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Communication

Cyclohexane oxidation: Small organic molecules as catalysts

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ABSTRACT

The catalytic activity of several small organic molecules including ketones, aldehydes, esters, alcohols and amines toward cyclohexane oxidation was investigated. The catalytic activity was found to be closely related to polarity, α-H activity, the strength of hydrogen bond formed with cyclohexane and the radical scavenging capability of these molecules. Based on the obtained results, the catalytic role of the organic solvent must be considered for cyclohexane oxidation. Tripropylamine has very high activity in cyclohexane oxidation and it might be further developed as a promising small-molecule organocatalyst for future application.
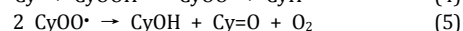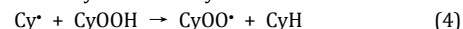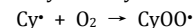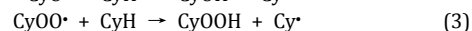
The oxidation of cyclohexane to cyclohexanone and cyclohexanol is an important industrial process and the products are precursors for the production of caprolactam and adipic acid, which are the building blocks for nylon-6 and nylon-6, 6 [1,2]. The auto-oxidation of cyclohexane is known to proceed through a complex radical chain mechanism as described in Scheme 1 [3]. Cyclohexane can react with oxygen to form cyclohexyl hydroperoxide. The chain initiation proceeds through the cleavage of cyclohexyl hydroperoxide (reaction (2)). Once oxygen-centered radicals are formed, they attack cyclohexane to form cyclohexyl radicals (reaction (3)). Cyclohexyl radicals are further oxidized to cyclohexyl peroxy radicals (reaction (4)). The cyclohexyl peroxy radicals are the main chain propagators. The chain is terminated by the mutual destruction of two cyclohexyl peroxy radicals [3]. Various byproducts are generated during the radical chain reaction. Commercially, cyclohexane oxidation is operated at a temperature of 140–160 °C and under a pressure of 1–1.5 MPa. The conversion is usually kept below 5% to prevent the deep oxidation of cyclohexane, giving 70%–85% selectivity toward cyclohexanone-cyclohexanol mixture (KA oil).

Transition-metal ions such as Co^{2+}, Cr^{3+}, or Mn^{2+}, which can accelerate free radical chain reactions [4], have been used to catalyze cyclohexane oxidation. However, these catalysts are difficult to separate from the products and can induce pipeline blocking. Heterogeneous catalysts such as modified zeolites [5–7], supported metal catalysts [8,9], metal organic frameworks [10–14] and carbon materials [15,16] have been used to catalyze cyclohexane oxidation and a certain activity can be

$$CyH + O_2 \rightarrow CyOOH \qquad (1)$$
$$CyOOH \rightarrow CyO^\bullet + {}^\bullet OH$$
$$CyOOH \rightarrow CyOO^\bullet + {}^\bullet H \qquad (2)$$
$$CyO^\bullet + CyH \rightarrow CyOH + Cy^\bullet$$
$$CyOO^\bullet + CyH \rightarrow CyOOH + Cy^\bullet \qquad (3)$$
$$Cy^\bullet + O_2 \rightarrow CyOO^\bullet$$
$$Cy^\bullet + CyOOH \rightarrow CyOO^\bullet + CyH \qquad (4)$$
$$2\ CyOO^\bullet \rightarrow CyOH + Cy{=}O + O_2 \qquad (5)$$
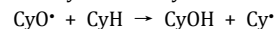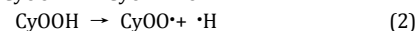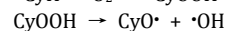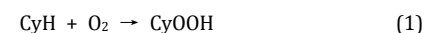
Scheme 1. Radical chain mechanism for cyclohexane oxidation.

obtained. Combined with Mn^{2+} or Co^{2+}, N-hydroxyphthalimide (NHPI) has been successfully applied to the functionalization of different hydrocarbons. Cyclohexane can also be directly oxidized to adipic acid by oxygen using NHPI as a catalyst [17]. In most cyclohexane oxidation reactions that have been reported, a solvent has been used and it has a significant impact on the reaction results. Based on our preliminary experimental results, considerable cyclohexane conversion can be achieved in the absence of catalysts when solvents such as methanol are used. That is, the solvent may play a catalytic role in cyclohexane oxidation. Therefore, the catalytic activity of small organic molecules toward cyclohexane oxidation was investigated in this study and a catalysis mechanism is proposed.

Several kinds of polar molecules with different functional groups were used as catalysts for cyclohexane oxidation under solvent-free conditions. Ultra-high purity reagents (>99.99%) were used throughout the reaction. The catalytic performance of several different ketones, aldehydes, esters, alcohols, and amines are summarized in Table 1. A blank experiment without any catalyst gave a cyclohexane conversion of 1.4% after reaction for 4 h because of auto-oxidation. Cyclohexanol and cyclohexanone were detected as exclusive products. Phenol and its oxidation product, quinone, are good radical scavengers. When phenol was used as the catalyst, no cyclohexane oxidation occurred, which confirmed that this reaction proceeds by a radical chain mechanism. However, cyclohexanone and acetone exhibit significant catalytic activity; their TOF values were 8.3 and 5.2 h^{-1}, respectively. Meanwhile, their selectivity toward cyclohexanone and cyclohexanol was only 74% and 76%, respectively. GC-MS analysis results (Fig. 1) show that the main products obtained when using acetone as a catalyst are cyclohexanone, cyclohexanol and cyclohexanone peroxides, which can induce ring opening reaction and deep oxidation. The catalytic activity of cyclohexanone implies that cyclohexane oxida-
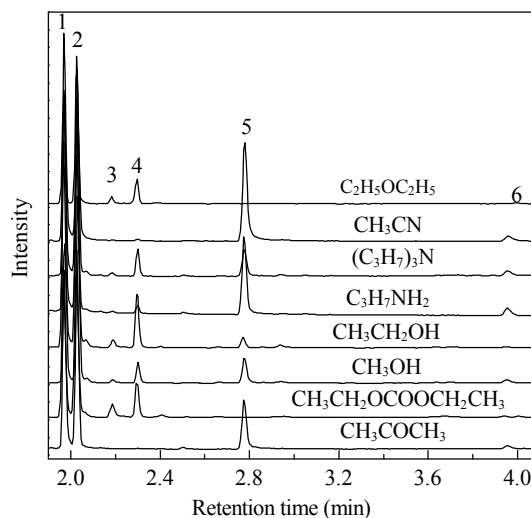
Fig. 1. GC-MS analysis of the products from cyclohexane oxidation over different small-molecule catalysts. 1, Cyclohexanol; 2, Cyclohexanone; 3, Caproic acid; 4, Cyclohexyl hydroperoxide; 5, Cyclohexanone peroxide; 6, Caprolactone.

tion is an autocatalytic reaction. The catalytic activity of diphenyl ketone is much lower than that of cyclohexanone and acetone. Cyclohexane conversion was only 2.1% after 4 h and the TOF value was calculated to be 2.7 h^{-1}.

Similar to ketones, aldehydes also have carbonyl groups and they are expected to be active in the cyclohexane conversion. Benzaldehyde and its homolog, phenylacetaldehyde, show considerable catalytic activity in cyclohexane oxidation. Cyclohexane conversion using benzaldehyde was 14.9%, which corresponds to a TOF value of 10.5 h^{-1}. In addition, the total selectivity toward cyclohexanone and cyclohexanol was 94%, which is distinctly higher than that using cyclohexanone and acetone.

Table 1
Cyclohexane oxidation catalyzed by small organic molecules.

Catalyst		C_6H_{12} conversion [a] (%)	TOF [b] (h^{-1})	$C_6H_{10}O$ selectivity (%)	$C_6H_{12}O$ selectivity (%)
Blank	—	1.4	—	67	32
Ketone	cyclohexanone	11.5	8.3	40	34
	CH_3COCH_3	10.3	5.2	40	36
	$C_6H_5COC_6H_5$	2.1	2.7	58	41
Aldehyde	C_6H_5CHO	14.9	10.5	46	48
	$C_6H_5CH_2CHO$	6.2	5.1	47	45
Ester	$CH_3COOCH_2CH_3$	11.0	7.5	39	46
	$C_3H_7COOCH_2CH_3$	7.3	5.8	30	48
	$CH_3CH_2OCOOCH_2CH_3$	11.2	6.5	43	34
Alcohol	CH_3OH	9.8	2.5	54	36
	CH_3CH_2OH	6.5	2.6	49	40
	$CH_3CH_2CH_2OH$	2.1	1.3	42	38
	CH_2OHCH_2OH	0.6	0.3	64	35
Amine	$C_3H_7NH_2$	13.1	7.5	48	34
	$(C_3H_7)_2NH$	11.2	10.6	47	32
	$(C_3H_7)_3N$	17.0	22.6	48	33
	$(C_2H_5)_3N$	13.7	13.3	42	38
Others	CH_3CN	13.2	4.8	46	32
	$C_2H_5OC_2H_5$	8.3	6.0	43	45
	C_6H_5OH	0	0	—	—

[a] Typical conditions: cyclohexane 3 mL, catalyst 10 μL (or 10 mg), O_2 1.5 MPa, 150 °C, 4 h. After the removal of peroxide by triphenyl phosphine, the reactants and products were analyzed by GC (flame ionization detector, DB-5 capillary column) using biphenyl as an internal standard.
[b] Calculated as mole of cyclohexane converted per mole of catalyst per hour.

The cyclohexane conversion when using phenylacetaldehyde was 6.2% (cyclohexanone and cyclohexanol selectivity of 92%), which corresponds to a TOF value of 5.1 h^{-1}. The catalytic activity of aldehydes obviously decreases with an increase in the length of the carbon chain.

Ethyl acetate, ethyl butyrate, and diethyl carbonate were used as catalysts for cyclohexane oxidation. TOF values of 7.5 and 5.8 h^{-1} were obtained for ethyl acetate and ethyl butyrate, respectively. The catalytic activity decreased with an increase in the length of the catalyst's carbon chain. This is consistent with the results obtained when using aldehydes as the catalyst. In addition, a TOF value of 6.5 h^{-1} was obtained for diethyl carbonate. Selectivity toward cyclohexanone and cyclohexanol was similar to that obtained when using ketones as the catalyst but lower than that obtained when using aldehydes as the catalyst. GC-MS analysis results indicate that the main products from cyclohexane oxidation are cyclohexanone, cyclohexanol, and cyclohexyl hydroperoxide when using diethyl carbonate as the catalyst. Traces of 6-hydroxy hexanoic acid and butyric acid were detected as well.

All the above-mentioned catalysts have carbonyl groups. Therefore, their activity might originate from their C=O bonds. In addition, C-O bonds are also present in the ester molecules. To investigate the role of oxygen in the C-O bonds, the ethers were evaluated as catalysts for cyclohexane oxidation. When diethyl ether was used as the catalyst, a cyclohexane conversion of 8.3% was obtained after 4 h (TOF: 6.0 h^{-1}). The selectivity toward cyclohexanol and cyclohexanone was 45% and 43%, respectively. GC-MS analysis results show that the byproducts are cyclohexyl hydroperoxide and caproic acid. These results indicate that the C-O bond in diethyl ether is also catalytically active during cyclohexane oxidation. The catalytic activity of diethyl ether is slightly less than that of ethyl acetate. Each diethyl carbonate molecule contains two C-O bonds and one C=O bond; however, the catalytic activity of diethyl carbonate and ethyl acetate is quite similar. Obviously, the catalytic activity of small organic molecules is not simply determined by the amount of functional groups but also by other physicochemical properties.

All the active small organic molecules mentioned above are polar molecules with O atoms. Hydrogen bonds can be formed between the H atoms in cyclohexane and O atoms in the catalysts. Therefore, we propose that polarity and hydrogen bonding play important roles in the cyclohexane oxidation reaction. The catalysis mechanism is proposed and described in Scheme 2. The C-H bond in cyclohexane becomes longer and weaker because of the induced polarization of polar molecules and hydrogen bond formation. Therefore, the C-H bond can be broken to produce a cyclohexyl radical. The formed cyclohexyl radical can react with molecular oxygen to produce CyOO radical. Alternatively, the oxygen atom can attack the weakened C-H bond to form a hydroperoxide, which is similar to cyclohexane auto-oxidation (Scheme 1). Obviously, a strongly polar catalyst will better conduct the reaction and higher catalytic activity might be expected. As for the evaluated catalysts, the polarity decreases with an increase in the length of the carbon chain and, therefore, the catalytic activity also decreases with it.
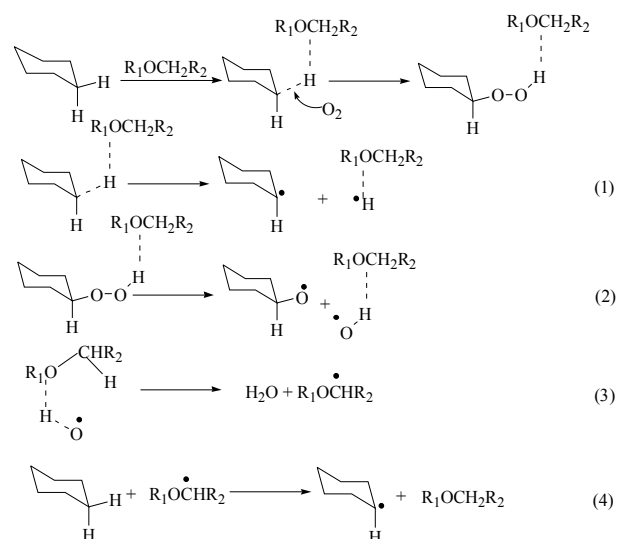
Scheme 2. Reaction mechanism for cyclohexane oxidation with small organic molecule as the catalyst. R_1, R_2 = H or alkyl.

Under our reaction conditions, the formed hydroperoxide is easily converted to a CyO radical and a hydroxyl radical via hemolytic cleavage. The hydroxyl radical is so active that it can easily abstract an α-H from the hydroperoxide of cyclohexanone to produce new radicals. Once new radicals form, β-cleavage begins and leads to ring-opened byproducts [18]. However, the activity of hydroxyl radicals decreases when they are attached to polar molecules by hydrogen bonds. Moreover, the α-H activity of polar molecules is usually higher than that of cyclohexane. Radical rearrangement and dehydration may occur (reaction (3)). The activity of the newly formed R_1OCHR_2 radicals is much lower than that of hydroxyl radicals. R_1OCHR_2 radicals can abstract H atoms from cyclohexane to produce Cy radicals, accompanied by the recovery of catalyst molecules. Diphenyl ketone has a large electronic conjugated system, which can stabilize free radicals. Therefore, when diphenyl ketone is used as a catalyst, the formed radicals will be captured and hinder subsequent reactions.

The O atoms in alcohols can also form hydrogen bonds with the H atoms in cyclohexane and, therefore, alcohols might be active in the cyclohexane oxidation reaction. Several kinds of alcohols were used as catalysts for cyclohexane oxidation and the results are shown in Table 1. Alcohols were found to be poor catalysts for cyclohexane oxidation and the catalytic activity of methanol (TOF: 2.5 h^{-1}) and ethanol (TOF: 2.6 h^{-1}) is very similar. Alcohols have a strong radical scavenging ability. Radicals can abstract H atoms from alcohols to produce alkoxy radicals, which will lose H atoms to aldehydes and can be further oxidized. Glycol has very low catalytic activity (TOF: 0.3 h^{-1}) because polyhydric alcohols are good free radical scavengers, which impedes this reaction. The products obtained using methanol or ethanol as the catalyst were identified by GS-MS. As shown in Fig. 1, cyclohexanol, cyclohexanone, cyclohexyl hydroperoxide and cyclohexanone peroxide were detected in both cases. ε-Caprolactone was detected when using methanol as the catalyst while more cyclohexyl hydroperoxide was detected when using ethanol as the catalyst.

Acetonitrile is a commonly used solvent for cyclohexane oxidation. However, its catalytic role has never been studied and, in fact, we found that acetonitrile is very active in cyclohexane oxidation. A cyclohexane conversion of 13.2% was obtained after 4 h using acetonitrile as the catalyst (TOF: 4.8 h⁻¹). The total selectivity toward cyclohexanol and cyclohexanone was 78% and the selectivity toward cyclohexanone peroxide was 18%. Traces of ε-caprolactone were also identified by GC-MS. The catalytic activity of acetonitrile was comparable with that of other heterogeneous catalysts. Acetonitrile is a strong polar molecule with active α-H, and hydrogen bonds can be formed between the H atoms of cyclohexane and the N atoms of acetonitrile. Therefore, the reaction pathway described in Scheme 2 also operates when acetonitrile is used as a catalyst. In another experiment, a cyclohexane conversion of 35% was obtained after 4 h when 4.5 mL acetonitrile and 0.5 mL cyclohexane were mixed and reacted at 140 °C under a pressure of 1.5 MPa (cyclohexanol 15%, cyclohexanone 66%, cyclohexyl hydroperoxide 1%, hexanol 8%, cyclohexanone peroxide 8%, ε-caprolactone 1%). Based on these experimental results, acetonitrile should be used as a solvent with caution for cyclohexane oxidation and the catalytic role of acetonitrile cannot be neglected.

Inspired by the catalytic role of small organic molecules in cyclohexane oxidation, we attempted to design highly active organocatalysts for this reaction. Since amines are strong polar molecules with active α-H, they were developed as possible catalysts for cyclohexane oxidation. As shown in Table 1, all the amines studied gave very high catalytic activity and the activity increased with an increase in the number of substituent groups. The TOF value was calculated to be 7.5, 10.6, and 22.6 h⁻¹ for propylamine, dipropylamine and tripropylamine, respectively. Compared with alcohols, amines cannot scavenge radicals and, therefore, exhibit much higher catalytic activity toward cyclohexane oxidation. Although the total selectivity toward cyclohexanol and cyclohexanone was similar (Ca 80%), the selectivity toward cyclohexyl hydroperoxide and cyclohexanone peroxide was quite different. The selectivity toward cyclohexyl hydroperoxide increased with an increase in the number of substituent groups at the N atom while selectivity

toward cyclohexanone peroxide decreased. Moreover, triethylamine (TOF: 13.3 h⁻¹) had lower catalytic activity than tripropylamine (TOF: 22.6 h⁻¹). In a general sense, triethylamine has a lower steric hindrance effect and stronger polarity, which should be good for the reaction. This can be explained by the different electron densities of the nitrogen atoms. The ethyl substituent has a far lower ability to supply an electron to the N atom than propyl and, therefore, the electron density of the N atom in triethylamine is lower than that in tripropylamine. The strength of the hydrogen bond decreases with a decrease in the electron density of the N atom, which influences the activation of cyclohexane.

In summary, several polar molecules such as ketones, aldehydes, esters, alcohols and amines were used as catalysts for cyclohexane oxidation and specific activity was observed. We propose a mechanism for cyclohexane oxidation by small organic molecule catalysis as follows. A hydrogen bond is formed between the catalyst and cyclohexane. The C-H bond in cyclohexane becomes longer and weaker because of polarization effects and hydrogen bond formation. The C-H bond can be broken to produce cyclohexyl radicals or the weakened C-H bond can be attacked by oxygen to produce COOH, which can undergo hemolytic cleavage to a CyO radical and a hydroxyl radical. The catalytic activity is controlled by the strength of the polarity and the hydrogen bond formed with cyclohexane, the activity of α-H and the radical scavenging ability. A strongly polar catalyst and hydrogen bonding are beneficial for cyclohexane oxidation. A specific α-H activity is also beneficial for the reaction while a high enough α-H activity resulting in free radical scavenging will impede the reaction.

The catalytic role of the organic solvent must be taken into account for cyclohexane oxidation. Small-molecule organocatalysts can be developed for use in industrial cyclohexane oxidation.

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Graphical Abstract

Cyclohexane oxidation: Small organic molecules as catalysts

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N- or O-containing small organic molecules were used as catalysts for cyclohexane oxidation. The polarity, α-H activity, strength of the hydrogen bond formed with cyclohexane and the radical scavenging capability of these molecules determine their catalytic activity.
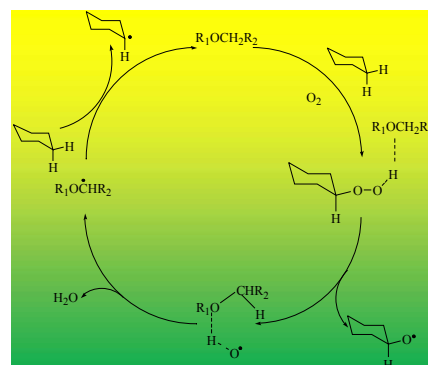
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