Pergamon

Tetrahedron Letters 43 (2002) 5487–5490

TETRAHEDRON
LETTERS

Stereoselective alkane hydroxylations by metal salts and *m*-chloroperbenzoic acid

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Received 4 March 2002; revised 27 May 2002; accepted 31 May 2002

Abstract—Simple metal (M = Mn, Fe, Co) perchlorates associated with *m*-chloroperbenzoic acid are able to conduct stereoselective alkane hydroxylations via a mechanism involving metal-based oxidants; the catalytic activity of the metal salts is in the order of $Co(ClO_4)_2$>$Mn(ClO_4)_2$>$Fe(ClO_4)_2$. © 2002 Elsevier Science Ltd. All rights reserved.

The selective hydroxylation of unactivated C–H bonds of alkanes by metal complexes are of significant importance in both synthetic chemistry and industrial processes. Since heme- and nonheme-containing monooxygenase enzymes catalyze the most energetically difficult hydroxylation of alkanes under physiological reaction conditions, biomimetic alkane hydroxylations using the model compounds of monooxygenase enzymes have received much attention in the communities of bioinorganic and oxidation chemistry.[1,2] It has been demonstrated that synthetic metal complexes with porphyrin and non-porphyrin ligands mimic the chemistry of the monooxygenases and that alkane hydroxylations by the model compounds proceed via a mechanism involving metal-based oxidants (e.g. high-valent metal oxo intermediates).[3] It has also been shown that metal salts associated with peracids conduct alkane hydroxylations via a non-radical type of oxidation reactions.[4,5]

Very recently, Burgess and co-worker reported that manganese(II) salts without organic ligands catalyze epoxidation of olefins by aqueous 30% H_2O_2 in bicarbonate buffer, yielding epoxides exclusively.[6] The authors suggested that an active oxidant that reacts with manganese salts is percarbonate (HCO_4^-), which is generated in situ by the reaction of H_2O_2 and bicarbonate.[7] As an initial attempt to find out whether metal salts without porphyrin and non-porphyrin ligands are able to conduct stereospecific alkane hydroxylations, we have studied alkane hydroxylations with simple metal salts and peracids. We now report that the first-row transition metal perchlorates associated with *m*-chloroperbenzoic acid (*m*-CPBA) are indeed able to hydroxylate alkanes stereospecifically via a mechanism involving metal-based oxidants and that, among the tested metal salts, cobalt perchlorate shows the highest reactivity.

The catalytic hydroxylation of alkanes by metal perchlorates and *m*-CPBA was carried out in a solvent mixture of CH_3CN and CH_2Cl_2 at room temperature. Among the tested first-row metal salts, manganese(II), iron(II), and cobalt(II) perchlorates yielded oxygenated products in the hydroxylation of cyclohexane by *m*-CPBA, whereas the formation of oxygenated products was not detected in the reactions of other metal perchlorates such as $Cr(ClO_4)_3$, $Ni(ClO_4)_2$, $Cu(ClO_4)_2$, and $Zn(ClO_4)_2$ (data not shown). Therefore, we have studied the alkane hydroxylation reactions with the perchlorate salts of manganese(II), iron(II), and cobalt(II) in detail. As the results show in Table 1 [see the column of $M(ClO_4)_2$], the reaction of $Co(ClO_4)_2$ with *m*-CPBA gave the highest yields of oxygenated products (e.g. ~90% yield based on *m*-CPBA used in the hydroxylation of *cis*-1,2-dimethylcyclohexane), whereas only small amounts of oxygenated products were yielded in the reaction of $Fe(ClO_4)_2$ with *m*-CPBA (e.g. ~15% yield based on *m*-CPBA in the hydroxylation of *cis*-1,2-dimethylcyclohexane).[8] These results indicate that cobalt salt is the most efficient catalyst in

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Keywords: biomimetic; alkane hydroxylation; metal perchlorate; monooxygenases; catalysis; *m*-chloroperbenzoic acid.

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PII: S0040-4039(02)01060-2

Table 1. Hydroxylation of alkanes by *m*-CPBA catalyzed by simple metal salts and their metalloporphyrin complexes[a,b]

Substrate	Products		Yields of products (%)[c]					
			$M(ClO_4)_2$			$M(TPFPP)(ClO_4)$[d]		
		M =	Co	Fe	Mn	Co[e]	Fe	Mn
cis-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol		81±4	10±2	25±2	60±3	55±3	40±3
	trans-1,2-Dimethylcyclohexanol		<1	<1	<1	<1	<1	<1
	2,3- and 3,4-Dimethylcyclohexanol[f]		8±1	4±1	12±2	7±1	20±2	16±2
trans-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol		0	0	0	0	0	0
	trans-1,2-Dimethylcyclohexanol		67±3	1±1	8±2	40±3	14±2	9±1
	2,3- and 3,4-Dimethylcyclohexanol[f]		16±2	4±1	22±3	16±2	42±3	36±3
Cyclohexane	Cyclohexanol		28±3	4±1	21±3	25±3	65±3	44±3
	Cyclohexanone		29±3	3±1	6±1	21±3	5±1	7±1

[a] **Caution**! Since perchlorate salts of metals and metal complexes with organic ligands are potentially explosive, only small amounts of perchlorate salts should be handled with great care. Into a reaction solution of a metal catalyst (1×10^{-3} mmol) and substrate (1 mmol) in a solvent mixture (0.5 mL) of CH_3CN and CH_2Cl_2 (1:1), *m*-CPBA (2×10^{-2} mmol, diluted in 40 μL of CH_3CN) was added in two additions (1×10^{-2} mmol each) at 30 min intervals at room temperature. After the reaction mixture was stirred for 1 h, the reaction solution was directly analyzed by GC and/or GC/MS. Product yields were determined by comparison with standard curves of known authentic samples. Since the hydroxylation reactions were not affected by molecular oxygen, all reactions were performed in air.

[b] A control reaction showed that hydroxylation of cyclohexane by *m*-CPBA does not occur in the absence of metal catalysts.

[c] Based on the amount of *m*-CPBA added. All reactions were run at least in triplicate, and the data reported represent the average of these reactions.

[d] All $M(TPFPP)(ClO_4)$ complexes were prepared by stirring equimolar amounts of M(TPFPP)Cl with $Ag(ClO_4)$ followed by filtering through a 0.45 μM filter. The resulting solutions were used immediately for further studies.

[e] *m*-CPBA was added in two additions at 2 h intervals due to the slow reaction of $Co(TPFPP)(ClO_4)_2$ with *m*-CPBA (see Fig. 2). Total reaction time was 4 h.

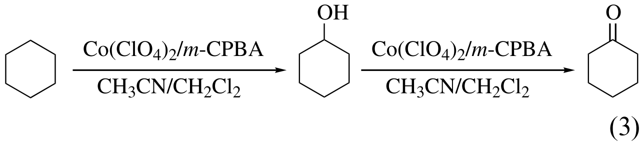
[f] The yields of alcohol products were calculated with commercially available 2,3-dimethylcyclohexanol, with an assumption that the response factors for the alcohols are identical.

terms of yielding oxygenated products and that the catalytic activity of the metal salts is in the order of $Co(ClO_4)_2>Mn(ClO_4)_2>Fe(ClO_4)_2$. We also found that the alkane hydroxylations by $Co(ClO_4)_2$ and $Mn(ClO_4)_2$ were highly stereoselective, in which the hydroxylation of *cis*-1,2-dimethylcyclohexane afforded *cis*-1,2-dimethylcyclohexanol with >98% retention and the hydroxylation of *trans*-1,2-dimethylcyclohexane yielded *trans*-1,2-dimethylcyclohexanol as a major product with no formation of its epimer. The high stereoselectivity observed in the hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexanes strongly indicate that the alkane hydroxylations do not proceed via a typical free-radical mechanism involving a long-lived alkyl radical.[3,9,10a] However, the formation of equal amounts of cyclohexanol and cyclohexanone in the hydroxylation of cyclohexane by $Co(ClO_4)_2$ and *m*-CPBA may suggest the generation of a long-lived alkyl radical followed by the formation of an alkylperoxyl radical by the reaction of the alkyl radical with O_2 (Eq. (1)).[10,11] Russell-type termination of the alkylperoxyl radical results in the formation of equimolar amounts of alcohol and ketone (Eq. (2)).[11]

$$c\text{-}C_6H_{11}^{\bullet}+O_2\rightarrow c\text{-}C_6H_{11}OO^{\bullet} \tag{1}$$

$$c\text{-}C_6H_{11}OO^{\bullet}+c\text{-}C_6H_{11}OO^{\bullet}\rightarrow c\text{-}C_6H_{11}OH+c\text{-}C_6H_{11}{=}O+O_2 \tag{2}$$

Since the result of the cyclohexane hydroxylation was inconsistent with that of the *cis*- and *trans*-1,2-dimethylcyclohexane hydroxylations, we carried out the following reactions and reached the conclusion that the formation of cyclohexanone was not the result of the generation of a long-lived alkyl radical but the result of further oxidation of cyclohexanol product. First, when the hydroxylation of cyclohexane by $Co(ClO_4)_2$ and *m*-CPBA was carried out in the absence and presence of O_2, the yields of cyclohexanol and cyclohexanone products were the same in both reactions (data not shown). This result indicates that the formation of the products was not affected by the presence of O_2 and that O_2 was not involved in the formation of cyclohexanone (see Eqs. (1) and (2)). Second, when the cyclohexane hydroxylation was carried out by adding *m*-CPBA incrementally, the formation of cyclohexanol was dominant at the beginning of the reaction (Fig. 1). As the amount of *m*-CPBA added to the reaction solution gradually increased, the amount of cyclohexanol product did not change, but the yield of cyclohexanone increased linearly and it became the major product. These results demonstrate that the formation of cyclohexanone was the result of further oxidation of cyclohexanol product (Eq. (3)).



(3)

Other supporting evidence for the latter conclusion was obtained by carrying out a competitive reaction with a

100:1 mixture of cyclohexane and cyclooctanol (Eq. (4)).[†]

$$\begin{array}{c}\text{cyclohexane (1 mmol)}\\ +\\ \text{cyclooctanol (0.01 mmol)}\end{array} \xrightarrow[m\text{-CPBA }(5 \times 10^{-3}\text{ mmol})]{Co(ClO_4)_2\ (1 \times 10^{-3}\text{ mmol})} \begin{array}{c}\text{cyclohexanol (22\%) and cyclohexanone (8\%)}\\ +\\ \text{cyclooctanone (66\%)}\end{array}$$

(Percentages are based on the amount of *m*-CPBA added.)

(4)

In the competitive reaction, the oxidation of cyclooctanol took place preferentially, and the ratio of alcohol to alkane oxidation was determined to be ~2700 after statistical correction (see footnote ‡ for the determination of product percentages). We therefore conclude that ketone is formed as the product of alcohol oxidation and that the intermediate generated in the reaction of $Co(ClO_4)_2$ and *m*-CPBA selectively oxidizes alcohols to give the corresponding ketone products.[12]

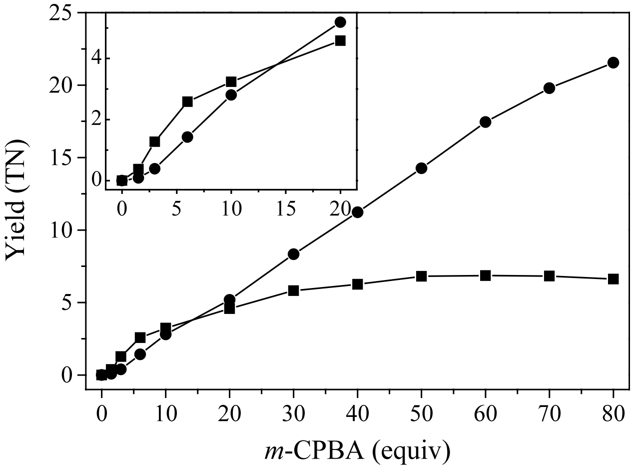


Figure 1. Yields (turnover number) of cyclohexanol (■) and cyclohexanone (●) as a function of equivalents of *m*-CPBA added. Inset: Magnification of the region of 0–20 equiv. of *m*-CPBA. Turnover numbers were calculated as moles of products per mole of $Co(ClO_4)_2$. Reaction conditions: Into a reaction solution of $Co(ClO_4)_2$ (1×10^{-3} mmol) and cyclohexane (1 mmol) in a solvent mixture (0.5 mL) of CH_3CN and CH_2Cl_2 (1:1), *m*-CPBA (diluted in 20 μL of CH_3CN) was added at 30 min intervals at room temperature. The yields of products were analyzed by sampling the reaction solution before the new addition of *m*-CPBA.

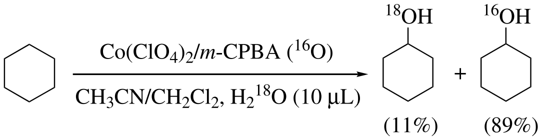
Then, the kinetic isotope effect (KIE) for the cyclohexanol formation by $Co(ClO_4)_2$ and *m*-CPBA was determined by carrying out an intermolecular competitive hydroxylation with cyclohexane and cyclohexane-d_{12} under the reaction conditions where cyclohexanol was yielded as a major product (Eq. (5)).[‡] The k_H/k_D ratio of 8±1 obtained in the KIE study was the same as that obtained in the reaction of $[Co^{III}(TPFPP)]^+$ [TPFPP = *meso*-tetrakis(pentafluorophenyl)porphinato dianion] and *m*-CPBA.[13]

$$\begin{array}{c}C_6H_{12}\\ +\\ C_6D_{12}\end{array} \xrightarrow[m\text{-CPBA }(5 \times 10^{-3}\text{ mmol})]{Co(ClO_4)_2\ (1 \times 10^{-3}\text{ mmol})} \begin{array}{c}C_6H_{11}OH\ (52\%)\\ +\\ C_6D_{11}OD\ (6.6\%)\end{array}$$

(Percentages are based on the amount of *m*-CPBA added.)

(5)

We also performed an ^{18}O-labeled water experiment in the reaction of $Co(ClO_4)_2$ and *m*-CPBA in order to understand whether the reactive species responsible for hydroxylating alkanes exchanges its oxygen with labeled water.[14] The result in Eq. (6) shows that some of the oxygen in the cyclohexanol product came from $H_2{}^{18}O$,[§] and the observation of the ^{18}O-incorporation from $H_2{}^{18}O$ into the alcohol product may suggest the involvement of a high-valent cobalt-oxo species as a reactive intermediate in the hydroxylation of alkanes by $Co(ClO_4)_2$ and *m*-CPBA.[15]



(6)

Lastly, the effect of porphyrin ligand on the reactivity of metal ions has been investigated by performing the alkane hydroxylations with metal salts and their metalloporphyrins under the identical reaction conditions. The results in Table 1 show that the reactivity of the iron ion markedly increased upon binding to an electron-deficient porphyrin ligand, resulting in high yields of oxygenated products with a high alcohol to ketone ratio and an almost complete retention of stereochemistry [Table 1, compare the results of $Fe(ClO_4)_2$ and $Fe(TPFPP)(ClO_4)$]. In the case of the manganese ion, the yields of oxygenated products were almost doubled in the reactions where $Mn(TPFPP)(ClO_4)$ was used as a catalyst [Table 1, compare the results of $Mn(ClO_4)_2$ and $Mn(TPFPP)(ClO_4)$]. In contrast to the iron and manganese cases, the yields of oxygenated products diminished slightly in the reactions where the cobalt ion was bound to a porphyrin ligand [Table 1, compare the

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[†] *m*-CPBA (5×10^{-3} mmol, diluted in 20 μL of CH_3CN) was added to a reaction solution containing $Co(ClO_4)_2$ (1×10^{-3} mmol) and substrates (1 mmol of cyclohexane and 0.01 mmol of cyclooctanol) in a solvent mixture (0.5 mL) of CH_3CN and CH_2Cl_2 (1:1). After the reaction mixture was stirred for 10 min, the reaction solution was analyzed by GC. The yields of products were determined to be cyclohexanol (1.1×10^{-3} mmol, 22% yield based on *m*-CPBA), cyclohexanone (0.4×10^{-3} mmol, 8%), and cyclooctanone (3.3×10^{-3} mmol, 66%).

[‡] The reaction conditions were the same as described in footnote † except that equal amounts (1 mmol each) of competing substrates were used.

[§] The ^{18}O-labeled water experiment was run in the presence of $H_2{}^{18}O$ (10 μL, 95% ^{18}O enriched) under the reaction conditions described in Table 1, footnote a. The yields of cyclohexanol and cyclohexanone were 27 and 26%, respectively. The ^{16}O and ^{18}O compositions in cyclohexanol were analyzed by GC/MS (Hewlett–Packard 5890 II Plus gas chromatograph interfaced with Hewlett–Packard Model 5989B mass spectrometer) and determined by the relative abundance of mass peaks at $m/z = 57$ for ^{16}O and 59 for ^{18}O. A control experiment showed that cyclohexanol does not exchange its oxygen with water under the experimental conditions.

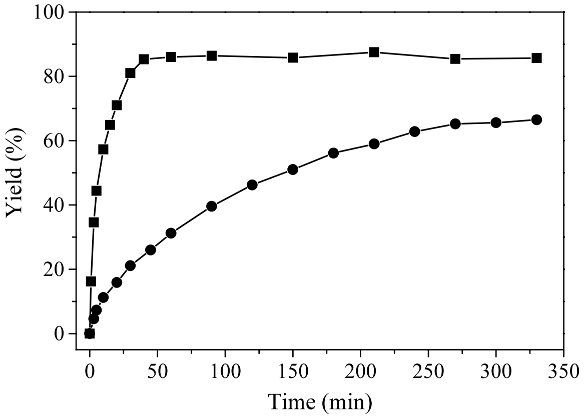

Figure 2. Yields (%, based on the amount of *m*-CPBA added) of *cis*-1,2-dimethylcyclohexanol obtained in the reactions of $Co(ClO_4)_2$ (■) and $Co(TPFPP)(ClO_4)$ (●) as a function of reaction time. Reaction conditions were the same as described in Table 1, footnote a except that *m*-CPBA (20 equiv.) was added all at once to the reaction solution. Aliquots of the reaction solutions were sampled at the given time and analyzed by GC.

results of $Co(ClO_4)_2$ and $Co(TPFPP)(ClO_4)$].[13] Moreover, the formation of oxygenated products was found to be much slower in the hydroxylation of *cis*-1,2-dimethylcyclohexane by $Co(TPFPP)(ClO_4)$ than by $Co(ClO_4)_2$ (Fig. 2). With the previous results that cobalt porphyrins containing electron-rich porphyrin ligand such as $[Co(TMP)]^+$ [TMP = *meso*-tetramesitylporphinato dianion] is a poorer catalyst in alkane hydroxylations by *m*-CPBA, the high reactivity of simple cobalt salt compared to cobalt porphyrin complexes suggests that as the electron-richness of cobalt ion increases, the activity of cobalt ion toward alkane hydroxylation becomes lower. In conclusion, the results presented above indicate that, as we have expected, there is a porphyrin ligand effect on the catalytic activity of metal ions, but the increase or decrease in the catalytic activity depends on the metal ions.

In summary, we have shown here that simple metal salts without porphyrin and non-porphyrin ligands are able to conduct stereospecific alkane hydroxylations via non-radical types of oxidation reactions. Interestingly, cobalt salt shows the highest catalytic activity in terms of product yields. Future studies will focus on attempts to develop an environmentally benign hydroxylation method, in which metal salts are used as catalysts and aqueous 30% H_2O_2 and bicarbonate are used to generate percarbonate as an active oxidant.[6,7]

Acknowledgements

This research was supported by the Korea Research Foundation (DP0270).

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15. Although the structure of the high-valent cobalt-oxo species is not clear at this moment, possible structures for the suggested cobalt-oxo species are $Co^V{=}O \leftrightarrow Co^{IV}{-}O^\bullet$.