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Mechanistic studies on the oxidation of thiols by a $\{\text{Mn}_4\text{O}_6\}^{4+}$ core in aqueous acidic media

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ABSTRACT

Described in this work is the kinetics of the oxidation of a series of thiols, viz. 2-mercaptoethanol (mercap), thioglycolic acid (tga) and L-cysteine (cys), a paradigm for aliphatic thiols, by a tetranuclear Mn oxidant, $[\text{Mn}_4(\mu\text{-O})_6(\text{bipy})_6]^{4+}$ (bipy = 2,2'-bipyridine), in weakly acidic aqueous media (pH 2.0–4.0) in the presence of added bipy (60.0–80.0 mM). The thiols were quantitatively oxidized to their respective disulfides and the Mn^{IV}_4 species was reduced to Mn^{II} . Excess bipy present in the reaction mixture removes any possibility of Cu^{2+} catalysis in these reactions. The reactions were acid-catalyzed and the oxo-bridged protonated Mn oxidant, $[\text{Mn}_4(\mu\text{-O})_5(\mu\text{-OH})(\text{bipy})_6]^{5+}$, was found to be a kinetically far superior oxidant than its deprotonated analog, $[\text{Mn}_4(\mu\text{-O})_6(\text{bipy})_6]^{4+}$. The reactions show kinetic isotope effects. The tga oxidation rate was increased in media enriched with D_2O whereas the rate of oxidation of the other two thiols was increased in H_2O . However, the increase/decrease in rate in H_2O – D_2O mixed media varied linearly with the D_2O content of the media, which might be indicative of transfer of a single proton in the rate step of the reactions, at least for cys and mercap. The increase in rate of tga oxidation in D_2O media could be explained by the relative abundance of the reactive species in D_2O in comparison to that in H_2O .

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1. Introduction

Photosynthetic water splitting, resulting in oxygen evolution, is the primary source of oxygen in the atmosphere. The water oxidation process proceeds through a cycle of at least five steps, known as the Kok cycle [1]; each step is characterized as a S_i ($i = 0\text{--}4$) state depending on the oxidation states of a cluster of four Mn atoms, along with related structural and electronic properties at each state [2,3]. Ligands derived from H_2O (O^{2-} or HO^-) act as bridges between the Mn atoms, along with carboxylato moieties, in the catalytic site of the oxygen evolving complex (OEC) in photosystem II (PS II) [4–6].

Successive changes in the redox states of the Mn atoms in the OEC during the cycle are associated with protonation/deprotonation of the oxo-bridges [5,7,8] and the nearby amino acid residues, along with simultaneous movement of protons and electrons within the OEC [6,9–11]. The large size and complexity of the PS II makes it difficult to prepare, store and handle. Reactivity studies of synthetic models could play a significant role in understanding the structure and mechanism of action of OEC. Effects of oxo-bridge protonation include a decrease in the exchange coupling between Mn^{IV} in a model tetranuclear system, and this has

an important bearing in interpreting the changes in the magnetic behavior of the OEC upon S-state advancement, and changes in the configurations [12], increase in the Mn···Mn distance [13,14] in multinuclear Mn complexes and a substantial increase in the reduction potential [15]. Investigations on the chemical aspects of reactivity resulting from oxo-bridge protonation, however, are scarce. It was observed that protonation of an oxo-bridge affects the catalase activity of a Mn^{IV} dimer [15], whereas disproportionation of a Mn^{III} dimer requires oxo-bridge protonation [16]. It was also reported that oxo-bridge protonation in multinuclear Mn complexes sometimes leads to cluster break up, rendering their redox chemistry proton coupled [17]. Formation of monomeric, trimeric and tetrameric Mn species resulting from the opening of oxo-bridges on protonation were also proposed [18–21]. Exchange of oxygen atoms between bulk water and μ -oxo bridges is also believed to involve elementary steps of bridge protonation and deprotonation [22–27]. The acid/base chemistry resulting from oxo-bridge protonations has been studied mostly in non-aqueous media [12–16,19–21,28–32]. However, how such protonations influence the kinetic pattern of oxidation of small substrates are rarely studied [33–35], despite the relevance of such knowledge to PS II. This is particularly true in water, the medium for PS II.

The title complex $[\text{Mn}_4(\mu\text{-O})_6(\text{bipy})_6]^{4+}$ (**1⁴⁺**, Fig. 1) formally corresponds to the fully oxidized S_3 or S_4 state of OEC [36,37] (although involvement of a higher state (Mn^{V}) is proposed in the water oxidation process [38–43]), and is stable in aqueous solution

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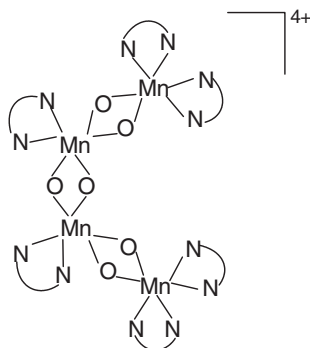


Fig. 1. Schematic drawing of $[\text{Mn}_4(\mu\text{-O})_6(\text{bipy})_6]^{4+}$. N–N is 2,2'-bipyridine.

over a wide acidity range (pH 1.5–6.0). Fig. S1 shows that the title tetramer is stable in aqueous solution over a long period of time, even at low pH. Its one-electron reduced, mixed-valent $\text{Mn}^{\text{IV}}_3\text{Mn}^{\text{III}}$ form is an EPR spectroscopic model for the S_2 state [44]. Exploration of the electron-transfer reactivity of the title Mn tetramer will thus be of potential interest. Oxidation reactions of thiols by metal-centered oxidants are catalyzed by metals ions, especially by Cu^{2+} [45–47]. Even, ubiquitous Cu^{2+} ions present as impurities in the solution affect the kinetics. However, by using a suitable masking agent, effective for Cu^{2+} , the catalytic path can be completely suppressed [48–51]. In the present work, we report the kinetics of the unanalyzed, direct oxidation of three thiols, viz. 2-mercaptoethanol (mercap), thioglycolic acid (tga) and L-cysteine (cys) (a paradigm for aliphatic thiols) by the title Mn tetramer in aqueous media in the presence of externally added 2,2'-bipyridine, which acts as a chelating ligand for Cu^{2+} thus scavenging Cu^{2+} from solution.

In this work we gained conclusive kinetic evidence that at higher acidity of the reaction media protonation of an oxo-bridge in $\mathbf{1}^{4+}$ results in the formation of a highly reactive species $\mathbf{1H}^{5+}$ that oxidizes the thiols much quicker than $\mathbf{1}^{4+}$ does. We also like to note here that no information is yet known on the thiol reduced Mn sites in PS II or their models.

2. Experimental

2.1. Materials

The complex salt hydrate $[\text{Mn}_4(\mu\text{-O})_6(\text{bipy})_6](\text{ClO}_4)_4 \cdot 2\text{H}_2\text{O}$ was prepared following the literature procedure [44]. One of its water molecules is easily lost [44] and the elemental analyses of the material match with the values expected for the monohydrate. The title tetramer thus appears to be the monohydrate. *Anal. Calc.* for $\text{C}_{60}\text{H}_{50}\text{Cl}_4\text{Mn}_4\text{N}_{12}\text{O}_{23}$: C, 43.16; H, 2.99; N, 10.07. *Found*: C, 43.40; H, 3.08; N, 10.16%.

2-Mercaptoethanol (mercap) (Aldrich), thioglycolic acid (tga) (Aldrich), L-cysteine (cys) (SRL, India) and cystine (SRL, India) solutions were prepared with 99% reagent grade thiols. The thiols were dissolved just prior to the kinetic studies and fresh solutions were always used. 2,2'-Bipyridine was used as received from Sigma. D_2O (99.9 atom-% D) and DNO_3 (99+ atom-% D) were also purchased from Sigma. All other chemicals were of reagent grade and used as received. Doubly distilled, deionized and then freshly boiled water was used throughout.

2.2. Equilibrium measurements

The acid dissociation constants of the reducing thiols in pure H_2O and in 95% D_2O –5% H_2O media were determined by pH-metric titration using a Metrohm (736 GP Titrino) autotitrator at 25

(± 0.1) $^\circ\text{C}$, $I = 1.0 \text{ M}$ (NaNO_3) using freshly prepared carbonate free NaOH solution as described earlier [52–54]. A similar pH-metric titration of $\mathbf{1}^{4+}$ was performed in the pH range 1.5–6.0 to examine the basicity of its oxo bridges.

2.3. Stoichiometric measurements

The stoichiometries of the reactions were determined under the conditions of both deficit and excess of reducing agent concentrations over $[\mathbf{1}^{4+}]$. Under the non-kinetic condition ($[\mathbf{1}^{4+}] > [\text{Reducing agent}]$), 0.20–0.50 mM of $\mathbf{1}^{4+}$ was reacted with less than a stoichiometric amount of reducing agents and when the reactions reached equilibrium, unreacted $[\mathbf{1}^{4+}]$ was measured at 420 nm ($\epsilon = 7.5 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ [33,34]). Unreacted mercap, tga or cys was quantified spectrophotometrically [55] in separate experiments when the reactions were studied under the condition $[\text{thiol}] > [\mathbf{1}^{4+}]$. For reactions with cysteine, the unreacted cysteine, along with cystine sulfinic acid, was additionally determined by titration of the product mixture with aqueous sodium nitrite [56]. From the difference, the cystine sulfinic acid produced, if any, was estimated. No attempt was made to determine sulfinic acid for mercap and tga oxidations.

2.4. Physical measurement and kinetics

Absorbance and electronic spectra were recorded on a Shimadzu (UV-1700) spectrophotometer using 1.0 cm quartz cells. The kinetic studies were monitored in the 'kinetic mode' of the instrument and in an electrically controlled thermostated 25.0 (± 0.1) $^\circ\text{C}$ cell housing (CPS-240A) at 420 nm, where the title Mn tetramer has sufficient absorption. The ionic strength was normally maintained at 1.0 M with NaNO_3 . An excess of 2,2'-bipyridine concentration, $C_{\text{bipy}} = [(\text{Hbipy}^+) + (\text{bipy})]$, in the range 60.0–80.0 mM was used in all the kinetic runs, and this acted as a good buffer in the pH range (2.0–4.0) and also masked the Cu^{2+} ions to suppress their catalytic activity (*vide infra*). A maximum drift in 0.05 pH units was observed in the reactions, measured with an Orion-Ross combined electrode system (Model 81-02) before and after the reaction.

The electrode was calibrated to read $-\log_{10}[\text{H}^+]$ using a calibration curve constructed by plotting the pH meter reading against $-\log_{10}[\text{H}^+]$ [57,58]. For reactions in D_2O , pD was calculated using the relation $\text{pH}_{\text{measured}} + 0.40$ [59–61]. An excess of reducing agent over $[\mathbf{1}^{4+}]$ was maintained in all the kinetic runs. The $\log_{10}(\text{absorbance})$ versus time plots were found to be good straight lines for up to at least 90% completion of the reactions and the observed first-order rate constants (k_0) were calculated in the usual way. The presence of Cu^{2+} in the reaction blank was measured with a Perkin–Elmer Atomic Absorption Spectrophotometer, A – Analyst 200.

2.5. Catalytic effect of Cu^{2+} and its suppression

The kinetic study of the reduction of $\mathbf{1}^{4+}$ with excess thiols showed that the reactions are much faster in the absence of externally added bipyridine as well as in the presence of added Cu^{2+} salts. Under either condition, however, the reactions obeyed good first-order kinetics. Moreover, the first-order rate constants significantly increased with an increase in $\text{Cu}(\text{II})$ concentration. Atomic absorption spectroscopy (AAS) quantified an impurity level of $[\text{Cu}^{2+}]$ of $2.6 \times 10^{-6} \text{ M}$ in the blank reaction media. Such an impurity level of Cu^{2+} ions catalyzes the conversion of cys, tga and mercap to such an extent that the catalyzed reaction interferes with the study of the direct reaction. 2,2'-Bipyridine is a good chelating agent for Cu^{2+} ions [62] and it can effectively mask the catalysis. Using the known equilibrium constants [62] for the reactions of 2,2'-bipy with H^+ and Cu^{2+} , it could be demonstrated that even at

pH 2, 80 mM 2,2'-bipy practically sequesters Cu^{2+} completely from the reaction media ($[\text{Cu}(\text{bipy})_2]^{2+}/[\text{Cu}^{2+}] \approx 10^7$). The kinetic studies were performed in presence of an excess of 2,2'-bipyridine (generally 80.0 mM for all three thiols and occasionally at 60.0 mM) so that the externally added Cu^{2+} ion lost its catalytic effect. Tables S1–S3 collect all such observations.

3. Results and discussion

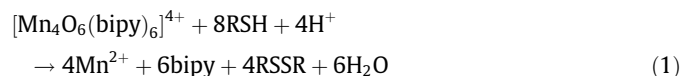
3.1. Equilibrium measurements

The observed acid dissociation constants of the thiols in pure H_2O and in 95% D_2O –5% H_2O media, along with some of their reported values [63,64] under similar experimental conditions, are collected in Table 1. In consonance with our earlier observations [33–35], the Mn oxidant did not show any ionization within the pH interval 1.5–6.0.

3.2. Stoichiometry

Measurements of the amount of unreacted reducing agents, mercap, tga and cys as well as unreacted $[\mathbf{1}^{4+}]$, suggested a consumption ratio $\Delta[\mathbf{1}^{4+}]/\Delta[\text{thiol}]$ of 1:8 (Table S4) that indicates all the three thiols are quantitatively oxidized to their respective disulfides. Moreover, titration of the cys reaction product with aqueous sodium nitrite [56] gave no indication of the formation of cystine sulfinic acid. Mn^{II} in the product solutions was estimated by EDTA titrations using EBT as an indicator [65]. For this purpose, excess reducing agents were treated with the Mn oxidant until the absorbance at 420 nm became less than 0.01, and then Mn^{II} was estimated. We verified that the thiols and bipy do not interfere in this complexometric titration.

All these observations confirm that we are dealing with the stoichiometric equation as shown in Eq. (1), where RSH represents the thiols.



3.3. Kinetics

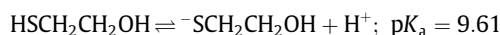
Under the employed reaction conditions, the reactions obeyed good first-order kinetics at least up to 90% decay in $[\mathbf{1}^{4+}]$. The observed first-order rate constants (k_0) remained practically unaltered when the reactions were monitored with varying wavelengths (380–500 nm) or in the presence of dissolved oxygen in the reaction media. The presence of excess bipy in the reaction media controls the pH drift during the reaction well, to within 0.05 units ($\text{p}K_{\text{a}}$ of $\text{Hbipy}^+ = 4.67$ and that of $\text{H}_2\text{bipy}^{2+} = 1.50$ [66]) besides masking the adventitious Cu^{2+} present in the reaction blank. Averages of k_0 values from at least three measurements were taken and the average coefficients of variation (CV) [67] for these measurements were within 4%.

We observed a linear variation of k_0 against T_{R} (T_{R} = analytical concentration of thiol) over the entire pH range studied (Figs. S2–S4) and found no indication of rate saturation even at the highest T_{R} studied.

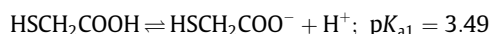
However, a strong pre-equilibrium (K) binding of the reducing species with the title oxidant followed by reaction of the intermediate thus formed with a second reducing species would lead to the observed kinetics (linear dependence of k_0 on T_{R}) provided that KT_{R} is much greater than 1 (unity), which requires a K value as high as 10^4 (lowest $T_{\text{R}} = 1.0 \times 10^{-3}$ M). But, as the d^3 Mn centers in the title oxidant are substitution inert [68] and coordinatively saturated at each Mn atom, such a strong association could not be feasible.

The thiols show the following protic equilibria [69,48,50] in aqueous solution.

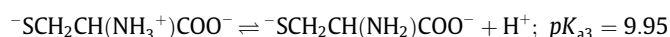
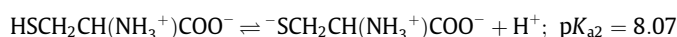
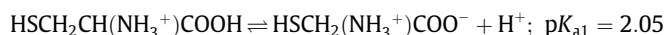
Mercaptoethanol (mercap):



Thioglycolic acid (tga):

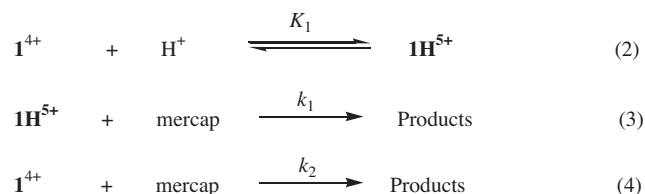


Cysteine (cys):



The rate of oxidation of all three thiols examined here show a remarkable acid-assisted path (Tables 2–4). From the known protolytic equilibria [69,48,50] of these thiols it is clear that in the investigated pH range, the available species in the solution for the said thiols are neutral 2-mercaptoethanol (for mercap), neutral thioglycolic acid and its mono-dissociated conjugate base (for tga) and the cationic and zwitterionic form (for cys). On increasing the acidity of the reaction media, the neutral or cationic forms of these reducing species are thus progressively generated, and these are expected to be kinetically slower reducing agents [48–50] than their anionic counterparts or conjugate bases. The observed acid-catalysis in these reactions should thus appear from the protonation of the oxo-bridges of the title Mn tetramer, generating an additional protonated oxidant ($\mathbf{1H}^{5+}$) over $\mathbf{1}^{4+}$. It is well-established that protonated oxidants react faster than their conjugate bases [33–35], and we observed a steady increase in the oxidation rate of all three thiols on increasing the acidity of the reaction media. Superior reactivity of $\mathbf{1H}^{5+}$ over $\mathbf{1}^{4+}$ has recently been found in the oxidation of ascorbic acid and hydroquinone by the title Mn tetramer [35].

Scheme 1, shown in Eqs. (2–4), thus represents the pathways for the oxidation of mercap.



Scheme 1.

Table 1

Proton dissociation constants for thiols in H_2O and D_2O medium at 25 °C, $I = 1.0$ M (NaNO_3) (maximum deviation ± 0.10).

Thiols	$\text{p}K_{\text{a}1}$		$\text{p}K_{\text{a}2}$		$\text{p}K_{\text{a}3}$	
	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O
L-Cysteine	2.05	2.52	8.07 [63]	8.42	9.95 [63]	10.38
Thioglycolic acid	3.49	3.74	10.25	10.65 [64]		
Mercapto ethanol	9.61	9.96 [64]				

Table 2

Some representative first-order rate constants for the oxidation of mercapto ethanol by the tetranuclear Mn oxidant at $[1^{4+}] = 0.1$ mM, $T = 25.0$ °C, $I = 1.0$ M (NaNO_3).

pH	T_R (M)	C_{bipy} (mM)	$10^3 k_0$ (s^{-1})
2.00	0.001	80.0	27.6
2.20	0.001	80.0	19.2
2.62	0.001	80.0	11.8
3.00	0.001	80.0	9.0
3.10	0.001	80.0	8.6
3.34	0.001	80.0	8.6
3.60	0.001	80.0	8.6
3.01	0.002	80.0	17.0
3.00	0.003	80.0	26.0
2.50	0.001	80.0	13.0 ^a
2.51	0.001	80.0	13.9 ^b

^a $I = 0.5$ M (NaNO_3).

^b $I = 0.1$ M (NaNO_3).

Table 3

Some representative first-order rate constants for the oxidation of thioglycolic acid by the tetranuclear Mn oxidant at $[1^{4+}] = 0.1$ mM, $T = 25.0$ °C, $I = 1.0$ M (NaNO_3).

pH	T_R (M)	C_{bipy} (mM)	$10^3 k_0$ (s^{-1})
2.11	0.002	80.0	5.00
2.26	0.002	80.0	4.31
2.43	0.002	80.0	3.80
2.60	0.002	80.0	3.42
3.07	0.002	80.0	2.77
3.46	0.002	80.0	3.01
3.70	0.002	80.0	3.08
4.00	0.002	80.0	3.20
3.06	0.001	80.0	1.33
3.06	0.004	80.0	5.57
3.05	0.002	80.0	1.53 ^a
3.05	0.002	80.0	3.62 ^b

^a $I = 1.5$ M (NaNO_3).

^b $I = 0.5$ M (NaNO_3).

Table 4

Some representative first-order rate constants for the oxidation of L-cysteine by the tetranuclear Mn oxidant at $[1^{4+}] = 0.1$ mM, $T = 25.0$ °C, $I = 1.0$ M (NaNO_3).

pH	T_R (M)	C_{bipy} (mM)	$10^3 k_0$ (s^{-1})
2.21	0.002	80.0	21.7
2.37	0.002	80.0	16.0
2.41	0.002	80.0	15.0
2.59	0.002	80.0	12.0
2.70	0.002	80.0	11.0
3.01	0.002	80.0	9.5
3.48	0.002	80.0	8.8
3.68	0.002	80.0	8.9
3.77	0.002	80.0	8.9
3.50	0.004	80.0	17.4
3.49	0.005	80.0	22.2
3.51	0.008	80.0	35.0
3.01	0.002	80.0	11.9 ^a
3.02	0.002	80.0	16.8 ^b

^a $I = 0.5$ M (NaNO_3).

^b $I = 0.1$ M (NaNO_3).

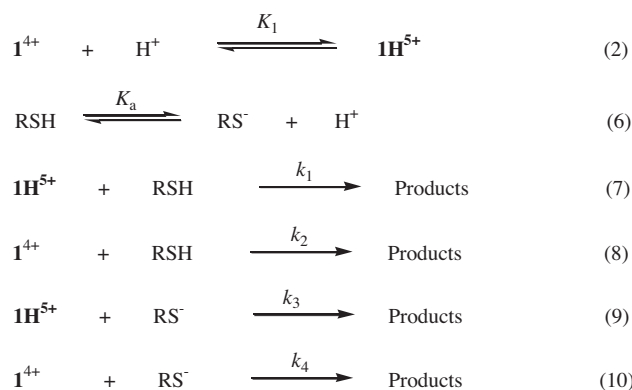
Scheme 1 leads to rate Eq. (5), approximating $K_1[\text{H}^+] \ll 1$.

$$k_0/[\text{mercap}] = k_1 K_1 [\text{H}^+] + k_2 \quad (5)$$

We propose Scheme 2, shown in Eqs. (6–10), along with Eq. (2) for the oxidation of tga and cys.

With the approximation $K_1[\text{H}^+] \ll 1$, Scheme 2 leads to rate Eq. (11).

$$k_0(K_a + [\text{H}^+])/T_R = k_1 K_1 [\text{H}^+]^2 + (k_2 + k_3 K_1 K_a)[\text{H}^+] + k_4 K_a \quad (11)$$



Scheme 2. (RSH = tga or cationic cys)

Fig. 2A shows plot of $k_0/[\text{mercap}]$ against $[\text{H}^+]$. Using Eq. (5), $k_1 K_1$ and k_2 values were evaluated (Table 5). The horizontal line parallel to the $[\text{H}^+]$ axis in Fig. 2A also shows that above pH c.a. 3.0, only the k_2 path describes the observed rate. Protonation of the oxo-bridges in the title Mn tetramer is thus believed to be effective below pH c.a. 3.0.

Non-linear least-squares solution of Eq. (11) yielded the values of $k_1 K_1$, $(k_2 + k_3 K_1 K_a)$ and k_4 for the oxidation of tga and cys (Fig. 2B and C). All such second-order rate constants or their composites in pure H_2O or in media enriched with D_2O are tabulated in Table 6. Fig. 2B and C show plots relevant to Eq. (11).

Tables 5 and 6 clearly demonstrate that 1H^{5+} is kinetically far superior to 1^{4+} in oxidizing the thiols as $K_1[\text{H}^+] \ll 1$ (that is, $K_1 \ll 1$, *vide infra*). The k_2 and k_3 paths for the oxidation of tga and cys cannot be resolved because they appear as a composite due to proton ambiguity. In fact, the very high reactivity of protonated oxo-bridged dinuclear Mn^{IV} species has been reported [13,33,34], and these species are quickly reduced to lower states in the presence of acids, illustrating that the Mn^{IV} oxidation level is destabilized upon protonation of the oxo-bridge. Table 6 shows that the maximum value of $k_3 K_1$ for the oxidation of cys is $\sim 5.3 \times 10^2 \text{ M}^{-2} \text{ s}^{-1}$ (using a $\text{p}K_a$ for cys of 2.05 and assuming the k_2 path is absent), which is smaller than $k_1 K_1$. It thus establishes an uncommon observation that RSH reacts quicker with 1H^{5+} than RS^- does – the protonated reductant is faster reacting than its conjugate base. For cys, RSH is a cationic species whereas RS^- is a neutral one. Stronger hydrogen bonding involving the protonated nitrogen center of the cationic RSH species than with the neutral RS^- species for cys with the oxo-bridges of the Mn oxidant, resulting in a close proximity of the redox agents, may be a reason for this difference in reactivity. Such a comparison does not appear reasonable for the oxidation of tga as here $(k_3 K_1)_{\text{max}}$ is much higher than $k_1 K_1$. It can, however, be commented that an almost invariant effect of the change of ionic strength on the mercap oxidation rate (Table 2) compared to a sufficient increase in the oxidation rates for cys and tga (Tables 3 and 4) on decreasing the ionic strength of the media supports the involvement of neutral mercap and cys but anionic tga species, as proposed in Schemes 1 and 2.

The inequality $K_1[\text{H}^+] \ll 1$ along with the $k_1 K_1$ values listed in Tables 5 and 6 set a range for K_1 between 10^{-9} and 1 M^{-1} . The fact that $K_1[\text{H}^+]$ is much less than 1 needs an upper limit for K_1 nearly at 1 M^{-1} as the maximum $[\text{H}^+]$ used in this study is c.a. 10^{-2} M , while assuming the diffusion control limit is $10^{11} \text{ M}^{-1} \text{ s}^{-1}$, the lower limit of K_1 estimated from the $k_1 K_1$ values listed in Tables 5 and 6 is c.a. 10^{-9} . Although it is not possible to have a more precise estimate of K_1 , a low value is anticipated as we got no UV–VIS spectral changes of the title Mn_4 complex in the pH range 1.5–4.0. Also, reports so

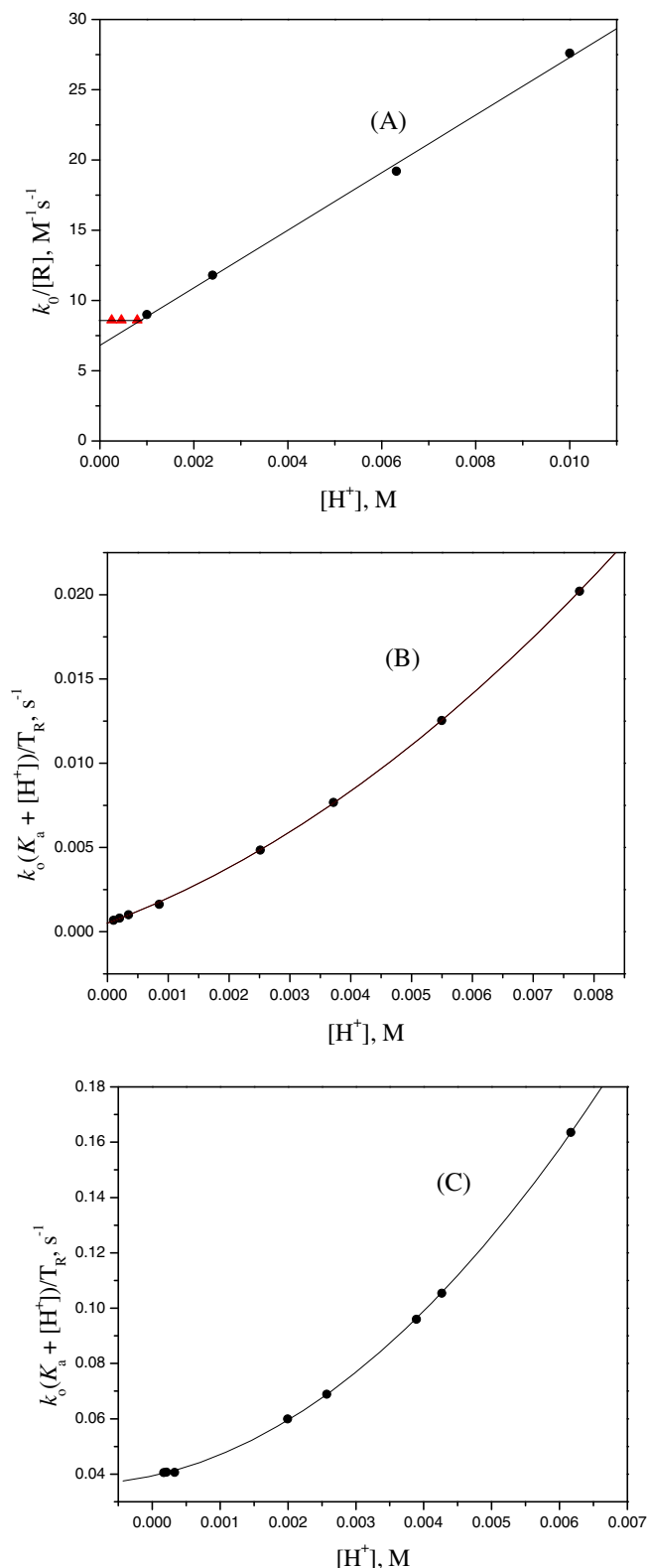


Fig. 2. Plot of the left-hand side of Eq. (5) vs. $[H^+]$. (A) Mercapto ethanol, $[T_R] = 1.0$ mM; left-hand side of Eq. (11) vs. $[H^+]$. (B) Thioglycolic acid, $[T_R] = 2.0$ mM. (C) L-Cysteine, $[T_R] = 2.0$ mM. $C_{bipy} = 80.0$ mM, $[complex] = 0.10$ mM, $T = 25.0$ °C, $I = 1.0$ M (NaNO₃) in all three plots.

far available for the very low basicities of oxo-bridges linked to high valent Mn₄ centers [18,30] support the approximations $K_1[H^+]$ and K_1 are both very small compared to 1. The strong acidity

Table 5

Second-order rate constants for the oxidation of mercapto ethanol by the tetranuclear Mn oxidant at $[1^{4+}] = 0.1$ mM, $T = 25.0$ °C, $C_{bipy} = 80$ mM, $I = 1.0$ M (NaNO₃).

Rate constants	Mercapto ethanol (H ₂ O) medium	Mercapto ethanol (95% D ₂ O) medium
k_1K_1 (M ⁻² s ⁻¹)	2050 ± 70	2435 ± 100
k_2 (M ⁻¹ s ⁻¹)	8.6 ± 0.04	6.2 ± 0.03

Table 6

Second-order rate constants for the oxidation of L-cysteine and thioglycolic acid by the tetranuclear Mn oxidant at $[1^{4+}] = 0.1$ mM, $T = 25.0$ °C, $C_{bipy} = 80$ mM, $I = 1.0$ M (NaNO₃).

Rate constants and its composites	L-Cysteine (H ₂ O medium)	Thioglycolic acid (H ₂ O medium)	L-Cysteine (95% D ₂ O medium)	Thioglycolic acid (95% D ₂ O medium)
k_1K_1 (M ⁻² s ⁻¹)	2405 ± 100	154 ± 6	1929 ± 60	770 ± 16
$(k_2 + k_3K_1K_a)$ (M ⁻¹ s ⁻¹)	5.28 ± 0.25	1.34 ± 0.06	7.69 ± 0.63	2.38 ± 0.14
k_4 (M ⁻¹ s ⁻¹)	4.40 ± 0.07	1.54 ± 0.12	1.30 ± 0.11	5.47 ± 0.43

of the protonated oxo-bridge in $1H^{5+}$ may thus be inferred. When the ligands ligated to Mn^{IV} centers are anionic and have strong donor ability, as compared to pyridine or related ligands like bipy, this leads to more electron density on the metal centers. Therefore, the oxo-bridges are not required to donate much electron density to the metal centers and a proton acceptor chemistry results. For example, the pK_a of $[Mn^{IV}_2(salpn)_2(\mu-O)(\mu-OH)]^+$ (salpn = 1,3-bis(salicylideneamino)propane) in H₂O is ca. 6 [13], whereas that for $[Mn^{IV}_4(\mu-O)_5(\mu-OH)(bpea)_4]^{5+}$ (bpea = N,N'-bis(2-pyridylmethyl)ethanamine) is ca. -6 [30]. This shows that the bridging oxo groups in the latter complex, compared to those we are using in this study, are much less 'proton hungry'.

3.4. Mechanism

The Mn^{IV}₄ to Mn^{II} reduction is an overall 8 electron transaction and must occur in steps. However, we observed that the decay of the title tetranuclear Mn oxidant follows a pure first-order kinetics, perhaps indicating a single rate-limiting step in the overall reaction. An initial one electron transfer rate step may be proposed which results in the formation of the mixed valent Mn^{IV}₃Mn^{III} species, and the follow-up steps leading to the end-product Mn^{II} are fast. The rapid redox decomposition of the mixed-valent Mn^{IV}₃Mn^{III} species is expected because the most likely one-electron reduced species of 1^{4+} , viz. $[Mn^{IV}_3Mn^{III}(\mu-O)_6(bipy)_6]^{3+}$ is very unstable, even at 190 K. The very high reactivity of this species, produced from the cryogenic radiolytic reduction of 1^{4+} , has been documented [70]. Moreover, during the conversion of 1^{4+} to Mn^{II}, tri- or dinuclear Mn species that might be generated could bear a number of water molecules bound to the Mn centers, and such aqua complexes are known to be very reactive in their redox chemistry [71–74].

The electrochemistry of the title Mn tetramer has been extensively studied by Dunand-Sauthier [75–78] and Girerd [44]. The cyclic voltammogram of 1^{4+} in Hbipy⁺/bipy buffers shows only an irreversible peak near at 0.40 V versus Ag/AgCl, leading to the formation of $[Mn(bipy)_3]^{2+}$ species [75–78]. Standard chemical reduction in solution also failed to generate the mono-reduced form [44]. All such facts clearly establish the very high reactivity of the one-electron reduced species of 1^{4+} . An initial one-electron transfer rate step results in the formation of the highly reactive mixed-valent Mn^{IV}₃Mn^{III} species, and it may thus be proposed that this species is likely to be reduced very quickly in solution by the excess reducing agents.

In order to further explore the electron-transfer mechanism, the kinetics were repeated in media enriched with D₂O. The first-order rate constants and the second-order rate constants or their com-

posites (Tables 5 and 6) were determined in the same way as those in pure H₂O, and the results clearly establish kinetic isotope effects in these reactions. The k_0 values in D₂O media for the oxidation of all three thiols are tabulated in ESI (Tables S5–S7). The lowering of rate in D₂O enriched media in comparison to that in pure H₂O media supports the occurrence of an electroprotonic mechanism [79–83].

Table 6 clearly shows that the naked second-order rate constant k_4 is lowered in D₂O enriched media for cys oxidation, whereas it is increased for the tga reaction. For the mercap oxidation, the pure second-order rate constant k_2 is decreased in D₂O enriched media, although the composite k_1K_1 increases. Also, for the composite constants, like k_1K_1 or $(k_2 + k_3K_1K_a)$, it is found that both are increased in D₂O for tga oxidation, whereas for the cys reaction, k_1K_1 decreases but $(k_2 + k_3K_1K_a)$ increases in D₂O. We believe the relative values of K_1 in H₂O and in D₂O enriched media are responsible for this scattered effect. It is known that D₂O has a smaller autoprotolysis constant than H₂O by a factor of 5 [84] and thus it is less basic than H₂O, which means that the oxo-bridges in the title oxidant will be able to compete with the solvent for the D⁺ ion in D₂O more effectively than for the H⁺ ion in H₂O. An increase in the K_1 value (Scheme 1 or 2) is thus expected in D₂O media. In support, we may recall that weak acids in H₂O become weaker in D₂O [84–90]. There are precedences in the literature [84–86] that rates increase significantly with D₂O content in an H₂O/D₂O mixture if acid–base pre-equilibrium steps are involved prior to the rate steps [84–86]. Occasional the reversal of composite values in Table 6 in D₂O media could thus be explained.

Interestingly, we find that the pure rate constant (k_4) increases in D₂O media (for tga oxidation) – a situation never encountered in the kinetics and reaction mechanism of multinuclear Mn systems. Deprotonated tga suffers a tautomeric equilibrium in aqueous solution:



Although the magnitude of K_1 has not been reported, from the known values of $\text{p}K_{a1}$ and $\text{p}K_{a2}$ of tga and the approximation that the two acid groups do not interact with each other very strongly, a value of about 7 is predicted for $\text{p}K_1$, and hence the equilibrium should lie far to the left [48].

Since the disulfide is the product detected for tga oxidation in this work and for all reactions leading to the disulfide product an S-centered oxidation was proposed [48,49], we propose a first electron capture from the sulfur center as the rate step. Thus it may be concluded that SCH_2COOH should be faster reacting than $\text{HSCH}_2\text{COO}^-$. Moreover, the less electronegative S atom (than O atom) favors the redox site. If SCH_2COOH has a greater concentration in D₂O than in H₂O, then we can expect an increase in rate in D₂O in comparison to that in H₂O.

It is known that D₂O has a smaller autoprotolysis constant than H₂O and thus D₂O is less basic than H₂O [84]; the acidity of any weak acid decreases in D₂O [33,34,52,64]. However, this decrease in acidity for an O–H bond will be greater than an S–H bond [91]. The relatively small magnitude of the isotope effect for the ionization of thiol acids is expected as a consequence of the low stretching and bending frequencies of the S–H bond [64]. Thus the species SCH_2COOH has a greater abundance in D₂O medium than in H₂O which explains the enhancement in rate in D₂O media.

Moreover, we observed that the increase in rate of tga oxidation in H₂O–D₂O mixed media varies linearly with the D₂O content of the media (Fig. 3B). However, the other two thiols (cys and mercap) show a decrease in rate in the mixed media and the decrease is linearly related to the D₂O content (Fig. 3A and C), suggesting transfer of a single proton [92,93] as the rate step of both reactions.

As discussed above, an initial one-electron transfer rate step results in the formation of a highly reactive mixed-valent Mn species, $\text{Mn}^{\text{IV}}_3\text{Mn}^{\text{III}}$, that is reduced quickly in solution by the excess reduc-

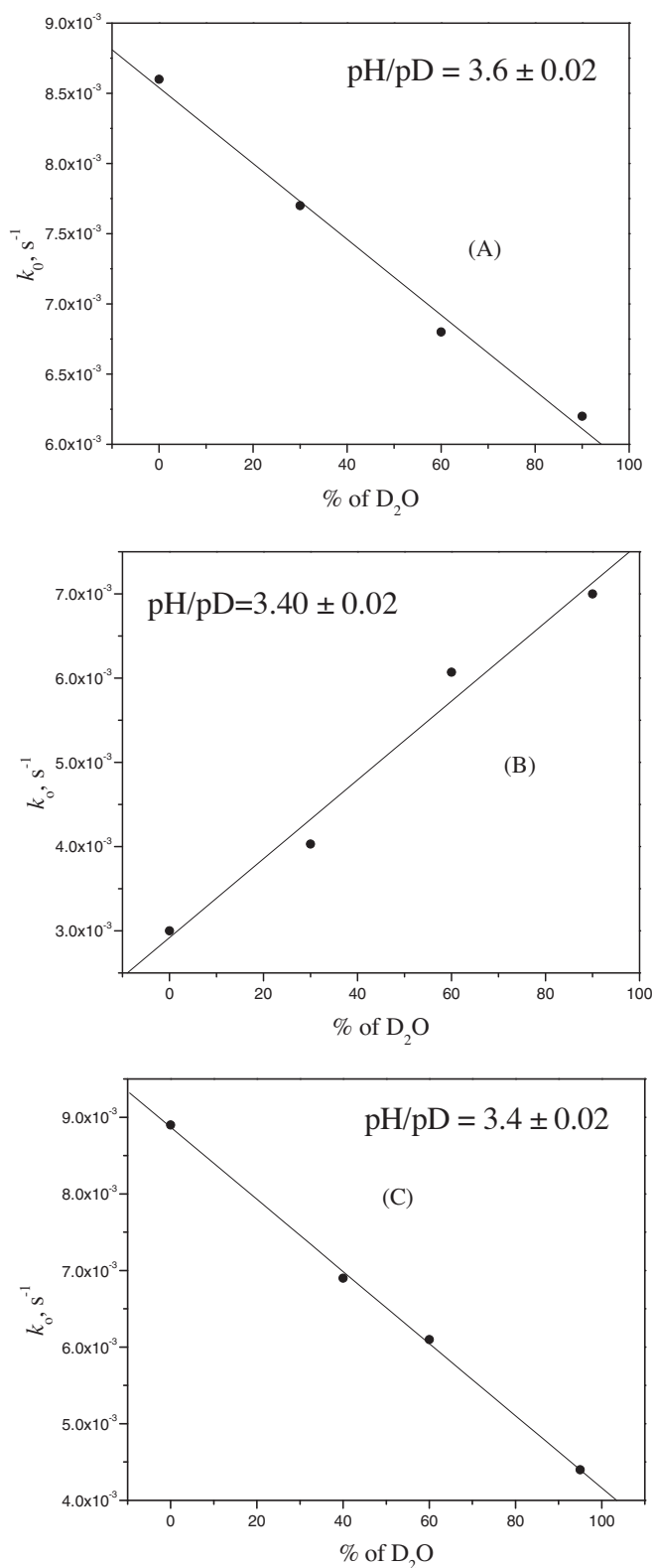


Fig. 3. Effect of the amount of D₂O (mol-%) on k_0 . [complex] = 0.10 mM, T = 25.0 °C, I = 1.0 M. (A) Mercapto ethanol, [T_R] = 1.0 mM, C_{bipy} = 80.0 mM. (B) Thioglycolic acid, [T_R] = 2.0 mM, C_{bipy} = 80.0 mM. (C) L-Cysteine, [T_R] = 2.0 mM, C_{bipy} = 80.0 mM.

ing agents. The one-electron reduced species of **1**⁴⁺ or **1H**⁵⁺ must have much more basic oxo-bridges in comparison to the oxo-bridges in **1**⁴⁺ or in **1H**⁵⁺, which immediately accept a proton from the reaction media thus removing thermodynamic or kinetic barriers to further reduction [94,95]. Results of our recent DFT studies

clearly established a substantial increase in the negative charge on the oxo-bridges of one-electron reduced species of 1^{4+} or $1H^{5+}$ [35]. A large increase in basicity of the oxo-bridges in the one electron reduced mixed-valent di- or polynuclear Mn species is well documented, [95,96] and is a key feature in the sequential redox steps of the Kok cycle in PS II [37,97]. An analogous situation is also seen for the μ -oxo diiron(III) species [95,96,98–108].

Among the four six coordinate Mn^{IV} centers in the title complex, the two terminal Mn atoms are equivalent in the sense that each is ligated to two bipy ligands along with two oxo ligands, whereas each of the two equivalent middle (central) Mn atoms are ligated to four oxo atoms and one bipy ligand (Fig. 1). Recently, we have conclusively established using DFT studies [35] that one of the two terminal Mn(IV) atoms is reduced to Mn(III) instead of a central Mn(IV) atom when one-electron is added to the tetranuclear Mn(IV) system, 1^{4+} or $1H^{5+}$. The one-electron rate steps (k_1 to k_4) shown in Schemes 1 and 2 should thus involve either of the two terminal Mn atoms.

The observed overwhelming dominance of $1H^{5+}$ over 1^{4+} in the kinetics (Tables 5 and 6) may be due, at least in part, to its more oxidizing nature than 1^{4+} because of one extra unit of cationic charge. Our recent DFT studies [35] showed that on protonation of 1^{4+} (that is in $1H^{5+}$) the covalent bond between one Mn(IV) and the oxygen atom of the OH group is broken which generates a somewhat 'opened' Mn(IV) center, leading to a unsaturated metal center that must be more reactive. In some known Mn^{IV} compounds with oxo- and hydroxo-bridges, crystallographic data show that Mn–OH bond distances are substantially larger than Mn–O distances [14], indicating an increase in reactivity of the Mn center connected to this protonated oxo-bridge (Mn–OH). In fact, we have observed much higher reactivity of $1H^{5+}$ over 1^{4+} in oxidizing α -keto acids [34], ascorbate and hydroquinone [35]. The optimized geometries of both $1H^{5+}$ and 1^{4+} and the one-electron reduced product $1H^{4+}$ show no covalency between one of the Mn atoms of the tetranuclear oxidant and the protonated oxygen [35], indicating a somewhat 'opened' Mn center with increased reactivity, and cluster break-up is anticipated. In fact, the chemistry of multi-nuclear Mn complexes are characterized by oxo-bridge protonation and its effects, like increased reactivity including cluster break-up, [17] inhibition of catalase activity [28] and commencement of disproportion [16].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.poly.2012.07.011>.

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