Aerobic Oxidations of Alkanes and Alkenes in the Presence of Aldehydes catalysed by Copper Salts

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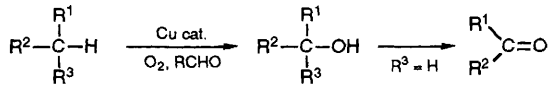
Oxidation of alkanes to the corresponding alcohols and ketones and epoxidation of alkenes can be performed efficiently at room temperature with molecular oxygen (1 atm) in the presence of an aldehyde and a copper salt catalyst such as $Cu(OH)_2$.

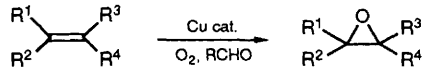
Copper as well as iron is predominantly contained in metalloenzymes that play important roles in biological dioxygen metabolism.[1] Although much effort has been devoted to mimicking haem-iron-containing enzymes such as cytochrome P-450, model studies for the copper-containing monooxygenases such as peptidylglycine α-amidating monooxygenase, which catalyse the oxidation of aliphatic C–H bonds, are limited to a few cases.[2] During the course of our systematic study of the simulation of enzymatic functions with metal complex catalysts,[3] we have found that novel copper salt-catalysed oxidations of alkanes and alkenes with molecular oxygen (1 atm) proceed efficiently at room temperature. Copper salt-catalysed oxidation of alkanes with molecular oxygen in the presence of aldehydes under mild conditions gives the corresponding alcohols and ketones highly efficiently [eqn. (1)], while treatment of alkenes gives epoxides, [eqn. (2)]. This is the practical example of copper-catalysed aerobic oxidation of alkanes and epoxidation of alkenes, although the oxidations of alkanes using hydrogen peroxide[4] and *tert*-butyl hydroperoxide[5] and the oxidations of alkenes using silyl-protected peroxy esters[6] and iodosylbenzene[7] have been reported. More recently, Barton *et al.* have reported oxidation of alkanes with molecular oxygen promoted by Cu power.[8]

The catalytic activity of various copper salts has been examined for the oxidation of adamantane with molecular oxygen (1 atm) in the presence of acetaldehyde. $Cu(OH)_2$ has proved to be the most effective among the catalysts examined, and the effect of copper salts is in the order of $Cu(OH)_2$ > $Cu(OAc)_2$ > CuCl ≈ $Cu(OCOCF_3)_2$ ≫ $CuCl_2$, indicating that a copper salt bearing a more basic ligand is suitable for the present oxidation and that a copper(I) salt is more effective than a copper(II) salt. It is noteworthy that both Cu powder and Cu_2O can be also used. The effect of aldehydes has been examined for the $Cu(OH)_2$-catalysed aerobic oxidation of adamantane and dec-1-ene. The oxidation of adamantane with acetaldehyde and the oxidation of dec-1-ene with cyclohexanecarbaldehyde gave excellent results. Without an aldehyde no oxidation occurs.

The representative results of the $Cu(OH)_2$-catalysed aerobic oxidations of alkanes and alkenes in the presence of aldehydes are summarized in Table 1. Various alkanes including poorly reactive linear alkanes such as n-decane are oxidized to give the corresponding alcohols and ketones highly efficiently under mild conditions. The distributions of the oxygenated products from adamantane and n-decane indicate that the selectivity of the present reaction is in the order of tertiary > secondary ≫ primary. The oxidation of alkenes gives the corresponding epoxides readily and selectively. Stereospecificity is not observed for the epoxidation of dec-5-enes. The reactivity of alkenes is in the order of tri- > di- ≫ mono-substituted ones, indicating that the active species has an electrophilic character.



(1)



(2)

In order to gain insight into the mechanism of the present oxidation of alkanes the relative reaction rates of the $Cu(OH)_2$-catalysed oxidation of four substituted toluenes (X-C_6H_4Me, X = *p*-Me, H, *p*-Cl, and *m*-Cl) with molecular oxygen in the presence of acetaldehyde in CH_2Cl_2 were determined by the GLC analysis of the products. The rate data correlate well (γ = 0.957) with the Hammett linear free-energy relationship with use of σ^+ values. The ρ value is −1.21, which indicates cationic intermediacy at the rate-determining step. The intramolecular deuterium isotope effect of the $Cu(OH)_2$-catalysed oxygenation of 1,1-dideuterio-1,3-diphenylpropane was determined to be 3.7 by GC–MS analysis of the product ketones. Furthermore, the intermolecular isotope effect of the oxygenation of cyclohexanes was determined to be 3.0 by GLC analysis of the ketones obtained from the competitive reaction of cyclohexane and [$^2H_{12}$]cyclohexane. The observed intra- and inter-molecular isotope effects suggest that the C–H bond breaking in the present reaction is a crucial step. Intermediacy of alkyl radicals is supported by the above isotope effects and detection of benzyl chloride from the oxidation of toluene in CH_2Cl_2. Although it is premature to discuss the precise mechanism at the present stage, the reaction can be rationalized by assuming the following pathways. The reaction of

Table 1 Copper-catalysed oxidation of alkanes and alkenes with molecular oxygen in the presence of aldehydes

Substrate	Condition[a]	Conversion (%)[b]	Product[c]	Yield (%)[d]
Cyclohexane	A	4.5	Cyclohexanol	38
			Cyclohexanone	58
Cyclooctane	A	9.9	Cyclooctanol	9
			Cyclooctanone	88
Adamantane	A	29	Adamantanol[e]	92
			Adamantan-2-one	3
n-Decane	A	4.6	Decanol[f]	15
			Decanone[g]	83
Indan	A	27	Indan-1-ol	22
			Indan-1-one	75
Dec-1-ene	B	32	1,2-Epoxydecane	83
Cyclohexene	B	100	1,2-Epoxycyclohexane	79
			2-Cyclohexen-1-ol	1
			2-Cyclohexen-1-one	4
trans-Dec-5-ene	B	83	5.6-Epoxydecane[h]	96
cis-Dec-5-ene	B	96	5,6-Epoxydecane[i]	86
α-Pinene	B	100	α-Pinene oxide	84

[a] Condition A: A mixture of substrate (2.00 mmol), $Cu(OH)_2$ (0.06 mmol), and acetaldehyde (6.00 mmol) in dry CH_2Cl_2 (12 ml) was vigorously stirred at room temperature under oxygen atmosphere (1 atm) for 17 h. Condition B: The similar conditions except cyclohexanecarbaldehyde instead of acetaldehyde and amount of $Cu(OH)_2$ (0.02 mmol). [b] Determined by GLC analysis based on the starting substrate. [c] The identity of the products were verified by coinjection with authentic samples and GC–MS analysis. [d] Determined by GLC analysis based on the converted substrate. [e] 1-ol : 2-ol = 93 : 7. [f] 2-ol : 3-ol : (4 + 5)-ols = 20 : 20 : 60. [g] 2-one : 3-one : (4 + 5)-ones = 27 : 27 : 46. [h] *trans* : *cis* = 100 : 0. [i] *trans* : *cis* = 23 : 77.

aldehydes with molecular oxygen in the presence of $Cu(OH)_2$ would give peracids,[9] which subsequently react with the metal copper salts to afford active species, Cu^{III}–O· or Cu^{IV}=O[8,10] along with carboxylic acids. Intermediacy of peracetic acid has been confirmed by ^1H NMR (270 MHz) analysis of the mixture of $Cu(OH)_2$-catalysed aerobic oxidation of adamantane in the presence of acetaldehyde (3 equiv.) in CD_2Cl_2 at room temp. After 1.5 h the signal of methyl protons of peracetic acid was observed as a singlet at δ 2.13 along with those of acetic acid (δ 2.07s), acetaldehyde (δ 2.15, d, *J* 2.9 Hz), and paraaldehyde (δ 1.32, d, *J* 5.1 Hz). The chemical shifts are identical with those of authentic samples. Indeed, the $Cu(OH)_2$-catalysed oxidation of adamantane with peracetic acid gave similar results to those obtained from the present oxidation reaction. Hydrogen abstraction of alkanes by the above active copper species, followed by electron transfer would give the cationic intermediate $Cu^{II}(OH)(R^+)$ which is converted into alcohols and Cu^{II}. Alcohols can be converted into ketones under the same reaction conditions. The nonstereospecific epoxidation of alkenes indicates that the present epoxidation is not due to the direct reaction of alkenes with peracids formed *in situ* but due to the reaction with active copper species.

Work is in progress to provide definitive mechanistic information and to apply the present method to other systems. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

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