

CHAPTER III

RESULTS AND DISCUSSION

This research concentrates on the development of a new system for the epoxidation of alkenes. Cyclohexene was selected as a substrate for reaction conditions optimization. In general, the system is composed of cobalt calix[4]pyrrole complex as a catalyst, 2-ethylbutyraldehyde and O₂ as a source of an oxidant in a reaction medium. Acetonitrile and toluene were mostly used as solvent. Other substrates including cyclic monoterpenes containing double bonds such as α -terpinene, γ -terpinene, *R*-(+)-limonene and *S*-(-)-limonene were employed for some specific purposes. Among cobalt calix[4]pyrrole complexes, dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -tetrspiroyl-calix[4]pyrrole cobalt(II) complex **15** and dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -tetrakis(4-methoxyphenyl)-tetramethyl-calix[4]pyrrole cobalt(II) complex **16** were thoroughly utilized as a catalyst. To our best knowledge under these particular conditions, there has never been reported in the literature for the epoxidation of alkenes.

3.1 Effect of cobalt calix[4]pyrrole complex, CoCl₂ and Co(acac)₂ on reactivity of cyclohexene epoxidation.

The epoxidation of unfunctionalized alkenes catalyzed by metal complexes is emerging as a useful synthetic transformation. For utilizing a wide variety of metal complexes for epoxidation system,^{43,44} cobalt complexes were found to be effective catalysts for many reported epoxidations of alkenes.⁴⁵ Although there have been some investigations on the use of Co(salen) complex for catalytic epoxidation of alkene, there is no report on the utilizing of cobalt calix[4]pyrrole as a catalyst. In this study, the effort focused on screening of dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -octaethyl-calix[4]pyrrole cobalt(II) complex **14** for its catalytic activity compared with CoCl₂ and Co(acac)₂. Under this particular condition, the

epoxidation of cyclohexene provided cyclohexene oxide (**25**) as a major product, while cyclohexenone (**26**) being a minor and cyclohexenol could not be detected. The outcomes are presented in Table 3.1 and Fig. 3.1.

Table 3.1 The effect of dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -octaethyl-calix[4]pyrrole cobalt(II) complex **14**, CoCl_2 and $\text{Co}(\text{acac})_2$ on cyclohexene epoxidation

Entry	Catalyst	Product (%)		Total yields (%)
		25	26	
1	none	9	0	9
2	14	57	trace	57
3	CoCl_2	49	0	49
4	$\text{Co}(\text{acac})_2$	20	0	20

Reaction conditions : cyclohexene (5 mmol), catalyst (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O_2 atmosphere

25 : cyclohexene oxide, **26** : cyclohexenone

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

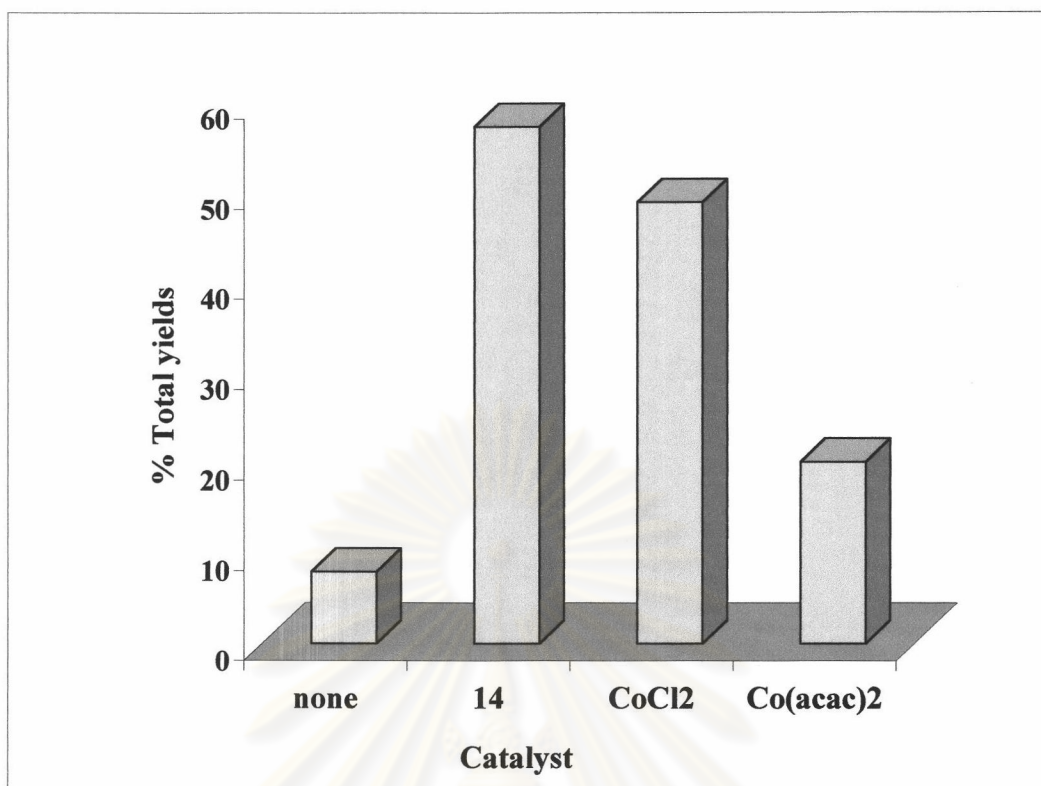


Fig. 3.1 The effect of dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -octaethyl-calix[4]pyrrole cobalt(II) complex **14**, CoCl₂ and Co(acac)₂ on cyclohexene epoxidation

The observations obtained from Table 3.1 and Fig 3.1 provided an interesting result. In the absence of catalyst, only about 9% of cyclohexene oxide was detected. Among cobalt calix[4]pyrrole complexes examined, cobalt calix[4]pyrrole **14** was found to be the most efficient catalyst providing a good productivity of cyclohexene oxide with superb selectivity and gave good yield compared with the case without catalyst. The epoxidation of this substrate greatly depended on a type of cobalt catalyst. While, cobalt calix[4]pyrrole **14** enhanced the yield of cyclohexene oxide, CoCl₂ and Co(acac)₂ could catalyze the epoxidation reaction to smaller extents (entries 3 and 4).

In this research, cobalt calix[4]pyrrole complex was selected to use as a catalyst for cyclohexene epoxidation. The usage of calix[4]pyrrole ligands to form a variety of Co complexes was examined and tested for its catalytic capability.

3.2 Study on the optimum conditions for the epoxidation of cyclohexene

Stemmed from the preliminary results mentioned in 3.1, various diverse factors needed to be assayed to optimize the epoxidation reaction were explored. Cyclohexene was chosen as the first substrate model. Variable parameters studied included type of calix[4]pyrrole complexes, the amount of 2-ethylbutyraldehyde, solvents and type of oxidants.

3.2.1 Effect of ligands of cobalt calix[4]pyrrole complexes

Since there has been no report concerning the use of this class of catalyst for alkene epoxidation, a search for efficient ligands coordinating to cobalt that could catalyze the reaction to transform cyclohexene into the corresponding cyclohexene oxide selectively was scrutinized. Six cobalt calix[4]pyrrole complexes **13-18** were investigated and the findings are intimated in Table 3.2 and Fig. 3.2.

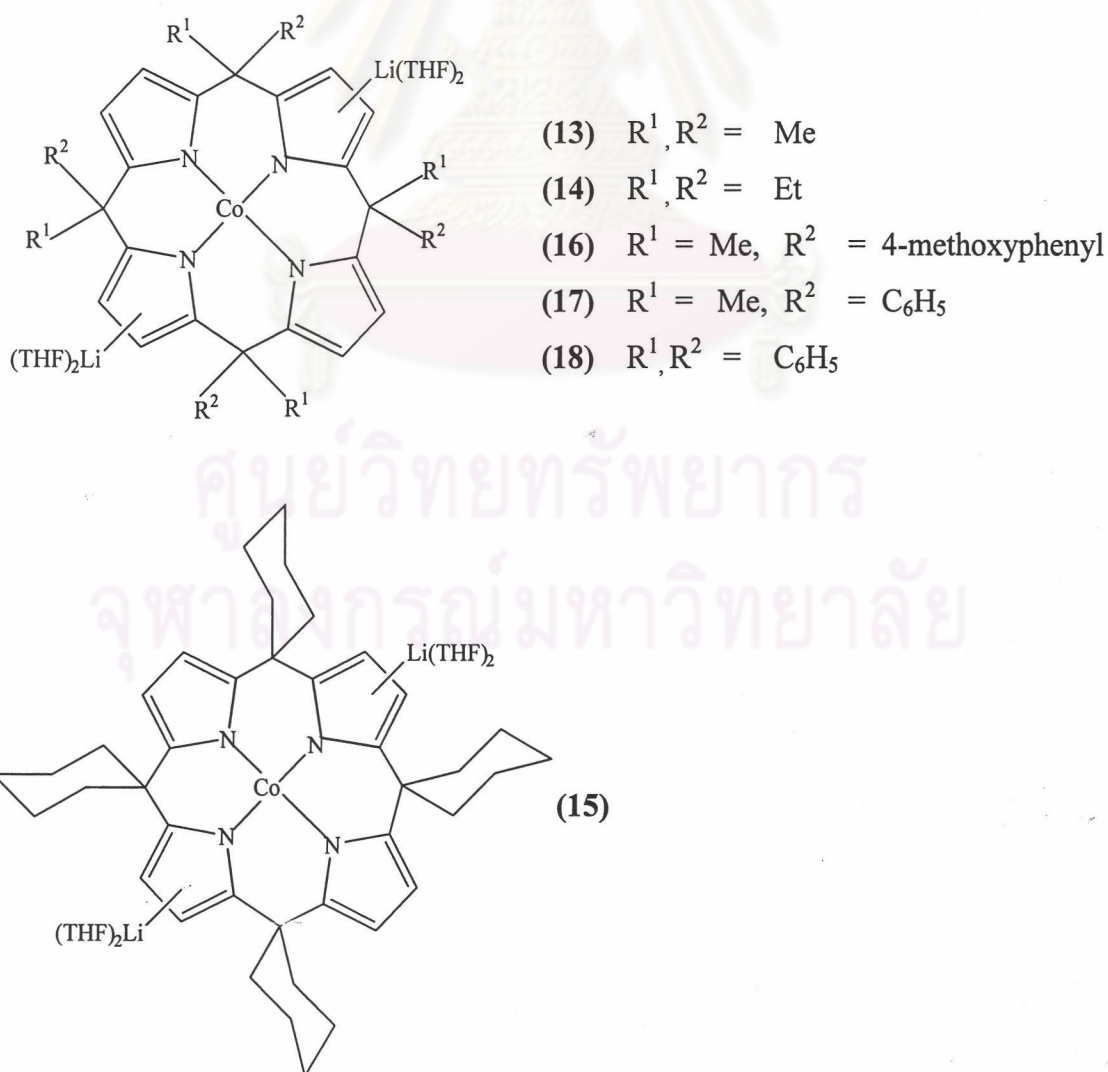


Table 3.2 The epoxidation of cyclohexene catalyzed by various cobalt calix[4]pyrrole complexes

Entry	Catalyst	Product (%)		Total yields (%)
		25	26	
1	13	44	0	44
2	14	57	trace	58
3	15	74	trace	75
4	16	85	trace	85
5	17	60	0	60
6	18	16	0	16

Reaction conditions : cyclohexene (5 mmol), cobalt calix[4]pyrrole (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O₂ atmosphere
25 : cyclohexene oxide, **26** : cyclohexenone

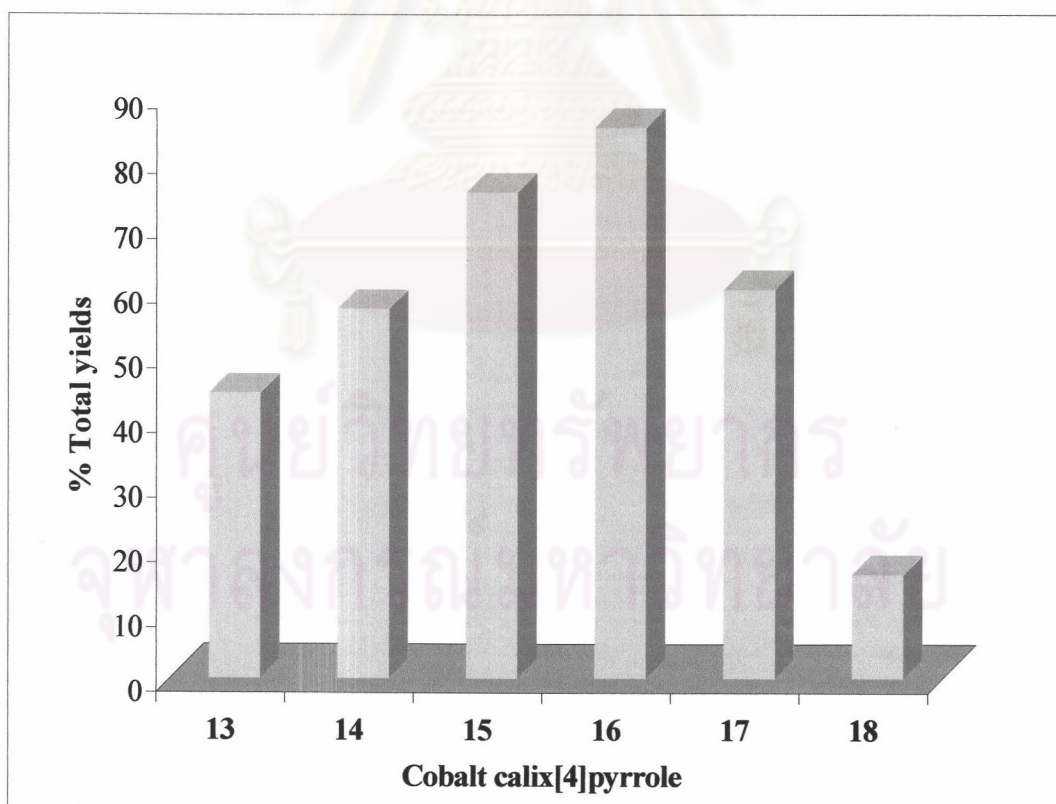


Fig. 3.2 The effect of various cobalt calix[4]pyrroles on cyclohexene epoxidation

From Table 3.2 and Fig. 3.2, it could be noticed that most of cobalt calix[4]pyrrole complexes could catalyze the cyclohexene epoxidation smoothly leading to the desired product cyclohexene oxide with a small amount of cyclohexenone. None of cyclohexenol was detected. The complexes bearing electron-donating substituent like methyl, ethyl group, **13** and **14** provided the lower yield than those containing more powerful electron-releasing substituent (complexes **15** and **16**). It could also be observed that highly steric-hindrance and electronic effects of phenyl ring substituents, complexes **17**, **18**, influenced the yield of the desired products. The very sterically complex **18** gave only small amount of cyclohexene oxide (entry 6). In addition, it could also be observed that the epoxidation of cyclohexene in this reaction was markedly dependent on the type of chelating ligand around the metal to achieve a high yield of oxygenated product by occurring *via* superoxo Co/O₂ intermediate to transfer oxygen to substrate. Considering the variation of ligands, *p*-methoxyphenyl group was found to be a good substituent that could assist the activation process of the catalyst. In all catalysts tested, electron-releasing substituents, dilithium-tetrakis(tetrahydrofuran)- $\alpha,\beta,\gamma,\delta$ -tetrakis(4-methoxyphenyl)-tetramethyl-calix[4]pyrrole cobalt(II) complex **16**, showed incomparable catalytic efficiency with the highest yields.

According to the results shown above, cobalt calix[4]pyrrole complexes **15** and **16** were selected to use as a catalyst for additional investigation.

3.2.2 Effect of solvents

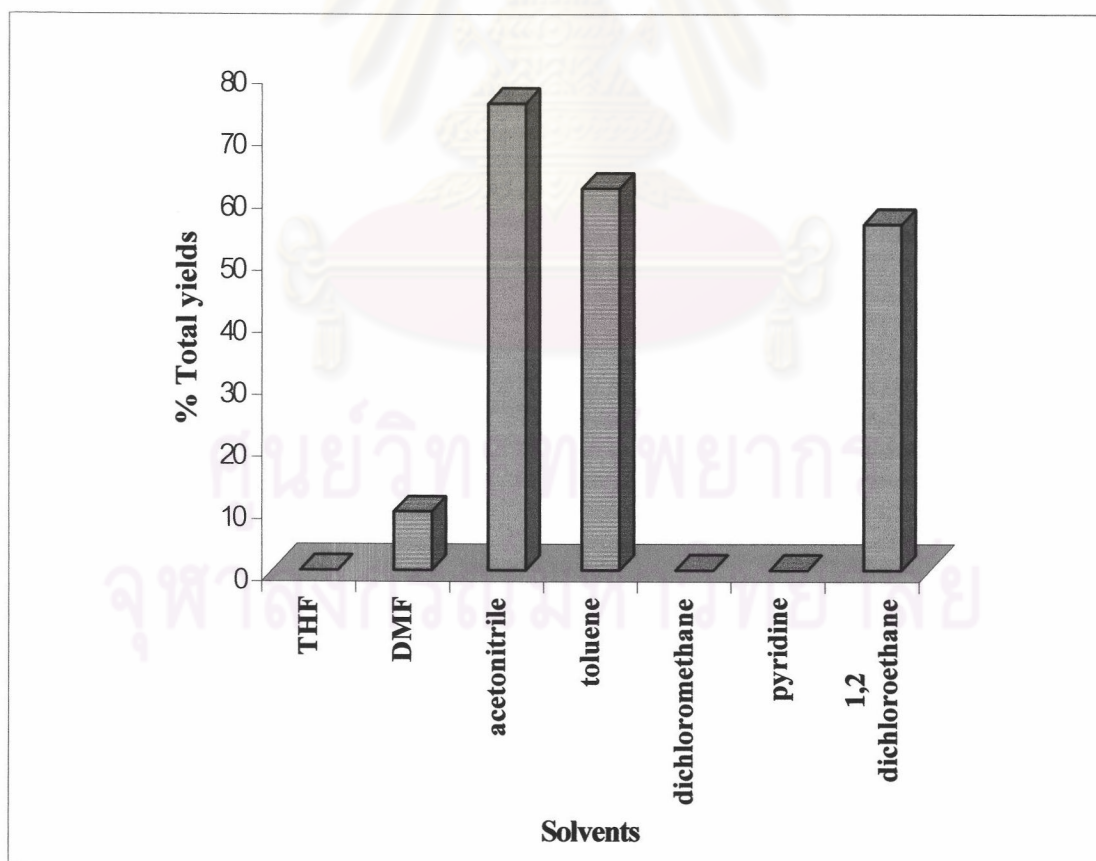
From the experimental conditions described above, acetonitrile was used as a homogeneous medium. Several solvents were chosen to evaluate the catalytic potentials of cobalt(II) calix[4]pyrrole complex **15** in these media and to observe whether they could replace acetonitrile. The results of the variation of solvents in cyclohexene epoxidation using catalyst **15** are presented in Table 3.3 and Fig. 3.3.

Table 3.3 The effect of solvents on cyclohexene epoxidation

Entry	Solvent	Products (%)		Total yields (%)
		25	26	
1	tetrahydrofuran	0	0	0
2	<i>N,N</i> -dimethylformamide	9	0	9
3	acetonitrile	75	trace	75
4	toluene	62	trace	62
5	dichloromethane	0	0	0
6	pyridine	0	0	0
7	1,2-dichloroethane	56	trace	56

Reaction conditions : cyclohexene (5 mmol), **15** (0.05 mmol), solvent (30 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O₂ atmosphere

25 : cyclohexene oxide, **26**: cyclohexenone

**Fig. 3.3** The effect of solvents on cyclohexene epoxidation

Among several diverse solvents studied, acetonitrile was the first solvent chosen as a reaction medium because it could dissolve both cobalt calix[4]pyrrole catalyst and a substrate. The yields of the desired products were higher than employing a relatively nonpolar solvent such as toluene. From the literature, it was found that acetonitrile had the highest value of the dielectric constant among all solvents examined.⁷⁰ Comparison with acetonitrile, both the polarity and dielectric constant of toluene were much lower. However, toluene also served as a suitable solvent because it provided in pretty high percentage yield of the desired product. In the case of employing tetrahydrofuran, dichloromethane and pyridine, the epoxidation reaction did not take place. The observation in the case of pyridine as a solvent offered an informative clue for the mechanistic pathway of the system which will be discussed later. From the above result, it seemed that the polarity and the dielectric constant of the solvent do not have any close correlation effect on this epoxidation reaction.

3.2.3 Effect of the amount of solvent on cyclohexene epoxidation

In order to gain the maximum yield of the desired products, the variation of the amount of acetonitrile was conducted. The results of the variation of the amount of acetonitrile in cyclohexene epoxidation using catalyst **16** are presented in Table 3.4 and Fig. 3.4.

Table 3.4 The effect of the amount of acetonitrile on cyclohexene epoxidation

Entry	Acetonitrile (mL)	Products (%)		Total yields (%)
		25	26	
1	10	24	0	24
2	15	46	0	46
3	25	53	0	53
4	30	64	0	64
5	36	85	trace	85
6	45	84	trace	84

Reaction conditions: cyclohexene (5 mmol), **16** (0.05 mmol), acetonitrile (varied) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O₂ atmosphere, **25** : cyclohexene oxide, **26** : cyclohexenone

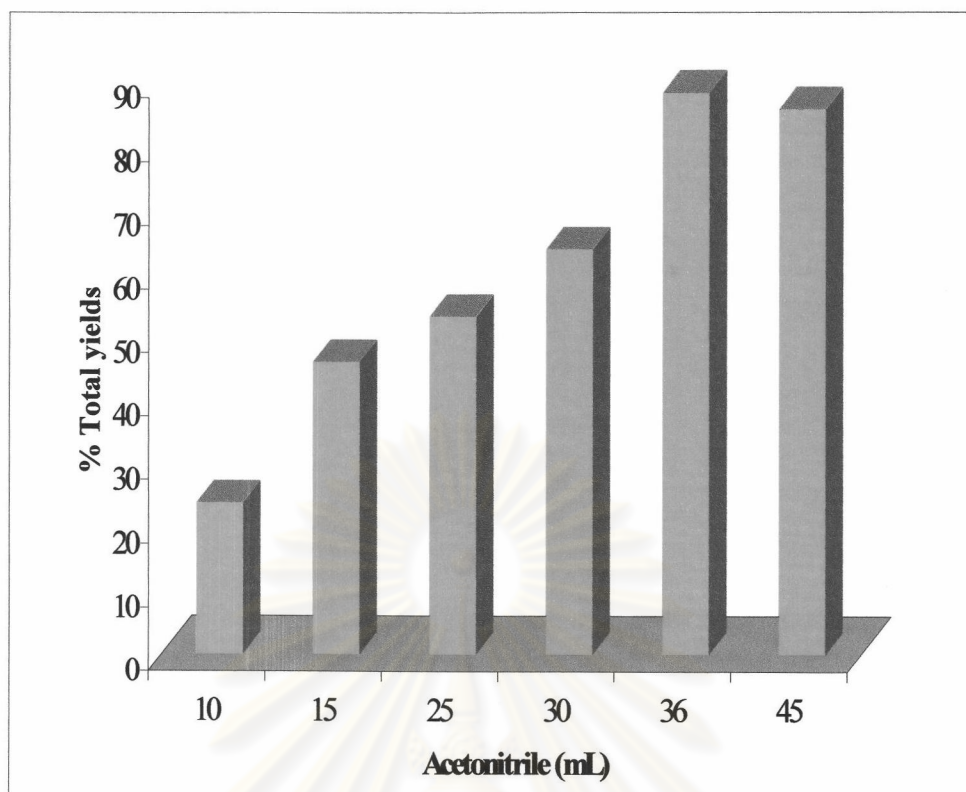


Fig. 3.4 The effect of the amount of acetonitrile on cyclohexene epoxidation

Judging from the yield of the desired products (Table 3.4, all entries), it was observed that the use of acetonitrile 36 mL was the most appropriate amount of solvent (entry 4). Using acetonitrile 10, 15 and 25 mL afforded lower yield of the desired product. In the case of employing solvent 30 and 36 mL, total yields were enhanced. The reason for this was probably due to the competition reactions between that yielding cyclohexene oxide and other side reactions that might concomitantly take place. Using appropriate amount of solvent 36 mL, cyclohexene oxide was preferentially occurred. This suitable volume implied that the epoxidation was prevailed to take place over other side reactions. However, the amount of the desired products could not be higher even 45 mL of acetonitrile was used. Thus 36 mL of acetonitrile was the most befitting amount for the further investigation under this particular condition.

3.2.4 Effect of the oxidants

The type of oxidant is another significant factor on the production of cyclohexene oxide. The results of the variation of oxidants in cyclohexene epoxidation using cobalt(II) calix[4]pyrrole catalyst **16** was examined. Various

oxidants besides 2-ethylbutyraldehyde/O₂ may affect this epoxidation reaction. The effect of several oxidants on the epoxidation reaction is listed in Table 3.5.

Table 3.5 The effect of various oxidants on cyclohexene epoxidation

Entry	Oxidant	Products%		Total yields (%)
		25	26	
1	2-ethylbutyraldehyde	85	3	88
2	H ₂ O ₂	0	0	0
3	TBHP ^a	0	0	0
4	2-ethylbutyraldehyde ^b	55	trace	55
5	<i>m</i> -CPBA ^b	49	trace	49

Reaction conditions : cyclohexene (5 mmol), **16** (0.05 mmol), oxidant 10 mmol, acetonitrile (36 mL) and reaction time (24 hrs) under O₂ atmosphere
25 : cyclohexene oxide, **26** : cyclohexenone, ^a 70°C, ^b oxidant 5 mmol was used

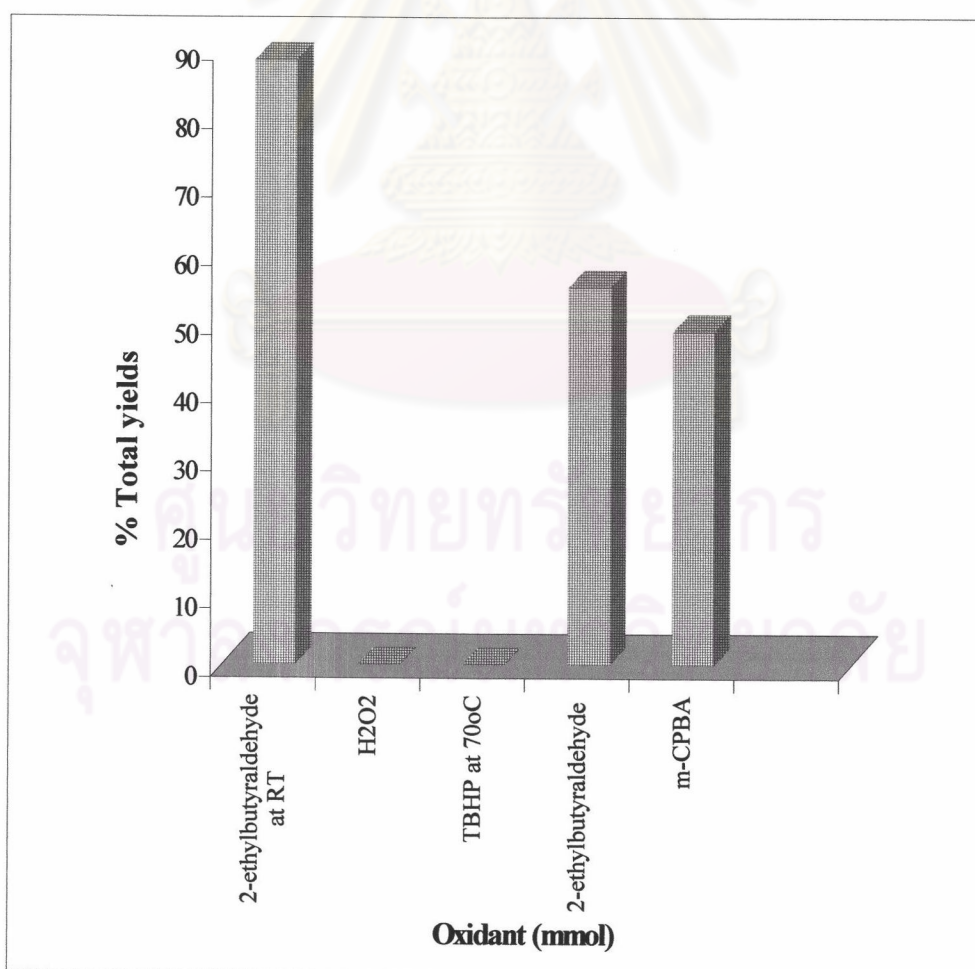


Fig. 3.5 The effect of oxidants on cyclohexene epoxidation

From Table 3.5 and Fig 3.5, H₂O₂ and TBHP (entries 2 and 3) were found not to be good oxidants under this particular condition. This result apparently presented that 2-ethylbutyraldehyde/O₂ and *m*-CPBA were more efficient oxidant affecting the epoxidation of cyclohexene. In addition, the results pointed out that 2-ethylbutyraldehyde still revealed a prevail result over *m*-CPBA under the same reaction conditions (entries 4 and 5). In conclusion, 2-ethylbutyraldehyde coupled with dioxygen was found to be the most efficient oxidant towards the transformation of cyclohexene to cyclohexene oxide (entry 1). This reaction condition was therefore kept constant for further optimization condition study.

3.2.5 Effect of the amount of 2-ethylbutyraldehyde on cyclohexene epoxidation

The amount of the oxidant is another crucial parameter that needed to be evaluated. The effect of the amount of 2-ethylbutyraldehyde present in the reaction was also examined in order to study the efficiency of 2-ethylbutyraldehyde. The results are described in Table 3.6 and Fig. 3.6.

Table 3.6 The effect of the amount of 2-ethylbutyraldehyde on cyclohexene epoxidation

Entry	2-Ethylbutyraldehyde (mmol)	Product (%)		Total yields (%)	% Efficiency based on 2-ethylbutyraldehyde
		25	26		
1	0	0	0	0	0
2	10	82	3	85	43
3	15	53	2	55	18
4	20	31	0	31	8

Reaction conditions : cyclohexene (5 mmol), **16** (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (varied) reaction time (24 hrs) under O₂ atmosphere

25 : cyclohexene oxide, **26** : cyclohexenone

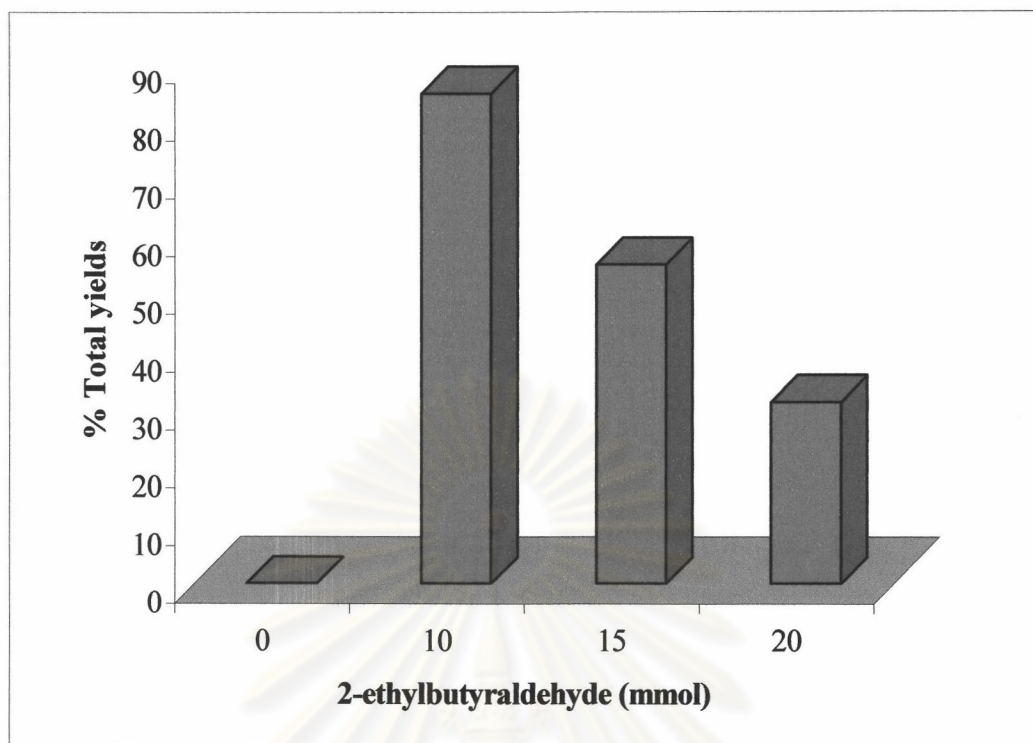


Fig. 3.6 The effect of the amount of 2-ethylbutyraldehyde on cyclohexene epoxidation

A blank experiment clearly revealed that in the absence of 2-ethylbutyraldehyde, cyclohexene oxide did not occur. Under the standard conditions, the utilization of 2-ethylbutyraldehyde 10 mmol provided the highest yield of the desired product (Table 3.6, entry 2). The more oxidants added, the less oxidized products obtained. The possible explanation may be because too much active species was generated at one time and unwanted side reactions may take place competitively with the main reaction. Moreover, the % efficiency based on 2-ethylbutyraldehyde was dropped dramatically as the increasing of the oxidant over 10 mmol in entries 3 and 4. The less amount of cyclohexene oxide was detected upon increasing the amount of 2-ethylbutyraldehyde. It was reasonable to rationalize that the over oxidation of the product may also be taken place. This upshot obviously indicated that the amount of oxidant had influence on the yield of product.⁷⁴

Hence, the optimized conditions for cyclohexene epoxidation can be summarized as: cyclohexene 5 mmol, complex **16** 0.05 mmol, acetonitrile 36 mL and 2-ethylbutyraldehyde 10 mmol using the reaction time for 24 hr under O₂ atmosphere.

3.3 Application of the developed epoxidation reaction for other alkenes

Under the optimized conditions as discussed in section 3.2.5, cyclohexene was transformed to cyclohexene oxide in a high yield with a superb selectivity. This developed system was therefore attempted to test for a variety of alkenes. For example, aliphatic alkenes such as 1-dodecene, *trans*-2-hexen-1-ol, aromatic containing double bond such as styrene, α -methylstyrene, monoterpenes containing double bonds such as α -terpinene, γ -terpinene, *R*-(+)-limonene and *S*-(-)-limonene, and 4-vinyl-1-cyclohexene which contained two kinds of double bonds were used as substrates. The epoxidation of selected alkenes is summarized in Table 3.7.

Table 3.7 Epoxidation of selected alkenes by developed epoxidation system




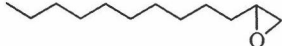
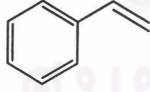
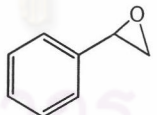
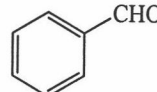
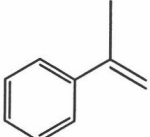
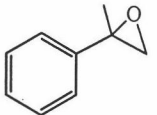
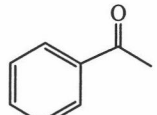
Entry	Substrate (5 mmol)	2-Ethyl butyraldehyde(mmol)	Product(s) (%)
1		10	 85, 74 ^b
2		10 20	 39 74, 65 ^a
3		10 20	 ,  34 68 , 19
4		10 20	 ,  52 76 , 25

Table 3.7 (cont)

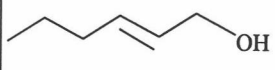
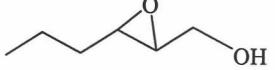
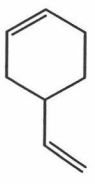
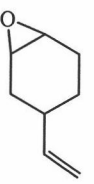
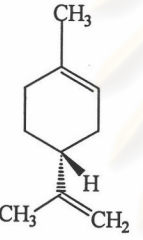
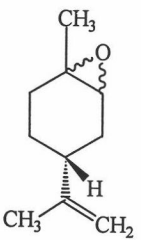
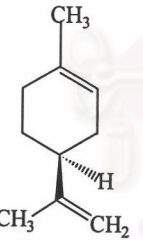
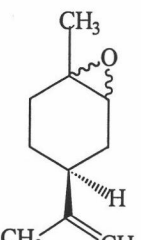
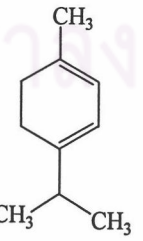
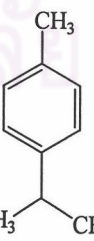
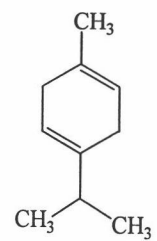
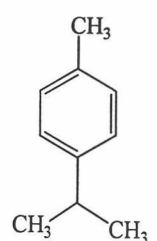
Entry	Substrate (5 mmol)	2-Ethyl butyraldehyde(mmol)	Product(s) (%)
5		10	 75
6		10	 78
		20	75
7	 R(+)-limonene	10	 93
8	 S(-)- limonene	10	 82
9	 α -terpinene	10	 <i>p</i> -cymene , 36

Table 3.7 (cont)

Entry	Substrate (5 mmol)	2-Ethyl butyraldehyde(mmol)	Product(s) (%)
10	 γ -terpinene	10	 43

Reaction conditions : alkene (5 mmol), **16** (0.05 mmol), toluene (36 mL) and 2-ethylbutyraldehyde (varied) reaction time (24 hrs) under O₂ atmosphere

- acetonitrile using as solvent
- using **15** as catalyst

Table 3.7 presents the outcomes from the epoxidation of alkenes under developed epoxidation conditions. These data clearly showed that, cobalt calix[4]pyrrole complexes **15**, **16** could catalyze the reaction to produce epoxides in good yields. In entries 2-10, toluene was employed as an appropriate solvent because it could dissolve all selected alkenes. However, in the case of cyclohexene, acetonitrile was used instead of toluene (entry 1). The epoxidation of endocyclic alkene such as cyclohexene proceeded smoothly to form cyclohexene oxide 85% yield when 10 mmol of 2-ethylbutyraldehyde was added (entry 1). 1-Dodecene chosen as an instance of aliphatic terminal alkenes could also be converted to 1-dodecene oxide; however to achieve the high yield of desired product, about twice of the amount of 2-ethylbutyraldehyde required for cyclohexene were necessary (entry 2). This study indicated that terminal monosubstituted alkene could transform to epoxide less than endocyclic disubstituted alkene.

In the presence of aromatic moiety, styrene which consisted of terminal double bond could also be epoxidized. Moderate yields of styrene oxide were obtained as the predominant product with a little concurrence of benzaldehyde as a minor product from cleaving of terminal double bond. When the amount of oxidant was increased, the total amount of the desired product was increased. Similar results were observed for the reactions of α -methylstyrene to yield α -methylstyrene oxide as a major

product. Acetophenone was detected as a minor one (entry 4). Conversely, increasing the amount of 2-ethylbutyraldehyde, the desired epoxidized product as α -methyl styrene oxide and styrene oxide gained were increased. Under the same conditions, allylic alcohol such as *trans*-2-hexen-1-ol was converted to *trans*-epoxy alcohol (*trans*-2-hexene oxide-1-ol) in good yield with the retention of the geometry.

4-Vinylcyclohexene was further tested for regioselectivity. This substrate contained both an internal and isolated terminal double bonds. From the examination result, the double bond in the ring of the substrate was preferentially oxidized over the isolated double bond in the side chain which remained intact under these conditions. In addition, 1,2-epoxy-4-vinylcyclohexane the main product of this oxidation reaction could be isolated from silica gel column chromatography (hexane : chloroform; 7 : 3). The $^1\text{H-NMR}$ (CDCl_3) spectrum clearly revealed the important signals at δ (ppm) : 4.88-5.70 (3H, m), 3.12 (epoxy protons, 2H, m) and 1.76-2.20 (alkyl protons, 7H, m). The GC chromatograms of both compounds; from authentic sample and normal reaction, were recorded to confirm this result (see section 2.4.4).

A similar study of the epoxidation of this substrate was addressed in literature. Kaneda and co-workers⁷⁰ reported that the use of the combinations of aldehyde and O_2 to provide 1,2-epoxide in 78 % yield in the presence of RuO_4 at 40 °C. The heterogeneous system using H_2O_2 ¹⁹ could be accomplished by $\text{Mg}_{10}\text{Al}_2(\text{OH})_{24}\text{CO}_3$, as catalyst at 70 °C. 1,2-Epoxide was appeared in 80 % yield without the detection of the oxidized product from exocyclic double bond. These two mentioned reactions were carried out at a high temperature and utilizing an expensive catalyst. In contrast to the epoxidation of the alkene catalyzed by cobalt(II) complex from this study, the reaction proceeded under mild conditions and gave a high yield of the desired product.

R-(+) and *S*-(-)-limonenes, another two naturally occurring monoterpenes were chosen as substrates for regioselectivity study. Concerning the obtained results, diastereomers were gained from the internal cyclic alkene epoxidation of each enantiomer (entries 7 and 8). These results should also be noted that the endocyclic double bond could be epoxidized more facile than exocyclic double bond. The explanation for this could be stemmed from the electron-rich trisubstituted double bond which was more active than the other.

Other terpenes were also selected as model substrates. These included monocyclic six-membered ring system with unsaturation: α -terpinene and γ -terpinene. The aromatization appeared to be more prevalent than other chemical processes (entries 9 and 10). To illustrate this, α - and γ -terpinene preferentially aromatized to *p*-cymene which was an aromatic compound instead of being epoxidized to their corresponding epoxides. This finding could be explained according to the stability and the existence of aromatic compound.

3.3.1 Regioselectivity study of 4-vinylcyclohexene

For further study on regioselectivity of this developed epoxidation reaction, the epoxidation of 4-vinylcyclohexene was comparatively investigated using Cobalt(II)calix[4]pyrrole **16**, 2-ethylbutyraldehyde / O₂ and *m*-CPBA under the same reaction conditions employed. The results are intimated in Table 3.8.

Table 3.8 The epoxidation of 4-vinylcyclohexene catalyzed by selected reaction condition

Entry	Reaction conditions	1,2-epoxy-4-vinylcyclohexane (%)	Mass balance (%)
1	Cobalt(II)calix[4]pyrrole ^a	41	100
2	<i>m</i> -CPBA ^b	46	102
3	Cobalt (II)calix[4]pyrrole, <i>m</i> -CPBA ^c	57	98

^a **Reaction conditions** : substrate (5 mmol), catalyst **16** (0.05 mmol), toluene 36 mL, 2-ethylbutyraldehyde (5 mmol) reaction time (24 hrs) and O₂ atmosphere

^b **Reaction conditions** : substrate (5 mmol), *m*-CPBA^b (5 mmol), toluene 36 mL, reaction time (24 hrs) at atmosphere

^c **Reaction conditions** : substrate (5 mmol), catalyst **16** (0.05 mmol), toluene 36 mL, *m*-CPBA (5 mmol), reaction time (24 hrs) atmosphere

From Table 3.8, 4-vinylcyclohexene was epoxidized under three different conditions. When utilizing *m*-CPBA, 1,2-epoxy-4-vinylcyclohexane was gained as a sole product in moderate yield (entries 2 and 3). The use of cobalt(II) calix[4]pyrrole **16** coupled with *m*-CPBA also yielded the desired product with the same extent of using

2-ethylbutyraldehyde / O₂ system. Thus, *m*-CPBA could be used as another choice of oxidant instead of aldehyde/ O₂. Nevertheless, the developed system still remained good features since the amount of aldehyde could be increased without affecting the reaction. The yield of the product could be increased when the higher amount of aldehyde was employed (see section 3.3, entries 3-4). In contrast to *m*-CPBA, the more *m*-CPBA used, the more by product, *m*-chlorobenzoic acid gained which made the reaction sluggish. In addition, *m*-CPBA was more expensive than 2-ethylbutyraldehyde.



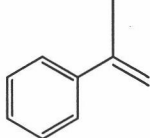
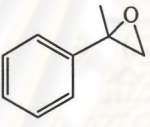
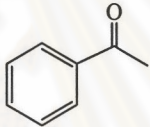
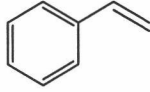
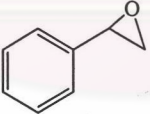
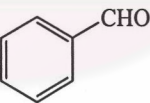
Furthermore, it has been clearly demonstrated that the high electron density position in double bond would lead to stabilized oxo-cobalt(IV) intermediate which would undergo epoxidation and eventually yielding the corresponding epoxide.

3.4 Effect of the amount of 2-ethylbutyraldehyde on the epoxidation of alkenes

The amount of 2-ethylbutyraldehyde was one of the essential parameters that needed to be scrutinized. Thus, the variation of the amount of 2-ethylbutyraldehyde was carried out according to the same manner as previously described, with the different amount of 2-ethylbutyraldehyde (0, 10, 15 and 20 mmol). 1-Dodecene, α -methylstyrene and styrene were selected as chemical models. The results are exhibited in Table 3.9 and Fig. 3.7.

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Table 3.9 The effect of the amount of 2-ethylbutyraldehyde on various selected alkenes

Substrate	Oxidant (mmol)	Oxidized products (%)		Total yields (%)	Ratio epoxide/oxidized products
	0			0	-
	10	0		39	-
	15	39		50	-
	20	50		74	-
	10			52	∞
	15	52	0	72	5.55
	20	61	11	100	3.00
		75	25		
	10			34	∞
	15	34	0	61	5.77
	20	52	9	87	3.58
		68	19		

Reaction conditions: alkene (5 mmol), **16** (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (varied) reaction time (24 hrs) under O₂ atmosphere

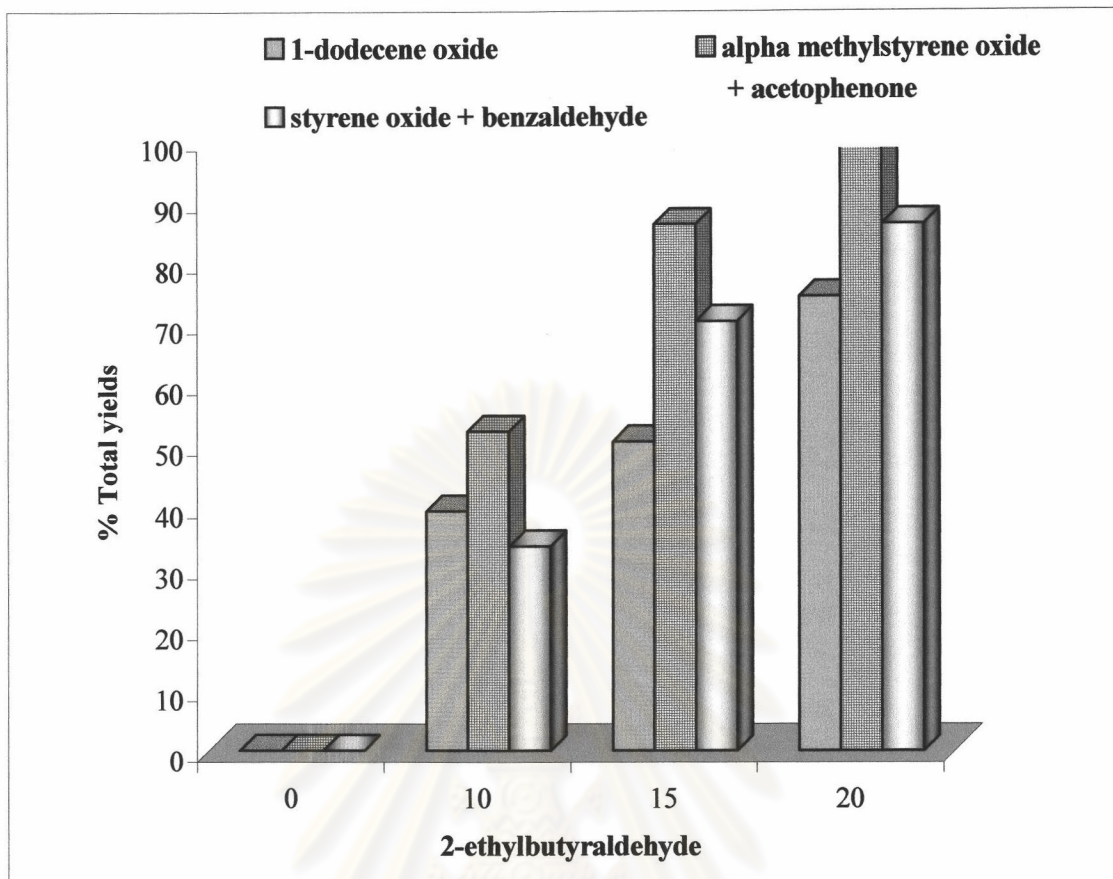


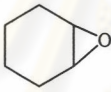
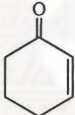
Fig. 3.7 The effect of the amount of 2-ethylbutyraldehyde on the variation of alkenes

It could clearly be seen from Table 3.9 and Fig. 3.7 that 1-dodecene, α -methylstyrene, and styrene could be transformed to the corresponding desired products. In the absence of the oxidant, there was no reaction taken place. The higher amount of 2-ethylbutyraldehyde was used, the greater yield of products were obtained. Therefore, these results showed that the amount of oxidant is a significant parameter for this system. For instance, the total yield of the epoxidation of α -methylstyrene with 20 mmol of 2-ethylbutyraldehyde was close to 100, which pointed out that the reaction could proceed almost completely. It should also be noted at this point that in the case of increasing the amount of oxidant from 15 mmol to 20 mmol, the ratio of epoxide/oxidized product was a bit altered from 5 to 3. The yield of the desired products gained was higher. Thus, it was clearly seen that one way to lift up the yield was to increase the amount of 2-ethylbutyraldehyde.

3.5 Comparative kinetic study of the epoxidation of cyclohexene and 1-dodecene

Various recent catalytic models that mimic enzymatic systems had an effort to develop the reactions to be of a capability to proceed at RT. Nevertheless, the rates of these reactions are generally slow and need to spend more time to complete the reaction. In order to investigate the reactivity of diverse alkenes, cyclohexene (endocyclic alkene) and 1-dodecene (terminal monosubstituted alkene) were selected as chemical probes to observe the rate of epoxidation reaction. The rates of the epoxidation of cyclohexene and 1-dodecene catalyzed by cobalt(II) calix[4]pyrrole complex **16** are presented in Tables 3.10 and Table 3.11.

Table 3.10 Kinetic study on cyclohexene epoxidation catalyzed by cobalt(II) calix[4]pyrrole complex **16**

Entry	Time (hrs)	Product (%)		Total yields (%)
				
1	1	2	0	2
2	3	5	0	5
3	5	30	0	30
4	7	44	0	44
5	10	54	trace	54
6	13	75	trace	75
7	18	79	trace	79
8	21	84	trace	84
9	24	87	trace	87
10	36	85	trace	85

Reaction conditions: cyclohexene (5 mmol), **16** (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O₂ atmosphere

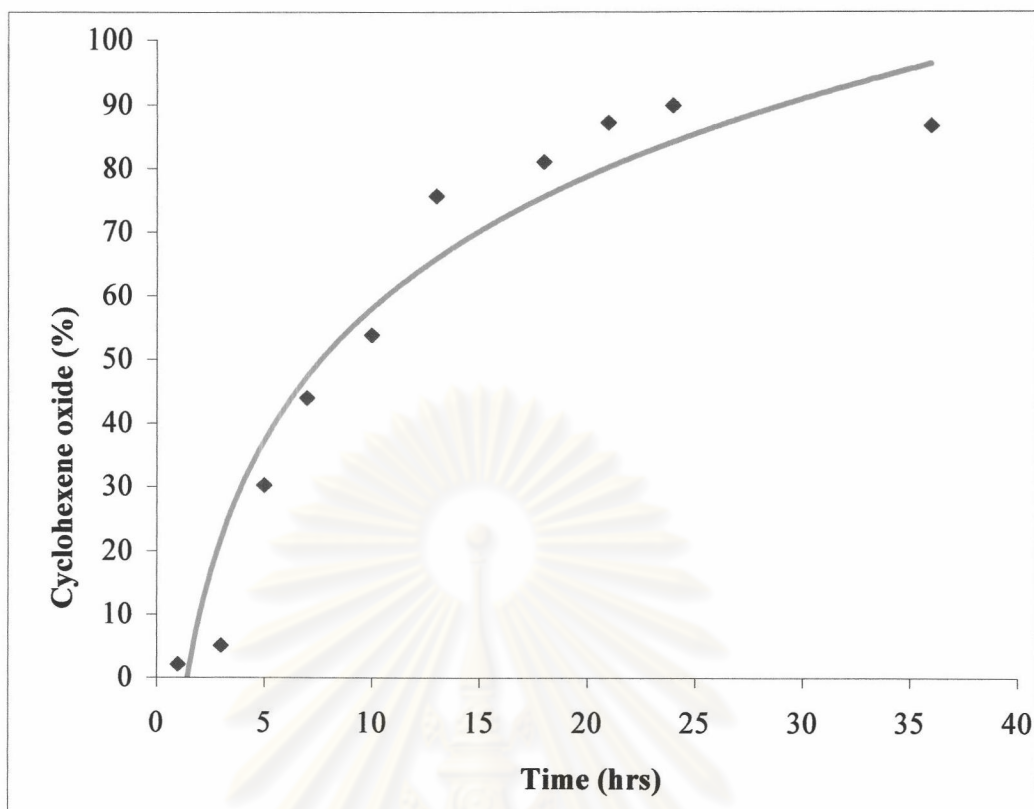




Fig. 3.8 Kinetic study on cyclohexene epoxidation catalyzed by Cobalt(II) calix[4] pyrrole 16

From the results obtained, Fig. 3.8 displays the productivity of the desired product, cyclohexene was smoothly converted to cyclohexene oxide in a high yield with a trace of cyclohexenone. As proceeding, 24 hours were taken as the most favorable reaction time at which the maximum epoxidation was occurred and the maximum yield was received about 87%. The half-life of cyclohexene epoxidation was approximately 7 hours.

3.5.1 Comparative kinetic study on the epoxidation of cyclohexene and 1-dodecene catalyzed by Co(II) calix[4]pyrrole complex in acetonitrile and toluene

Half-life of the reaction is an influential factor to reflect the kinetic epoxidation. The kinetic study on the epoxidation of cyclohexene and 1-dodecene by various solvents: acetonitrile and toluene was conducted at room temperature. The outcomes are shown in Table 3.11 and Fig. 3.9.

Table 3.11 Comparative kinetic study on the epoxidation of cyclohexene and 1-dodecene catalyzed by cobalt(II) calix[4]pyrrole **16**

Entry	Time (hrs)	Product (%) in			
					
		acetonitrile	toluene	acetonitrile	toluene
1	1	2	1	1	4
2	5	30	22	9	15
3	10	54	39	14	21
4	15	77	47	18	25
5	24	90	74	30	36

Reaction conditions: substrate each (5 mmol), **16** (0.05 mmol), solvent (36 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrS) under O₂ atmosphere

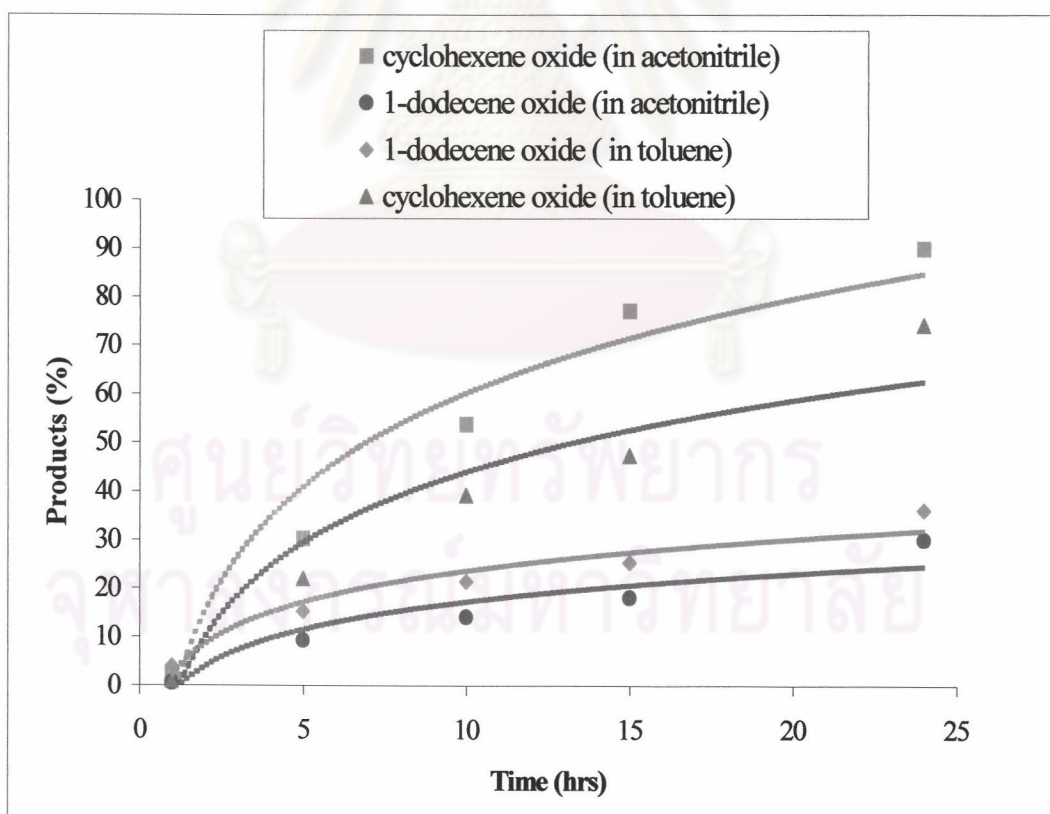


Fig. 3.9 Comparative kinetic study on the epoxidation of cyclohexene and 1-dodecene catalyzed by cobalt(II) calix[4] pyrrole **16**

As seen from Fig 3.9, it was found that the rate of the reaction depended greatly on the solvents. In the case of cyclohexene, the reaction conducted in acetonitrile could afford smoothly faster than that in toluene. The half-life of the reaction was increased from approximately 7 hrs in acetonitrile to 9 hrs in toluene and the yields detected at 24 hrs were 90% and 74% respectively. Hence, an appropriate solvent for cyclohexene in this system was acetonitrile. On the contrary, in the case of 1-dodecene, the better trend could be observed when using toluene as solvent. The half-life of the reaction was decreased from 10 hrs in acetonitrile to 8 hrs in toluene. The yields observed at 24 hrs were 30% and 36%, respectively. Hence, the following examinations would be made use of acetonitrile for cyclohexene and toluene for 1-dodecene.

Moreover, the influence of the amount of 2-ethylbutyraldehyde (10 and 20 mmol) was investigated in the epoxidation of 1-dodecene. The results are tabulated in Table 3.12 and Fig. 3.10.

Table 3.12 Kinetic study on 1-dodecene epoxidation catalyzed by cobalt(II) calix[4]pyrrole complex **16**

Entry	Time (hrs)	1-Dodecene oxide (%)	
		Oxidant 10 mmol used	Oxidant 20 mmol used
1	1	4	10
2	3	10	16
3	5	15	24
4	7	18	35
5	10	22	44
6	13	24	61
7	18	29	67
8	21	33	71
9	24	36	74
10	36	39	77

Reaction conditions : 1-dodecene (5 mmol), **16** (0.05 mmol), toluene (36 mL) and 2-ethylbutyraldehyde (10 or 20 mmol), reaction time (24 hrs) under O₂ atmosphere

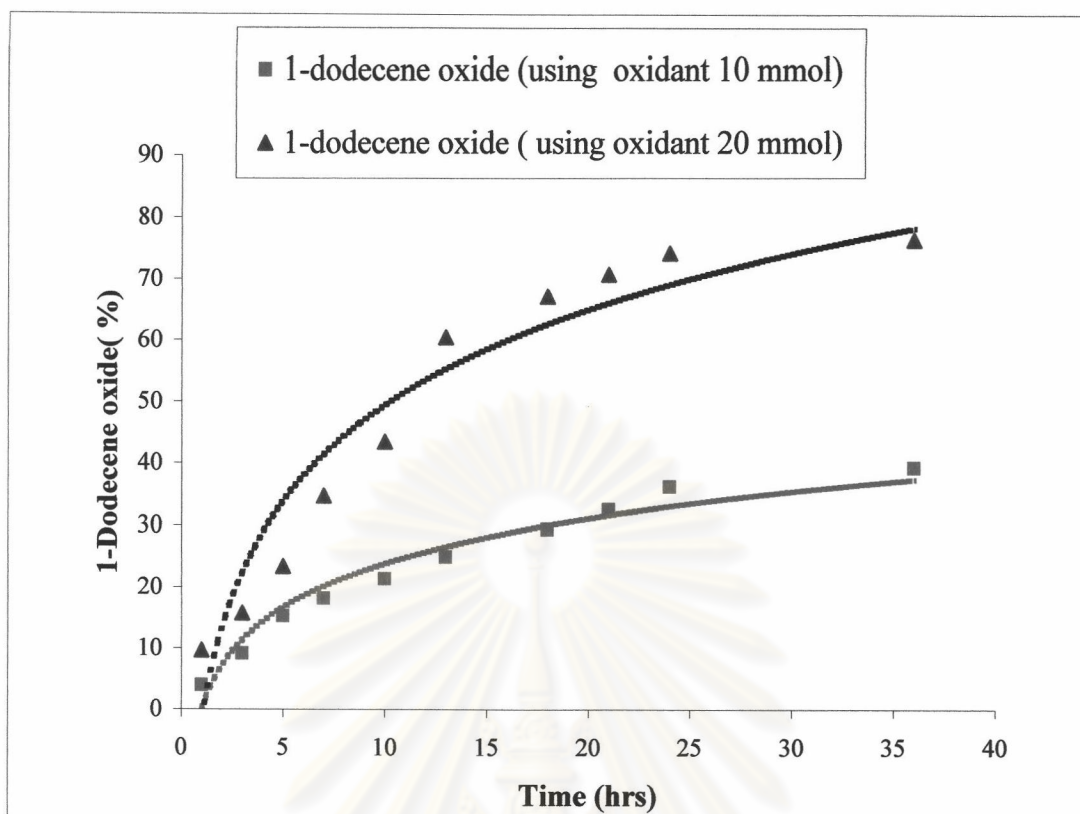


Fig. 3.10 Kinetic study on 1-dodecene epoxidation catalyzed by cobalt(II) calix[4] pyrrole **16**


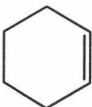
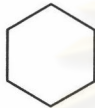
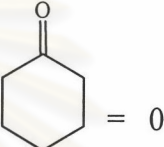

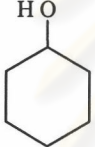
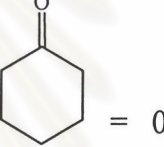
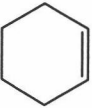
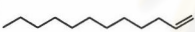
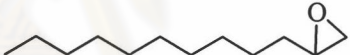
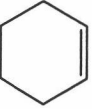
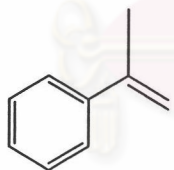
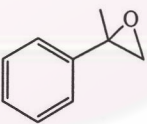
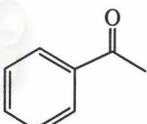

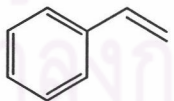
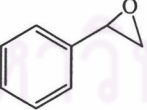
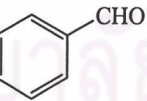
When using 20 mmol of 2-ethylbutyraldehyde, the desired product was attained in a higher yield than using 10 mmol of oxidant. The maximum yield was received about 76 %. The half-life of 1-dodecene epoxidation was approximately 10 hours by using cobalt(II) calix[4]pyrrole catalyst **16** in terms of employing oxidant 10 or 20 mmol.

3.6 Competitive studies on the oxidation of cyclohexene, cyclohexane, cyclohexanol, 1-dodecene, α -methyl styrene and styrene

In order to examine the characteristics of this developed catalytic system, the competitive studies on the oxidation of cyclohexene and saturated hydrocarbons such as cyclohexane, and alcohol such as cyclohexanol were carried out. The competitive studies on the oxidation between cyclohexene and other alkenes such as 1-dodecene, α -methylstyrene and styrene were also performed. In most cases of the exploration inquired, the alkene epoxidation was carried out under the condition using cobalt(II)

complex **16** as a catalyst, 2-ethylbutyraldehyde and oxygen as oxidant and toluene as a reaction medium. The upshots of the results are shown in Table 3.13.

Table 3.13 Competitive studies of the reactivity for the oxidation of saturated hydrocarbon and selected alkenes.

Cyclohexene (A)	Other substrates (B)	Products (mmol)		Relative Reactivity (B) / (A)
			Other oxidized products	
		2.15	 = 0	-
		1.76	 = 0.55	0.31
		4.82	 1.88	0.39
		3.25	 3.02  1.50	1.39
		3.20	 2.40  1.22	1.13

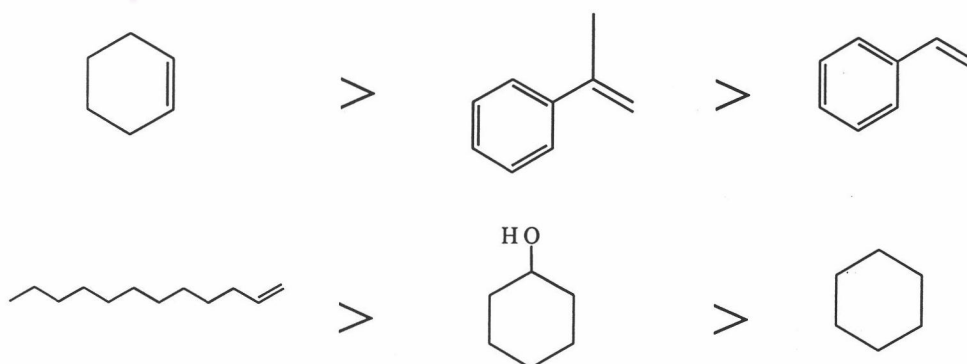
Reaction conditions : substrate 10 mmol each, **16** (0.05 mmol), toluene (36 mL)
2-ethylbutyraldehyde 20 mmol, reaction time (24 hrs) under O₂ atmosphere

From Table 3.13, it was observed that the epoxidation of cyclohexene yielding cyclohexene oxide took place faster than the oxidation of cyclohexanol and cyclohexane, respectively. In both cases, allylic oxidation was not occurred. Cyclohexane was not oxidized to either cyclohexanone or cyclohexanol. This competition reaction explicitly showed that alkene functional group was more sensitive than the C-H bond of saturated hydrocarbon.

For the competitive studies between cyclohexene and 1-dodecene mentioned above, cyclohexene could be epoxidized faster than 1-dodecene. This was clearly understandable because the epoxidation of terminal alkene, generally, was difficult to perform. This finding was supported that the active species of this reaction preferred interacting at more electron rich site and implied that it should possess the electrophilic in character.

Unlike the previously mentioned substrates, α -methylstyrene or styrene did not produce only the corresponding epoxides but also yielded the minor products (acetophenone and benzaldehyde from α -methylstyrene and styrene, respectively). These products were obtained from the cleavage of the terminal double bond. Therefore, there were at least two competitive reactions taken place simultaneously under this condition.

Comparison to the terminal aliphatic alkene; 1-dodecene, aromatic bearing double bond such as α -methylstyrene and styrene, the epoxidation of cyclohexene was still prevailed. The presence of conjugated double bond in both substrates might be a good reason to explain the outcome of the reaction. Considering the relative reactivity which could calculate from the ratio of the desired products from the competitive reaction between cyclohexene and α -methylstyrene, it gave the highest value, 1.39. This data indicated that cyclohexene was easier to be epoxidized to the desired products. From the above results for the comparison of relative reactivity of a series of substrates selected, the order could be as follows:



The information derived from competitive studies provided important clues for chemoselectivity study. The observation implied that high valent oxo cobalt(IV) of calix[4]pyrrole generated should be of selectivity for the oxidation of alkenes prevailing the other function groups. This result was different from other systems reported. For example, The oxidation utilizing by Schiff base oxovanadium(IV) complex, cyclohexenone was produced as a major product while cyclohexene oxide being minor.⁷² In the presence of VO(acac)₂-AIBN as a catalyst, the corresponding epoxy alcohol was detected in high yield.⁷³

3.7 Effect of the radical inhibitor in the epoxidation of alkene

Mechanistic study of the epoxidation of alkenes by dioxygen in the presence of aldehyde and metal complexes was carried out. Generally, the reaction proceeded *via* radical pathway. To prove this, appropriate radical inhibitor, pyridine was added to the reaction for the mechanistic study. The results are exhibited in Table 3.14.

Table 3.14 Effect of pyridine on the epoxidation of cyclohexene

Entry	2-ethylbutyraldehyde (mmol)	Pyridine (mL)	Total yields (%)	Recovered cyclohexene (%)	Mass balance (%)
			25+26		
1	0	-	0	99	99
2	10	-	84	14	98
3	10	0.5	0	100	100

Reaction conditions : alkene (5 mmol), **16** (0.05 mmol), acetonitrile (36 mL) and 2-ethylbutyraldehyde (10 mmol) reaction time (24 hrs) under O₂ atmosphere

25 : cyclohexene oxide, **26 :** cyclohexenone

The results presented in Table 3.14 manifestly revealed that there was the effect of the radical inhibitor on the cyclohexene epoxidation. The mechanism of this epoxidation reaction supposed to proceed *via* free radical pathway.⁷⁴

3.8 Separation of 2-ethylbutanoic acid

Upon the analysis of the product from the epoxidation reaction, it was noticed that there was another peak present in the gas chromatogram besides the epoxidized product peaks. Therefore, the attempt to separate this byproduct from the reaction was made as described in Section 2.6.1

According to GC-MS analysis of this component (Figs. 3.11 and 3.12) using DB-5 column, the results clearly indicated that the isolated product was 2-ethylbutanoic acid.

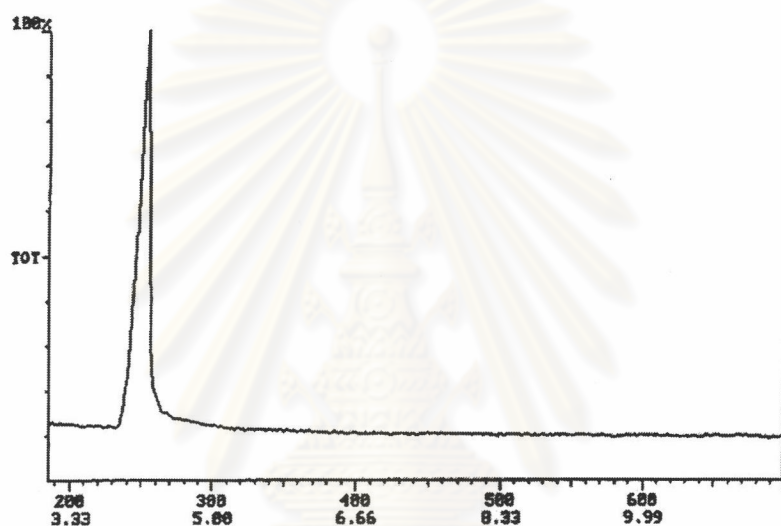


Fig. 3.11 Chromatogram of 2-ethyl butanoic acid

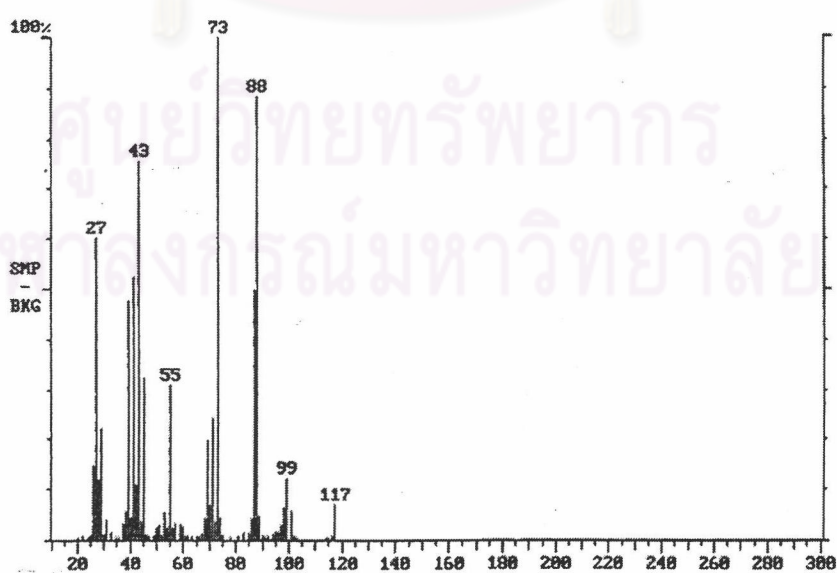


Fig. 3.12 Mass spectrum of 2-ethyl butanoic acid

This compound was isolated as liquid pale yellow, R_f 0.44 (hexane: ethyl acetate; 1:1). To confirm the structure of this compound, IR and $^1\text{H-NMR}$ spectra were recorded. IR (neat): 3400-2800 (O-H stretching vibration), 1705 (C=O stretching vibration) and 1275 (C-O stretching vibration) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , δ (ppm)): 10.98 (acid proton, 1H, bs), 2.03-1.87 (1H, m), 1.69-1.43 (4H, m) and 0.92-0.87 (methyl protons, 6H, t = 12 Hz).

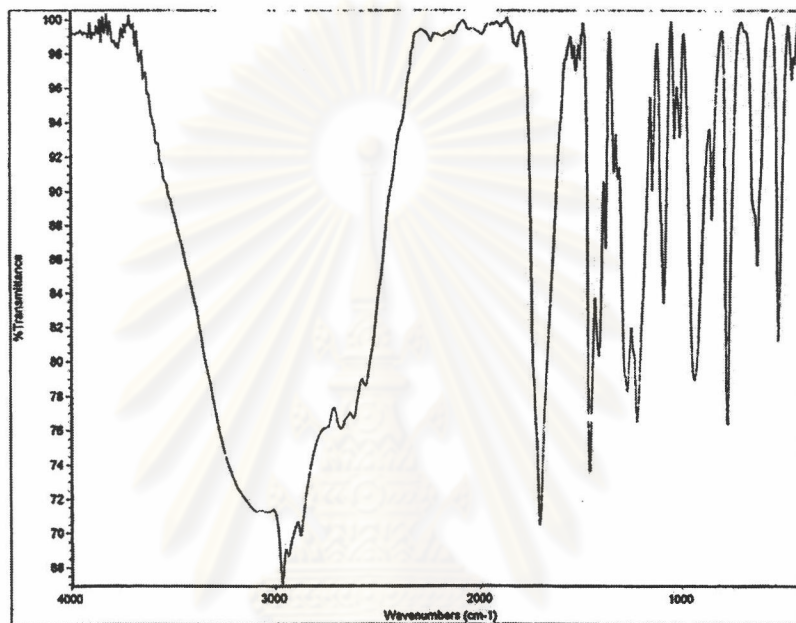


Fig. 3.13 IR spectrum of 2-ethyl butanoic acid

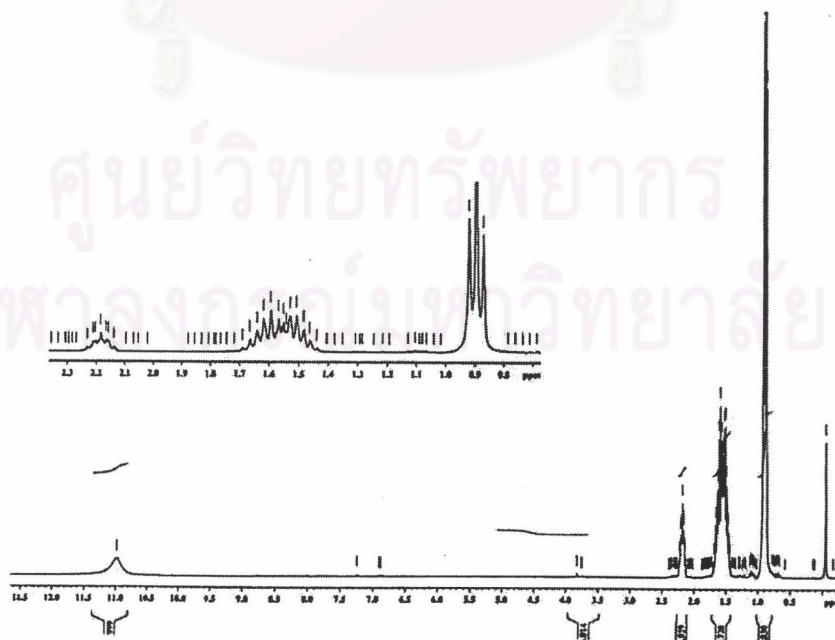
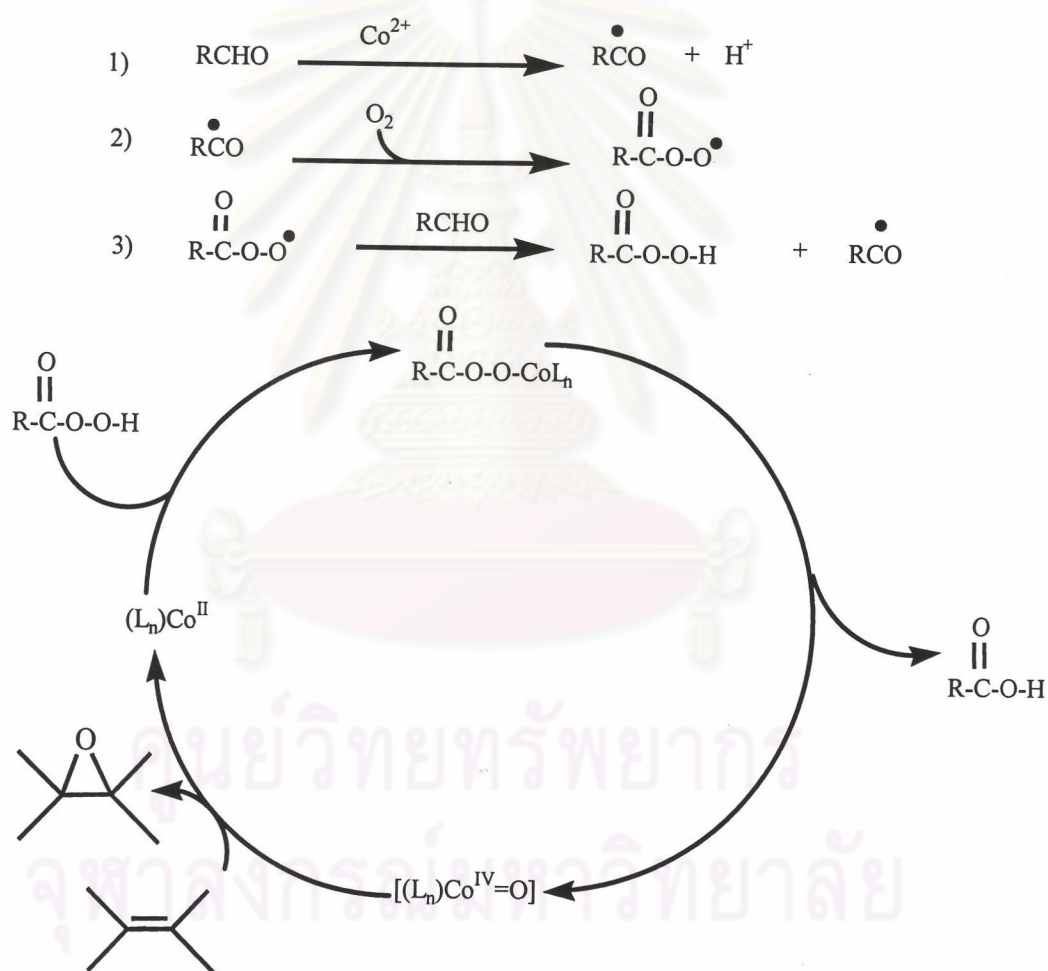


Fig. 3.14 ^1H NMR spectrum of 2-ethyl butanoic acid

3.9 Proposed mechanism for cobalt-catalyzed epoxidation of alkene utilizing 2-ethylbutyraldehyde/ O₂ system

Based upon the detection of 2-ethylbutanoic acid as by product from the epoxidation of alkenes catalyzed by cobalt calix[4]pyrrole complex (section 3.8) and the effect of radical inhibitor (pyridine) study (section 3.7), these evidences led to the confirmation that carboxylic acid was the byproduct from the epoxidation of alkene using aldehyde and O₂ as an oxidant. The epoxidation was therefore believed to occur *via* free radical pathway.⁷⁴ The proposed mechanism is shown below in Scheme 3.1.



Scheme 3.1 The proposed mechanism for the cobalt-calix[4]pyrrole complex catalyzed epoxidation of alkenes using 2-ethylbutyraldehyde/ O₂ system

The mechanistic study of this epoxidation was assumed to initiate from the cobalt complex reacting with the aldehyde to generate an acyl radical (RC(O)^\bullet). The acyl radical was then reacted with dioxygen to give an acyl peroxy radical (RC(O)OO^\bullet). The acyl peroxy radical acted as a carrier in a chain mechanism by reacting with another aldehyde molecule to yield peroxy acid, thereby generating another acyl radical. The peroxy acid reacted with cobalt complex to proceed cobalt (IV)-peroxy complex which occurred *via* reactive high-valent oxo cobalt (IV) intermediate, known to be an active oxidizing agent by the oxygen-oxygen bond cleavage of the peroxy group and gave the corresponding acid species as byproduct which could be confirmed by isolation from the reaction mixture. The oxo-cobalt (IV) complex reacted with alkenes in a fashion analogous to transfer an oxygen atom directly to alkenes yielding epoxides. The cobalt(II) complex was driven back to the catalytic system.⁷⁴



ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย