การสังเคราะห์แนฟโทควิโนนโดยอาศัยตัวเร่งปฏิกิริยาโคบอลต์ซาเลน

นายองอาจ ธเนศนิตย์

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SYNTHESIS OF NAPHTHOQUINONES UTILIZING COBALT-SALEN CATALYST

Mr. Ong-art Thanetnit

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Chemistry

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องอาจ ธเนศนิตย์: การสังเคราะห์แนฟโทควิโนนโดยอาศัยตัวเร่งปฏิกิริยาโคบอลต์ซาเลน (SYNTHESIS OF NAPHTHOQUINONES UTILIZING COBALT-SALEN CATALYST) อ. ที่ปรึกษา: ผศ. ดร.วรินทร ชวศิริ, 46 หน้า. ISBN 974-53-2050-1

ภายใต้ภาวะในการออกซิเดชันที่ไม่รุนแรงโดยอาศัยตัวเร่งปฏิกิริยาโคบอลต์ซาเลน และออกซิเจนสามารถออกซิไดซ์ 1-แนฟทอล เป็นผลิตภัณฑ์ 1,4- แนฟโทควิโนนในปริมาณที่น่าพอใจ ภาวะที่เหมาะสมในการทำปฏิกิริยาขึ้นกับเวลา อุณหภูมิ ชนิดและปริมาณของลิแกนด์ ชนิดของตัวออกซิไดซ์และชนิดของตัวทำละลาย ภายใต้ภาวะในการออกซิเดชันที่ถูกพัฒนาพบว่า 2-แนฟทอล สามารถถูกออกซิไดซ์เป็นผลิตภัณฑ์ 4-(2-ไฮดรอกซี-1-แนพทิล)-1,2-แนฟโทควิโนนในปริมาณที่น่าพอใจ นอกจากนี้ได้นำระบบออกซิเดชันที่ พัฒนามาประยุกต์ใช้ในการทำปฏิกิริยากับสารตั้งต้นไทมอล, 1,5-ไดไฮดรอกซีแนฟทาลีน 6-เมทอกซี-2-แนฟทอล และ 7-เมทอกซี-2-แนฟทอล ได้ผลิตภัณฑ์หลักเป็นไทโมควิโนน จัคโลน 6-เมทอกซี-1,2-แนฟโทควิโนน และ 4-(2-ไฮดรอกซี-7-เมทอกซี-1-แนพทิล)-7-เมทอกซี-1,2-แนฟโทควิโนน ตามลำดับในปริมาณปานกลาง

ภาควิชา…….เคมี…… ลายมือชื่อนิสิต…….

สาขาวิชา……...เคมี…… ลายมือชื่ออาจารย์ที่ปรึกษา……..

ปีการศึกษา…...2547…….. ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……-……..

4472478723: MAJOR CHEMISTRY

KEY WORD: OXIDATION/ NAPHTHOQUINONE/ CATALYST

ONG-ART THANETNIT: SYNTHESIS OF NAPHTHOQUINONES UTILIZING COBALT-SALEN CATALYST: ADVISOR: ASSISTANT PROFESSOR WARINTHORN CHAVASIRI, Ph.D., 46 pp. ISBN 974-53-2050-1

Under mild condition, utilizing cobalt-salen catalyst with oxygen, 1-naphthol could be oxidized to the corresponding 1,4-naphthoquinone product at room temperature in good yield. The optimum reaction conditions studied including reaction time, type of oxidant, type and amount of ligand, temperature and type of solvent were explored. The oxygenation of 2-naphthol under the developed oxidation process could yield a dimeric compound, namely 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone in satisfactory. In addition, this developed condition was applied to the oxidation of thymol, 1,5-dihydroxynaphthalene, 6-methoxy-2-naphythol, 7-methoxy-2-naphthol into the corresponding thymoquinone, juglone, 6-methoxy-1,2-naphthoquinone and 4-(2-hydroxy-7-methoxy-1-naphthyl)-7-methoxy-1,2-naphtho-quinone in moderate yield.

Department…..Chemistry…… Student's signature……...

Field of study…Chemistry….. Advisor's signature……..

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Special thanks are expressed to my family for their love, affection, best wishes, understanding and encouragement, without them, the author would have never been able to be successful on this goal.

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LIST OF ABBREVIATIONS

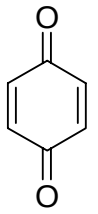
CH_3-	alkanic proton of methyl
CH-	alkanic proton of methine
ArH	aromatic proton
br	broad spectrum (NMR)
°C	degree of celsius
δ	chemical shift
J	coupling constant (NMR)
d	doublet (NMR)
equi-	equivalent (s)
Fig	Figure
g	gram (s)
OH	hydroxy proton
QH	quinolic proton
Hz	hertz
IR	infrared
lit.	literature
m.p.	melting point
mL	milliliter (s)
mmol	millimole (s)
m	multiplet (NMR)
NMR	nuclear magnetic resonance
q	quartet (NMR)
R_f	retardation factor
sep	septet (NMR)
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography
cm^{-1}	unit of wave number

CHAPTER I

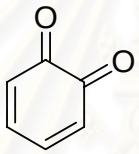
INTRODUCTION

1.1 Quinones

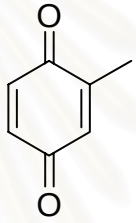
Quinones are cyclohexadiones whose names are derived from those aromatic systems, for instance, benzoquinone is derived from benzene, toluquinone from toluene and naphthoquinone from naphthalene, *etc*. In addition, quinone is used both as generic term and as common name for *p*-benzoquinone [1].



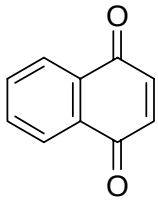
***p*-benzoquinone**



***o*-benzoquinone**

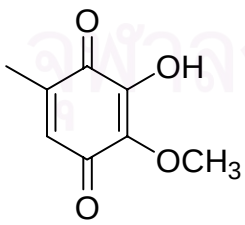


toluquinone

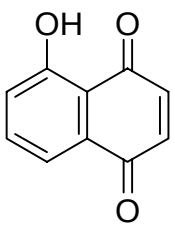


1,4-naphthoquinone

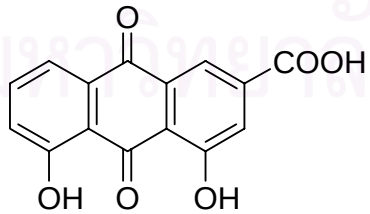
Many quinones, especially hydroxyquinones, occur in nature. Some examples are antibiotics fumigatin and phitiocol [2-5]. Hydroxynaphthoquinones and hydroxyanthraquinones such as juglone and rhien are also common as free forms or bound to sugar moiety [6-11]. Furthermore, many natural pigments possess quinone structures [12-13]. Quinone structures are frequently associated with color and the following structure units are referred to as "*quinonoid*".



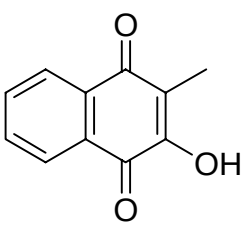
fumigatin



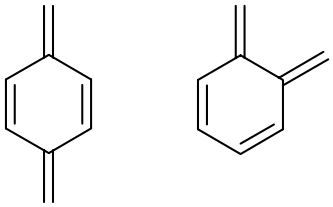
juglone



rhein



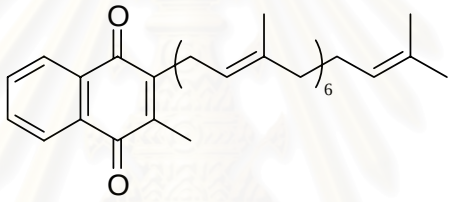
phthiocol



quinonoid structure

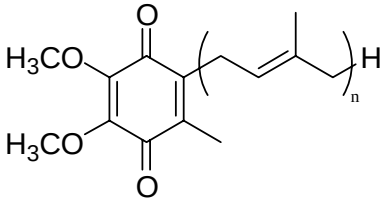
Quinones, which are readily produced by oxidation of 1,2- and 1,4-hydroxybenzenes, are easily reduced, forming the dihydroxy derivatives.

The oxidation-reduction reactions of hydroquinone and quinone derivatives play an important role in physical redox process. There are a number of Vitamin K, such as K_1, K_2, K_3 that naturally relate to this process and they concern to 1,4-naphthoquinone in the redox process [14-17]. For example, Vitamin $K_{2(30)}$ is



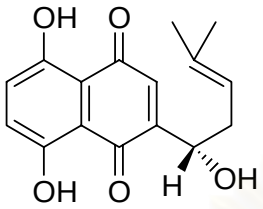
vitamin $K_{2(30)}$

The K vitamins are present in blood as coagulation factor [18-19].Their function as cofactors for an enzymes that carboxylates glutamic side chains in proteins. The resulting carboxy glutamic acid groups are probably important in chelation of calcium ion. The relative series of compounds is coenzyme Q, which occurs in many kinds of cells with n = 6, 8 or 10 (n = 10 in mammalian cells, ubiquinone). Coenzyme Q is involved in electrontransport systems and the long isoprenoid chain is designed to promote solubility in phospholipid bilayers of cell or mitochondrial membrane [20].

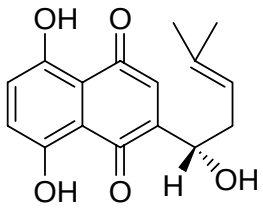


coenzyme Q

Alkanin and shikonin, bear both the naphthoquinone and the phenolic moiety, are potent pharmaceutical substances with a wide spectrum of biological properties and comprise the active ingredients of several pharmaceutical [21-22] and cosmetic [23-24] preparations, and are used as food colorants [25-26].



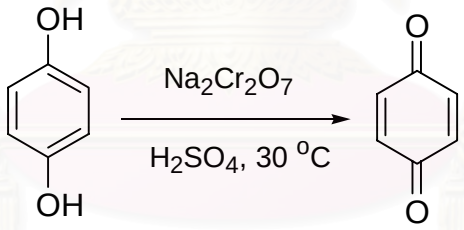
alkanin



shikonin

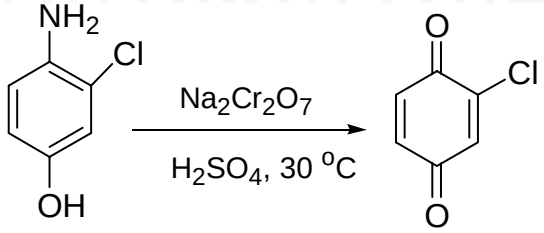
1.2 The oxidation methods for quinone formation

Quinones have considerable potential for the synthesis of organic molecules owing to their highly functionalized character [27-28]. The common method for preparation of quinones is oxidation of substituted aromatic alcohol [29-30] or aniline derivatives [32]. For example, *p*-benzoquinone can be prepared by oxidation of some benzene or aniline with variety of oxidizing agents, but the usual laboratory preparation involves the oxidation of hydroquinone.



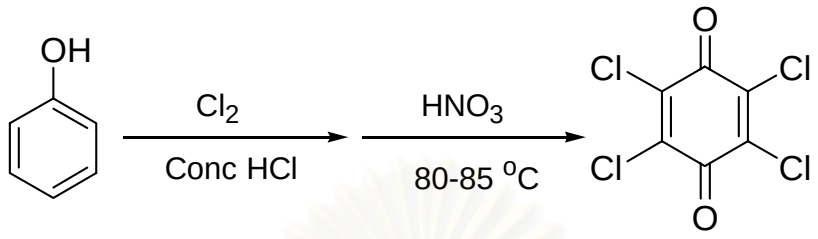
hydroquinone **quinone (86-92%)**

Amino phenols are easily oxidized to quinones, and this route constitutes one of the best methods for the preparation of substituted quinones.



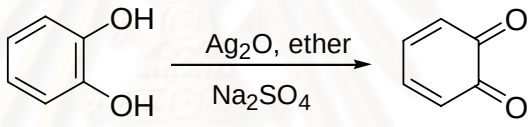
2-chloro-1,4-benzoquinone

Many other oxidizing agents have also been used, and the best one for any given compound must be determined by experiment. For example, the preparation of tetrachloro-*p*-benzoquinone (chloranil) makes advantageous use of nitric acid [33].



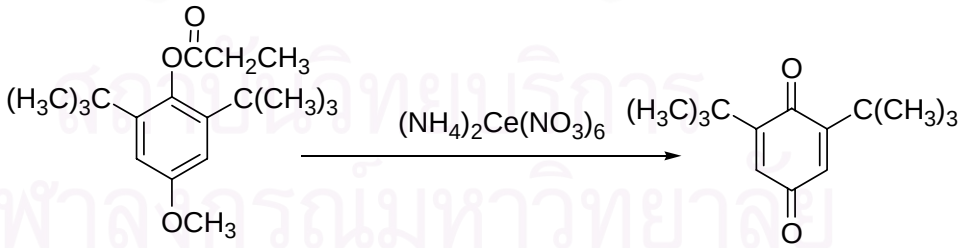
chloranil (60%)

The oxidation of *o*-dihydroxybenzenes to *o*-quinones can be carried out with silver oxide in ether [34].



catechol **o-benzoquinone**

In many cases phenyl ethers and esters undergo oxidation to the corresponding quinones with loss of the alkyl or acyl group. An example is the oxidation of 2,6-di-*t*-butyl-4-methoxyphenyl propionate by ceric ammonium nitrate [35-37].

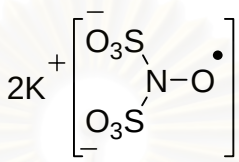


Direct oxidation of aromatics with H_2O_2 can be accomplished by increasing the electrophilicity of the oxidant through the use of Lewis acid as, for example, with aluminium chloride ($AlCl_3$) or boron trifluoride etherate ($BF_3.OEt_2$) or by carrying out the reaction in super acidic media [38]. However, these systems are not catalytic and often requiring large excess of the activating agent.

The naphthol oxidation products are used for the successful synthesis of natural products, vitamin and their intermediates. It is also known that the effective

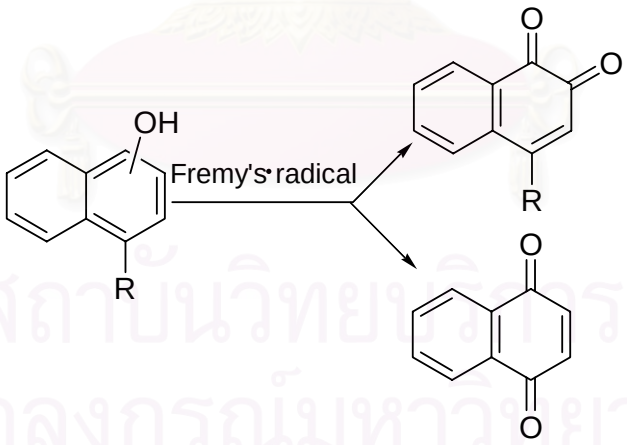
reagents such as chromic trioxide [39-40], silver oxide [41-42], cerric ammoniumnitrate [43-44] could proceed the oxidation reaction of naphthols into naphthoquinones with the satisfied result.

One of the major trends in modern organic synthesis is the development of very selective reagent. In the area of oxidation reaction of organic compound, the number of such selective oxidizing agents is still fairly small. One of few of those agent is potassium nitrodisulfunate or Fremy's radical [45].



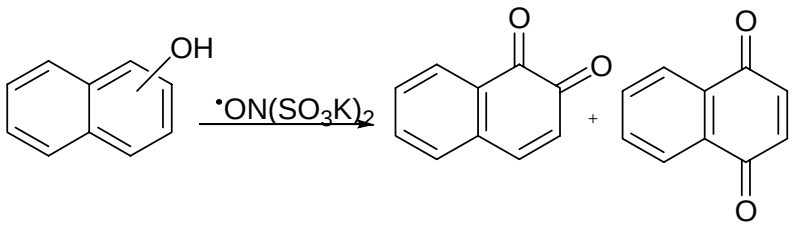
Fremy's radical

Because of its radical character, that gives the reagent as a rather unstable compound. It could oxidize organic compound, especially phenol very easily. Oxidation of 1-naphthol on which position 4 is unsubstituted (R=H) generally leads to the formation of 1,4-naphthoquinone, while 1,2-naphthoquinone will be formed if an alkyl group occupies position 4 or a hydroxy group occupies position 2 [46].



When a hydroxy group occupies position 5- of 1-naphthol, approximately equal amount of the 1,2- and 1,4-naphthoquinones are formed. In addition, 2-naphthol are generally oxidized to give 1,2-naphthoquinone. The radical intermediates which would lead to 1,2-naphthoquinone is described as presented into Table 1.1

Table 1.1 The oxidation of 1- and 2-naphthol with Fremy's radical reagent



Chemical Substance	% yield of the product	
	1,2-naphthoquinone	1,4-naphthoquinone
1-naphthol	-	91
1,2-dihydroxynaphthalene	95	-
1,3-dihydroxynaphthalene	-	81
1,4-dihydroxynaphthalene	-	95
1,5-dihydroxynaphthalene	51	49
1,6-dihydroxynaphthalene	-	91
4-methoxy-1-naphthol	97	-
3-methoxy-1,2-dihydroxynaphthalene	99	-
2-naphthol	91	-
2,6-dihydroxynaphthalene	92	-
2,7-dihydroxynaphthalene	80	-
3-methoxy-2-naphthol	99	-
4-methoxy-2,3-dihydroxynaphthalene	66	-

However, the lack of stability of Fremy's radical could cause a violent explosion when the reaction was employed with chloride, nitrite ion or manganese oxide.

In 1976, Barton *et al.* [47] reported the oxidation of phenols *via* diphenylseleninic anhydride in tetrahydrofuran to the corresponding *o*-quinones in good yield. In addition, the reaction was efficiently worked at 50^{o}C after 15 min. However, diphenylseleninic anhydride oxidant was limited to use due to its toxicity.

In 1986, Inoue *et al.* [48] reported that the palladium catalyst supported on sulfonated polystylene type resin could be applied to the oxidation of naphthalene. The experiment was carried out with aqueous 60% H_2O_2 for 8 hr at 50 ^{o}C and found that methylnaphthalene were oxidized easily to give methylnaphthoquinones 54%,

while 2-methyl-2,3-dimethylnaphthalene, and 2,6-dimethylnaphthalene gave the corresponding 1,4-naphthoquinones 53 and 66%, respectively.

In 1987, Rao and Murali [49] reported that substituted 1-naphthols were oxidized by iodoxybenzene to afford a mixture of the corresponding 1,2- and 1,4-naphthoquinones. Furthermore, it was found that the oxidation did not affect labile structure features such as a benzylic tertiary hydroxy group or a hydro aromatic.

In 1988, Thomson *et al.* [50] reported that naphthols underwent autooxidation when adsorbed on the silica gel and exposed to air, the main product as quinones, 2-naphthol yields 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone, and 4-methoxy-1-naphthol gives 4,4-dimethoxy-2,2-binaphthyl-1,1-quinone. The reason was explained that silica gel was normally slightly basicity so that quinone formation presumeably proceeded *via* the naphthoxide which reacted with oxygen to give first the corresponding naphthoxyl and then the hydroperoxide followed by base-catalysed dehydration.

In 1988, Asakawa *et al.* [51] reported that the oxidation reaction utilizing *m*-chloroperbenzoic acid in chloroform could transform aromatic terpenoids and nonnatural aromatic compounds to 1,2- and 1,4-quinones or hydroxylated products with their yield around 2- 50%.

In 1993, Adam and Ganeshpure [52] reported that the oxidation of 2-methylnaphthalene with hydrogen peroxide catalyzed by hexafluoroacetone hydrate yielded 2-methyl-1,4-naphthoquinone. The optimized condition was 100 mmol of 70% H_2O_2, 4 mmol of hexafluoroacetone hydrate, at 45 ^oC, for 3 hr could provide 56% of conversions and 45% yields of the desired product.

In 1994, Mukaiyama *et al*. [53] reported that oxygenation of naphthalene and naphthol derivatives was successfully carried out by the combined use of molecular oxygen and crotonaldehyde under an atmospheric pressure and the corresponding 1,4-naphthoquinones was formed when oxovanadium (IV) complex having lower oxidation potential such as bis(3-*n*-butyl-2,4-pentanedionato)oxovanadium(IV), $VO(^nbuac)_2$ was employed as a catalyst.

In 1994, Sakamoto *et al*. [54] reported that the oxidative coupling of 2-naphthols catalyzed by alumina supported copper(II) sulfate under bubble air condition was successfully carried out under the reaction condition at 140 ^oC for 8 hr.

In 1994, Mukaiyama *et al*. [55] reported that, in the presence of crotonaldehyde and a catalytic amount of oxovanadium(IV) complexs coordinated

with 1,3-diketones, having electron-donating substitutents such as $VO(^{n}buac)_2$, direct oxygenations of benzene, *tert*-butylbenzene, biphenyl and chlorobenzene into the corresponding hydroxylated product were performed under an atmospheric pressure of molecular oxygen.

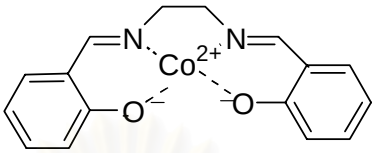
In 1997, Korh *et al.* [56] discovered that the oxidation of a number of naphthols by oxygen was carried out with copper-collidine and copper-pyridine complexes as catalyst. It was shown that phenols could be specifically oxygenated to give *o*-quinone by a combination of transition metal complexes: $Ti(OiPr)_4$, $VO(acac)_4$, $Zr(OiPr)_4$ and *tert*-butylhydroperoxide (TBHP) or by $(Mo(O_2))_2$.Py.HMPT. Under this developed condition, naphthols and mononuclear phenols were converted into the corresponding 1,2-naphthoquinone. However, unhindered *o*-naphthoquinones could yield binaphthyls from unreacted starting material by Michael addition. The type of C-C coupling, with the formation of a binaphtyl system was observed in the auto-oxidation of naphthol as well as in molybdenum-catalyzed oxidations. Dimerization of 2-naphthol could also lead to the formation of 1, 1-bis-(2-naphthol).

In 1999, Yan *et al.* [57] reported that the oxidation reaction of 1- and 2-naphthols in the presence of H_2O_2 over metalloporphyrin catalyst led to the formation of 2-hydroxy-1,4-napthoquinone. In order to get high selectivity and reactivity, the catalytic process was required to perform under strong alkali medium at low temperature.

In 2002, Villemin *et al.* [58] addressed that supported metalated phthalocyanine on K10 or on lamellar zirconium phosphate catalyses the oxidation of hydroquinones and phenols into quinones such as menadione, lawsone and phthiocol, in satisfied yield.

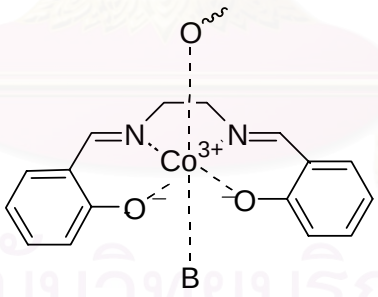
Recently, the development of efficient catalysts for the selective oxidation of organic compounds in mild and ecological friendly conditions is highly an active field of research. An interesting line of study is the research for the effective environmentally clean catalytic reaction to transform cheap natural compounds into valuable intermediates for organic synthesis both in the laboratory and industry [59]. Much attention has been given to the selective oxidation of the organic compounds with dioxygen metal-complex and metal-ion activation of oxygen since these reactions could mimic some biological oxidation. From this point, cobalt(II)-schiff base [Co(II)(SB)] complexs are highly interesting catalyst because of their catalytic activities in oxidation reaction [60]. For example, [Co(II)(SB)] in aprotic solvents

could catalyze the dioxygenase-type reaction of phenols, indoles, flavonols and nitroalkanes. Moreover, it was found that cobalt(II)-[bis-(salicylaldehyde)-ethylenediiminato), common name as Co(II)-salen or sacomine, could catalyze TBHP oxidation of phenols, giving (*t*-butyl peroxide)quinol ethers [61].



Co(II) salen

In 1987, Chen and Martell [62] reported the chemical absorption ability to dioxygen of Co(II)-salen in the solid state. According to their research study, Co(II) center could not bind oxygen strongly. Only suitable monodentate Lewis base could strongly support the binding ability of metal center to dioxygen under suitable conditions as the result of increase in electron density at the metal center provided by the axial base. In addition, dioxygen ligand binds in a position *trans* to axial base. The axial bases (B) that promoted oxygenation of Co(II)-salen might be aliphatic or aromatic amines.



dioxygen complex of Co(II)-salen

In 1990, Nishinaga *et al.* [63] reported that cobalt(II)-Shiff base complexs in alcohols results in irreversible oxidation by molecular oxygen could give the corresponding alcoholatcobalt(II)complexs which could convert to hydroxocobalt(III) species by treatment with water.

In 1990, Nishinaga *et al.* [64] reported that Co(II)-salen could catalyze 4-substuituted phenylacetylenes, incorporation of oxygen, converting to the corresponding acetophenones, mandelic and phenylglyoxylic esters in highly selective.

In 1995, Hames and Bozell [65] reported that in the presence of catalytic Co(II)-Shiff base complexs, *p*-substituted phenolics could be oxidized to the corresponding benzoquinone with oxygen gas. It was found that the reaction product was depended on the structure of catalyst. In addition, The 5-coordinate catalysts, namely (pyridine)- [bis(salicylidene)ethylenediamine)cobalt] and [bis-((salicylideneamino) ethyl)amine]-cobalt could convert 3,5-dimethoxy-4-hydroxybenzyl alcohol to 2,6-dimethoxybenzoquinone in satisfactory.

In 1985, Nishinaga *et al.* [61] reported that Co(salen)-catalyzed oxidation of 2,4-and 2,6-di-*tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at room temperature, results predominantly in the formation of *tert*-butyl peroxylated products. The position of *tert*-butylperoxylation depended on the nature of the unsaturated side chain.

1.3 Objectives of this research

This research was focused on the catalytic oxidation system for transforming naphthols to naphthoquinones catalyzed by Co(II)-salen. Many parameters such as temperature, axial ligand type, oxidant type, reaction time, were considered in this study. The major goals of this research were:

1. To investigate for the optimum oxidation condition for transforming naphthols to naphthoquinones catalyzed by Co(II)-salen.

2. To synthesize some interesting chemical compounds such as juglone, thymoquinone by using the developed oxidation system.

CHAPTER II

EXPERIMENTAL

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2.1 General Procedure

Melting points were measured by a Fisher-Johns melting point apparatus and are further uncorrected. The FT-IR spectra were recorded on a Nicolet Fourier transform infrared spectrophotometer model Impact 410. Solid samples were incorporated to potassium bromide to form pellet. The ^{1}H and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$) solvent, with a Bruker model ACF200 spectrometer and Jeol, Model JNM-A500.

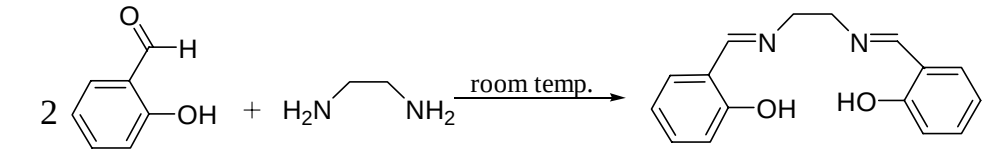
Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's, Kieselgel 60 PF_{254}). High performance liquid chromatography was carried out using following equipments: pump (Water as 600E), autosampler (Water 917), and diode array detector (Waters 996). The Column used for HPLC technique was HPLC reverse phase column: Merck's Lichrospher 100(C18, 5 μm).

2.2 Chemicals

All solvents used in this research were purified prior to use by standard method except for those which were reagent grades. The reagents used for synthesizing salen, Co(II)-salen and all naphthols were purchased from Fluka chemical company and were used without further purification.

2.3 Synthesis

2.3.1 Bis(salicylaldehyde)*N,N* –ethylenediimine (salen) [62]



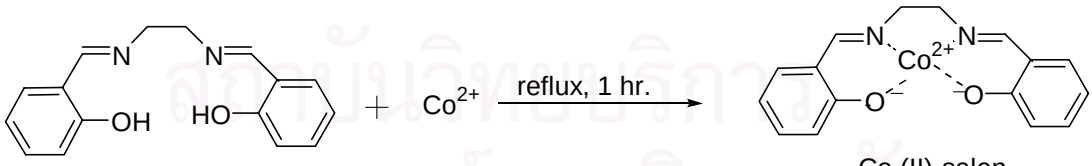
Salicyladehyde Ethylenediamine Bis(salicylaldehyde)N,N -ethylenediimine (Salen)

Procedure

2 Mol-equivalents of salicylaldehyde were slowly added dropwise to 1 mol-equivalent of ethylenediamine in methanol. The solution was stirred at room temperature until precipitate was formed. The precipitate was filtered off and recrystallized by cold methanol.

Bis(salicylaldehyde)*N,N* –ethylenediimine (salen): Bright yellow crystals, 99% yield; m.p. 124 ^{o}C: R_f 0.77 (Silica gel: dichloromethane); IR (KBr): 3500(w), 3010-3050(w), 2870-2950(w), 1750-2000(w), 1640(s), 1450-1600(s), 1280(s) and 1170(s) cm^{-1}; ^{1}H-NMR($CDCl_3$) δ(ppm): 3.84(s, 4H), 6.83(2H, dt, J =7.5, 1.5), 6.93 (2H, d, J = 8.2), 7.18 (2H, dd, J = 7.8, 1.5), 8.29 (2H, s) and 13.2 (2H, s); ^{13}C-NMR ($CDCl_3$) δ(ppm): 59.5 (2C), 116.8 (2C), 118 (2x 2C), 131.4 (2C), 132.2 (2C), 160.9 (2C) and 166.3 (2C).

2.3.2 Co (II)-salen [62]



Salen Co (II)-salen

Procedure

Salen 2.7 g (0.01 mol) was dissolved in ethanol 50 mL at 70 ^{o}C. After stirring the solution until homogeneity, cobalt(II)acetate tetrahydrate 2.08 g (0.01 mmol) dissolved in ethanol was slowly added dropwise and refluxed for 1 hr. After that, the precipitate of Co(II)-salen complex was formed. The product was filtrered off and washed with cold ethanol.

Co(II)-salen : yield 76%, m.p. 229 ^{o}C: IR (KBr): 3500 (w), 3020 (w) and 1640 (m).

2.4 Study on the optimum conditions for the oxidation of 1-naphthol

General Procedure

1-Naphthol (1.0 mmol) was taken in dimethylformamide (DMF) (10 mL) containing cobalt(II)-salen (0.1 mmol) in a round bottle flask with a ballon filled with oxygen (O_2). The mixture was stirred at room temperature. After the reaction was completed, 0.5 mL of reaction mixture was taken and extracted with diethyl ether. The combined extracts were washed with 10% HCl and saturated aqueous solution of $NaHCO_3$, respectively. The organic layer was dried over anhydrous Na_2SO_4 and analyzed by HPLC technique.

2.4.1 Effect of reaction time

The oxidation reaction was carried out at different reaction times preceded: 4, 6, 7, 9, 12 and 24 hr. The sampling reaction mixture (0.5 mL) was taken, worked up and analyzed by HPLC technique.

2.4.2 Effect of type of oxidant

The oxidation reaction was carried out as previously described. In addition, H_2O_2 (30%) and TBHP (70%) were used to compare the yields of 1,4-naphthoquinone product to that obtained from using the standard oxidant, oxygen (balloon) at 70 ^{o}C and reflux temperature at 153 ^{o}C.

2.4.3 Effect of temperature

The reaction temperature was varied into 3 conditions: room temperature (28^{o}C), 70 ^{o}C and reflux temperature. Other parameters were still controlled as same as the previous study.

2.4.4 Effect of axial ligand

2.4.4.1 Effect of type of axial ligand

The oxidation reaction was carried out as previously described with the additional 0.1 mmol of axial ligand in solution before filling oxygen (balloon). The diaxial ligand was varied: 4-quinoline, triethylamine, diethylamine, benzalamine,

cyclohexamine, pyridine and imidazole. It must be noted that the reaction time was kept constant at 4 hr.

2.4.4.2 Effect of amount of ligand

The oxidation reaction was carried out as previously described. The amount of pyridine: 1, 2, 3 and 4 equiv-, based upon Co(II)-salen, was added to the reaction flask before the oxidation initially proceeded.

2.4.5 Effect of solvents

The oxidation reaction was carried out in the same manner as aforementioned except for that acetonitrile, acetone, dichloromethane, chloroform, THF and carbontetrachloride were employed instead of DMF. It must be noted that the reaction time was maintained at 4 hr.

2.4.6 Kinetic study of the oxidation of 1-naphthol catalyzed by Co(II)-salen

The oxidation reaction was carried out at different reaction times preceded: 2, 4, 6, 8 and 10 with a presence of pyridine under previously described condition.

2.5 Oxidation of 1-naphthol deviratives

Selected naphthols named 1-TBDMS naphthyl ether, 1-naphthylacetate, 1-methoxy naphthyl ether and 1-naphtylamine were used as alternative substrates under the optimum condition.

2.6 Oxidation of 2-naphthol

To campare the reactivity with 1-naphthol, 2-naphthol was used as a substrate under the developed conditions. The oxidation reaction was also carried out under the optimum condition.

2.7 Applications of the developed oxidation process

A phenol, namely thymol, together with four selected naphthols, namely 2,3-dihydroxy naphthalene, 1,5-dihydroxy naphthalene, 6-methoxy-2-naphthol and 7-methoxy-2-naphthol were oxidized under the optimum conditions. The products were analyzed after 6 hr of oxidation reaction proceeded.

General isolation procedure

After the reaction was completed (monitored by TLC), the oxidation product was separated as follows: the whole reaction mixture was extracted according to the general procedure and all solvents were removed. The crude product was purified by silica gel column chromatography using dichloromethane or dichloromethane–ethyl acetate as an eluent. The equivalent fractions observed by TLC were combined and the solvents were completely evaporated by rotatory evaporator. The residue was crystallized by appropriate solvent such as methanol, petroleum ether to yield the desired naphthoquinone.

CHAPTER III

RESULTS AND DISCUSION

The main feature of this research was focused on the oxidation of naphthols to naphthoquinones catalyzed by transition metal complex, cobalt(II)-salen, using oxygen as an oxidant. This chapter could be divided into 3 parts: the approached idea to develop a naphthoquinone formation in the oxidation reaction, the search for the optimized condition for the oxidation process catalyzed by cobalt(II)-salen, and the synthesis of some interesting chemical compounds, such as thymoquinone utilizing this developed oxidation conditions.

3.1 The approached idea to develop naphthoquinone formation *via* oxidation process

Naphthoquinone, one of the highly interesting natural products, in organic synthesis is generally taken by two reactions. The first one is an oxidation reaction while the second one involves Diels-Alder reaction [66]. Anyhow, Diels-Alder reaction could bring the quantity of naphthoquinone in poor to moderate yields because of a number of steps required. On the other hand, the oxidation reaction is generally simple to work with and it always gives the yield of the desired product in satisfaction. Unfortunately, the selective reagents, normally employed in oxidation processes, are basically toxic, harmful, non-stoichiometric and expensive. Thus, the attention to use transition metal catalysts is highly interesting because those problems could be solved. According to the literature review [66], the quantity of benzoquinone and its derivatives could be accelerated by Co(II)-salen in satisfied yields. From this point the study of the oxidation naphthol to naphthoquinone utilizing Co(II)-salen would be performed in this research.

3.2 Study on the optimization conditions for the oxidation naphthols to naphthoquinones

Regarding to the report of Imurai [67], the optimized conditions for the oxidation of phenol to benzoquinone required 1.0 mmol of phenol as substrate, 5 mL of DMF as solvent, 1 atm of oxygen gas as oxidant and 0.1 mmol of Co(II)-salen as catalyst. In addition, this mild condition was performed at room temperature for 5 hr. In this research, that mentioned condition was employed as the standard for the oxidation of 1-naphthol to 1,4-naphthoquinone. However, a number of parameters must be reviewed to study due to the different nature of substrates: 2,6-dimethylphenol and 1-naphthol. The studied variable parameters include the effect of reaction time, temperature, type and amount of axial ligand, solvent and kinetic study.

3.2.1 Effect of reaction time on the oxidation of 1-naphthol

The effect of reaction time on the oxidation of 1-naphthol was varied from 4, 6, 7, 9, 12 and 24 hr. After carrying out the reaction for the specific period of time, the target product, 1,4-naphthoquinone, was cautiously analyzed *via* HPLC technique. The results are reported in Table 3.1

Table 3.1 The effect of reaction time for the oxidation of 1-naphthol

Entry	Reaction time (hr)	1,4-naphthoquinone (%)
1	4	30.9
2	6	59.7
3[(a)]	7	70.7
4	9	66.8
5	12	68.5
6	24	71.1

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature

(a) 15.1% recovery of 1-naphthol

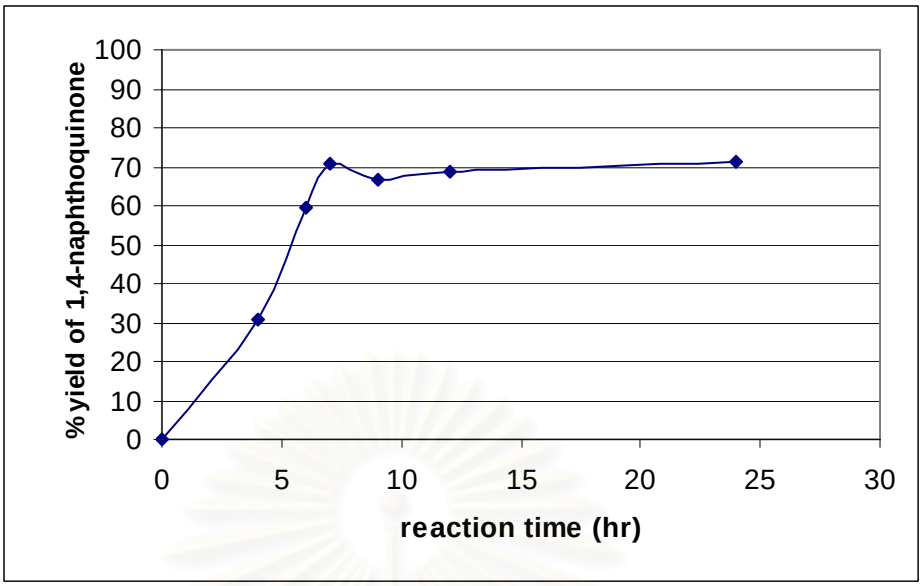


Figure 3.1 Effect of reaction time for the oxidation of 1-naphthol

According to the result presented in Table 3.1 and Figure 3.1, the oxidation of 1-naphthol was completed after 7 hr. with 70% yield of 1,4-naphthoquinone. In addition, the half-life of this oxidative reaction was required for 5 hr. From this point, it was reasonable to use the reaction time of 7 hr to be as a standard time for the study.

3.2.2 Effect of type of oxidant for the oxidation of 1-naphthol

In order to study the effect of the oxidant, the selected oxidants: TBHP (70%) and H_2O_2 (30%) were used to compare with oxygen (balloon). It must be noted that the temperature of the oxidation reaction was controlled into 2 conditions: room temperature (28^{o}C) and reflux temperature. The results are collected in Table 3.2

Table 3.2 The effect of oxidant for the oxidation of 1-naphthol

Entry	Oxidant	Yield of 1,4-naphthoquinone,%	
		rt (28°C)	reflux
1	O_2	70.7	-
2	TBHP	trace	1.5
3	H_2O_2	trace	trace

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 7 hr

Regarding to the result shown above, oxygen was appreciated as the oxidant for this research. While both of TBHP and H_2O_2 gave a poor yield of 1,4-naphthoquinone on both at room and reflux temperatures. In addition, it was found that % conversion of 1-naphthol in the presence of TBHP and H_2O_2 completely turned to 100. This might be expected that both oxidants could proceded other reaction products because an absence of 1,4-naphthoquinone could be observed in this oxidative reaction.

3.2.3 Effect of temperature for the oxidation of 1-naphthol

Reaction temperature normally plays an important factor in the catalytic oxidation. In this study, the temperature for the oxidation was varied into 3 conditions: room temperature (28°C), 70 °C and reflux temperature (153°C). In each conditions, an aliquot (0.5 mL) of the reaction was collected at 4 and 7 hr and analyzed by HPLC technique**.** The results are tabulated in Table 3.3.

Table 3.3 The effect of temperature for the oxidation of 1-naphthol

Entry	Reaction time (hr)	Yield of 1,4-naphthoquinone,%		
		rt (28°C)	70 °C	reflux
1	4	30.9	38.5	9.6
2	7	70.7	41.4	0.1

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature

The data lists in Table 3.3 indicated that the yield of 1,4-naphthoquinone decreased with increment of reaction temperature. This could be explained that the vapor pressure of solvent could affect the solubility of oxygen gas in media. When the reaction temperature increased, the amount of oxygen soluble in the media should be lesser that gave the substrate, 1-naphthol, was worked insufficiently. From this point, it could be relied that the oxidation was suitably preceded at room temperature.

3.2.4 Effect of axial ligand for the oxidation of 1-naphthol

3.2.4.1 Effect of type of axial ligand for the oxidation of 1-naphthol

According to the references cited in literature reviews [62], a selective axial ligand could bring up the yield of the desired product. In this study, seven diaxial ligands: 4-quinoline, triethylamine, diethylamine, benzylamine, cyclohexylamine, pyridine and imidazole, are promptly considered. The yield of the desired product was collected at room temperature after 4 hr of the reaction and the results were exhibited in Table 3.4.

Table 3.4 The effect of type of ligand for the oxidation of 1-naphthol

Entry	Axial ligand	1,4-naphthoquinone (%)
1	None	30.9
2	Diethylamine	47.8
3	Triethylamine	61.5
4	Cyclohexylamine	10.2
5	Benzylamine	23.2
6	4-Picoline	36.3
7	Imidazole	0
8	Pyridine	67.9

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 4 hr

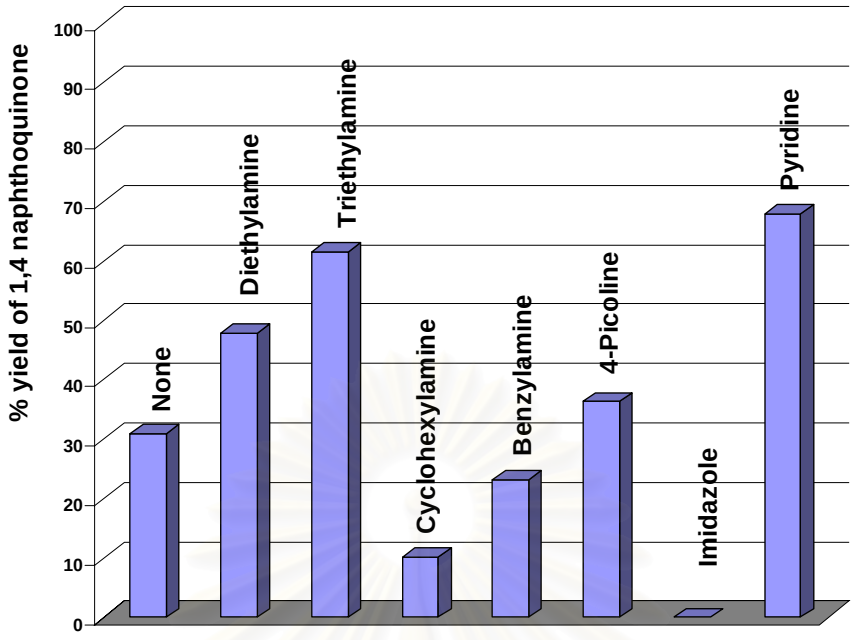


Figure 3.2 Effect of axial ligand for the oxidation of 1-naphthol

The data lists in Table 3.4 and Figure 3.2 could indicate that either pyridine, triethylamine, 4-picoline and diethylamine could bring up the yields of the corresponding product, 1,4-naphthoquinone, higher than an absence of axial ligand. The order of the high efficient axial ligands could be arranged as pyridine, triethylamine and diethylamine (entries 2, 3 and 8), respectively. Although, it could not completely be clear why they were beneficially to work with Co(II)-salen, it was expected that these ligands could convey their cloud of electron to the central Cobalt(II) ion that could give the rest active site of hexagonal complex, to be highly active [62]. Hence, it was obviously that pyridine was required as the standard axial ligand for the research.

3.2.4.2 Effect of amount of pyridine on the oxidation of 1-naphthol

The amount of preferable axial ligand, pyridine, was varied: 1, 2, 3 and 4 equivalent based on the molarity of the catalyst, Co(II)-salen. The results were accumulated into Table 3.5 as described.

Table 3.5 The effect of amount of pyridine for the oxidation of 1-naphthol

Entry	Pyridine (mmol)	1,4-naphthoquinone (%)
1	None	30.9
2	0.1	67.9
3	0.2	46.2
4	0.3	40.5
5	0.4	49.2

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 4 hr

According to the result given in Table 3.5, the amount of pyridine played an important factor towards the oxidation of 1-naphthol to 1,4-naphthoquinone in this system. When the oxidation reaction employed pyridine, the yield of 1,4-naphthoquinone was significantly higher than in the reaction without pyridine. Furthermore, 1 equiv- of pyridine showed the best result, comparable with the others: 2, 3 and 4 equiv- of pyridine. It was noted that the yield of the desired product when the reaction was employed 1 equiv- of pyridine could reach to 68%. As the cited literatures [62], it could explain that when a single molecule of pyridine bind to molecule of Co(II)-salen on hexagonal position, it could transfer a cloud of electron to another site of hexagonal, that could give a complex to be highly reactive to oxygen and gave 1-naphthol substance worked in sufficient. On the other hand, when the number of pyridine was more than 2 equivalents, the complete bond of the hexagonal side of the metal complex with pyridines might take place. In that case the complex did not have a site to bind with oxygen and gave oxygen insufficiently work with 1-naphthol substance. Form this point, it must be completely clear to use only an equivalent of pyridine for this research.

3.2.5 Effect of solvent for the oxidation of 1-naphthol

The oxidation of 1-naphthol catalyzed by Co(II)-salen was carried out in various organic solvents. According to the previous studies, DMF was the first media used, that was because it could dissolve both Co(II)-salen catalyst and 1-naphthol substrate. Other solvents such as acetonitrile, acetone, THF, dichloromethane,

chloroform and carbontetrachloride were chosen to examine whether they could replace with DMF in this oxidation reaction. The results are presented in Table 3.6.

Table 3.6 The solvent effect for the oxidation of 1-naphthol

Entry	Solvent	1,4-naphthoquinone(%)
1	DMF	67.9
2	Acetonitrile	35.1
3	Acetone	26.8
4	THF	29.1
5	Dichlomethane	20.9
6	Chloroform	0
7	Carbontetrachloride	0

Reaction conditions: 1-naphthol (1 mmol), Co(II)-salen (0.1 mmol), pyridine (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 4 hr

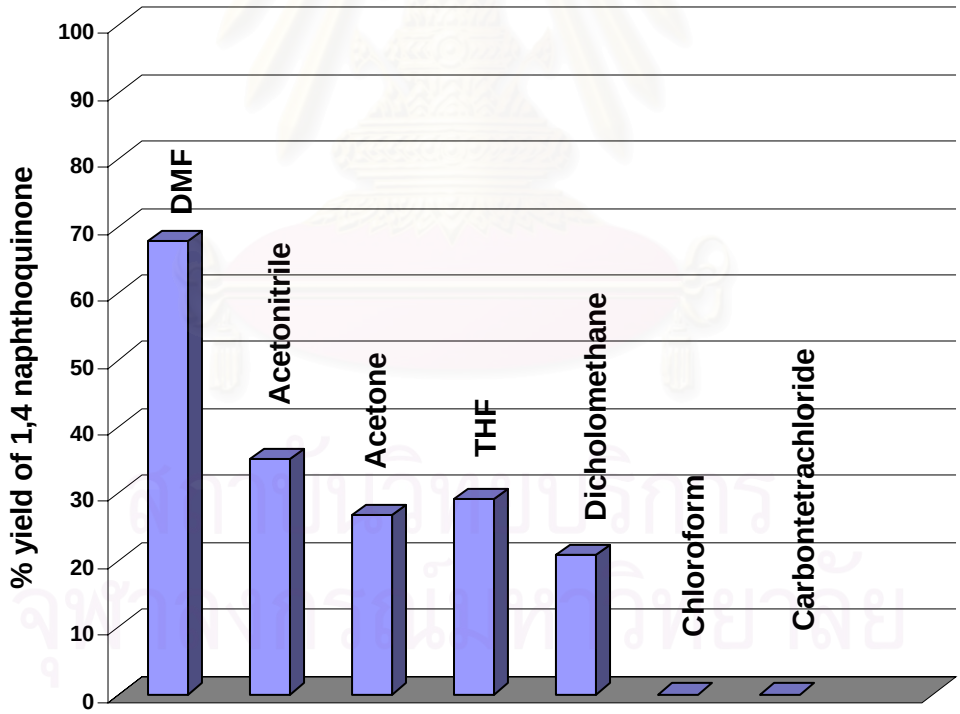


Figure 3.3 The solvent effect for the oxidation of 1-naphthol

As shown in Table 3.6 and Figure 3.2, it was revealed that when DMF was used as solvent, the highest yield of 1,4-naphthoquinone was clearly observed. When the reaction employed acetonitrile, acetone, THF and dichloromethane as solvent, the

yield of the desired product was quite fair with the result around 20-35%. Furthermore, no reaction took place when chloroform and dichloromethane were used as solvent. It must be noted that the reaction performed with good result when polar aprotic solvent was used, especially in DMF. From this point, the suitable solvent for this oxidation reaction was DMF.

3.2.6 Kinetic studies on the oxidation of 1-naphthol catalyzed by Co(II)-salen

The kinetic studies on the oxidation of 1-naphthol catalyzed utilizing Co(II)-salen in the presence of 0.1 mmol of pyridine were investigated at room temperature. The results are obtained as shown in Table 3.7

Table 3.7 Kinetic study on the oxidation of 1-naphthol catalyzed by Co(II)-salen

Entry	Reaction time (hr)	1,4-naphthoquinone (%)	% Conversion
1	2	38.5	43.6
2	4	61.3	76.2
3	6	67.6	83.2
4	8	68.1	84.3
5	10	68.5	85.1

Reaction conditions: Substrate (1 mmol), Co(II)-salen (0.1 mmol), pyridine (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature

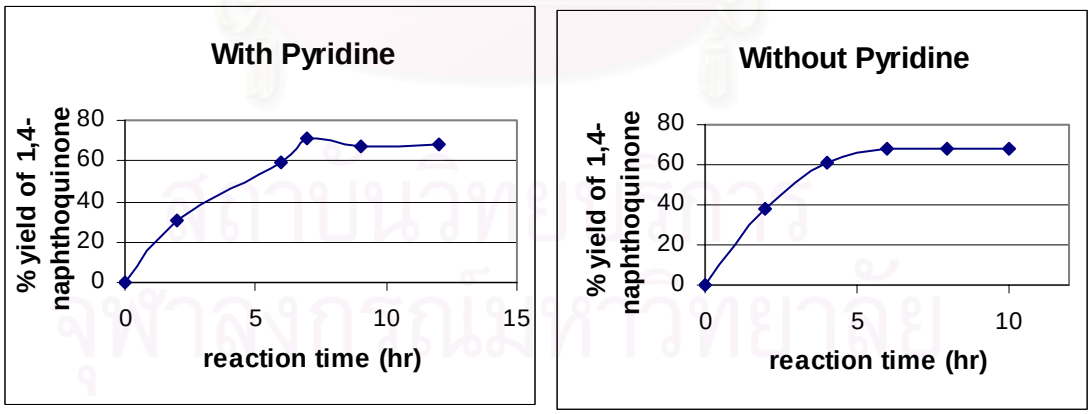


Figure 3.4 Comparative kinetic study on the oxidation of 1-naphthol catalyzed by Co(II)-salen with and without pyridine ligand (referring to Figure 3.1)

As it was seen from Table 3.7 and Figure 3.2 when pyridine was added to the reaction, the optimized time for the oxidation was reasonably reduced from 7 (non-

pyridine used) to 6 hr (pyridine used) of the reaction and gave the yield of the desired product achieved to 67.6% with 83.2% of conversion when the reaction was performed in the presence of pyridine. In addition, the half-life of the reaction with pyridine added was quite short to 2 hr. In case of pyridine used, when the reaction was preceded after 6 hr, mass balance of the system was totally constant to 83%.

Therefore, it is worth concluding that the optimization of the reaction condition for the oxidation of 1-naphthol was clearly proceeded as follows: 1 mmol of 1-naphthol as a substrate, 5 mL of DMF as solvent, 0.1 mmol of Co(II)-salen as catalyst, O_2 as oxidant and 6 hr of reaction time at room temperature

Without interrupting the system during the developing condition, 1-naphthol could be effectively oxidized to 1,4-naphthoquinone in high yield, 75.3%. Furthermore, the attempt to isolate the quinone product by column chromatography was proceeded. The procedure to isolate the desired 1,4-naphthoquinone product was already mentioned in chapter II. The product quinone was obtained as yellow needles 75.3%, m.p. 126-127 ^{o}C (lit.[66] 126 ^{o}C), R_f 0.82 (CH_2Cl_2). IR (KBr): 3054 (C-H stretching vibration), 1660 (C=O stretching vibration of diketone) and 1579-1291 (C=C streching) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.0 (2H, s, QH), 7.8 (2H, m, ArH) and 8.26 (2H, m, ArH); 1.63 (impurity) and 7.25 ($CDCl_3$). The IR and NMR spectra are presented in Figures 3.5 and 3.6

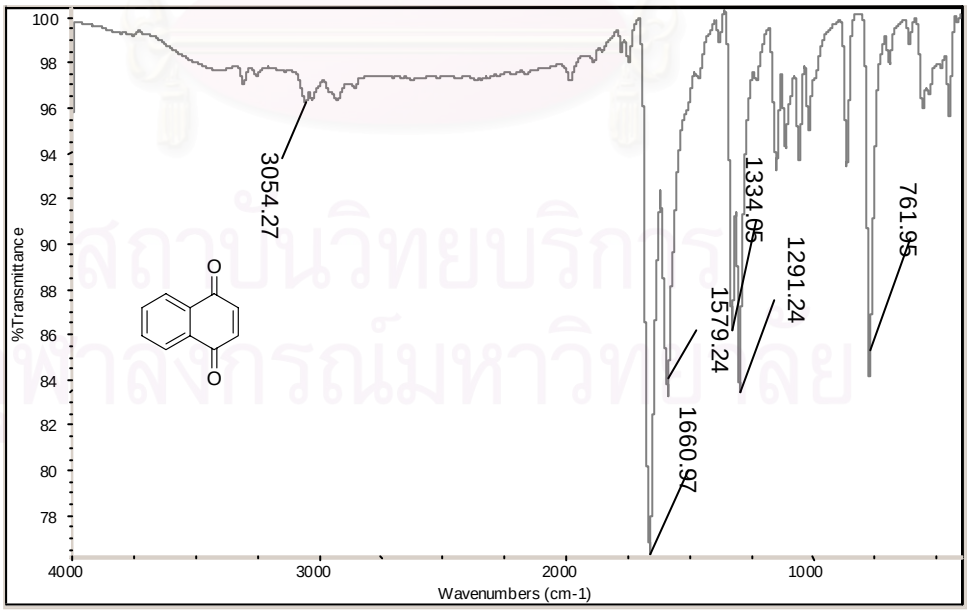


Figure 3.5 IR spectrum of isolated 1,4-naphtoquinoine

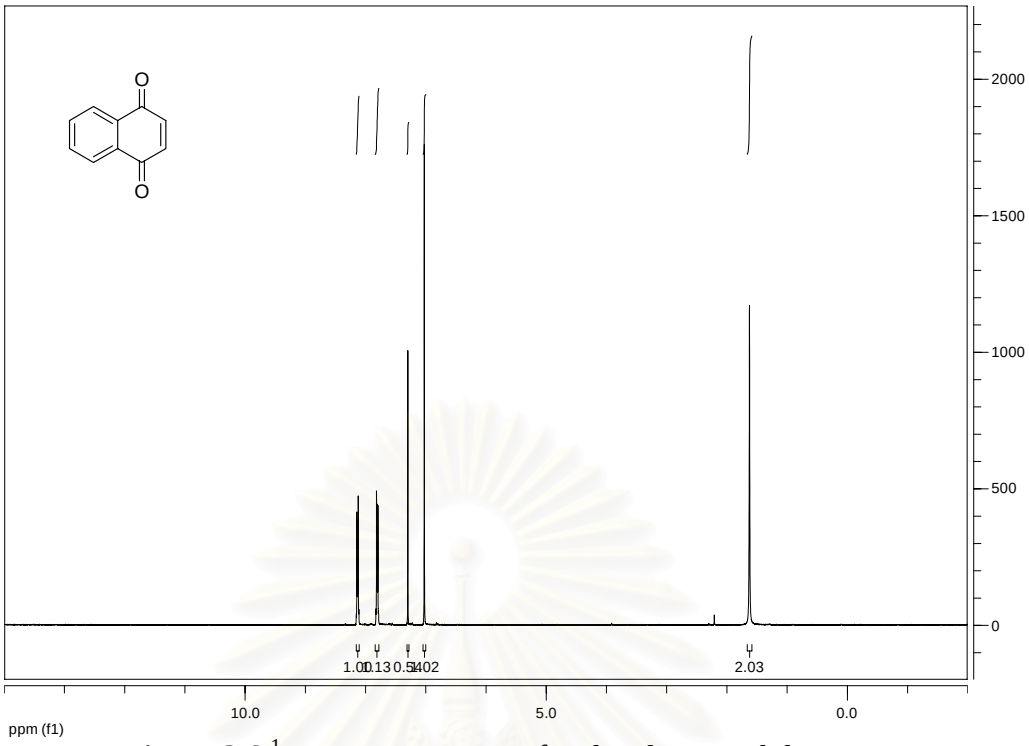
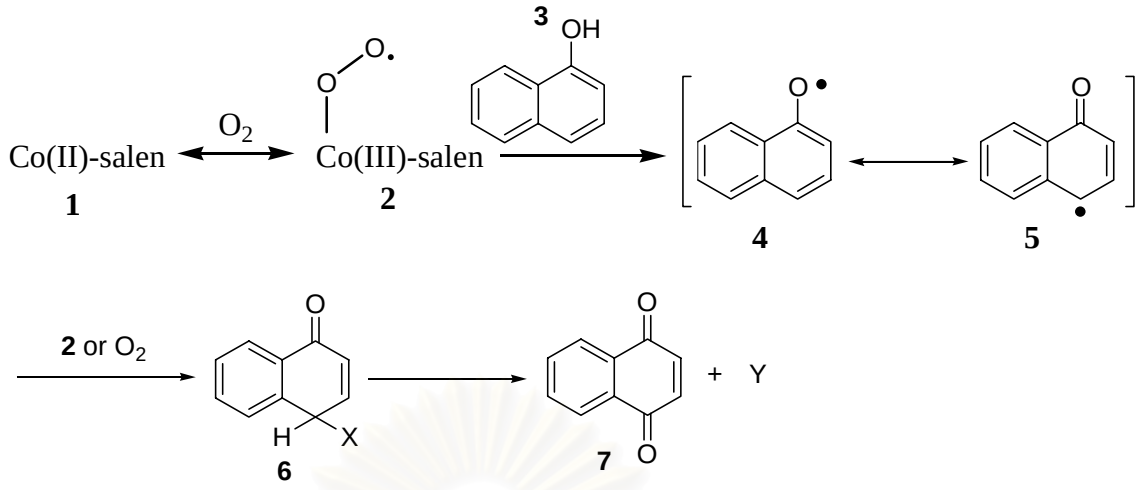


Figure 3.6 ^{1}H-NMR spectrum of isolated 1,4-naphthoquinone

3.2.7 Proposed mechanism for the oxidation of 1-naphthol to 1,4-naphthoquinone catalyzed by Co(II)-salen

According to the report of Bozell [65], the mechanism for the oxidation of phenols, catalyzed by Co(II) shiff base and used molecular oxygen as oxidant, was proceeded as free radical reaction. From this point, the oxidation of 1-naphthol should be performed in the same pathway. The mechanism of the oxidation of 1-naphthol catalyzed by Co(II)-salen was proposed in Scheme 3.1



X = O-O-Co(III)-salen or O-O•

Y = H-O-Co(III)-salen or OH^-

Scheme 3.1 Proposed mechanism for the oxidation of 1-naphthol to 1,4-naphthoquinone catalyzed by Co(II)-salen with oxygen

As presented in Scheme 3.1, the reaction of Co(II)-salen and molecular oxygen gave a highly active superoxo Co/O_2 adduct (**2**). This active specie would abstract the naphthol hydrogen and gave products as free radical species (**4** and **5**). After that, intermediate **5** was trapped by the second molecule of superoxo Co/O_2 or molecular oxygen, giving the intermediate **6**. An elimination of hydrogen of intermediate **6** could give the product, 1,4-naphthoquinone (**7**).

3.3 Oxidation of 1-naphthol derivatives

Four alternative substances, namely 1-TBDMS naphthyl ether, 1-naphthylacetate, 1-naphthylmethyl ether and 1-naphtylamine, were used to compare their reactivity to the standard model, 1-naphthol under the optimum conditions. The yield of the product, 1,4-naphthoquinone on the oxidation reactions are collected in Table 3.8.

Table 3.8 Oxidation of 1-naphthol derivatives

Entry	Substrate	%1,4-naphthoquinone
1	1-naphthol	75.3
2	1-TBDMS naphthyl ether	15.4
3	1-naphthyl acetate	3.4
4[a)]	1-naphthylmethyl ether	0
5	1-naphthylamine	2.6

Reaction conditions: substrate (1 mmol), Co(II)-salen (0.1 mmol), pyridine (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 6 hr

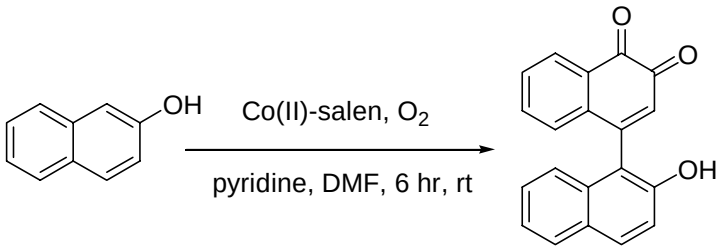
a) 95.4% recovery of 1-naphthol

According to Table 3.8, it could be clearly observed that 1-naphthol gave the highest yields of 1,4-naphthoquinone product (75.3%), while the others could give the yield of the product in poor except 1-naphthyl methyl ether that 1,4-naphthoquinone could not detected. This could be estimated that the reaction would be highly selective for the substrate to work with, only an appropriated model like 1-naphthol could generate the desired product. The low yield of the desired product when the reaction was 1-TBDMS naphthyl ether as substrate could be estimated that the steric effect of large functional group, TBDMS, might affect to an abstracting process of superoxo Co(III)-salen complex even though Si-O bond was easily cleavage. In case of using 1-naphthyl acetate as substrate, the aromatic ring of substrate was electron poor system that might cause the reaction being ineffectively proceed.

3.4 Oxidation of 2-naphthol

3.4.1 Oxidation of 2-naphthol catalyzed by Co(II)-salen

In order to study the reactivity of the oxidation reaction on other naphthols, the selected naphthol, 2-naphthol was used as the substrate under the optimized oxidation conditions. The chemical equation as Scheme 3.2, is the result of this study.



Scheme 3.2 The oxidation of 2-naphthol catalyzed by Co(II)-salen

From the result obtained as shown in Scheme 3.2, the substrate model, 2-naphthol could be oxidized to an analog naphthoquinone, namely 4-(2-hydroxy-1-naphthyl)1,2-naphthoquinone under the developed condition. The product quinone was obtained as red solid, 59.3%, R_f 0.25 (CH_2Cl_2), m.p. 147-149 ^oC (lit [50] 148 ^oC), ^{1}H-NMR (Acetone-d_6) δ (ppm): 5.64 (1H, s, OH), 6.48 (1H, s, QH), 6.91 (1H, d, J = 7.5, ArH), 7.41 (3H, m, ArH), 7.60 (2H, m, ArH), 7.81 (1H, d, J = 9.0, ArH), 7.96 (1H, d, J = 7.3, ArH), 8.02 (1H, d, J = 9.0, ArH) and 8.19 (1H, d, J = 8.9, ArH); 2.15 (Acetone-d_6), 2.81, 2.98 and 2.99 (impurities).

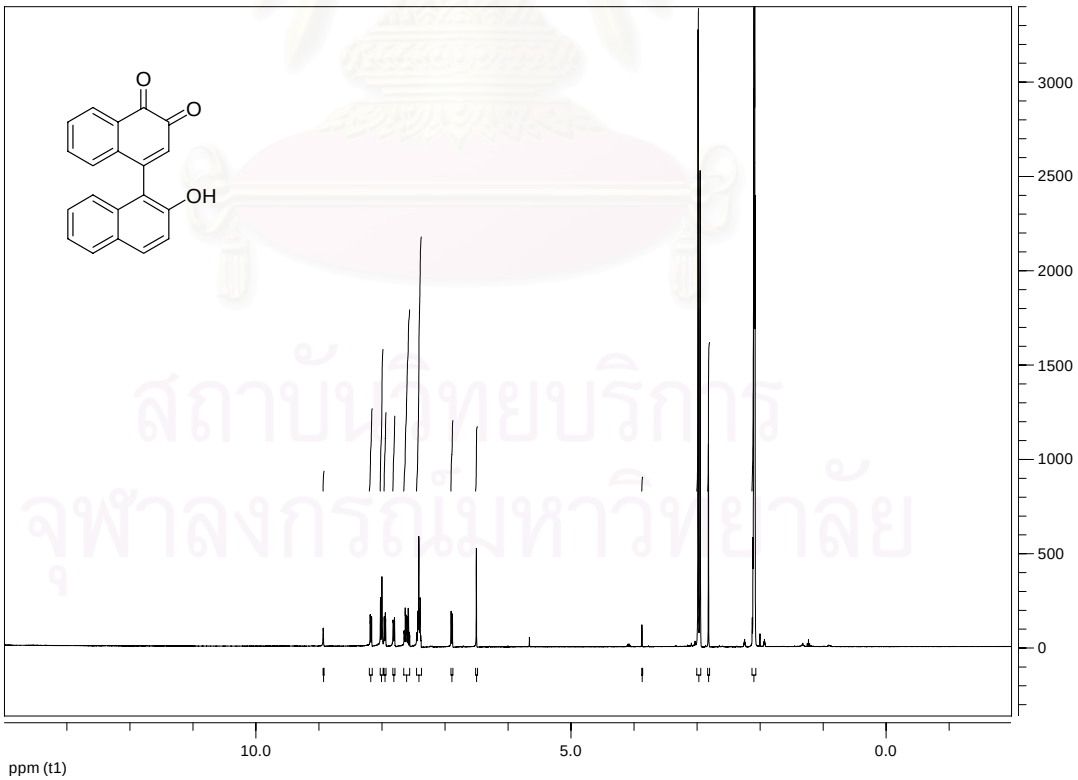
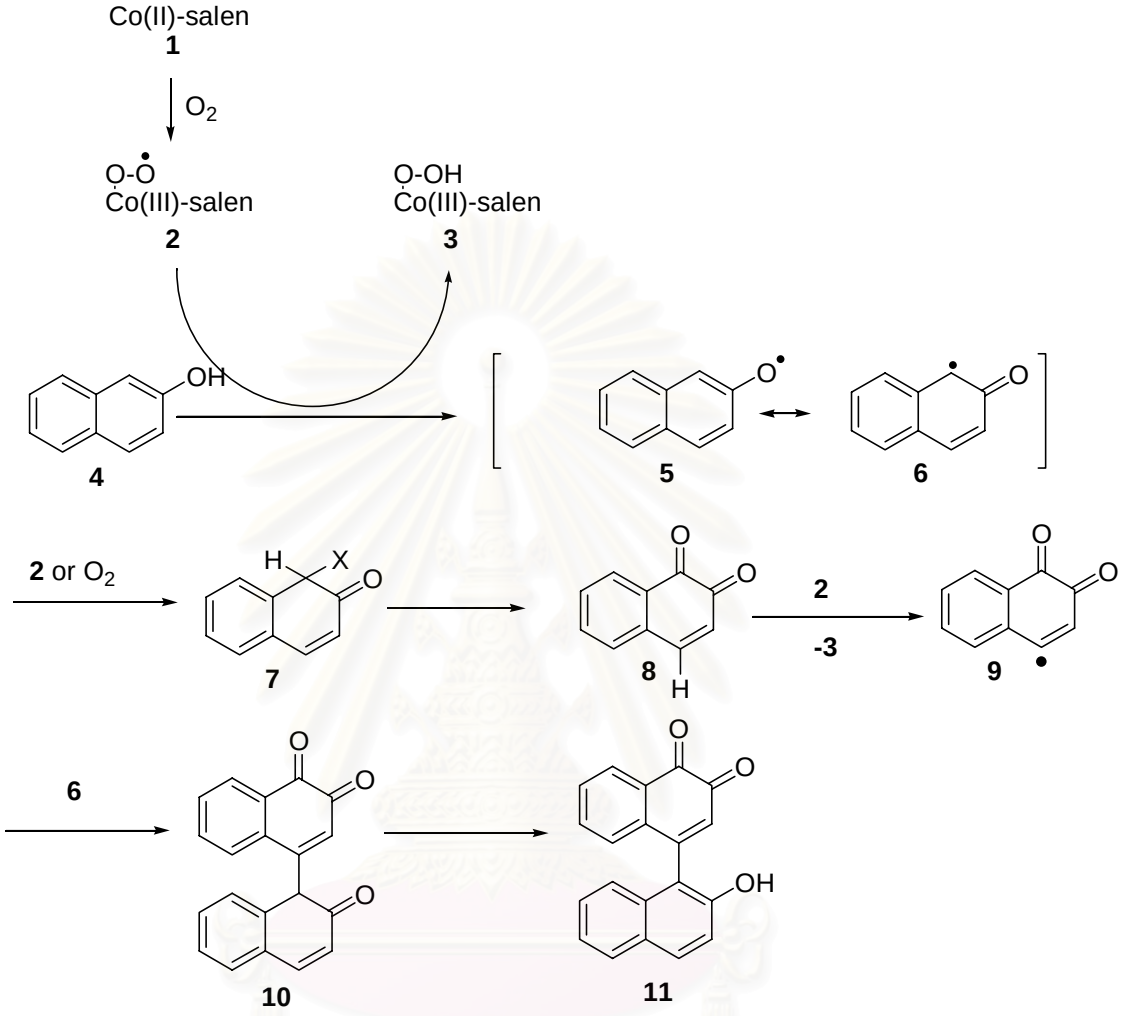


Figure 3.7 ^{1}H-NMR spectrum of isolated 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone

3.4.2 Proposed mechanism for the oxidation of 2-naphthol to 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone catalyzed by Co(II)-salen



X = O-O-Co(III)-salen or O-O•

Y = H-O-Co(III)-salen or OH^-

Scheme 3.6 Proposed mechanism for the oxidation of 2-naphthol catalyzed by Co(II)-salen

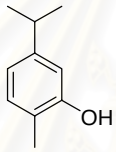
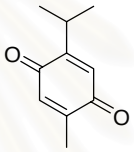
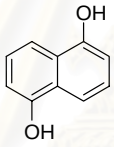
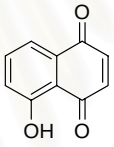
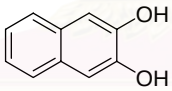
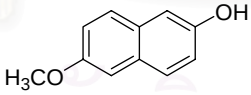
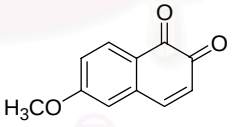
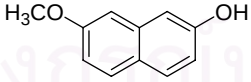
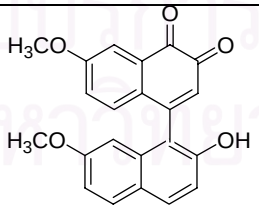
The reaction of Co(II)-salen and molecular oxygen produced a highly active superoxo Co/O_2 adduct (**2**). The abstraction of naphthol hydrogen on 2-naphthol, by superoxo adduct would generate free radical species (**5** and **6**). After that, the second molecule of superoxo Co/O_2 or molecular oxygen trapped free radical species, giving the intermediate **7**. An elimination of hydrogen of intermediate **7** would give the corresponding product, 1,2-napthoquinone (**8**). The abstraction of hydrogen on

compound **8** could provide an free radical specie (**9**) that would react to intermediate **6**, forming to the adduct **10**. Finally, the adduct **10** were tautomerized to 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone (**11**)

3.5 Applications of the developed oxidation process

The application of the developed oxidation condition to a phenol, namely thymol, and four selected naphthols, namely, 1,5-dihydroxynaphthalene, 2,3-dihydroxynaphthalene, 6-methoxy-2-naphthol and 7-methoxy-2-naphthol, was considered in this part. The results are shown in Table 3.9

Table 3.9 Oxidation of a phenol and other naphthols catalyzed by Co(II)-salen

Entry	Substrate	Product	Product yield (%)
1			59.0
2			40.7
3		-	-
4			46.3
5			42.6

Reaction conditions: Substrate (1 mmol), Co(II)-salen (0.1 mmol), pyridine (0.1 mmol), DMF (5 mL), 1 atm O_2 at room temperature for 6 hr

As seen from Table 3.9, the oxidation of thymol (entry1) yielded the corresponding thymoquinone as the main product in moderate yield (59.0 %), m.p. 45-46 ^{o}C (lit [68] 43-44 ^{o}C). It must be noted that the use of this developed oxidation

process provided the best result of thymoquinone formation comparable with the previous methods such as the oxidation *via* MCPBA [69], H_2O_2 catalyzed by H_3ReO_3 [70], H_2O_2 catalyzed by Fe (III) meso-tetraphenylporphyrin [71] and $(HDTMA)_4H_2[Mn(H_2O)BW_{11}O_{39}].10H_2O$ incoperating H_2O_2 [72]. Which were reported to yield thymoquinone 4-47%. The ^{1}H-NMR spectral, presented in Figure 3.8 could confirm the structure of the corresponding product as thymoquinone: ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.19 (6H, d, J = 6.9, CH_3-), 2.02 (3H, s, CH_3-), 3.05 (1H, sep, J = 6.9, CH-), 6.55 (1H, d, J = 0.9, QH) and 6.62 (1H, s, QH); 7.25 ($CDCl_3$). In addition, this desired product, thymoquinone, could be found in the essential oils of many aromatic plants, that beneficially used as a diabetic drug in pharmaceutical field [73].

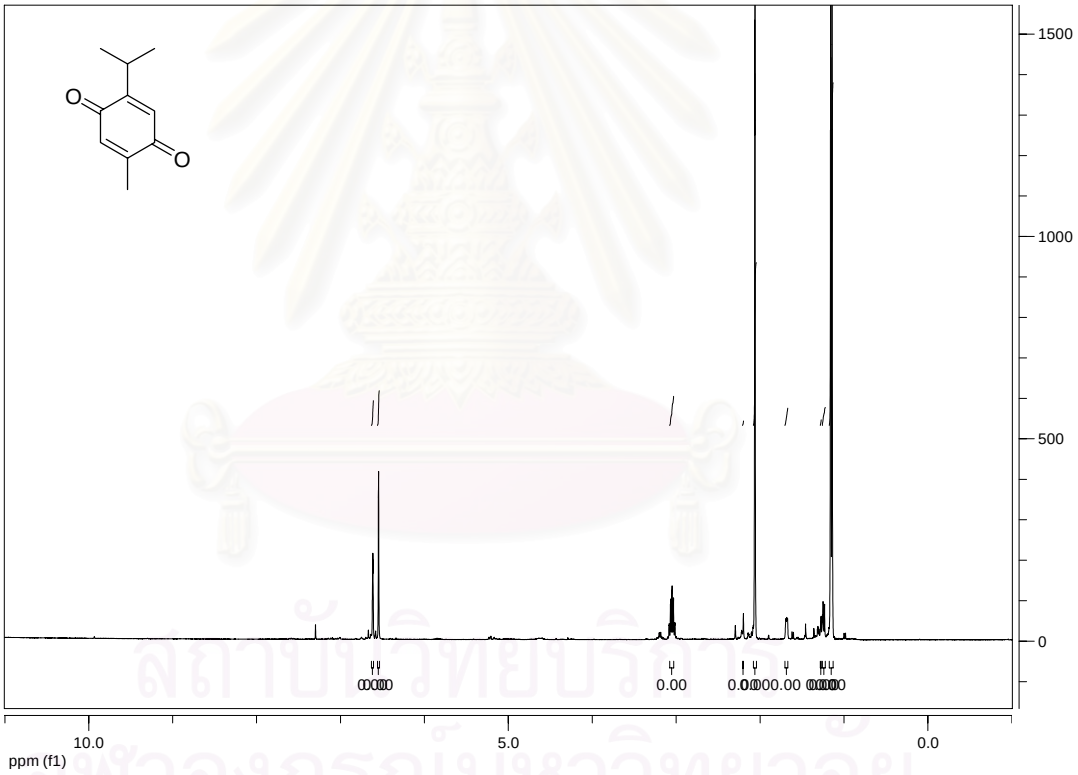


Figure 3.8 ^{1}H-NMR spectrum of isolated thymoquinone

The conversion of 1,5-dihydroxynaphthalene (entry 2) to the naphthoquinone analog, namely juglone with the satisfied yield (40.7%) was accomplished, m.p.161-164 ^oC (lit [74] 162 ^oC). The ^{1}H-NMR spectral data, presented in Figure 3.9, could endorse the structure of the corresponding product as juglone δ (ppm): 6.93 (2H, s, QH), 7.21 (1H, dd, J = 2.1, 7.5, ArH) and 7.59 (2H, m, ArH), 12.8 (1H, s,

OH); 1.64 (impurities) and 7.23 ($CDCl_3$). According to the literature review, juglone, has a board spectrum antimicrobial activity killing many bacteria and fungi. Furthermore, this adduct was also applied as a drug for chemotheraphy [75].

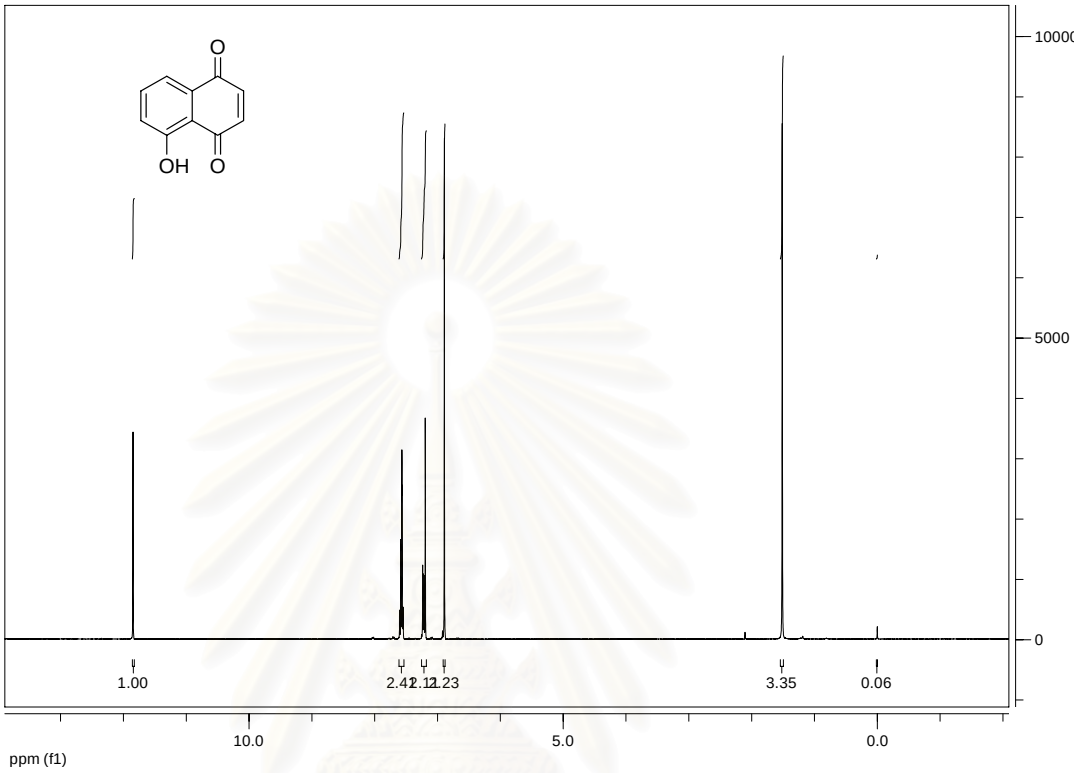


Figure 3.9 ^{1}H-NMR spectrum of isolated juglone

Under the optimized oxidation conditions, 6-methoxy-2-naphthol (entry 3) could be converted to the corresponding naphthoquinone product, namely 6-methoxy-1,2-naphthoquinone, in moderate yield (46.3%), m.p. 137-149 ^oC (lit [76] 135-140 ^oC). The ^{1}H-NMR spectral data, shown in Figure 3.10, could confirm the structure of the corresponding quinone product as 6-methoxy-1,2-naphthoquinone, δ (ppm): 4.02 (3H, s, OMe), 6.53 (1H, d, J = 11.0, QH), 6.85 (1H, s, ArH) 6.98 (1H, d, J = 9.2, QH), 7.39 (1H, d, J = 10.5, ArH) and 8.18 (1H, d, J = 9.1, ArH); 1.25, 1.27 (impurities) and 7.25 ($CDCl_3$).

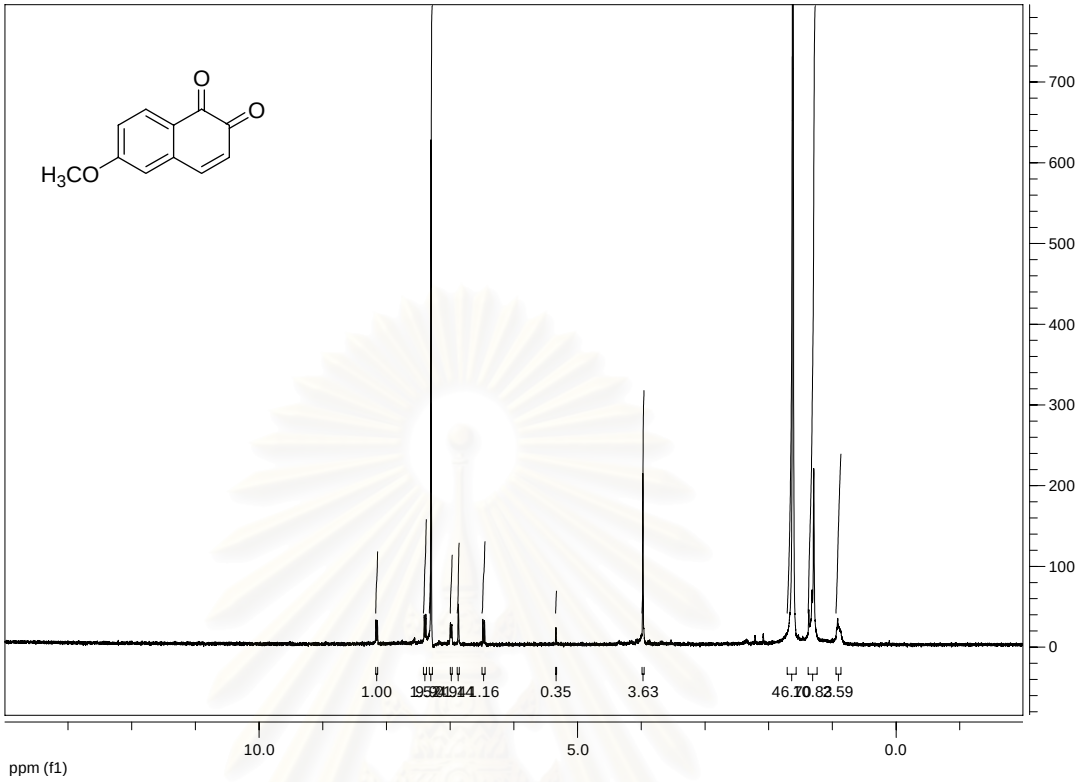


Figure 3.10 ^{1}H-NMR spectrum of isolated 6-methoxy-1,2-naphthoquinone.

In case of 7-methoxy-2-naphthol (entry 4), 4-(2-hydroxy-7-methoxy-1-naphthyl)-7-methoxy-1,2-naphthoquinone was obtained as the sole product of the oxidation reaction in moderate yield (42.6%), m.p. 235-238 ^{o}C (lit [50] 237-240 ^{o}C).. The ^{1}HNMR data, presented in Figure 3.11, could confirm the structure of the corresponding product as 4-(2-hydroxy-7-methoxy-1-naphthyl)-7-methoxy-1,2-naphthoquinone: δ (ppm): 3.78 (3H, s, OMe), 3.98 (3H, s, OMe), 5.59 (1H, s, OH), 6.48 (1H, s, QH), 6.82 (2H, m, J = 2.3, ArH), 6.93 (1H, dd, J = 2.8, 8.6, ArH), 7.13 (1H, dd, J = 2.4, 9.0, ArH), 7.16 (1H, d, J = 2.4, ArH), 7.77 (1H, d, J = 2.8, ArH), 7.78 (1H, d, J = 9.0, ArH) and 7.91 (1H, d, J = 8.8, ArH); 1.63 (impurities) and 7.25 ($CDCl_3$).

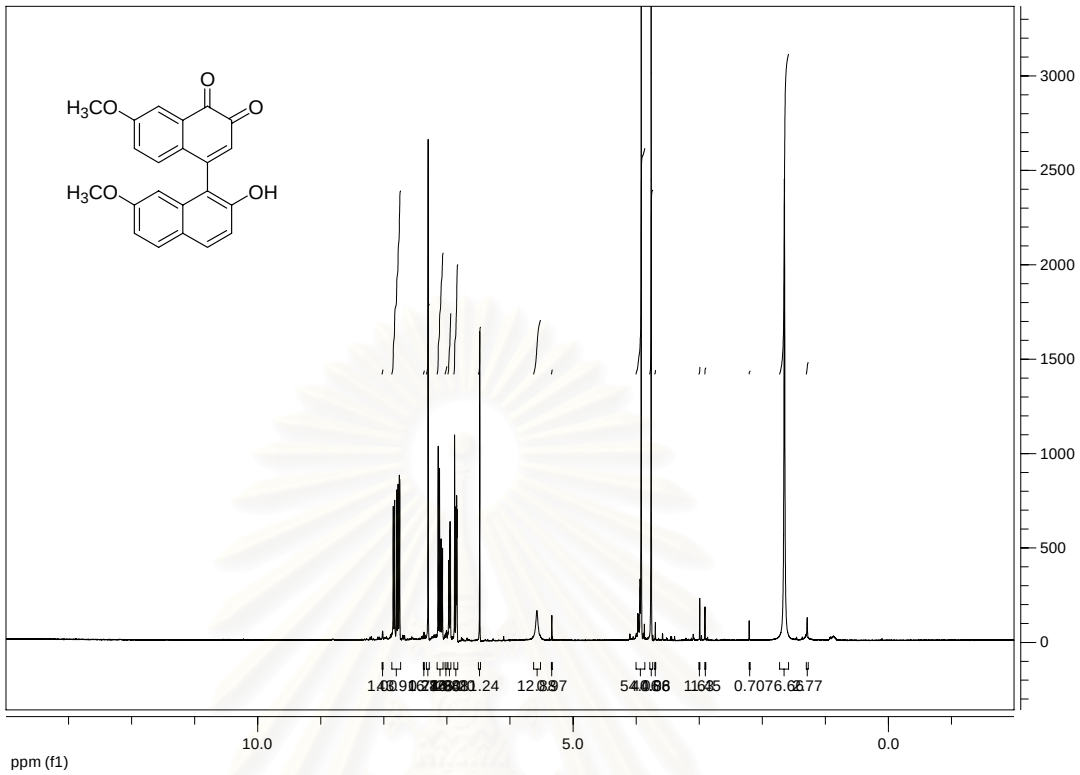


Figure 3.11 ^{1}H-NMR spectrum of isolated 4-(2-hydroxy-7-methoxy-1-naphthyl)-1,2 naphthoquinone.

According to the result of oxidation of 2,3-dihydroxynaphthalene (entry 3) in Table 3.9, it was shown that the oxidation reaction of 2,3-dihydroxynaphthalene could not take place due to the high recovery of 2,3-dihydroxynaphthalene (92.1%).

CHAPTER IV

CONCLUSION

The main feature for this research is to search for suitable conditions for oxidizing naphthols utilizing transition metal Shiff base, namely Co(II)-salen, to analogs of naphthoquinones. This developed condition was also used to apply for the synthesis a number of interesting compounds.

According to this research study, the important factors that controlled the formation of naphthoquinones on the oxidation are type of oxidant, reaction temperature, axial ligand, and time of reaction. It must be concluded that the optimized conditions for this research study are: 1 mmol of substrate, 0.1 mmol of Co(II)-salen, 0.1 mmol of pyridine, excess oxygen gas, at room temperature ($28^{o}C$) for 6 hrs. In addition, under this particular condition, the oxidation of 1-naphthol to the desired product, 1,4-naphthoquinone could be successfully accomplished. The isolated yields of 1,4-naphthoquinone were 75.3 %. Furthermore, the half-life of the reaction was obviously as 2 hr.

The oxygenation of 2-naphthol under the developed oxidation process could provide a dimeric compound, 4-(2-hydroxy-1-naphthyl)-1,2-naphthoquinone, in good yield (59.3%).

Under this developed catalytic system, 1-naphthol derivatives, namely 1-TBDMS naphthyl ether, 1-naphthylacetate, 1-naphthylmethyl ether and 1-naphtylamine could generate 1,4-naphthoquinone in poor yields except for 1-naphthylmethyl ether that the oxidation did not take place. It was indicated that Co(II)-salen was selectively oxidized the functional group of the substrate.

The application of the developed condition to oxidize other selective phenol and naphthols: thymol, 1,5-dihydroxynaphthalene, 2,3-dihydroxynaphthalene, 6-methoxy-2-naphthol and 7-methoxy-2-naphthol were considered. It was obviously found that all studied substrates could generate analogs of naphthoquinone with satisfied yield except for 2,3-dihydroxynaphthalene that could not produce quinone

product. This finding revealed that Co(II)-salen catalyst could selectively oxidize naphthols. Under this particular mild condition, it was clearly found that thymol could successfully generate thymoquinone with the best result compared with other methods. Furthermore, there is no report concerning the oxidation of 6-methoxy-2-naphthol to 6-methoxy-1,2-naphthoquinone, therefore, this research was the first one to report the successive formation of 6-methoxy-1,2-naphthoquinone.

Suggestion for the future work

The important experiments for the further studies based upon this research are: to carry out the oxidation reaction into expanded solvent systems such as super critical fluid carbon dioxide, to study bi- and tri-catalysts of oxidation, to apply the developed oxidation into pilot scale of chemical industry, and to apply for synthesizing some complex natural products, naphthoquinone structures.

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VITAE

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