Chapter 5
Mechanistic study of an *in situ* prepared Mn$^{II}$/pyridine-2-carboxylic acid catalytic system

*In this chapter a range of spectroscopic techniques were employed to obtain kinetic information regarding the reaction, employing Mn$^{II}$/pyridine-2-carboxylic acid/butanedione and a base, to elucidate the mechanism. The equilibrium between butanedione and H$_2$O$_2$ and a competitive reaction to form acetic acid in situ in the reaction mixture are demonstrated as well as the roles played by butanedione and acetic acid.*

*Part of this chapter has been published:*
5.1 Introduction

The decomposition of polypyridyl amine based ligands such as TPTN and their aminal precursors under the conditions employed for catalysis was described in Chapter 3. It was also demonstrated that pyridine-2-carboxylic acid and its derivatives formed in situ are responsible for the activity observed.\(^1\) The application of an in situ formed catalyst system for the epoxidation and cis-dihydroxylation of alkenes with \(\text{H}_2\text{O}_2\) based on pyridine-2-carboxylic acid, Mn\(^{\text{II}}\), a base (e.g. NaOH or NaOAc) and a ketone either as solvent or co-solvent was described in Chapter 4.\(^2\)

The presence of a ketone either as a solvent or co-solvent was found to be essential to the activity of the catalytic system. Subsequently, butanedione was identified as a ketone that provided a highly active catalytic system and it could be used substoichiometrically.\(^3\) Importantly, the reaction times were dramatically reduced. The system is especially suited for the epoxidation of electron rich alkenes and shows good to excellent selectivity in the epoxidation of dienes and bifunctional substrates. In the case of electron deficient alkenes the method exhibits exceptional selectivity and activity in their cis-dihydroxylation (Scheme 1).\(^3\)

\[
\text{Scheme 1} \quad \text{Conversions and yields (isolated) obtained for a) the epoxidation of electron rich alkenes and b) cis-dihydroxylation of electron deficient alkenes under the standard conditions employing Mn}^{\text{II}}/\text{pyridine-2-carboxylic acid/butanedione/base system.}
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In this chapter the system employing butanedione in the combination with Mn\(^{\text{II}}/\text{pyridine-2-carboxylic acid and a base is investigated in more detail in an attempt to elucidate the reaction mechanism, with particular focus on the role of the ketone and acids in controlling the reaction rate. For details of substrate scope and optimisation of reaction conditions using butanedione please refer to reference.}^3
5.2 Mechanistic considerations

5.2.1 Information from substrate scope

Several mechanistically relevant observations can be made based on the substrate scope.\(^3\)

![Scheme 2](image)

**Scheme 2** Oxidation of cis-/trans-2-heptene, cis-/trans-1-methyl-styrene and cis-/trans-stilbene catalysed by Mn\(\text{II}\)/pyridine-2-carboxylic acid/butanedione/base.\(^a\)

\(^a\) For conditions see the experimental section. Yields determined by \(^1\)H NMR spectroscopy. Note that the trans-dihydroxylation products were not observed in any of the examples and side products were overoxidation products, i.e. \(\alpha\)-hydroxyl ketone.

The degree of retention of configuration in the epoxidation of cis-/trans-2-heptene is relatively low. For cis-2-heptene, 75% of the epoxide product was obtained as a mixture of cis-2-heptene oxide and trans-2-heptene oxide (2 : 1) (Scheme 2). Similarly, trans-2-heptene provided 45% trans-2-heptene oxide and only 9% cis-2-heptene oxide. This indicates that the epoxidation of alkenes is not a concerted reaction but is instead stepwise and favours the trans-epoxide product. In strong contrast, the heptane-1,2-diol that was formed as a minor product was in both cases the result of cis-dihydroxylation only. This
is remarkable as it suggests that dihydroxylation is a concerted process. Essentially the same trends were observed with both cis- and trans-1-methylstylene and cis- and trans-stilbene. In addition, it is clear that, in contrast to Mn-TMTACN (see Table 4, Chapter 2), trans-alkenes are much more reactive under the present conditions.

However, the absence of significant allylic oxidation, for example cyclohexene, indicates that the low retention of configuration observed for 2-heptene is not due to a radical oxidation pathway involving hydroxyl radicals.4

5.2.2 Kinetic analysis: order of reaction with respect to various components and the rate determining step

The present system is highly active and can achieve up to 300,000 turnovers with respect to MnII with turnover frequencies of up to 40 s\(^{-1}\) with 1.5 equiv. of H\(_2\)O\(_2\). However, the high activity and low catalyst loadings required (0.01-0.3 mol%) and the absence of spectroscopic signals assignable to manganese species involved in this system (e.g. by EPR or UV/Vis spectroscopy) means that direct identification of the ‘active species’ or even the catalyst in its resting state is essentially impossible. These aspects pose a massive challenge in mechanistic studies for this system. Nevertheless, the techniques and experiments that have been used to understand how individual components are involved in the reaction and, more importantly, why components affect reactions in a negative or positive manner will be described in the following sections.

Kinetic analysis employing Raman spectroscopy was used to obtain mechanistically relevant information for the present system. The conversion of substrate, the formation of products and the changes of butanedione concentration and H\(_2\)O\(_2\) concentration can be monitored by following individual Raman bands relating to each component over time (see Figure 1 for an example). UV/Vis absorption spectroscopy was also used for kinetic analysis in monitoring the butanedione concentration since it has a strong absorption at 417 nm.

Most of the experiments for kinetic analyses by Raman spectroscopy described in this chapter were performed using cyclooctene representing electron rich alkene substrates with 1,2-dichlorobenzene (DCB) as internal standard. The intensity or peak area of Raman bands between 1550-1800 cm\(^{-1}\) relating to stretching modes of C=C and C=O bonds were used to follow substrate conversion (band at 1650 cm\(^{-1}\) for cyclooctene) and the change of butanedione concentration (band at 1724 cm\(^{-1}\)). Moreover Raman bands between 600-900 cm\(^{-1}\) relating to bending modes of C=C and C=O bonds were used also for reaction monitoring such as following the band at 682 cm\(^{-1}\) for butanedione, 701 cm\(^{-1}\) for cyclooctene and at 870 cm\(^{-1}\) for H\(_2\)O\(_2\).
Mechanistic study of an in situ prepared MnII/pyridine-2-carboxylic acid catalytic system

1.5 equiv. H2O2
0.01 mol% Mn(ClO4)2·6H2O
0.5 mol% pyridine-2-CO2H
1.0 mol% NaOAc (aq.)
0.5 equiv. DCB
1.5 equiv. butanedione
MeCN, r.t.

a)

b)

Figure 1 Online monitoring of a catalytic oxidation reaction using Raman spectroscopy (λexc 785 nm). Kinetic information is obtained by monitoring individual bands with 1,2-dichlorobenzene as internal standard a) Raman bands of individual components in reaction mixture and b) plot of intensity of bands of individual components in the reaction mixture against time.

5.2.2.1 Order of reaction with respect to manganese

The oxidation of cyclooctene using optimised conditions but varying the concentration of MnII was performed and followed in real time by Raman spectroscopy (λexc 785 nm). A lag time was observed over the first 10 min after the addition of H2O2 (Figure 2), which will be discussed in detail in Section 5.2.4.

The rate of reaction, obtained from the slope of the curve, varied depending on the MnII concentration. The reaction reaches maximum conversion faster at higher MnII concentration. Importantly, however, after the lag period the reaction rate is constant until conversion stops. The change in rate with change in MnII concentration confirms that manganese is involved in the rate determining step of the reaction. Again, the shape of the curve is particularly interesting because after the lag phase there is a fast linear part in which the reaction reaches maximum conversion which is unexpected. Normally the rate of a reaction (slope of the curve) changes as the reaction proceeds and the amount of substrate and H2O2 changes. However, as this is not observed it would suggest that the substrate (cyclooctene) does not participate in the rate determining step, i.e. zero order in substrate. This also applies to H2O2 to a certain extent (vide infra).
1.5 equiv. H₂O₂
X mol% Mn(ClO₄)₂·6H₂O
0.5 mol% pyridine-2-CO₂H
1.0 mol% NaOAc (aq.)
0.5 equiv. butanedione
0.5 equiv. DCB
r.t., MeCN (0.5 M)

**Figure 2** Conversion of cyclooctene versus time for reactions using various concentrations of Mn²⁺ measured by Raman spectroscopy (λexc 785 nm).

### 5.2.2.2 Order of reaction with respect to pyridine-2-carboxylic acid

The correlation between the peak area of the substrate and time shows similar behaviour to that observed in Figure 2. A lag time is again observed, however, it is longer when less pyridine-2-carboxylic acid (PCA) is used. Reaction rates varied with the concentration of pyridine-2-carboxylic acid (Figure 3). This indicates that the reaction is non-zero order with respect to pyridine-2-carboxylic acid.
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5.2.2.3 Order of reaction with respect to substrate

As observed and discussed in section 2.2.1, the reaction appeared to show zero order kinetics with respect to substrate. To confirm this observation, reactions with different initial concentrations of cyclooctene were performed (Figure 4). In all cases, a lag time was observed that lasted ca. 10 min. The rate at which the substrate is consumed is almost equal for all three concentrations of substrate for both concentrations of catalyst examined. This confirms that the reaction is zero order with respect to substrate under the conditions employed. Notably the reaction reaches higher conversion when a lower initial concentration of substrate is used (e.g. with 0.01 mol% Mn; 80% conversion is obtained with [0.5 M] substrate and with [0.25 M] substrate full conversion is obtained). This is a useful observation for practical applications as it can be applied for substrates that gave low conversion at normal substrate concentration (0.5 M) such as phenanthrene.$^3$
1.5 equiv. $\text{H}_2\text{O}_2$
$X \text{ mol}\% \text{Mn(ClO}_4\text{)}_{2.6}\text{H}_2\text{O}$
0.5 mol% pyridine-2-$\text{CO}_2\text{H}$
1.0 mol% NaOAc (aq.)
0.5 equiv. butanedione
0.5 equiv. DCB
r.t., MeCN (vary [SM])

**Figure 4** Conversion of cyclooctene versus time for reactions using various concentrations of cyclooctene monitored by Raman spectroscopy ($\lambda_{\text{exc}} \ 785 \text{ nm}$).

### 5.2.2.4 Order of reaction with respect to butanedione

From the correlation in Figure 5, it can be concluded that when the amount of butanedione added decreases the rate of the reaction also decreases. This indicates that the order with respect to butanedione is not zero. This implies that butanedione is involved at or before the rate determining step for the reaction. Interestingly, the lag time observed is shorter when a higher concentration of butanedione is used (*vide infra*). The data suggests that butanedione might be involved in the processes occurring during the lag phase of the reaction. In order to obtain more evidence to support this hypothesis, the effect of butanedione concentration in the reaction mixture was studied (see Section 5.2.3).
Mechanistic study of an in situ prepared Mn$^{II}$/pyridine-2-carboxylic acid catalytic system

1.5 equiv. H$_2$O$_2$
0.01 mol% Mn(ClO$_4$)$_2$.6H$_2$O
0.5 mol% pyridine-2-CO$_2$H
1.0 mol% NaOAc (aq.)

X equiv. butanedione
0.5 equiv. DCB
r.t., MeCN (0.5 M)

Figure 5 Conversion of cyclooctene versus time for reactions using various concentrations of butanedione monitored by Raman spectroscopy ($\lambda_{exc}$ 785 nm).

5.2.3 Role(s) of ketone in the catalytic reaction

Although the initial objective was to find safer alternatives to acetone as solvent (see Chapter 4), it was discovered that butanedione was a substoichiometrically active ketone for the manganese catalysed oxidation of alkenes.$^3$ Indeed at low Mn$^{II}$ loadings the requirement for butanedione to be present, even when acetone was used as solvent, indicated that the ketone was directly involved in the reaction and not simply acting as (co)solvent. Actually, full conversion observed with sub-stoichiometric amounts of butanedione implies that it is involved in the oxidation directly and is catalytic. Furthermore, the broad solvent scope$^3$ and the absence of activity when butanedione was omitted, together with the increased activity that allows for the use of low Mn$^{II}$ (<0.01 mol%) and PCA (<0.05 mol%) catalyst loadings, with much shorter reaction times than in acetone alone, hinted that hydrogen peroxide/butanedione adducts (i.e. 3-hydroperoxy-3-hydroxybutan-2-one) could be involved. UV/Vis absorption and Raman spectroscopic analysis of the reaction mixture confirmed that the butanedione reacts immediately (<10 s) with H$_2$O$_2$ in a 1 : 1 ratio, manifested in a decrease and blue shift in both the carbonyl
stretch (1722 cm$^{-1}$) in the Raman spectrum (Figure 6) and the absorption band at 417 nm (n-π* absorption of the butanedione) in the UV/Vis absorption spectrum of the reaction mixture (Figure 7).

That the changes observed are due to the formation of a mono-hydroperoxy acetal (Scheme 3) is supported by the 1:1 stoichiometry required to see almost loss in the intensity of both the 1722 cm$^{-1}$ Raman band (Figure 6) and the 417 nm UV/Vis absorption band (Figure 7). With 1 equiv. of H$_2$O$_2$ with respect to substrate, the 1722 cm$^{-1}$ Raman band and the 417 nm absorption began to recover after approximately 66% of the H$_2$O$_2$ was consumed (i.e. <1 equiv. of H$_2$O$_2$ with respect to butanedione remained). This is also consistent with the formation of 1:1 adduct of H$_2$O$_2$ and butanedione (Scheme 3).$^6$

![Scheme 3 Equilibrium between ketone/H$_2$O$_2$ and hydroperoxy acetal species.](image)
Figure 6 Changes in the Raman spectrum (upper spectrum 1500-1800 cm⁻¹ region, lower spectrum 500-1100 cm⁻¹ region), $\lambda_{\text{exc}}$ 785 nm, of the reaction mixture during the epoxidation of cyclooctene. Conditions: 0.01 mol% Mn$^{II}$, 0.5 mol% pyridine-2-carboxylic acid, 1.0 mol% NaOAc (aq.), 0.5 mol% butanedione, 1.5 equiv. H$_2$O$_2$, MeCN, r.t., substrate concentration = 0.5 M. Spectra prior to (black) and at $t = 5$ (red), 15 (blue), 20 (green) and 30 (pink) min after addition of H$_2$O$_2$. Directions of change are identical with arrows.
The partial recovery of the butanedione is observed to occur concomitantly with the end of the conversion of cyclooctene (i.e. after t > 25 min, Figures 8 and 9), as the H$_2$O$_2$ concentration decreases below that of the butanedione.

When 1.5 equiv. of H$_2$O$_2$ was employed with respect to substrate the recovery of the 1722 cm$^{-1}$ and 417 nm bands of butanedione was ca. 25% indicating that decomposition of butanedione occurs as a competing reaction (Figure 7). The reaction of butanedione with H$_2$O$_2$ to form the active hydroperoxy acetal could in principle lead to decomposition to acetic acid (Scheme 4).$^{7,8,9,10}$
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Figure 8 Equivalents of butanedione remaining (determined by monitoring absorbance at 417 nm) 1 min after the addition of H$_2$O$_2$ and after 40 min (i.e. after conversion of cyclooctene has stopped) showing partial recovery of butanedione after the reaction.

Figure 9 Conversion of cyclooctene and butanedione (expressed as equivalents with respect to cyclooctene) for various equivalents of H$_2$O$_2$ measured by Raman spectroscopy ($\lambda_{exc}$ 785 nm) and UV/Vis absorption spectroscopy, respectively. The total conversion of cyclooctene and butanedione is shown as black squares.

Scheme 4 Decomposition of butanedione/H$_2$O$_2$ adduct to form acetic acid. Although the reaction could proceed uncatalysed, in fact the formation of acetic acid is a catalysed reaction under the reaction conditions employed (vide infra).

The formation of hydroperoxy acetal and acetic acid was confirmed by $^{13}$C NMR spectroscopy (Figures 10 and 11). In Figure 10, the formation of hydroperoxy acetal (signal at 208 ppm) was observed within 4 min after addition of H$_2$O$_2$ and the butanedione signal at 198 ppm disappeared completely as observed earlier by UV/Vis
absorption and Raman spectroscopy (Figures 6 and 7, respectively). After 34 min, the signal of acetic acid at 174 ppm appeared while the butanedione signal at 198 ppm reappeared after 44 min. Moreover, products of the reaction which are cyclooctene oxide (major product) and cyclooctane diol (minor product) can also be observed after 4 min at 58 and 76 ppm, respectively. Some of $^{13}$C NMR signals have not been identified yet. Acetic acid might form earlier in the reaction than indicated by $^{13}$C NMR spectroscopy, however, the detection limit of the technique has not been determined for the present case.

Furthermore, when the loss of butanedione as well as the conversion of cyclooctene are both taken into account, it is apparent that almost all of the $\text{H}_2\text{O}_2$ consumed is used in these two processes only (Figure 9). This observation is important as it indicates that the efficiency of the system can be increased by outcompeting the oxidation of the butanedione (e.g., by accelerating the catalytic oxidation of the alkene).

It should be noted from reactions in either the absence or presence of acetic acid (vide supra) that the breakdown of butanedione or its $\text{H}_2\text{O}_2$ adduct is observed only when both manganese and pyridine-2-carboxylic acid are present. This strongly indicates that acetic acid is formed by the same species responsible for the oxidation of alkenes (as will be discussed further in Section 5.2.4).
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3.0 equiv. H$_2$O$_2$
0.02 mol% Mn(ClO$_4$)$_2$.6H$_2$O
1.0 mol% pyridine-2-CO$_2$H
2.0 mol% NaOAc (aq.)
0.5 equiv. DCB
r.t., MeCN (0.5 M)

Figure 11 $^{13}$C NMR spectrum of the reaction mixture (in CD$_3$CN) a) after 40 min showing the presence of acetic acid and butanedione and b) reaction mixture from a) spiked with additional acetic acid.
5.2.4 Effect of acetic acid on the catalytic oxidation of alkenes

When the reaction was performed in acetone the rate of reaction was dramatically reduced in the presence of acetic acid, albeit with relatively little effect on the overall conversion after 24 h as demonstrated in Chapter 4. The confirmation that acetic acid is formed by decomposition of butanedione in the present system (see Section 2.3) raises a question to its affect on the conversion and reaction rate also. The formation of acetic acid could potentially inhibit the catalytic system in one or more ways including: (i) the loss of butanedione could result in reduced activity since this is required for catalysis, (ii) the acetic acid could affect the equilibrium between butanedione/H₂O₂ and 3-hydroperoxy-3-hydroxybutan-2-one through reducing the effective nucleophilicity of H₂O₂, and (iii) could destabilise a putative Mn^{II}/PCA complex.

\[
\text{1.5 equiv. H}_2\text{O}_2 \\
0.01 \text{ mol\% Mn(ClO}_4)_2.6\text{H}_2\text{O} \\
0.5 \text{ mol\% pyridine-2-CO}_2\text{H} \\
1.0 \text{ mol\% NaOAc (aq.)} \\
0.5 \text{ equiv. butanedione} \\
0.2 \text{ equiv. AcOH or none} \\
0.5 \text{ equiv. DCB} \\
15^\circ\text{C, MeCN (0.5 M)}
\]

Chart 1 Effect of added acetic acid on the catalytic oxidation of cyclooctene and the omission of individual components from the catalyst system on conversion. Note that in all cases except when butanedione was omitted, the formation of 3-hydroperoxy-3-hydroxybutan-2-one was observed by Raman spectroscopy. Notably, when manganese or pyridine-2-carboxylic acid were omitted this hydroperoxy species is stable for 24 h. This observation indicates that decomposition to acetic acid is “Mn/pyridine-2-carboxylic acid” catalysed.
Addition of acetic acid to the reaction (0.2 equiv. w.r.t substrate) either before or after addition of H$_2$O$_2$ did not affect conversion or yield significantly (Chart 1). The kinetics of the reactions obtained by Raman spectroscopy still showed the same reaction rate for all conditions (Figure 12). Interestingly, both reactions with extra acetic acid start immediately after adding H$_2$O$_2$, i.e. a lag time is not observed compared to standard conditions when acetic acid is not added. This confirms that, although acetic acid is formed in significant amounts during the reaction, it does not interfere with the present butanedione based system. Instead, it aids the formation of an active catalyst, manifested in the absence of a lag time.

The absence of an effect of acetic acid on reaction rate when butanedione is employed is in stark contrast to reactions carried out in acetone. It is possible that under acidic conditions the formation of the hydroperoxy species (Scheme 3) will be affected more in the presence of acetone (the equilibrium in this case lies to the left) than in the presence of butanedione. Hence, in the latter case the presence of acetic acid does not affect the availability of the proposed oxidant, 3-hydroperoxy-3-hydroxybutan-2-one, sufficiently to retard the reaction. However, an alternative hypothesis for the difference in the effect of acetic acid between acetone and butanedione should also be considered. Specifically, potential differences in the ability of acetate to compete with the hydroperoxy acetal of acetone and of butanedione for coordination to the manganese catalyst should be
recognised. Regardless of which effect is most important it is clear that the formation of acetic acid does not lead to catalyst deactivation in the present system.

Chart 2 Oxidation of cyclooctene (red) and diethylfumarate (blue) with peracetic acid in the presence and absence of butanedione under standard reaction conditions (stated in Figure 1).

An additional consideration that must be made with regard to the formation of acetic acid is the possibility of subsequent *in situ* formation of peracetic acid, which is itself capable of oxidizing alkenes.\(^\text{11}\) This possibility was investigated in a series of control experiments with cyclooctene and diethylfumarate. Under the present conditions (Figure 1) stoichiometric peracetic acid was found to be effective in the epoxidation of cyclooctene in the absence and presence of butanedione. Importantly, however, no activity in the oxidation of diethylfumarate was observed (Chart 2). Taken together with the absence of activity in the oxidation of cyclooctene with added acetic acid when butanedione is omitted (Chart 1), this confirms that the *in situ* formation of peracetic acid does not occur significantly under these conditions.

To understand more about whether this reaction is a general acid catalysed or specific acid catalysed reaction, the reactions with and without added acetic acid were carried out in both a polar aprotic solvent, acetonitrile, and a polar protic solvent, ethanol (Figure 13).

The rate of reaction is different when using different solvents, however, the same overall result can be seen from reactions in ethanol and acetonitrile, *i.e.* the lag phase is absent upon the addition of acetic acid (as the reaction in the presence of acetic acid shows conversion earlier than without acetic acid). Furthermore, using ethanol allows the determination of solvent kinetic isotope effects (Figure 14). Deuterated ethanol
Mechanistic study of an in situ prepared MnII/ pyridine-2-carboxylic acid catalytic system (CH₂CH₃OD) and deuterated acetic acid (CH₃CO₂D) were used with H₂O₂ or D₂O₂ as terminal oxidant, but a solvent kinetic isotope effect was not observed indicating that proton transfer may not be involved at or before the rate determining step.

Figure 13 Correlation between peak areas of substrate and time for the oxidation of cyclooctene using conditions stated in Chart 1 in acetonitrile and in ethanol monitored by Raman spectroscopy (λexc 785 nm).

5.2.5 Effect of other acids on catalysis with butanedione
As discussed above acetic acid is formed in situ in the reaction mixture by decomposition of the butanedione/H₂O₂ adduct. Acetic acid eliminates the lag time of the reaction but does not affect the rate of reaction. Several other acids with different pKₐ12,13,14,15 were studied under standard reaction condition both in acetonitrile and in ethanol (Figures 15 and 16, respectively).

All reactions from Figures 15 and 16, except those that contained trichloroacetic acid or perchloric acid, showed conversion under the reaction conditions employed, but gave different conversions. However, there is no clear correlation between pKₐ and conversion. The fact that conversion was not observed with trichloroacetic acid or perchloric acid could be ascribed to the effect of pKₐ. These acids are the only acids employed that have a pKₐ lower than the pKₐ of pyridine-2-carboxylic acid (pKₐ 1.07 for CO₂H and 5.25 for PyH⁺, Scheme 5), and hence will protonate pyridine-2-carboxylic acid inhibiting the formation of the active catalyst.
Figure 14 Correlation between peak areas of substrate and time for the oxidation of cyclooctene using conditions stated in Chart 1 in acetonitrile and in ethanol monitored by Raman spectroscopy ($\lambda_{exc}$ 785 nm).

The kinetics of the reactions (Figure 17) showed a dependence on the acid added and can be classified into three categories. Type one are those acids that completely inhibit the reaction and consists of acids with $pK_a$ lower than pyridine-2-carboxylic acid (Table 1, entry 2 and 3). Type two are those that retard the reaction compared to conditions without any added acid. This group consists of acids such as 2,6-dichlorobenzoic acid, 2-nitrobenzoic acid, chloroacetic acid, 2-hydroxybenzoic acid, 3-nitrobenzoic acid ($pK_a$ range 1.69-3.45) (Table 1, entries 3-8). The third type are those that remove the lag period that follows addition of $H_2O_2$, but do not affect the rate of reaction significantly (Table 1, entry 9-11).
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$1.5$ equiv. H$_2$O$_2$
$0.01$ mol% Mn(ClO$_4$)$_2.6$H$_2$O
$0.5$ mol% pyridine-2-CO$_2$H
$1.0$ mol% NaOAc (aq.)
$0.5$ equiv. butanedione
$0.2$ equiv. acid
$0.5$ equiv. DCB
$15$ °C, MeCN (0.5 M)

Figure 15 Conversion of cyclooctene using standard conditions with various acids (different pK$_a$) in acetonitrile monitored by Raman spectroscopy ($\lambda_{exc}$ 785 nm). a) Table shows conversion of reactions after 1 and 4 h with various acids used. b) Correlation between conversion of reactions and pK$_a$ of acids.
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1.5 equiv. H₂O₂
0.01 mol% Mn(ClO₄)₂·6H₂O
0.5 mol% pyridine-2-CO₂H
1.0 mol% NaOAc (aq.)
0.5 equiv. butanedione
0.2 equiv. acid
0.5 equiv. DCB
15 °C, EtOH (0.5 M)

Figure 16 Conversion of cyclooctene using standard conditions with different acids in ethanol monitored by Raman spectroscopy ($\lambda_{exc}$ 785 nm) a) Table shows conversion of reactions after 1 and 4 h and b) relation between conversion and $pK_a$ of acids.

<table>
<thead>
<tr>
<th>acid</th>
<th>$pK_a$</th>
<th>conversion (%) after 1 h</th>
<th>conversion (%) after 4 h</th>
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<tr>
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<td>-</td>
<td>32</td>
<td>55</td>
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<tr>
<td>Cl₃C₆H₄CO₂H</td>
<td>0.65</td>
<td>0</td>
<td>6</td>
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<td>2,6diCl-PhCO₂H</td>
<td>1.69</td>
<td>31</td>
<td>61</td>
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<td>2NO₂-PhCO₂H</td>
<td>2.17</td>
<td>59</td>
<td>70</td>
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<tr>
<td>ClCH₂CO₂H</td>
<td>2.86</td>
<td>53</td>
<td>61</td>
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<td>13</td>
<td>33</td>
</tr>
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<td>3NO₂-PhCO₂H</td>
<td>3.45</td>
<td>69</td>
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<tr>
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<td>3.83</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>PhCO₂H</td>
<td>4.20</td>
<td>73</td>
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</tr>
<tr>
<td>AcOH</td>
<td>4.76</td>
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</tr>
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</table>

$Scheme\ 5$ $pK_a$ of pyridine-2-carboxylic acid. $^{16}$
Figure 17 Intensities of substrate band at 1650 cm\(^{-1}\) against time for the oxidation of cyclooctene using conditions stated in Figure 15 monitored by Raman spectroscopy (\(\lambda_{\text{exc}} 785\) nm).

Thus it can be concluded that acids have different effects on the reaction depending on their pK\(_a\). Some completely inhibit the reaction, some retard the reaction rate and some only remove the lag period.

The next question that arises is the effect of acid on the equilibrium between butanedione and H\(_2\)O\(_2\). One of the acids in each category (from Table 1) was used to study this. UV/Vis absorption spectroscopy was used to monitor the butanedione concentration in the reaction (Figure 18). From the results, only acetic acid gives similar behaviour compared to the original conditions. Butanedione reacts directly with H\(_2\)O\(_2\) manifested in an immediate decrease in absorption at 417 nm upon addition of H\(_2\)O\(_2\). Since the reaction with acetic acid showed no lag time after addition of H\(_2\)O\(_2\) (as discussed above) and reaction reached its maximum conversion sooner than in the absence of acid and the recovery of butanedione occurred earlier here also. So it can be concluded that the equilibrium between butanedione and H\(_2\)O\(_2\) and the adduct are unaffected by acetic acid.
Table 1 Classification of acids and their effects on the oxidation of cyclooctene using conditions stated in Figure 15 (effect on the reaction are based on kinetic analysis in Figure 17)

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>pK_a</th>
<th>type</th>
<th>effect on the reaction</th>
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<td>none</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>HClO₄</td>
<td>-10</td>
<td>1</td>
<td>inhibit the reaction completely</td>
</tr>
<tr>
<td>3</td>
<td>Cl₃CCO₂H</td>
<td>0.65</td>
<td>1</td>
<td>retard the reaction</td>
</tr>
<tr>
<td>4</td>
<td>2,6-diCl-PhCO₂H</td>
<td>1.69</td>
<td>2</td>
<td>remove the lag period but do not affect the reaction rate</td>
</tr>
<tr>
<td>5</td>
<td>2-NO₂-PhCO₂H</td>
<td>2.17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ClCH₂CO₂H</td>
<td>2.86</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2-OH-PhCO₂H</td>
<td>2.97</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3-NO₂-PhCO₂H</td>
<td>3.45</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3-Cl-PhCO₂H</td>
<td>3.83</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PhCO₂H</td>
<td>4.20</td>
<td>3</td>
<td>do not affect the reaction rate</td>
</tr>
<tr>
<td>11</td>
<td>AcOH</td>
<td>4.76</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The equilibrium in the presence of chloroacetic acid and trichloroacetic acid was different, however, with a slow decrease in the absorption of butanedione indicating that the equilibrium is shifted to the left (back to butanedione) instead of the butanedione/H₂O₂ adduct (see the reaction of butanedione and H₂O₂ in Scheme 3). This supports the kinetic data for conversion obtained with chloroacetic acid, which shows that it retards the oxidation of cyclooctene. The gradual decrease of the absorbance of butanedione with trichloroacetic acid indicates that hydroperoxy acetal is built up slowly in the reaction as was detected by¹³C NMR with a signal at 208 ppm observed (data not shown). Moreover, the exponential decay of butanedione suggests that it decomposed to form other species, albeit, not acetic acid. The ¹³C NMR signal at 174 ppm (C=O of acetic acid) cannot be detected even 45 min after addition of H₂O₂. Instead an unidentified species at 117 ppm formed in the reaction (data not shown). The fact that the hydroperoxy acetal was formed but no conversion of cyclooctene was observed implied that the formation of the active catalyst did not occur either employing trichloroacetic acid.

The data described above can be rationalised as follows. An acid can have more than one effect on the reaction, for example trichloroacetic acid, inhibits the reaction, possibly because it protonates pyridine-2-carboxylic acid and thus inhibits the formation of the active catalyst and also shifts the equilibrium between butanedione and H₂O₂ reducing the effective concentration of 3-hydroperoxy-3-hydroxybutan-2-one. Secondly, because of the effect on the equilibrium shown above, some acids retard the reaction. Finally, some acids remove the lag phase because they promote the formation of an active catalyst.
Mechanistic study of an in situ prepared MnII/ pyridine-2-carboxylic acid catalytic system

Figure 18 Changes in the UV/vis absorption spectrum of butanedione at 417 nm in the oxidation reaction of cyclooctene using standard conditions with various acids stated in Figure 15.

5.2.6 18O-labelling studies

As discussed in Chapter 1, one of the most powerful tools available in studying mechanisms in oxidation catalysis is isotopic labelling, *i.e.* atom tracking of oxygen.17 Labelled hydrogen peroxide (H218O2) and/or labelled water (H218O) were used in the reaction in order to identify the origin of oxygen atoms in the products. The oxidation of cyclooctene employing H218O and H216O2 provided cyclooctene where only 16O was incorporated in the epoxide product (Figure 19). This indicates that the oxygen in the epoxide product is not from water. For the complementary experiment with H216O and H218O2, surprisingly *ca.* 1 : 1 ratio of epoxide incorporating 16O or 18O was observed. This means only 50% of the oxygen atoms in the product are from H2O2. The other source is possibly from butanedione. O2 (from air) is excluded as a source since the reaction can be performed under N2 or Ar atmosphere.
Figure 19 $^{16}$O and $^{18}$O isotopic distribution in the oxidation product of cyclooctene measured by mass spectrometry.

Figure 20 $^{16}$O and $^{18}$O isotopic distribution in the oxidation product of diethylfumarate measured by mass spectrometry.
Mechanistic study of an in situ prepared Mn^{II} / pyridine-2-carboxylic acid catalytic system

Diethylfumarate was used also for this study as it provided cis-diol as the major product (Figure 20). Similar results were observed with the reaction employing H_{2}^{18}O and H_{2}^{16}O_{2}. In agreement, the oxygen atoms in the product are not from water as purely cis-diol with both ^{16}O is observed. Interestingly, only cis-diol with one atom each of ^{16}O and ^{18}O in the same molecule was observed as the sole product when H_{2}^{16}O and H_{2}^{18}O_{2} were used. Again this supports the hypothesis that oxygen atoms in the product are from both H_{2}O_{2} and butanedione.

5.3 Proposed mechanism

The goal of this discussion is not to propose a microkinetic description of the catalytic system but instead to rationalise the empirical observation made under the conditions employed in the present system (0.005-0.1 mol% Mn^{II}/0.02-0.5 mol% pyridine-2-carboxylic acid/1.0 mol% NaOAc (aq.)/1.5 equiv. H_{2}O_{2}/MeCN). The most striking observation for this system is the equilibrium between butanedione and H_{2}O_{2} towards 3-hydroperoxy-3-hydroxybutan-2-one (A, Scheme 3). From kinetic analyses, it can be concluded that the reaction is zero order with respect to H_{2}O_{2} when in excess with respect to butanedione. However, the reaction is not-zero order with respect to butanedione (Figure 5). The reason for this difference is that the equilibrium between butanedione and H_{2}O_{2} lies almost completely towards A. The concentration of A formed in the reaction depends on the primary concentration of butanedione (when H_{2}O_{2} is present in excess). The formation of A was confirmed by Raman (Figure 6) and ^{13}C NMR (Figure 10) spectroscopy and the rate of reaction depends on the concentration of A.

Under the conditions employed, butanedione decomposes to form acetic acid in situ, which is catalysed by manganese and pyridine-2-carboxylic acid (Figures 10 and 11 and Chart 1). The formation of acetic acid in the reaction is a competitive process to alkene oxidation. In addition, loss of butanedione reduces the effective concentration of A. Acetic acid does not inhibit the present butanedione based system and does not participate in the oxidation through formation of peracetic acid under the conditions employed (Chart 1 and 2). However, it is essential for catalysis, possibly for the formation of the active catalyst as a lag time is eliminated when acetic acid is present. Acids showed several effects on the reaction depending on their pK_a. Some acids completely inhibit the reaction, some only retard the rate of the reaction and some do not affect the reaction rate but only eliminate the lag time (Table 1).

The reaction shows zero order kinetics with respect to substrate (Figure 4). This means that the formation of the oxygen transferring species is the rate determining step. The product distribution of cis- and trans-alkenes showed that epoxidation of alkenes is not a concerted reaction, in contrast to cis-dihydroxylation, is a concerted reaction (Scheme 2). However, it is still possible that these two transformations go through a common intermediate. Moreover, the present system provides high activity for both epoxidation of electron rich alkenes and cis-dihydroxylation of electron deficient alkenes.
and low activity for \( \alpha,\beta \)-unsaturated alkenes. This suggests that the catalyst simultaneously has both electrophilic and nucleophilic properties.

As mentioned above the formation of the oxygen transferring species is the rate determining step under the reaction conditions employed. It can also be concluded from kinetic analyses that the reaction is non-zero order with respect to both manganese and pyridine-2-carboxylic acid (Figure 2 and 3). However, varying these two components over a wide range of concentrations showed a concentration dependence, where the concentration of one compound is dependent on the concentration of the other compound, but in general a ratio greater than \( ca. 3 : 1 \) of pyridine-2-carboxylic acid : manganese provides good activity. A base is also necessary for forming the active catalyst unless sodium pyridine-2-carboxylate is used. This observation is still not fully understood since even addition of the base after addition of acetic acid is sufficient. The characterisation of the active catalyst is challenging and it is not practical to determine its structure due to the low concentration of catalyst used in the reaction. EPR spectroscopy of the reaction mixture showed that no EPR active species were present (perpendicular mode, at 77 K). This indicates that mononuclear Mn\( \text{II} \) is not present.\(^{18,19}\) Hence multinuclear Mn\( \text{II} \) and mononuclear Mn\( \text{III} \) are possible candidates.

Data obtained from labelling studies provided some insight as to the active species (Figures 19 and 20). Both epoxidation and \textit{cis}-dihydroxylation of alkenes showed that oxygen is not incorporated from water but that half of the oxygen comes from H\(_2\)O\(_2\) and half, possibly, from butanedione.\(^{20}\) These data suggest that the active species should contain two equivalent oxygen atoms which are available for transfer to the product. Thus a peracid type or cyclic oxidant, \textit{e.g.} B and D (Scheme 6), can be excluded. In addition Mn\( \text{IV}=\text{O} \) or HO-Mn\( \text{IV}=\text{O} \) (E and F, respectively) are unlikely since generally Mn\( \text{IV} \) oxo complexes are not that reactive for oxidation of alkenes.\(^{21}\) So a possible active species in this case could be Mn\( \text{V}=\text{O} \), \textit{i.e.} C (Scheme 6).
Mechanistic study of an in situ prepared Mn$^{II}$/pyridine-2-carboxylic acid catalytic system

Scheme 6 Proposed mechanism for the oxidation of alkenes under the present system based on data from kinetic analyses and orders of the reaction.

5.4 Summary and conclusions

In this chapter, kinetic analyses using Raman and UV/Vis spectroscopy provided important data in which the relationship between individual components in the reaction and their effects on the reaction can be inferred. It can be concluded that the reaction is zero order with respect to H$_2$O$_2$ and substrate and non-zero order with respect to Mn$^{II}$, pyridine-2-carboxylic acid and butanedione under the conditions employed.

Both the equilibrium between butanedione and H$_2$O$_2$ to form the hydroperoxy acetal and its decomposition to form acetic acid in situ were demonstrated using Raman spectroscopy, UV/Vis absorption and NMR spectroscopy. Acetic acid formed in the reaction is not directly responsible for catalysis as no peracetic acid is formed, however, it aids the formation of the active catalyst manifested in a lack of the lag period. Other acids showed different effects on the reaction depending on their pK$_a$.

It can be concluded as well that the rate determining step of the reaction is the formation of the oxygen transferring species. In order to identify the structure of active catalyst,
more experiments need to be performed such as $^{18}$O-exchange to butanedione which can provide more evidence for the origin of oxygen atom in the products.

The consequences of the mechanistic understanding for the catalytic system developed here are explored further with regard to future work in Chapter 6.

5.5 Experimental section

All reagents are of commercial grade and used as received unless stated otherwise. Hydrogen peroxide was used as received as a 50 wt. % solution in water; note that the grade of H$_2$O$_2$ employed can affect the outcome of the reaction where sequestrants are present as stabilisers. $^1$H NMR (400.0 MHz) and $^{13}$C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to $^1$H NMR CDCl$_3$ (7.26 ppm), CD$_3$CN (1.94 ppm) and $^{13}$C NMR CDCl$_3$ (77 ppm), CD$_3$CN (118 ppm).

Caution. The drying or concentration of solutions that potentially contain H$_2$O$_2$ should be avoided. Prior to drying or concentrating, the presence of H$_2$O$_2$ should be tested for using peroxide test strips followed by neutralization on solid NaHSO$_3$ or another suitable reducing agent. When working with H$_2$O$_2$, 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 exposure to its vapours. It should be handled in a properly ventilated fumehood and exposure to vapours should be avoided.

General procedures for catalytic oxidation of alkenes described in Scheme 2

To a solution of Mn(ClO$_4$)$_2$·6H$_2$O (0.01 mol%, 0.0361 mg) and pyridine-2-carboxylic acid (0.5 mol%, 0.123 mg) in acetonitrile was added the alkene (1 mmol) to give a final concentration of the substrate of 0.5 M, NaOAc (aq. 0.6 M, 1 mol%, 16.7 $\mu$l) and 2,3-butanedione (0.5 equiv. 43.5 $\mu$l) to give a final volume of 2 ml. The solution was stirred in an ice/water bath before addition of H$_2$O$_2$ (50 wt. %, 1.5 equiv., 85 $\mu$l). The reaction mixture was stirred for 1 h. After 1 h, brine (10 ml) was added and the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine. The product was dried over Na$_2$SO$_4$ (anh.), filtered, and the dichloromethane was removed in vacuo. 1,2-Dichlorobenzene was employed as internal standard for Raman and $^1$H NMR spectroscopy. The products were isolated by flash column chromatography on silica gel 230-400 or neutral aluminum oxide 70-230.

Note: For some reactions CD$_3$CN was used as solvent with analysis after the reaction carried out by $^1$H NMR spectroscopy directly.
5.6 References and notes


7. The mechanism for the decomposition, e.g. dioxetane, epoxide or Baeyer-Villiger, is not certain. See references: 8-10.


12. These values were measured in water.


18. It should be noted, however, that although preliminary EPR spectroscopic studies show that Mn$^{II}$ at 0.01 mol% shows the expected 6-line signal, under reaction conditions, no EPR signals were observed at room temperature indicating that mononuclear Mn$^{II}$ is not present in significant amounts.

19. The absence of evidence for manganese species in higher oxidation states does not preclude the involvement of such species in a catalytic cycle, however, if such species do form, then the rate at which they react must be significantly faster than their rate of formation. A possibility is that the reaction proceeds via an electron transfer mediated mechanism; see for example J. Piera and J. E. Bäckvall, *Angew. Chem. Int. Ed.*, 2008, **47**, 3506.

20. The exchange between oxygen atom of butanedione and H$_2$O is possible, however, the exchange rate is relatively slow compared to the reaction time as observed by the new Raman band at 1690 cm$^{-1}$ which belongs to C=O appeared in the reaction mixture after addition of H$_2$O$_2$. 

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40 min. In order to assign the exact origin of oxygen atom in the products, $^{18}$O-labelled butanedione is required and this will be studied in the near future.


