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Spectroscopic and kinetic evidence for redox cycling, catalase and degradation activities of Mn^{III}(TPPS) in a basic aqueous peroxide medium†

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Mn^{III}(TPPS) was found to react rapidly with hydrogen peroxide in basic aqueous solution to form intermediate (TPPS)Mn^V=O and (TPPS)Mn^{IV}=O species which, in the presence of excess H₂O₂, are reduced fully back to Mn^{III}(TPPS) with clear evidence for redox cycling of Mn^{III}(TPPS). The system shows very strong catalase and degradation activities.

Many model biomimetic complexes can mimic the efficient reaction of hydrogen peroxide with Fe(III) states of heme-containing peroxidases and catalases in a two-electron redox reaction.^{1,2} In a recent study,³ direct evidence was reported for the catalase activity of [Ru^V(edta)O][−], formed in the reaction of [Ru^{III}(edta)(H₂O)][−] with H₂O₂, in the presence of a large excess of H₂O₂ in weakly acidic aqueous solution (pH ≈ 5). In terms of the catalase activity of Mn(III) complexes, detailed studies have revealed the reaction mechanism for competitive substrate oxidation and catalase activity of Mn^V=O complexes in the presence of relatively high H₂O₂ concentrations. In general, lower H₂O₂ concentrations were selected to use Mn^{IV}=O and Mn^V=O complexes as catalysts for substrate oxidation processes in order to avoid the destructive catalase activity of these complexes.⁴

In this study we report spectroscopic and kinetic evidence for the catalase activity and redox cycling of Mn^{III}(TPPS), TPPS = 5,10,15,20-tetrakis(4-sulphonatophenyl)-21H,23H-porphine, in the presence of H₂O₂ in basic aqueous solution. We report direct spectroscopic evidence for the formation of (TPPS)Mn^V=O and (TPPS)Mn^{IV}=O upon the addition of excess H₂O₂ to Mn^{III}(TPPS) in the pH range of 9 to 12, followed by reformation of Mn^{III}(TPPS) and the release of molecular oxygen. As far as we know, such a direct redox cycling in the absence of a substrate has not been observed before for Mn^{III}(porphyrin) systems. Furthermore, the observed redox cycling was dramatically accelerated by the

presence of a carbonate buffer at pH 9, which is ascribed to the formation and participation of peroxocarbonate in the redox cycling of the Mn^{III}/Mn^{IV/V}=O system in the case of the TPPS porphyrin.

The pK_a values of [Mn^{III}(TPPS)(H₂O)₂]^{3−} were determined from spectrophotometric pH titrations, for which the data are reported in the ESI.† The pK_a values for reactions (1) and (2) are approximately 6.6 and 12.0, respectively. Complexes of Mn(III) with different tetrapyrrolic ligands exhibit similar properties and appear mainly in their diaqua form at pH < 7.5. The values found in this study are in close agreement with related data reported in the cited literature.⁵

Reaction of Mn^{III}(TPPS) with H₂O₂ at pH = 12. Under these conditions the Mn^{III}(TPPS) complex exists in solution as a mixture of [Mn^{III}(TPPS)(H₂O)OH]^{4−} and [Mn^{III}(TPPS)(OH)₂]^{5−} based on the pK_a values reported above. Since the pK_a value of H₂O₂ is 11.3, it will mainly be present as HOO[−] under the selected conditions. Upon addition of H₂O₂ to an aqueous solution of Mn^{III}(TPPS) at pH 12, an immediate decrease in the absorbance at 466 nm was accompanied by the rapid formation of a new broad band with a maximum at 422 nm (Fig. 1). The spectrum of Mn^{III}(TPPS) in 0.01 M NaOH solution is characterized by the presence of two bands of medium intensity at 379 and 401 nm, a strong Soret band at 466 nm and two much less intense Q bands at 564 and 596 nm. The new species rapidly formed upon the addition of H₂O₂ shows two bands at 422 and 520 nm.

Reactions between Mn(III) porphyrins with various oxidizing agents were studied before. A hypsochromic shift observed during the oxidation of Mn^{III}(TMPyP) (TMPyP = tetra-(N-methylpyridyl)-porphyrin),^{4b} Mn^{III}(TF₄TMAP) (TF₄TMAP = *meso*-tetrakis-(2,3,5,6-tetrafluoro-*N,N,N*-trimethyl-4-aniliniumyl)porphyrin),^{4e}

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Fig. 1 Typical spectral changes observed for the reaction of 3.4 μM $\text{Mn}^{\text{III}}(\text{TPPS})$ with 195 μM H_2O_2 at pH = 12 and 25 $^\circ\text{C}$. Inset: Corresponding kinetic trace at 466 nm.

and $\text{Mn}^{\text{III}}(\text{TDMImP})$ ($\text{TDMImP} = 5,10,15,20\text{-tetrakis}[1,3\text{-}N\text{-dimethylimidazol-2-yl}]porphyrin$),⁶ has in all cases been ascribed to the oxidation of $\text{Mn}(\text{III})$ to $\text{Mn}(\text{V})=\text{O}$ species. This interpretation was confirmed by EPR experiments. The very similar spectral changes observed in our system strongly suggest the formation of a $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ complex.

Fig. 1 shows the spectral changes observed immediately after the addition of H_2O_2 to $\text{Mn}^{\text{III}}(\text{TPPS})$ measured using the rapid-scan modus of a stopped-flow instrument in the H_2O_2 concentration range of 20 to 195 μM (see Fig. S2 and S3 in the ESI[†]). The reaction is accompanied by clean isosbestic points at 387, 447, 487 and 542 nm. The kinetic trace in the inset of Fig. 1 shows very good pseudo-first-order behaviour. The observed rate constant exhibits a linear dependence on the H_2O_2 concentration with a small intercept as shown in Fig. S2 (ESI[†]). The intercept is ascribed to a parallel decomposition reaction that occurs at low H_2O_2 concentration, as seen from the kinetic trace in Fig. S3 (ESI[†]). The second-order rate constant for the reaction is $(2.9 \pm 0.1) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 25 $^\circ\text{C}$.

In a subsequent slow step, the spectral changes observed in Fig. 1 were reversed and the initial spectrum of $\text{Mn}^{\text{III}}(\text{TPPS})$ was restored as shown in Fig. 2. The complete reformation of $\text{Mn}^{\text{III}}(\text{TPPS})$ in the presence of an excess of H_2O_2 is shown in

Fig. 2 Spectral changes observed during the reformation of $\text{Mn}^{\text{III}}(\text{TPPS})$ in the reaction of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ with H_2O_2 at pH = 12. Inset: Spectra recorded before and after the completion of the catalase redox cycle. Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 7.9 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 147 \mu\text{M}$, total time = 241 min, $T = 25 \text{ }^\circ\text{C}$.

Fig. 3 Typical kinetic traces recorded at 466 nm over long (a) and short (b) reaction times during the catalase activity of the $\text{Mn}^{\text{III}}(\text{TPPS})\text{-H}_2\text{O}_2$ system at pH = 12. Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 5.1 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 8$ (a and b), 25 (c) and 100 μM (d), $T = 25 \text{ }^\circ\text{C}$.

the inset of Fig. 2. It is much slower than the formation of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ due to the competitive nature of the processes, *viz.* the oxidation of $\text{Mn}^{\text{III}}(\text{TPPS})$ to $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ and the competing reduction of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ to $\text{Mn}^{\text{III}}(\text{TPPS})$ accompanied by the catalytic disproportionation of H_2O_2 .

Depending on the selected H_2O_2 concentration, it was possible to introduce an apparent induction period during which the concentration of the $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ complex remained stable in solution as a result of redox cycling of the $\text{Mn}^{\text{III}}(\text{TPPS})/(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ system. The steady state concentration of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ results from an exact balance of its formation and decay rates (see Fig. 3a and b). The length of the redox cycling period increases with increasing H_2O_2 concentration as illustrated in Fig. 3c and d. Thus at higher H_2O_2 concentration the reformation of $\text{Mn}^{\text{III}}(\text{TPPS})$ is significantly delayed for 400 s as seen in Fig. 3d. During the redox cycling, H_2O_2 undergoes disproportionation into water and oxygen, *i.e.* the system shows catalase activity as summarized in reactions (3) and (4).

The change in H_2O_2 concentration during the redox cycling period of up to 600 s was monitored with a standard iodide/iodine/thiosulfate titration, for which the results and further information are given in Fig. S4 (ESI[†]). Under the selected conditions where the concentration of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ remains constant, the observed pseudo-first order rate constant is independent of the H_2O_2 concentration and depends linearly on the $\text{Mn}^{\text{III}}(\text{TPPS})$ concentration. The second order rate constant for the catalase activity was found to be $1.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ at 25 $^\circ\text{C}$ (see the ESI[†]), which is seven orders of magnitude larger than for other Cu, Mn, Fe and Ru systems reported in the literature.³ As far as we know, only the $\text{Fe}^{\text{III}}(\text{TAML})$ system has a higher activity of $2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.⁷

Fig. 4 Changes in the concentration of oxygen during the reaction of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 under an argon atmosphere. Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 11.9 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 3.92 \text{ mM}$ (a) and 1.96 mM (b), $\text{pH} = 9$ (a) and $\text{pH} = 12$ (b), $T = 25^\circ\text{C}$.

During the observed redox cycling, oxygen should be produced in solution, which was checked using an oxygen sensitive electrode (Fig. 4) calibrated with a saturated oxygen solution. The experimental data demonstrate that the oxygen concentration increases almost linearly during the first 150 s after the addition of H_2O_2 to the reaction mixture. This corresponds to the time of the observed induction period during which $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ reacts with H_2O_2 to form dioxygen and $\text{Mn}^{\text{III}}(\text{TPPS})$, which in turn is oxidized to $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ to undergo redox cycling as presented in reactions (3) and (4). The data in Fig. 4 suggest that a steady state concentration of oxygen is reached in solution, which depends on the pH and H_2O_2 concentration used. This is related to the redox cycling and limited solubility of oxygen in aqueous solution.

Reactions of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 at different concentration ratios (2 : 1, 1 : 1, 1 : 2) favour the formation of different oxidation states of manganese. The results in Fig. S5 (ESI[†]) show that upon increasing the H_2O_2 concentration, the concentration of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ (maximum at 422 nm) also increases at the expense of $(\text{TPPS})\text{Mn}^{\text{IV}}=\text{O}$ (maximum at 402 nm). The shift in the peak maximum by about 20 nm is very typical for the formation of $\text{Mn}^{\text{IV}}=\text{O}$ versus $\text{Mn}^{\text{V}}=\text{O}$ porphyrin complexes as shown for the corresponding complexes of TMPyP , TF_4TMAP and TDMImP in the literature.^{4a,e,6}

The ability to stabilize the high oxidation state $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ complex as long as H_2O_2 is present in solution is of significance for the potential use of this species in degradation reactions of dyes and other inert organic substrates (see further discussion).

Reaction of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 at $\text{pH} = 9$ in tris buffer. In order to check the catalase activity of $\text{Mn}^{\text{III}}(\text{TPPS})$ under conditions where hydrogen peroxide is mainly present in the protonated form, H_2O_2 , we turned to $\text{pH} 9$. At this pH the $\text{Mn}^{\text{III}}(\text{TPPS})$ complex is mainly present as $[\text{Mn}^{\text{III}}(\text{TPPS})(\text{H}_2\text{O})\text{OH}]^{4-}$ in aqueous solution. The *trans*-hydroxo ligand is expected to labilize the coordinated water molecule, making the $\text{Mn}^{\text{III}}(\text{TPPS})$ complex significantly more labile than at $\text{pH} 12$ where *ca.* 50% of the complex is in the inert $[\text{Mn}^{\text{III}}(\text{TPPS})(\text{OH})_2]^{5-}$ form. However, H_2O_2 is a much weaker nucleophile than HOO^- under such conditions.

Alternatively, recent work showed that H_2O_2 can protonate a hydroxo ligand in an intramolecular way by which a labile water molecule is formed and displaced by HOO^- .^{8,9} The reactions do not go to completion at lower $[\text{H}_2\text{O}_2]$ (see Fig. 5), presumably due to the interference of the back reaction. At higher $[\text{H}_2\text{O}_2]$,

Fig. 5 Spectral changes observed during the reaction of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 to form $(\text{TPPS})\text{Mn}^{\text{IV/V}}=\text{O}$ at $\text{pH} = 9$ in tris buffer (0.1 M). Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 2.7 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 196 \mu\text{M}$, tris buffer $\text{pH} = 9.04$, $T = 25^\circ\text{C}$, total time = 245 min.

Fig. 6 Typical kinetic trace recorded at 466 nm (a) and plot of k_{obs} versus H_2O_2 concentration for the formation of $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ (b) at $\text{pH} = 9$. Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 2.7 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 196 \mu\text{M}$ (a) and 8–1500 μM (b), tris buffer (0.1 M) $\text{pH} = 9.0$, $T = 25^\circ\text{C}$.

the kinetic traces had to be fitted with a double exponential function due to the parallel decomposition of the $\text{Mn}^{\text{III}}(\text{TPPS})$ complex (see Fig. 6). The plot of k_{obs} versus $[\text{H}_2\text{O}_2]$ shows a significant intercept that can be associated with the back reaction in which $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ is reduced by H_2O_2 to $\text{Mn}^{\text{III}}(\text{TPPS})$. The second-order rate constant for the reaction with H_2O_2 at $\text{pH} 9$, *viz.* $0.99 \pm 0.04 \text{ M}^{-1} \text{ s}^{-1}$, is four orders of magnitude slower than the reaction with OOH^- at $\text{pH} 12$, *viz.* $(2.9 \pm 0.1) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, due to the much stronger oxidant present in solution at $\text{pH} 12$.

Reaction of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 at $\text{pH} = 9$ in carbonate buffer. In earlier work dealing with the catalytic degradation of organic dyes by H_2O_2 at $\text{pH} 9.2$, we found that the reaction was much faster in carbonate than in tris buffer due to the rapid formation of peroxocarbonate, HCO_4^- (reaction (5)), being a much stronger oxidant than H_2O_2 under such conditions.^{10,11}

In the present study we observed a huge acceleration of the reaction in carbonate buffer as compared to tris buffer. This is also true for the back reaction as illustrated by the typical absorbance-time traces observed under such conditions (see Fig. S6, ESI[†]). The spectral changes recorded under such conditions are shown in Fig. 7 and illustrate the significant acceleration in carbonate buffer.

Fig. 7 Spectral changes observed during the reaction of $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 at pH = 9.3 in carbonate buffer (black line – spectrum before mixing $\text{Mn}^{\text{III}}(\text{TPPS})$ with H_2O_2 , red line – spectrum recorded immediately after mixing the reactants, blue line – final spectrum measured after 175 min). Experimental conditions: $[\text{Mn}^{\text{III}}(\text{TPPS})] = 5.9 \mu\text{M}$, $[\text{H}_2\text{O}_2] = 343 \mu\text{M}$, [carbonate buffer] = 0.5 M, $T = 25^\circ\text{C}$.

Moreover, the new species has an absorbance maximum at about 402 nm, which suggests that $\text{Mn}^{\text{III}}(\text{TPPS})$ is oxidized to $(\text{TPPS})\text{Mn}^{\text{IV}}=\text{O}$ under the present conditions. The presence of a less intense band with a maximum at 422 nm indicates the contribution from $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ species. Information on the influence of the H_2O_2 and carbonate concentrations is given in the ESI†.

Degradation of substrates under catalytic conditions. The catalytic activity of the $\text{Mn}^{\text{III}}(\text{TPPS})/\text{H}_2\text{O}_2$ system was studied for the degradation of Orange II (ORII), which belongs to the group of azo dyes. We have studied in the past the catalytic activity of manganese, iron and ruthenium complexes in the degradation of such dyes.^{10–12} Preliminary experiments for the present system show promising results (see the ESI†).

In summary, the results clearly show that hydrogen peroxide can easily oxidize $\text{Mn}^{\text{III}}(\text{TPPS})$ to $(\text{TPPS})\text{Mn}^{\text{IV}}=\text{O}$ or $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ in basic aqueous medium. In addition, an excess of H_2O_2 leads to the subsequent reduction of the oxidized intermediates fully back to $\text{Mn}^{\text{III}}(\text{TPPS})$ to close the catalytic cycle in terms of catalase activity of the studied complex. Molecular oxygen is released during the observed redox cycling of the system, resembling catalase activity responsible for decomposition of hydrogen peroxide to water and oxygen. The catalase activity is characterized by a second-order rate constant of $1.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and TOF of 1.5 s^{-1} at pH 12 and 25°C . This rate constant is seven orders of magnitude higher than reported for most other synthetic catalysts. Such processes are lately recognized to play a crucial role in oxidative stress modulation, therapeutic aspects of Mn porphyrins and redox cycling of related heme and non-heme metal complexes.¹³ The fact that the starting complex $\text{Mn}^{\text{III}}(\text{TPPS})$ is fully regenerated in the catalytic cycle enforces the medical potential of this class of compounds. At pH = 12, $\text{Mn}^{\text{III}}(\text{TPPS})$ is oxidized to $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ several orders of magnitude faster than at pH = 9 when a tris buffer solution is used.

This can be ascribed to the presence of the much stronger oxidant OOH^- at pH 12 than at pH 9 where H_2O_2 is the oxidizing species. When a carbonate buffer is used, evidence for the relatively rapid formation of both $(\text{TPPS})\text{Mn}^{\text{IV}}=\text{O}$ and $(\text{TPPS})\text{Mn}^{\text{V}}=\text{O}$ was observed. This can be accounted for by the rapid formation of peroxocarbonate, HCO_4^- , which is a significantly stronger oxidant than H_2O_2 under the selected conditions.¹⁰ In the latter case, the carbonate buffer also induces the back reaction to $\text{Mn}^{\text{III}}(\text{TPPS})$, which is not observed in tris buffer, and indicates that peroxocarbonate can induce a more effective catalase type activity than hydrogen peroxide under these conditions. The catalase activity is characterized by a second-order rate constant of $1.6 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ and TOF of 0.07 s^{-1} at pH = 9 (carbonate buffer) and 25°C .

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