

Alkane Oxidation Catalyzed by Manganese-tmtacn Complexes with H₂O₂

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Received July 22, 2003

Key Words : Manganese complexes, Mn-tmtacn, Alkane oxidation, Oxidation with H₂O₂

The C-H bond activation of alkanes for selective hydroxylation by metal complexes has been the subject of intense research for application in synthetic chemistry and industrial processes. As metal-containing enzymes functionalize the energetically difficult C-H bonds of alkanes, biomimetic alkane hydroxylations using the model complexes of the enzymes have received much attention in the communities of bioinorganic and oxidation chemistry.¹ Among the reported model complexes, manganese complexes using N, N', N''-trimethyl-1,4,7-triazacyclononane (tmtacn) are known to catalyze various oxidation reactions, such as epoxidation of olefins, hydroxylation of saturated and aromatic hydrocarbons, and oxidation of alcohols, by peroxides.²⁻⁴ In the oxidation reactions of alkane and alkene, the nature of carboxylate buffers was reported to have a significant effect on the activities of the Mn-tmtacn catalysts.⁴⁻⁷ The differences in the activity observed in different carboxylate buffers were suggested perhaps to arise from differences in the structures of the active Mn species involved in the oxidation reactions. As an attempt to get an additional insight into the reactivity and selectivity features of the catalytic alkane oxidation process based on our experience with porphyrin catalysts,⁸ we have studied the alkane oxidation using the Mn-tmtacn catalyst and H₂O₂ in the presence of an oxalate buffer under mild conditions. We now report that this Mn catalyst is able to oxidize alkanes with moderate yields at 0 °C and perform a stereospecific hydroxylation via a mechanism involving metal-based oxidants.

Experimental Section

All reagents purchased from Aldrich Chemical Co. were the best available purity and used without further purification unless otherwise indicated. H₂O₂ (35% aqueous) were purchased from Aldrich.

The catalyst system was prepared *in situ* in the catalytic reaction by mixing MnSO₄, tmtacn, and Na-oxalate. In a typical oxidation reaction, MnSO₄·H₂O (2.0 mmol) in 0.1 mL H₂O was mixed with 3.0 μmol of tmtacn in 0.1 mL acetone and then 3.0 μmol of sodium oxalate (Na-oxalate). After substrate (0.67 mmol) in 0.8 mL acetone were added, the reaction started by treating 3.0 mmol H₂O₂ diluted with

0.3 mL acetone over a 30 min period at 0 °C, and the solution was stirred for additional 2.5 hours. The total volume of the reaction solution was 2 mL. Then, the products were monitored by GC (Donam Systems 6200 gas chromatograph) and identified by GC-MS (Hewlett-Packard 5890 II Plus gas chromatograph interfaced with Model 5989B mass spectrometer).

Results and Discussion

The catalytic oxidation of cyclohexane by Mn(II) and tmtacn with H₂O₂ was carried out in the presence of Na-oxalate as co-catalyst in acetone at 0 °C. With the treatment of 4.5 equivalent of oxidant, 73% conversion of cyclohexane was achieved; however cyclohexanone was produced in 40% yield as a major product with the formation of cyclohexanol and a variety of overoxidized byproducts (entry 1 in Table 1). Such a high conversion with Mn(II) and tmtacn was not observed in the alkane oxidation under different reaction conditions at a similar reaction temperature.³ In the control experiment using cyclohexanol as substrate, a similar amount of cyclohexanone was generated, demonstrating that the cyclohexanone product derived from the further oxidation of cyclohexanol (Scheme 1). Also the low alcohol to ketone ratio of 0.15 indicates that the formation of cyclohexanol and cyclohexanone was not the result of generation of a cyclohexylperoxy radical resulting in the formation of equal amount of alcohol and ketone by a Russell-type termination. Without tmtacn or co-catalyst decreased the yields dramatically, proving that all components are essential for the formation of a reactive metal species.⁴⁻⁶

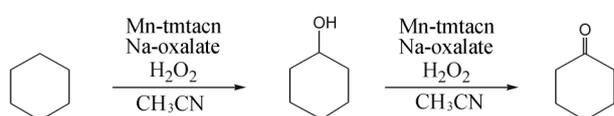
As the acid structure used as co-catalyst was reported to have a significant effect on the epoxidation of olefins and benzylic hydroxylation, we performed the oxidation of cyclohexane in the presence of various additives as co-catalyst (Table 1). Interestingly, the addition of Na-oxalate/oxalic acid afforded a little lower yield and conversion than Na-oxalate, but the use of oxalic acid did not show any reactivity (entry 2, 3). These results indicate that the ionization degree of the co-catalyst affects the catalyst performance. As the addition of oxalic acid in the epoxidation reaction of olefins by the Mn-tmtacn system afforded the similar yield as oxalate/oxalic acid only with the longer reaction time,⁷ no reactivity in the presence of oxalic acid

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Table 1. Oxidation of cyclohexane by Mn(II)/tmtacn/H₂O₂ in the presence of various additives^a

Entry	Additives	Yields of products (%) ^b			Conversion (%)
		cyclohexanol	cyclohexanone	total	
1	Na-oxalate	9	39	48	78
2	oxalic acid	0	0	0	14
3	Na-oxalate/oxalic acid	6	40	46	73
4	malonic acid	5	10	15	29
5	Na-malonate	5	12	17	36
6	succinic acid/Na-succinate	2	9	11	12
7	phthalic acid/Na-phthalate	0	0	0	5
8	acetic acid	3	5	8	41
9	trifluoroacetic acid	1	3	4	35
10	2-ketoglutaric acid	3	7	10	3
11	2-hydroxy 2-methoxyacetic acid	1	2	3	0

^aAll reactions were run at least in duplicate, and the data reported represent the average of these reactions. See the Experimental Section for detailed reaction conditions. ^bBased on the amount of substrate added.

**Scheme 1**

implies that a different reactive species is involved in the C-H bond activation of alkane. The malonic acid and malonate additives which afforded a similar reactivity to the oxalate buffer in the benzylic oxidation³ showed much lower reactivity than Na-oxalate/oxalic acid. All acid additives including acetic acid did no or poor reactivities. In contrast, Mn(IV)-tmtacn complexes were reported to catalyze hydrocarbons efficiently in the presence of acetic acid.^{2,4}

In the hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane, we found that the alkane hydroxylation was highly stereoselective, in which the hydroxylation of *cis*-1,2-dimethylcyclohexane afforded (1R,2R or 1S,2S)-1,2-dimethylcyclohexanol with > 99% retention and that of *trans*-1,2-dimethylcyclohexane yielded (1R,2S or 1S,2R)-1,2-

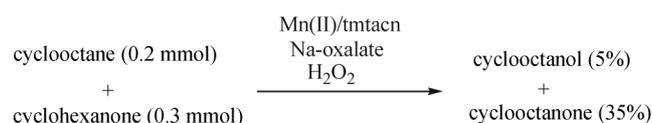
dimethylcyclohexanol with a trace amount of its epimer and 2,3- and 3,4-dimethylcyclohexanones (entry 1 and 2 in Table 2). The high stereoselectivity observed in alcohol products strongly indicates that the alkane hydroxylation do not proceed via a typical free-radical mechanism including a long-lived alkyl radical. The stereoselectivity in the alkane oxidation with Mn(IV)-tmtacn complexes were also reported,^{2,5} but their selectivities were lower than that observed in this study.⁹ In case of cyclooctane oxidation, the catalyst showed the similar reactivity to cyclohexane. The oxidation of *n*-hexane appeared to functionalize 2 and 3 positions without discrimination still with the preferred formation of ketone products, but the oxidation of *n*-alkane by Mn(IV)-tmtacn was reported to generate more alcohol products than ketone and prefer the 2 position.^{4,5}

Other information about the oxidation of alkane was obtained by carrying out a competitive reaction with a 2 : 3 mixture of cyclooctane and cyclohexanone (Scheme 2). Even though 14% of cyclohexanone was further oxidized, the conversion of cyclooctane and the product ratio of

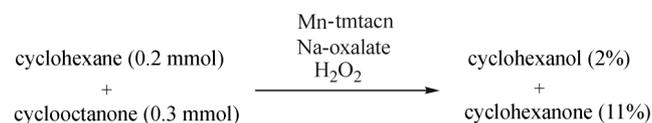
Table 2. Oxidation of alkanes catalyzed by Mn(II) and tmtacn with H₂O₂ in the presence of Na-oxalate^a

Entry	Substrate	Products	Yields of Products (%) ^b	Conversion (%)
1	<i>cis</i> -1,2-dimethylcyclohexane	(1R,2R or 1S,2S)-1,2-dimethylcyclohexanol	8	23
		(1R,2S or 1S,2R)-1,2-dimethylcyclohexanol	0	
		2,3- and 3,4-dimethylcyclohexanones	1	
2	<i>trans</i> -1,2-dimethylcyclohexane	(1R,2R or 1S,2S)-1,2-dimethylcyclohexanol	trace	20
		(1R,2S or 1S,2R)-1,2-dimethylcyclohexanol	6	
		2,3- and 3,4-dimethylcyclohexanones	7	
3	cyclooctane	cyclooctanol	4	66
		cyclooctanone	37	
4	<i>n</i> -hexane	2-hexanol	2	50
		3-hexanol	2	
		2-hexanone	13	
		3-hexanone	13	

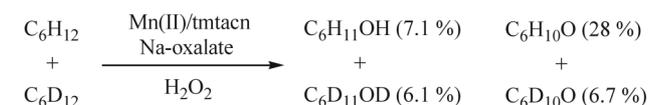
^aAll reactions were run at least in duplicate, and the data reported represent the average of these reactions. See the Experimental Section for detailed reaction conditions. ^bBased on the amount of substrate added.



Scheme 2



Scheme 3



Scheme 4

cyclooctanol and cyclooctanone was not changed compared to the results obtained without cyclohexanone. These results indicate that the oxidation of cyclooctane was not hindered by the presence of cyclohexanone. However, in another competitive experiment with a 2 : 3 mixture of cyclohexane and cyclooctanone, the conversion and product yield decreased with the conversion of cyclooctanone to further oxidized products (9%), but the ratio of oxidation products did not change (Scheme 3).

Then, the kinetic isotope effect (KIE) for the cyclohexane oxidation was determined by carrying out an intermolecular competitive oxidation with cyclohexane and cyclohexane- d_{12} . As cyclohexanol is further oxidized to cyclohexanone, it is complicated to extract the KIE value for each step. Considering that the ratios of $\text{C}_6\text{H}_{11}\text{OH}/\text{C}_6\text{H}_{10}\text{O}$ and $\text{C}_6\text{D}_{11}\text{OD}/\text{C}_6\text{D}_{10}\text{O}$ formed from normal and deuterated cyclohexane are 3.9 and 1.1, respectively, we believe there is a significant KIE in the C-H activation step of cyclohexanol. On the assumption that all cyclohexanone derives directly from cyclohexanol, the KIE for the cyclohexanol formation step of $(\text{C}_6\text{H}_{11}\text{OH} + \text{C}_6\text{H}_{10}\text{O})/(\text{C}_6\text{D}_{11}\text{OD} + \text{C}_6\text{D}_{10}\text{O})$ is calculated as 2.7 (Scheme 4).

In summary, we have shown here that the Mn complex formed *in situ* with the addition of tmtacn and the oxalate co-catalyst is able to conduct alkane hydroxylation stereospecifically *via* non-radical types of oxidation reactions under mild conditions. Future studies will focus on attempts to understand the precise role of the oxalate co-catalyst and to elucidate the structures of reactive species.

Acknowledgement. This work was supported by the Korea Research Foundation (KRF-2001-002-D00154 to J. K.).

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- The *cis/trans* ratio was about 2 in the case of the oxidation of *cis*-decalin, and the *trans/cis* ratio about 30 in the case of *trans*-decalin.