VI}O_2(O_2CC(S)Ph_2)_2]^{2-}$ in $Zn^{II}$–$Al^{III}$-layered double hydroxide[16] and cobalt chlorate[17] all having been used as catalysts. The subject has been comprehensively reviewed by Uemura.[18] Among the transition metals, iron is singled out as being non-toxic[19] and more emphasis is being given on the use of iron-based systems for oxidation.[20] Earlier, we reported iron(III)–ethylenediaminetetraacetic acid ($Fe^{III}$–EDTA) mediated autoxidation of 2,6-di-*tert*-butylphenol and substituted hydroquinones.[21] We now report for the first time $Fe^{III}$–EDTA[22] catalysed oxidation of thiols (**1**) to disulfides (2) with molecular oxygen (Scheme 1).



$$\underset{\mathbf{1}}{R{-}S{-}H} \xrightarrow[\text{pH 7.8–9.6, aq. MeOH}]{Fe^{III}\text{–EDTA, } O_2} \underset{\mathbf{2}}{R{-}S{-}S{-}R}$$

R = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 2-pyridyl, $PhCH_2$, $Bu^n$, $n$-$C_5H_{11}$, $n$-$C_7H_{15}$, $n$-$C_8H_{17}$

**Scheme 1**

An $Fe^{III}$–EDTA (0.1 M) solution was prepared by adding EDTA disodium salt solution to an ammonium iron(III) sulfate solution and raising the pH of the mixture to 8.0 by addition of sodium carbonate solution. The oxidation experiments were carried out by bubbling molecular oxygen into a solution of the thiol in 80% aqueous methanol containing $Fe^{III}$–EDTA (10 mol% of the thiol) at specified pH under ambient conditions (Table 1). A wide variety of thiols (aromatic, aliphatic and heterocyclic) were selectively oxidized to their corresponding disulfides in near quantitative yields without any evidence for the formation of the corresponding sulfonic acid. Under these reaction conditions aromatic thiols in general were found to be more reactive than aliphatic ones. Among the aliphatic thiols the reactivity was found to decrease with increasing carbon chain length and was strongly dependent upon the pH of the medium. While aromatic thiols could be oxidized at a pH of about 8 in a reasonable reaction time, the aliphatic thiols required a higher pH. To evaluate the catalytic effect of $Fe^{III}$–EDTA in this reaction, a parallel blank experiment was carried out with benzenethiol. The conversion of benzenethiol into its disulfide was 73% after 4 h without $Fe^{III}$–EDTA, while conversion was quantitative within 20 min in the presence of $Fe^{III}$–EDTA.

**Table 1** $Fe^{III}$–EDTA catalysed oxidation of thiols (**1**) to disulfides (**2**) by molecular oxygen[a]

| Disulfide (**2**) | R | pH | Reaction (*t*/h) | Yield[b] (%) | Mp or bp (Torr) (*T*/°C) Found | Lit. |
|---|---|---|---|---|---|---|
| **a** | Ph | 7.8 | 0.33 | 96 | 59–61 | 59–60[14] |
| **b** | 4-$MeC_6H_4$ | 7.9 | 0.75 | 95 | 47–48 | 46–48[25] |
| **c** | 4-$MeOC_6H_4$ | 7.8 | 1.0 | 87 | 44–45 | 43.8[25] |
| **d** | 2-Pyridyl | 8.0 | 0.50 | 84 | 52–53 | 52–53[25] |
| **e** | $PhCH_2$ | 7.8 | 8 | 97 | 70–71 | 69–70[14] |
| **f** | $PhCH_2$ | 8.5 | 3 | 98 | 70–71 | 69–70[14] |
| **g** | $Bu^n$ | 9.5 | 8 | 93 | 94(6) | 88–91(3)[14] |
| **h** | $n$-$C_5H_{11}$ | 9.5 | 9 | 86 | 117(6) | 90–92(1)[26] |
| **i** | $n$-$C_7H_{15}$ | 9.5 | 12 | 87 | 152–154(6) | 143–147(5)[27] |
| **j** | $n$-$C_8H_{17}$ | 9.6 | 18 | 88 | 185–187(6) | 178–83(5)[27] |

[a] The reaction was carried out with 40 mmol of alkanethiol or 10 mmol of arenethiol. [b] Yield of pure product isolated by crystallization or distillation.

The oxidation of thiols to disulfides by molecular oxygen under alkaline conditions has been reported to proceed through a radical pathway involving one-electron transfer from the thiolate anion to the molecular oxygen. Metal ions are known to catalyse this reaction.[23] Accordingly, the mechanistic pathway for the present reaction could be through the formation of a thiyl radical by single-electron transfer from the thiolate anion to the $Fe^{III}$–EDTA, followed by coupling

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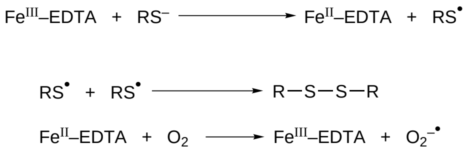
of the radical to yield the disulfide. The Fe$^{II}$–EDTA thus formed is oxidized to Fe$^{III}$–EDTA by the molecular oxygen (Scheme 2).

Wubs and Beenackers[24] postulated Fe$^{III}$(OH$^-$)EDTA to be the active species in the oxidation of $H_2S$ by Fe$^{III}$–EDTA under alkaline conditions. In accordance with their mechanism, thiols may form complexes with Fe$^{III}$–EDTA by way of replacement of OH$^-$ and intramolecular electron transfer from Fe$^{III}$ to the thiolate anion generating a thiyl radical (Scheme 3).

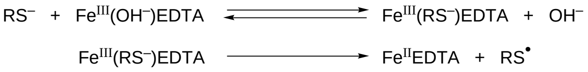


$$\mathrm{Fe^{III}\text{–}EDTA + RS^- \longrightarrow Fe^{II}\text{–}EDTA + RS^\bullet}$$

$$\mathrm{RS^\bullet + RS^\bullet \longrightarrow R\text{—}S\text{—}S\text{—}R}$$

$$\mathrm{Fe^{II}\text{–}EDTA + O_2 \longrightarrow Fe^{III}\text{–}EDTA + O_2^{-\bullet}}$$

**Scheme 2**



$$\mathrm{RS^- + Fe^{III}(OH^-)EDTA \rightleftharpoons Fe^{III}(RS^-)EDTA + OH^-}$$

$$\mathrm{Fe^{III}(RS^-)EDTA \longrightarrow Fe^{II}EDTA + RS^\bullet}$$

**Scheme 3**

The wine red colour of Fe$^{III}$–EDTA is changed to bluish green on addition of a thiol to an alkaline solution of Fe$^{III}$–EDTA, and again to wine red on complete oxidation of the thiol to the disulfide, suggesting complex formation between the thiolate anion and the Fe$^{III}$–EDTA. In line with the postulated mechanism, the rate of oxidation would depend on the concentration of thiolate anion. Since aromatic thiols have lower p$K_a$ values than aliphatic thiols, sufficient availability of the thiolate anion is expected at lower pH. This is in line with their fast oxidation at pH ~8 while aliphatic thiols require higher pH.

The simplicity of the system, excellent yields, and the reasonable reaction time thus make Fe$^{III}$–EDTA an attractive, environmentally acceptable synthetic tool for the oxidation of thiols to disulfide by molecular oxygen.

## Experimental

*General Procedure for the Oxidation of Thiols by Molecular Oxygen in the Presence of Fe$^{III}$–EDTA.*—A solution of the thiol (10 mmol) in 80% aqueous methanol (50 ml) containing Fe$^{III}$–EDTA (0.1 mmol; 10 ml of 0.1 M solution) was taken in a two-necked round-bottomed flask fitted with gas delivery tube and a condenser. The pH of the solution was adjusted by adding a few drops of an alkali solution and oxygen gas was passed into the solution at 30 °C for a specified period (Table 1). The completion of the reaction was indicated by the colour change of the reaction mixture from bluish green to wine red. The major portion of the methanol was then removed by distillation under reduced pressure, followed by dilution of the reaction mixture with water (40 ml) and extraction with dichloromethane (3 × 30 ml). The combined dichloromethane extract was washed with water and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure yielded the desired disulfide. The disulfides were purified either by recrystallization or by vacuum distillation. The identity of the products was established by comparison of their mps (wherever possible), IR and NMR spectra and GC retention times.

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