Formation of a third liquid phase and its reuse for dibenzyl ether synthesis in a tetraalkylammonium salt phase transfer catalytic system

Gong Jin [a,*], Harald Morgner [a], Tadaatsu Ido [b], and Shigeo Goto [b]

[a] *Wilhelm-Ostwald Institute of Physical and Theoretical Chemistry, University of Leipzig, Linnestrasse 2, D-04103 Leipzig, Germany*
[b] *Department of Chemical Engineering, Nagoya University, Chikusa, Nagoya 464-8603 Japan*

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This paper describes the formation of a third liquid phase in a phase transfer catalytic system in the presence of benzyl alcohol and potassium hydroxide, where dodecane and tetraalkylammonium bromide serve as organic solvent and catalyst, respectively. In this kind of system, a symmetrical ether (dibenzyl ether) was synthesized from benzyl chloride and benzyl alcohol at 323 K. In particular, the investigation demonstrates that the observed reaction rate constant depends on the length of the alkyl group of the catalyst. Tetrabutylammonium bromide exhibits the highest catalytic activity among the catalysts explored. With respect to the reuse of the third liquid phase, the results confirm that there is no decrease in phase transfer catalytic activity in three consecutive runs.

KEY WORDS: chemical reaction; phase transfer catalyst; symmetrical synthesis; third liquid phase; repeated use.

1. Introduction

Phase transfer catalysis (PTC) is a fascinating technique in organic synthesis, bringing the reactants dissolved in two immiscible phases together by adding a phase transfer agent, and has found wide application in the production of fine chemicals and pharmaceuticals in the past few decades [1].

One of the primary drawbacks of such a traditional kind of liquid–liquid PTC is that separation and recovery of the catalyst from the products and organic solvent are difficult [2]. One strategy to overcome this hurdle is to form a catalyst-rich third liquid phase which can be achieved under certain conditions. The third liquid phase usually contains a high concentration of catalyst, accompanied by some water and organic solvent. This not only improves the chances for recovery of the PTC but also, as a welcome consequence, owing to the high concentration of the catalyst and reactants in the third phase, the observed overall reaction rate increases dramatically once the third liquid is formed [3–6].

There have been a few examples in the literature demonstrating halogen exchange, dehydrohalogenation, alkoxylation and asymmetric ether synthesis reactions in three liquid-phase PTC systems [4–8]. Nevertheless, so far, no attempts have succeeded in the synthesis of symmetrical ethers applying this novel technique, although this kind of ether is of special importance in commercial applications. In this paper we report the first application of a three-phase PTC system to the synthesis of a symmetrical ether.

We report the formation of the third liquid phase in a PTC system, which means that the system becomes liquid (aqueous phase)–liquid (third liquid phase)–liquid (organic phase). Further, we demonstrate its repeated use by means of dibenzyl ether synthesis from benzyl chloride and benzyl alcohol. This study also opens up a new possibility to synthesize a symmetrical ether at low temperature (323.15 K).

The PTC catalytic reaction is represented by the reaction

$$C_6H_5CH_2Cl + C_6H_5CH_2OH \xrightarrow[\text{PTC}]{\text{KOH}} (C_6H_5CH_2)_2O + HCl \quad (1)$$

This reaction is usually catalyzed by OH^- ions in the aqueous phase. The product, dibenzyl ether, a symmetrical ether, is used in several commercial processes, *e.g.*, as a carrier in dyeing and a solvent in organic chemistry and in perfumes. Quaternary ammonium salts are of special interest for phase transfer purposes.

2. Experimental

2.1. *Catalysts and reagents*

Tetramethyl-, tetrapropyl-, tetrabutyl-, tetrapentyl- and tetrahexylammonium bromide were employed as phase transfer catalysts. Tetrahexylammonium bromide was purchased from Aldrich Chemical (99% purity).

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* To whom correspondence should be addressed.
E-mail: jingongch@hotmail.com

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Table 1
Properties of the tetrabutylammonium salts

Property	Tetramethylammonium bromide	Tetrapropylammonium bromide	Tetrabutylammonium bromide	Tetrapentylammonium bromide	Tetrahexylammonium bromide
Molecular formula	$(CH_3)_4NBr$	$(C_3H_7)_4NBr$	$(C_4H_9)_4NBr$	$(C_5H_{11})_4NBr$	$(C_6H_{13})_4NBr$
Molecular weight (g/mol)	154.04	266.26	322.37	378.48	435.58
Melting point (K)	573	539	373	373	373
Phase number	2	3	3	3	2
k_{obs} (s^{-1})	0	7.12	9.51	4.98	2.55

All other catalysts and reagents were of GR grade from Wako Pure Chemical Industries. All chemicals were used without any further purification.

2.2. *Solubility experiments*

Solubility of tetrabutyl- and tetrahexylammonium bromide in dodecane was determined by means of ^1H NMR spectrometry (Gemini 2000, Varian, USA). Supersaturated ammonium salt was introduced into a test-tube with dodecane. After vigorous mixing in a vortex mixer for 5 min, the tube was immersed in a constant-temperature water bath (323 K) for 1 h. Finally, a drop of the liquid was dissolved in CD_3OD to form a homogeneous solution for NMR analysis. The solubilities of tetrabutyl- and tetrahexylammonium bromide in dodecane are 6.67 and 16.08 mol/m^3 org., respectively, according to the NMR results.

2.3. *Kinetic measurements*

A stirred tank batch reactor at a constant temperature of 323.15 K was used as described elsewhere [5], except for adding tetradecane as an internal standard. The initial volume of both organic and aqueous bulks was 50 cm^3.

3. Results and discussion

3.1. *Formation of the third liquid phase*

In all systems investigated dodecane served as the organic solvent in the presence of benzyl alcohol (at a concentration of 200 mol/m^3 org.) whereas the polar phase was made up of water with a constant concentration of potassium hydroxide (6.42 kmol/m^3 H_2O).

First, we explored which of the different quaternary ammonium salts used as phase transfer catalysts led to the formation of the third liquid phase. The properties of the different catalysts are shown in table 1. It is obvious that an increase in the number of atoms surrounding the central N atom of an ammonium cation will increase its lipophilic property, which results in enhanced segregation of the ammonium salt from the water. Only if the lipophilic group is larger than C_2H_5 is the third liquid phase formed. The third liquid phase, intermediate in density, builds up at the interface, growing in thickness as more catalyst is added. We note, however, that there is an upper limit for the size of the lipophilic group since for C_6H_{13} no third liquid phase can be observed. Apparently, the solubility of the phase transfer catalyst must be sufficiently low in both the polar and the organic phase.

The last row of table 1 shows the values of the observed rate constant k_{obs}, for each catalyst investigated, which was obtained from the plot of $y_{R,org}$ *versus* time shown in figure 1. Once the third phase is formed, the observed reaction rate rises substantially. It is also found that k_{obs} shows a maximum value when tetrabutylammonium bromide is used as the catalyst. As tetrahexylammonium bromide does not form a third phase, the corresponding reaction rate is fairly low.

This latter behavior differs from our previous results in a study concerning dehydrohalogenation reactions of 2-bromooctane in a PTC system [5], where a third liquid was obtained for tetrahexylammonium bromide when dodecane served as the organic solvent and this catalyst showed a higher reaction activity than tetrabutylammonium bromide. Comparison of the different experimental situations implies that this deviation may be attributed to the presence of benzyl alcohol in the organic phase or else to the concentration of the catalyst.

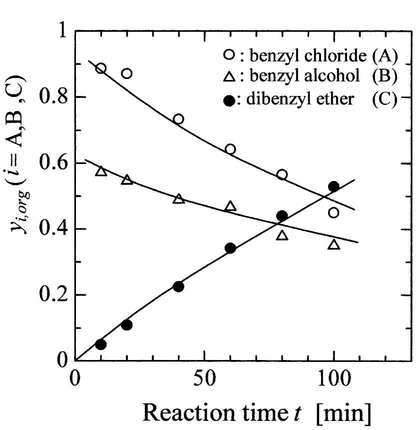

Figure 1. Concentrations of benzyl chloride, benzyl alcohol and dibenzyl ether in the organic bulk as a function of time with tetrabutylammonium bromide as a phase transfer catalyst. Aqueous phase: KOH, 6.42 kmol/m^3 H_2O. Organic solvent: dodecane. Reactants: 200 mol benzyl chloride/m^3 org. and 200 mol benzyl alcohol/m^3 org. PTC: 20 mol/m^3 org.

With respect to the first possible reason, one could argue that the dissolved benzyl alcohol in dodecane may increase the miscibility of tetrahexylammonium bromide in the organic bulk owing to the change in the polarity of the mixture. However, the ^{1}H NMR determination of the tetrahexylammonium bromide distribution among the three phases indicates that there is little influence in such a case.

The reason may be related to the concentration of the catalyst used in the two studies. In contrast to the 100 mol/m^3 org. in the previous study, this time we added only 10 mol/m^3 org. catalyst in the system. Since the ^{1}H NMR results show that the solubility of tetrahexylammonium bromide in dodecane is 16.08 mol/m^3 org., which is larger than the amount added to the system in the present study, no third phase is formed. However, as the solubility of tetrabutylammonium bromide is 6.67 mol/m^3 org, and thus lower than the amount added in the present study, the third phase is formed for this compound.

3.2. *Reactants and product in the course of time*

Equal concentrations of benzyl chloride and benzyl alcohol were added to the reactor and the concentrations of the two reactants and the product, dibenzyl ether, were measured *versus* time when tetrabutylammonium bromide was used as catalyst. Figure 1 shows their concentrations in the organic bulk as a function of time.

Although the reactants are added in equal amounts, the concentration of benzyl alcohol is lower than that of benzyl chloride already at $t = 0$. The behavior of benzyl alcohol during the reaction may be due to the association of three molecules of benzyl alcohol with one hydroxide anion. This aggregate is extracted into the polar phase according to the following sequence of reactions [1].

First, the PTC reacts with the KOH in the system:

$$\mathrm{QBr} + \mathrm{KOH} \rightleftharpoons \mathrm{Q^+OH^-} + \mathrm{HBr} \tag{2}$$

where Q^+ represents the phase transfer catalyst cation. Then, Q^+OH^- reacts with three benzyl alcohol molecules according to

$$\mathrm{Q^+OH^-} + 3\mathrm{ROH} \rightleftharpoons \mathrm{Q^+(HO{\cdot}3ROH)^-} \tag{3}$$

with the product being accumulated in the third phase.

The effect of the formation of the third phase on the kinetics can be explained in the following way: because the catalyst exists mainly in the third phase, it is reasonable to assume on the basis of solubility arguments that the OH^- can be ferried to the third phase much more easily than to the organic bulk. Therefore, another reactant, benzyl chloride, will be dissolved in the third liquid phase more easily for the same reason. It has been found that this kind of concentration effect in the catalyst-rich third phase would lead to an increase in the reaction rate [4,5]

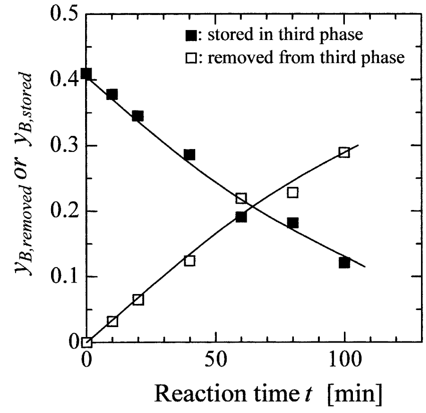

Figure 2. Amounts of benzyl alcohol stored in and removed from third phase as a function of time. Aqueous phase: KOH, 6.42 kmol/m^3 H_2O. Organic solvent: dodecane. Reactants: 200 mol benzyl chloride/m^3 org. and 200 mol benzyl alcohol/m^3 org. PTC: 10 mol/m^3 org.

3.3. *Behavior of benzyl alcohol in the third phase*

As seen in figure 1, almost half the amount of benzyl alcohol dissolves in the third phase by cooperating with the catalyst. This implies that benzyl alcohol is a main component in the third phase at the beginning of the reaction. To gain insight into the reactant behavior in the third phase, the amounts of benzyl alcohol stored in and removed from the third phase were investigated. Figure 2 shows their concentrations as a function of time.

Two parameters are used to describe the situation:

$$y_{\mathrm{B,removed}} = y_{\mathrm{R,org}} - (y_{\mathrm{B,org,0}} - y_{\mathrm{B,org},t}) \tag{4}$$

$$y_{\mathrm{B,stored}} = 1 - y_{\mathrm{B,org},t} - y_{\mathrm{R,org}} \tag{5}$$

where $y_{\mathrm{B,removed}}$ and $y_{\mathrm{B,stored}}$ represent the fraction of benzyl alcohol removed from and stored in the third phase, respectively, $y_{\mathrm{B,org,0}}$ and $y_{\mathrm{B,org},t}$ are the fractions in the organic bulk at time zero and t, respectively, and $y_{\mathrm{R,org}}$ is the fraction of product dissolved in the organic solvent.

Unlike the catalyst, the amount of benzyl alcohol stored in the third phase steadily decreases as the reaction proceeds and finally vanishes if the reaction is completed. The amount of this species removed from the third phase increases approximately in proportion.

The behavior of benzyl chloride in the third phase is essentially the same; however, the amount of this species stored in and removed from the third phase is fairly small.

3.4. *Reuse of third phase*

After the reaction as a function of time following formation of the third phase had been established as shown in figure 1, experiments on the repeated use of the catalyst were performed in order to evaluate the possibility of reuse. In these experiments interest was focused on the reappearance of the catalytic activity of

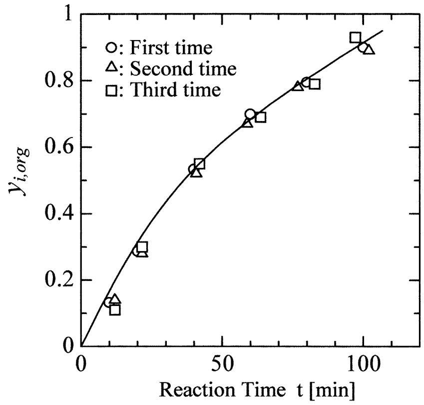

Figure 3. Repeated use of the phase transfer catalyst at 323 K. Aqueous phase: KOH, 6.42 kmol/m^3 H_2O. Organic solvent: dodecane. Reactants: 200 mol benzyl chloride/m^3 org. and 200 mol benzyl alcohol/m^3 org. PTC: 20 mol/m^3 org.

the catalyst. Prior to the following run, an amount of potassium hydroxide equal to the amount of the product was added and dissolved in the aqueous phase in order to compensate for the consumption of KOH as consequence of the production of HCl [*cf.* equation (1)] according to

$$KOH + HCl \longrightarrow KCl + H_2O. \quad (6)$$

Further, benzyl chloride and benzyl alcohol reactants were added to the batch reactor stoichiometrically. Three-times repeated experiments were conducted and the results are shown in figure 3. Obviously the results at each time are the same and hence it is possible to reuse the third phase without any decrease in its catalytic activity. For quantitative comparison between the figures, one should note that in the runs in figure 3 the concentration of PTC is twice that in the single run shown in figure 1.

4. Conclusion

For dodecane as nonpolar solvent in the presence of benzyl alcohol in contact with aqueous potassium hydroxide solution as polar liquid with quaternary ammonium bromide salts as phase transfer catalyst, we investigated the conditions for forming a third liquid phase as a function of the alkyl chain length of the ammonium ion. It turns out that the third liquid phase shows up only for intermediate chain lengths. Tetrabutylammonium bromide gives the highest reaction rate for the production of dibenzyl ether from benzyl chloride and benzyl alcohol at 323.15 K. Further, the experimental results demonstrate that the catalyst can be reused without any decrease in catalytic activity in three consecutive runs.

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