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Novelties of selective synthesis of 3-methyl-4′-nitro-diphenyl ether under solid–liquid phase transfer catalysis

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Abstract

3-Methyl-4′-nitro-diphenyl ether, an important agrochemical, is normally synthesized by employing aprotic polar solvents, or Ullmann reaction at elevated temperatures leading to a number of by-products and the process is costly. The current paper presents a cost effective and simpler process of synthesis of 3-methyl-4′-nitro-diphenyl ether from sodium salt of *m*-cresol and *p*-chloronitrobenzene (PCNB) by using *o*-xylene as a solvent under solid–liquid phase transfer catalysis (S–L PTC), at 120 °C, which is 100% selective. The liquid–liquid (L–L) PTC process does not work at the same conditions due to poor reactivity of the ion-pair. A novel mathematical model is developed to determine simultaneously the rate constant and anion exchange equilibrium constant from the same set of data. This will be helpful in reactor design and scale up. The activation energy and Gibb's free energy for a combined ion exchange and partitioning of ion pairs is are also calculated. The reactivity of sodium salts of *o*- and *p*-cresol with PCNB is also tested.
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1. Introduction

Phase transfer catalysis (PTC) has been successfully applied for the manufacture of large number of chemicals useful in several industries such as intermediates, dyestuffs, agrochemicals, perfumes, flavours, pharmaceuticals and polymers [1–5]. The most common operations involve the liquid–liquid (L–L) mode of operation. PTC has been quite successful for C, N, O and S alkylations involving S_N2 type reactions in fine chemical industries, apart from dehydro-halogenations. When the halogen exchange of alkoxide is conducted in L–L PTC, there is always a formation of alcohol due to hydrolysis. One of the ways to suppress by-product formation and also intensify the rates of reactions of L–L PTC is

through the use of solid–liquid (S–L) PTC in which the aqueous phase promoted reactions can be totally suppressed and better selectivities obtained [6,7]. S–L PTC involves reaction of an anionic reagent in a solid phase (usually an alkali metal salt) with a reactant located in a continuous organic phase [8–11]. 3-Methyl-4′-nitro-diphenyl ether also known as "HE-314" is an important agrochemical [12,13] which is normally synthesized by Ullmann reaction [14] or employing aprotic polar solvents [15]. Ullmann's method requires elevated temperatures and leads to formation of by-products like hydro-dehalogenated compounds. When halogen exchange of alkoxides is conducted in L–L PTC, sometimes there is a formation of alcohols due to hydrolysis. Solid–liquid (S–L) PTC offers the way to suppress the by-product formation due to total absence of *hydrolysis* and enhances the reaction rates. The current work discusses the selective reaction between sodium salt of *m*-cresol and *p*-chloro-nitrobenzene in *o*-xylene as a solvent towards 3-methyl-4′-nitro-diphenyl ether under solid–liquid PTC including its kinetics.

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2. Experimental

2.1. Chemicals and catalysts

p-Chloronitrobenzene (PNCB), *m*-cresol, sodium hydroxide and *o*-xylene were obtained from s.d. Fine Chemicals Pvt. Ltd., Mumbai, India. Tetra-*n*-butyl ammonium bromide (TBAB), tetra-*n*-butyl ammonium hydrogen sulphate (TBAHS), tetra-ethyl ammonium bromide (TEAB), ethyl triphenyl phosphonium bromide (ETPB) and tetra-*n*-butyl phosphonium bromide (TBPB) were received as gift samples from Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India.

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 a six blade-pitched turbine impeller (2 cm diameter) and a reflux condenser. The impeller was located at a distance of 2 cm from the bottom. This arrangement ensured excellent solid–liquid mixing for high mass transfer rates. The assembly was kept in an isothermal bath at the desired temperature and mechanically stirred at a known speed with an electrical motor. Predetermined quantities of reactants and solvent were added to the reactor and the temperature was increased to the desired value. The catalyst was added when the temperature reached the set value.

Typically the reaction was carried out as follows. Initially, a suspension of 0.03 mol sodium salt of *m*-cresol in 50 ml of *o*-xylene was made. The reaction was carried out at the set temperature after the addition of 0.03 mol of *p*-nitro chlorobenzene (PCNB) and 20 mol.% of catalyst on the basis of PCNB at 120 °C in the control experiments. A zero time sample was collected and sampling was done periodically to get concentration–time profiles of reactants and products. Initial experiments were done at 90 °C for S–L PTC to get a conversion of 90% in 2 h and the same reaction under liquid–liquid PTC conditions did not occur at 90 °C, under otherwise similar conditions.

The reaction scheme is as given below.
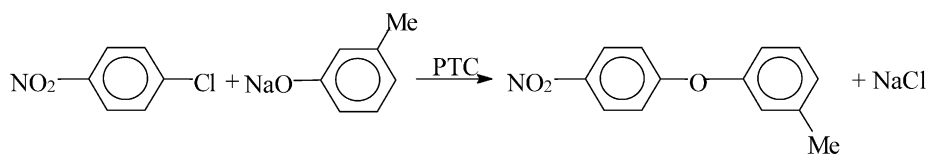
PCNB (RX)   Sodium salt of m-cresol (MY)   3-Methyl-4'-nitro- diphenyl ether   sodium chloride
(liquid)   (solid)   (liquid)   (solid)

2.3. Analysis

Analysis was performed on GC (Chemito Gas Chromatograph, model 8510) by using a 2 m × 3.8 mm stainless steel column packed with 10% OV-17 on Chromosorb WHP, coupled with a flame ionisation detector. The product was confirmed by GC–MS. Analyses showed that only 3-methyl-4'-nitro-diphenyl ether was the sole product in the reaction.

2.4. Isolation of product

After completion of the reaction, the mixture was filtered to remove unreacted sodium salt of *m*-cresol and solid NaCl. The filtrate was collected contained the catalyst, PCNB and the product. The catalyst TBAB was removed by extracting the filtrate with 2% NaOH. *o*-Xylene was recovered by distillation of filtrate while product (3-methyl-4'-nitro-diphenyl ether) was separated by fractional crystallisation.

3. Results and discussion

3.1. Mechanism and kinetic model

The solid particles of the reactant provide a very large surface area per unit volume of the organic phase and the reaction can occur on the surface of the particle if is poorly soluble in the liquid or they could dissolve in the liquid due to ion-exchange reaction. Thus, the first step in solid–liquid PTC involves the transport of a reactant anion (substrate, Y$^-$) from the solid phase to the organic phase by a phase transfer cation (Q$^+$). This is an organophilic quaternary cation which exchanges the anion (X$^-$) with the nucleophile (Y$^-$) 3-methyl phenoxide to form the ion-pair [Q$^+$Y$^-$], which is organophilic and is freely transported to the bulk organic phase. There could be a resistance associated with the transfer of this ion-pair across the liquid film next to solid–liquid interface. The second step involves the reaction of the ion-pair [Q$^+$Y$^-$] with the reactant PCNB (RX) located in the organic phase, leading to the formation of the product (RY) with simultaneous generation of [Q$^+$X$^-$]. There are several possibilities by which this reaction can occur depending on relative rates of mass transfer and chemical reaction. Finally the third step involves the transport of the co-product anion [X$^-$], the leaving group, as an ion-pair [Q$^+$X$^-$] and the transport of another nucleophile [Y$^-$] into the organic phase. In the current case, the S–L PTC mechanistic description is the implication that the reaction takes place in anhydrous condition, since both solid and liquid phases were dry. So the formation of the omega phase was discounted.
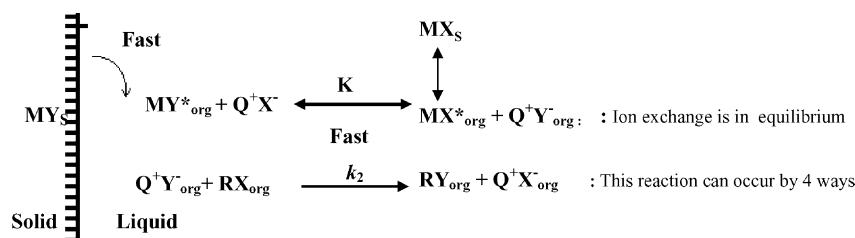
Fig. 1. Homogeneous solubilization S–L PTC.

There are two types of mechanisms for S–L PTC, the homogeneous solubilization mechanism of Yadav and Sharma [6] and heterogeneous solubilization of Doraiswamy and Naik [16]. In the heterogeneous solubilization, the particles are totally insoluble and the catalyst get adsorbed on to the solid whereas in the case of homogeneous solubilization model, the particles are sparingly soluble in the organic phase and the particle solubility is augmented by the phase transfer agent (Q^+X^-) as shown in Fig. 1. There is an instantaneous exchange of anions and formation of an ion-pair (Q^+Y^-) with the quaternary cation Q^+ with the nucleophile Y^- which diffuses from the solid–liquid interface to the organic phase through the organic film. The particle size goes on decreasing with time due to the reaction in the organic phase. Depending on the relative rate of transfer of Q^+Y^- in the organic film next to the solid and the reaction of the species, four different regimes can be identified just like the L–L PTC [17] for homogeneous solubilisation. Yadav and Subramanian [18] have proposed new model for solid–liquid PTC.
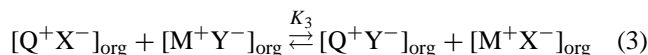
Preliminary experiments suggested that the homogeneous solubilization model illustrated by the S_N2 type of reaction of the substrate RX with the nucleophile Y of the solid reactant MY. M^+ is the inorganic metallic counter-ion of the nucleophile Y^- was applicable to the current work. The overall reaction is:

$$RX_{(org)} + MY_{(s)} \xrightarrow{k_{obs}, [QX]_{(org)}} RY_{(org)} + MX_{(s)} \qquad (1)$$
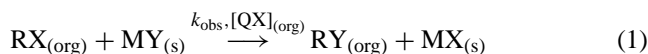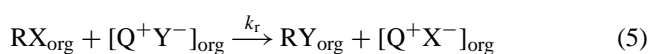
where Q^+ is the quaternary cation of the catalyst. Q^+X^- is a loosely bound ion pair shown in squared brackets. The solid reactant is in equilibrium with its solution in the organic phase.

$$MY_{(s)} \overset{K_2}{\rightleftarrows} [M^+Y^-]_{(org)} \qquad (2)$$

The quaternary salt (Q^+X^-) reacts with the dissolved part of the solid reactant in the organic phase.

$$[Q^+X^-]_{org} + [M^+Y^-]_{org} \overset{K_3}{\rightleftarrows} [Q^+Y^-]_{org} + [M^+X^-]_{org} \qquad (3)$$

$$[M^+X^-]_{(org)} \overset{1/K_4}{\rightleftarrows} M^+X^-_{(s)} \qquad (4)$$

The substrate RX reacts with $[Q^+Y^-]$ according to

$$RX_{org} + [Q^+Y^-]_{org} \xrightarrow{k_r} RY_{org} + [Q^+X^-]_{org} \qquad (5)$$

The quaternary salt is thus generated repeatedly to catalyze the reaction. However, there is no transfer of the catalyst across the interface as is normally observed in the case of liquid–liquid phase transfer process.

The equilibrium constant K_e which is a sort of a solubility parameter is defined by combining steps (3) and (4) as follows:

$$K_e = \frac{[Q^+Y^-]_{org}[M^+X^-]_s}{[Q^+X^-]_{org}[M^+Y^-]_s} = \frac{K_2 K_3}{K_4} \qquad (6)$$

The rate of reaction for Eq. (5) is given by

$$-\frac{d[RX]_{org}}{dt} = k_r[RX]_{org}[Q^+Y^-]_{org} \qquad (7)$$

$$= k_r K_e \frac{[M^+Y^-]_s}{[M^+X^-]_s}[RX]_{org}[Q^+X^-]_{org} \qquad (8)$$

But

$$Q_0 = [Q^+Y^-]_{org} + [Q^+X^-]_{org}$$
$$= \text{total concentration of catalyst in organic phase,}$$
$$\text{mol/cm}^3. \quad (9)$$

Let fractional conversion of RX at time t,

$$X_A = \frac{N_{RX_0} - N_{RX}}{N_{RX_0}} \qquad (10)$$

where N_{RX_0} are the initial moles of RX at time $t = 0$.

Let $M = \dfrac{N_{MY}}{N_{RX_0}}$

= initial mole ratio of the nucleophile to substrate.

$\qquad (11)$

From the stoichiometry of the reaction, all terms in Eq. (8) can be written in terms of X_A and Q_0. Separation of variables and integration leads to the following:

$$\int_0^{X_A} \left[\frac{X_A + K_e M - K_e X_A}{K_e(M - X_A)(1 - X_A)} \right] dX_A = k_r Q_0 t \qquad (12)$$

This integral is solved by the method of partial fractions to get the following:

$$\left(\frac{M}{M-1}\right)\ln\left(\frac{M-X_A}{M}\right)-\left(\frac{1-K_e+K_eM}{M-1}\right)$$
$$\ln(1-X_A)=k_rQ_0t \quad \text{for } M\neq 1 \tag{13}$$

Eq. (13) can be further manipulated to the following to extract both K_e and k_r:

$$\left[\frac{\ln(M-X_A/M)}{\ln(1-X_A)}\right]-\left[\frac{1-K_e+K_eM}{M}\right]$$
$$=\left[\frac{(M-1)k_rQ_0}{M}\right]\frac{t}{\ln(1-X_A)} \tag{14}$$

A plot of $[(\ln(M-X_A/M))/(\ln(1-X_A))]$ versus $t/\ln(1-X_A)$ should give

$$\text{slope}=\left[\frac{(M-1)k_rQ_0}{M}\right] \text{ and intercept}$$
$$=-\left[\frac{1-K_e+K_eM}{M}\right] \tag{15}$$

Thus, both K_e and k_r can be obtained from the slope and intercept the from knowledge of M and Q_0. Further for equimolar quantities of substrate and nucleophile, the following form of the integrated equation results.

$$\left(\frac{X_A}{1-X_A}\right)+(1-K_e)\ln(1-X_A)=k_rQ_0t \quad \text{for } M=1 \tag{16}$$

Eq. (16) is also manipulated to the following.

$$\left[\frac{X_A/(1-X_A)}{\ln(1-X_A)}\right]+(1-K_e)=k_rQ_0\frac{t}{\ln(1-X_A)} \tag{17}$$

A plot of $[X_A/(1-X_A)/\ln(1-X_A)]$ versus $t/\ln(1-X_A)$ will give a straight line with slope equal to k_rQ_0 and intercept equal to $1-K_e$.

The validation of the above model was verified by conducting several experiments. The rate of reactions were calculated at each point on conversion–time profile. In the following discussions, the conversion trends in each case are given and the initial rates of reaction in each case are mentioned to suggest the trends to describe the effect of different variables on rates of reactions to deduce the kinetics. Ultimately the derived model is verified by plotting the appropriate parameters.

3.2. Effect of various catalysts

Tetra-*n*-butyl ammonium bromide, tetra-*n*-butyl ammonium hydrogen sulphate, tetra-ethyl ammonium bromide, ethyl triphenyl phosphonium bromide and tetra-*n*-butyl phosphonium bromide were screened for their efficacy for the reaction under otherwise similar concentrations of catalysts at 120 °C and 1000 rpm (Fig. 2). The order of activity was as
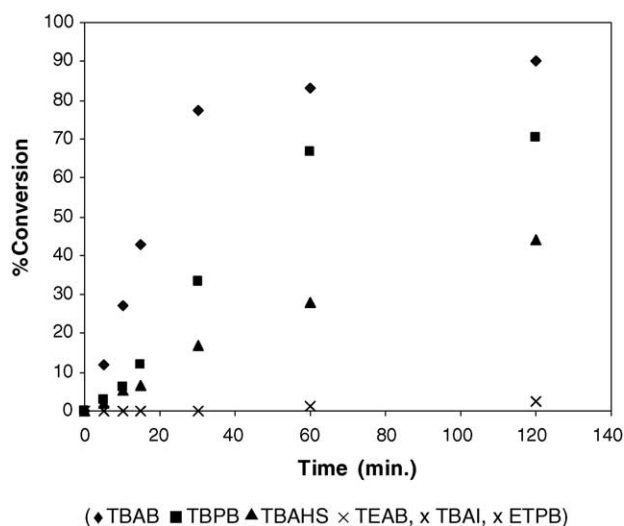

Fig. 2. Effect of different catalysts. Sodium salt of *m*-cresol 0.03 mol, PCNB 0.03 mol, catalyst 0.006 mol, *o*-xylene (solvent) up to 50 ml, speed of agitation 1000 rpm, temperature 120 °C.

follows:

TBAB > TBPB > TBAHS > ETPB(v. small),

TEAB, TBAI, (nil)

TBAB gave the maximum rates of reaction and conversion whereas. There is no question of distribution of catalyst between two phase in the current case since all cation is available in the organic phase and its availability as Q^+Y^- in organic phase as an activated ion-pair in *o*-xylene as a non-polar medium needs to be considered. The ion exchange reaction of TBAB with MY is very fast in comparison with others and majority of catalyst is in the Q^+Y^- as an activated form. TEAB, ETPB and TBAI catalysts were inactive. Tetraethylammonium cation is less reactive than tetrabutyl ammonium cations for exchange with large anions. Similarly ethyltriphenyl cation, although is more stable, is not as effective due to the formation of strong ion-pairs with bromides [1] in comparison *m*-cresolate anion. Iodides as anions are known to be strongly associated with quaternary cations, can act as poisons and are difficult to replace with bulky organic anions like *m*-cresolate. Hence, these catalysts were found to be ineffective.

Thus, further experiments were conducted with TBAB. Apart from its high reactivity TBAB is inexpensive and commercially available in high purity. The selectivity towards the ether was 100%.

3.3. Effect of speed of agitation

The reaction was carried out at four different speeds of agitation with TBAB as catalyst under otherwise similar conditions. There was a significant increase in the conversion of sodium salt of m-cresol from 500 to 1000 rpm but it
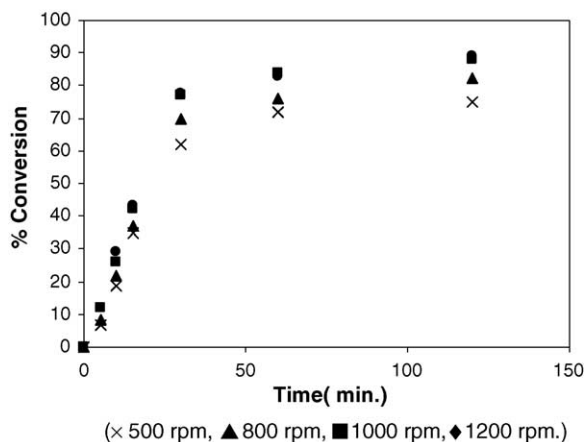
Fig. 3. Effect of speed of agitation. Sodium salt of *m*-cresol 0.03 mol, PCNB 0.03 mol, TBAB 0.006 mol *o*-xylene (solvent) up to 50 ml, temperature 120 °C, time 2 h.

remained almost constant at 1000 and 1200 rpm. This observation suggested that there was no external mass transfer resistance. The calculations of mass transfer rates vis-à-vis observed rates of reactions showed that the mass transfer rates were higher by two orders of magnitude. Estimation of mass transfer coefficients was done by following standard texts. The reactions were in kinetic regime. All subsequent reactions were carried out with 1000 rpm while assessing the effect of other variables on the rate of reaction (Fig. 3).

3.4. Effect of catalyst loading

The reaction rate was found to vary significantly with catalyst concentration. The concentration of the catalyst was varied from 3×10^{-5} to 1.8×10^{-4} mol cm^{-3}. It was observed that as the concentration of sodium salt of *m*-cresol was increased, its conversion increased (Fig. 4). The increase in conversion with concentration of catalyst concentration can be properly quantified by invoking the rate Eq. (7) which shows that the rate of reaction is linear in catalyst concentration. The initial rate of reaction increased with catalyst concentration up to 1.2×10^{-4} mol cm^{-3}. The rate of reaction at 1.8×10^{-4} mol cm^{-3} was very high and the reaction was over practically within 10 min. It could bring mass transfer resistance in picture at higher catalyst concentration. Therefore, all further experiments were done at catalyst concentration of 1.2×10^{-4} mol cm^{-3}.

3.5. Effect of mole ratio

Mole ratio of sodium salt of *m*-cresol to *p*-chloronitrobenzene was varied from 1:1 to 2:1(Fig. 5). The conversion increases with concentration of PCNB under otherwise similar conditions. The reaction rate was found to increase with an increase in the initial concentration of
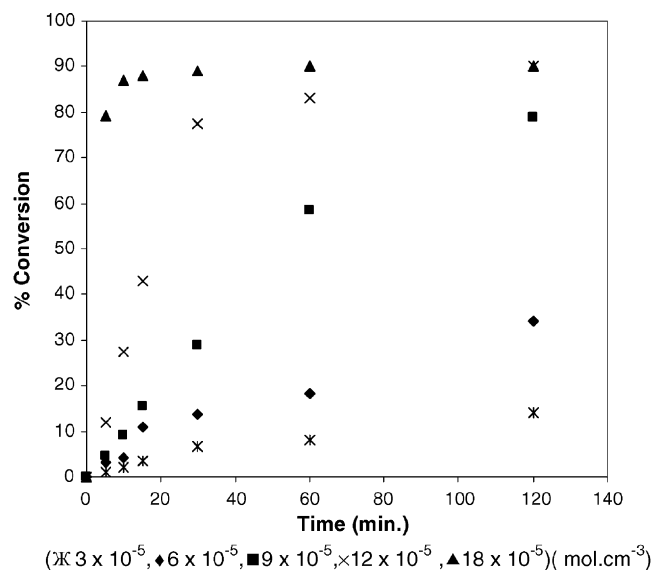

Fig. 4. Effect of catalyst loading. Sodium salt of *m*-cresol 0.03 mol, PCNB 0.03 mol, *o*-xylene up to 50 ml, Speed of agitation 1000 rpm, temperature 120 °C.

PCNB. The highest reaction rate was observed for mole ratio of 1:1, so it was selected for further studies. The kinetic modal was tested for mole ratio ($M \neq 1$) of 1:1.5, 1:2 (Na-salt of *m*-cresol:PCNB) and it was found to be in agreement with the observed data (Fig. 6). Thus, it was possible to get the rate constant k_r and equilibrium constant K_e at 120 °C as 176.68 and 2.88 cm^3 mol^{-1} s^{-1}, respectively.
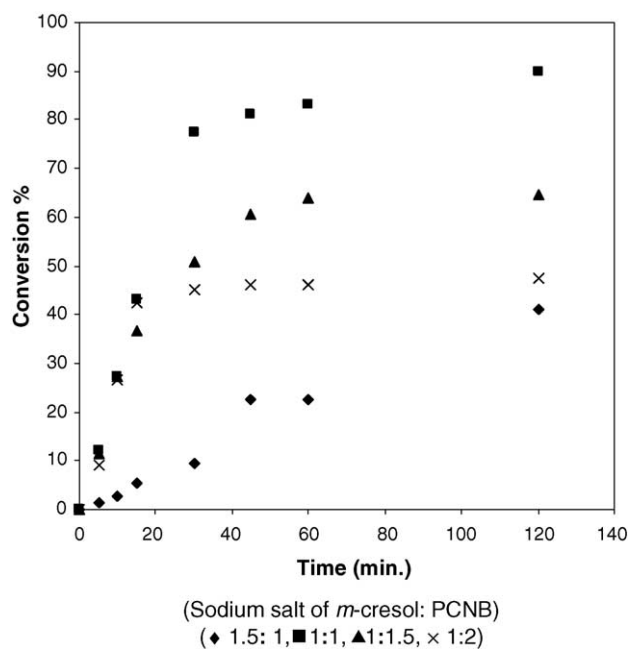

Fig. 5. Effect of different mole ratios on conversion of limiting reactant. *o*-Xylene (solvent) up to 50 ml, speed of agitation 1000 rpm, TBAB 0.006 mol, temperature 120 °C.
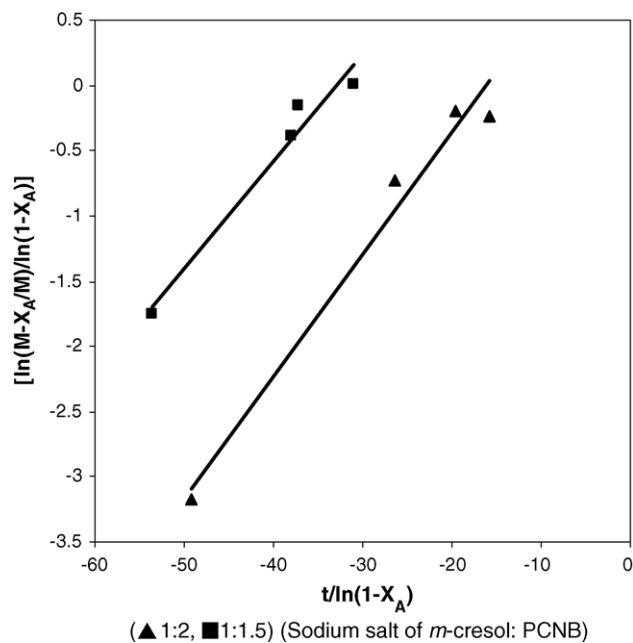
Fig. 6. Model validation: plot of $[\ln(M - X_A/M)/\ln(1 - X_A)]$ vs. $t/\ln(1 - X_A)$.

3.6. Effect of temperature

The effect of temperature was studied under otherwise similar reaction conditions in the range of 90–120 °C (Fig. 7). It was found that the initial reaction rate increased with increase in the temperature. The model was again tested for each temperature to get a good statistical fit (Fig. 8). The apparent activation energy was calculated as 16.43 kcal/mol (Fig. 9) and Gibbs free energy as 2.54 kcal/mol (Fig. 10).
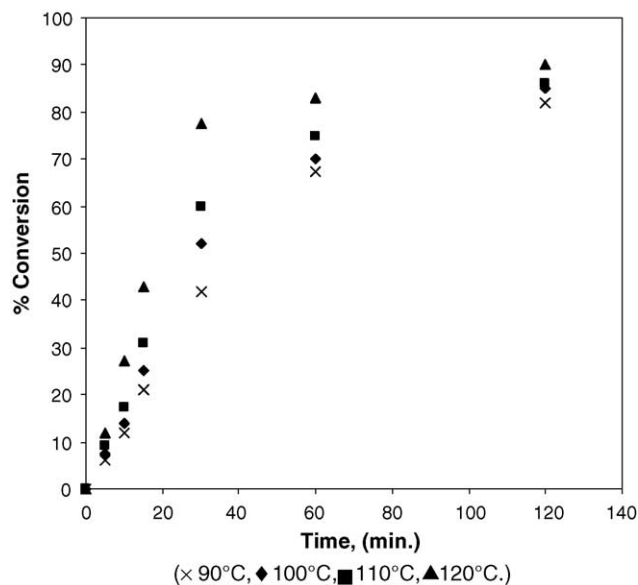

Fig. 7. Effect of temperature. Sodium salt of *m*-cresol 0.03 mol, PCNB 0.03 mol, TBAB 0.006 mol *o*-xylene (solvent) up to 50 ml, speed of agitation 1000 rpm, time 2 h.
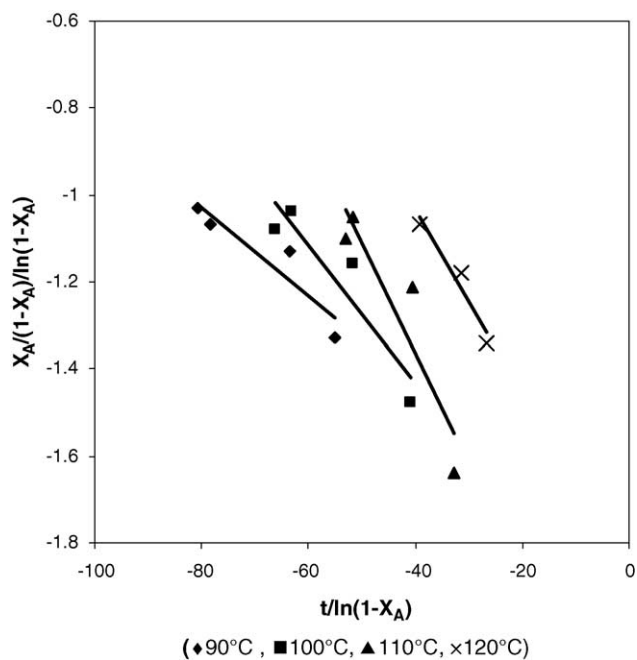

Fig. 8. Model validation at different temperatures: plot of $[X_A/(1 - X_A)/\ln(1 - X_A)]$ vs. $t/\ln(1 - X_A)$.

This should be treated as an apparent value since three different equilibria are combined in Eq. (6) to get the equilibrium constant K_e.

3.7. Effect of different cresol isomers

Sodium salts of *o*-cresol and *p*-cresol were also prepared in situ in *o*-xylene phase and the water was removed by azeotropic distillation to dry the solids. These salts were reacted under identical conditions with PCNB using TBAB as the catalyst. Ethers were the only products of these reactions. The conversions after 90 min were 44, 90 and 91%, respec-
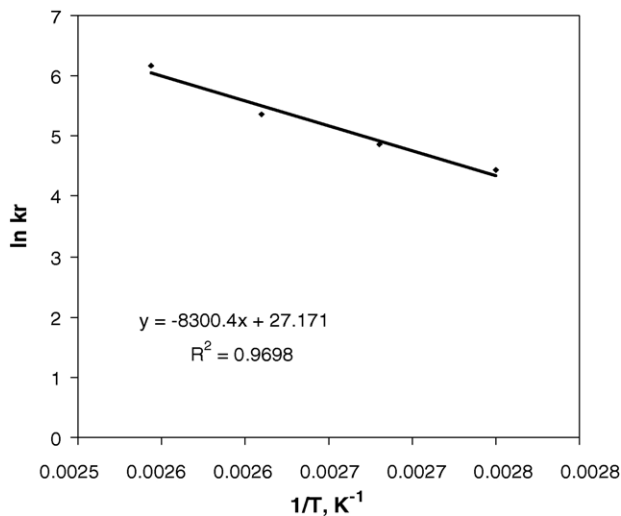

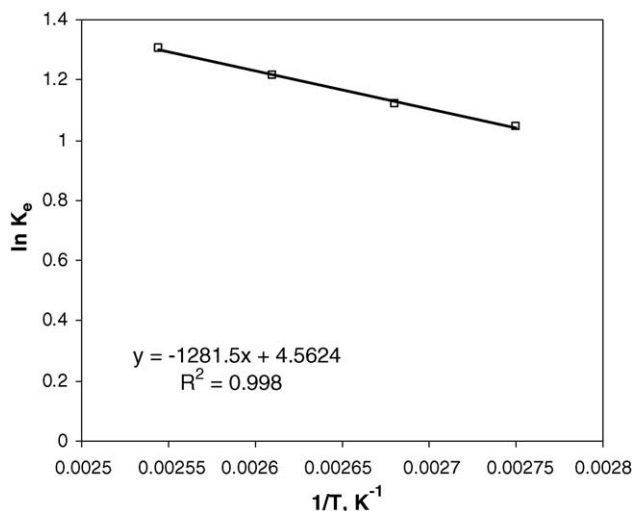$$y = -8300.4x + 27.171$$
$$R^2 = 0.9698$$

Fig. 9. Arrhenius plot.

Fig. 10. Plot of $\ln(K_e)$ vs. $1/T$ to get Gibb's free energy.

tively for the sodium salts of o-, m- and p-cresols. Sodium salts of m- and p-cresols showed almost similar reactivity towards PCNB while o-cresol was found to be much less reactive towards PCNB. Low reactivity of o-cresol can be accounted by steric hindrance caused by methyl group adjacent to phenolic group.

4. Conclusions

A simple process was developed to prepare 3-methyl-4′-nitro-diphenyl ether from p-chloronitrobenzene and solid sodium salt m-cresol with 100% selectivity by using inexpensive solvent like o-xylene under solid–liquid phase transfer catalysis. Tetra-n-butyl ammonium bromide was found to be the best catalyst. Since 3-methyl-4′-nitro-diphenyl ether was the sole product obtained in this reaction it can be easily separated from the reaction mixture. A comprehensive theoretical analysis of the process was carried out to explain the observed rate data. Apparent activation energy is $16.43\,\text{kcal mol}^{-1}$ while Gibb's free energy of the dissolution of sodium salt of m-cresol with anion exchange in o-xylene is $2.54\,\text{kcal mol}^{-1}$. The solid–liquid PTC is better than Ullmann's synthesis. The reactivity of sodium salts of o- and p-cresols was also studied. o-Cresol is less reactive than p- and m-cresol. Only the ethers were formed in these two cases as well.

Acknowledgment

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