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OXIDATION OF EXOGENOUS SUBSTRATES BY THE O_2-EVOLVING CENTER OF PHOTOSYSTEM II AND RELATED CATALYTIC AIR OXIDATION OF SECONDARY ALCOHOLS VIA A TETRANUCLEAR MANGANESE(IV) COMPLEX

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Abstract: The O_2-evolving center of Photosystem II (PSII) contains a tetranuclear Mn complex that acts as the catalyst for photosynthetic H_2O oxidation. The catalytic cycle for H_2O oxidation is thought to involve the light-driven generation of a very strongly oxidizing state of the Mn complex prior to the formation of the O-O bond. However, the Mn complex also exhibits oxidation chemistry in its lower oxidation states. Exogenous ligands, such as primary amines and hydroxylamines, have been shown previously to interact with the O_2-evolving center in the dark S_1 oxidation state by coordinating to a Cl^--binding site near the Mn complex. In this paper, we present evidence that primary and secondary amines irreversibly inactivate the Mn complex in the S_1 state by a reductive mechanism, leading to the liberation of Mn(II) ions and a concomitant loss of O_2-evolution activity. Hence, the Mn complex in the O_2-evolving center acts as a strong oxidant even in the dark-stable S_1 state. The synthetic tetranuclear Mn(IV) complex $[(TACN)_4Mn_4O_6]Br_4$, which has been suggested as a model for the Mn complex in the O_2-evolving center, is a strong oxidant as well. We find that it catalyzes the air oxidation of secondary alcohols to ketones and triphenylphosphine to triphenylphosphine oxide.

Introduction

The selective, metal-catalyzed oxidation of organic molecules is an area of continuing interest among synthetic chemists.[1] Of the many efficient transition-metal based oxidation systems known, those involving high-valent Mn ions are among the most numerous and well-studied.[2a] Permanganate oxidations of secondary alcohols to ketones, aldehydes to carboxylic acids, olefins to diols and the hydroxylation of benzylic and tertiary C-H bonds have been documented. MnO_2 oxidizes allylic and benzylic alcohols to α,β-unsaturated carbonyl compounds, and Mn(III) acetate is an effective reagent for the oxidation of alkenes to γ-lactones and for the radical acetoxylation of arenes.[2b] Also, several groups have recently reported the biomimetic oxygen-atom transfer oxidation of alkenes using Mn(III) porphyrin and related compounds.[3]

Mn also plays an essential role in plant biochemistry. A tetranuclear Mn complex in the O_2-evolving center of photosystem II (PSII) acts as the catalyst for photosynthetic H_2O oxidation.[4] The catalytic cycle involving the Mn complex is characterized by five intermediate oxidation states S_i, where i represents the number of stored

oxidation equivalents.[5] It has been suggested that coordination of substrate H_2O molecules to the Mn complex occurs only after the S_3 state is formed,[6,7] and the O-O bond is likely to be formed only after formation of the highest oxidation state, S_4.[8,9] However, the Mn complex can oxidize hydroxylamine,[10,11] hydrazine,[12] and hydrogen peroxide[13] in the S_1 and S_2 states. The mechanism for the oxidation of these compounds is proposed to involve a series of dark two-electron reactions leading to reduction of the Mn complex to a configuration containing labile Mn(II) ions.[14] Hydroxylamine and related compounds bind in the O_2-evolving center to the Cl^--binding site rather than to the substrate H_2O-binding site prior to reaction with the Mn complex .[14b]

Mn ions are also displaced from the O_2-evolving center by alkaline tris(hydroxymethyl)aminomethane (Tris) treatments.[15-18] The mechanism for the Tris-induced inactivation of the Mn complex is not known, though chelation of functional Mn ions by Tris molecules, leading to disruption of the Mn complex and eventual release of Mn(II) ions, has been considered as a possibility. We have found that Tris is not unique in having this inhibitory property; we show in this paper that treatment of the dark-stable S_1 state with several primary amines and a secondary amine results in irreversible inhibition of O_2-evolution activity. The amines probably reduce the Mn complex to a super-reduced oxidation state containing labile Mn(II) ions, which subsequently are released from the O_2-evolving center. In view of evidence that the rate of the amine inhibition depends inversely on the Cl^- concentration, the mechanism is likely to be similar to that involved in the liberation of Mn(II) ions by hydroxylamine.

We have also examined the possibility that synthetic tetranuclear high-valent Mn complexes might catalyze oxidative transformations. We report preliminary results showing that a tetranuclear Mn(IV) model for the Mn complex in the O_2-evolving center catalyzes the air oxidation of secondary alcohols.

Materials and Methods

O_2-evolving preparations of PSII-enriched membranes were isolated from market spinach leaves by using a modified version of the Berthold, Babcock, and Yocum procedure,[19] as described previously.[20] PSII membranes were stored at 77 K suspended at 5-10 mg chlorophyll/mL in a buffer solution containing 20 mM 2-(N-morpholino)ethanesulfonic acid (MES)-NaOH, pH 6.0, 15 mM NaCl, and 30% (v/v) ethylene glycol. All steps in the isolation procedure and subsequent handling of PSII membranes were performed under a green safe light. This procedure afforded extensively dark-adapted PSII membrane preparations,[20] insuring that the O_2-evolving centers were poised in the S_1 state prior to treatment with reagents.[21] Chlorophyll concentrations were determined spectrophotometrically by the method of Arnon.[22]

O_2-evolution rates were measured at 25.0 °C with the apparatus described previously.[20] Assays consisted of a suspension of PSII membranes at 2.5 μg chlorophyll/mL in a buffer solution containing 20 mM MES-NaOH, pH 6.0, 5 mM $CaCl_2$, 2.5 mM sodium ferricyanide, and 250 μM 2,5-dichloro-*p*-benzoquinone.

Rates for the irreversible inhibition of O_2-evolution activity by amines were obtained by assaying the O_2-evolution activity of aliquots of an amine-treated PSII membrane suspension during a seventy-minute incubation period at 0 °C in complete darkness. The treated PSII membrane suspension (0.5 mg chlorophyll/mL) contained 0.8 M of the indicated amine and 20 mM MES, pH 8.0. Owing to the 2000-fold dilution of the amine and the lower pH in the O_2-evolution assay suspension, the residual amines had no effect on the measured O_2-evolution rates.

Results and Discussion

Irreversible Inhibition of Photosynthetic O_2-Evolution Activity by Amines. Cheniae and Martin[15] first showed that treatment of spinach thylakoid membranes with Tris under alkaline conditions resulted in inhibition of O_2-evolution activity and the release of about four Mn ions, providing early evidence that a Mn complex is the catalytic site for photosynthetic H_2O oxidation. Lozier *et al.*[23] demonstrated that the Mn ions freed by the alkaline Tris treatment were detectable by electron paramagnetic resonance (EPR) spectroscopy at room temperature; a six-line spectrum characteristic of $Mn(H_2O)_6^{2+}$ was observed. Since it is likely that the S_1 state contains four Mn(III) ions,[4] release of Mn(II) ions as a result of alkaline Tris treatment requires a reduction of the Mn complex. In the presence of Tris, O_2-evolution activity is lost more rapidly under illumination than in complete darkness;[16,17,24] work by Frasch and Cheniae[17] showed that the S_2 state in particular reacts much more rapidly with Tris than does the S_1 state. These results suggest that Tris is oxidized by the Mn complex, producing a reduced state of the Mn complex that releases Mn(II) ions.

In order to examine the mechanism of Tris's action on the S_1-state Mn complex, we measured the rate at which O_2-evolution activity was lost in dark-adapted PSII membranes when treated with one of several amines, at pH 8.0. Figure 1 shows that exposure of PSII membranes to 0.8 M NaCl for seventy minutes at 0 °C in complete darkness results in a negligible loss of O_2-evolution activity; however, activity was slowly lost irreversibly in PSII membranes treated with 0.8 M ethanolamine, $(CH_3)_2NH$, or Tris. Similar behavior was observed when PSII membranes were treated with 2-amino-2-ethyl-1,3-propanediol (AEPD), NH_3, or CH_3NH_2 (not shown). The loss of activity in the presence of each of the amines could be well described by a single-exponential rate function, as indicated by the examples in Figure 1.

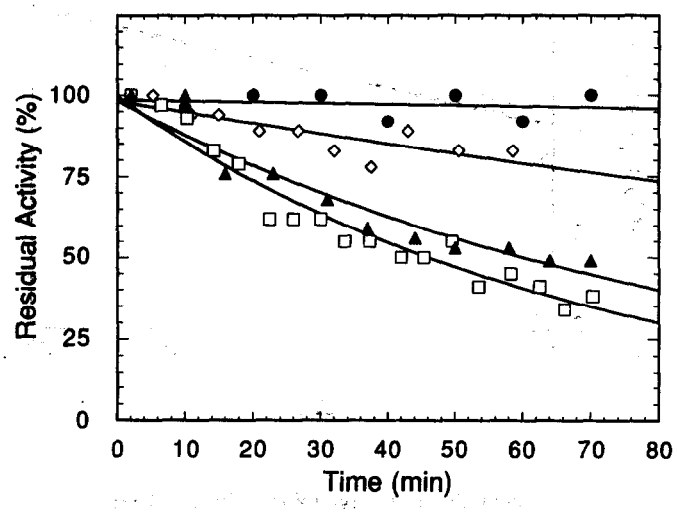


Figure 1. Time course for irreversible inhibition of O_2-evolution activity in PSII membranes treated with 0.8 M NaCl (●), 0.8 M ethanolamine (▲), 0.8 M dimethylamine (◇), or 0.8 M Tris (□) at pH 8.0, 0 °C, and in darkness. The activities are normalized with respect to the activity recorded after a 2 min incubation. The solid lines through the data points were obtained by least-squares regression to the equation $A(t) = 100 \exp(-k t)$, where A(t) is the residual activity at time t and k is the rate constant for irreversible inhibition.

Table I
Rates for Irreversible Inhibition of O_2-Evolution Activity in the S_1 State by Amines

Amine	pK_a	k_{obs}, $M^{-1}s^{-1}$	Rank
Tris	8.06	0.625×10^{-3}	6
AEPD	8.80	1.14×10^{-3}	5
NH_3	9.25	2.08×10^{-3}	4
ethanolamine	9.50	7.38×10^{-3}	3
CH_3NH_2	10.62	8.61×10^{-3}	2
$(CH_3)_2NH$	10.77	44.4×10^{-3}	1

Table I compares the observed second-order inhibition rate constant, k_{obs}, obtained with each of the amines studied. Note that the free base form of the amine has been identified as the active species in both reversible and irreversible inhibition of O_2-evolution activity by amines;[25] hence, the measured k values have been scaled by the calculated concentration of free base present in the amine-treatment buffer solution at pH 8 to obtain k_{obs}. The analogous rate constants for the reduction of the Mn complex from the S_1 state to the S_{-1} state by hydroxylamines are, on the average, larger than the rate constants shown in Table I by three orders of magnitude.[14]

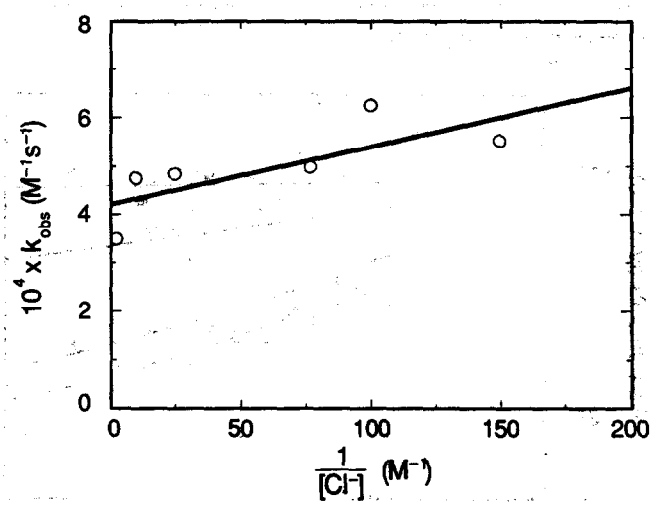


Figure 2. Rates for the irreversible inhibition of O_2-evolution activity in PSII membranes treated with 0.8 M Tris at pH 8.0, 0 °C, and in darkness, plotted as a function of the reciprocal of the Cl^- concentration. The second-order rate constant, k_{obs}, was obtained by dividing the measured rate constant, k, obtained as shown in Figure 1, by the calculated free-base amine concentration at pH 8.0.

Inverse Cl^- concentration dependences have been previously noted in the *reversible* inhibition of O_2-evolution activity by amines at lower concentrations and less basic media,[25] in the *irreversible* inhibition of O_2-evolution activity caused by treatment of the S_1 state with hydroxylamine,[26] and in the rate at which hydroxylamines reduce the Mn complex from the S_1 state to the S_{-1} state.[14b] Therefore, we have examined the Cl^- concentration dependence for the irreversible inhibition of O_2-evolution by amines. Figure 2 shows that a linear trend is indicated by a plot of the observed rate constant, k_{obs}, for inactivation in the presence of Tris as a function of the reciprocal of the Cl^- concentration. Similar results were obtained for ethanolamine and AEPD (data not shown). By analogy with the conclusions of Sandusky and Yocum,[25] our results indicate that the irreversible inhibition of the O_2-evolving center by the amines involves the Cl^--binding site. The present results do not determine the mode of competition between amines and Cl^-; that the rate of amine-induced irreversible inhibition is apparently not zero at very high Cl^- concentrations (Figure 2) may implicate additional binding sites for amines near the Mn complex, possibly including the H_2O-binding site(s).

A variation of a simple redox model, proposed previously to account for the reaction of hydroxylamine and related compounds with the Mn complex in the S_1 state,[14] can explain the irreversible inhibition of O_2-evolution activity by amines. We propose that an amine molecule binds in competition with Cl^- to the site at which Cl^- functions as a cofactor in the H_2O-oxidizing reaction (equation 1). After binding, the amine is oxidized by the Mn complex, forming a hydroxylamine molecule as a product (equation 2).

$$S_1(Cl^-) + RNH_2 \overset{K_{eq}}{\rightleftharpoons} S_1(RNH_2) + Cl^- \quad (1)$$

$$S_1(RNH_2) + H_2O \xrightarrow{k_1} S_{-1}(RNHOH) + 2\,H^+ \quad (2)$$

The equilibrium in equation 1 simply scales the concentration of the reactive, bound amine species. The bound hydroxylamine species produced in equation 2 is capable of reducing the Mn complex further, producing a nitroso compound and the hypothetical, labile S_{-3} state.[14]

$$S_{-1}(RNHOH) \xrightarrow{k_2} S_{-3} + RHNO^+ + H^+ \quad (3)$$

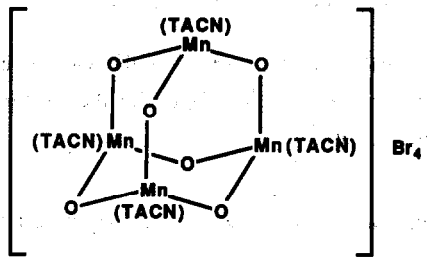
While the S_{-1} state is stable and can be reoxidized to higher S states, leading eventually to oxidation of H_2O,[14] the Mn complex in the S_{-3} state would be irreversibly disabled owing to release of Mn(II) ions. That the inhibition rates show a dependence on the Cl^- concentration implies that equation 3 is not the rate-limiting step under our conditions.

Since the *reversible* inhibition of O_2-evolution activity by amines occurs at amine concentrations much lower that those employed in the experiments reported here,[25] the displacement of Cl^- from sites near the Mn complex by the binding of an amine molecule can inhibit the turnover of the Mn catalyst without resulting in a high rate of Mn reduction only if equation 2 is the rate-limiting step. In the limiting case in which $k_2 \gg k_1$, the observed single-exponential rate constant, k_{obs}, is defined in terms of K_{eq} and k_1 by equation 4.

$$k_{obs} = k_1 K_{eq} \frac{1}{[Cl^-]} \quad (4)$$

Note that k_{obs} appears to increase with increasing basicity of the amine (Table 1), suggesting that the equilibrium constant for the binding of the amine in the S_1 state (equation 1) dominates the observed rates for the reductive inactivation of the Mn complex. This observation, taken together with evidence from low-temperature EPR measurements that amines are more tightly bound in the S_2 state than in the S_1 state,[27] might account for the more rapid loss of O_2-evolution activity in the presence of alkaline Tris when the S_2 state is present.[17] A similar explanation is consistent with the observation that reactions of H_2O_2 and hydroxylamines occur more rapidly in the S_2 state than in the S_1 state[13,14,28] and with the recently reported effects of H_2S on the O_2-evolving center.[29] The tighter binding of ligands in the S_2 state reflects the probable role of Cl^- in the H_2O-oxidation cycle;[25,30] in the absence of Cl^-, the S_3 state cannot be formed in a stable manner from the S_2 state.[30] We have previously proposed that the presence of Cl^- is required so that substrate H_2O molecules can bind to an especially electron-deficient form of the Mn complex in the S_3 state.[7]

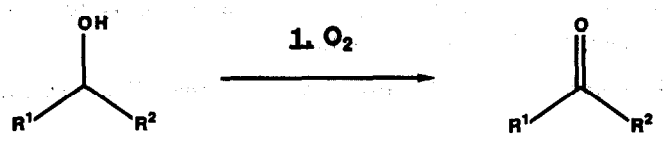
Oxidation of Secondary Alcohols by Model Mn Complexes. Several groups have reported the synthesis and structural characterization of tetranuclear Mn complexes that represent the initial models for the Mn complex in the O_2-evolving center.[31,32] We now consider the possibility that these complexes can catalyze the oxidation of organic substrates. Our initial experiments focused upon the use of Wieghardt's tetranuclear Mn(IV) complex $[(TACN)_4Mn_4O_6]Br_4$, **1** (TACN = 1,4,7-triazacyclononane),[33] because it is easily formed with air as the sole oxidant.



1

As a probe to determine whether aerobic re-oxidation is possible, we found that complex **1** catalyzes the oxidation of triphenylphosphine to triphenylphosphine oxide in refluxing acetonitrile under a stream of air at a rate of 38.4 turnovers in 16 hours. Other sources of high-valent Mn appeared to be less active as catalysts: Mn(III) acetate hydrate gave only 7.8 turnovers under identical conditions. This suggests that the phosphine oxidation proceeds via an atom transfer rather than electron transfer mechanism. Similarly, Mn(II) or (III) acetate plus one equivalent of TACN produced only traces of phosphine oxide. The dimeric complex, $[(TACN)_2Mn(III)_2(\mu\text{-}O)(\mu\text{-}OAc)_2]^{2+}$, which forms under these conditions,[34] must therefore be catalytically inactive, possibly due to increased steric hindrance at the bridging oxygen site. No phosphine oxide was formed in the absence of catalyst.

Other substrates are also oxidized by complex **1**. Cyclohexanol and 1-phenylethanol are oxidized to the ketones in refluxing acetonitrile (equation 5), at rates of 25.1 turnovers/25 hours and 13.5 turnovers/20 hours, respectively.[35]



(5)

$R^1, R^2 = (CH_2)_5$

$R^1 = Ph, R^2 = CH_3$

The oxidation of secondary alcohols by Ru(IV)-oxo complexes by a hydride transfer mechanism has been reported;[36] such a mechanism may be operative in the present case. Cyclooctane, cyclooctene and ethylbenzene are inert under the reaction conditions.

Although many methods exist for the oxidation of secondary alcohols to ketones,[2a] air oxidations of organic compounds are rather rare; Shapley has recently reported similar air oxidation of alcohols to carbonyl compounds using a binuclear osmium(VIII)-chromate complex.[37]

Conclusions

Our results indicate that amines are oxidized by the O_2-evolving center in the S_1 state, producing a labile, super-reduced state of the Mn complex that releases Mn(II) ions. The rate of reaction is inversely dependent on the Cl^- concentration. Therefore, in addition to its probable role in the substrate H_2O-binding step,[7] Cl^- may also act as a cofactor for the photosynthetic H_2O-oxidation reaction by impairing the access of oxidizable substrates other than H_2O to the Mn complex. We are currently examining the implications of these results with respect to the structure and ligation of the Mn complex and the location of the Cl^- and substrate H_2O binding sites.

In the related area of oxidation of organic molecules by synthetic models for the Mn complex in the O_2-evolving center, we believe that the use of powerful electron-donor ligands, which are known to promote the facile air-oxidation of Mn(II) to higher oxidation states,[38] may lead to the discovery of efficient, synthetically useful catalysts for organic oxidations. We are currently investigating the scope of this and other catalytic systems for this purpose.

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35. Experimental procedure: A solution of cyclohexanol (422 mg, 4.3 mmol) and **1** (5.0 mg, 0.043 mmol, 0.008 equiv) was refluxed in 20 mL of acetonitrile under a slow stream of house compressed air, bubbled through via a pipette, for 20 h. The resulting homogeneous solution was diluted with ether, extracted with water (3 x 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The yield of cyclohexanone was determined using gas-liquid chromatography.

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