[Chem. Pharm. Bull.
33(8)3101—3106(1985)]

Kinetic Studies on an Improved Williamson Ether Synthesis Using a Polymer-Supported Phase-Transfer Catalyst[1]

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(Received December 5, 1984)

An improved Williamson ether synthesis was conducted under phase-transfer conditions by using a polymer-supported quaternary salt. Benzyl butyl ether was produced from benzyl alcohol and butyl bromide, and it was shown that the rate of reaction was influenced by the concentrations of benzyl alcohol and butyl bromide in the organic phase and the concentration of KOH in the aqueous phase. Based on kinetic studies, the rate-determining step was found to depend on the concentrations of the reactants. The content of water in the organic phase, which increased with the concentration of benzyl alcohol, was found to be closely related to the decrease in the rate of raction.

Keywords——triphase catalysis; phase-transfer catalysis; polymer-supported quaternary salt; Williamson ether synthesis; kinetics; benzyl butyl ether

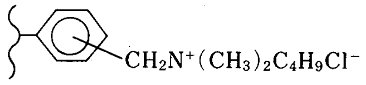
Phase-transfer catalysis has been established as a generally useful synthetic technique.[3] Recently, much attention has been given to immobilization of the phase-transfer catalyst because the work-up is greatly simplified by using an immobilized catalyst. A polymer-supported quaternary cation is one of the most popular immobilized catalysts (triphase catalyst[4]), and the catalytic effectiveness and mechanism have been studied by several workers.[5] We also investigated the kinetic features,[6] the effect of quaternary cation structure on the catalytic activity,[7] and the effect of mass-transfer resistance on the global rate of reaction.[8] Most of the studies, however, have been concerned with nucleophilic substitution of the anion extracted from the aqueous phase. In order to develop the practical use of immobilized phase-transfer catalysts, more investigations regarding hydroxide ion-initiated reactions will be required.

O-Alkylation of an alcohol is one of the more interesting hydroxide ion-initiated reactions under phase-transfer catalytic conditions. This reaction is conducted in a liquid (alcohol and alkyl halide)–liquid (alkaline solution) system and has been established as an improved Williamson ether synthesis.[9] This method does not involve the rigorous conditions usually required for the standard Williamson ether synthesis, and therefore many applications are expected in the laboratory or in industry.[10] Although it has been found that many unsymmetrical ethers can be obtained by means of this method, the detailed mechanism remains unknown.[11] Few reports have dealt with the utilization of immobilized catalysts for this reaction.[12]

We report here the effectiveness of a polymer-supported quaternary cation for the *O*-alkylation of an alcohol. The reaction mechanisms are also discussed on the basis of detailed kinetic investigations. The reaction of benzyl alcohol ($PhCH_2OH$) with butyl bromide (reaction (1)) was chosen as a model reaction.

$$PhCH_2OH + C_4H_9Br \xrightarrow[\text{cat.}]{50\%\ KOH_{aq.}} PhCH_2OC_4H_9 \qquad (1)$$

cat.:


$$\text{[resin]}-C_6H_4-CH_2N^+(CH_3)_2C_4H_9Cl^-$$

Experimental

Materials——All reagents were obtained commercially and used without further purification. Chloromethylated polystyrene cross-linked by 1% divinylbenzene (Bio-Beads S-X1, 1.26 meqchlorine/g-resin, 200—400 mesh) was purchased from Bio-Rad Laboratories.

Catalyst——Catalysts were prepared by the reaction of the chloromethylated resin with tertiary amines. The reaction was conducted in a culture tube for 70 h at 70 °C. Toluene was used as a solvent. The resin was filtered off, and washed first with toluene then with methanol and distilled water successively. It was dried overnight under reduced pressure at 70 °C. The contents of quaternary salt in catalyst samples were determined by elemental analysis.

Procedure——A test tube (cross-sectional area: $2.7\,cm^2$) equipped with a Teflon-lined screw cap was used as a reaction vessel. In a typical run the test tube was charged with 16.6 mg of the catalyst and 2 ml of 50% w/w KOH, and placed in a water bath (40 °C). The reaction was started by adding a preheated organic solution (2 ml) containing benzyl alcohol, butyl bromide, and *n*-tridecane (as an internal standard) to the test tube. The mixture was stirred by using a magnetic stirrer with a Teflon-coated chip. The stirring speed was sufficiently high to produce turbulence in the vessel. The reaction was followed by withdrawing samples ($1\,\mu l$ each) from the organic phase at appropriate intervals. Stirring was stopped for 10—20 s each time for sampling. The concentrations of reactants and product in the sample were analyzed by gas chromatography on a column packed with 2% silicone GE SE 30 on Chromosorb W (AW-DMCS, 80—100 mesh). The content of water in the organic solution was measured by the Karl Fisher method.

Results and Discussion

Kinetic Features

As shown in Fig. 1, the reaction proceeded rapidly in the presence of polymer-supported quaternary cation. Benzyl butyl ether was produced selectively and no by-products were observed, while a part of the benzyl alcohol had apparently disappeared even at zero time. Under similar conditions, but in the absence of the catalyst or in the presence of unfunctionalized resin (Bio-Beads S-X1), no yield of the ether was detected after 200 min. The initial rate of reaction (r) was determined by dividing the ether concentration by the reaction time, because the ether concentration was proportional to the reaction time until the yield of product reached about 50% (Fig. 1).

The same initial rate of reaction was observed when the stirring speed was changed. The activation energy obtained from an Arrhenius plot in the range of 20—40 °C was 19.8 kcal

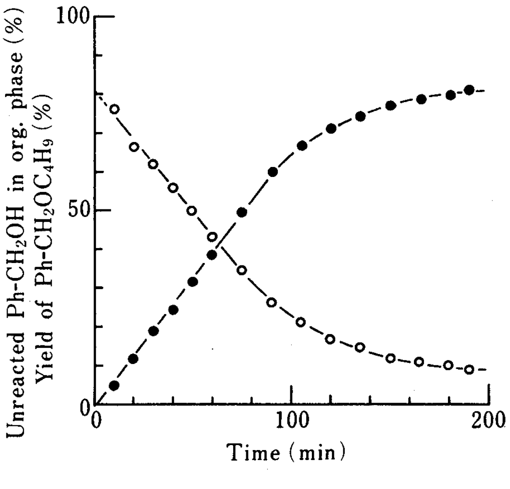


Fig. 1. Concentration of Benzyl Alcohol and Benzyl Butyl Ether *vs*. Reaction Time

○, benzyl alcohol; ●, benzyl butyl ether.
Reaction conditions; Organic phase: $PhCH_2OH$ ($0.3 \times 10^{-3}\,mol \cdot cm^{-3}$), C_4H_9Br (solvent), *n*-tridecane ($0.1 \times 10^{-3}\,mol \cdot cm^{-3}$, internal standard), $2\,cm^3$. Aqueous phase: 50% w/w KOH, $2\,cm^3$. Catalyst: $[resin]\text{-}CH_2N^+(CH_3)_2C_4H_9Cl^-$, N content $= 1.2 \times 10^{-3}\,mol\,g\text{-cata.}^{-1}$, $16.6 \times 10^{-3}\,g$. Reaction temperature: 40 °C

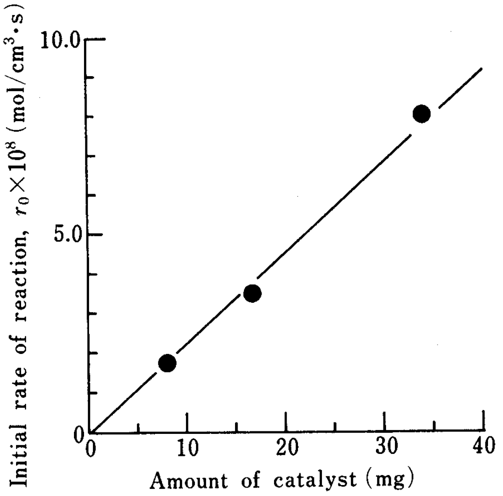


Fig. 2. Effect of the Amount of Catalyst on the Rate of Reaction

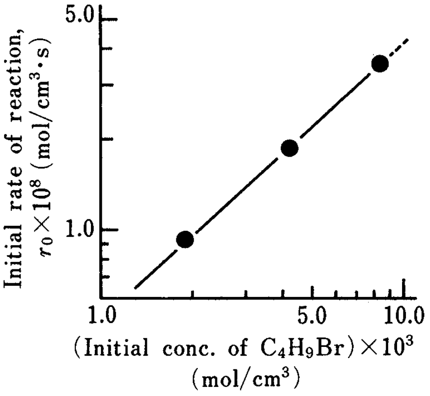


Fig. 3. Effect of the Concentration of Butyl Bromide on the Rate of Reaction

mol^{-1}. Based on these results, both inter- and intraparticle mass-transfer resistances are considered to be insignificant under the conditions shown in Fig. 1.

The initial rate of reaction was proportional to the amount of catalyst used (Fig. 2). In order to examine the dependency of the rate of reaction on the concentration of butyl bromide, the initial concentration of butyl bromide was changed by using toluene as a solvent. As shown in Fig. 3, the initial rate of reaction was found to be first-order with respect to butyl bromide.

Reaction Mechanism

From the results described above, the rate-determining step of the reaction is considered to be the reaction between $Q^+PhCH_2O^-$ and butyl bromide. $PhCH_2O^-$ may be produced in the aqueous phase or at the interface of the two phases by a hydroxide ion, and may then form an ion-pair with the quaternary cation. The proposed reaction mechanism can be summarized as follows.

$$PhCH_2OH + KOH \rightleftarrows PhCH_2O^-K^+ + H_2O \tag{2}$$

$$PhCH_2O^-K^+ + Q^+Br^- \rightleftarrows Q^+PhCH_2O^- + K^+Br^- \tag{3}$$

$$Q^+PhCH_2O^- + C_4H_9Br \longrightarrow PhCH_2OC_4H_9 + Q^+Br^- \tag{4}$$

where Q^+ is the polymer-supported quaternary cation, reactions (2) and (3) are in equilibrium and reaction (4) is the rate-determining step.

This mechanism is essentially the same as that for the anion displacement reaction under triphase catalytic conditions. Therefore, a similar structural effect of the supported cation on the catalytic activity to that in the case of the anion displacement reaction is expected. Thus, we tested the catalytic activity of several catalysts having different quaternary cations. The results are summarized in Table I. The catalytic activity increased with the bulkiness of the supported quaternary cation. Moreover, the relative catalytic activities of these catalysts were nearly the same as those observed for the anion displacement reaction.$^{7)}$ This result is consistent with the above-mentioned reaction mechanism.

Next, the effect of the concentration of benzyl alcohol on the rate of reaction was tested by changing the initial concentration of benzyl alcohol over a wide range. By plotting the logarithm of the initial rate of reaction against that of the initial concentration of benzyl

Table I. Comparison of Catalytic Activity

Catalyst		$r_0 \times 10^8$ ($mol \cdot cm^{-3} \cdot s^{-1}$)	(relative rate) (—)	Relative catalytic activity for anion displacement reaction[a]	
No.	Structure of cation			Experimental	Calculated
2	$-N^+(CH_3)_2C_4H_9Cl^-$	3.5	(0.50)	0.48	—
5	$-N^+(C_2H_5)_3Cl^-$	4.0	(0.57)	0.53	0.60
6	$-N^+(C_3H_7)_3Cl^-$	5.5	(0.79)	0.71	0.82
7	$-N^+(C_4H_9)_3Cl^-$	7.0	(1.0)	(1.0)	(1.0)

Data were taken from reference 7. a) $n\text{-}C_8H_{17}OSO_2CH_3 + KI\ (aq.) \rightarrow n\text{-}C_8H_{17}I + KOSO_2CH_3\ (aq.)$.

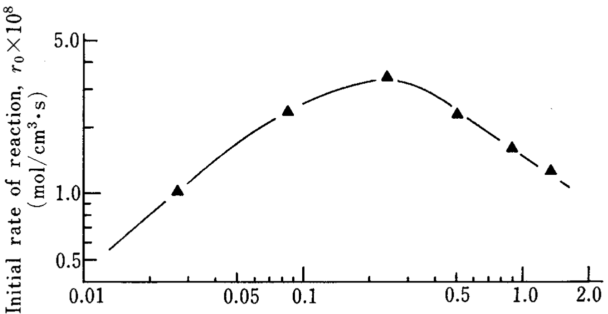


Fig. 4. Effect of the Concentration of Benzyl Alcohol on the Rate of Reaction

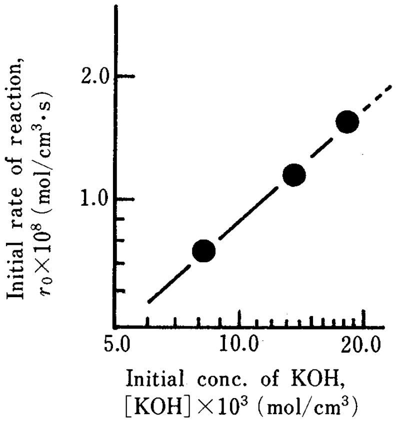


Fig. 5. Effect of the Concentration of KOH on the Rate of Reaction

Concentration of $PhCH_2OH$: 0.03×10^{-3} mol·cm^{-3}.

alcohol, the rate of reaction was found to show a first-order dependence on the concentration of benzyl alcohol at low concentrations (Fig. 4). When the alcohol concentration was low the rate of reaction also showed first-order dependency with respect to the concentration of KOH as shown in Fig. 5. Therefore, it can be concluded that reaction (2) is the rate-determining step at low concentrations of benzyl alcohol.

When the concentration of benzyl alcohol was higher than about 0.3 M, the rate of reaction decreased with increase in the concentration of benzyl alcohol. According to the reaction mechanism mentioned before, the rate-determining step is reaction (4), and therefore the rate of reaction should be independent of the concentration of benzyl alcohol. This inconsistency can be explained by taking account of the effect of the concentration of benzyl alcohol on the reactivity of the anion in reaction (4). It is well known that the reactivity of an anion is changed by the nature of the organic phase and/or by water molecules entrapped in the organic phase under phase-transfer catalytic conditions. As an alcohol is more protic and hydrophilic than both butyl bromide and toluene, the nature of the organic phase becomes more protic with increase in the concentration of benzyl alcohol. The content of water molecules in the organic phase may also increase with the concentration of benzyl alcohol. Actually, the content of water in the organic phase was found to increase dramatically under the reaction conditions used when the concentration of benzyl alcohol was higher than 0.3 M (Fig. 6). This increase in the water content in the organic phase suggestes that an increasing amount of water molecules accompanies the nucleophile $PhCH_2O^-$. Therefore, the decrease in the rate of reaction shown in Fig. 6 (and Fig. 4) can be ascribed to the increase in the water content in the organic solution, which in turn is caused by the change in the nature

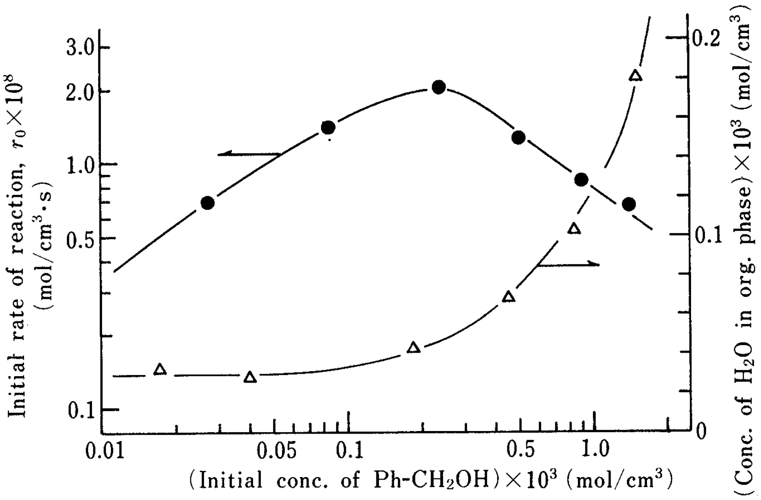


Fig. 6. Effect of the Concentration of H_2O in the Organic Phase on the Rate of Reaction

●, initial rate of reaction; △, concentration of H_2O in the organic phase. Concentration of KOH: 35% w/w.

of the organic solution.

Conclusion

The improved Williamson ether synthesis can be successfully conducted by using polymer-supported quaternary cations. In this reaction, $K^+PhCH_2O^-$ is produced at the interface between the organic phase and the aqueous phase and/or in the aqueous phase by reaction of the alcohol with a hydroxide ion. If the concentration of the alcohol is very low, this reaction is the rate-determining step. When the concentration of the alcohol becomes higher than about 0.1 M, the rate-determining step is the reaction of butyl bromide with the alcoxide anion accompanied by a quaternary cation, and therefore the rate of reaction is independent of the concentration of benzyl alcohol. The rate of reaction decreases with increase in the concentration of benzyl alcohol when the concentration of benzyl alcohol is higher than 0.3 M. This decrease in the rate of reaction can be attributed to the increase of the water content in the organic phase.

In conclusion, the rate of the improved Williamson ether synthesis in the presence of a phase-transfer catalyst is very sensitive to the concentration of reactants. In particular, the concentration of the alcohol, which affects the content of water in the organic phase, is an important factor in determining the optimum reaction conditions.

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