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Organosulfur oxidation by hydrogen peroxide using a dinuclear Mn-1,4,7-trimethyl-1,4,7-triazacyclononane complex

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Abstract—A mechanistic study of organosulfide oxidation by H_2O_2, using a dinuclear manganese complex as the catalyst, has revealed an unusual switch in the philicity of the oxidant for the first and the second oxygen transfer steps; this switch has been exploited to tune selectivity for each of the products.

Sulfoxides and sulfones often display useful biological and medicinal properties.[1] Both compounds can be prepared by oxidation of the corresponding sulfide; the versatility of this synthetic route is limited, however, as over-oxidation to the sulfone can be a problem. In addition, the mild and chemoselective oxidation of sulfides to sulfones remains an important challenge in modern synthetic chemistry. Accordingly, there is much interest in developing selective catalytic methods to perform these oxidations.[2]

The dinuclear manganese 1,4,7-trimethyl-1,4,7-triazacyclononane complex, $[(Me_3TACN)_2Mn_2^{IV}(\mu\text{-}O)_3](PF_6)_2$ (**1**), has shown considerable potential as a catalyst for oxidations with H_2O_2 in aqueous and organic solution.[2–9] However, details of the mechanisms of many of these reactions remain unclear. We report here a study of the oxidation of methyl 4-substituted phenyl sulfides and sulfoxides using this system, revealing an unusual and atypical switch in the philicity of the oxidant from electrophilic for sulfides to nucleophilic for sulfones.

In a typical oxidation, hydrogen peroxide (2.2×10^{-3} mol, 31%, w/w) was added to a stirred solution of sulfide or sulfoxide (1.5×10^{-4} mol) and manganese complex **1** (3.7×10^{-7} mol, 0.25 mol %) in acetone (5 cm^3) at 25 °C. Aliquots (0.18 cm^3) were removed at selected time intervals, diluted with acetonitrile and analysed by UV–vis spectroscopy. Deconvolution of the spectra from sulfide oxidations gives reaction profiles showing [sulfide], [sulfoxide] and [sulfone] versus time and provides initial rate data and maximum yields of sulfoxides (see e.g., Fig. 1). The same procedure was used to follow the sulfoxide oxidations. Under these reaction conditions, the rates of the uncatalysed oxidations of the substrates were at least two orders of magnitude less than those of the corresponding catalysed reactions. Repeating the sulfide oxidations using the

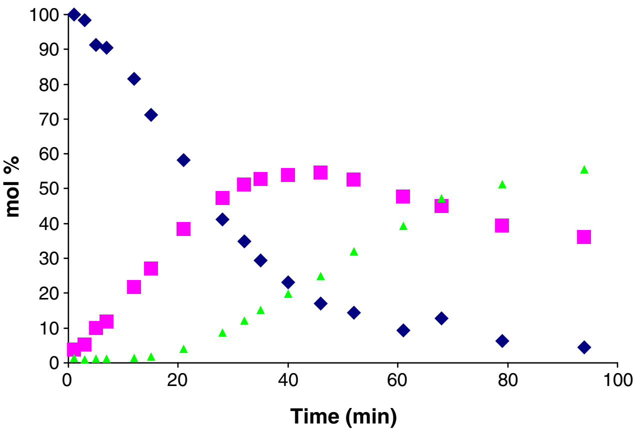

Figure 1. Reaction profile for the oxidation of 4-methoxyphenyl methyl sulfide using H_2O_2 (15 equiv) and **1** (1 mol %) in acetone, (◆) sulfide, (■) sulfoxide and (▲) sulfone.

Keywords: Oxidation; Sulfide; Sulfoxide; Catalysis; Manganese 1,4,7-trimethyl-1,4,7-triazacyclononane complexes; Hydrogen peroxide.

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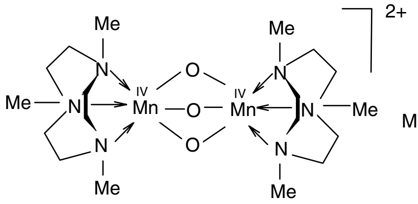
mononuclear Mn catalyst **2** gave identical reaction profiles.



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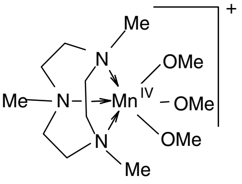

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Substituent effects on the initial rates of substrate consumption were analysed using the Hammett equation. The plot of log relative rate data versus σ^+, for the monooxidation of methyl 4-substituted phenyl sulfides, gives a good linear correlation with a negative ρ value of -0.28 ± 0.01 ($r = 0.987$) (Fig. 2a), indicating that the active oxidant for the first oxidation step is an electrophile. However, the comparable plot for sulfoxide oxidations (vs σ), performed under identical experimental conditions, has a positive slope ($\rho = 0.2 \pm 0.01$, $r = 0.990$) (Fig. 2b). The change in the sign of ρ indicates that there is a switch in the nature of the active oxidant from electrophilic in the first oxidation step to nucleophilic in the second. Bonchio et al. have reported that sulfoxide–sulfone oxidations, using Ti^{IV}/homochiral *C*3 symmetric trialkanolamine-hydroperoxo complexes, can proceed by either an electrophilic or a nucleophilic pathway.[10] Similarly, Huang and Espenson, in their study of the methyltrioxorhenium-catalysed oxidation of sulfines (thioketone *S*-oxides) with hydrogen peroxide, noted that the active oxidant changed from electrophilic with electron-rich to nucleophilic with electron-deficient sulfines.[11] However, in our system the linear Hammett plot suggests a uniquely nucleophilic pathway operates in the sulfoxide oxidation step.

Sulfide/sulfoxide oxidations that are performed using electrophilic oxidants typically exhibit $k_S/k_{SO} \approx 10^3$, due to the greater nucleophilicity of sulfide compared with sulfoxide.[12] However, in our system $k_S/k_{SO} \approx 1$. We propose that this decrease in chemoselectivity arises from the switch in the nature of the oxidant for the two steps. Thus sulfoxides, which are unreactive towards the electrophilic oxidant are relatively susceptible to nucleophilic attack (see mechanism below).

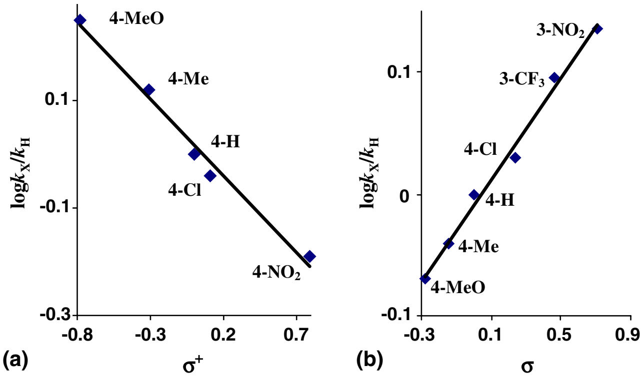


Figure 2. Hammett plots for the oxidation of methyl 3- and 4-substituted phenyl sulfides (a) and sulfoxides (b) using H_2O_2 (15 equiv) and (**1**) (0.25 mol %) in acetone.

To investigate the fate of complex **1** in the oxidation system, ESI-MS was used to monitor the reaction. On addition of H_2O_2 to **1**, a new species with *m*/*z* 500, corresponding to $[(Me_3TACN)_2Mn_2^{III/IV}(\mu\text{-}O)_3]^+$ (**3**) was detected. This one-electron reduction of **1** by H_2O_2 in acetone has previously been observed by Feringa and coworkers using EPR spectroscopy.[13] On subsequent addition of phenyl methyl sulfide, new signals at *m*/*z* 277 and 259 were also detected. These cations, assigned to the mononuclear manganese species $[(Me_3TACN)Mn^{IV}(OH)_3]^+$ and $[(Me_3TACN)O{=}Mn^{IV}(OH)]^+$, respectively, have been observed before in the equivalent oxidations of azo dyes[14] and cinnamic acids,[15] and suggest that the active oxidant is a mononuclear Mn species.

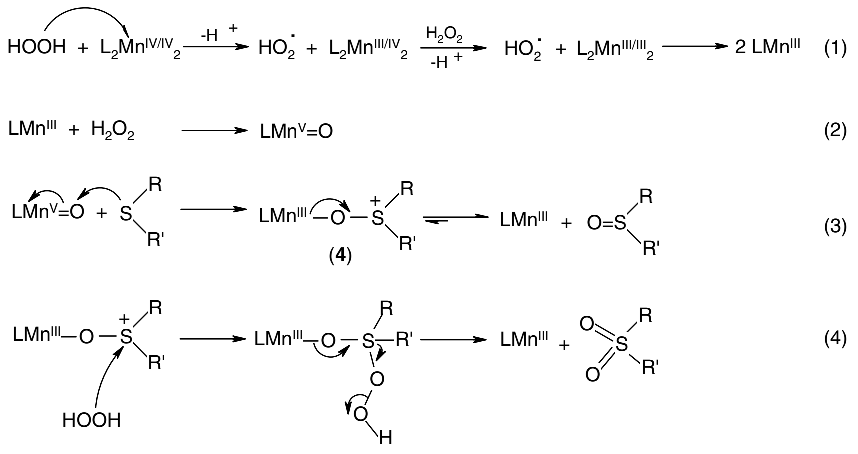
We next applied the reaction profiles, described above, to improve the maximum sulfoxide yield using methyl 4-nitrophenyl sulfide, the most electron deficient sulfide, with the poorest sulfoxide selectivity of all the substrates screened. Changing the mole percent of catalyst from 1.0 to 0.25 increased the maximum yield of sulfoxide from 28% to 47% and improved the sulfoxide:sulfone ratio from 1.1 to 2.1 (Table 1). A similar improvement in sulfoxide yield was observed for all methyl 4-substituted aryl sulfides. The selectivity for sulfoxide over sulfone was further enhanced by switching the solvent from acetone to acetonitrile and by adding carboxylic acid/carboxylate co-catalysts (Table 1). The best of the co-catalysts tested was 3,3-dimethylbutanoic acid, which gave a sulfoxide:sulfone ratio of 13.3.

We can account for all the results above with the mechanism in Scheme 1. Reduction of $L_2Mn_2^{IV/IV}$ (**1**) by H_2O_2 generates the dinuclear $L_2Mn_2^{III/IV}$ species (**3**), which following a second reduction is cleaved to give two LMn^{III} species (Reaction 1). Subsequent oxidation yields the proposed active oxidant, $LMn^V{=}O$ (Reaction 2).[8,14–16] This reacts with the sulfide to form a LMn^{III}–sulfoxide complex, **4**, which is in equilibrium with free sulfoxide and LMn^{III} (Reaction 3). The further oxidation to

Table 1. The effect of solvents and co-catalysts on the maximum yield of sulfoxide and yield of sulfone in the oxidation of methyl 4-nitrophenyl sulfide with H_2O_2 (5 equiv) catalysed by complex **1** (0.25 mol %) at 25 °C

Solvent	Co-catalyst	Max yield (%) sulfoxide	Yield (%) sulfone	Sulfoxide/sulfone ratio
Me_2CO[a]	—	28	26	1.1
Me_2CO	—	47	22	2.1
MeCN	—	55	14	3.9
MeCN	$MeCO_2H$	60	11	5.5
MeCN	$MeCO_2Na$	70	8	8.8
MeCN	$^tBuCH_2CO_2H$	80	6	13.3

[a] Complex **1**, 1.0 mol %.



Scheme 1.

sulfone (Reaction 4) occurs by nucleophilic attack by hydrogen peroxide on the positive sulfur in the Mn–sulfoxide complex, **4**.

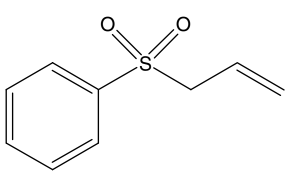
An alternative electron-transfer oxidation of sulfide to sulfoxide by the oxo-manganese(V) species would also be in agreement with the measured ρ value. However, this mechanism was ruled out by a competitive oxidation, which showed that *tert*-butyl methyl sulfide is >10-times more reactive than methyl phenyl sulfide. Two-electron oxygen transfer is known to occur more rapidly with dialkyl sulfides whereas single electron transfer is faster with aryl sulfides.[17]

The experimental changes leading to improved sulfoxide selectivity (Table 1) can all be rationalised in terms of discouraging the reaction of free sulfoxide with LMn^{III} to form complex **4** that is needed for sulfone formation. These include decreasing the catalyst concentration and using a solvent or oxidatively stable co-catalyst that competes with the sulfoxide as a ligand for the manganese centre.[15,17–22] The greater efficiency of sodium acetate over acetic acid, in suppressing over-oxidation to sulfone, is attributed to the ability of the Na^+ counterion to bind to the sulfoxide, which further inhibits sulfoxide complexation to manganese. The improved performance of 3,3-dimethylbutanoic acid over acetic acid may arise from the steric bulk of the ligand hindering sulfoxide ligation.

Further support for the mechanism in Scheme 1 comes from labelling experiments using $H_2{}^{18}O_2/H_2{}^{16}O$ and $H_2{}^{16}O_2/H_2{}^{18}O$. With labelled H_2O_2 (90 at %), the isotopic incorporation in sulfoxide and sulfone was 96.5% and 89.2%, respectively, whereas with labelled water (98 at %) it was 8.6% and 10.4%, respectively. These results show that the large majority of the oxygen in the products arises from hydrogen peroxide. For sulfoxidation (Steps 2–3), this is in agreement with oxygen atom-transfer being the main (if not the only), oxidation route. The small amount of unlabelled oxygen in the sulfoxide (ca. 5–8%) could arise from a minor electron-transfer pathway in which water traps the sulfide cation radical or alternatively from protropic oxygen exchange with coordinated water in the oxo-manganese(V) species. The latter reaction, has been observed previously in oxidations with oxo-manganese(V) porphyrins[23,24] and salens.[25]

Hitherto, we had concentrated on performing reactions under conditions that inhibited Mn–sulfoxide complex formation in order to limit over-oxidation to the sulfone. However, by performing reactions under conditions that favour formation of the Mn–sulfoxide complex, sulfones can be prepared in a mild and chemoselective manner using our system.

Competition experiments revealed that sulfides could be selectively oxidised to the corresponding sulfones in the presence of other easily oxidised substrates/functional groups, including alkenes and alcohols. For example, sulfones **5** and **6** could be prepared in excellent yields (94% and 91%, respectively), from the corresponding sulfides by performing the reactions using 0.5 mol % catalyst, in acetone, in the absence of co-catalyst.



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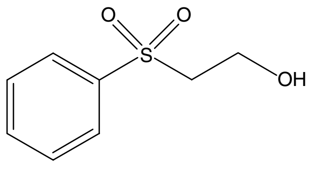

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In conclusion, we have shown that an unusual oxidation mechanism operates in this system, which allows the products to be tuned to either sulfoxide or sulfone. The key to controlling the selectivity in these reactions is the equilibrium between the $(Me_3TACN)Mn^{III}$–sulfoxide complex and $(Me_3TACN)Mn^{III}$ and sulfoxide. Conditions that disfavour complex formation lead to sulfoxide and discourage sulfone—a common by-product when performing sulfoxidation. Alternatively, conditions that promote the complex can be used for the chemoselective preparation of sulfones.

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