

# Reaction of 4,4'-bis(chloromethyl)-1,1'-biphenyl and phenol in two-phase medium via phase-transfer catalysis

Maw-Ling Wang<sup>a,\*</sup>, Ze-Fa Lee<sup>b</sup>

<sup>a</sup> Department of Environmental Engineering, Hung Kuang University, Shalu, Taichung County 433, Taiwan, ROC

<sup>b</sup> Department of Chemical Engineering, National Chung Cheng University, Ming Hsiung, Chiayi County 621, Taiwan, ROC

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## Abstract

Kinetic study of the phase-transfer catalyzed etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol in an alkaline solution of KOH/organic solvent two-phase medium was investigated. The reaction was carried out in a stirred batch reactor under mild operating conditions. During or after completing the reaction, the mono-substituted product (4,4'-(chloromethylphenoxy-methyl)-1,1'-biphenyl) and the di-substituted product (4,4'-bis(phenoxy-methyl)-1,1'-biphenyl) are both produced. Effects on the reaction due to various operating conditions, such as agitation speed, amount of water, amount of organic solvent, amount of phase-transfer catalyst, amount of potassium hydroxide, kind of phase-transfer catalyst, kind of organic solvent, inorganic salt and temperature were studied in detail. A rational mechanism of the etherification was proposed based on the experimental observation and a kinetic model was developed. In examining nine kinds of phase-transfer catalyst, tetraoctylammonium bromide was found to be the best for increasing the reaction rate. The inorganic salts, such as potassium iodide or sodium iodide play an important role in enhancing the reaction rate. Hoffmann elimination is used to explain the peculiar behavior in studying the effect of the KOH on the apparent rate constants. The apparent activation energies for the etherification were  $E_{a1} = 23.7$  kcal/mol and  $E_{a2} = 31.5$  kcal/mol, respectively, using tetra-*n*-butyl-ammonium bromide (TBAB) as the catalyst.

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## 1. Introduction

The liquid–liquid phase-transfer catalysis (LL-PTC), discovered by Jarrouse [1], is a process favoring reactions between a lipophilic substrate dissolved in an organic phase, with a hydrophilic reactant solubilized in water. It is an advantageous method in many organic reactions and it consists of transferring an anionic reactant from the water phase via a lipophilic ion-pair, to the organic phase, where the reaction with the lipophilic substrate takes place [2–4]. The role of the catalysts, which are usually quaternary ammonium salts, is to maintain the presence of reacting anions in the reaction medium [5]. Catalysis is considered to be helpful in the development of eco-friendly processes [6,7]. There are several processes in the specialty chemical industry which employ catalytic routes in order to make them eco-friendly and cost effective [8–10]. Currently,

phase-transfer catalysis is widely applied for manufacturing pharmaceuticals, agricultural chemicals, perfumes, flavors, dyes and specialty polymers, and is also extended to pollution and environmental control processes [11–13]. Phase-transfer catalysis is a versatile, potential synthetic technique that has been applied with advantage to a number of organic bi-phase reactions. The ether compounds which are versatile chemicals, can be used as an additive in gasoline to increase its octane number. Some ether compounds have been used as pharmaceuticals for applications such as Alzheimer's disease combination therapy, metabolism disorders, thrombotic syndrome, obesity hypertension, renal inflammation therapeutics, etc. [14–16]. Thus, it is worthwhile to develop industrial production of high added-value ether compounds.

This study investigated the etherification in phase-transfer catalytic system. The reaction of 4,4'-bis(chloromethyl)-1,1'-biphenyl and phenol catalyzed by phase-transfer catalysts to synthesize 4,4'-bis(phenoxy-methyl)-1,1'-biphenyl was carried out in an alkaline solution of KOH/organic solvent two-phase medium. The mono-substituted product (4,4'-(chloromethyl-

\* Corresponding author.

E-mail address: [chmmlw@sunrise.hk.edu.tw](mailto:chmmlw@sunrise.hk.edu.tw) (M.-L. Wang).

phenoxyethyl)-1,1'-biphenyl) and the di-substituted product (4,4'-bis(phenoxyethyl)-1,1'-biphenyl) which were produced from the sequential reactions, were both observed during or after completing the reaction. This study investigated in detail the effects on the conversion and the reaction rate. Kinetics of this reaction system, including the effect of the agitation speed, amount of water, amount of organic solvent, amount of phase-transfer catalyst, amount of potassium hydroxide, kind of phase-transfer catalyst, kind of organic solvent, inorganic salt and temperature. A rational mechanism was proposed based on the experimental data. A kinetic model was built, in which a pseudo-first order rate law is applied to find the two rate constants and the activation energies of the two sequential reactions. The peculiar behavior noted in studying the effect of the KOH in the apparent rate constant was satisfactorily explained by the change of the environment of the reaction solution at high KOH concentration.

## 2. Experimental

### 2.1. Materials

All reagents, benzene, biphenyl, chlorobenzene, dichloromethane, dibutyl ether, ethylbenzene, hexane, methanol, octane, acetonitrile, phenol, potassium bromide, potassium chloride, potassium iodide, potassium hydroxide, sodium bromide, sodium chloride, sodium iodide, 3-(*N,N*-dimethyloctylammonio)propanesulfonate (SB-8), 4,4'-bis(chloromethyl)-1,1'-biphenyl, polyethylene glycol 600 (PEG 600), 18-crown-6-ether (1,4,7,10,13,16-hexaoxacyclooctadecane), Aliquat 336 (tricaprylylmethylammonium chloride, a trademark of Cognis Corporation), tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC), tetrabutylammonium iodide (TBAI), tetrahexylammonium bromide (THAB), tetraoctylammonium bromide (TOAB) and toluene were guaranteed grade (G.R.) chemicals.

### 2.2. Procedures

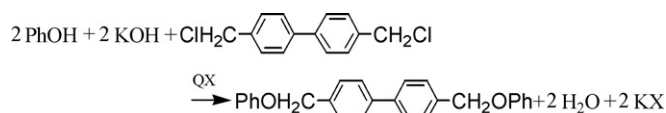
(i) *Synthesis of 4,4'-(chloromethylphenoxyethyl)-1,1'-biphenyl and 4,4'-bis(phenoxyethyl)-1,1'-biphenyl and their purification.* The reactor was a 150-mL three-necked round-bottomed Pyrex flask. Measured quantities of 4,4'-bis(chloromethyl)-1,1'-biphenyl (4 mmol), phenol (60 mmol), potassium hydroxide (20 g) and TBAC (1 mmol) were dissolved in a mixture of 50 mL of chlorobenzene and 20 mL of water at 85 °C. The mixture was stirred continuously at 600 rpm using a mechanical mixer equipped with a PTFE half-moon blade. After 1 h of reaction, the two-phase solution was separated and the portion of organic solution was washed five times with an alkaline solution of KOH to remove the TBAC catalyst. Then, the mixture was separated by pressurized column chromatography. The mono-substituted product and the di-substituted product were separated using silica gel as adsorbent and 60% hexane/40% dichloromethane (v/v) as

mobile phase. Finally, the products were identified by mass spectrum (VG Quattro GC/MS/MS/DS) for molecular weight, by element analyzer (Heraeus CHN-O-S-Rapid Analyzer) for carbon, and by hydrogen analyzer and NMR (Bruker Avance 600 MHz NMR) for functional groups.

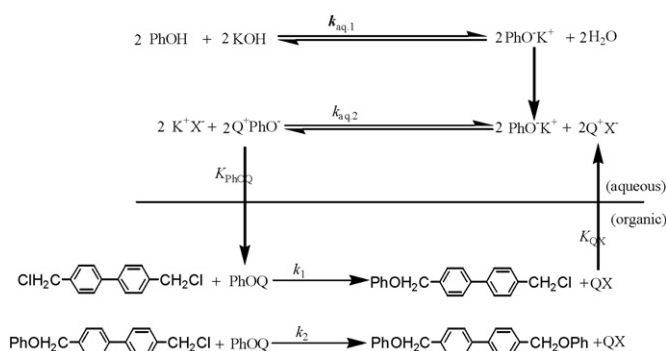
(ii) *Kinetic study of the experimental runs.* All experiments were carried out in a 150-mL reactor which was the same as that used in (i). The temperature was maintained at  $\pm 0.1$  °C of the desired value. Known quantities of reactants and catalyst were charged into the reactor. Samples were withdrawn at periodic intervals up to 3 h. A standard experiment consisted of 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 25 g of potassium hydroxide, 50 mL of chlorobenzene, 40 mL of water, 0.5 mmol of tetrabutylammonium bromide (phase-transfer catalyst) and biphenyl (internal standard). The HPLC analysis was done with a Shimadzu SCL-M10AVP high performance liquid chromatograph equipped with an SPD-M10AVP photo-diode array detector, LC-10ATVP binary pump, and a Lichrospher® 100 RP-18e(5  $\mu$ m) column.

## 3. Reaction kinetics and mechanism

The overall reaction of the etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol is



In this work, tetra-*n*-butylammonium bromide was used as a liquid–liquid phase-transfer catalyst (LL-PTC). Potassium phenoxide ( $\text{PhO}^- \text{K}^+$ ) was synthesized *in situ* directly by reacting phenol with potassium hydroxide in the aqueous phase. 4,4'-(Chloromethylphenoxyethyl)-1,1'-biphenyl was first synthesized by reacting phenoxide with 4,4'-bis(chloromethyl)-1,1'-biphenyl in an organic solvent. Afterward, 4,4'-bis(phenoxyethyl)-1,1'-biphenyl was produced by further reacting phenoxide with 4,4'-(chloromethylphenoxyethyl)-1,1'-biphenyl. The reaction scheme is depicted in the following where Q represents phase-transfer catalytic cation [2].



Usually, the reaction mechanism of the phase-transfer catalyst prevails. The first step of the reaction involves the transport

of a reactant anion (substrate,  $\text{PhO}^-$ ) from the aqueous phase to the organic phase by a phase-transfer cation ( $\text{Q}^+$ ). This is an organophilic quaternary cation which exchanges the anion ( $\text{X}^-$ ) with the nucleophile of potassium salt of phenol ( $\text{PhO}^- \text{K}^+$ ) to form the organophilic  $\text{PhO}^- \text{Q}^+$ , which is freely transported to the bulk organic phase. There could be a resistance associated with the transfer of this ion-pair across the liquid film next to liquid–liquid interface. The second step involves the reaction of the PhOQ with the reactant 4,4'-bis(chloromethyl)-1,1'-biphenyl located in the organic phase. Then, a  $\text{S}_{\text{N}}2$  type reaction occurs. Finally, the third step involves the transport of the co-product anion  $\text{Cl}^-$  (the leaving group) by the phase-transfer cation to the aqueous solution and the transport of another nucleophile  $\text{PhO}^-$  into the organic phase.

The phenoxide is sparingly soluble in the organic phase. However, its solubility is augmented by the phase-transfer catalyst. In this study, [PhOQ] and [QX] are all kept at constant values by using a large excess of phenol. Based on the experimental data, no by-product was observed. There is an instantaneous exchange of anion and formation of an ion-pair ( $\text{PhO}^- \text{Q}^+$ ) with the quaternary cation  $\text{Q}^+$  with the nucleophile  $\text{PhO}^-$  which was transported from the aqueous phase to the organic phase. Therefore, the etherification in the organic phase is the rate-determining step for the whole reaction system. Material balances for the regenerated catalyst QX and the active catalyst PhOQ in the organic and aqueous phases are

$$\begin{aligned} \frac{d[\text{PhOQ}]_o}{dt} &= K_{\text{PhOQ}}A \left( [\text{PhO}^- \text{Q}^+]_a - \frac{[\text{PhOQ}]_o}{M_{\text{PhOQ}}} \right) \\ &\quad - k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o[\text{PhOQ}]_o \\ &\quad - k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o[\text{PhOQ}]_o \quad (1) \end{aligned}$$

$$\begin{aligned} \frac{d[\text{PhO}^- \text{Q}^+]_a}{dt} &= k_{\text{aq},2}[\text{PhO}^- \text{K}^+]_a[\text{Q}^+ \text{X}^-]_a \\ &\quad - K_{\text{PhOQ}}Af \left( [\text{PhO}^- \text{Q}^+]_a - \frac{[\text{QOR}]_o}{M_{\text{PhOQ}}} \right) \quad (2) \end{aligned}$$

$$\begin{aligned} [\text{PhOQ}]_o &= \frac{Q_0}{V_o} \left\{ \left( 1 + \frac{1}{fM_{\text{PhOQ}}} \right) + (1 + fM_{\text{QX}}) \frac{k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o + k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o}{k_{\text{aq},2}[\text{PhO}^- \text{K}^+]_a} \right. \\ &\quad \left. + \left( \frac{1}{K_{\text{QX}}A} + \frac{1}{fK_{\text{PhOQ}}A} \right) (k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o + k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o) \right\}^{-1} \quad (9) \end{aligned}$$

$$\begin{aligned} \frac{d[\text{QX}]_o}{dt} &= k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o[\text{PhOQ}]_o \\ &\quad + k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o[\text{PhOQ}]_o \\ &\quad - K_{\text{QX}}A([\text{QX}]_o - M_{\text{QX}}[\text{Q}^+ \text{X}^-]_a) \quad (3) \end{aligned}$$

$$\begin{aligned} \frac{d[\text{Q}^+ \text{X}^-]_a}{dt} &= K_{\text{QX}}Af([\text{QX}]_o - M_{\text{QX}}[\text{Q}^+ \text{X}^-]_a) \\ &\quad - k_{\text{aq},2}[\text{PhO}^- \text{K}^+]_a[\text{Q}^+ \text{X}^-]_a \quad (4) \end{aligned}$$

$$Q_0 = V_o([\text{PhOQ}]_o + [\text{QX}]_o) + V_a([\text{PhO}^- \text{Q}^+]_a + [\text{Q}^+ \text{X}^-]_a) \quad (5)$$

where  $\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2$ ,  $\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})$  and  $\text{C}_{12}\text{H}_8(\text{CH}_2\text{OPh})_2$  are 4,4'-bis(chloromethyl)-1,1'-biphenyl, 4,4'-(chloromethylphenoxy)methyl)-1,1'-biphenyl (mono-substituted product) and 4,4'-bis(phenoxy)methyl)-1,1'-biphenyl (di-substituted product), respectively.  $f$  is the volume ratio of organic solution ( $V_o$ ) to the aqueous solution ( $V_a$ ). The subscript “o” and “a” denote the characteristics of the species in the organic and aqueous phase, respectively.  $k_1$  and  $k_2$  are the intrinsic rate constants of the two sequential reactions in the organic phase.  $k_{\text{aq},1}$  and  $k_{\text{aq},2}$  are the intrinsic rate constants of the two ionic reactions in the aqueous phase.  $A$  is the interfacial area between two phases is defined as the interfacial area between the two phases/per unit volume of organic solution.  $Q_0$  is the total catalyst.  $K_{\text{QX}}$  and  $K_{\text{PhOQ}}$  are the mass-transfer coefficients of QX and PhOQ between two phases, respectively.  $M_{\text{QX}}$  and  $M_{\text{PhOQ}}$  are the distribution coefficients of QX and PhOQ between two phases, respectively, i.e.

$$M_{\text{PhOQ}} = \frac{[\text{PhOQ}]_{o,s}}{[\text{PhO}^- \text{Q}^+]_{a,s}} \quad (6)$$

$$M_{\text{QX}} = \frac{[\text{QX}]_{o,s}}{[\text{Q}^+ \text{X}^-]_{a,s}} \quad (7)$$

The subscript “s” denotes the characteristic of the species at the interface.

Based on the experimental observation, the concentrations of PhOQ and QX in the organic and aqueous phase both reach constant values at the beginning of the reaction [17,18]. Therefore, a pseudo-steady-state hypothesis (PSSH) is applied, i.e.

$$\begin{aligned} \frac{d[\text{PhOQ}]_o}{dt} &= 0, & \frac{d[\text{PhO}^- \text{Q}^+]_a}{dt} &= 0, \\ \frac{d[\text{QX}]_o}{dt} &= 0, & \frac{d[\text{Q}^+ \text{X}^-]_a}{dt} &= 0 \quad (8) \end{aligned}$$

Combining Eqs. (1)–(5) and (8), we obtain

The following Damkohler numbers,  $Da_{\text{QX},1}$ ,  $Da_{\text{QX},2}$ ,  $Da_{\text{PhOQ},1}$ , and  $Da_{\text{PhOQ},2}$  are defined as

$$\begin{aligned} Da_{\text{QX},1} &= \frac{k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o}{K_{\text{QX}}A}, \\ Da_{\text{QX},2} &= \frac{k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o}{K_{\text{QX}}A}, \\ Da_{\text{PhOQ},1} &= \frac{k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o}{K_{\text{PhOQ}}A}, \\ Da_{\text{PhOQ},2} &= \frac{k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o}{K_{\text{PhOQ}}A} \quad (10) \end{aligned}$$

$R_1$  and  $R_2$  are defined as the ratio of the organic-phase reaction rate to the aqueous-phase reaction rate, i.e.

$$R_1 = \frac{k_1[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o}{k_{\text{aq},2}[\text{PhO}^-\text{K}^+]_a},$$

$$R_2 = \frac{k_2[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o}{k_{\text{aq},2}[\text{PhO}^-\text{K}^+]_a} \quad (11)$$

Thus, Eq. (9) can be written in a dimensionless form:

$$[\text{PhOQ}]_o = \frac{Q_0}{V_o} \left\{ \left( 1 + \frac{1}{fM_{\text{PhOQ}}} \right) + (1 + fM_{\text{QX}})(R_1 + R_2) \right. \\ \left. + (Da_{\text{QX},1} + Da_{\text{QX},2}) + \frac{Da_{\text{PhOQ},1} + Da_{\text{PhOQ},2}}{f} \right\}^{-1} \quad (12)$$

Several experiments were carried out to measure the PhOQ concentration in aqueous and organic phases. It is found that the transfer of PhOQ from aqueous phase to organic phase is rapid. Therefore, the concentrations of PhOQ between two phases reaches to an equilibrium state within 1 min. This result indicates that the mass transfer of PhOQ or QX is rapid compared to the organic-phase reaction. Based on the experimental evidence, both the Damkohler numbers, and  $R_1$  as well as  $R_2$  are all small. Therefore, Eq. (12) is reduced to

$$[\text{PhOQ}]_o = \frac{fM_{\text{PhOQ}}}{1 + fM_{\text{PhOQ}}} \frac{Q_0}{V_o} \quad (13)$$

From Eq. (13), it is obvious that  $[\text{PhOQ}]_o$  is kept at a constant value. Therefore, a pseudo-first order rate law can be applied to describe the reaction.

Material balances for the compounds in the reaction solution are

$$-\frac{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o}{dt} = k_{\text{app},1}[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o \quad (14)$$

$$\frac{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o}{dt} = k_{\text{app},1}[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o - k_{\text{app},2}[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o \quad (15)$$

$$\frac{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{OPh})_2]_o}{dt} = k_{\text{app},2}[\text{C}_{12}\text{H}_8(\text{CH}_2\text{OPh})_2]_o \quad (16)$$

The concentration of PhOQ in the organic phase is at a constant value immediately after starting the reaction.  $k_{\text{app},1}$  and  $k_{\text{app},2}$  are the two apparent rate constants of the two sequential reactions in the organic phase and are defined as

$$k_{\text{app},1} = k_1[\text{PhOQ}]_o \quad (17)$$

$$k_{\text{app},2} = k_2[\text{PhOQ}]_o \quad (18)$$

The data obtained from the kinetic runs were analyzed using the integral method of rate data analysis. A pseudo-first order rate

expression was tried first for all the kinetic runs and was found to be sufficient for rate data analysis. Integrating Eq. (14) yields

$$-\ln(1 - X) = k_{\text{app},1}t \quad (19)$$

where  $X$  is defined as the conversion of  $\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2$ , i.e.

$$X = 1 - \frac{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_o}{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_{o,i}} \quad (20)$$

In which  $[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_{o,i}$  denotes the initial concentration of 4,4'-bis(chloromethyl)-1,1'-biphenyl (reactant) in the organic phase. The subscript 'i' represents the initial concentration of the species. Thus, the value of  $k_{\text{app},1}$  can be obtained from experimental data in conjunction with Eq. (19). Substituting Eq. (19) into Eq. (15), we obtain

$$\frac{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OR})]_o}{[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})_2]_{o,i}} = \frac{k_{\text{app},1}}{k_{\text{app},2} - k_{\text{app},1}} [\exp(-k_{\text{app},1}t) - \exp(-k_{\text{app},2}t)] \quad (21)$$

Based on the experimental data for  $[\text{C}_{12}\text{H}_8(\text{CH}_2\text{Cl})(\text{CH}_2\text{OPh})]_o$  versus time, the value of  $k_{\text{app},2}$  can be obtained from Eq. (21) with the previous knowledge of  $k_{\text{app},1}$ . The kinetic parameters of the equation were obtained using a computer program (software Fortran 90).

## 4. Results and discussion

### 4.1. Effect of agitation speed

To determine the influence of mass-transfer resistance of the reactants to the reaction phase, the speed of agitation was varied over the range of 0–1200 rpm. In Fig. 1, the experimental results show that the observed reaction rate constants increased linearly with the increase in the stirring rate from 0 to 200 rpm. However, the reaction rate did not increase for stirring rate higher than 200 rpm. The rate constant is dependent on the agitation

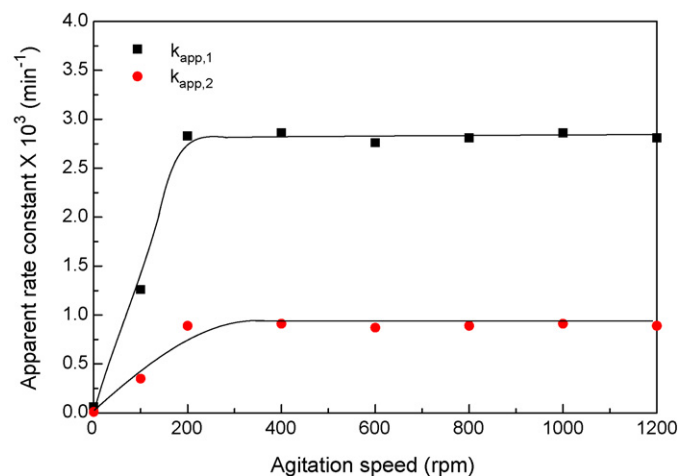


Fig. 1. Effect of the agitation speed on the two apparent rate constants,  $k_{\text{app},1}$  and  $k_{\text{app},2}$ ; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 0.5 mmol of TBAB, 25 g of potassium hydroxide, 40 mL of water, and 55 °C.



speed up to 200 rpm and becomes constant beyond 200 rpm, providing that further increase in rpm does not increase the mass-transfer rate of  $\text{PhO}^- \text{Q}^+$  ion-pair to organic phase. This means that the mass transfer of  $\text{PhO}^- \text{Q}^+$  from aqueous phase to organic phase plays an important role in enhancing the conversion of 4,4'-bis(chloromethyl)-1,1'-biphenyl and the reaction rate for agitation speed less than 200 rpm. Thus, the reaction is controlled by the chemical reaction in the organic phase for stirring rates greater than 200 rpm. In other words, at stirring level of 200 rpm, anion exchange equilibrium is fast relative to the organic displacement reaction, and the substrate consumption rate becomes independent of the stirring speed. Below 200 rpm, the mass transfer of the anion does not sufficiently meet the requirement of the reaction. Thus, diffusion and kinetics both dominate the reaction. Hence, the constancy of the reaction rate constants on the stirring speed above 200 rpm indicates that in the present study the reaction is a type of extraction mechanism. Thus, the reaction was not influenced by mass-transfer resistance (or the mass-transfer resistance remained at a constant value) for agitation speeds higher than 200 rpm. All further experiments in the following were carried out at 800 rpm for kinetic investigation.

#### 4.2. Effect of the phase-transfer catalysts

Several phase-transfer catalysts were employed to evaluate their efficacy in the etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol at 55 °C and 800 rpm. These phase-transfer catalysts were tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC), 3-(*N,N*-dimethyloctylammonio)propane sulfonate (SB-8), tetrabutylammonium iodide (TBAI), tetraheptylammonium chloride (THAC), 18-crown-6-ether, polyethylene glycol 600 (PEG 600), tricaprilmethylammonium chloride (Aliquat 336) and tetraoctylammonium bromide (TOAB). Table 1 depicts the two apparent rate constants for these nine catalysts. Among these, TOAB exhibited the maximum rate of reaction and conversion. Compared with the other catalysts, the greater efficiency of the TOAB catalyst is attributed to the higher lipophilic character of the cation ( $\text{Q}^+$ ) supplied by the catalyst, leading to the

Table 1  
Effect of the phase-transfer catalysts on the two apparent rate constants

| Kinds of phase-transfer catalysts | $k_{\text{app},1} (\times 10^{-3} \text{ min}^{-1})$ | $k_{\text{app},2} (\times 10^{-3} \text{ min}^{-1})$ |
|-----------------------------------|--|--|
| TBAC                              | 2.08   | 0.34   |
| TBAI                              | 2.99   | 0.57   |
| THAB                              | 7.32   | 1.39   |
| TOAB                              | 7.70   | 1.60   |
| SB-8                              | 0.90   | 0.21   |
| Aliquat 336                       | 2.54   | 0.69   |
| 18-Crown 6-ether                  | 0.10   | 0.03   |
| PEG 600                           | 0.66   | 0.19   |
| TBAB                              | 2.81   | 0.89   |

Reaction conditions: 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 0.5 mmol of phase-transfer catalyst, 3 mmol of an internal standard (biphenyl), 50 mL of chlorobenzene, 25 g of potassium hydroxide, 40 mL of water, 800 rpm, and 55 °C.

formation of an ion-pair with the phenoxide anion ( $\text{PhO}^-$ ). The ion-pairs are able to enter the less polar organic media in which the displacement reaction takes place. In general, a more oleophilic cation is more effective to transfer anions into the organic phase. Therefore, the order of catalytic reactivity are  $\text{TOAB} > \text{THAB} > \text{TBAB}$  and  $\text{Aliquat 336} > \text{TBAC}$ . The accessibility of the positive charge of Aliquat 336, due to the short methyl group, results in a tight ion-pairs with the phenoxide which in turn reduces the  $\text{S}_{\text{N}}2$  reactivity. In addition, the role of counter anion is also important. Comparing the results for TBAB, TBAC and TBAI, the order of the reactivity of these anions is  $\text{I}^- > \text{Br}^- > \text{Cl}^-$ . Since softer and more oleophilic anions are more effective than harder and less oleophilic anions, the order of catalytic reactivity is  $\text{TBAI} > \text{TBAB} > \text{TBAC}$ . In general, the iodide of a quaternary cation is a co-catalyst, forming iodomethylbiphenyl *in situ* and rapidly which is more reactive than the chloromethyl derivative. It is noteworthy that crown ether, which usually shows superior activity for phase-transfer systems, but in this work, performed poorly activity. This phenomenon is unusual and the reason for this result is still not well understand. Although polyethylene glycol 600, which is considered an open chain crown ether, often offers poor reactivity, its reactivity was greater than that of crown ether here. Furthermore, 3-(*N,N*-dimethyloctylammonio)propane sulfonate (SB-8) is a zwitterionic reagent which shows good reactivity in other reaction systems. But, the reactivity of SB-8 in this reaction system was low. In summary, the activity of quaternary ammonium salts was higher than those of other kinds of phase-transfer catalysts.

#### 4.3. Effect of the amount of phase-transfer catalyst

The effect of the catalyst loading on the conversion of reactant was studied for its amount between 0 and 8 mmol. The conversion is plotted against time for different catalyst loadings. As shown in Fig. 2, the conversion of the present etherification reac-

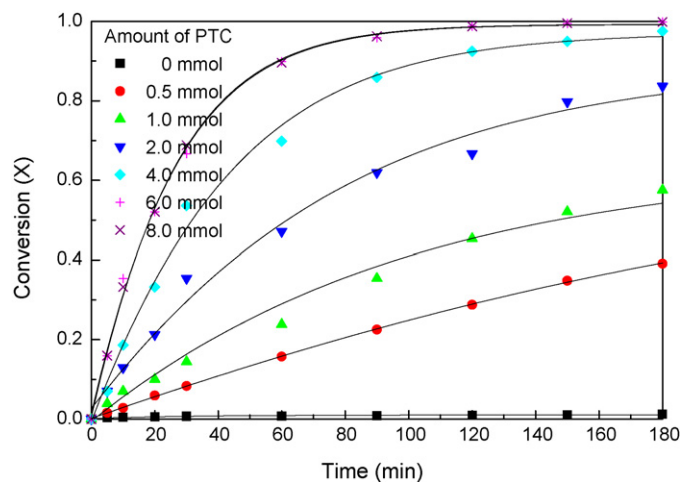


Fig. 2. Effect of the amount of phase-transfer catalyst on the conversion; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 25 g of potassium hydroxide, 40 mL of water, 800 rpm, and 55 °C.

tion also increased with increased loading. It stands to reason that the higher catalyst loading, the higher its solubilizing power and its transporting catalysis efficiency will result in higher conversion. In the absence of TBAB catalyst, almost no reaction takes place after 3 h of reaction. However, the conversion is dramatically increased to 39% after 3 h of reaction when only 0.5 mmol of TBAB catalyst is added to the reaction solution. These results indicate that the phase-transfer catalysts improve this etherification reaction substantially. Furthermore, the conversion would reach 100% when 8 mmol of TBAB was added to this reaction system.

#### 4.4. Effect of the amount of water

In the present work, the effect of water on the conversion was also explored. Fig. 3 shows the effect of the amount of water over a range of 20–80 mL on the conversion, demonstrating that the reaction follows the pseudo-first order rate law well. The water quantity affects the interfacial area between aqueous phase and organic phase, solvation of PhOQ and the concentration of potassium hydroxide in the aqueous phase. As stated above in the section on the effect of agitation speed, the mass-transfer resistance is neglected or is kept at a constant value for the agitation speed at 800 rpm. Thus, the reaction rate does not increase with increased amount of water in order to increase the interfacial area. It is commonly recognized that the dominant reason for the increase in reaction rate at low water level is the dramatic effect of reduced hydration of the phenoxide nucleophile. The activity of KOH is also not important since phenol ( $pK_a$  9) will instantaneously be neutralized at all concentrations of KOH at which pH is higher than about 9. The solvation of PhOQ with water is increased by increasing the amount of water, by which the activity of PhOQ is decreased. Furthermore, the concentration of potassium hydroxide decreases with the increase in the amount of water and it is also unfavorable for this etherification. With 20, 25, 30, 35, 40, 60 and 80 mL of water, the conver-

Table 2

Effect of the organic solvents on the two organic-phase apparent rate constants

| Kinds of organic solvents | Dielectric constant ( $\epsilon$ ) | $E_T^N$ | $k_{app,1}$ ( $\times 10^3 \text{ min}^{-1}$ ) | $k_{app,2}$ ( $\times 10^3 \text{ min}^{-1}$ ) |
|---------------------------|------------------------------------|---------|--|--|
| Benzene                   | 2.3                                | 0.111   | 1.65   | 0.26   |
| Ethylbenzene              | 2.5                                | –       | 0.79   | 0.13   |
| Dibutyl ether             | 2.8                                | 0.071   | 0.97   | 0.19   |
| Toluene                   | 2.4                                | 0.099   | 0.56   | 0.12   |
| Octane                    | 2.0                                | 0.012   | 2.58   | 0.65   |
| Chlorobenzene             | 5.6                                | 0.188   | 2.81   | 0.89   |

Reaction conditions: 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 0.5 mmol of TBAB, 3 mmol of internal standard (biphenyl), 50 mL of organic solvent, 25 g of potassium hydroxide, 40 mL of water, 800 rpm, and 55 °C.

sion of 4,4'-bis(chloromethyl)-1,1'-biphenyl levels were 94%, 92%, 89%, 75%, 39%, 34% and 30%, respectively. Therefore, a higher conversion of reactant was obtained when using less water. For example, when using 20 mL of water, the values of the two apparent rate constants are  $k_{app,1} = 0.0157 \text{ min}^{-1}$  and  $k_{app,2} = 0.0038 \text{ min}^{-1}$ , respectively.

#### 4.5. Effect of the organic solvents

The distribution of a phase-transfer catalyst between water and an organic medium depends, to a large extent, on the nature of the latter, i.e. the polarity, the lipophilic property, etc. In this work, catalytic etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol has been carried out over a series of organic solvents including benzene, chlorobenzene, dibutyl ether, ethylbenzene, octane and toluene. The results of experiments using different kinds of organic solvents are listed in Table 2. The information on dielectric constant and Dimroth–Reichardt parameter of organic solvents are also listed in Table 2 for comparison. The order of the reactivities for these organic solvents was chlorobenzene > octane > benzene > diethyl ether > ethylbenzene > toluene. Chlorobenzene and octane showed by far the most favorable behavior with respect to reaction rate constant. In this work, a small third phase in the reaction solution was observed when octane is used as the organic solvent and TBAB is used as the phase-transfer catalyst at high concentration of KOH (25 g). Therefore, higher reaction rate is obtained when the reaction was carried out in octane at high concentration of KOH. The formation of a third phase often leads to different solvent dependency for TBAB than for Aliquat 336 which is fully soluble in octane. However, the activity of the TBAB catalysts in different organic solvents does not correspond to the order of dielectric constant or the Dimroth–Reichardt parameter of organic solvents. This can be ascribed to the effect of the degree of ionization, extraction, solubility, and chemical circumstances which were all in relation to kinds of organic solvents; all of the effects were complicated and interactive. Therefore, the activity of the phase-transfer catalyst in different organic solvents is not monotonously increasing with dielectric constant or Dimroth–Reichardt parameter of organic solvents. In other words, there is not a

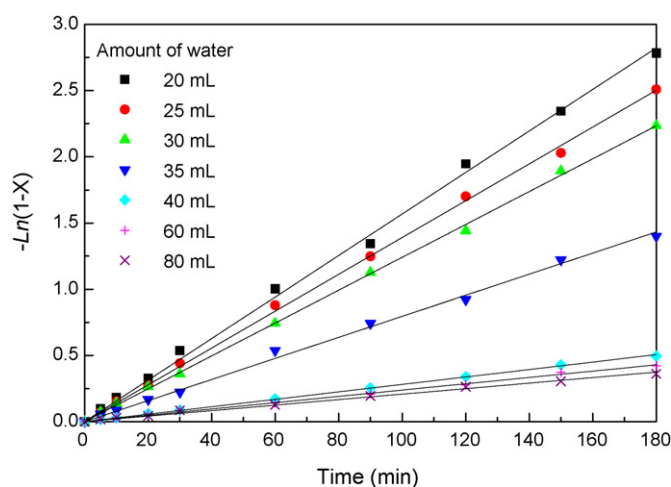


Fig. 3. A plot of  $-\ln(1-X)$  of 4,4'-bis(chloromethyl)-1,1'-biphenyl vs. time with different amount of water; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 0.5 mmol of TBAB, 25 g of potassium hydroxide, 800 rpm, and 55 °C.

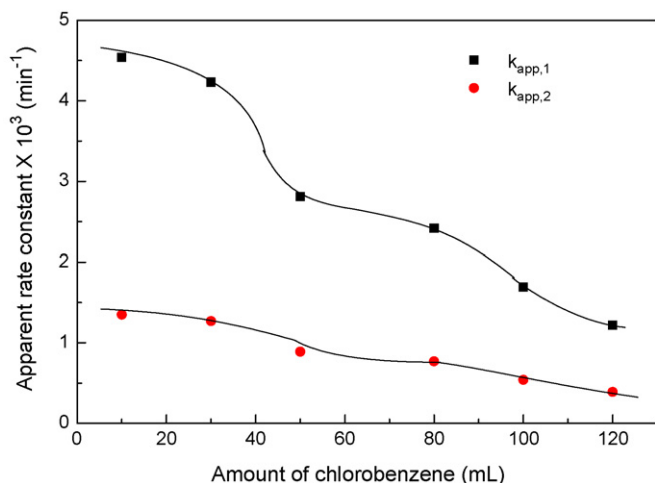


Fig. 4. Effect of the amount of organic solvent on the two apparent rate constants,  $k_{app,1}$  and  $k_{app,2}$ ; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 0.5 mmol of TBAB, 25 g of potassium hydroxide, 40 mL of water, 800 rpm, and 55 °C.

simple rule to predict their effects by only using the dielectric constant or Dimroth–Reichardt parameter of organic solvents.

#### 4.6. Effect of the amount of chlorobenzene (organic solvent)

In this work, chlorobenzene was chosen as the organic solvent. The effect of the amount of organic solvent on etherification was also investigated over the range of 10–120 mL. As shown in Fig. 4, the apparent rate constant is decreased with increased chlorobenzene, even though the interfacial contact area is increased with the increase in the amount of organic solvent. At the same time, the concentration of the active intermediate (PhOQ) and of 4,4'-bis(chloromethyl)-1,1'-biphenyl both decrease with the increase in the amount of chlorobenzene. For these reasons, less organic solvent is favorable to the etherification in this biphasic LL-PTC system. Nevertheless, a sufficient amount of organic solvent would be required to dissolve a certain amount of organic reactant, which is 4,4'-bis(chloromethyl)-1,1'-biphenyl.

#### 4.7. Effect of inorganic salt adding

In phase-transfer catalytic reactions, the inorganic salts added sometimes influence the conversion. To investigate the effect of inorganic salts on etherification, potassium bromide, potassium chloride, potassium iodide, sodium bromide, sodium chloride and sodium iodide were chosen as the extra inorganic agents. Fig. 5 shows the influence of different kinds of inorganic salt adding on the conversion of 4,4'-bis(chloromethyl)-1,1'-biphenyl. It shows that the addition of potassium iodide or sodium iodide would promote this etherification reaction. Nevertheless, with the addition of other inorganic salts such as potassium chloride, potassium bromide, sodium chloride and sodium bromide would diminish the conversion of 4,4'-bis(chloromethyl)-1,1'-biphenyl. In general, the addition of inorganic salts affects not only the concentration of the active catalyst

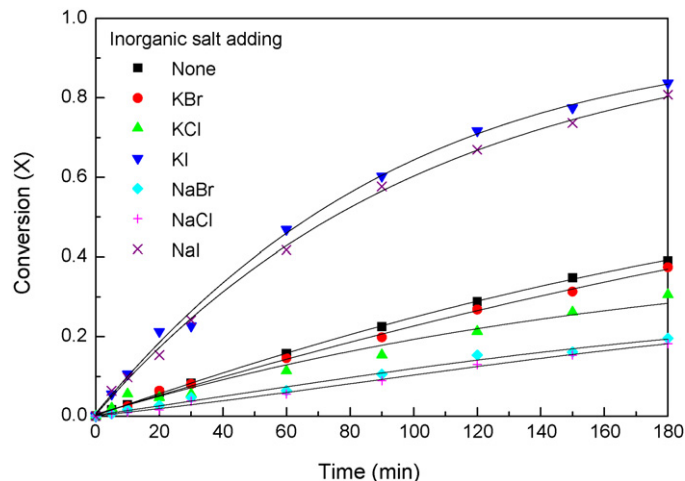


Fig. 5. Effect of the inorganic salt adding on the two apparent rate constants; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 0.5 mmol of TBAB, 25 g of potassium hydroxide, 40 mL of water, 10 mmol of inorganic salt, 800 rpm, and 55 °C.

in the organic phase but also the reaction environment. It also ties up water molecules for the dehydrating effect on the ions present in the system. The existence of iodide ions of a quaternary cation makes the aqueous phase more lipophilic than the existence of chloride ions or bromide ions which would make the aqueous phase more compatible with the organic solvents. Also, the iodide of a quaternary cation is a co-catalyst, forming iodomethylbiphenyl *in situ* and rapidly which is more reactive than the chloromethyl derivative. Therefore, less expensive inorganic salts of such as potassium iodide or sodium iodide can be used to promote dramatically the conversion in this phase-transfer catalytic system.

#### 4.8. Effect of the amount of potassium hydroxide

Since there is a base-initial reaction for the etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol, it is meaningful when the conversion of 4,4'-bis(chloromethyl)-1,1'-biphenyl is correlated to the amount of potassium hydroxide. The amount of potassium hydroxide amount was varied from 0 to 40 g. The amount of potassium hydroxide affects the distribution and amount of the active catalyst PhOQ between the phases. Meanwhile, the hydration number of PhOQ is also decreased with increased potassium hydroxide. Hence, the reaction rate is increased by increasing the amount of potassium hydroxide. Nevertheless, the apparent rate constants were not monotonously increased by increased potassium hydroxide. As shown in Fig. 6, the apparent rate constants would decrease when the amount of potassium hydroxide is greater than 20 g. At this point, the solution would become more viscous and thicker. Also in this situation, tetrabutylammonium bromide decomposes and loses its activity due to Hoffmann elimination at higher KOH concentration. This would cause in the apparent rate constants to decrease when the amount of potassium hydroxide is greater than 20 g.

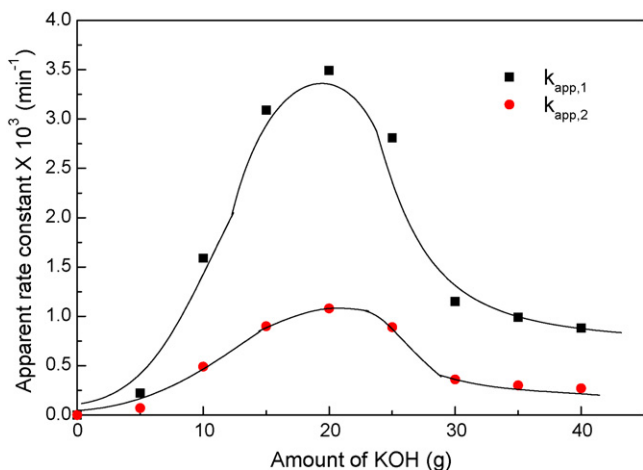


Fig. 6. Effect of the amount of potassium hydroxide on the two apparent rate constants,  $k_{app,1}$  and  $k_{app,2}$ ; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 0.5 mmol of TBAB, 40 mL of water, 800 rpm, and 55 °C.

Table 3  
Effect of temperature on the two organic-phase apparent rate constants

| Temperature (°C) | $k_{app,1}^a$ ( $\times 10^3 \text{ min}^{-1}$ ) | $k_{app,2}^b$ ( $\times 10^3 \text{ min}^{-1}$ ) |
|------------------|--|--|
| 45               | 1.07   | 0.23   |
| 50               | 1.83   | 0.38   |
| 55               | 2.81   | 0.89   |
| 60               | 5.25   | 2.14   |
| 65               | 10.65  | 3.14   |
| 70               | 15.21  | 7.99   |
| 75               | 24.97  | 15.65  |

Reaction conditions: 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 0.5 mmol of TBAB, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 25 g of potassium hydroxide, 40 mL of water, and 800 rpm.

<sup>a</sup>  $E_{a1} = 23.7 \text{ kcal/mol}$ .

<sup>b</sup>  $E_{a2} = 31.5 \text{ kcal/mol}$ .

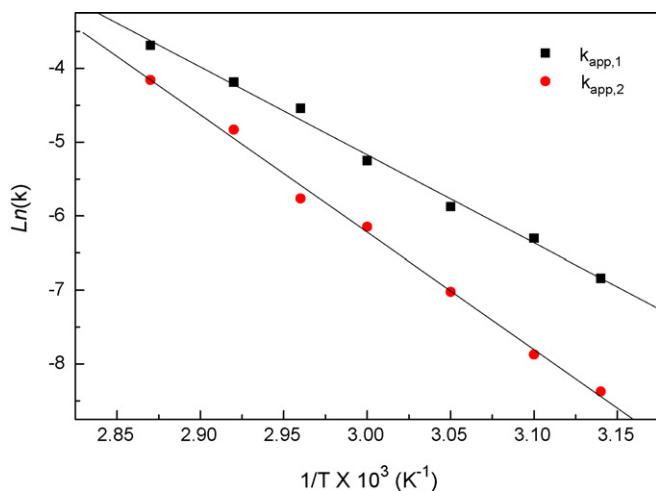


Fig. 7. Arrhenius plot for  $k_{app}$  vs.  $1/T$ ; 4 mmol of 4,4'-bis(chloromethyl)-1,1'-biphenyl, 60 mmol of phenol, 3 mmol of internal standard (biphenyl), 50 mL of chlorobenzene, 0.5 mmol of TBAB, 25 g of potassium hydroxide, 40 mL of water, and 800 rpm.

#### 4.9. Effect of temperature

The effect of temperature on rate of etherification was studied for the temperature range from 45 to 75 °C. The conversion was found to increase substantially with increasing temperature, which suggested that the reaction was intrinsically controlled kinetically and by activation energy values. The experimental data are listed in Table 3 and the results are depicted in an Arrhenius plot, as shown in Fig. 7, from which the activation energy was determined. From the slope of the plot ( $= -E_a/R$ ), it follows that the apparent activation energy equals  $E_{a1} = 23.7 \text{ kcal/mol}$  and  $E_{a2} = 31.5 \text{ kcal/mol}$ , respectively. This value supports the conclusion that there are no mass-transfer limitations. A high value of apparent activation energy implies a high dependence of the reaction rate on temperature.

#### 5. Conclusion

The phase-transfer catalyzed etherification of 4,4'-bis(chloromethyl)-1,1'-biphenyl with phenol was successfully carried out in a biphasic LL-PTC system by TBAB catalyst. A complete theoretical analysis of the reaction was achieved to describe the experimental results. This study investigated factors affecting the overall reaction rate, such as agitation speed, amount of water, amount of organic solvent, amount of phase-transfer catalyst, amount of potassium hydroxide, kind of phase-transfer catalyst, kind of organic solvent, inorganic salt and temperature. The reaction rate was not affected by agitation speed higher than 200 rpm. It increases with increasing temperature and catalyst amount and decreases with increasing amount of water and organic solvent. Nevertheless, there is an optimum value of the amount of potassium hydroxide. Of all the chosen catalysts, TOAB provides the best reactivity. Of all organic solvents, chlorobenzene provides the best reaction environment for this etherification. The addition of less expensive inorganic salts such as potassium iodide or sodium iodide promotes the conversion of 4,4'-bis(chloromethyl)-1,1'-biphenyl. The apparent activation energies for formation of 4,4'-(chloromethylphoxymethyl)-1,1'-biphenyl and 4,4'-bis(phoxymethyl)-1,1'-biphenyl are 23.7 and 31.5 kcal/mol, respectively.

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