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Biomimetic alkane hydroxylation by cobalt(III) porphyrin complex and *m*-chloroperbenzoic acid†

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The catalytic hydroxylation of alkanes by an electron-deficient cobalt(III) porphyrin complex and *m*-chloroperbenzoic acid yielded alcohols as major products with a high k_H/k_D value, > 99% retention of stereochemistry, and a high regioselectivity; a high-valent cobalt–oxo porphyrin complex was suggested as a reactive hydroxylating intermediate.

Cytochrome P-450 enzymes are capable of catalyzing a variety of oxidation reactions, including the most energetically difficult hydroxylation of unactivated C–H bonds of alkanes.[1] Since selective oxygenations of hydrocarbons under mild conditions are of importance in both synthetic chemistry and industrial processes, biomimetic hydroxylation reactions with synthetic metalloporphyrins have been intensively studied over the past two decades.[2] It has been shown that metalloporphyrins containing iron, manganese, and ruthenium ions, especially with electron-deficient porphyrin ligands, are efficient catalysts for the hydroxylation of alkanes by various oxidants.[2,3] However, cobalt porphyrin complexes have been rarely used as catalysts in alkane hydroxylation reactions, since the reactions of cobalt complexes with hydroperoxides often proceed *via* free-radical type of oxidation reactions.[4] In the present study, we report for the first time that an electron-deficient cobalt(III) porphyrin complex catalyzes the hydroxylation of alkanes by *m*-chloroperbenzoic acid (*m*-CPBA) *via* a non-radical type of oxidation reaction.

The catalytic hydroxylation of alkanes by Co(TPFPP)(CF_3SO_3) [**1**, TPFPP = *meso*-tetrakis(pentafluorophenyl)porphinato dianion] and *m*-CPBA was carried in a solvent mixture of CH_3CN and CH_2Cl_2 at rt.‡ The results in Table 1 show that alcohols were yielded as major products with high alcohol to ketone ratios under mild reaction conditions, indicating that *m*-CPBA is a competent terminal oxidant for the alkane hydroxylations by the cobalt porphyrin complex.§¶‖ The kinetic isotope effect (KIE) for the cyclohexanol formation by **1** and *m*-CPBA was determined to be 8 ± 1 by carrying out intermolecular competitive hydroxylation with cyclohexane and cyclohexane-d_{12} (Table 1, entry 5).[5,6]

The stereochemistry of the alkane hydroxylations by **1** and *m*-CPBA was investigated with *cis*- and *trans*-1,2-dimethylcyclohexane. The alkane hydroxylations were highly stereospecific with > 99% retention; no formation of isomerized alcohol products (*e.g.* the formation of *trans*-1,2-dimethylcyclohexanol in the hydroxylation of *cis*-1,2-dimethylcyclohexane was observed (Table 1, entries 2 and 3). Interestingly, only small amounts of secondary alcohol products such as 2,3- and 3,4-dimethylcyclohexanol were formed in these reactions, and these results are different from those of the hydroxylations of *cis*- and *trans*-1,2-dimethylcyclohexane by iron complexes of porphyrin and non-porphyrin ligands.[6] In the latter reactions, moderate to high amounts of secondary alcohol products were yielded. In a competitive hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane, the former was found to react 2.9 times faster than the latter (Table 1, entry 6). The alkane hydroxylation by **1** and *m*-CPBA was also found to be highly

Table 1 Hydroxylation of alkanes by **1** and *m*-CPBA[a]

Entry	Substrate	Products	Yields (%)[b,c]
A. Hydroxylation of alkanes			
1	Cyclohexane	Cyclohexanol	39 ± 4
		Cyclohexanone	8 ± 2
2	*cis*-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol	65 ± 5
		trans-1,2-Dimethylcyclohexanol	< 1
		2,3- and 3,4-Dimethylcyclohexanol[d]	5 ± 1
3	*trans*-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol	0
		trans-1,2-Dimethylcyclohexanol	43 ± 4
		2,3- and 3,4-Dimethylcyclohexanol[d]	8 ± 2
4	Adamantane[e]	Adamantan-1-ol	53 ± 3
		Adamantan-2-ol	9 ± 2
		Adamantan-2-one	> 1
B. Competitive hydroxylation of alkanes[f]			
5	Cyclohexane + Cyclohexane-d_{12}	Cyclohexanol Cyclohexanol-d_{12}	32 ± 3 4 ± 1
6	*cis*-1,2-Dimethylcyclohexane + *trans*-1,2-Dimethylcyclohexane	*cis*-1,2-Dimethylcyclohexanol *trans*-1,2-Dimethylcyclohexanol	41 ± 3 14 ± 1

[a] See footnote ‡ for detailed reaction procedures. Since the hydroxylation reactions were not affected by molecular oxygen, all the reactions were performed in air. [b] All reactions were run at least triplicate, and the yields reported represent the average of these reactions. [c] Based on the amount of *m*-CPBA added. [d] The yield of 3,4-dimethylcyclohexanol was determined with commercially available 2,3-dimethylcyclohexanol, with an assumption that the response factors for these alcohols are identical. [e] Reaction was run with 0.2 mmol of adamantane in CH_2Cl_2 (0.5 mL) due to the low solubility of adamantane. [f] Equal amounts of competing substrates (1 mmol each) were used.

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† Electronic supplementary information (ESI) available: Fig. S1. See http://www.rsc.org/suppdata/cc/b1/b103986p/

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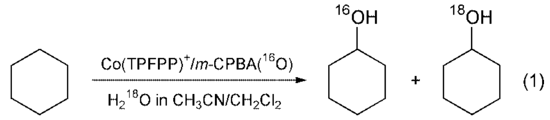
regioselective, in which a high degree of selectivity for tertiary C–H bond over secondary C–H bond was observed in the hydroxylation of adamantane (Table 1, entry 4). The ratio of 3°/2° oxygenated products was ~18 after statistical correction; such a high 3°/2° ratio was usually observed in iron and manganese porphyrin-catalyzed hydroxylation of adamantane.[7]

The results presented above demonstrate unambiguously that the alkane hydroxylations by **1** and *m*-CPBA occur *via radical-free* oxidation reactions:[6] (1) the fact that alcohols were the major products with high alcohol to ketone ratios and the ratios of alcohol to ketone products were not affected by the presence of O_2, (2) a high KIE value for the formation of cyclohexanol, and (3) a complete retention of stereochemistry in the hydroxylations of *cis*- and *trans*-alkanes. Then, what is the nature of a hydroxylating intermediate? Is a high-valent cobalt–oxo porphyrin complex involved as a reactive species? Since isotopically labeled water ($H_2{}^{18}O$) experiments are a useful mechanistic probe to test the involvement of high-valent metal oxo intermediates in metal-mediated oxygen atom transfer reactions,[8] the hydroxylation of cyclohexane by **1** and *m*-CPBA was conducted in the presence of a small amount of $H_2{}^{18}O$ [eqn. (1)].** As the results show in Table 2 (entries 1 and 2), some of the oxygen in the cyclohexanol product came from $H_2{}^{18}O$ and the percentage of ^{18}O in the alcohol product was dependent on the amount of $H_2{}^{18}O$ present in the reaction media. These results imply that a reactive hydroxylating intermediate generated in the reaction of **1** and *m*-CPBA exchanges its oxygen with labeled water prior to the oxygen atom transfer from the intermediate to cyclohexane.[8,9] For comparison, the ^{18}O-labeled water experiment was carried out with an iron porphyrin complex, Fe(TPFPP)(CF_3SO_3), under the identical reaction conditions, since we have shown previously that an oxoiron(IV) porphyrin cation radical complex was generated as a reactive hydroxylating intermediate in the hydroxylation of alkanes by Fe(TPFPP)(CF_3SO_3) and *m*-CPBA.[10] The degree of ^{18}O-incorporation in the Fe(TPFPP)(CF_3SO_3) reaction was about two times greater than that in the Co(TPFPP)(CF_3SO_3) reaction (Table 2, entries 3 and 4). Since the observation of ^{18}O-incorporation from $H_2{}^{18}O$ into oxygenated products is indirect evidence for the involvement of high-valent metal oxo intermediates in metal-catalyzed oxygenation reactions,[8–10] we suggest that a high-valent cobalt–oxo porphyrin complex participates as a reactive species in the cobalt porphyrin-catalyzed hydroxylation of alkanes by *m*-CPBA.



(1)

In conclusion, we have shown for the first time that an electron-deficient cobalt(III) porphyrin complex catalyzes the hydroxylation of alkanes by *m*-CPBA *via* a non-radical type of oxidation reactions. We suggest that a high-valent cobalt–oxo porphyrin complex is generated as a reactive hydroxylating intermediate in the reaction of the cobalt porphyrin complex and *m*-CPBA. Future studies will focus on attempts to understand the exact nature of the reactive intermediate.

Table 2 Percentages of ^{18}O incorporated from $H_2{}^{18}O$ into cyclohexanol product[a]

Entry	Catalyst	Amount (μL) of $H_2{}^{18}O$ present in reaction soln.	Cyclohexanol	
			^{18}O (%)	Yield (%)[b]
1	Co(TPFPP)(CF_3SO_3)	5	5 ± 1	18 ± 2
2		10	10 ± 1	17 ± 3
3	Fe(TPFPP)(CF_3SO_3)	5	11 ± 2	51 ± 4
4		10	18 ± 2	53 ± 4

[a] See footnote ** for detailed reaction procedures. All reactions were run at least triplicate, and the data reported represent the average of these reactions. [b] Based on the amount of *m*-CPBA added.

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Notes and references

‡ Reaction conditions: *m*-CPBA (5×10^{-3} mmol, diluted in 20 μL of CH_3CN) was added to a reaction solution containing **1** (1×10^{-3} mmol) and substrate (1 mmol) in a solvent mixture (0.5 mL) of CH_3CN and CH_2Cl_2 (1 : 1) at rt. After the reaction mixture was stirred for 1 h, the reaction solution was directly analyzed by a Hewlett-Packard 5890 II Plus gas chromatograph with a FID detector and 30 m capillary column (Hewlett-Packard HP-1 or HP-5). Product yields were determined by comparison of peak area with that of decane or dodecane standard.

§ By following the time course of the hydroxylation of cyclohexane by **1** with 5 eq. of *m*-CPBA, we found that the alkane hydroxylation by **1** and *m*-CPBA takes place slowly, and the formation of cyclohexanol lasted for 1 h (data not shown).

¶ A control reaction carried out in the absence of the cobalt porphyrin catalyst did not show the formation of cyclohexanol and cyclohexanone products. Also, other cobalt porphyrin complexes such as Co(TMP)(CF_3SO_3) [TMP = *meso*-tetramesitylporphinato dianion] yielded only small amounts of cyclohexanol (~8%) and cyclohexanone (~2%). All cobalt(III) porphyrin complexes were obtained from Mid-Century and used without further purification.

‖ The catalytic activity of the cobalt porphyrin complex was examined by adding 50 eq. of *m*-CPBA (10 aliquots of 5 eq. of *m*-CPBA each at 1 h time intervals) into a reaction solution containing **1** (1×10^{-3} mmol) and *cis*-1,2-dimethylcyclohexane (1 mmol). Total reaction time was 10 h (see footnote ‡ for detailed experimental procedures). The yield of *cis*-1,2-dimethylcyclohexanol was 40% based on *m*-CPBA added, equivalent to 20 turnovers (see Fig. S1 for a plot of eq. of *m*-CPBA added *vs.* turnover number). By comparing UV-vis spectra of **1** taken before and after the reaction, we found that about 20% of the cobalt porphyrin catalyst was degraded.

** ^{18}O-labeled water experiments were performed under the identical reaction conditions described in footnote ‡ except that $H_2{}^{18}O$ (5 μL, 95% ^{18}O enriched), cyclohexane (0.5 mmol), and 15 eq. of *m*-CPBA (3 aliquots of 5 eq. of *m*-CPBA each at 1 h time intervals) were used. The ^{16}O and ^{18}O compositions in cyclohexanol were determined by the relative abundances of mass peaks at m/z = 57 for ^{16}O and 59 for ^{18}O (HP 5989B mass spectrometer). A control experiment showed that cyclohexanol does not exchange its oxygen with water under the experimental conditions.

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