CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 30, No. 11 November 1982

Regular Articles

[Chem. Pharm. Bull. 30(11)3865—3871(1982)]

Studies on Triphase Catalysis: Kinetics of Anion Displacement Reactions

Hirofumi Takeuchi, Masahiro Kikuchi, Yoshihisa Miwa, and Jutaro Okada*

Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan

(Received April 21, 1982)

The kinetics of liquid (organic)-liquid (aqueous) two-phase reactions on an immobilized phase transfer catalyst (triphase catalysis) was investigated. The displacement reactions of anions (aq. phase) on benzyl bromide or benzyl chloride (org. phase) were carried out at 90°C using tri-*n*-butylphosphonium chloride bound to 1% cross-linked polystyrene resin as a catalyst. The system was not stirred and all catalyst particles existed at the liquid–liquid interface.

The observed sequence of nucleophilic reactivity of anions ($CN^- \sim I^- > Br^-$, Cl^-) is similar to that in a protic solvent. The reaction of benzyl bromide with potassium chloride was studied kinetically in detail. Under the experimental conditions used, all the mass transfer resistances had no significant effect and the rate of reaction was directly proportional to the amount of catalyst. The reaction order with respect to benzyl bromide was 0.73. From a consideration of the effects of concentrations of both chloride and bromide anions and the reverse reaction, a rate equation was developed.

Keywords——triphase catalysis; phase transfer catalysis; anion displacement; reaction kinetics; nucleophilicity of anion; reaction model; polystyrene resin; phosphonium salt; benzyl halide

The principle of phase transfer catalysis (PTC) is now well established[1] and this technique has been widely applied to synthetic processes in pharmaceutical chemistry.[2] Recently the immobilization of phase transfer catalysts has been investigated by several workers.[3] Such a phase transfer catalyst bound to a support can be easily separated from the reaction mixture by simple filtration and product isolation is greatly simplified. Moreover, the catalyst can be used in a flow system such as a fixed-bed reactor. Regen[4] was the first to study the reaction catalyzed by onium salts bound to polystyrene resins and termed this system "triphase catalysis (TC)." Montanali *et al.*[5] also reported the immobilization of various phase transfer catalysts, such as onium salts, crown ethers and cryptands.

There are many reports on TC, but the mechanistic details have not been well interpreted because of the complexity of the system. The rate of TC reaction is influenced by many physical and chemical factors, such as inter- and intra-particle diffusion, swelling of the polymer catalyst, the structure of the active site, *etc.* Regen[6] reported that a diffusion-limited chemical reaction is the rate-determining step in TC and that the main role of stirring is to increase the resin contact with the liquid–liquid interface. Tomoi *et al.*[7] found that inter- and intra-particle diffusion governs the rate of simple displacement reactions under TC conditions.

The purpose of this work was to examine the kinetic features of TC in detail. The anion displacement reaction on benzyl halide was investigated in the toluene–water system. A cross-linked polystyrene resin carrying tri-*n*-butylphosphonium groups was used as a catalyst. The reactivities of anions and the kinetics of the reaction were studied.

Experimental

Materials——Benzyl bromide, benzyl chloride, tri-*n*-butylphosphine, *n*-decane, *n*-dodecane, *n*-tridecane, toluene and all inorganic salts were used as obtained. Dimethylformamide (DMF) was used after further distillation. Chloromethylated polystyrene cross-linked by 1% divinylbenzene (Bio-Beads S-X1, 1.34 meq. chlorine/g-resin, 200—400 mesh) was purchased from Bio-Rad Laboratories.

Catalyst——The catalyst was prepared according to the previously described procedure.[5] Chloromethylated polystyrene was soaked in a DMF solution of tri-*n*-butylphosphine in a culture tube sealed with a Teflon-lined screw cap. The tube was placed in an oil bath at 90°C for 70 h. The resin was filtered off, washed with excess distilled water, and dried overnight under a vacuum at 80°C.

Two kinds of catalysts with different contents of phosphonium groups (catalysts 1 and 2) were prepared by changing the concentration of tri-*n*-butylphosphine. Elemental analysis showed that catalysts 1 and 2 contained 0.69 and 0.17 mmol phosphine/g-catalyst, respectively. Unless otherwise stated, catalyst 1 was used in all experiments.

Procedure——A test tube equipped with a Teflon-lined screw cap was used as the reaction vessel. Three different sizes of test tubes were used. The cross-sectional areas were: No. 1, 1.43 cm^2; No. 2, 2.68 cm^2; No. 3, 3.80 cm^2.

As a typical procedure, 5 mg of catalyst was placed in the test tube, then 2 ml of aqueous solution saturated with potassium chloride was added and the catalyst was well dispersed on the surface of the solution. The tube was sealed and placed in an oil bath (90°C), then 1 ml of toluene solution of benzyl bromide (3.0×10^{-4} mol·cm^{-3}) containing *n*-decane as an internal standard was added. The reaction was followed by withdrawing samples (1 μl each) from the organic phase at appropriate intervals. The concentrations of reactant and product in the sample were analyzed by gas chromatography. A column packed with silicone DC550 on Celite 545BW (60—80 mesh) was used.

The initial rate of reaction (r_0) was determined in the following way. The logarithm of (1 − conversion of organic reactant) was plotted against reaction time. Linearity of the plot was good in the low conversion range. The initial rate of reaction was calculated from the slope of the line (a) and the initial concentration of organic reactant (C_0);

$$r_0 = -a \cdot C_0$$

The reaction in the stirred system was conducted by using a magnetic stirrer at 70°C. The stirring speed was sufficiently high to produce turbulence in the vessel.

Results and Discussion

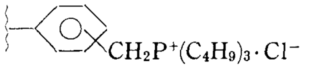
Reactivity of Anions

Anion displacement reactions under PTC and TC conditions have been well investigated,[1,8] but only a few quantitative studies on the reactivities of anions have been reported, especially in TC. In advance of the kinetic study, the reactivities of halide and cyanide anions under TC conditions were evaluated from the initial rates of the following reactions.

$$C_6H_5-CH_2X + KY \xrightarrow{\text{catalyst}} C_6H_5-CH_2Y + KX$$

$X = Cl, Br$
$Y = F, Cl, Br, I, CN$

catalyst:



The initial rates obtained under the same reaction conditions are summarized in Table I. In the case of F$^-$, no conversion was detected even after 5 h. The observed sequence of nucleophilic reactivity (CN$^-$∼I$^-$>Br$^-$ or CN$^-$∼I$^-$>Cl$^-$) is in accordance with the results reported under TC conditions.[8]

Table I. Initial Rate of Reaction of Benzyl Bromide or Benzyl Chloride with Halogen and Cyanide Anions

	$(r_A)_0 \times 10^8$ $(\mathrm{mol \cdot cm^{-3} \cdot s^{-1}})$	$(r_B)_0 \times 10^8$ $(\mathrm{mol \cdot cm^{-3} \cdot s^{-1}})$
F	—	—
Cl	5.8	—
Br	—	0.64
I	12.8	1.20
CN	12.9	1.27

$(r_A)_0$=initial rate of reaction of benzyl bromide with anions.
$(r_B)_0$=initial rate of reaction of benzyl chloride with anions.
Reaction conditions
Init. conc. of org. reactant: 3.0×10^{-4} mol·cm^{-3}.
Solvent: toluene.
Init. conc. of inorg. salt: saturated.
Volume: org. phase, 1 cm^3; aq. phase, 2 cm^3.
Amount of catalyst: 5 mg.
Test tube: No. 1. React. temp.: 90°C.

The reactivity sequences of anions in dipolar aprotic solvents ($CN^- > Cl^- > Br^- > I^-$) and in protic solvents ($I^- > CN^- > Br^- > Cl^-$) are well known.[9] Landini *et al.*[10] reported that the sequence under PTC conditions ($C_{16}H_{33}P^+(C_4H_9)_3$ Hal$^-$ catalyst, chlorobenzene–water system) is $CN^- > Br^- \sim I^- > Cl^-$ and that this anomalous sequence is due to the specific solvation of anions by a limited number of water molecules in the organic phase. The sequence observed in the present study resembles that in protic solvents. It can, therefore, be presumed that the reaction environments within the polymer matrix are more protic than those in the organic phase under PTC conditions.

In order to carry out detailed kinetic studies, the reaction of benzyl bromide (in the org. phase) with potassium chloride (in the aq. phase) was chosen as a typical example of TC. In this reaction, only benzyl chloride was produced and the material balance was simple, as shown in Fig. 1. Under similar conditions, but in the absence of catalyst or in the presence of unfunctionalized resin (Bio Beads S-Xl), no appreciable conversion was detected even after 3 h.

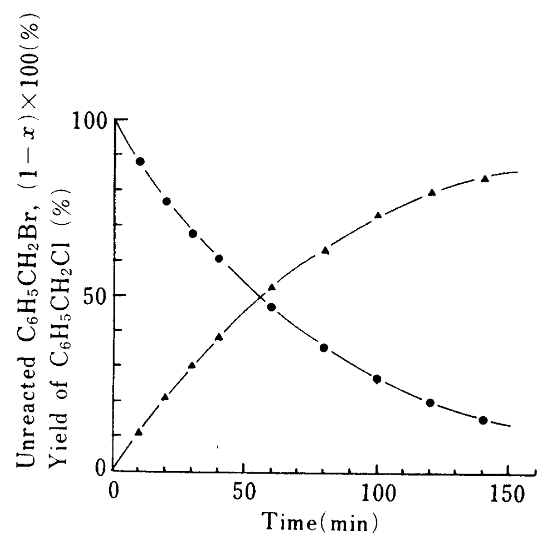


Fig. 1. Reaction of Benzyl Bromide with Potassium Chloride

—●—, benzyl bromide; —▲—, benzyl chloride. Init. conc. of benzyl bromide, 0.3×10^{-3} mol·cm^{-3}; solvent, toluene; init. conc. of KCl, saturated. Volume: org. phase, 1 cm^3; aq. phase, 2 cm^3. Amount of catalyst: 5 mg. Test tube: No. 1. React. temp.: 90°C.

Effect of Mass Transfer Resistance

The effect of mass transfer resistances was first examined by measuring the initial rate of reaction. As shown in Fig. 2, in the unstirred system, the initial rate is linearly dependent on the catalyst loading (m (g·cm^{-3})),[11] up to a critical value. This value is proportional to the liquid–liquid interfacial area, that is, the cross-sectional area of the test tube. This result suggests that the rate of reaction is proportional to the amount of the catalyst present at the liquid–liquid interface, and this is also supported by the results in the stirred system, as shown in Fig. 3. In the stirred system, the reaction occurred slowly even when the catalyst was absent, and a by-product (benzyl alcohol) was produced. The initial rate of this non-catalytic

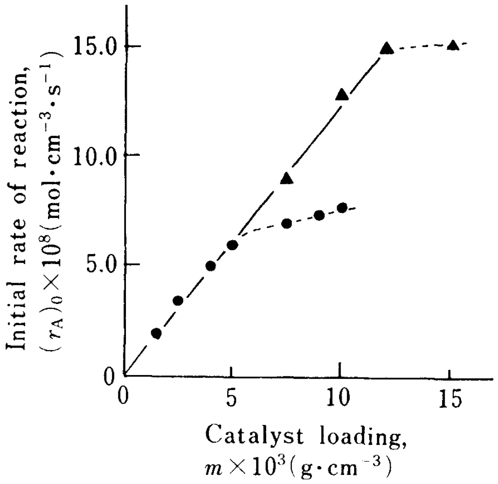


Fig. 2. Effect of Catalyst loading on Rate of Reaction in the Unstirred System

—●—, test tube No. 1; —▲—, test tube No. 3. Init. conc. of benzyl bromide, 0.3×10^{-3} mol·cm^{-3}; solvent, toluene; init. conc. of KCl, saturated. Volume: org. phase, 1 cm^3; aq. phase, 2 cm^3. React. temp.: 90°C.

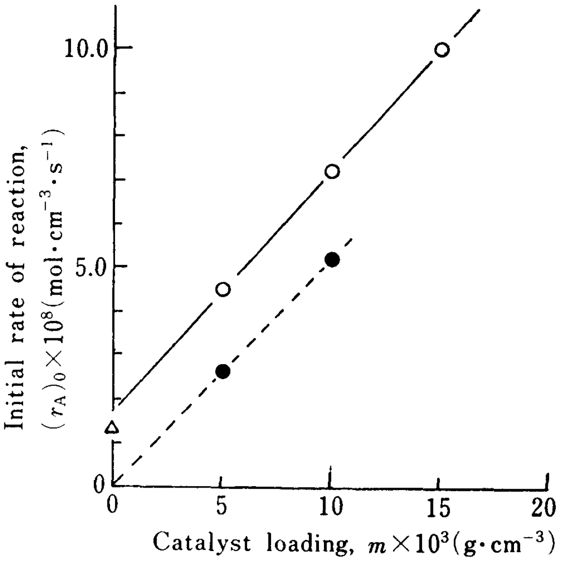


Fig. 3. Effect of Catalyst loading on Rate of Reaction in the Stirred System

—○—, —△—, in stirred system; —●—, in unstirred system. Init. conc. of benzyl bromide, 0.3×10^{-3} mol cm^{-3}; solvent, toluene; init. conc. of KCl, saturated. Volume: org. phase, 1 cm^3; aq. phase, 2 cm^3. Test tube: No. 2 for stirred system, No. 3 for unstirred system. React. temp.: 70°C.

reaction is shown by the mark (△) in Fig. 3. Taking account of this non-catalytic reaction, the initial rate of TC reaction in the stirred system is found to be directly proportional to the catalyst loading, and the slope is almost the same as that in the unstirred system (------). In the stirred system, the critical value is not observed, as all catalyst particles might contact the liquid–liquid interface owing to the stirring. These observations may support the conclusion reported by Regen[6] and also suggest that external mass transfer resistance is insignificant under our experimental conditions.

Tomoi *et al.*[7] reported a 20% increase in the rate constant when the catalyst particle size was reduced from 50—90 μm to 20—50 μm. Thus in our study, the catalyst (200—400 mesh: 74—38 μm) was divided into two groups of different particle sizes (200—250 mesh and 250—400 mesh) by sieving, and the initial rate of reaction for each group was measured. No difference in initial rate was observed between these particle sizes. To test whether all active sites inside the catalyst particles were effective or not, the effect of content of phosphonium groups on the rate of reaction was examined. As mentioned in the experimental section, the number of active sites of catalyst 2 was 4 times less than that of catalyst 1. The initial rate of reaction observed was proportional to the number of active sites as shown below.[12]

catalyst 1: $r_0 = 5.8 \times 10^{-8} (\mathrm{mol \cdot cm^{-3} \cdot s^{-1}})$
catalyst 2: $r_0 = 1.4 \times 10^{-8} (\mathrm{mol \cdot cm^{-3} \cdot s^{-1}})$

These results imply that the intraparticle diffusion of reactants is not a limiting factor for the rate of reaction, and that all active sites participate in the catalysis.

Kinetic Analysis

By analogy with the mechanism of PTC reactions,[1] this TC reaction is assumed to proceed according to the following two steps.

(*i*) *Halogen exchange reaction* between phosphonium salt bound to polystyrene matrix (P–X, X=Br$^-$ or Cl$^-$) and halogen anion in the aqueous phase.

$$\text{P-Br} + \text{Cl}^-(\text{aq.}) \overset{K}{\rightleftharpoons} \text{P-Cl} + \text{Br}^-(\text{aq.}) \tag{1}$$

(ii) Displacement reaction of phosphonium chloride on benzyl bromide.

$$\underset{(\text{A})}{C_6H_5CH_2Br(\text{org.})} + \text{P-Cl} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{(\text{B})}{C_6H_5CH_2Cl(\text{org.})} + \text{P-Br} \tag{2}$$

Step(i) may be considered to be very rapid and in equilibrium, and the equilibrium constant (K) can be expressed as

$$K = \frac{\theta_{Cl} \cdot C_{Br}}{\theta_{Br} \cdot C_{Cl}} \tag{3}$$

where θ_{Cl} and θ_{Br} are the molar fractions of phosphonium chloride and bromide in the resin matrix, and C_{Cl} and C_{Br} are the concentrations of chloride and bromide anions in the aqueous phase, respectively. It can be considered that all phosphomium groups are in the form of chloride or bromide ($\theta_{Cl}+\theta_{Br}=1$). Thus, θ_{Cl} and θ_{Br} can be expressed as

$$\theta_{Cl} = \frac{K \cdot C_{Cl}}{C_{Br} + K \cdot C_{Cl}} \tag{4}$$

and

$$\theta_{Br} = \frac{C_{Br}}{C_{Br} + K \cdot C_{Cl}} \tag{5}$$

As shown in Table I, the reverse reaction of step(ii) could not be neglected. If this step is assumed to be the rate determining step, the reaction rate of benzyl bromide (r_A) can be written as

$$\begin{aligned} r_A &= -dC_A/dt = k_1 \cdot m \cdot \theta_{Cl} \cdot C_A{}^{\alpha} - k_2 \cdot m \cdot \theta_{Br} \cdot C_B{}^{\beta} \\ &= k_1 \cdot m \cdot \frac{K \cdot C_{Cl}}{C_{Br} + K \cdot C_{Cl}} \cdot C_A{}^{\alpha} - k_2 \cdot m \cdot \frac{C_{Br}}{C_{Br} + K \cdot C_{Cl}} \cdot C_B{}^{\beta} \end{aligned} \tag{6}$$

where k_1 and k_2 are the respective rate constants, m is the catalyst loading, α and β are the reaction orders with respect to benzyl bromide and benzyl chloride, and C_A and C_B are the concentrations of benzyl bromide and benzyl chloride, respectively, in the organic phase.

When a large excess of potassium chloride is used, the amount of potassium bromide produced is negligible compared to that of potassium chloride ($C_{Cl} \gg C_{Br}$), and then $\theta_{Cl} \approx 1$. As the reverse reaction is negligible at low conversion, the initial rate of reaction $(r_A)_0$ can be represented by

$$(r_A)_0 = -dC_A/dt|_{t=0} = k_1 \cdot m \cdot (C_A)_0{}^{\alpha} \tag{7}$$

where $(C_A)_0$ is the initial concentration of benzyl bromide.

Figure 4 shows the relationship between log $(r_A)_0$ and log $(C_A)_0$. In the kinetics of PTC and TC reactions, first order dependency on the concentration of organic reactant has been reported.[1,3] However, in the present study, the observed order with respect to benzyl bromide (α) was 0.73, as shown in Fig. 4. Similarly, the order with respect to benzyl chloride (β) was estimated to be 0.92 (Fig. 4), and the values of k_1 and k_2 were estimated to be as follows.

$$k_1 = 4.18 \times 10^{-3} \quad (\text{mol}^{1-\alpha} \cdot \text{cm}^{3\alpha} \cdot \text{s}^{-1} \cdot \text{g-catalyst}^{-1})$$

$$k_2 = 2.35 \times 10^{-3} \quad (\text{mol}^{1-\beta} \cdot \text{cm}^{3\beta} \cdot \text{s}^{-1} \cdot \text{g-catalyst}^{-1})$$

The value of K can be determined by the following method. If the initial concentration of potassium chloride is equal to that of potassium bromide ($(C_{Cl})_0 = (C_{Br})_0$), and their molar amounts are in excess compared to that of benzyl bromide, the initial rate of reaction can be expressed as

$$(r_A)_0 = k_1 \cdot m \cdot \frac{K}{1+K} \cdot (C_A)_0{}^{\alpha} \tag{8}$$

Then, the value of K can be calculated by comparing the observed initial rate in the presence of equimolar potassium bromide (eq. (8)) with that in the absence of potassium bromide (eq. (7)), at the same initial concentration of benzyl bromide. The results are shown in Table II, and the value of K was obtained as 0.142.

Finally, the adequacy of the above mentioned model will be discussed. Equation (6) can be expressed in terms of the conversion of benzyl bromide, x, as follows.

$$dx/dt = \frac{k_1 \cdot m}{(C_A)_0{}^{1-\alpha}} \cdot \frac{K\cdot(n-x)}{x+K\cdot(n-x)} \cdot (1-x)^{\alpha} - \frac{k_2 \cdot m}{(C_A)_0{}^{1-\beta}} \cdot \frac{x}{x+K\cdot(n-x)} \cdot x^{\beta} \tag{9}$$

where n represents the intial molar ratio of potassium chloride to benzyl bromide. The value of K, as noted above, is rather small so that the value of n should affect the rate of reaction,

Table II. Estimated Equilibrium Constant (K)

	Amount of salt (mmol) KCl	KBr	$(r_A)_0 \times 10^8$ ($\text{mol}\cdot\text{cm}^{-3}\cdot\text{s}^{-1}$)	K (—)
Run 1	0.9	0.9	0.70	0.139
Run 2	3.0	3.0	0.73	0.145
Run 3	6.0	6.0	0.72	0.143

Reaction conditions

$(C_A)_0 = 3.0\times10^{-4}$ mol·cm^{-3}; volume of org. phase, 1cm^3. Aq. phase: KCl and KBr were dissolved in 2 cm^3 water. $m=5\times10^{-3}$ g·cm^{-3}. Test tube: No.1. React. temp.: 90°C.

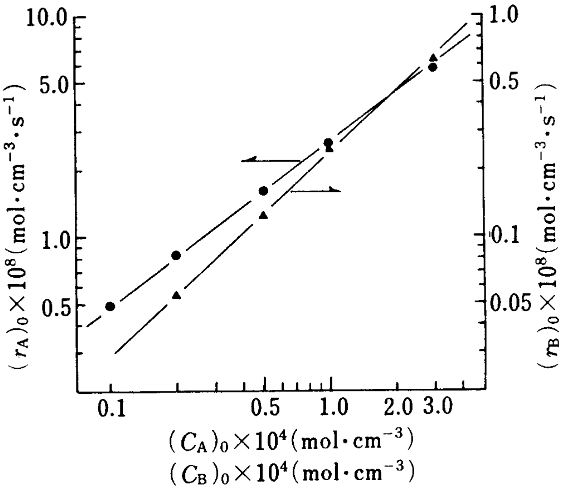


Fig. 4. Effect of Initial Concentration of Benzyl Bromide or Benzyl Chloride on Rate of Reaction

—●—, reaction of benzyl bromide with KCl; —▲—, reaction of benzyl chloride with KBr. Init. conc. of KCl or KBr: saturated. Volume: org. phase, 1 cm^3; aq. phase, 2 cm^3. $m=5\times10^{-3}$ g·cm^{-3}. Test tube: No. 1. React. temp.: 90°C.

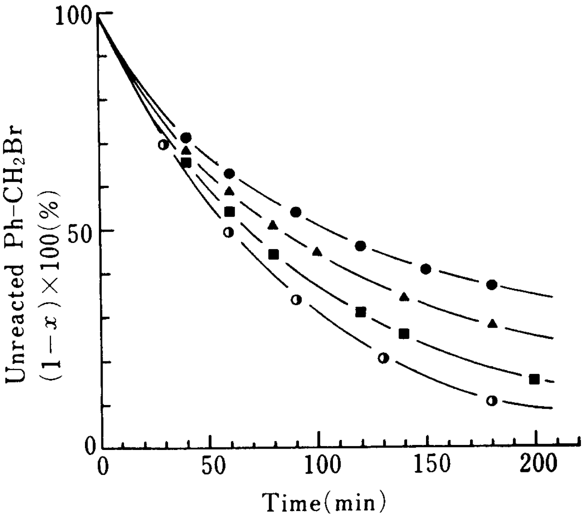


Fig. 5. Unreacted Benzyl Bromide *vs.* Time; Theoretical Curves and Experimental Data

$(C_A)_0=0.3\times10^{-3}$ mol·cm^{-3}; solvent, toluene; volume of org. phase, 1 cm^3. $m=5\times10^{-3}$ g·cm^{-3}. Test tube: No.1. React. temp.: 90°C.

Symbol	n	$(C_{Cl})_0\times10^3$ [mol·cm^{-3}]	Volume of aq. phase [cm^3]
●	3.0	1.8	0.5
▲	5.0	3.0	0.5
■	10.0	3.0	1.0
◐	24.0	3.6[a]	2.0

[a] Saturated solution.

especially at high conversion. Based on the obtained values of k_1, k_2, α, β, and K, equation (9) was numerically integrated. The calculated curves are shown in Fig. 5 for various values of n. These curves agree well with the experimental data, and therefore this model appears to be adequate for this reaction.

Conclusion

Under our experimental conditions, as long as the solid catalyst particles remain in contact with the liquid–liquid interface, the effects of mass transfer resistance are insignificant and all phosphonium groups bound to the polystyrene matrix are effective in the catalysis. From the kinetic analysis, it is concluded that the rate of this reaction is controlled by the displacement reaction of phosphonium salt on benzyl halide. Our experimental results are well interpreted by the rate equation (6).

If the step(ii) is a simple reaction, the observed orders with respect to benzyl bromide (0.73) and benzyl chloride (0.92) cannot be explained. We suppose that (i) the adsorption of organic reactant on the catalyst surface or (ii) its entrapment into the polymer matrix occurs with the formation of a relatively stable intermediate in step(ii). If this is the case, the observed rate order (0.73 or 0.92) could be well explained by a Langmuir–Hinshelwood or Michaelis–Menten type equation.

Since the mechanism of this reaction is not very clear as yet, further studies are planned with other reactants using various other related catalysts.

References and Notes

1) *a*) W.P. Weber and G.W. Gokel, "Phase Transfer Catalysis in Organic Synthesis," Springer-Verlag, N.Y., 1977; *b*) C.M. Starks and C. Liotta, "Phase Transfer Catalysis, Principles and Techniques," Academic Press, N.Y., 1978.
2) L. Lindblom and M. Elander, *Pharmaceutical Technology*, **1980**, 59.
3) S.L. Regen, *Angew. Chem. Int. Ed. Engl.*, **18**, 421 (1979).
4) S.L. Regen, *J. Am. Chem. Soc.*, **97**, 5956 (1975); *idem*, *ibid.*, **98**, 6270 (1976).
5) M. Cinouini, S. Colonna, H. Montanari, and P. Tundo, *J. Chem. Soc.*, *Chem. Commun.*, **1976**, 394.
6) S.L. Regen and J.J. Besse, *J. Am. Chem. Soc.*, **101**, 4059 (1979).
7) M. Tomoi and W.T. Ford, *J. Am. Chem. Soc.*, **102**, 7140 (1980).
8) *a*) S.L. Regen, *J. Org. Chem.*, **42**, 875 (1977); *b*) S.L. Regen, J.C.K. Heh, and J. McLick, *ibid.*, **44**, 1961 (1979); *c*) H. Molinari, F. Montanari, and P. Tundo, *J. Chem. Soc.*, *Chem. Commun.*, **1977**, 639; *d*) H. Molinari, F. Montanari, S. Quici, and P. Tundo, *J. Am. Chem. Soc.*, **101**, 3920 (1979); *e*) P. Tundo, *Synthesis*, **1978**, 315; *f*) M. Tomoi, T. Takubo, M. Ikeda, and H. Kakiuchi, *Chemistry Lett.*, **1976**, 473; g) M.S. Chiles, D.D. Jackson, and P.C. Reeves, *J. Org. Chem.*, **45**, 2915 (1980).
9) K. Okamoto, "Kyukaku-Chikanhanno S_N2 Hanno; Kouza Yuukihannokiko 3," ed. by M. Imoto, Tokyo-Kagakudozin, 1969, Chapters IV and VI.
10) D. Landini, A. Maia, and F. Montanari, *J. Am. Chem. Soc.*, **100**, 2796 (1978).
11) The catalyst loading is catalyst weight (g) per volume of organic phase (cm^3).
12) For the reaction conditions, see the typical procedure described in the experimental section.