Engineering Selectivity in Novel Synthesis of 3-(Phenylmethoxy)phenol from Resorcinol and Benzyl Chloride under Liquid–Liquid−Liquid Phase Transfer Catalysis

Ganapati D. Yadav* and Omprakash V. Badure

Department of Chemical Engineering, University Institute of Chemical Technology, University of Mumbai, Matunga, Mumbai - 400 019, India

Abstract:

Monobenzyl ether of resorcinol, namely, 3-(phenylmethoxy)phenol is used as an intermediate for the synthesis of various chemically and biologically active molecules. The synthesis of 3-(phenylmethoxy)phenol can be accomplished by using phase transfer catalysis (PTC), either as liquid–liquid (L−L) or solid–liquid (S−L) PTC. Creation of a third phase in a biphasic reaction leads to several advantages in this type of reaction. A catalyst rich middle phase is formed between the other two phases wherein the main reaction takes place in the liquid–liquid−liquid (L–L–L) PTC and this offers a number of advantages over L−L PTC in terms of intensification of rate, higher selectivity and the possibility to reuse the catalyst. It is an excellent way for waste reduction and improving profitability. The catalyst rich phase is recovered and reused to up to six times with little impact to reactivity. This also helps in waste minimization which is a major theme of Green Chemistry. In the current work, synthesis of 3-(phenylmethoxy)phenol was accomplished by the reaction of resorcinol with benzyl chloride using tetrabutylammonium bromide (TBAB) under liquid–liquid−liquid phase transfer catalysis (L−L−L PTC) at 90 °C. The studies cover the effects of various kinetic and process parameters which lead to enhancement in rates and selectivities. A theoretical model was developed and validated against experimental data. It follows zero-order kinetics in the mono-*O*-benzylation of resorcinol. There is 100% selectivity for 3-(phenylmethoxy)phenol with no discernible amount of bis-alkylated product detectable. *O*-Alkylation of hydroquinone and catechol were also studied using the same technique to realise the same high selectivity. The order of reactivity and apparent activation energy is as follows: hydroquinone > resorcinol> catechol.

1. Introduction

O-Alkylation of dihydroxybenzenes leads to mono- and dialkylated products which are highly valuable in the fine chemical and pharmaceutical industry. Catechol, resorcinol, and hydroquinone have been used to create a family of intermediates and fine chemicals though *C*- and *O*-alkylations, by using a variety of alkylating agent, both through acid catalysis and phase transfer catalysis (PTC). Monobenzyl ether of resorcinol, namely 3-(phenylmethoxy)phenol, for instance, is used as a precursor for the synthesis of various chemically and biologically active molecules. 3-(Phenylmethoxy)phenol is also used in the prepa-

ration of an intermediate for an oral bactericide drug.[1] Most of the routes for the manufacture of the 3-(phenylmethoxy)phenol involve reaction of resorcinol with benzyl chloride in presence of potassium carbonate.[2] Other synthetic routes include: (a) demethylation of the bis-methyl ether of resorcinol,[3] (b) hydrogenolysis of resorcinol dibenzyl ether using hydrogen and Pd/C acetic acid,[4] (c) reaction of benzyl bromide with 10-fold excess of resorcinol,[5] (d) using PEG as a multipurpose soluble polymer, monoprotection group and phase transfer catalyst,[6] and (e) Mitsunobu reaction of resorcinol monobenzoate and alcohol followed by hydrolysis using a strong base.[7] All of these methods give low yields of 3-(phenylmethoxy)phenol, and some methods require expensive and not readily available reagents. *O*-Alkylation can be most conveniently carried out by using phase transfer catalysis (PTC), and in the case of dihydroxy-benzenes, the reaction needs to be engineered to get only the monoether. In this paper, a very convenient method is reported to synthesize monobenzyl ether of resorcinol by using liquid–liquid−liquid (L−L−L) PTC, and also a mechanistic and kinetic analysis of the process is presented to generalize the findings for other dihydroxybenzenes.

PTC is now a text-book technique, which is practised in over 600 processes in different industries such as intermediates, dyestuffs, agrochemicals, perfumes, flavours, pharmaceuticals, and polymers.[8–11] A majority of PTC reactions are conducted under liquid–liquid (L−L) conditions. L−L PTC is also disadvantageous for systems where the presence of water can lead to side reactions, such as hydrolysis; for instance, when halides are used as alkylating agents it leads to byproduct formation such as alcohols and ethers. In order to suppress byproduct formation and also to intensify the rates, the biliquid PTC ought to be converted to triliquid PTC. In the case of

---

* Author to whom correspondence should be addressed. Telephone: 91-22-410 2121. Fax: 91-22-414-5614. E-mail: gdyadav@yahoo.com, gdyadav@udct.org.

(1) Wissner, A.; Carrol, M. L.; Green, K. E.; Kerwar, S. S. *J. Med. Chem.* **1992**, *35*, 1650.
(2) Fitton, A. O.; Ramage, G. R. *J. Chem. Soc.* **1962**, 4870.
(3) Karpov, O. N.; Fedosyuk, L. G. *Khim. Tekhnol.* **1976**, *3*, 59;*Chem. Abstr.* **1976**, *85*:159566r.
(4) Maleski, R. J.; Kluge, M.; Sicker, D. *Synth. Commun.* **1995**, *25*, 2327.
(5) Amabilino, D. B.; Ashton, P. R.; Boyd, S. E.; Gómez-López, M.; Hayes, W.; Stoddart, J. F. *J. Org. Chem.* **1997**, *62*, 3062.
(6) Yang, G.; Chen, Z.; Zhang, Z.; Qiu, X. *Synth. Commun.* **2002**, *3*, 3637.
(7) Boxhall, J. Y.; Page, P. C. B.; Chan, Y.; Hayman, C. M.; Heaney, H.; McGrath, M. J. *Synlett* **2003**, *7*, 997.
(8) Starks, C. M.; Liotta, C.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications and Perspectives*; Chapman and Hall: New York, 1994.
(9) Sasson, Y., Neumann, R., Eds. *Handbook of Phase Transfer Catalysis*; Blackie Academic and Professional: New York, 1997.
(10) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: New York, 1993.
(11) (a) Yadav, G. D. *Top. Catal.* **2004**, *29*, 145. (b) Yadav, G. D.; Naik, S. S. *Catal. Today* **2001**, *66*, 345.
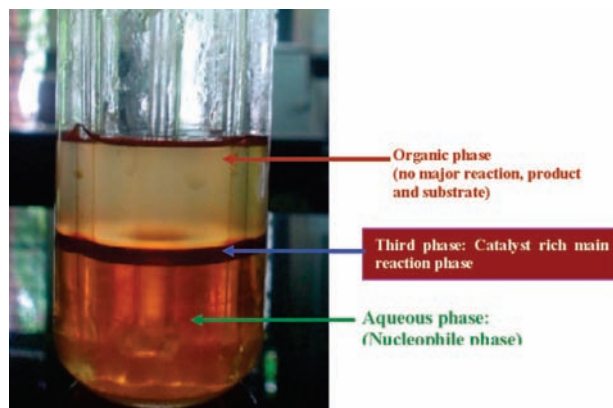
L−L−L PTC, the middle phase (or the so-called third phase) is the catalyst-rich phase, with two interfaces on either side, namely, (i) aqueous phase−middle phase, (ii) organic phase−middle phase, which prohibit direct contact of aqueous and organic phases. Therefore, there is no coextraction of water and the aqueous-phase promoted reactions are totally suppressed. Indeed, we have found in a number of reactions, not only the rates of reaction but also the selectivity can be enhanced dramatically thereby reducing reaction times; reactor volumes and separation costs.[11−19] Besides, the catalyst phase can be recycled along with the aqueous phase to reuse the catalyst, which leads to waste minimization, one of the tenets of Green Chemistry. The third liquid phase is the main reaction phase and, the recovery and reuse of the catalyst is easier since it forms an immiscible middle liquid phase.[11−23] The current work addresses L−L−L PTC catalyzed monobenzylation of resorcinol with benzyl chloride to produce 3-(phenylmethoxy)phenol. The mono-*O*-benzylation of catechol and hydroquinone was also studied since the corresponding products are also important in fine chemical and pharmaceutical industry.

2. Experimental Section

2.1. Materials. Benzyl chloride, toluene, resorcinol, catechol, hydroquinone, potassium hydroxide, potassium chloride, 3-(phenylmethoxy)phenol of AR grade were obtained from M/S s.d. Fine Chem. Pvt. Ltd. Mumbai, India. Tetrabutylammonium bromide (TBAB) of pure grade was obtained as a gift sample from M/s Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India. All other chemicals were A.R. grade procured from reputed firms.

2.2. Experimental Procedure. The reaction was studied in a 5 cm. i.d. fully baffled mechanically agitated glass reactor of 100 cm^3 total capacity which was equipped with four baffles and a six-bladed turbine impeller and a reflux condenser. The stirrer was centrally located, and the dimensions of the impeller were as follows: Disc turbine impeller of 1.7 cm o.d., made of s.s. 316, located at a distance of 0.9 cm from the bottom. The entire reactor assembly was immersed in a thermostatic water bath, which was maintained at the desired temperature with an accuracy of ±1 °C. The reaction mixture was agitated mechanically with the help of an electric motor. Typical L−L−L PTC runs were conducted by taking 0.04 mol resorcinol, 0.02 mol potassium hydroxide, 0.13 mol of potassium chloride, and 0.0062 mol TBAB in 30 cm^3 of water. This ensured that the formation of the third liquid phase took place at room temperature and also at reaction temperature (Figure 1). The organic phase was composed of 0.02 mol benzyl chloride which was made up to 30 cm^3 toluene. All the typical runs were carried

Figure 1. Photograph of the L−L−L PTC Reactor. The stirrer is stationary.

Organic phase (no major reaction, product and substrate)

Third phase: Catalyst rich main reaction phase

Aqueous phase: (Nucleophile phase)

out at 90 °C and 1000 rpm for which the reactions were intrinsically kinetically controlled, which will be discussed later. L−L PTC reactions were also conducted at a catalyst concentration a little lower than the critical concentration which formed the third phase.

2.3. Method of Analysis. Samples of the organic phase were withdrawn periodically and analysed by gas chromatography on a Chemito 8510 model. A 2 m × 3.18 mm internal diameter stainless steel column packed with 10% SE-30 on chromosorb WHP was used for analysis in conjunction with a flame ionization detector. The conversion was based on the disappearance of benzyl chloride in the organic phase. Synthetic mixtures of pure components and possible products were made and used to quantify the data. Under three liquid phases, only 3-(phenylmethoxy)phenol was produced. The product was confirmed by GC−MS and also by product isolation and purification.

2.4. Determination of the Composition of the Third Phase. The composition of the third phase was analyzed on gas phase chromatography by using a thermal conductivity detector with a stainless steel column (3.25 mm × 2 m) packed with a liquid stationary phase of 10% SE-30. A Karl Fischer apparatus was used to analyze the amount of water present in the third phase. The third phase contains 14.87% toluene, 22.56% TBAB, 0.89% benzyl chloride, 20.79% resorcinol, 1.24−3% (phenylmethoxy)phenol, 39.65% water. In a typical experiment, the third-phase volume was 7.0 mL.

2.5. Reaction Scheme. The overall reaction is shown in Scheme 1 for dihydroxybenznes. Resorcinol reacts with benzyl chloride in the presence of the phase transfer catalysis to give selectively 3-(phenylmethoxy)phenol in triliquid PTC. When dihydroxybenzene is taken as a limiting reactant with reference to KOH and benzyl chloride, byproduct formation is significant due to a series (consecutive) reaction of dihydroxybezene and a parallel reaction of benzyl chloride as shown in Scheme 1, particularly in L−L PTC.

3. Results and Discussion

Figure 1 shows the photograph of the reactor with three distinct liquid phases. The photograph was taken without any agitation at the reaction temperature. These phases were stable under experimental conditions, and only the desired monoalkylated product was formed. Scheme 2 depicts the mechanism of

(12) Yadav, G. D.; Reddy, C. A. *Ind. Eng. Chem. Res.* **1999**, *38*, 2245.
(13) Yadav, G. D.; Jadhav, Y. B. *Clean Technol. Environ. Policy* **2003**, *6*, 32.
(14) Yadav, G. D.; Bisht, P. M. *J. Mol. Catal. A: Chem.* **2004**, *223*, 93.
(15) Yadav, G. D.; Lande, S. V. *Appl. Catal., A* **2005**, *287* (2), 267.
(16) Yadav, G. D.; Lande, S. V. *Adv. Synth. Catal.* **2005**, *347* (9), 1235.
(17) Yadav, G. D.; Desai, N. M. *Org. Process. Rec. Dev.* **2005**, *9*, 749.
(18) Yadav, G. D.; Desai, N. M. *Catal. Commun.* **2006**, *7*, 325.
(19) Wang, D. H.; Weng, H. S. *Chem. Eng. Sci.* **1988**, *43*, 2019.
(20) Wang, D. H.; Weng, H. S. *Chem. Eng. Sci.* **1995**, *50*, 3477.
(21) Neumann, R.; Sasson, Y. *J. Org. Chem.* **1984**, *49*, 3448.
(22) Masson, D.; Magdassi, S.; Sasson, Y. J. *Org. Chem.* **1991**, *56*, 7229.
(23) Huang, C. C.; Yang, H. M. *Appl. Catal., A* **2005**, *290*, 65.

Scheme 1. *O*-Alkylation of dihydroxybenzene with benzyl chloride; complex reaction network consisting of two parallel reactions of benzyl chloride and a consecutive reaction of dihydroxybenzene; L−L−L allows only one reaction (b) to give the desired product; L−L also leads to byproduct formation

Mono-O-benzylated product [1]

Mono-O-benzylated product [1]   Di-O-benzylated byproduct [3]
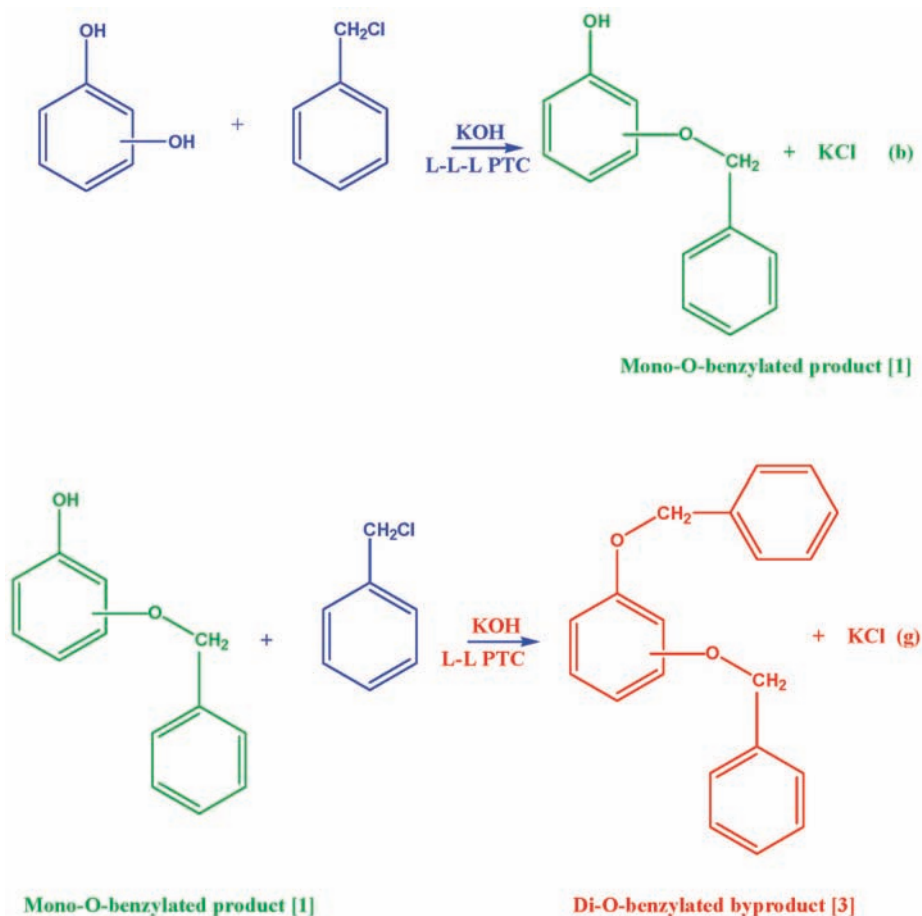
Scheme 2. Mechanism of L−L−L PTC mono-*O*-benzylation of resorcinol with benzyl chloride
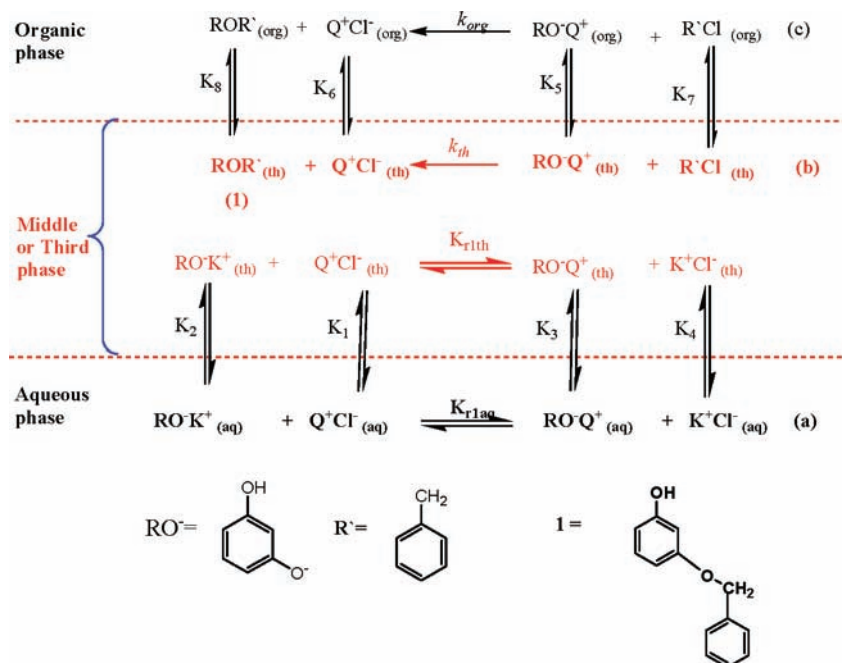
the L−L−L PTC. It shows the various reactions taking place in different phases and the products getting transferred across the two interfaces. The locale of the rate-controlling reaction (reaction b) is the middle phase, and no side reactions occur here because benzyl chloride is not allowed to transfer to the aqueous third-phase interface. Scheme 3 depicts the L−L PTC mechanism and shows why there are byproducts in the biphasic system where the rate-controlling reaction takes place in the

Scheme 3. Mechanism of L−L PTC alkylation of resorcinol with benzyl chloride
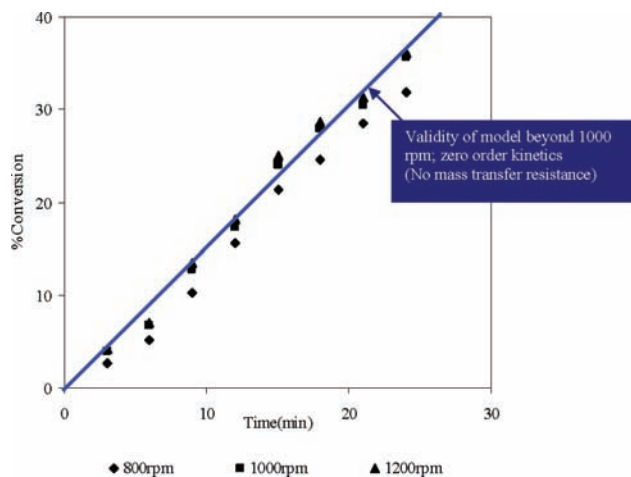
Organic phase

$$RO^{-}Q^{+}{}_{(org)} + R'Cl_{(org)} \xrightarrow{k_{rorg}} ROR'_{(org)} + Q^{+}Cl^{-}{}_{(org)} \quad \text{(desired reaction) (b)}$$
$$[1]$$

$$R^{1}OR'O^{-}Q^{+}{}_{(org)} + R'Cl^{-}{}_{(org)} \longrightarrow R^{1}OR'OR'_{(org)} + Q^{+}Cl^{-}{}_{(org)} \text{(g)}$$
$$[3]$$

$$R'OH_{(org)} + RO^{-}Q^{+}{}_{(org)} \longrightarrow R^{1}OR'O^{-}Q^{+}{}_{(org)} + H_2O_{(org)} \quad \text{(f)}$$

$$R'O^{-}Q^{+}{}_{(org)} + R'Cl_{(org)} \longrightarrow R'OR'_{(org)} + Q^{+}Cl^{-}{}_{(org)} \quad \text{(e)}$$
$$[4]$$

Interfacial region

$$Q^{+}OH^{-}{}_{(int)} + R'OH_{(int)} \rightleftharpoons R'O^{-}Q^{+}{}_{(int)} + H_2O_{(int)}$$

$$Q^{+}OH^{-}(int) + R'Cl_{(int)} \longrightarrow R'OH_{(int)} + Q^{+}Cl^{-}{}_{(int)} \quad \text{(d)}$$
$$[2]$$

Aqueous phase

$$Q^{+}OH^{-}(aq) + Cl^{-} \rightleftharpoons OH^{-}{}_{(aq)} + Q^{+}Cl^{-}{}_{(aq)} \quad \text{(c)}$$

$$RO^{-}Q^{+}{}_{(aq)} + K^{+}Cl^{-}{}_{(aq)} \xrightleftharpoons{K_{a\text{-}aq}} RO^{-}K^{+}{}_{(aq)} + Q^{+}Cl^{-}{}_{(aq)} \quad \text{(a)}$$

Products of reaction

Main product :
[1]= 3-(phenylmethoxy) phenol

Byproducts :
[2]=benzyl alcohol
[3]= 3-(phenylmethoxy)benzyl ether
[4]= dibenzyl ether

organic phase (reaction b). The formation of the $Q^{+}OH^{-}$ ion-pair due to ion exchange (reaction c in Scheme 3) near the interface influences the selectivity. This ion-pair has a very limited partitioning into the organic phase; hence, benzyl chloride is hydrolyzed to benzyl alcohol at the interfacial region (reaction d) and subsequently a series of reactions take place such as e, f, and g (in that order). As a result, byproducts are formed which are benzyl alcohol **[2]**, 3-(phenylmethoxy)benzyl ether **[3]**, and dibenzyl ether **[4],** apart from some C-alkylated products. Particularly when resorcinol was used as a limiting reactant with a little excess of KOH and BzCl in the L−L PTC, all byproducts were formed in the current work. When the moles of KOH and BzCl were taken equivalent to, or less than, half of resorcinol, the byproduct formation was reduced in L−L PTC. No byproduct was formed, when the L−L PTC system was converted into a L−L−L PTC. The comparison of Schemes 2 and 3 also reveals why there is 100% selectivity in L−L−L PTC, whereas the selectivity to 3-phenylmethoxy phenol was 80% in L−L PTC.

3.1. Effect of Speed of Agitation. To ascertain the influence of mass transfer resistance for the transfer of reactants to the reaction phase and products into the organic phase, the speed of agitation was varied from 800 to 1200 rpm under otherwise similar conditions, with TBAB as the catalyst, at 90 °C (Figure 2). Experiments were also done at 500 rpm to find that there was a reduction in conversion (23% after 25 min), but there was no change in selectivity. The conversion was found to be nearly the same within experimental errors as that at 1000 and 1200 rpm. Further increase in the speed of agitation had practically no effect on the conversion. So there was no mass transfer resistance, and all further experiments were conducted at 1000 rpm. A typical analysis was done for mass transfer rates and overall reaction rates by using theoretical correlations on overall mass transfer coefficients; also to reiterate, there were

no mass transfer effects at and beyond 1000 rpm. Thus, further experiments were carried out at 1000 rpm. The inspection of the data suggested that the conversions were linear with the time, suggesting a zero-order kinetics. As will be discussed later, the effect of temperature on rates of reaction also showed that the activation energy was much greater (i.e., 15.52 kcal/mol) than a typical value, which is realized for mass transfer controlled reaction (i.e., 4 kcal/mol). The reaction was intrinsically kinetically controlled, and hence, the reaction mechanism and kinetic model could be developed and tested through the effects of various parameters.

3.2. Mechanism and Kinetic Model. The reaction mechanism for L−L−L PTC system is shown in Scheme 2. Since

**Figure 2.** Effect of speed of agitation on conversion of benzyl chloride - 0.02 mol; organic phase made up to 30 cm³ with toluene. Resorcinol - 0.04 mol. TBAB - 6.21 × 10⁻³ mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Temperature - 90 °C.

the selectivity to 3-(phenylmethoxy)phenol (R′OR) [1] was 100%, the mechanism depicted here is straightforward. Here

$$RO^- = $$

(structure: benzene ring with OH at top and O⁻ substituent)
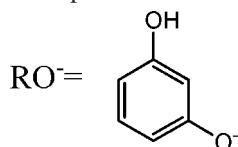
The potassium 3-hydroxyphenoxide ion-pair (RO⁻K⁺) generated in situ in the aqueous phase is equivalent to moles of KOH, and the anion exchange takes place between the quaternary salt (Q⁺Cl⁻) and RO⁻K⁺ in the aqueous phase to form an ion-pair (RO⁻Q⁺) (reaction a in Scheme 2), which is then transferred into the third liquid phase (or the middle phase, which is referred to as the third phase for the sake of consistency). All the species involved have equilibrium concentrations. The substrate benzyl chloride R′Cl is transferred from the organic phase to the third phase, where the subsequent reaction occurs between RO⁻Q⁺ and R′Cl to produce the desired product, R′OR [1] (reaction b in Scheme 2), which is transferred to the organic phase.

Thus, the overall reaction is:

$$KOR_{(aq)} + R'Cl_{(org)} \xrightarrow{L-L-L\ PTC} R'OR_{(org)} + KCl_{(aq)}$$

(1)
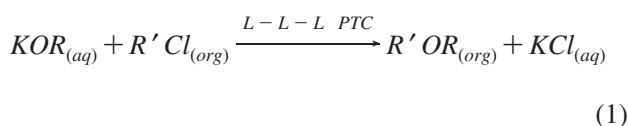
The rate equation is derived as given in the Appendix. (Equation 27) becomes

$$\frac{dX}{dt} = k_{app}(1-X)N_{Qtot}$$

(29)

where X is the fractional conversion of R′Cl (benzyl chloride), k_{app} is the apparent rate constant for the third phase reaction, and N_{Qtot} is the total moles of catalyst added to the reaction mass. When the third phase was saturated with R′Cl for the conditions employed in these studies, it was observed that the conversions were linear in time. Thus, from eq 10, by following the above procedure, the rate of change of fractional conversion is given by:

$$\frac{dX}{dt} = \frac{k_0 N_{Qtot}}{N_{R'Cl0}} = k'_0 = \text{constant}$$

(30)

Integrating eq 30 leads to:

$$X_A = X = k'_0 N_{Qtot} t$$

(31)

Thus, conversion of R′Cl is linear in time with apparent zero-order reaction.

When the concentrations of KOH and benzyl chloride are taken in stoichiometrically excess over 0.5 mol of resorcinol, the second hydroxyl group is also converted; then by integrating eq 29 it leads to

$$-\ln(1-X) = k_{app}N_{Qtot} t$$

(32)

The above theory was tested by conducting further experiments.
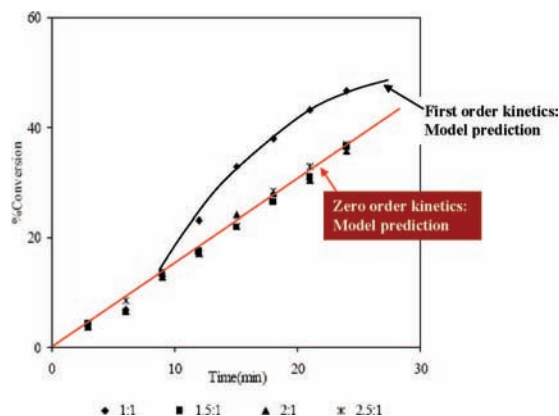
Figure 3. Effect of resorcinol:KOH mole ratio on conversion of benzyl chloride. Mole ratio: resorcinol:KOH, resorcinol:BzCl 2:1. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. TBAB - 6.21 × 10⁻³ mol. KCl - 0.13 mol. Aqueous phase made up to 30 cm³ with water. Speed of agitation - 1000 rpm. Temperature - 90 °C.
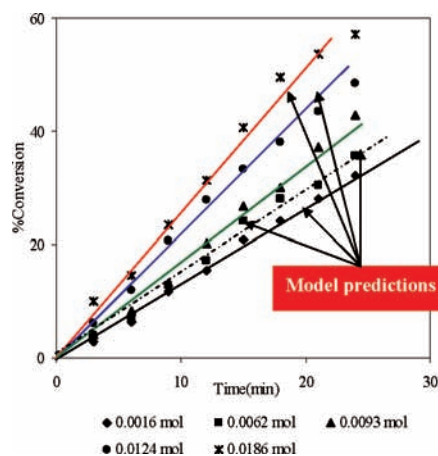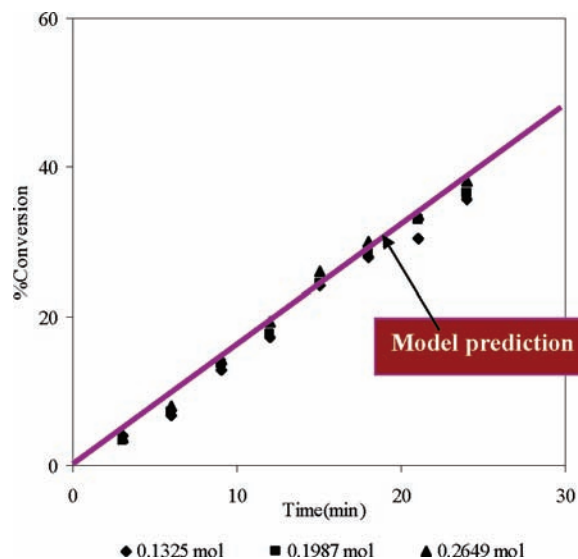

Figure 4. Effect of catalyst loading on conversion of benzyl chloride. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. Resorcinol - 0.04 mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Temperature - 90 °C. Agitation speed - 1000 rpm

3.3. Effect of Mole Ratio of Resorcinol to KOH. The amount of resorcinol was varied from 0.02 to 0.05 mol, which corresponds to a mole ratio of 1 to 2.5 of resorcinol to potassium hydroxide by keeping the amount of potassium hydroxide constant. Increasing the concentration of resorcinol increases the selectivity of monobenzylated product (Figure 3). Inspection of Figure 3 shows that the conversions are linear in time only when the mole ratio of resorcinol to KOH was above 1:1.5, thereby showing a zero-order reaction. At a mole ratio of 1:1, there is no zero-order dependence; the reaction follows a first-order dependence as given by eq 32, and there was a formation of the byproducts. After 0.04 mol of resorcinol there is no increase in the selectivity under otherwise similar conditions. Therefore, 0.04 mol of resorcinol was taken as the optimum quantity for further experiments. The selectivity to 3-(phenylmethoxy)phenol was 100%.

3.4. Effect of Catalyst Loading. The catalyst amount was varied from 1.6 × 10⁻³ mol to18.6 × 10⁻³ mol under otherwise similar conditions. It was observed that the formation of the third phase takes place only after a certain critical amount of catalyst was added to the reaction mixture. In the present case,
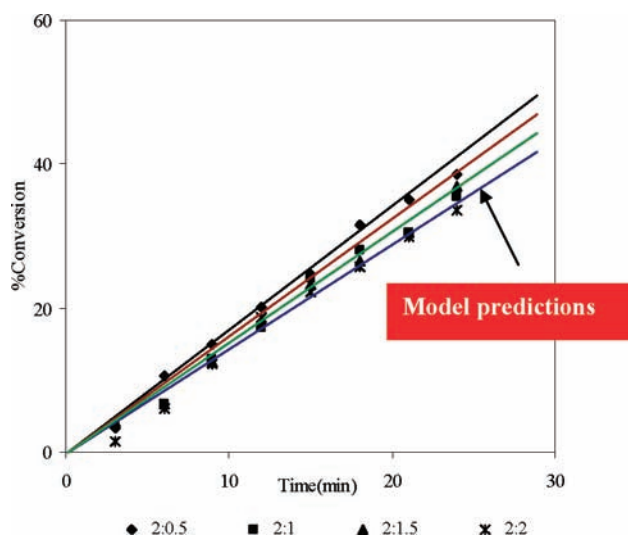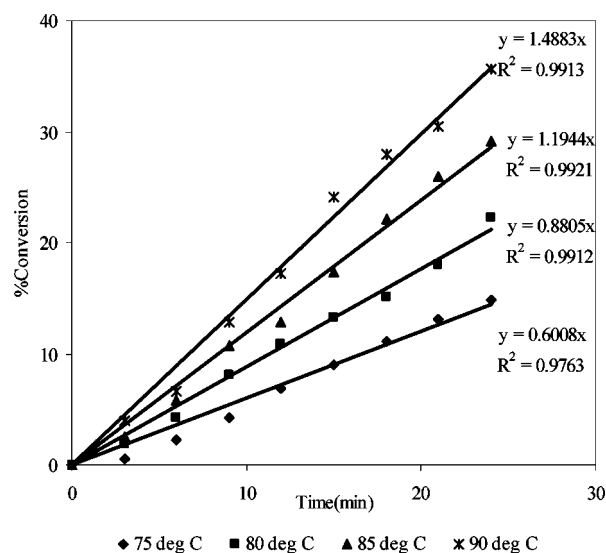
Figure 5. Effect of resorcinol:benzyl chloride mole ratio on conversion of benzyl chloride. Mole ratio - resorcinol:BzCl. Resorcinol:KOH - 2:1. Organic phase made up to 30 cm³ with toluene. TBAB - 6.21×10^{-3} mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Speed of agitation - 1000 rpm. Temperature - 90 °C.


Figure 6. Effect of potassium chloride on conversion of benzyl chloride. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. Resorcinol - 0.04 mol. TBAB - 6.21×10^{-3} mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. Speed of agitation - 1000 rpm. Temperature - 90 °C.

the formation of the third phase takes place at the catalyst concentration of 6.2×10^{-3} mol TBAB. At any amount of catalyst below this value, the third phase disappears, and the system becomes L−L PTC system. Figure 4 shows the percentage conversion as a function of time at different catalyst amounts. It was observed that at amounts less than 1.6×10^{-3} mol, the third phase rich in catalyst was not formed. Only at higher amounts of catalyst, i.e. at and beyond 1.6×10^{-3} mol, was the third phase formation observed. When the catalyst amount increased from 6.2×10^{-3} to 18.6×10^{-3} mol, the rate of reaction increased substantially. The conversions were linear with time at all catalyst loadings as predicted by the model (see Figure 4).
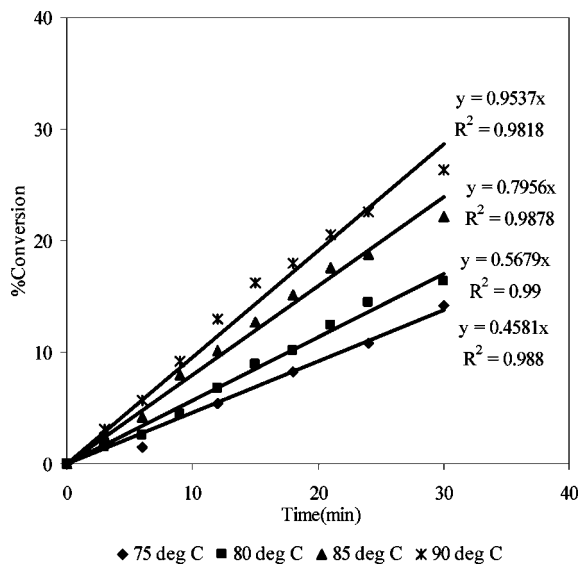
Figure 7. Effect of temperature on conversion of benzyl chloride for monobenzylation of resorcinol. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. TBAB - 6.21×10^{-3} mol. Resorcinol - 0.04 mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Agitation speed - 1000 rpm.
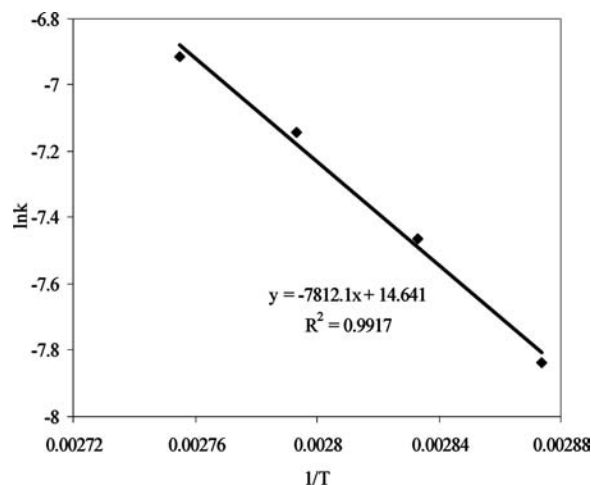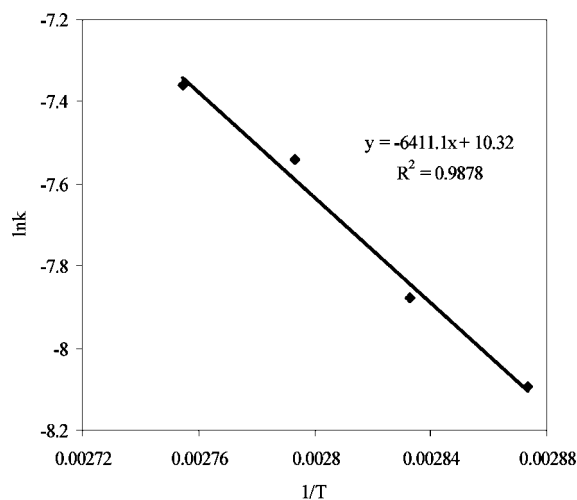

Figure 8. Arrhenius plot for monobenzylation of resorcinol.

3.5. Effect of Concentration Benzyl Chloride as a Limiting Reactant. The effect of the mole ratio of benzyl chloride to resorcinol (with a resorcinol to KOH mole ratio of 2:1) was studied from 0.5:2 to 2:2. The conversion was found to decrease with increasing mole ratio up to 1:2 (Figure 5). The rate constant k'_0 contains the term $N_{R'Clo}$, and thus, the constant k_0 is calculated from the slopes of the lines in Figure 5 to get an average value by the fit within 98% correlation coefficient.

3.6. Effect of Potassium Chloride Concentration. The amount of potassium chloride was varied from 0.13 to 0.26 mol under similar reaction conditions (Figure 6). The role of KCl is to salt out the catalyst along with the nucleophile in the form of the RO^-Q^+ ion-pair from the aqueous phase into the third phase as well as to increase the rate of aqueous phase ion-exchange reaction, which leads to equilibrium. As the concentration of potassium chloride was increased from 0.13 mol, no significant increase in the rate of reaction was observed, and almost constant conversions were obtained as is seen in Figure 6. This is because there was no further increase in the

Figure 9. Effect of temperature on conversion of benzyl chloride for monobenzylation of catechol. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. TBAB - 6.21 × 10³ mol. Catechol - 0.04 mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Agitation speed - 1000 rpm.
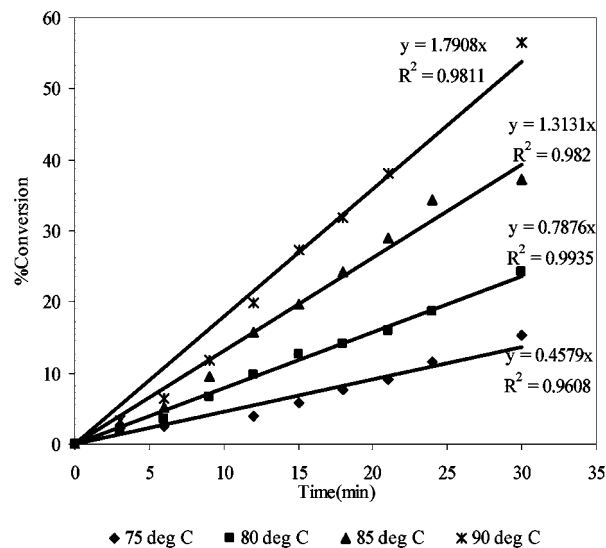

Figure 11. Effect of temperature on conversion of benzyl chloride for monobenzylation of hydroquinone. Benzyl chloride - 0.02 mol. Organic phase made up to 30 cm³ with toluene. TBAB - 6.21 × 10–3 mol. Hydroquinone - 0.04 mol. KOH - 0.02 mol. Aqueous phase made up to 30 cm³ with water. KCl - 0.13 mol. Agitation speed - 1000 rpm.

Figure 10. Arrhenius plot for monobenzylation of catechol.

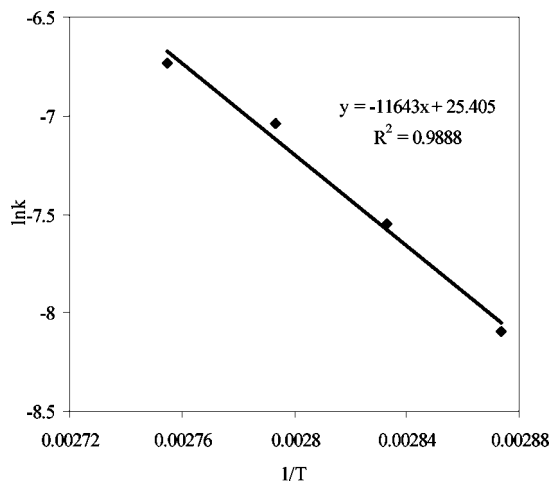**Figure 12.** Arrhenius plot for monobenzylation of hydroquinone.

catalyst concentration in the middle phase. Addition of KCl beyond the saturation concentration has no significant effect on the rate of reaction because it forms an additional solid phase.

3.7. Effect of Temperature. The effect of temperature on the rate of reaction between resorcinol and benzyl chloride was studied under otherwise similar conditions. The temperature was varied from 75 to 90 °C. The conversion of benzyl chloride was observed to increase with an increase in the reaction temperature. The effect of temperature on the conversion of benzyl chloride is given in Figure 7. The conversions were linear with time at all temperatures. These observations show that the reaction is zero order in substrate concentration and the model is validated at different temperatures. The Arrhenius plot was made to determine the energy of activation (Figure 8). The energy of activation has been found to be 15.52 ± 0.1 kcal/mol.

3.8. Effect of Different Dihydroxybenzene Isomers. Reactions of hydroquinone and catechol with benzyl chloride were studied under identical conditions by using TBAB as a catalyst. The effect of temperature on the rate of reaction of benzyl chloride was studied in the range of 75−90 °C. The conversion of benzyl chloride was observed to increase with an increase in the reaction temperature. Once again it was observed that the reaction followed zero-order kinetics. Catechol was found to be more reactive and hydroquinone was found to be less reactive towards benzyl chloride. The effect of temperature on the conversion of benzyl chloride is given in Figure 9 for catechol with the corresponding Arrhenius plot in Figure 10. Similar plots are also made for hydroquinone (Figure 11 and Figure 12, respectively). The energy of activation has been found to be 12.74 ± 0.1 kcal/mol and 23.13 ± 0.1 kcal/mol for catechol and hydroquinone, respectively. Activation energy for the monobenzylation of catechol was found to be lower than that for monobenzylation of resorcinol and hydroquinone. The reactivity of dihydroxybenzenes as well as activation energy is in the following order:

Hydroquinone> resorcinol > catechol

3.9. Catalyst Reusability. The catalyst-rich phase along with the aqueous phase was used six times in which the organic phase along with the solvent was replenished with benzyl chloride. The reaction mass was cooled to lower temperatures (<15 °C) while maintaining the three phases, and the organic phase was recovered and processed to get the product. The middle phase and the aqueous phase were reused. The purpose of using the aqueous phase was to use the catalyst distributed in the aqueous phase using the conditions of the control experiment. The merits of such a strategy are discussed elsewhere.[17] The selectivity to the product 3-(phenylmethoxy)phenol was 100% in all cases. There was a marginal decrease in conversion (5%) from the first use to the sixth use. This is reasonable.

4. Conclusion

3-(Phenylmethoxy)phenol is used in the preparation of a drug intermediate used in the inhibition of oral bacteria. This reaction can be accomplished by L−L−L PTC instead of L−L or S−L PTC. The synthesis of this compound was done under L−L−L PTC by using resorcinol and benzyl chloride. The best results were obtained by employing 0.02 mol of each benzyl chloride and potassium hydroxide, 0.04 mol of resorcinol, and 0.0062 mol of TBAB. A theoretical model has been proposed and validated against experimental data. The reaction follows zero-order kinetics. The studies were also extended to catechol and hydroquinone for monobenzylation.

Creation of a third phase from the two-phase reaction leads to several advantages in PTC. A catalyst-rich third phase or the middle phase is formed between other two phases, wherein the main reaction takes place, and it intensifies the rates of reaction as well as offers better selectivity including catalyst reusability unlike the L−L PTC. L−L−L PTC is an excellent technique for reducing waste, reactor volume, and processing time, and thus increasing profitability. The catalyst-rich phase is recovered and reused to some extent. This also helps in waste minimization which is a major theme of green chemistry. The reactivity of dihydroxybenzenes with benzyl chloride for the mono-*O*-alkylation as well as activation energy is in the following order:

Hydroquinone > resorcinol > catechol

Appendix
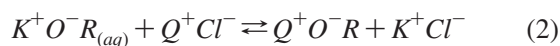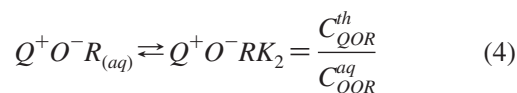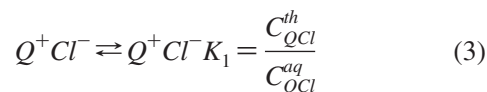### Derivation of Kinetic Equation

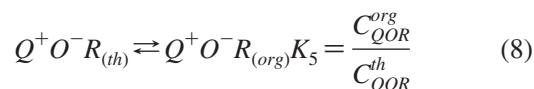The steps involved in the overall reaction 1 are as follows:
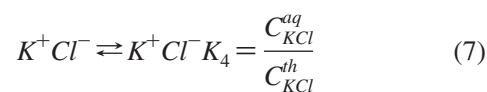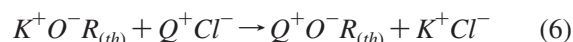
1. Ion-exchange reaction of K^+O^-R and Q^+Cl^- in the aqueous phase to form the ion-pair with the nucleophile Q^+O^-R:

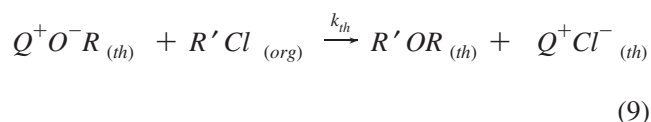$$K^+O^-R_{(aq)} + Q^+Cl^- \rightleftharpoons Q^+O^-R + K^+Cl^- \quad (2)$$

2. Mass transfer of Q^+Cl^-, K^+O^-R and Q^+O^-R from the aqueous phase into the third liquid phase with equilibrium constants K_1, K_2, and K_3 respectively:

$$Q^+Cl^- \rightleftharpoons Q^+Cl^- \quad K_1 = \frac{C_{QCl}^{th}}{C_{QCl}^{aq}} \quad (3)$$

$$Q^+O^-R_{(aq)} \rightleftharpoons Q^+O^-R \quad K_2 = \frac{C_{QOR}^{th}}{C_{QOR}^{aq}} \quad (4)$$

$$K_3 = \frac{C_{KOR}^{th}}{C_{KOR}^{aq}} \quad (5)$$

3. Ion-exchange reaction of K^+O^-R and Q^+Cl^- can also take place in the third liquid phase to form catalytic intermediate Q^+O^-R and K^+Cl^-, transferring into aqueous phase with equilibrium constants K_4 and K_5 respectively:

$$K^+O^-R_{(th)} + Q^+Cl^- \rightarrow Q^+O^-R_{(th)} + K^+Cl^- \quad (6)$$

$$K^+Cl^- \rightleftharpoons K^+Cl^- \quad K_4 = \frac{C_{KCl}^{aq}}{C_{KCl}^{th}} \quad (7)$$

$$Q^+O^-R_{(th)} \rightleftharpoons Q^+O^-R_{(org)} \quad K_5 = \frac{C_{QOR}^{org}}{C_{QOR}^{th}} \quad (8)$$

4. Reaction of Q^+O^-R with R′Cl in the third liquid phase:

$$Q^+O^-R_{(th)} + R'Cl_{(org)} \xrightarrow{k_{th}} R'OR_{(th)} + Q^+Cl^-_{(th)} \quad (9)$$

There is a very insignificant contribution by the reaction in organic phase, although it is shown in Scheme 2 for the sake of clarity and for comparison with an L−L PTC process. The critical analysis of rate data suggested that the conversions of benzyl chloride were linear in time, suggesting zero-order reaction.

The rate of formation of R′OR can be written from eq 9. At the same time, the stoichiometry suggests that for every one mole of R′Cl, one mole of product R′OR is formed. Here,
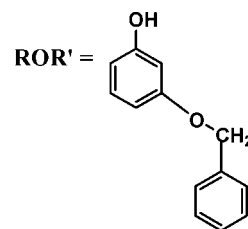
Thus, the rate of formation of the product per unit volume of the third phase is given by:

$$\frac{dC_{R'OR}^{th}}{dt} = k_{th}C_{QOR}^{th}C_{R'Cl}^{th} \quad (10)$$

Further $K_7 = \dfrac{C_{R'Cl}^{th}}{C_{R'Cl}^{org}}$ and $K_8 = \dfrac{C_{R'OR}^{th}}{C_{R'OR}^{org}}$ (11)

The fractional conversion of R'Cl is given by:

$$X = \frac{N_{R'Cl0} - N_{R'Cl}}{N_{R'Cl0}} \quad (12)$$

where 0 denotes the zero time or initial condition.

The rate of formation of R'OR in mol/time is equal to that of reaction of R'Cl as shown below.

$$\frac{dN_{R'OR}}{dt} = V^{th}\frac{dC_{R'OR}^{th}}{dt} = V^{th}k_{th}C_{QOR}^{th}C_{R'Cl}^{th} = \frac{-dN_{R'Cl}}{dt} \quad (13)$$

$$\frac{-dN_{R'Cl}}{dt} = V^{th}k_{th}C_{QOR}^{th}K_7C_{R'Cl}^{org} \quad (14)$$

The volumes of the aqueous, third, and organic phases are given by V^{aq}, V^{th}, and V^{org}, respectively. The total number of moles of R' Cl at any time are distributed between the organic and third phase and none in the aqueous phase:

$$N_{R'Cl} = N_{R'Cl}^{th} + N_{R'Cl}^{org} \quad (15)$$

$$K_7 = \frac{C_{R'Cl}^{th}}{C_{R'Cl}^{org}} = \frac{N_{R'Cl}^{th}V^{org}}{N_{R'Cl}^{org}V^{th}} \quad (16)$$

therefore, the following can be derived:

$$C_{R'Cl}^{org} = \frac{N_{R'Cl}}{(V^{org} + K_7V^{th})} \quad (17)$$

$$\frac{-dN_{R'Cl}}{dt} = \frac{V^{th}k_{th}K_7C_{QOR}^{th}N_{R'Cl}}{(V^{org} + K_7V^{th})} = \frac{k_{th}K_7N_{QOR}^{th}N_{R'Cl}}{(V^{org} + K_7V^{th})} \quad (18)$$

Taking mass balance for the catalyst (N_{Qtot}, the total moles added initially) which is distributed in six different species in the three phases:

$$N_{Qtot} = V^{aq}(C_{QOR}^{aq} + C_{QCl}^{aq}) + V^{th}(C_{QOR}^{th} + C_{QCl}^{th}) + V^{org}(C_{QOR}^{org} + C_{QCl}^{org}) \quad (19)$$

As stated earlier, the contribution of the organic phase reaction is negligible since the amount of Q in the organic phase is negligible, and thus eq 20 becomes:

$$N_{Qtot} = V^{aq}(C_{QOR}^{aq} + C_{QCl}^{aq}) + V^{th}(C_{QOR}^{th} + C_{QCl}^{th}) \quad (20)$$

Let the amount of catalyst in the third phase be denoted by

$$C_Q^{th} = C_{QOR}^{th} + C_{QCl}^{th} \quad (21)$$

$$C_{QOR}^{th} = \eta C_Q^{th} \quad (22)$$

In eq 23, η is the molar ratio of Q^+ in the form of QOR at any time in the third-phase.

Substituting eqs 3, 4, and 23 into eq 21, the following is obtained.

$$N_{Qtot} = \left[\left(\frac{1}{K_2} + \frac{V^{th}}{V^{aq}}\right) + \left(\frac{1}{K_1} + \frac{V^{th}}{V^{aq}}\right)\left(\frac{1-\eta}{\eta}\right)\right]C_{QOR}^{th}V^{aq} \quad (23)$$

$$C_{QOR}^{th} = \frac{N_{QOR}^{th}}{V^{th}} = \frac{\dfrac{N_{Qtot}}{V^{aq}}}{\left[\left(\dfrac{1}{K_2} + \dfrac{V^{th}}{V^{aq}}\right) + \left(\dfrac{1}{K_1} + \dfrac{V^{th}}{V^{aq}}\right)\left(\dfrac{1-\eta}{\eta}\right)\right]} \quad (24)$$

$$\frac{-dN}{dt} = \frac{k_{th}K_7N_{QOR}^{th}N_{R'Cl}}{(V^{org} + K_7V^{th})} = \frac{k_{th}K_7N_{R'Cl}}{(V^{org} + K_7V^{th})} \times$$
$$\left(\frac{\dfrac{N_{Qtot}V^{th}}{V^{aq}}}{\left[\left(\dfrac{1}{K_2} + \dfrac{V^{th}}{V^{aq}}\right) + \left(\dfrac{1}{K_1} + \dfrac{V^{th}}{V^{aq}}\right)\left(\dfrac{1-\eta}{\eta}\right)\right]}\right) \quad (25)$$

$$\frac{-dN_{R'Cl}}{dt} = \frac{k_{th}K_7N_{QOR}^{th}N_{R'Cl}}{(V^{org} + K_7V^{th})} =$$
$$\frac{\alpha k_{th}K_7N_{R'Cl}N_{Qtot}}{V^{org}(1 + K_7\beta)\left[\left(\dfrac{1}{K_2} + \alpha\right) + \left(\dfrac{1}{K_1} + \alpha\right)\left(\dfrac{1-\eta}{\eta}\right)\right]} \quad (26)$$

$$\alpha = \frac{V^{th}}{V^{aq}} \qquad \text{and} \qquad \beta = \frac{V^{th}}{V^{org}} \quad (27)$$

In eq 27, α, β, K_7 and k_{th} are constant and hence can be suitably written as an apparent rate constant k_{app} constant. The volume of the third phase remains practically the same since the product is transported back into the organic phase. This was also confirmed through measurements and is assumed to be constant. Further N_{Qtot}, the catalysts quantity added is also constant.

In terms of fractional conversion, eq 27 becomes,

$$\frac{dX}{dt} = k_{app}(1 - X)N_{Qtot} \quad (28)$$

Nomenclature and Symbols

A	benzyl chloride
C_A^{org}	concentration of benzyl chloride in the organic phase, mol/cm³ of organic phase
C_A^{th}	concentration of benzyl chloride in the third phase, mol/cm³ of third phase
C_{QOR}^{aq}	concentration of RO^-Q^+ (also QOR) in aqueous phase, mol/cm³ aqueous phase

C^{aq}_{QCl}	concentration of Q^+Cl^- (also QCl) in aqueous phase, mol/cm^3 aqueous phase
C^{th}_{QOR}	concentration of RO^-Q^+ (also QOR) in third phase, mol/cm^3 third phase
C^{th}_{QCl}	concentration of Q^+Cl^- (also QCl) in third phase, mol/cm^3 third phase
C^{org}_{QOR}	concentration of RO^-Q^+ (also QOR) in organic phase, mol/cm^3 organic phase
C^{org}_{QCl}	concentration of Q^+Cl^- (also QCl) in organic phase, mol/cm^3 organic phase
K_1	$\dfrac{C^{th}_{QCl}}{C^{aq}_{QCl}}$
K_2	$\dfrac{C^{th}_{QOR}}{C^{aq}_{QOR}}$
K_3	$\dfrac{C^{th}_{ROK}}{C^{aq}_{ROK}}$
K_4	$\dfrac{C^{aq}_{KCl}}{C^{th}_{KCl}}$
K_5	$\dfrac{C^{org}_{QOR}}{C^{th}_{QOR}}$
K_7	$\dfrac{C^{th}_{R'Cl}}{C^{org}_{R'Cl}}$
K_8	$\dfrac{C^{th}_{R'OR}}{C^{org}_{R'OR}}$
k_{app}	apparent first-order reaction rate constant, cm^3/(mol of catalyst s)
k_0	zero-order constant, mol^{-1} s^{-1}
k_0	apparent zero-order constant, s^{-1}
k_{th}	rate of reaction in the third phase, cm^3/(mol of catalyst s)
N_{Qtot}	total moles of catalyst added to the system, mol
N^{th}_A	moles of A in third phase, mol
N^{org}_A	moles of A in organic phase, mol
N^{th}_{QOR}	moles of QOR in third phase, mol
$R'Cl$	benzyl chloride
ROH	dihydroxybenzene
$R'OR$	mono-O-benzylated product
t	time of reaction, s
V^{aq}	volume of aqeous phase, cm^3
V^{org}	volume of organic phase, cm^3
V^{th}	volume of the third phase, cm^3
X_a	$\dfrac{N_{A0} - N_A}{N_{A0}}$, fractional conversion

Greek symbols

α	V^{th}/V^{aq} = ratio of third to aqueous phase volumes
β	V^{th}/V^{org} = ratio of third to organic phase volumes
η	$\dfrac{C^{th}_{QOR}}{C^{th}_{QOR} + C^{th}_{QCl}}$ = molar ratio of Q^+ in the form of QOR at any time in the third phase