

Articles

The Effect of Iron Catalysts on the Formation of Alcohol and Ketone in the Biomimetic Oxidation of Cyclohexane

Seong-Bo Kim[†], Kyu-Wan Lee^{†*}, Yong-Joon Kim[‡], and Seog-In Hong[‡]

[†]Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejeon 305-606

[‡]Department of Chemical Engineering, Korea University, Seoul 136-701

Received August 31, 1993

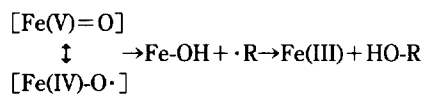
Effects of iron compounds in known biomimetic oxidation systems (Gif IV and GoAgg II) have been studied on activity and ketone/alcohol selectivity of cyclohexane oxidation. Both ketone/alcohol ratio and cyclohexane conversion were affected by counter-ion Z of iron compounds Z-Fe. When Z has a more electron withdrawing property, the reactivity is increased and the formation of ketone is favored. From these experimental results, a new mechanism is proposed for the biomimetic oxidation system.

Introduction

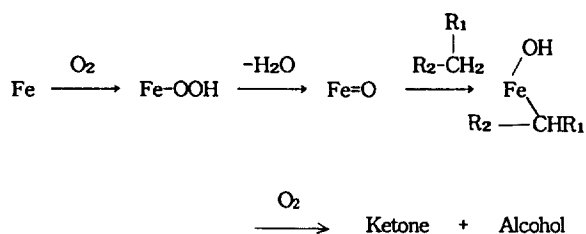
The oxidation of saturated hydrocarbons, especially cyclohexane, under mild conditions has an important industrial significance. In nature, selective functionalization of non-activated carbon-hydrogen bonds takes place by enzyme catalysis. Among all the enzymes capable of catalyzing such biochemical reactions, the best known and most interesting enzymes are methane monooxygenase¹, proyl 4-hydroxylase², isopenicilline N-synthase³, γ -butylobetaine hydroxylase⁴ and other biologically active systems such as bleomycine⁵. Despite all the efforts devoted to the subject, the use of model systems *in vivo* has so far given only low hydrocarbon oxidation yields. Moreover, in many instances, the important problem of dioxygen activation has been ignored and alternative sources of active oxygen such as iodosobenzene or alkylhydroperoxides are used. The oxidation system using Cytochrome P-450 and porphyrin has many problems for industrialization in the catalyst preparation and the catalyst separation from reaction mixtures. Thus, the studies to mimic the cytochrome P-450 have been performed by many researchers.

Recently, Barton and coworkers developed a family of new biomimetic systems which allows the oxidation and functionalization of saturated hydrocarbons under mild reaction conditions of ambient temperature, atmospheric pressure and nearly neutral pH.⁶⁻⁸ They have been called as "Gif systems". All of them contain a pyridine-acetic acid (or other carboxylic acid) solution of a hydrocarbon to be oxidized, an iron-based catalyst, an oxidant and an electron source. The two most practical members of the Gif family are Gif IV (with FeCl₂·H₂O as a catalyst, air as the oxidant, and zinc powder as the electron source) and GoAgg II (with FeCl₃·H₂O as a catalyst, and hydrogen peroxide as a combined oxidant and electron source). Gif systems were originally designed to emulate the non-heme enzymatic oxidation of alkanes.

The oxidation of saturated hydrocarbons using Gif systems showed many differences compared with the case of porphyrin system. Ketones were major products in the Gif type oxidations. But in the case of porphyrin systems, alcohols



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



Scheme 2. Gif reaction mechanism proposed by Barton.

were formed as major products. Thus we have been interested in the selectivity of the alcohol and ketone in biomimetic system.

Studies on mechanism using various Cytochrome P-450 type monooxygenase have been carried out by various researchers⁹⁻¹¹. This reaction is known to proceed *via* a radical mechanism. A high valent porphyrin-iron oxo complex corresponding formally to Fe(V)=O structure has radical resonance forms as in Scheme 1.

Also, Barton proposed that the activation of saturated hydrocarbons by the Gif system can be represented by the following three steps¹²,

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

(2) Activation of the 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 the alkyl hydroperoxide intermediate.

These steps are shown in Scheme 2.

Recently, we found that substrate conversion and reaction selectivity (ketone to alcohol ratio) depend on the counter-

Table 1. Gif IV oxidation of cyclohexane using different iron-catalysts

Fe salt	Cyclohexanol (wt%)	Cyclohexanone (wt%)	Cyclohexane conversion (wt%)	Ketone/Alcohol
FeCl ₂	0.97	4.45	5.42	4.56
FeCl ₃	1.08	3.83	4.91	3.55
FeSO ₄	1.10	3.65	4.75	3.31
Fe(NO ₃) ₃	0.89	3.39	4.28	3.80
FeO	1.85	1.80	3.65	1.02
Acetyl ferrocene	1.61	2.47	4.08	1.53

*Reaction conditions: Room temperature, Reaction Time (16 hr), Cyclohexane (46 mmole), Fe compounds (0.005 mmole), Zn (40 mmole), Acetic acid (35 mmole) Pyridine (40 ml).

Table 2. Effects of Fe compounds in GoAgg II reaction of cyclohexane

Fe compound	Cyclohexanol (wt.%)	Cyclohexanone (wt.%)	Conversion (wt.%)	ON/OL ratio
FeCl ₂	2.60	2.83	5.43	1.08
FeCl ₃	0.21	1.45	1.66	6.90
FeSO ₄	0.29	0.35	0.64	1.20
Fe(NO ₃) ₃	2.38	6.19	8.57	2.60
FeO	0	0	0	

*Reaction conditions: Reaction temp (10°C), Reaction time (10 min), Cyclohexane (46 mmole), Fe compounds (0.59 mmole), Acetic acid (35 mmole), Pyridine (40 ml).

ion of iron(III) catalyst.

We report here the relationship between the nature of iron catalysts, and the activity and ketone-to-alcohol selectivity of Gif systems in cyclohexane oxidation.

Experimental section

Experimental methods (including work-up procedures and gas chromatographic analysis) used throughout this work are as reported previously¹². Gif IV and GoAgg II reactions were carried out as described elsewhere^{7,8}. Quantitative analysis of reaction mixture was performed on a Shimadzu model 14A gas chromatograph equipped with a FID and using diisopropyl benzene as an internal standard.

General procedure for Gif IV reaction under an atmosphere of O₂. Zinc, cyclohexane, pyridine, acetic acid and the corresponding iron catalyst were placed in an 125 ml Erlenmeyer flask. The amounts are presented in Table 1. The reaction mixture was stirred vigorously under air at room temperature for 16 hr.

General procedure for GoAgg II reactions. Cyclohexane, pyridine, acetic acid and the corresponding iron catalyst were placed in an 125 ml Erlenmeyer flask. The amounts are presented in the Table 2 and 3. The reaction was initiated by addition of hydrogen peroxide (30% in water). The reaction mixture was stirred vigorously under air at room temperature for 5 hr.

General work-up procedure. The reaction mixture was chilled in an ice-salt mixture and 60 ml of 25% (v/v) H₂SO₄ was slowly added with stirring. Then the mixture was extracted (3×50 ml) with ethylether and the combined

Table 3. The results in the GoAggII reaction for various reaction temperature

Rx. Temp. (°C)	Consumption of peroxide (%)	Cyclohexanone (mole%)	Cyclohexanol (mole%)
30	0	0	0
45	0	0	0
60	98	1.64	0.21

*Reaction conditions: Reaction Time (12 hr), FeO (1 mmole), Cyclohexane (40 mmole), Acetic acid (35 mmole), Pyridine (40 ml).

acidic ethylether layer was washed successively with 75 ml of 5% (w/v) NaHCO₃ solution and brine, and dried over MgSO₄. The ethereal layer was mixed with a solution of an internal standard and analyzed by G.C.

Result and Discussion

Effect of various iron catalysts on the performance of the Gif IV system. So far, Gif IV reactions have been conducted in the presence of FeCl₂·4H₂O as the catalyst. Recently, we observed that iron catalysts having different counterions affected the ketone-to-alcohol ratio of Gif reactions. Therefore, we screened the various iron catalysts to examine their effects on the ketone to alcohol ratio in the oxidation of cyclohexane under Gif IV reaction conditions. As shown in Table 1, the ratio between cyclohexanone and cyc-

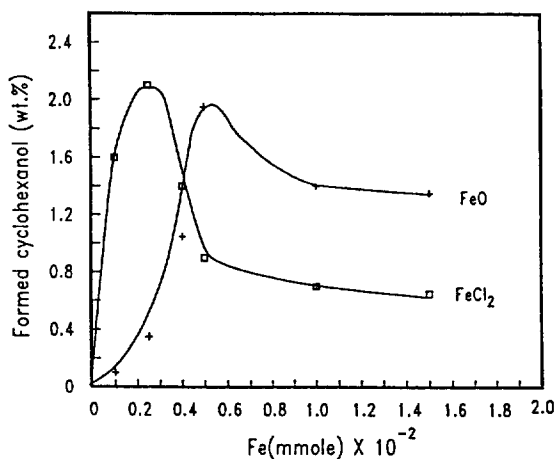


Figure 1. Effects on the amounts of iron compounds for alcohol formation in the Gif IV reaction of cyclohexane.

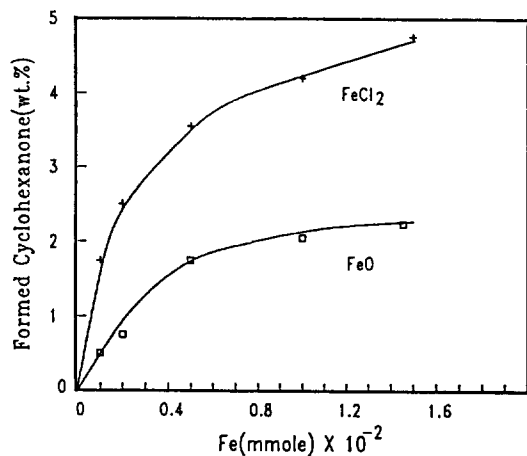


Figure 2. Effects on the amounts of iron compounds for ketone formation in the Gif IV reaction of cyclohexane.

lohexanol depends on the counter-ion of iron catalyst although all catalysts provided similar cyclohexane conversions. When the counter-ion has electron withdrawing property, the relative formation of ketone is largely increased.

On the other hand, when counter-ion has an electron donating property, the relative formation of alcohol is increased.

Effects of the amount of catalyst used were examined for $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and FeO . Interestingly, the pattern for each reaction product was different. As the amount of catalyst increased, the formation of the alcohol shows a maximum point, in yield as shown in Figure 1. On the other hand, the production of cyclohexanone showed a monotonic increase as shown in Figure 2. Both FeCl_2 and FeO showed similar trends in Figure 1 and 2 although absolute values of the yield and the amounts of catalysts to give the maximum alcohol yield were different each other. The dependance of ketone to alcohol on the amount of catalyst used is shown in Figure 3. The catalyst FeO showed a maximum ratio at the concentration of 0.1×10^{-2} mmol. In contrast, a steady increase of the ratio was observed for increasing amount of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$. These results seemed to be originated from further oxidation of part of alcohol to ketone. This was demonstrated

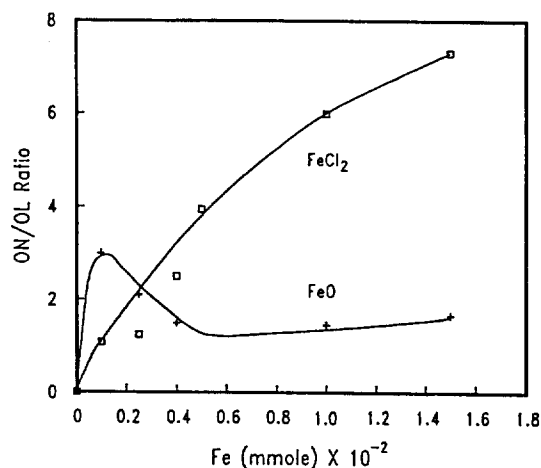


Figure 3. Effects on the amounts of iron compounds for ketone/alcohol ratio in the Gif IV reaction of cyclohexane.

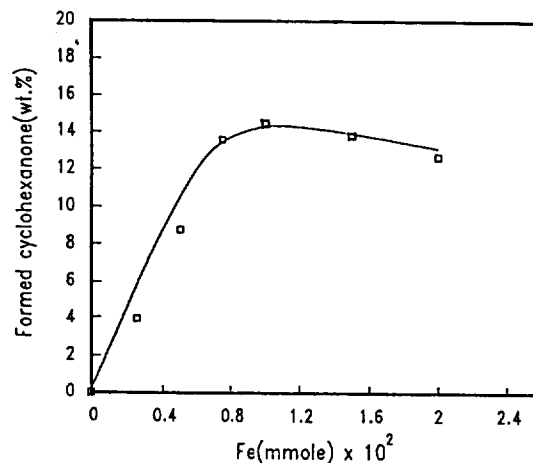


Figure 4. Effects of the amounts of FeCl_2 for the formation of ketone in the Gif IV reaction of cyclohexanol.

in Figure 4 which indicated that cyclohexanol readily converted to cyclohexanone under the same conditions with FeCl_2 catalyst.

Effect of Fe compounds in GoAgg II reaction. The reactivity of various iron compounds were also examined for the GoAgg II system.

The GoAgg II system has been developed from the Gif IV system by using hydrogen peroxide as the oxidant and is known to be more effective than any other biomimetic systems.

As shown in Table 2, the reaction rate showed marked difference among various catalysts. This provides an interesting contrast to Gif IV system whose activity does not show on the nature of the iron compound. When counter-ion of iron compound was more electron withdrawing, the reactivity increased. Especially, FeO catalyst showed no conversion under this reaction condition of 10°C for 10 min.

However, the catalytic effect was observed by increasing the reaction temperature up to 60°C as shown in Table 3. Figure 5 also shows that the reaction rate depends on the nature of the iron salt catalyst used.

The experimental results using the various Fe compounds

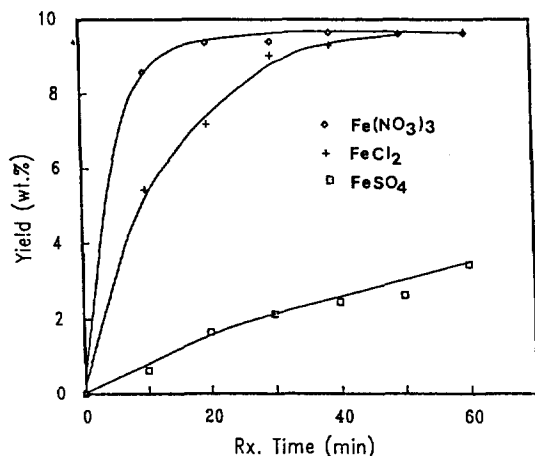
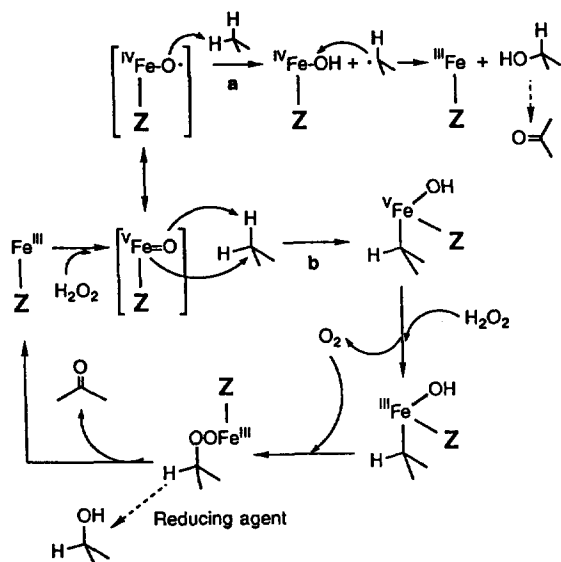


Figure 5. Yields on cyclohexanone and cyclohexanol for the reaction time in the GoAgg II reaction of cyclohexane.



Scheme 3. New reaction mechanism in biomimetic oxidation using the Gif reaction.

clearly indicate that the formation of alcohol and ketone from the biomimetic oxidation of cyclohexane with Gif systems are affected by the electronic state of Fe compounds. A new reaction mechanism could be speculated as shown in Scheme 3. When iron catalysts having electron-withdrawing group Z are used, the oxometal ($Z\text{-Fe=O}$) becomes unstable and reacts rapidly with hydrocarbons. Therefore, the reactivity

is substantially increased and reaction mainly proceeds though path *b* to produce ketone. On the other hand, when iron catalysts have electron-donating group Z, the formed *oxo*-metal ($Z\text{-Fe=O}$) seems to be stable and reaction proceeds *via* radical intermediate through the path *a* to produce alcohol.

Conclusions

The effect of the nature of the iron catalyst was examined amount of reaction products (cyclohexanone and cyclohexanol) and the reaction rate from the Gif IV and the GoAgg II oxidation of cyclohexane.

The counter-ion of iron salts was found to have significant influence on both activity and selectivity. Also, the effect of the amounts of catalyst ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ or FeO) on the yield of alcohol and ketone was examined. The results were different for each reaction product. The formation of alcohol required an optimal amount of catalyst, which affords the highest yield. In the case of ketone, increasing amounts of catalyst afforded higher yields of cyclohexanone.

References

- Woodland, M. P.; Patil, D. S.; Cammack, R. *Biochim. Biophys. Acta* **1986**, 2330.
- Kivirkko, K. I.; Myllyla, R.; Pihalajaniemi, T. *FASEB*, **1989**, 3, 1609.
- Baldwin, J. E. *J. Heterocycle. Chem.* **1990**, 27, 71.
- Ziering, D. L.; Pascal, Jr. R. A. *J. Am. Chem. Soc.* **1990**, 112, 834.
- Suga, A.; Sugiyama, T.; Otsuka, M.; Sugiura, M. Y.; Maeda, K. *Tetrahedron* **1991**, 47, 1191.
- Barton, D. H. R.; Gastiger, M. J.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 41, 731.
- Barton, D. H. R.; Lee, K. W.; Mehl, W.; Ozbalik, N.; Zhang, L. *Tetrahedron* **1990**, 46, 3753.
- Lee, K. W.; Kim, S. B.; Barton, D. H. R.; Doller, D. *Bull. Kor. Chem. Soc.* **1991**, 12(5), 459.
- Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T. Ray Buck, S. A. *J. Am. Chem. Soc.* **1985**, 107, 2000.
- Oritz, P. R.; Mico, B. B. A. *Mol. Pharmacol* **1980**, 18, 128.
- Garrison, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, 111, 191.
- Barton, D. H. R.; Beviere, S. D.; Chavasiri, W.; Cshuai, E.; Doller, D. *J. Am. Chem. Soc.* **1992**, 114, 2147.