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Mechanism of Alkene, Alkane and Alcohol Oxidation with H₂O₂ by an in situ prepared Mn^{II}/ Pyridine-2-Carboxylic Acid Catalyst

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ABSTRACT: The oxidation of alkenes, alkanes and alcohols with H_2O_2 is catalyzed efficiently using an in situ prepared catalyst comprising of a Mn^{II} salt and pyridine-2-carboxylic acid (PCA) together with a ketone in a wide range of solvents. The mechanism by which these reactions proceed is elucidated, with a particular focus on the role played by each reaction component, i.e. ketone, PCA, Mn^{II} salt, solvent etc. It is shown that the equilibrium between the ketone co-catalysts, in particular butanedione, and H_2O_2 is central to the catalytic activity observed and that a gem-hydroxyl-hydroperoxy species is responsible for generating the active form of the manganese catalyst. Furthermore the oxidation of the ketone to a carboxylic acid is shown to antecede the onset of substrate conversion. Indeed addition of acetic acid either prior to or after addition of H_2O_2 eliminates a lag-period observed at low catalyst loading. Carboxylic acids are shown to affect both the activity of the catalyst and the formation of the gem-hydroxyl-hydroperoxy species. The molecular nature of the catalyst itself is explored through the effect of variation of Mn^{II} and PCA concentration, with the data indicating that a Mn^{II} :PCA ratio of 1:2 is necessary for activity. A remarkable feature of the catalytic system is that the apparent order in substrate is zero indicating that the formation of highly reactive manganese species is rate limiting.

KEYWORDS. manganese, oxidation, catalysis, Raman spectroscopy, epoxidation.

Introduction

Catalytic systems for the oxidation of alkenes to epoxides or cis-diols and for C-H and alcohol oxidation, based on 1st row transition metals, continue to attract substantial attention,¹ not least those systems that use the atom economic and environmentally friendly terminal oxidants O₂ and H₂O₂. Manganese² and iron³ based catalysts, due to negligible toxicity and environmental impact, have seen rapid progress in terms of cost and reactivity. The development of new ligand systems to control reactivity and selectivity has focused most notably on polyalkyl amine/pyridyl frameworks, e.g., the 1,4,7-triazacylononane⁴ and pyridyl-amine based ligand families (*e.g.*, TPA, TPEN, TPTN).⁵

Over the last two decades, manganese complexes of the pyridyl-amine based ligand families (**Figure 1**) have been applied to a wide range of oxidative transformations.^{6,7} Although, many of these complexes showed good activity in the epoxidation of alkenes, they presented severe limitations in regard to application. Most critically, 8-10 equiv. of H_2O_2 w.r.t. substrate were required. This inefficiency was due to extensive H_2O_2 disproportionation during a lag period that preceded the oxidation of organic substrates.⁸ Furthermore, these catalyst systems were active only in ketone based solvents such as acetone, which presents additional risks in oxidations with H_2O_2 .



Figure 1. Ligands discussed in the text and conversion of pyridyl-amine based ligands to pyridine-2-carboxylic acid (PCA) under oxidizing conditions.^{9,10}

Later mechanistic studies by our group revealed that during the lag period pyridyl-amine ligands, such as TPEN, and its aminal precursors, underwent oxidative degradation to pyridine-2-carboxylic acid (PCA)

(Figure 1).¹⁰ It was, in fact, the PCA formed through ligand degradation, together with manganese and a ketone that was responsible for the catalytic activity and selectivity observed. Indeed, where PCA was used in place of the more complex ligands, the efficiency with respect to H_2O_2 became essentially

complete with elimination of the wasteful disproportionation of H_2O_2 .

The catalytic system based on Mn^{II}/PCA that was discovered through these mechanistic studies still presented the disadvantage that ketone solvents were necessary for activity to be observed.¹⁰ Subsequently, it was found that ketones such as acetone and CF₃COCH₃ could be used as co-solvents,¹¹ and in particular, that butanedione¹² could be used substoichiometrically. In addition, with sub-stoichiometric butanedione the reaction times were reduced dramatically from several hours to several minutes, in comparison to reactions carried out in acetone. Furthermore, the use of a ketone substoichiometrically enabled the application of this system in a wide range of polar protic and aprotic solvents, e.g., ethanol and acetonitrile (Scheme 1).



Scheme 1. Oxidation of alkenes, alkanes and alcohols using an in situ prepared Mn^{II}/PCA catalyst system.^{11,12}

The preparation of catalysts in situ from readily available components is advantageous as it circumvents the need for prior ligand and catalyst synthesis. The in situ formed catalyst system based on PCA, a Mn^{II} salt and a base (e.g., NaOH, NaOAc, etc.), together with a ketone, either as solvent or co-solvent, enabled high turnover numbers (>300,000) and turnover frequencies (40 s⁻¹) to be achieved in the epoxidation and cis-dihydroxylation of alkenes^{11,12} and in alcohol and C-H bond oxidation¹³ with H₂O₂. The system provides good to excellent multigram conversions and yields, as well as a broad functional group tolerance.

Despite that the catalyst system is prepared in situ, it was apparent that the mechanism by which it works is complex. From UV/Vis absorption, ¹³C NMR and Raman spectroscopy it was apparent that the ketone forms a gem-hydroxy-hydroperoxy species (Scheme 2), which is essential to the generation of the active (oxidizing) form of the catalyst.¹²



Scheme 2. Equilibrium between butanedione/H₂O₂ and 3-hydroperoxy-3-hydroxybutanone.

Furthermore, initial mechanistic studies established¹² that the ketones, i.e. acetone, butanedione, undergo oxidation to yield carboxylic acids also; i.e. acetic acid in the case of butanedione and acetone. Notably, however, the deliberate addition of acetic acid did not affect the conversion and selectivity of the reaction,¹² and the in situ formation of peracetic acid was excluded. These observations raise questions regarding the role, if any, of the acetic acid formed during the reaction and indeed the effect of carboxylic acids on the reaction in a general sense.

In this contribution, the mechanism by which Mn^{II}/PCA in combination with butanedione and a base engages in the catalyzed oxidation of alkenes, alkanes and alcohols with H₂O₂ is explored. The high activity and low catalyst loadings required and the absence of spectroscopic signals assignable to manganese species involved in this system (e.g., by EPR or UV/Vis spectroscopy)¹² means that direct identification of the 'active species' or even the catalyst in its resting state is impractical.¹⁴ Nevertheless, insight into the role of each reaction component can be gained through reaction progress monitoring, from which a global mechanistic understanding of the reaction emerges. The aim is not to propose a microkinetic description of the catalytic system but instead to rationalize the empirical observations made with regard to all reaction components and hence to establish the understanding needed to facilitate rapid optimization of reaction conditions.

Results

Although the Mn^{II}/PCA catalyst system shows a broad substrate scope, including alkene, alcohol and alkane oxidation, alkenes undergo oxidation preferentially. Furthermore, it is expected that a common active oxidant is responsible for all three transformations. Hence, cyclooctene, styrene, 1phenyethanol and 3-vinyl-benzaldehyde were chose as representative substrates with which to probe the mechanism of the reaction. The conversion of substrate, the formation of products and the changes of butanedione and H_2O_2 concentration were determined by monitoring changes in characteristic Raman bands relating to each component over time (see for example in Figure 2).¹² Page 3 of 12

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Figure 2. Reaction progress monitoring of styrene oxidation by Raman spectroscopy (λ_{ex} 785 nm). Selected characteristic bands and changes observed during oxidation are indicated.

At low concentrations of Mn^{II} (e.g., 0.05 mM) a lag period follows addition of H_2O_2 , after which substrate oxidation is observed (**Figure 3**). The duration of the lag period is dependent [Mn^{II}] (vide infra). By contrast, the absorbance band at λ_{max} 417 nm (vide infra) and carbonyl stretching band of butanedione (Figure 2) decrease within a few seconds of addition of H_2O_2 . The lag period observed is, therefore, not due to a delay in the formation of 3-hydroxy-3-hydroperoxy-butanone (Scheme 2). Furthermore the lag period shows little sensitivity to substrate (e.g. diethylfumarate, cyclooctene).¹⁵ Hence, a second slower process occurs prior to the onset of catalytic oxidation of substrates; possibly the oxidation of the ketone to the corresponding carboxylic acid.



Figure 3. Change in [cyclooctene] over time in acetonitrile under the conditions stated in Scheme 1, without (green) and with addition of acetic acid (0.1 M) before (red) and after (black) addition of H_2O_2 . Points of addition are indicated by arrows. Conditions: 0.5 M cyclooctene, 0.75 M H_2O_2 , 0.25 M 1,2-dichlorobenzene (internal reference), 0.25 M butanedione, 0.05 mM Mn(ClO₄)₂, 2.5 mM PCA, 5 mM NaOAc, at 15 °C.

Effect of acetic acid on reaction progress

A notable feature of the Mn^{II}/PCA system is that oxidation of the ketone (e.g., α -oxidation of acetone and butanedione) is observed in addition to oxidation of the substrate (e.g., cyclooctene). As noted earlier¹² addition of acetic acid (0.2 equiv. w.r.t substrate) to the reaction either before or after addition of H₂O₂ did not affect conversion or vield significantly.¹² ¹³C NMR spectroscopy confirmed that, in the case of butanedione, acetic acid forms prior to the end of the lag period. However, addition of acetic acid (0.2 equiv. w.r.t substrate) before H₂O₂ results in an immediate reaction upon addition of H_2O_2 (i.e. the lag period was eliminated). Similarly, when acetic acid was added after addition of H₂O₂, conversion started immediately also. Notably, however, the reaction rate (at maximum TOF) was the same regardless of whether acetic acid was added or not (Figure 3). Indeed addition of acetic acid after the onset of substrate oxidation has no effect on the reaction rate (i.e. neither on the rate of oxidation of the alkene nor butanedione itself). These data confirm that acetic acid is essential to the onset of catalytic activity and its formation in situ from butanedione is an autocatalytic reaction that is manifested in a lag time followed by the rapid onset of catalytic activity. Furthermore, oxidation of butanedione continues at an essentially constant rate concomitant with oxidation of the substrate, e.g., cyclooctene (vide infra,).



Figure 4. Change in [cyclooctene] over time during oxidation in ethanol and in acetonitrile without and with addition of acetic acid (0.1 M) prior to addition of H_2O_2 . Conditions: 0.5 M cyclooctene, 0.75 M H_2O_2 , 0.25 M 1,2-dichlorobenzene (internal reference), 0.25 M butanedione, 0.05 mM $Mn(ClO_4)_2$, 2.5 mM PCA, 5 mM NaOAc, at 15 °C.



Figure 5. Change in [cyclooctene] over time in C_2H_5OH and in C_2H_5OD , without and with acetic acid (0.1 M) added prior to addition of H_2O_2 and D_2O_2 , respectively. Conditions: 0.5 M cyclooctene, 0.75 M (H/D)₂O₂, 0.25 M 1,2-dichlorobenzene (internal reference), 0.25 M butanedione, 0.05 mM Mn(ClO₄)₂, 2.5 mM PCA, 5 mM NaOAc, at 15 °C.

The Mn^{II}/PCA catalyzed oxidation of cyclooctene with H_2O_2 and butanedione, proceeds in both the polar aprotic solvent, acetonitrile, and the polar protic solvent, ethanol (**Figure 4**). The reaction rate is solvent dependent, however, as for acetonitrile, the lag time observed in ethanol is eliminated also by the addition of acetic acid. Raman and UV/Vis absorption spectroscopy confirm that the decrease in reaction rate in ethanol is not due to an effect of solvent on the extent of formation of the 3-hydroxy-3-hydroperoxybutanone (Scheme 2) and indeed equilibrium is reached within several seconds in both solvents.

The reaction does not show a solvent kinetic isotope effect (i.e. KIE = 1 is observed) in ethanol, i.e. the use of CH₂CH₃OD, CH₃CO₂D and D₂O₂ in D₂O has no effect on reaction rate with and without acetic acid (Figure 5). Furthermore, both the lag time and reaction rate in acetonitrile shows relatively little sensitivity to temperature with only a doubling in reaction rate between 0 and 45 °C. The origin of the minor dependence on temperature is due in small part to the rapid prior equilibrium between butanedione and H₂O₂, which is shifted to the left as temperature is increased, thereby decreasing the concentration of the perhydrate. The lag phase observed in the absence of acetic acid is, however, reduced as the temperatures increases.

These data raise questions regarding the role, if any, of acetic acid during the reaction and indeed the effect of carboxylic acids on the reaction in a general sense.

Effect of carboxylic acids on the oxidation of cyclooctene

Perchloric acid and a series of carboxylic acids, covering a pK_a range from -10 to 4.76,¹⁶ were added under standard reaction conditions both in acetonitrile and in ethanol (Figure 6).¹⁷ Except with trichloroacetic acid and with perchloric acid, the same maximum conversion was reached typically within 4 h (Table S1). The lack of substrate conversion in the presence of trichloroacetic acid or perchloric acid can be ascribed to their pK_a . These are the only acids in the series for which their pK_a is lower than that of PCA { $pK_{a1} = 1.07$ (CO₂H/CO₂⁻) and $pK_{a2} = 5.25$ (PyH⁺/Py)},¹⁸ and hence are expected to protonate PCA and thereby inhibit formation of the catalyst by reducing the effective concentration of PCA (vide infra).



Figure 6. Conversion (after 1 and 4 h) of cyclooctene using standard conditions (upper) in acetonitrile and (lower) in ethanol w.r.t. the *p*Ka of various acids (0.1 M) added prior to addition of H_2O_2 . Conditions: 0.5 M cyclooctene, 0.75 M H_2O_2 , 0.25 M 1,2-dichlorobenzene (internal reference), 0.25 M butanedione, 0.05 mM Mn(ClO₄)₂, 2.5 mM PCA, 5 mM NaOAc, at 15 °C.

With all other carboxylic acids examined, the progress of the reactions over time (Figure 7) shows a dependence on the acid added. In addition to those acids that prevent oxidation of cyclooctene completely (i.e. with a pK_a lower than PCA, e.g., CCl_3CO_2H), the presence of acids with pK_{as} in the range 1.69-3.45, (e.g. CH₂ClCO₂H) leads to a considerable reduction in reaction rate. For acids with pKa's > 3.5, the lag period that follows addition of H₂O₂ was eliminated, although the reaction rate was not affected. In the case of salicylic acid, the decrease in reaction rate is likely to be due to competition with PCA for binding to Mn^{II}, thereby reducing the effective concentration of the catalyst. Thus it is apparent that the pK_a of the acid present determines its effect on the reaction with acids with a $pK_a < 0.7$ inhibiting the reaction completely, those with a pK_a < 3.5 retard the reaction and those with a $pK_a > 3.5$ only eliminate the lag period.

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Figure 7. Conversion of cyclooctene in acetonitrile under conditions shown in Figure 6 without added acid, with acetic acid (0.1 M), with CH_2CICO_2H (0.1 M), and with CCI_3CO_2H (0.1 M).

The effect of several of the acids on the equilibrium between butanedione and H2O2 was examined by UV/Vis absorption and Raman spectroscopy. The intense near-UV absorption band of butanedione (Figure 8), together with the Raman band at 640 and 702 cm⁻¹ of 3-hydroperoxy-3hydroxybutanone (Figure 2), allows for in-line monitoring the concentration of both species. Only acetic acid gives behavior comparable with that observed in the absence of added acid, i.e. a sudden decrease in absorbance and concomitant increase in the Raman band at 850 cm⁻¹ due to formation of 3-hydroxy-3-hydroperoxybutanone. The reaction in the presence of acetic acid does not show a lag time after addition of H₂O₂ (vide supra) and maximum conversion is reached within 5 min (Figure 7), which is concomitant with the partial recovery of the absorbance and Raman bands of butanedione (Figure 8). Hence, the equilibrium between butanedione and H_2O_2 and its adduct is unaffected by the presence of acetic acid.



Figure 8. Change in absorbance of butanedione at 450 nm^{19} after addition of H_2O_2 with various acids in the oxidation of cyclooctene; for conditions see Figure 6.

The effect of addition of H_2O_2 on the UV/Vis absorption spectrum of the reaction mixture with butanedione in the presence of chloroacetic acid or trichloroacetic acid was different

to that observed with and without acetic acid. In the case of chloroacetic acid the decrease was biphasic with a moderately rapid phase (over 3 min) and a subsequent slower phase, while for trichloroacetic acid only a slow (exponential) decrease in absorbance was observed. Importantly in both cases a concomitant appearance of the Raman bands of 3-hydroxy-3hydroxyperoxy-butanone was observed. Hence the decrease in reaction rate in the former case and absence of reactivity in the latter case, are not due to the absence of 3-hydroxy-3hydroperoxybutanone. Furthermore, the consumption of H_2O_2 in each case corresponded to the extent of alkene conversion, excluding the occurrence of H₂O₂ disproportionation. In both cases, however, the butanedione and the 3-hydroxy-3hydroxyperoxy-butanone are both consumed over the course of the reaction. An additional signal observed at 117 ppm by ¹³C NMR spectroscopy after the reaction is consistent with loss of butanedione due to aldol condensations. Hence the lack of conversion in the case with CCl₃CO₂H is most likely due to a reduction in the effective concentration of PCA through protonation (vide supra).

It should be noted that almost full conversion of diethylfumarate is observed earlier using CF₃COCH₃ (10 vol%) as ketone in acetonitrile, whereas conversion was not observed with CF₃COCF₃ or CCl₃COCCl₃.¹¹ The differences in behavior cannot be ascribed to differences in the extent to which a 3hydroperoxy-3-hydroxy species forms. Instead it is more likely that the lack of reactivity in the latter cases is due to the fact that oxidation of CF₃COCF₃ and of CCl₃CO₂H, respectively. In contrast, with CF₃COCH₃, oxidation will likely produce acetic acid and not CF₃CO₂H. Since trihaloacetic acids inhibit the reaction completely (vide supra) then their formation can rationalize the lack of conversion observed.

Dependence of reaction on [Mn^{II}]

The lag time and reaction rate showed a dependence on $[Mn^{II}]$ in the oxidation of cyclooctene (Figure S1), 3vinylbenzaldehyde (Figure 9) and styrene. Decreasing $[Mn^{II}]$ resulted in a lengthening of the duration of the lag time and a reduction in the rate of substrate oxidation (M s⁻¹). In all cases, however, after the lag period, the rate of substrate oxidation increases to a maximum rapidly and then proceeds at that rate until conversion ceases. In the presence of 0.2 equiv. of acetic acid w.r.t. substrate, the reaction commences immediately upon addition of H₂O₂, however, the maximum rate of substrate oxidation is the same as without acid. The maximum conversion reached at higher [Mn^{II}] was found to be essentially constant. The dependence of the maximum rate of oxidation of substrate on [Mn^{II}] confirms that the manganese catalyst formed is involved at the rate determining step of the reaction. For all substrates the turnover frequency once the reaction had reached a maximum rate of substrate oxidation (i.e. the linear part of the graphs) was relatively independent of catalyst concentration (ranging from 15 to 30 s⁻¹), indicative of a 1st order dependence on $[Mn^{II}]$. Notably, with a $[Mn^{II}] > 0.5$ mM, the maximum conversion reached decreases substantially, in part due to the low [PCA] to $[Mn^{II}]$ ratio (vide infra).



Figure 9. Conversion of 3-vinylbenzaldehyde (0.5 M) during oxidation in acetonitrile with 0.01 (light blue), 0.025 (blue), 0.05 (red), and 0.5 mM (black) Mn(ClO₄)₂. Conditions: 0.5 M cyclooctene, 0.75 M H₂O₂, 0.25 M 1,2-dichlorobenzene (internal reference), 0.25 M butanedione, 2.5 mM PCA, 5 mM NaOAc, at 15 °C. H₂O₂ was made at t = 1 min.

Dependence of reaction on [pyridine-2-carboxylic acid]

Both the reaction rate and maximum conversion are dependent on [PCA] (Figure 10), however, this dependence is linked to [Mn^{II}] also. With 0.5 mM Mn^{II} the reaction rate decreases as [PCA] is decreased and below a [PCA]:[Mn^{II}] of 1:1, negligible conversion of substrate and also of H_2O_2 is observed (Figure 10, lower). Above a 1:1 ratio the reaction rate increases sharply with increasing [PCA]. A more complex situation arises with a [Mn^{II}] of 0.05 mM (Figure 10, upper). The rate of oxidation increases moderately with [PCA] and then decreases with a large excess of PCA w.r.t. Mn^{II}. The most pronounced effect of variation in [PCA] is on the maximum conversion achieved, with conversion increasing with [PCA]. The time over which conversion is observed appears to be dependent on [PCA] also. PCA was shown earlier to eventually undergo oxidation to the corresponding N-oxide under reaction conditions, which together with the absence of conversion when the corresponding N-oxide was used in place of PCA,¹⁰ indicates that PCA oxidation may be an important deactivation channel.





Figure 10. Dependence of change in concentration of styrene over time on [PCA] with (upper) 0.05 and (lower) 0.5 mM $Mn^{II}(ClO_4)_2$, with an initial concentration of 0.5 M styrene, 5 mM NaOAc, 0.25 M butanedione, and 0.1 M acetic acid in acetonitrile. A single addition of H_2O_2 (to a final concentration of 0.75 M) was made at the time indicated.

In the absence of acetic acid a lag time is observed also (Figure 11), the duration of which increases, together with a decrease in reaction rate (at highest TOF), as the [PCA] is decreased. The increase in the duration of the lag-time is consistent with a model in which the same catalyst is responsible for oxidation of butanedione to acetic acid as well as for al-kene oxidation.

These data confirm that the reaction rate is dependent on [PCA], i.e. that PCA is involved before or at the rate determining step of the reaction. Furthermore, the inhibition seen at high [PCA] and the loss of activity observed at low [PCA] support the conclusion that PCA acts as a ligand in the active catalyst.



Figure 11. Conversion of cyclooctene over time for various [PCA] (2.5 mM (black), 1.25 mM (red), 0.5 mM (green), 0.25 mM (blue) and 0.125 mM (light blue)). With 0.5 M cyclooctene, 5 mM NaOAc, 0.25 M butanedione, 0.25 M 1,2-dichlorobenzene (internal reference), 0.05 mM Mn^{II}(ClO₄)₂ in acetonitrile. A single addition of 1.5 equiv. of H_2O_2 was made at t = 2 min.

Dependence of reaction on [substrate]

In early studies it was noted that the reaction appeared to show a zero-order dependence on substrate concentration (in the case of alkenes), which was taken advantage of to achieve full conversion simply by lowering substrate concentration and holding the concentration of all other reaction components constant.¹² The success of this approach is apparent from **Figure 12**. With 0.2 M styrene, full conversion is observed. Notably, neither the reaction rate nor (in the absence of acetic acid, Figure S2) the duration of the lag-time show sensitivity to substrate concentration, in the case of styrene, cyclooctene and sec-phenyl ethanol (Figure S3). These data confirm that the reaction is zero order with respect to substrate under the conditions employed.



Figure 12. Conversion (change in concentration) over time, of styrene, with an initial concentration of 0.2 M and 1.0 M; 2.5 mM PCA, 5 mM NaOAc, 0.25 M butanedione, 0.05 mM $Mn^{II}(ClO_4)_2$ and 0.2 M acetic acid in acetonitrile. A single addition of H_2O_2 (to a final concentration of 0.75 M) was made at t = 0 s.

Dependence of reaction on [butanedione] and [H₂O₂]

The reaction rate is strongly dependent on the concentration of butanedione with a 4 fold decrease in concentration resulting in a 10 fold decrease in reaction rate (**Figure 13**), confirming that butanedione is involved at or before the rate determining step of the reaction. Notably, in the absence of added acetic acid, the lag time observed is dependent on [butanedione] also; decreasing with increasing concentration (Figure S4). This later observation is expected since the decomposition of butanedione to acetic acid occurs prior to the onset of substrate oxidation (vide supra).



Figure 13. Conversion of styrene over time with 0.125 and 0.500 M butanedione; with 2.5 mM PCA, 5 mM NaOAc, 0.5 M cyclooctene, 0.25 M 1,2-dichlorobenzene (internal reference), 0.05 mM $Mn^{II}(CIO_4)_2$ in acetonitrile. A single addition of 1.5 equiv. of H_2O_2 was made at the time indicated.

In addition to the near complete decrease in the carbonyl stretching band of butanedione upon addition of H₂O₂, the loss in conjugation by formation of 3-hydroxy-3-hydroperoxybutanone, results a concomitant loss of the absorbance of butanedione at 417 nm (Figure 14). Importantly, since 3hydroperoxy-3-hydroxybutanone forms within several seconds after addition of H₂O₂, the lag phase cannot be due to a delay in its formation (vide supra). Furthermore, the absorbance of butanedione does not recover further after 30 min and the amount of butanedione consumed is approximately linearly dependent on the amount of H₂O₂ added, and hence the extent of oxidation and the time taken for this to occur is dependent primarily on the amount of H2O2 added. The oxidation of butanedione proceeds at a constant rate over the course of the reaction analogous to the oxidation of substrates (e.g. styrene, Figure S4).





Figure 14. (a) Change in absorbance of butanedione at 417 nm over time after addition of H2O2 at t = 0 min (0.125 to 0.875 M; 0.25, 0.50, 0.75, 1.00, 1.25, 1.35, and 1.50 eq. w.r.t. cyclooctene); 0.05 mM Mn^{II}(ClO₄)₂, 0.5 M cyclooctene, 5 mM NaOAc, 0.25 M butanedione, 2.5 mM PCA in acetonitrile. (b) Dependence of butanedione consumed on amount of H_2O_2 added.

The reaction rate is unaffected by the initial concentration of H_2O_2 where $[H_2O_2] > [butanedione]$ (Figure 15) and the conversion increases linearly with increase in [H₂O₂] (Figure S5). The lag phase observed prior the onset of oxidation of cyclooctene, however, was absent for $[H_2O_2]$:[butanedione] < 2 and above 2 it increased with the initial concentration of H_2O_2 . These data can be rationalised by considering that the reaction requires the formation of acetic acid by oxidation of butanedione. As the [H₂O₂] is increased the [butanedione] decreases (Figure 14b) due to formation of 3-hydroxy-3hydroperoxybutanone. Hence, although 3-hydroxy-3hydroperoxybutanone is the species responsible for generating the active oxidant (manganese species), the rate of this process requires acetic acid which is formed only by oxidation of butanedione - which is scarcely available at high [H₂O₂]. Overall, these data confirm that the lack of a significant dependence of reaction rate on [H2O2] is due to a prior rapid equilibrium (Scheme 2).



Figure 15. Conversion of cyclooctene over time for various equivalents of H_2O_2 (0.25 to 1.5 w.r.t cyclooctene). With 2.5 mM PCA, 5 mM NaOAc, 0.25 M butanedione, 0.25 M 1,2-dichlorobenzene (internal reference), 0.05 mM Mn^{II}(ClO4)2 in acetonitrile. A single addition of H_2O_2 was made at the t = 4 min.

In most cases the reaction proceeds at an essential constant rate (i.e. rate of oxidation of substrate) for a defined period after which substrate conversion ceases. If the initial concentration of substrate is greater than the maximum amount that can undergo oxidation before the reaction ceases then conversion will be incomplete. In the case of substrates such as styrene the cessation of catalytic activity is due to the loss of butanedione and H₂O₂ and addition of both butanedione and H_2O_2 results in a further oxidation. Importantly, there is no evidence for oxidation of the PCA to 2-carboxy-pyridine-Noxide. For less reactive substrates, in particular diethylmaleate, although some conversion is observed initially, the reaction ceases with only a minor amount of H₂O₂ and butanedione consumed even after 30 min. Subsequent addition of styrene does not result in conversion (Figure S7). ¹H NMR analysis shows complete conversion of PCA to 2-carboxy-pyridine-Noxide. Notably, with a 1:1 mixture of styrene and diethylmaleate conversion of styrene proceeds as expected, confirming that neither diethylmaleate nor its oxidation product mesotartrate inhibit the catalyst.

Discussion

A first step in elucidating the mechanism by which the catalyzed oxidation of organic substrates with Mn^{II}/PCA lies in examination of its substrate scope and product distributions. Indeed, several observations of mechanistic relevance can be gleaned from the substrate scope.¹² Most notably the lack of retention of configuration in the epoxidation of cis- and trans-2-heptene, with a 75% yield of a 2:1 mixture of cis- and trans-2-heptene oxide from cis-2-heptene.¹² Similarly, a 1:5 mixture of cis- and trans-2-heptene epoxide was obtained from trans-2heptene. These data indicated that the epoxidation of alkenes is a stepwise reaction in which an intermediate is formed that allows free rotation around the C-C bond of the epoxide. Similar results were obtained with cis- and trans-methylstyrene and stilbene. By contrast, examination of the product distribution of cis- and trans-alkenes showed that cis-dihydroxylation occurred only, i.e. it is a concerted reaction.^{11,12} The absence of allylic oxidation, e.g., with cyclohexene, indicates that the lack of retention of configuration is not due to radical oxidation pathways.20 Nevertheless, it is still possible that these two transformations go through a common intermediate. Moreover, the high activity for both the epoxidation of electron rich alkenes and cis-dihydroxylation of electron deficient alkenes and low activity for α,β -unsaturated alkenes, indicates that the catalyst operates electrophilically in the case of epoxidation and nucleophilically in the case of syn-dihydroxylation.

From a mechanistic perspective, the most striking observation for this system is the equilibrium between butanedione and H_2O_2 with 3-hydroperoxy-3-hydroxybutanone (Scheme 2). It was shown earlier¹² that this equilibrium is established rapidly (< 10 s) and that the formation of this hydroxyl-peroxy species is essential in order to achieve catalytic activity. In the present study it is shown that the oxidation of butanedione is catalyzed by the Mn^{II}/PCA catalyst and that the acetic acid 1

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59 60 formed through this reaction is key to achieving a significant rate of oxidation (Scheme 3). The role of acetic acid (or indeed any carboxylic acid) in the reaction is intriguing since although its presence is essential for catalytic activity to be observed, the reaction rate is essentially unaffected by variation in its concentration. Furthermore, acetic acid does not affect, significantly, the equilibrium between butanedione/H₂O₂ and 3-hydroperoxy-3-hydroxybutanone (Scheme 2). The absence of an effect of adding acid once substrate conversion has commenced indicates that the acid is responsible primarily for formation of the active form of the catalytic species but its role as a proton donor in the reaction between the perhydrate and the catalyst cannot be excluded.

The equilibrium between butanedione/ H_2O_2 and 3hydroperoxy-3-hydroxybutanone together with the zero order dependence of reaction rate on $[H_2O_2]$ and the non-zero order dependence on [butanedione] indicates that the rate determining step in the reaction is the formation of the active oxidizing species by reaction of 3-hydroperoxy-3-hydroxybutanone with the manganese catalyst. Once formed this species reacts with substrates at a rate much faster than the rate of its formation and hence reaction shows a zero order dependence on all substrates (Figure S8). Notably, however, the oxidation of substrates competes with oxidation of butanedione, and hence the extent of conversion observed for a particular substrate is dependent on the ease with which it undergoes oxidation relative to butanedione.

The dependence of the reaction rate on both $[Mn^{II}]$ and [PCA] is non-zero order, which together for the necessity that the ratio of PCA:Mn^{II} > 2: 1, indicates that the catalyst is a Mn-PCA complex. The characterization of the active form catalyst is challenging and indeed it is not practical to determine the structure of the resting state of the catalyst at the low concentrations of catalyst used in the reaction. It is notable, however, that EPR spectra of the reaction mixtures were featureless (perpendicular mode, at 77 K), which suggests the absence of octahedral mononuclear Mn^{II} are possible candidates for the oxidation state of the resting state. The essentially 1st order dependence of the reaction rate on the concentration of manganese indicates that a mononuclear catalyst is involved.

A notable feature of the reaction is that conversion stops after a certain period for all reactions, with the time dependent on catalyst concentration, in particular the relative concentration of Mn^{II} and PCA. The lack of activity observed, even in the presence of acetic acid, when the concentration of PCA is less than that of Mn^{II} , indicates that the limited time over which conversion is observed is due to oxidation of the PCA to its corresponding N-oxide. Furthermore, the effect of other carboxylic reactions on reaction rate is consistent with the reduction in the effect concentration of PCA (i.e. through protonation).

The decomposition of butanedione to acetic acid is catalyzed by Mn^{II}/PCA and indeed in the absence of Mn^{II} , oxidation is not observed even over several hours. However, in order for oxidation to proceed acetic acid needs to be present which presents an interesting mechanistic conundrum. The oxidation of butanedione by the catalyst therefore can compete with alkene oxidation. However, for most of the reaction, i.e. while $[H_2O_2] > [butanedione]$, the absolute concentration of

butanedione is low and the 3-hydroperoxy-3-hydroxybutanone itself is likely to be relatively unreactive towards oxidation. Hence, although some butanedione is initially oxidized to acetic acid, it is only towards the end of the reaction, where $[H_2O_2] < [butanedione]$, that it is present at sufficient concentrations to compete with substrates such as alkenes. That this is the case is supported by the fact that a rapid oxidation of butanedione would reduce the effective concentration of 3-hydroxy-3-hydroperoxy-butanone, and thereby the reaction rate would decrease; which is not observed.



Scheme 3 Proposed mechanism for the oxidation of alkenes under the present system based on data from kinetic analyses and orders of the reaction.

Conclusions

A combination of reaction monitoring by Raman and UV/Vis absorption spectroscopy has enabled a detailed picture of the mechanisms involved in the manganese catalyzed oxidation of alkenes with H₂O₂. Overall, it is apparent that an attempt to reveal the nature of the active oxidizing species through kinetic analyses is limited by the interdependence of reaction components, not least the Mn^{II} and PCA. Nevertheless it is clear that a prior rapid equilibrium (i.e. butanedione/ $H_2O_2 \Leftrightarrow$ 3-hydroxy-3-hydroperoxybutanone) is followed by the reaction of 3-hydroxy-3-hydroperoxybutanone with the reduced form of the catalyst to yield an active oxidizing species. This latter step is rate limiting and hence the substrate does not influence the overall reaction rate. The nature of both the reduced and oxidized form of the Mn/PCA catalyst can be speculated on. The absence of a 6-line EPR signal (characteristic of mononuclear Mn^{II}) and the high the essentially 1st order dependence on $[\ensuremath{\mathsf{Mn}}^{\ensuremath{\mathrm{II}}}]$ are consistent with a mononuclear Mn^{III} resting state and a reasonable hypotheses, in our view, is that the reaction between 3-hydroxy-3-hydroperoxybutanone and a Mn^{III}(PCA)₂ complex yields a highly reactive species, e.g., $[(PCA)_2Mn^V(=O)(OH)]$ (Scheme 3).

In a wider context, the data reported here highlights that, although the catalytic system is relatively simple in terms of composition, the intricate relations between individual components in the reaction and the multiple effects each component can have on the system as a whole complex. Understanding the complex interactions will certainly be key to expanding the systems scope and utility in synthesis. In the present contribution the interactions and reactions leading to the rate determining step have been explored. In future studies we will attempt to look beyond the rate determining step to elucidate the molecular nature of the manganese catalyst itself.

Experimental section

All reagents are of commercial grade and used as received unless stated otherwise. Hydrogen peroxide was used as received (ACROS chemicals) as a 50 wt. % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. D_2O_2 was obtained from Icon isotopes. ¹H NMR (400.0 MHz) and ¹³C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts²² are relative to ¹H NMR CDCl₃ (7.26 ppm), CD₃CN (1.94 ppm) and ¹³C NMR CDCl₃ (77 ppm), CD₃CN (118 ppm).

Caution. The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid Na-HSO₃ or another suitable reducing agent. When working with H_2O_2 , suitable protective safeguards should be in place at all times due to the risk of explosion.

Caution. Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fumehood and exposure to vapors should be avoided.²³

Typical procedure for catalytic oxidations described in Scheme 1

The substrate (1 mmol) was added to a solution containing Mn(ClO₄)_{2.6}H₂O and PCA in acetonitrile to give a final concentration of the substrate of 0.5 M. NaOAc (aq. 0.6 M) and butanedione (0.5 mmol) were added to give a final volume of 2 ml. The solution was stirred in an ice/water bath before addition of H₂O₂ (50 wt. %). Conversion was verified ¹H NMR by dilution of a part of the reaction mixture in CD₃CN. Product isolation involved addition of brine (10 ml) and extraction with dichloromethane. The combined organic layers were washed with brine and dried over Na₂SO₄ (anh.), filtered, and the dichloromethane was removed in vacuo. 1,2-Dichlorobenzene, which has a negligible effect on the reaction, was employed as internal standard for Raman and ¹H NMR spectroscopy. Reaction monitoring with Raman spectroscopy focused primarily on the intensity of the C=C and C=O stretching bands between 1550-1800 cm⁻¹ (e.g., at 1650 cm⁻¹ for cyclooctene, and 1724 cm⁻¹ for butanedione) and between 600-900 cm⁻¹ relating to the C=C and C=O bending modes (682 cm⁻¹ for butanedione, 701 cm⁻¹ for cyclooctene), and the O-O stretching mode of H₂O₂ at 870 cm⁻¹. UV/Vis absorption spectroscopy were recorded in 1 or 10 mm pathlength cuvettes on a AnalytikJena Specord 600. Raman spectra at 785 nm were recorded using a Perkin Elmer Raman Station and at 532 nm using a custom made Raman spectrometer; a 532 nm DPSS laser (25 mW, Cobolt Lasers) was fiber coupled to a low cost Raman probe (inphotonics) and the collected scattering feed into a Shamrock163 spectrograph (500 nm blaze, 1200 l/mm grating, Andor Technology) and dispersed onto a Newton EMCCD (Andor Tehcnology) operated in conventional CCD mode.

ASSOCIATED CONTENT

Supporting Information. Additional graphs showing substrate conversion over time. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The range of [Mn^{II}] that can be used in the reaction is between from 0.01-0.25 mM. At higher concentrations reactivity is reduced substantially, indicating the formation of noncatalytically active manganese species.

(15) The reaction rate observed with phenylethanol as substrate is lower than for alkenes (see SI Figure S₃), however, this is most likely to be due to solvent effects considering the differences in rate of alkene oxidation in acetonitrile and in ethanol.

(16) It should be noted that the pK_a values are determined in water. These values can differ substantially in acetonitrile and to a lesser extent in ethanol. However, an excess of water w.r.t. acid is added to the reaction both through the addition of NaOAc and upon addition of H_2O_2 .

(17) The reaction mixture contains a considerable amount of water (> 100 mol% w.r.t. substrate) due to its presence in the H_2O_2 added and hence the maximum acidity is limited by the pK_a of water (c.f. levelling effect).

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(21) It should be noted, however, that although EPR spectroscopy shows that Mn^{II} at 0.05 mM shows the expected 6-line signal, under reaction conditions before addition of H_2O_2 no EPR signals were observed at room temperature indicating that mononuclear Mn^{II} is not present in significant amounts. See ref. 12 for details.

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