Gif-KRICT Biomimetic Oxidation of Cyclohexane: The Influence of Metal Oxides

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Various metal oxides such as Fe_2O_3, FeO, TiO_2, MnO_2, MoO_3, WO_3 and ZnO have been used as a catalyst for Gif-KRICT type cyclohexane oxidation. In this reaction, the conversion of cyclohexane to cyclohexanone and cyclohexanol and the selectivity ratio of cyclohexanone to cyclohexanol were greatly affected by the acidity of metal oxides. When metal oxide has more acidic property, the reactivity on oxidation is increased and the formation of cyclohexanone is more favored. From this result, we proposed a new mechanism for the biomimetic Gif-KRICT oxidation system.

Introduction

The oxidation of saturated hydrocarbons under mild condition has recently become of considerable interest. In nature, the selective functionalization of non-activated carbon-hydrogen bonds takes place via enzymatic catalysis. Among all the enzymes catalyzing biological reactions, the best known and the most interesting ones are Cytochrome P-450,[1] Methane monooxygenase,[2] proyl 4-hydroxylase,[3] isopenicilline *N*-synthase,[4] γ-butyrobetaine hydroxylase[5] and other biologically active systems such as bleomycine.[6] The Cytochrome P-450 monooxygenase is a heme containing porphyrin which is capable of oxygenating hydrocarbon readily in a catalytic way, yielding alcohols from alkanes at ambient conditions. Despite the considerable efforts given to the subject, the use of model systems *in vivo* only produces lower reactivity on the saturated hydrocarbon oxidation. Moreover, in many instances, the important problem of dioxygen activation is bypassed and alternative sources of active oxygen such as iodosobenzene or alkyl hydroperoxides of active oxygen are used.

Barton *et al.* have developed a new biomimetic systems that allow oxidation and functionalization of satured hydrocarbons under mild reaction conditions (ambient temperature, atmospheric pressure, and nearly neutral pH).[7~9] These are called Gif systems, and is originally designed to emulate the non-heme enzymatic oxidation of alkanes. Two most practical members of the Gif system are Gif IV (catalyst: $FeCl_2 \cdot 4H_2O$, oxidant: air, electron source: zinc powder), and GoAgg II (catalyst: $FeCl_3 \cdot 6H_2O$, combined oxidant and electron source: hydrogen peroxide). However, both Gif IV and GoAgg II systems are homogeneous reaction. These present the seperation problem of reaction products which contain excess of starting material, solvent mixture, and the catalyst. To overcome this, we developed a new heterogeneous catalyst system, Gif-KRICT system,[10] in which active iron catalyst was bound to solid support. This catalyst system proceeds at a sufficiently high rate and provides an easy means of separation from the reaction mixture. This system provides a possibility of industriallization of Gif system.

However, this system is greatly affected by oxidation states and acidity of metal oxides. To clear these, the effect of various metal oxides having different oxidation states and acidity on the activity and the selectivity of cyclohexane oxidation to cyclohexanone and cyclohexanol are reported in this paper.

Experimental Section

Gif-KRICT System. Cyclohexane, pyridine, acetic acid, zinc, and the corresponding heterogeneous metal oxide (Fe_2O_3, FeO, TiO_2, MnO_2, MoO_3, WO_3, and ZnO) catalyst were placed in an 125 mL Erlenmeyer flask. These were stirred vigorously under air (1 atm) at room temperature for 16 hrs. The detailed reaction procedure was described in elsewhere.[10] The reaction mixture was chilled in an ice-salt mixture and 60 ml of 25% (v/v) H_2SO_4 was slowly added with stirring. Then this mixture was extracted (3 × 50 mL) with ethylether. The combined acidic ethylether layer was washed successively with 75 ml of 5% (w/v) $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The ethereal layer was mixed with an internal standard solution and analyzed by gas chromatography on a chromosorb column (5% OV-17) equipped with a flame ionization detector.

Fe/silica Catalyst System. Fe/silica catalyst was prepared by impregnating silica with iron chloride. The catalyst was dried at 393 K and calcined at 773 K for 4 hrs in air. The catalyst was characterized by XRD, ESCA, and Mõssbauer. It was readily seen that the iron species of the Fe/silica catalyst was existed mainly form of Fe_2O_3.[10]

Acid Strength Measurement. The acid strength was determined by a titration method.[11] Each dried catalyst (0.1 g) was weighed with a test tube (10 mL screw cap septum vials, Pierce Chem. Corp.). As a probe, 5 mL of dry benzene (analytical grade, redistilled and stored over molecular sieve 3A) was added to this test tube and the catalyst sample was equilibrated with n-butylamine. Indicators were added to the portion of the catalyst suspension and tested with Hammett indicators. The end-point was determined by a series of successive approximations. Ho max values measured are shown

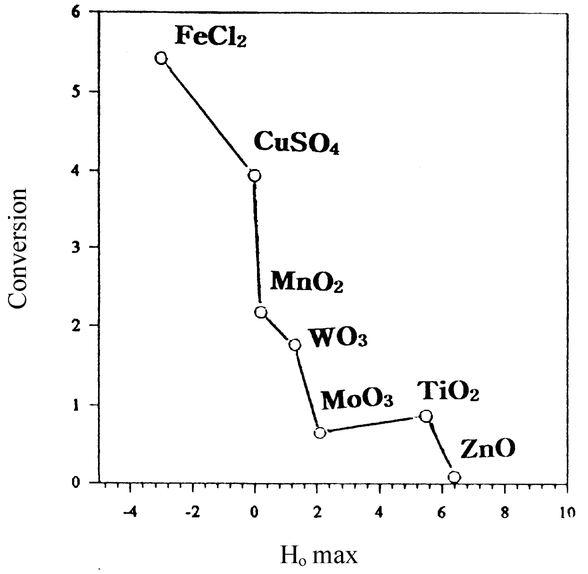


Figure 1. Relationship between conversion and Homax of various metal oxides.

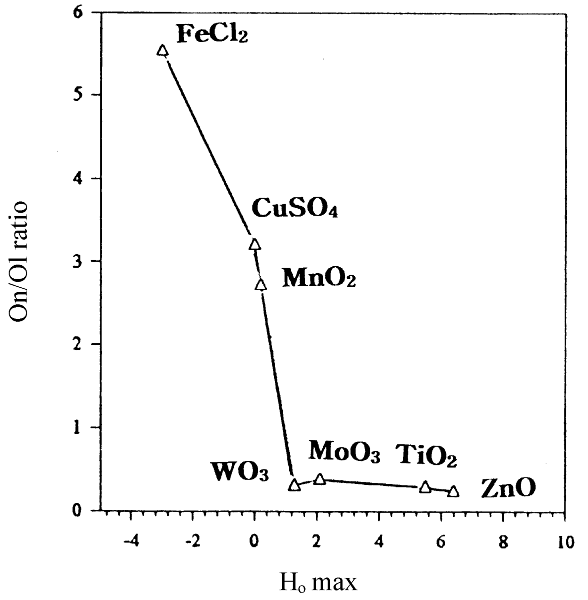


Figure 2. Relationship between On/O1 ratio and Homax of various metal oxides.

in the Figure 1 and 2. The obtained values are similar to the reported ones.[11]

Results and Discussion

The Comparison of Iron Catalysts with Porphyrin on the GifIV System. The Gif type oxidation systems of saturated hydrocarbons showed many differences compared with the porphyrin system. In the Gif type oxidations, ketone was the major product. Whereas, in the porphyrin systems, alcohol was the major product. Therefore, we were more concerned about the selectivities toward both alcohol and ketone.

Table 1. The effect of various iron catalysts on the formation of cyclohexanone and cyclohexanol

Fe salt	Selectivity		Conversion (mole%)	Selectivity ratio
	Cyclohexanol (mole%)	Cyclohexanone (mole%)		Ketone/ Alcohol
FeTPP	1.33	1.20	2.53	0.90
FeFTP	0.95	2.98	3.93	3.14
$Fe(CH_3COCHCOCH_3)_2$	0.77	1.89	2.66	3.83
$FeCl_2$	0.83	4.59	5.42	5.53
$FeCl_3$	1.08	3.83	4.91	3.56
$FeSO_4$	1.10	3.65	4.75	3.31
$Fe(NO_3)_3$	0.89	3.39	4.28	3.80
Acetyl-ferrocene	1.61	2.47	4.08	1.53

*Reaction condition: Reaction Temp. (15 °C), Reaction Time (16 hr), Cyclohexane (20 mmole), Fe compounds (0.005 mmole), Zn (40 mmole), Acetic acid (35 mmole), Pyridine (40 ml). FeTPP: 5,10,15,20-tetraphenyl-21H,23H-Porphine iron(III) chloride. FeTFP: 5,10,15,20-tetra kis (pentafluorophenyl) -21H,23H-Porphine iron(III) chloride.

Gif IV reactions were conducted in the presence of various iron catalysts. In the meanwhile, Iron-porphyrin catalysts were compared with the various iron catalysts. As shown in Table 1, FeTFP with fluorine showed the higher conversion and On/Ol ratio. Porphyrin catalysts showed the similar trends as those of iron catalysts having different counter-ions affected the cyclohexanone to cyclohexanol ratio in the oxidation of cyclohexane under Gif IV reaction conditions. When the counter ion had an electron withdrawing property, the relative formation of cyclohexanone was increased. $FeCl_2$ and $FeCl_3$ with stronger withdrawing group showed the higher conversion of cyclohexane to cyclohexanone and cyclohexanol and the higher selectivity ratio of cyclohexanone to cyclohexanol.

The Effect of Various Iron Oxides on Gif-KRICT System. Direct use of $FeCl_2$ and $FeCl_3$ on the cyclohexane oxidation presented the separation problem from the reaction mixture. Thus, Lee *et al.*[10] developed the heterogenized Gif-KRICT system designed iron catalyst supported on solid support. This heterogenized iron species of Fe/silica existed mainly in the form of Fe_2O_3 and counter-ions contained in iron catalyst greatly impacted on the conversion and the selectivity ratio in the Gif IV system.[12] According to our earlier results,[12] various iron oxides having various oxidation states showed different values of conversion of cyclohexane to cyclohexanone and cyclohexanol and selectivity ratio of cyclohexanone to cyclohexanol as shown in Table 2. Presently, Fe_3O_4 catalyst showed the best result in this system.

After reaction, these catalysts were filtered, dryed, and reused. The results showed these catalysts did not lose their activity. Therefore, oxidation states of metals play an important role on reactivity and formation of cyclohexanone and cyclohexanol.

Table 2. The effect of various iron oxides in the Gif-KRICT system

Solid catalyst	Selectivity		Conversion (mole%)	Selectiviy Ratio
	Cyclohexanol (mole%)	Cyclohexanone (mole%)		Ketone/ Alcohol
Fe powder	0.72	0.99	1.71	1.38
Fe/silica	1.02	4.50	5.52	4.41
FeO	2.58	2.47	5.05	0.96
Fe_3O_4	0.49	5.06	5.55	10.32
Fe_2O_3	0.76	4.10	4.86	5.39

The Effect of Various Metal Oxides. As shown in previous results, oxidation states of iron catalysts gave a great effect on the formation of cyclohexanone and cyclohexanol. Subsequently, various metal oxides such as Fe_2O_3, FeO, Fe_3O_4, MnO_2, MoO_3, WO_3, TiO_2 and ZnO were tested in this system.

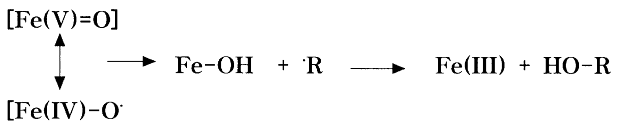
The conversion of cyclohexane to cyclohexanone and cy-clohexanol and the selectivity ratio of cyclohexanone to cyclohexanol were decreased with decreasing the acidity of metal oxides (Table 3). It could be explained the fact that these results were very well fitted with various acidity values (H_o max) of metal oxides obtained by titration method.[13] As shown in Figure 1 and 2, when $FeCl_2$ (Ho max: -3.0) catalyst was used in this reaction, the conversion and the selectivity ratio showed the highest value. These values were drastically decreased upto MoO_3 (Ho max: 2.0).

Therefore these biomimetic oxidation data showed the large difference from the catalytic partial oxidation system which involves redox cycles so-called Mars-van Krevelen mechanism.[14] In this mechanism, lattice oxygen oxidizes the organic molecule and leaves a reducing center, that is reoxidized by O_2.

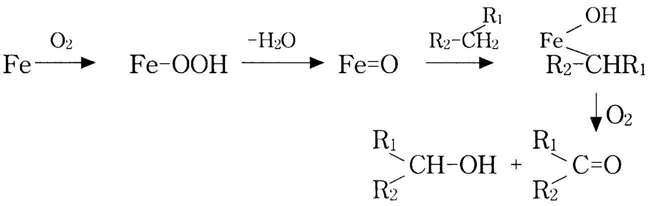
Table 3. Effect of various metal oxides in Gif-KRICT system

Metal oxide	Selectivity		Conversion (mole%)	Selectiviy Ratio
	Cyclohexanol (mole%)	Cyclohexanone (mole%)		Ketone/ Alcohol
$FeCl_2$*	0.83	4.59	5.42	5.53
Fe_2O_3	0.76	4.10	4.86	5.39
$CuSO_4$	0.93	2.97	3.90	3.20
MnO_2	0.58	1.59	2.17	2.71
WO_3	1.19	0.36	1.76	0.30
MoO_3	0.52	0.19	0.65	0.37
TiO_2	0.67	0.19	0.86	0.28
ZnO	0.64	0.15	0.08	0.23

*: A standard catalyst in Gif reaction to compare with other metal oxides.



Scheme 1. Possible mechanism for alkane hydroxylation by Cytochrome p-450.



Scheme 2. Proposed mechanism by Barton in Gif system.

Many researchers have been studied on the mechanism with various Cytochrome p-450 type monooxygenase. They found this reaction was proceeded via a radical mechanism.[15,16] A high valent porphyrin-iron oxo complex corresponding formally to Fe(V)=O structure showed resonance forms as in Scheme 1.[17]

Barton also proposed that the activation of saturated hydrocarbons by the Gif system could be represented by the following three steps,[18]

(1) Activation of dioxygen molecule, formally as an Fe=O species

(2) Activation of hydrocarbon through insertion of the Fe(V)=O species into a carbon-hydrogen bond

(3) Insertion of dioxygen into a carbon-iron bond and formation of ketone or alcohol from alkyl hydroperoxide intermediate.

Those steps were shown in Scheme 2.

The effects of the iron catalysts were already examined and the counter-ions of iron salts were found to show significant influence on both activity and selectivity.[12] Based on these data, we proposed a new reaction mechanism of biomimetic oxidation system containing various metal oxides (Figure 3).

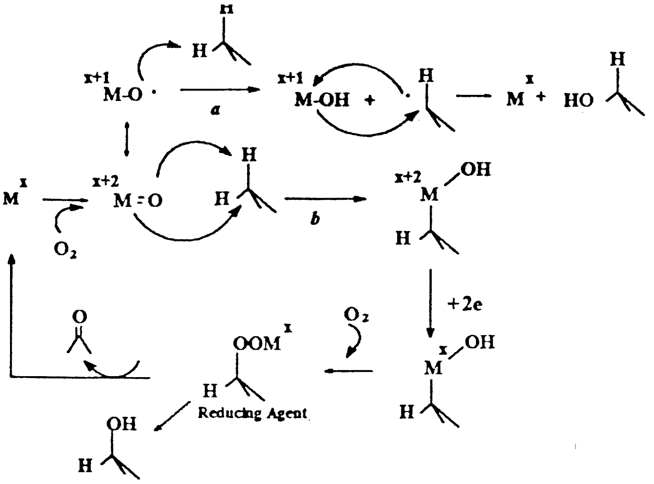


Figure 3. Proposed new reaction mechanism in biomimetic oxidation using various metal oxides in the Gif-KRICT reaction.

When metal oxides (M) are more acidic, the oxometal becomes unstable and reacts rapidly with hydrocarbons. Therefore, the reactivity is substantially increased and the reaction mainly proceeds through path *b* to produce ketone. On the other hand, when metal oxides are less acidic, the formed oxo-metal is stable and reaction proceeds via radical intermediate through path *a* and finally produces alcohol as in porphyrin mechanism.

Conclusions

The effect of metal oxides on the Gif-KRICT oxidation of cyclohexane were examined. In this system, we found that the acidity of metal oxides influenced both on activity and on selectivity. In the presence of strong acidic and high oxidation state metal oxide such as MnO_2 or Fe_2O_3, the conversion of cyclohexane to cyclohexanone and cyclohexanol and the selectivity ratio of cyclohexanone to cyclohexanol showed larger values.

Based on the experimental results, we proposed a new reaction mechanism on biomimetic oxidation using various metal oxides. In this, when metal oxides having strong acidity are used, the oxo-metal becomes unstable and reacts rapidly with hydrocarbons.

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