

Novelties of cyanide displacement reaction in ibuprofen amide process by phase transfer catalysis: Solid–liquid versus solid–liquid (ω)–liquid systems

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Abstract

This work deals with the phase transfer catalysed cyanide displacement reaction on 1-(4-isobutyl phenyl) ethyl chloride to synthesize 2-(4-isobutyl phenyl) propionitrile, which is an intermediate for the synthesis of ibuprofen analogs, belonging to a class of NSAID (nonsteroidal anti-inflammatory drugs). The reaction was studied using solid–liquid phase transfer catalysis (S-L PTC) with trace quantities of water, forming the so-called omega phase at 90 °C. The rates of reaction and selectivity to the product are enhanced in the S-L(org.)-L (ω) PTC in comparison with S-L PTC, which in turn is superior to L-L PTC; the latter suffers from the disadvantage of side reactions in the aqueous phase. In the current work, the effects of various parameters such as catalyst structure, catalyst loading, substrate loading and temperature were studied on the conversion and rates of reaction of 1-(4-isobutyl phenyl) ethyl chloride with solid sodium cyanide under S-L and S-L(ω)-L PTC at 90 °C with toluene as the organic solvent. Tetrabutylammonium bromide (TBAB) was found to be the best catalyst. The role of omega liquid phase in intensification of the S-L PTC was theoretically and experimentally investigated. The kinetic constants have been determined and the apparent activation energy is found as 4.2 kcal/mol, which suggests that the reaction is quite fast, which is likely to bring in mass transfer effects.

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Keywords: Solid–liquid phase transfer catalysis; Omega phase; Liquid–liquid PTC; Liquid–liquid (ω)–liquid PTC; Cyanide displacement; 1-(4-Isobutylphenyl)-ethylchloride; 2-(4-Isobutylphenyl)propionitrile; Ibuprofen; Ibuprofenamide; NSAID

1. Introduction

The nitrile substitution in organic moieties is a reaction of great commercial significance. As with other anions, cyanide can be extracted by a well chosen phase transfer catalyst from water into an organic liquid, where the subsequent desired substitution reactions can be performed. Before the advent of PTC, polar aprotic solvents such as DMSO/DMF were often chosen to co-solubilise the inorganic cyanide and the organic substrate, such as an alkyl halide or aryl halide. After the cyanide/chloride displacement reaction performed in DMSO, the reaction mixture is usually diluted with water to separate the product nitrile (if insoluble in water) from the solvent. Since an excess of

cyanide is used, a very hazardous waste stream of cyanide in DMSO/water is generated, usually of large volume due to multiple water washes. DMSO is usually not recoverable since the separation of DMSO and water is difficult and expensive. This leads to disposal problems.

On the contrary, in a typical PTC cyanide/chloride displacement, a solvent is chosen which is immiscible with water, such as toluene and the workup consists of a simple phase separation and water wash of low volume to assure the absence of cyanide in the product. Overall, cyanation reactions proceed rapidly in high yield due to very low hydration of the cyanide ion, loose ion pairing with the phase transfer catalyst and co-location with alkyl or aryl halide in the bulk organic phase. A solvent such as toluene is generally very recoverable by distillation at a reasonable temperature.

A challenge when performing certain cyanations is that the cyanide ion can act both as a nucleophile and a base. In the

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Nomenclature

K_{R1}	rate constant for forward anion-exchange reaction in the ω -phase
$N_{Q\text{-org}}$	moles of catalyst in organic phase (mol)
$N_{QX\text{-org}}$	moles of QX in organic phase
$N_{QY\text{-org}}$	moles of QY in organic phase (mol)
$N_{Q\text{ total}}$	feed mole of catalyst (mol)
$N_{Q\text{-}\omega}$	moles of catalyst in omega phase (mol)
$N_{QX\text{-}\omega}$	moles of QX in omega phase (mol)
$N_{QY\text{-}\omega}$	moles of QY in omega phase (mol)
$[QX]_{\omega}$	concentration of QX in ω -phase (mol/cm ³)
$[QX]_{\text{org}}$	concentration of QX in organic phase (mol/cm ³)
$[QY]_{\omega}$	concentration of QY in ω -phase (mol/cm ³)
$[RX]_{\text{org}}$	concentration of RX in the organic phase (mol/cm ³)
$[X^{-}]_{\omega}$	concentration of X ⁻ in ω -phase (mol/cm ³)
$[Y^{-}]_{\omega}$	concentration of Y ⁻ in the ω -phase (mol/cm ³)

reaction of cyanide with an alkyl halide, especially a secondary alkyl halide, some other side reactions such as dehydrohalogenations can be observed. In such cases, the conversion of a L-L PTC reaction into a solid-organic liquid (S-L) reaction proves to be advantageous from the viewpoint of not only suppression of side reactions but also the intensification of rates due to the increase in particle surface area by orders of magnitude in comparison to that available in a liquid–liquid dispersion. Furthermore, in a S-L PTC process, addition of a third aqueous phase in trace amounts to form the so-called omega (ω)-phase

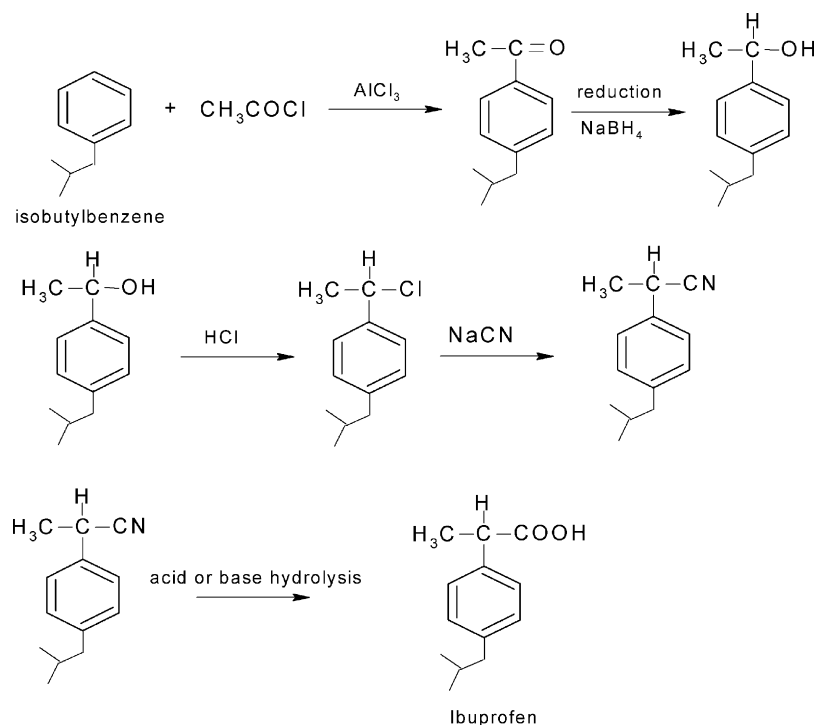
catapults the rates greatly [1–6]. Although several papers emphasizing the advantages of conducting reactions under S-L PTC conditions are available [7–15], very few publications deal with the modeling aspects of the process [16–18]. The recent book by Doraiswamy [2] covers some important aspects of phase transfer catalysis from modeling and engineering viewpoints, and recently kinetics and modeling of ω -phase concept has been dealt [19,20].

The conversion of 1-(4-isobutylphenyl)ethylchloride to 2-(4-isobutylphenyl) propionitrile was studied in detail by using sodium cyanide and tetrabutylammoniumbromide (TBAB) as catalyst, under both S-L PTC and S-L (ω)-L PTC system. 2-(4-Isobutyl phenyl) propionitrile is the intermediate of ibuprofen analogs, a well known NSAID (nonsteroidal anti-inflammatory drug). In the manufacture of ibuprofen (2-(4-isobutylphenyl) propionic acid), by the traditional route which is still in use in many parts of the world, several steps are involved as given in Scheme 1. Some of these steps are amenable to PTC but still no open literature exists. This work was thus undertaken for its commercial significance as well as for its academic relevance.

2. Experimental

2.1. Chemicals and catalysts

1-(4-Isobutylphenyl) ethylchloride was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad, India. Sodium cyanide was procured from M/s. Amrut Industries Ltd., Mumbai and toluene of AR grade was obtained from M/s. s.d.



Scheme 1. Traditional process for ibuprofen synthesis.

Fine Chem. Pvt. Ltd., from Mumbai, India. The phase transfer catalysts, tetrabutylammonium bromide (TBAB), tetrabutylammonium iodide (TBAI), ethyltriphenylphosphonium bromide (ETPPB), and tetrabutylammonium hydrogen sulfate (TBAHS), of pure grade were procured as gift samples from M/s. Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India. All other chemicals were analytical reagents obtained from M/s. s.d. Fine Chem. Pvt. Ltd., Mumbai.

2.2. Setup and reaction procedure

The reactions were studied in a 3.0 cm i.d. fully baffled mechanically agitated reactor of 50 cm³ total capacity, which was equipped with a six-blade pitched turbine impeller and a reflux condenser. The reactor was kept in an isothermal bath whose temperature could be maintained at the desired value using a temperature indicator controller. Standard runs were conducted with 0.03 mol of 1-(4-isobutylphenyl) ethyl chloride dissolved in toluene to make up 11 cm³ volume of organic phase. For a standard reaction, 0.03 mol of solid NaCN was used and 1 cm³ of water added for the 'ω'-phase formation. All standard reactions were conducted at 90 °C with 10 mol% of catalyst (TBAB) under 1000 rpm.

2.3. Method of analysis

Samples of the organic phase were withdrawn periodically and analyzed by gas chromatography (Chemito model 8510). A 4.0 m × 3.2 mm i.d. stainless steel column packed with Chromosorb WHP, which was impregnated with 10% OV-17, was used for analysis in conjunction with a FID. Synthetic mixtures were prepared for calibration and used to calculate the concentrations of 1-(4-isobutylphenyl) ethyl chloride and 2-(4-isobutylphenyl) propionitrile quantitatively. The rates of reaction were based on the disappearance of 1-(4-isobutylphenyl) ethyl chloride. Only one product was formed.

3. Results and discussion

3.1. Comparison of S-L PTC versus S-L (ω)-L PTC

The efficacy of S-L(ω)-L PTC in which trace quantities of water (so called ω-phase) are used, in comparison with S-L PTC was studied under otherwise similar conditions with TBAB as the catalyst. Preliminary experiments had suggested that TBAB was a better catalyst. Fig. 1 gives the effect of water on the conversion.

It was interesting to know whether the 'ω'-phase retains its identity by forming a third aqueous film around the particle. If the particle solubility increases substantially with temperature, then it is also important to know the fate of the 'ω'-phase. It is known that the 'ω'-phase enhances the rate in S-L PTC in certain cases, and there is an optimum quantity beyond which the rate falls dramatically. Thus, careful experiments were done by adding trace quantities of water in the range of 0.5–3.0 cm³ in 11 cm³ of organic phase. A model reaction was also conducted

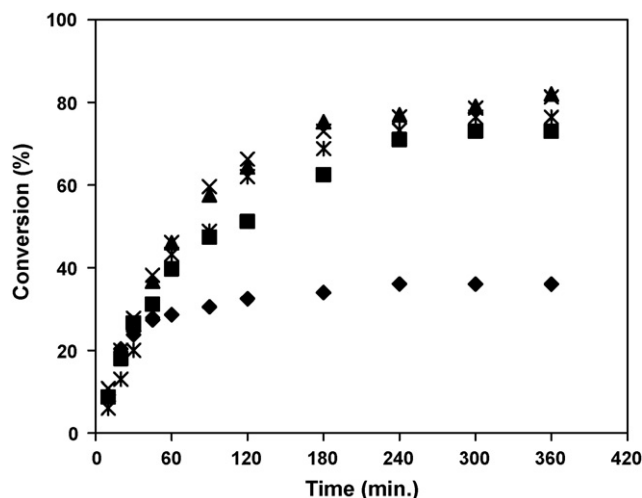


Fig. 1. Effect of trace quantities of water. 1-(4-isobutylphenyl) ethyl chloride 0.03 mol, NaCN 0.03 mol, toluene 5.0 ml, TBAB 0.003 mol, temperature 90 °C, speed of agitation 1000 rpm. (♦) 0 ml, (■) 0.5 ml, (▲) 1 ml, (×) 2 ml, and (*) 3 ml.

in the absence of water under nearly anhydrous conditions as S-L PTC.

A typical calculation done for the film thickness is given below. For solid NaCN, M_s is the molecular weight of solid, 49 g/mol; r_p the particle radius, 1000 μm (0.1 cm); ρ_p the particle density, 1.62 g/cm³; W_s is the solid loading, 1.47 g. Now,

$$W_s = \frac{4}{3}\pi\rho_p r_p^3 N = 1.47 \text{ g (where } N \text{ is the number of particles).}$$

Therefore, $N = 217$

$$\text{The available surface area} = 4\pi r_p^2 N = 27.25 \text{ cm}^2$$

$$a_p = \text{total surface area/volume of organic phase} \\ = 27.25/11 = 2.47 \text{ cm}^{-1}$$

Now for the volume of ω-phase 1.0 cm³

$$\frac{4}{3}\pi\rho_p(r_{p+\omega}^3 - r_p^3)N = 1.0 \text{ cm}^3$$

The radius of the particle surrounded by the film is: $r_{p+\omega} = 0.1188$ and the ω film thickness is 0.0188 cm or 188 μm.

As the amount of water is increased, the mode of operation could change from solid–liquid (org) to solid–liquid (ω)–liquid (org) to liquid (aq.)–liquid (org). It was observed that small amounts of water substantially increase the rates of reaction compared to those under anhydrous conditions, and a sudden rate enhancement was observed. The rate of reaction increases with the volume of water added. In all further experiments, 1 cm³ of water was added to the reaction mixture for the 'ω'-phase formation. The role of the 'ω'-phase is to enhance the local concentration of the nucleophile for the ion-exchange reaction with Q^+X^- , which is also partitioned in the 'ω'-phase. It appears that the thin film surrounding the solid particle gets saturated with CN^- , thereby increasing its concentration in the 'ω'-phase. The reaction scheme is given below.

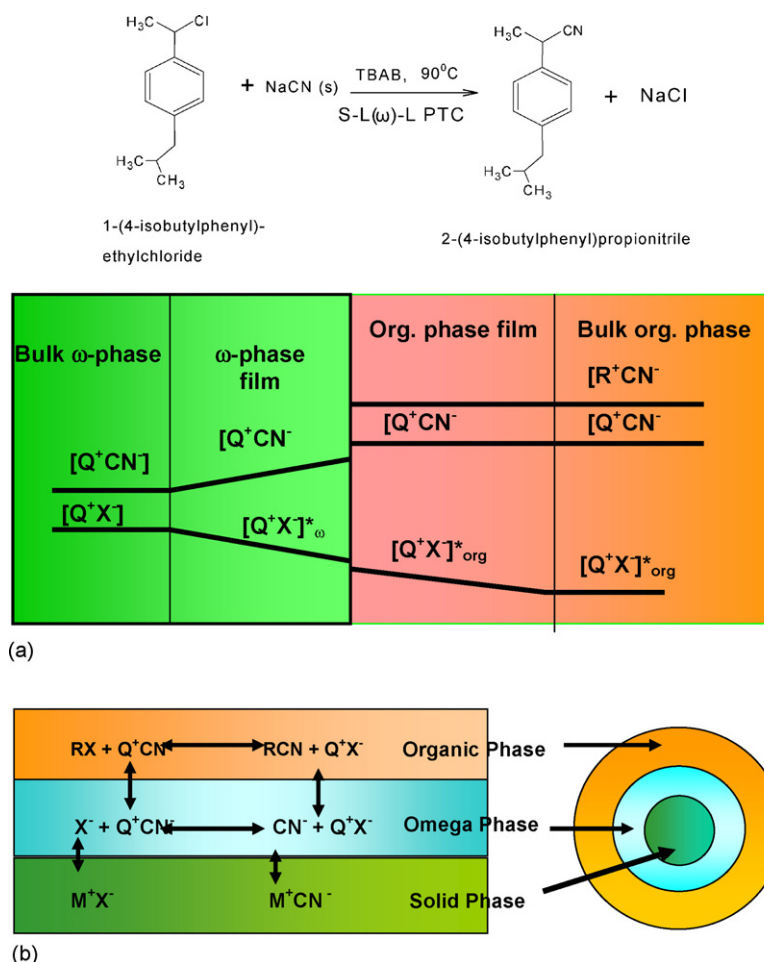


Fig. 2. General mechanism for S-L PTC in the presence of ω-phase: S-L (ω)-L PTC. (a) Enlarged view of ω and organic phase and (b) three phase reaction system.

A general mechanism for the reaction and mode of operation is shown in Fig. 2, which involves the dissolution of solid CN⁻ into the 'ω'-phase, followed by the anion-exchange reaction with the catalyst to form the active ion-pair Q⁺CN⁻ in the 'ω'-phase. Q⁺CN⁻ is then transferred to the organic phase, where the cyanide displacement on 1-(4-isobutylphenyl) ethyl chloride takes place. Addition of small quantities of water thus facilitates the distribution of the quaternary salt between the organic and solid phases. To determine the actual mechanism of the reaction, the effects of various parameters on the rate of reaction were studied. In all further experiments 1 cm³ of water was used as the ω-phase.

3.2. Effect of different catalysts

There was no reaction in the absence of any catalyst. Various catalysts with different cationic as well as anionic structures, such as TBAB, TBAHS, ETPPB and PEG-400 were employed under otherwise similar experimental conditions (Fig. 3). The order of activity of these catalysts was as follows:

TBAB ≈ TBAI > TBHS > ETPPB > PEG-400

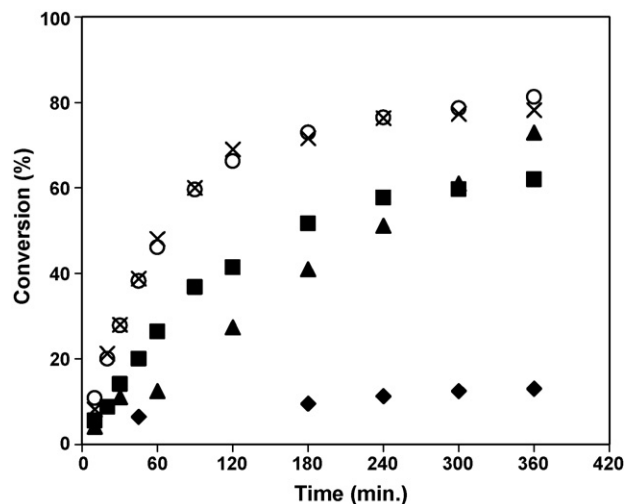


Fig. 3. Effect of different catalysts. 1-(4-Isobutylphenyl) ethyl chloride 0.03 mol, NaCN 0.03 mol, toluene 5.0 ml, water 1.0 cm³, temperature 90 °C, speed of agitation 1000 rpm. (◆) PEG-400, (■) TBAHS, (▲) ETPPB, (×) TBAI, and (○) TBAB.

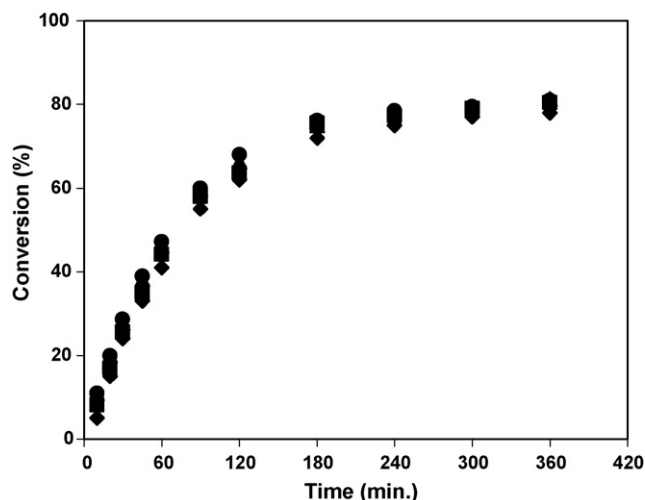


Fig. 4. Effect of speed of agitation. 1-(4-Isobutylphenyl) ethyl chloride 0.03 mol, NaCN 0.03 mol, toluene 5.0 ml, TBAB 0.003 mol, water 1.0 cm³, temperature 90 °C. (◆) 600 rpm, (■) 800 rpm, (▲) 1000 rpm, and (●) 1200 rpm.

Amongst the tetrabutylammonium salts, TBAHS was found to give minimum conversion due to its poor partitioning in the 'ω'-phase. TBAB and TBAI gave practically the same conversions. TBAB was employed as the catalyst for all further S-L reactions, as it is easily and economically available.

3.3. Effect of speed of agitation

To ascertain the influence of mass transfer resistance on the transfer of ion-pairs to the reaction phase (organic phase) through the ω-phase, the speed of agitation was varied in the range of 600–1200 rpm. Fig. 4 shows that the conversion is practically same even though the increase in speed of agitation was done from 600 to 1200 rpm. Therefore, a speed of agitation of 1000 rpm was employed in all further experiments to get a maximum rate and for assessing the effect of other variables on the rate of reaction.

3.4. Effect of catalyst concentration

The quantity of catalyst (TBAB) was varied from 3×10^{-4} to 6×10^{-3} mol under otherwise similar experimental conditions. The conversion of 1-(4-isobutylphenyl) ethyl chloride is plotted against time for different catalyst concentrations (Fig. 5). The initial rate of reaction increased with catalyst concentration due to the fact that the concentration of Q^+CN^- extracted into the organic phase increases with increasing catalyst concentration. All further experiments were done at catalyst concentration of 3×10^{-3} mol.

3.5. Effect of molar ratio

The effect of change in molar ratio of 1-(4-isobutylphenyl) ethyl chloride to NaCN was studied by varying in the range of 1:0.5–1:2 (Fig. 6). Increase in the concentration of the nucleophile (NaCN) increases the conversion, since more and more nucleophile in the Q^+CN^- form is available for the reaction.

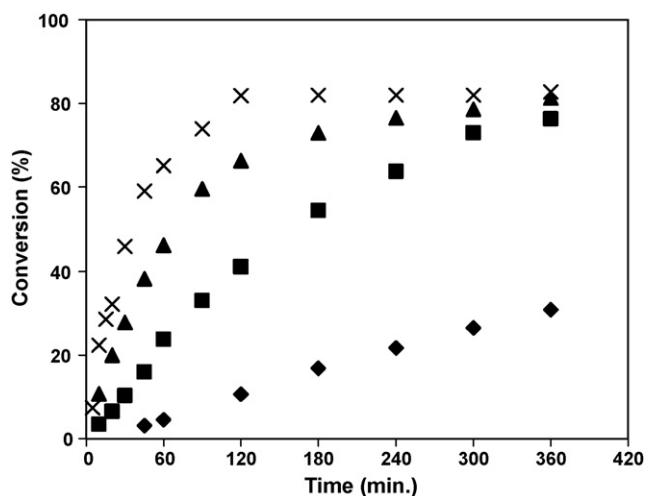


Fig. 5. Effect of catalyst concentration. 1-(4-isobutylphenyl) ethyl chloride 0.03 mol, NaCN 0.03 mol, toluene 5.0 ml, water 1.0 cm³, temperature 90 °C, speed of agitation 1000 rpm. (◆) 0.0003 mol, (■) 0.0015 mol, (▲) 0.003 mol, and (×) 0.006 mol.

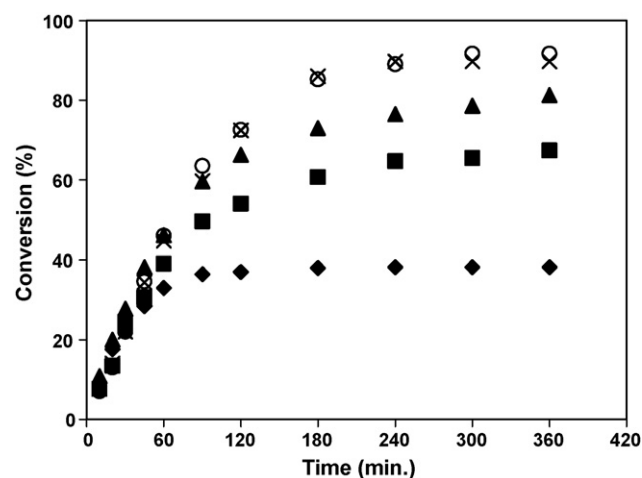


Fig. 6. Effect of mole ratio. 1-(4-Isobutylphenyl) ethyl chloride 0.03 mol, NaCN, toluene 5.0 ml, TBAB 0.003 mol, water 1.0 cm³, temperature 90 °C, speed of agitation 1000 rpm. (◆) 0.015 mol, (■) 0.024 mol, (▲) 0.03 mol, (×) 0.045 mol, and (○) 0.06 mol.

ophile (NaCN) increases the conversion, since more and more nucleophile in the Q^+CN^- form is available for the reaction.

3.6. Effect of temperature

The effect of temperature on the rate of the reaction of 1-(4-isobutylphenyl) ethyl chloride was studied in the range of 70–95 °C. The conversion of 1-(4-isobutylphenyl) ethyl chloride was observed to increase with an increase in the reaction temperature up to 95 °C (Fig. 7). However, there was a marginal increase in conversion at 95 °C over than at 90 °C, bringing into play the mass transfer effects.

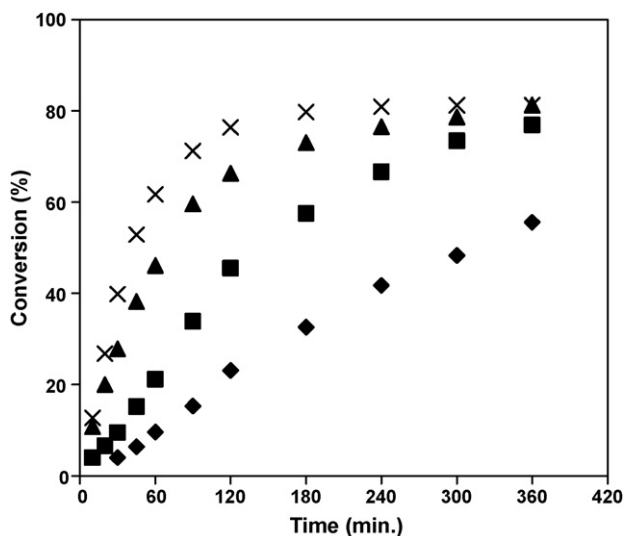


Fig. 7. Effect of temperature. 1-(4-Isobutylphenyl) ethyl chloride 0.03 mol, NaCN 0.03 mol, toluene 5.0 ml, water 1.0 cm³, TBAB 0.003 mol, speed of agitation 1000 rpm. (◆) 70 °C, (■) 80 °C, (▲) 90 °C, and (×) 95 °C.

4. Kinetics of reaction: model describing instantaneous phase saturation with shrunk particle

This model is valid for solids which are soluble in the aqueous phase or in ω -phase in the presence of other dissolved species. Since the quantity of ω -phase used is small, that phase is saturated with the nucleophile, with the core of particle retaining its identity and also there is quaternary salt distributed in the ω -phase.

The solubility of MY, the solid substrate, is very high and increases with temperature substantially. It would mean that on addition of trace quantities of water which forms the ω -phase, instantaneous dissolution of particles should occur thereby saturating the ω -phase with interior core of the particle retaining its identity for sometime. Besides NaCl (MX) which is generated in-situ as the reaction proceeds will also be dissolved within the ω -phase. This would suggest that $[Q^+Y^-]$ ion-pair which is formed in the ω -phase is immediately distributed in the organic phase and the reaction proceeds there. It is a typical L (ω)-L (org) PTC reaction, which occurs in the organic phase, either near the aqueous (ω)-organic interface in the liquid film on organic side or in the bulk organic phase.



Mass transfer to and from and reaction in organic phase.



Equilibrium constants

$$K_{QX} = \frac{[QX]_{\omega}}{[QX]_{org}}, \quad K_{QY} = \frac{[QY]_{org}}{[QY]_{\omega}} \quad (6)$$

Rate equations:

$$\frac{d[QX]_{\omega}}{dt} = k_{L\omega} a_{\omega} \{ [QX]_{\omega}^* - [QX]_{\omega} \} - k_{R1} [QX]_{\omega} [Y^-]_{\omega} + k'_{R1} [QY]_{\omega} [X^-]_{\omega} \quad (7)$$

$$-\frac{d[RX]_{org}}{dt} = k_{R2} [QY]_{org} [RX]_{org} \quad (8)$$

$$\frac{d[QY]_{\omega}}{dt} = k_{R1} [QX]_{\omega} [Y^-]_{\omega} - k'_{R1} [QY]_{\omega} [X^-]_{\omega} + k_{L\omega} a_{\omega} \{ [QY]_{\omega} - [QY]_{\omega}^* \} \quad (9)$$

$$\frac{d[QY]_{org}}{dt} = k_{L\omega} a_{\omega} \{ [QY]_{org}^* [QX]_{org} \} - k_{R2} [QY]_{org} [RX]_{org} \quad (10)$$

The total quantity of catalyst added $N_{Qtotal} = N_{Q-\omega} + N_{Q-org}$, which is distributed in four ion-pairs.

$$= N_{QX-\omega} + N_{QY-\omega} + N_{QX-org} + N_{QY-org} \quad (11)$$

$$= \{ [QX]_{\omega} + [QY]_{\omega} \} V_{\omega} + \{ [QX]_{org} + [QY]_{org} \} V_{org} \quad (12)$$

$$= \{ [QX]_{org} K_{QX} V_{\omega} + [QX]_{org} V_{org} \} + \left\{ \frac{[QY]_{org}}{K_{QY}} V_{\omega} + [QY]_{org} V_{org} \right\} \quad (13)$$

$$= [QX]_{org} \left\{ K_{QX} + \frac{V_{org}}{V_{\omega}} \right\} + [QY]_{org} \left\{ \frac{1}{K_{QY}} + \frac{V_{org}}{V_{\omega}} \right\} \quad (14)$$

$$\text{Let } \frac{V_{org}}{V_{\omega}} = \gamma$$

$$N_{Qtotal} = [QX]_{org} \{ K_{QX} + \gamma \} + [QY]_{org} \left\{ \frac{1}{K_{QY}} + \gamma \right\} \quad (15)$$

$$\{ K_{QX} + \gamma \} = \alpha \quad \text{and} \quad \left\{ \frac{1}{K_{QY}} + \gamma \right\} = \beta \quad (16)$$

$$N_{Qtotal} = \alpha [QX]_{org} + \beta [QY]_{org} \quad (17)$$

$$[QY]_{org} = \frac{N_{Qtotal} - \alpha [QX]_{org}}{\beta} \quad (18)$$

$$\frac{d[RX]_{org}}{dt} = k_{R2} [RX]_{org} \left[\frac{N_{Qtotal} - \alpha [QX]_{org}}{\beta} \right] \quad (19)$$

If $[QX]_{org} = \text{constant}$, then the above equation can be integrated to get

$$-\ln(1 - X_A) = k_{R2} \left[\frac{N_{Qtotal} - \alpha [QX]_{org}}{\beta} \right] t \quad (20)$$

Table 1
Model fitting for cyanide displacement on 1-(4-isobutylphenyl)-ethylchloride

	Temperature			
	343 K	353 K	363 K	368 K
k_{R2} (min^{-1})	361.27	440.89	510.7	552.43
β	54.38	45.05	37.91	34.48
$[\text{QX}]_{\text{org}}$ (mol/cm^3)	2.03×10^{-4}	1.968×10^{-4}	1.919×10^{-4}	1.869×10^{-4}
K_{QY}	0.023	0.029	0.037	0.042

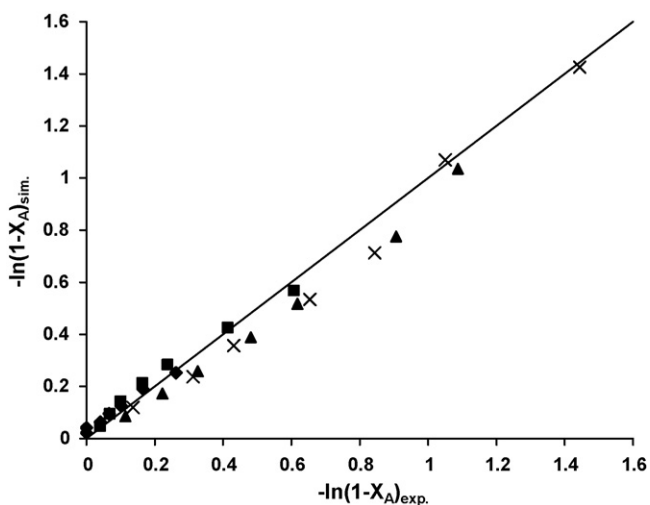


Fig. 8. Parity plot of experimental and simulated values of $-\ln(1 - X_A)$. (◆) 343 K, (■) 353 K, (▲) 363 K, and (×) 368 K.

This equation was fitted to the experimental data using Polymath 5.1 and the constants K_{QY} , $[\text{QX}]_{\text{org}}$ and k_{R2} were obtained as shown in Table 1. The parity plot of $-\ln(1 - X_A)$ calculated with these values was plotted against the experimental data and it showed a good fit (Fig. 8). It also shows that as the temperature is increased, the distribution of the active ion-pair in the organic phase increases substantially. The rate constants obtained at dif-

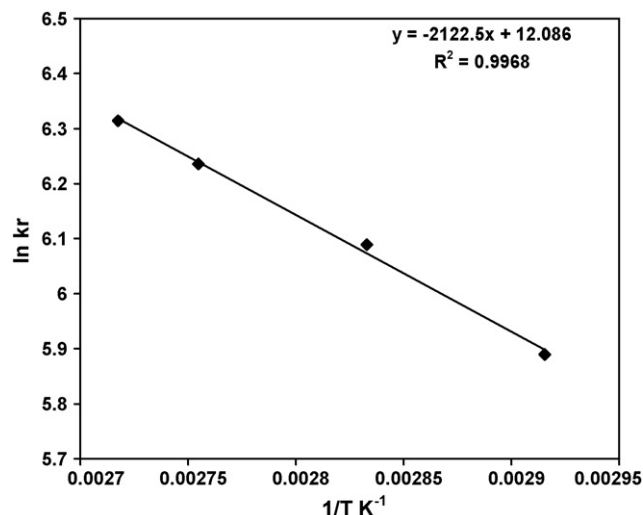


Fig. 9. Arrhenius plot.

ferent temperature were used to make the Arrhenius plot (Fig. 9). The frequency factor and activation energy for k_{R2} were obtained from an Arrhenius plot as $1.77 \times 10^5 \text{ min}^{-1}$ and 4.2 kcal/mol, respectively. This activation energy is on lower side but it suggested that it is an intrinsically kinetically controlled reaction.

5. Conclusion

The S-L PTC displacement reaction on 1-(4-isobutylphenyl) ethyl chloride with sodium cyanide was studied by using tetrabutylammonium bromide as the catalyst at 90 °C. The role of addition of small quantities of water, leading to intensification in reaction rates through 'ω'-phase formation, is highlighted. The kinetic model could take into account the role of different parameters. The presence of a limited amount of water is found to be very important in enhancing the rate of a S-L PTC reaction. The kinetic constants have been determined and the apparent activation energy is found as 4.2 kcal/mol, which suggests that the reaction is quite fast, which is likely to bring in mass transfer effects.

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