

Novelties of microwave irradiated solid–liquid phase transfer catalysis (MISL-PTC) in synthesis of 2'-benzyloxyacetophenone

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Abstract

2'-Benzyloxyacetophenone is an important pharmaceutical intermediate for the manufacture of drugs used as diuretics, antihypertensive, platelet, antiaggregant, lipoxygenase, analgesics and prostaglandin, and for treatment of metabolic disorders. Microwave irradiation has been widely used for the rapid synthesis of a variety of compounds. In the current work, for the first time, novelties of low power microwave irradiated solid–liquid phase transfer catalysis, named as MISL-PTC, has been brought out in enhancements of the rates of selective O-alkylation of sodium salt of *o*-hydroxyacetophenone (OHAP) with benzyl chloride by using tetra-*n*-butylammonium bromide as a catalyst. The advantages of solid–liquid (S–L) PTC are that the reaction is conducted at controllable temperatures, the rates of reaction are increased by orders of magnitude and the reaction is 100% selective at 80 °C, in comparison with the liquid–liquid (L–L) PTC which is slow and produces by-products. The microwave irradiation further enhances the rates of reaction. The system elegantly forms a synergistic combination of S–L PTC and microwave irradiation. The mechanism based on homogeneous solubilization of solid resulting in the formation of an active ion pair with the nucleophile was found to prevail in the system. A new theoretical analysis is presented to determine both the rate constant and equilibrium constant from the same set of data. The reaction is intrinsically kinetically controlled. The Gibbs free energy for solid dissolution with anion exchange reaction could be also evaluated.

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1. Introduction

Phase transfer catalysis (PTC) has been applied to over 600 industrial processes for the manufacture of a variety of intermediates for dyestuffs, agrochemicals, perfumes, flavours, pharmaceuticals and polymers [1–3]. A large number of PTC processes use the liquid–liquid (L–L) mode of operation. PTC has been quite successful in C-, N-, O- and S-alkylations involving SN₂ type reactions in fine chemical industries, apart from dehydrohalogenations. Several attempts have been made in the past to synthesize ethers by using different tech-

niques such as PTC alkylation with sulfate esters in methylene chloride–water system [4], ion-exchange resins [5], base catalysts [6,7], isomerization [8], O-alkylation with tri-liquid PTC [9,10] and acidic clay catalysis [11].

When the halogen exchange of alkoxides is conducted in L–L PTC, there is always formation of alcohols 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. The aqueous phase promoted reactions can thus be totally suppressed and better selectivities are obtained. While L–L PTC involves heterogeneous reaction between two reagents located in aqueous and organic phases, S–L PTC involves reaction of an anionic reagent in a solid phase (usually a salt) with a reactant located in a continuous organic phase. Yadav and Sharma proposed the first

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mechanistic and kinetic model of S–L PTC for the reaction of benzyl chloride with solid sodium acetate and benzoate, to produce the commercially important benzyl esters, which has been commercialised [12]. Apart from our fundamental work on S–L PTC, Doraiswamy's group has done substantial work on modelling of PTC processes [13]. We have carried out the detailed mechanistic and modelling studies for industrially important fine chemical reactions under S–L PTC conditions [14,15]. The role of small amounts of water, the so-called omega phase, in S–L PTC was analysed in our earlier work, and a rigorous model of S–L PTC with omega phase has been established [16].

Of late, microwave irradiation has been increasingly used as a synthetic tool in a number of studies. Microwave technology is a novel approach towards clean and green chemistry and it is relatively a very convenient, safe and rapid methodology. The slow uptake of the technology has been attributed to its initial lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating, but a number of papers have appeared [17–23]. When multi-mode power input at higher rates is used, it leads to evaporation of the solvent [21]. A large number of papers which appeared in several journals are based on the use of multi-mode domestic ovens with high power input which have a serious drawback of non-reproducibility of results, since the intensity of energy supplied to the reaction mixture is a strong function of the position of the sample on the rotating platform in the oven [23,24]. This fact was grossly overlooked since several different types of reactions occurred in a short time, in some cases as solid–liquid or solid–solid reactions. However, scale-up of microwave assisted reactions has become a formidable task as has been brought out recently [25]. Obviously, no kinetic studies have been reported, and such data essential for scale-up are missing from published literature.

Rates of PTC reactions, as well as selectivity of the desired product, can be synergistically enhanced by using microwave irradiation. The MW assisted solid–liquid phase transfer catalyzed synthesis of *o*-ethoxyphenol has been reported [26]. The solid composite copper–copper chloride assisted alkylation of naphthols promoted by microwave irradiation has been developed [26]. Loupy et al. have given a detailed account of the microwave activation in various solid–liquid phase transfer catalyzed reactions [27]. Several large pharmaceutical companies have reported dramatic productivity increases in switching from conventional synthesis to microwave assisted organic synthesis [28]. Organic synthesis of various ethers employing solid–liquid phase transfer catalysts under microwave conditions has been reported [29–34]. However, all work reported so far deals with input of very high power microwaves (>600 W) leading to reaction temperatures of more than 140–180 °C depending on solvents or reactants. At such high temperatures, most of the quaternary phase transfer catalysts degrade and the process no longer remains a true PTC. We have brought out the importance of low

energy microwave irradiation including in-depth analysis of greener aspects of PTC very recently [35–37].

The current work deals with the novelties of selective synthesis of 2'-benzyloxyacetophenone at low power inputs and attempts to understand the role of microwaves in enhancement of rates of reaction and selectivities. 2'-Benzyloxyacetophenone is an important pharmaceutical intermediate for the manufacture of drugs used as diuretics, antihypertensive, platelet, antiaggregant, lipoxygenase, analgesics, prostaglandin, and for treatment of metabolic disorders. The research has an academic impact and industrial applications and demonstrates the prowess of low energy microwave irradiated solid–liquid phase transfer catalysis, named MISL-PTC. Further, another novelty of the work is the development of a general modelling method by which it would be possible to determine the intrinsic reaction rate constant and also the overall equilibrium constant for exchange of anions, using the same set of data.

2. Experimental

2.1. Chemicals and catalysts

o-Hydroxyacetophenone (OHAP), benzyl chloride, toluene, diphenyl ether and sodium hydroxide, all of A.R. grade, were procured from M/s E. Merck Ltd., Mumbai. The phase transfer catalysts used in this work were received as gift samples from M/s Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India.

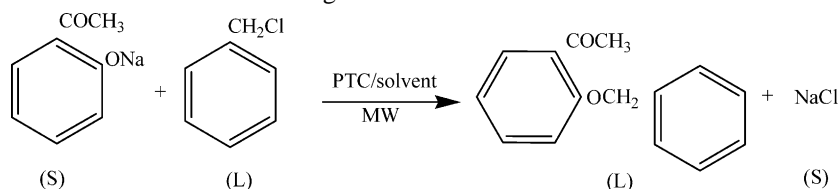
2.2. Experimental procedure

The experimental set-up for the microwave experiment was the commercially available "Discover" system of CEM Corporation, USA (Model CEM-SP 1245), with a proper temperature and pressure control. It is a mono-mode microwave system. The reactor consisted of 3.5 cm i.d. fully baffled mechanically agitated reactor of 150 cm³ capacity, which was equipped with four equispaced baffles and a six-bladed pitched turbine impeller and a reflux condenser. The impeller was located at a distance of 1 cm from the bottom. This arrangement ensured excellent solid–liquid mixing for high mass transfer rates. Control experiments were also done in the absence of the microwave effect using the same reactor assembly. The reactor was kept in a thermostatic bath whose temperature could be maintained within ± 1 °C of the desired value.

Typically, the reaction was carried out as follows. Initially, a suspension of 0.01 mol of sodium salt of *o*-hydroxyacetophenone was prepared in situ from 0.01 mol *o*-hydroxyacetophenone and 0.012 mol sodium hydroxide by heating in toluene at 105 °C for 30 min with microwave irradiation (140 W). The reaction was very facile. Water was removed by azeotropic distillation, and a completely dry solid particulate suspension of sodium salt of *o*-

hydroxyacetophenone was formed in situ. By this way, all traces of water were removed in order to ensure that no omega phase was formed in the S–L PTC process. Then the mixture was cooled down to 80 °C at which 40 W power input was given to maintain the temperature. The reaction was carried out at the set temperature after the addition of 0.01 mol of benzyl chloride. The total volume was made to 30 mL by adding toluene. 0.002 mol of catalyst was added when the desired temperature has been attained. A zero time sample was collected and sampling was done periodically to get concentration–time profiles of reactants and products. All the typical reactions were carried out at 80 °C and 1000 rpm. It is important to note here that the power supplied to the system, during the actual reaction (after tetra-*n*-butyl ammonium bromide (TBAB) addition), was below 40 W. Conventional heating was also used for the reaction which was carried out at 80 °C as a control experiment.

The reaction scheme is as given below:



2.3. Analysis

Samples were withdrawn periodically and GC analyses were performed (Chemito Model 8610) by using a stainless steel column (3.25 mm × 4 m) packed with 10% (w/w) OV-17/WHP. The quantification was done by calibration using synthetic mixtures. The products were also confirmed by GC-MS. Initial rates of reactions were also evaluated.

3. Results and discussions

Almost any type of organic reaction requiring heating or thermal conditions can be performed using microwave irradiation. Microwave dielectric heating is dependent on the ability of the solvent or matrix to absorb microwave energy and convert into heat. When irradiated at microwave frequencies, the ions or dipole of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field tries to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have time to realign, or it reorients too quickly with the applied field, no heating occurs. Microwave irradiation produces efficient in situ heating, resulting in even temperature throughout the sample, as compared with the conventional heating. The initial rate of reaction with TBAB in the presence of microwaves was 30 times greater than that under the same conditions with conventional heating at 80 °C. The

conversion profile is shown in Fig. 1. The reaction was 100% selective to the ether formation. Thus, it was decided to probe the reaction systematically for microwave irradiation and develop a kinetic model.

3.1. Mechanism and kinetic model

The basic mechanism of the reaction is not changed due to the influence of microwaves and enhancement is due to more collisions of the excited species, without any change in activation energy [35–37]. Thus, the usual PTC reaction mechanism prevails and the first step in the reaction 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 of sodium salt of OHAP ($R_1O^-Na^+$) to form the $[Q^+Y^-] = [Q^+OR_1^-]$, 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 $[Q^+Y^-]$ with the reactant (RX) (=BzCl) located in the organic phase. There are several possibilities by which this reaction can occur. Finally, the third step involves the transport of the co-product anion $[X^-]$, the leaving group, by the phase transfer cation to the solid 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 reac-

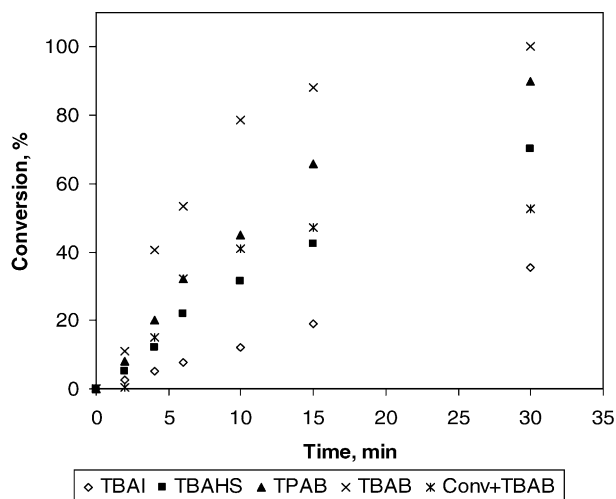
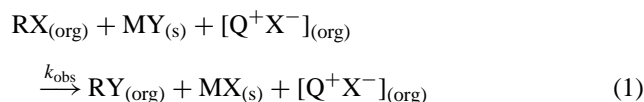


Fig. 1. Effect of different catalysts. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene 30 mL, catalyst 0.002 mol, temperature 80 °C, speed 1000 rpm.

tion takes place in anhydrous condition since both solid and liquid phases were dry. So the formation of the omega phase was discounted.

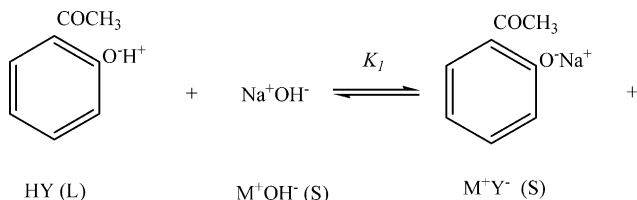
It is worthwhile to briefly mention the earlier modelling efforts. There are two types of mechanisms for S–L PTC: the homogeneous solubilization mechanism of Yadav and Sharma and heterogeneous solubilization of Naik and Doraiswamy [12,13]. In the heterogeneous solubilization, the particles are totally 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^-). 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 [15,16].

Preliminary experiments suggested that the homogeneous solubilization model, illustrated by the SN_2 type of reaction of the substrate RX with the nucleophile Y of the solid reactant MY , was applicable to the current work. Here M^+ is the inorganic metallic counter-ion of the nucleophile Y^- . The overall reaction is:

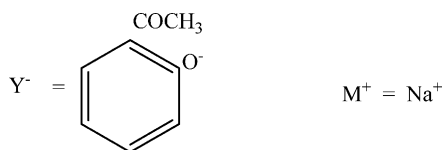


where Q^+ is the quaternary cation of the catalyst. Q^+X^- is a loosely bound ion pair shown in squared brackets. The solid reactant is in equilibrium with its solution in the organic phase.

The salt MY was generated in situ from OHAP as given below:



where the various anions are as follows:



Hence, the concentration of the organo-metallic salt generated in situ is given by:

$$[M^+Y^-]_S = K_1 \frac{[M^+OH^-]_S [HY]_L}{[W]_L} \quad (3)$$

In all control experiments, water was removed as an azeotrope with toluene before starting the experiment. When the water is removed from the reaction mixture and also the solid alkali $[MOH]$ is taken in stoichiometric excess, then all OHAP will be converted into a dry particulate sodium salt:

$$[MY]_S \cong [HY]_L \quad (4)$$

If while converting OHAP into its sodium salt, the water of reaction is not removed from the organic phase or some trace amount of water is retained in the reaction mixture, without leading to ω phase formation and also when $[MOH] \leq [HY]$, then:

$$[MY]_S < [HY]_L. \quad (5)$$

When Eq. (4) holds, then the alkali concentration will have no effect (if it is taken in little above stoichiometric requirement). The salt is transferred into the organic phase:

$$[M^+Y^-]_S \xrightleftharpoons{K_2} [M^+Y^-]_{org} \quad (6)$$

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

$$[Q^+X^-]_{org} + [M^+Y^-]_{org} \xrightleftharpoons{K_3} [Q^+Y^-]_{org} + [M^+X]_{org} \quad (7)$$

$$[MX^-]_{org} \xrightleftharpoons{1/K_4} [M^+X^-]_S \quad (8)$$

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



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.

W(L)

The equilibrium constant K_e which is a sort of a solubility parameter is defined by combining steps 6, 7 and 8 as follows:

$$K_e = \frac{[Q^+Y^-]_{org} [M^+X^-]_S}{[Q^+X^-]_{org} [M^+Y^-]_S} = \frac{K_2 K_3}{K_4} \quad (10)$$

When condition 5 is applicable, then Eq. (10) takes the following form:

$$K_e = \frac{[Q^+Y^-]_{org} [M^+X^-]_S [W]_L}{[Q^+X^-]_{org} [M^+OH^-]_S [HY]_L} = \frac{K_1 K_2 K_3}{K_4} \quad (11)$$

The rate of reaction in the organic phase between the substrate RX and the nucleophile Q^+Y^- is given by:

$$-\frac{d[RX]_{\text{org}}}{dt} = k_r [RX]_{\text{org}} [Q^+Y^-]_{\text{org}} \quad (12)$$

When Eq. (4) holds, then substituting for $[Q^+Y^-]_{\text{org}}$ from Eq. (10) in Eq. (12), the rate is given by:

$$-\frac{d[RX]_{\text{org}}}{dt} = k_r K_e \frac{[M^+Y^-]_S}{[M^+X^-]_S} [RX]_{\text{org}} [Q^+X^-]_{\text{org}} \quad (13)$$

On the contrary, when condition 5 is applicable, then the rate of reaction is given by:

$$-\frac{d[RX]_{\text{org}}}{dt} = k_r K_e \frac{[M^+OH^-]_S [HY]_L}{[M^+X^-]_S [W]_L} [RX]_{\text{org}} [Q^+X^-]_{\text{org}} \quad (14)$$

Now,

$$Q_0 = [Q^+Y^-]_{\text{org}} + [Q^+X^-]_{\text{org}} \quad (15)$$

=total concentration of catalyst in organic phase.

Let the fractional conversion X_A of RX at time t ,

$$X_A = \frac{N_{RX_0} - N_{RX}}{N_{RX_0}} \quad (16)$$

where N_{RX_0} are the initial moles of RX at time $t = 0$. Let $M = N_{MY_0}/N_{RX_0}$ = initial mole ratio of nucleophile to substrate. From the stoichiometry of the reaction, all terms in Eqs. (13) and (14) can be written in terms of X_A and Q_0 . Separation of variables and integration of these two equations respectively leads to the following:

$$\int_0^{X_A} \left[\frac{X_A + K_e M - K_e X_A}{K_e (M - X_A)(1 - X_A)} \right] dX_A = k_r Q_0 t \quad (17)$$

$$\int_0^{X_A} \left[\frac{X_A + K_e M - K_e X_A}{K_e (M - X_A)(1 - X_A)} \right] dX_A = k_r \frac{[M^+OH^-]_S [HY]_L}{[W]_L} Q_0 t \quad (18)$$

These integrals are solved by the method of partial fractions to get the following:

$$\left(\frac{M}{M-1} \right) \ln \left(\frac{M-X_A}{M} \right) - \left(\frac{1-K_e+K_e M}{M-1} \right) \times \ln(1-X_A) = k_r Q_0 t \quad \text{for } M \neq 1 \quad (19)$$

and

$$\left(\frac{M}{M-1} \right) \ln \left(\frac{M-X_A}{M} \right) - \left(\frac{1-K_e+K_e M}{M-1} \right) \times \ln(1-X_A) = k_r \frac{[M^+OH^-]_S [HY]_L}{[W]_L} Q_0 t \quad \text{for } M \neq 1 \quad (20)$$

Eqs. (19) and (20) can be further manipulated to the following equations of a straight line, for the above two cases, to extract both K_e and k_r :

$$\frac{\ln[(M-X_A)/M]}{\ln(1-X_A)} = \left[\frac{(M-1)k_r Q_0}{M} \right] \frac{t}{\ln(1-X_A)} + \left(\frac{1-K_e+K_e M}{M} \right) \quad (21)$$

$$\frac{\ln[(M-X_A)/M]}{\ln(1-X_A)} = \left[\frac{(M-1)k_r Q_0}{M} \frac{[M^+OH^-]_S [HY]_L}{[W]_L} \right] \times \frac{t}{\ln(1-X_A)} + \left(\frac{1-K_e+K_e M}{M} \right) \quad (22)$$

A plot of $[\ln\{(M-X_A)/M\}/\ln(1-X_A)]$ versus $t/\ln(1-X_A)$ should give for the straight lines according to Eqs. (21) and (22) and should give slopes = $[(M-1)k_r Q_0/M]$ and $[(M-1)k_r Q_0/M]([M^+OH^-]_S [HY]_L/[W]_L)$, respectively, and intercepts will be equal to $[(M-1)K_e + 1/M]$ in both the cases.

Thus, both K_e and k_r can be obtained from the slope and intercept since all other experimental conditions are known such as M and Q_0 . Further, for equimolar quantities of substrate and nucleophile, the following form of the integrated equation results.

$$\left(\frac{X_A}{1-X_A} \right) + (1-K_e) \ln(1-X_A) = k_r Q_0 t \quad \text{for } M = 1 \quad (23)$$

Eq. (18) is also manipulated to the following

$$\frac{X_A/(1-X_A)}{\ln(1-X_A)} = k_r Q_0 \frac{t}{(1-X_A)} + (K_e - 1) \quad (24)$$

and when Eq. (5) is applicable, then the rate of reaction is given by

$$\frac{X_A/(1-X_A)}{\ln(1-X_A)} = \left[\frac{k_r Q_0 [M^+OH^-]_S [HY]_L}{[W]_L} \right] \times \frac{t}{(1-X_A)} + (K_e - 1) \quad (25)$$

According to Eqs. (24) and (25), a plot of $[X_A/(1-X_A)/\ln(1-X_A)]$ versus $t/\ln(1-X_A)$ will give a straight line with respective slopes equal to $k_r Q_0$ and $[k_r Q_0 [M^+OH^-]_S [HY]_L/[W]_L]$, and the intercepts will be equal to $(K_e - 1)$ for both lines.

The validation of the above model was verified by conducting several experiments.

3.2. Effect of various catalysts

Four different catalysts, tetra-*n*-butylammonium iodide (TBAI), tetra-*n*-propylammonium bromide (TPAB), tetra-*n*-butylammonium hydrogensulfate (TBAHS) and tetra-*n*-butyl

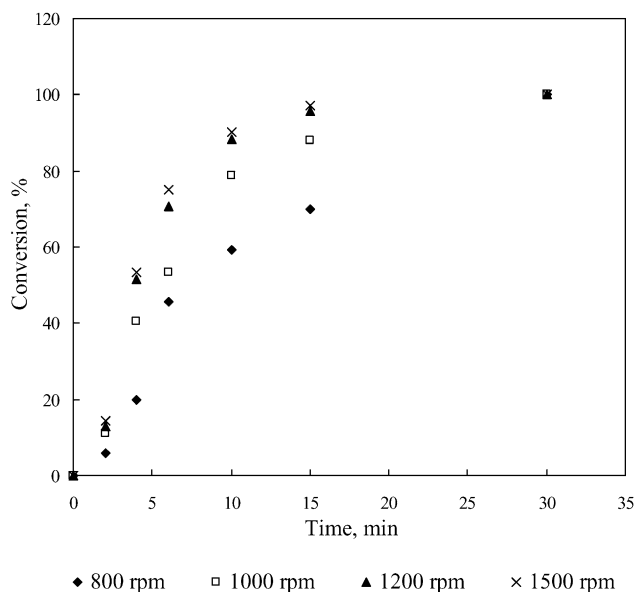


Fig. 2. Effect of speed of agitation. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene 30 mL, TBAB 0.002 mol, temperature 80 °C.

ammonium bromide were selected for the reaction under otherwise similar concentrations of catalysts at 80 °C and 1000 rpm (Fig. 1). Out of these, TBAB gave the maximum rates of reaction and conversion. This is a solid–liquid PTC process in which the entire catalyst is in the organic liquid phase and the solubility of solid nucleophile is affected by the type of cations and anions present. Indeed, the PTC breaks the crystal lattice and transports the nucleophile as Q^+Y^- whose concentration depends on the type of PTC. This is the case of homogeneous solubilization. Therefore, the activity of TBAB is much greater. Thus, further experiments were conducted with this catalyst. The selectivity to the ether was 100%.

3.3. Effect of speed of agitation

The reaction was carried out at four different speeds of agitation i.e. 800, 1000, 1200 and 1500 rpm (Fig. 2). There was no significant change in the rate of reaction beyond 1000 rpm. This indicated the absence of external mass transfer resistance beyond 1000 rpm. All subsequent reactions were carried out with 1000 rpm while assessing the effect of other variables on the rate of reaction. A calculation was done to find out if the theory of mass transfer with reaction could be invoked to find the locale of reaction in the absence of mass transfer resistance and to which regime the system belonged.

The observed initial rate of reaction, for a typical experiment was equal to $3 \times 10^{-7} \text{ mol cm}^{-3} \text{ s}^{-1}$, whereas the rate of mass transfer was estimated from the knowledge of solid–liquid mass transfer coefficient (k_{SL-A}), particle surface area ($a_p = 600 \text{ cm}^{-1}$) and the solubility of sodium salt of OHAP in toluene ($3.5 \times 10^{-5} \text{ mol/cm}^3$). The solid–liquid mass transfer coefficient (k_{SL-A}) was found from the Sher-

wood number ($k_{SL-A}d_p/D_A = 2$). A limiting value of the Sherwood number was taken as 2 since the particles were very fine. The Wilke–Chang equation was used to calculate the bulk diffusivity. The mass transfer rate was equal to $6.3 \times 10^{-5} \text{ mol cm}^{-3} \text{ s}^{-1}$, which is 210 times greater than the rate of reaction. Thus, the observed reaction rate was slower than the mass transfer rate, and the organic phase was always saturated with the ion pair $Q^+OR_1^-$, thereby making it as a pseudo first order reaction. That is, the reaction occurred in the bulk liquid phase and not in the film surrounding the solid particle.

3.4. Effect of NaOH concentration

Two types of experiments were done. All control experiments were performed with dry sodium salt of OHAP, prepared in situ, wherein all water was removed from the reaction mass before adding the substrate and catalyst. So the model developed for this purpose did not have any sodium hydroxide concentration in it.

In the case of studies on the effect of NaOH concentration at 80 °C, two types of studies were done. The sodium salt was generated with OHAP in situ, and water generated due to the reaction was not removed and therefore, not all OHAP was converted into the sodium salt and hence, as the mole ratio of NaOH to OHAP was increased, the conversion increased. This is due to complete conversion to the sodium salt of OHAP beyond a certain excess concentration of NaOH. Fig. 3 shows the effect of NaOH concentration for type 1 experiments over a range of 0.33–0.67 M on the conversion of benzyl chloride. In these experiments, equimolar quantities of OHAP and benzyl chloride (0.01 mol each) were used and the mole ratio of NaOH to *p*-tert-butylphenol was varied at 1:1, 1.2:1, 1.5:1 and 2:1 which correspond to 0.33, 0.4, 0.5 and 0.67 M. To ensure complete conversion of OHAP to its sodium salt, 1.2 mol of NaOH per mol OHAP was taken for all the reactions. The purpose was to see if omega phase

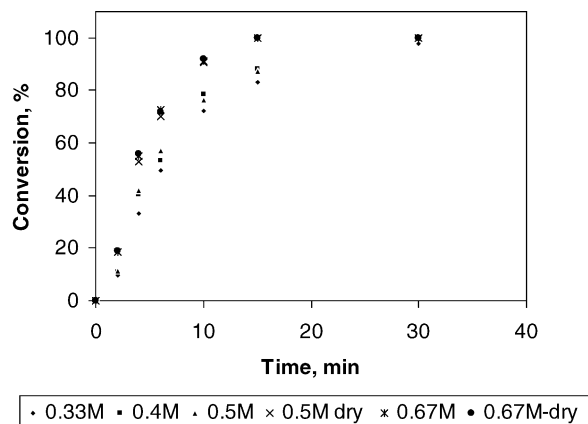


Fig. 3. Effect of NaOH concentration. OHAP 0.01 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene to make 30 mL, TBAB 0.002 mol, 1000 rpm, temperature 80 °C.

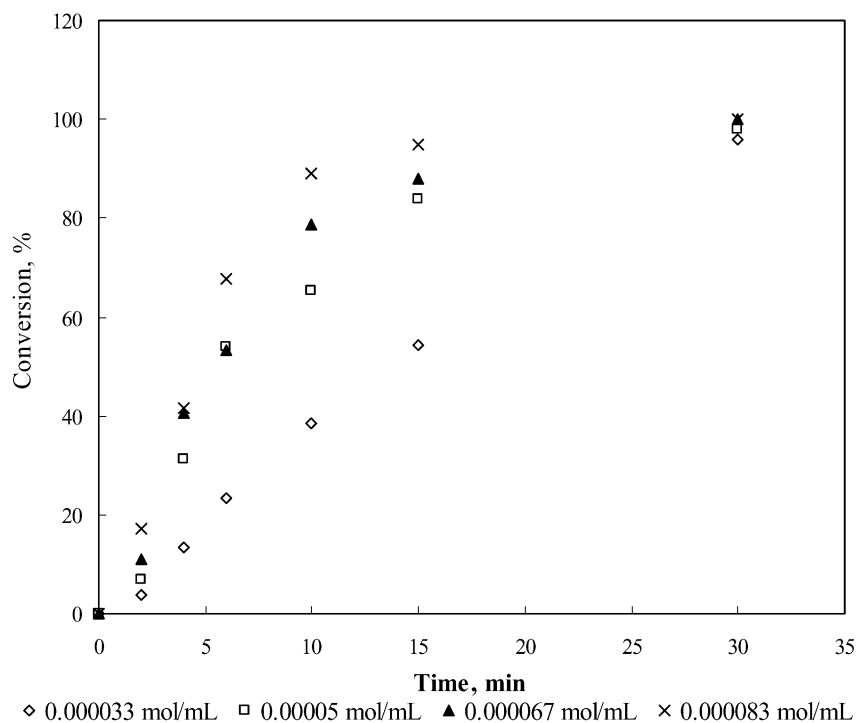


Fig. 4. Effect of catalyst concentration. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene to make 30 mL, 1000 rpm, temperature 80 °C.

was formed, which could enhance the rate. The higher NaOH concentration also picks up water and decreases the concentration of catalyst in aqueous phase. There was no omega phase formation. The effect of NaOH could be accounted as

given by the rate Eq. (14). The integrated forms of Eq. (14) are given by Eqs. (20) and (25) for $M \neq 1$ and $M=1$, respectively.

In the case of experiments, wherein water generated due to the formation of sodium salt of OHAP was removed totally

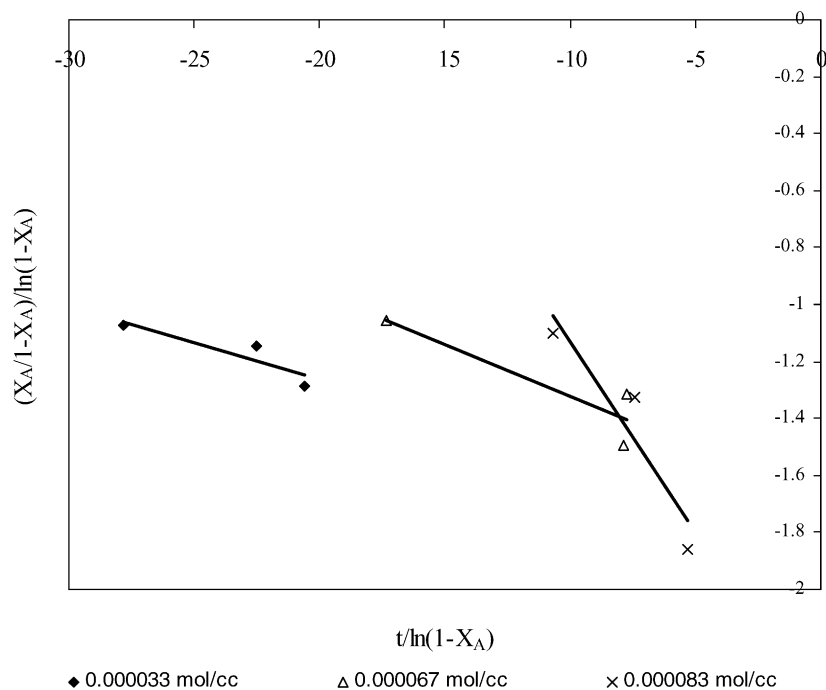


Fig. 5. Effect of catalyst concentration. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene to make 30 mL, 1000 rpm, temperature 80 °C.

before the experiment was started (e.g. 0.5 M-dry and 0.67 M-dry points in Fig. 3), the conversions were the same, within experimental error, as those for the control experiment shown by 0.4 M-dry data point which was for dry sodium salt of OHAP, which is also shown in Fig. 3. The theory developed was thus validated for both the cases.

3.5. Effect of catalyst concentration

The concentration of the catalyst was varied from 0.33×10^{-4} to 0.83×10^{-4} mol/cm³ (Fig. 4). As the concentration was increased, the conversion increased, but above a concentration of 6.7×10^{-5} mol/cm³, there was no further increase in the conversion. This suggested that the reaction rate was fast and thus, mass transfer of ion pair $Q^+R_1^-$ from the liquid film to the bulk liquid was controlling beyond 6.7×10^{-5} mol/cm³ of catalyst. Here the rate of mass transfer was less than the rate of reaction. The validity of Eq. (24) was tested (Fig. 5). There is an excellent fit for different catalyst concentrations.

3.6. Effect of mole ratio

The effect of mole ratio of benzyl chloride to sodium salt of OHAP was studied from 1:0.8 to 1:2, keeping the total volume of the reaction mass constant at 30 cm³ with toluene. The catalyst loading was kept at 0.67×10^{-4} mol/cm³. The

conversion was found to increase marginally and remained almost the same at the mol ratios of 1:1, 1:1.33 and 1:2 (Fig. 6). This is obvious from the fact that the concentration of the ion pair $Q^+R_1^-$ in the organic phase remains constant as is evident from Eqs. (2) and (3). So, further addition of sodium salt of OHAP does not help in enhancement of the rate of reaction. Eqs. (13) and (19) were used for $M \neq 1$ and $M = 1$ to make the plots to validate the theory.

3.7. Effect of temperature

The effect of temperature was studied under otherwise similar reaction conditions from 60–90 °C (Fig. 7). It was found that the conversion increased substantially with increase in temperature from 60 to 80 °C. However, there was a marginal increase in conversion when the temperature was increased from 80 to 90 °C, due to the mass transfer effects. The same theory was again validated at all temperatures up to 80 °C (Fig. 8). Thus, the Arrhenius plot was made and the activation energy was found to be 47.6 kcal/mol, which suggested that the reaction was kinetically controlled (Fig. 9). The Gibbs free energy, $\Delta G = -RT \ln K_e = -RT \ln(K_2K_3/K_4)$, for the solid dissolution with anion exchange reaction in the organic phase was estimated as 2.4 kcal/mol (Fig. 10). The solubility of both ion pairs increases with temperature and also the ion exchange reaction increases with temperature.

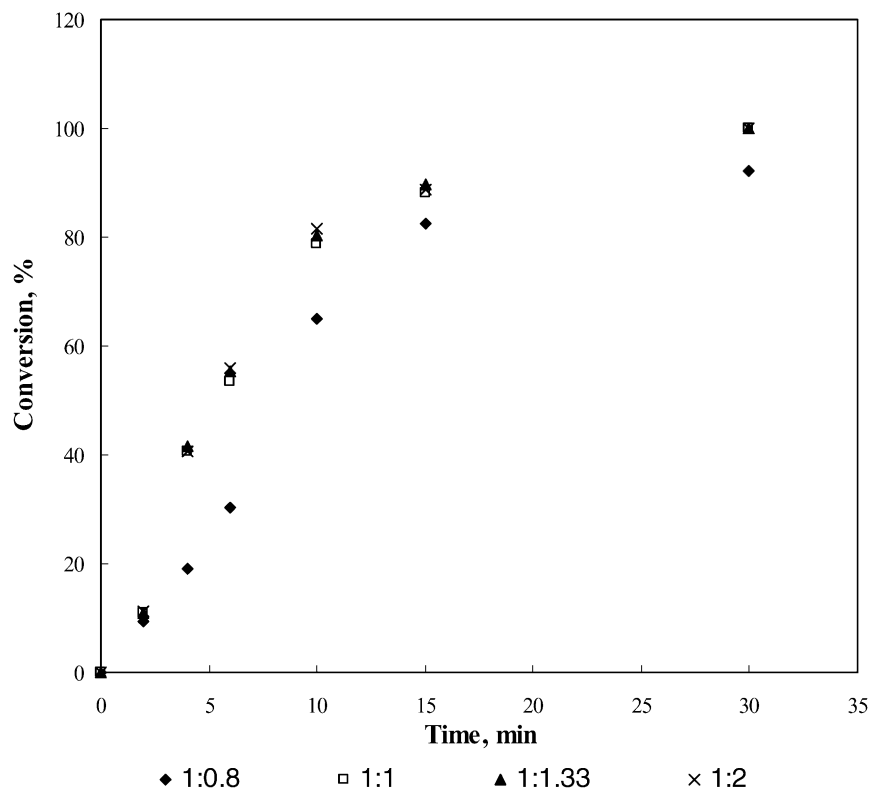


Fig. 6. Effect of various mole ratios of benzyl chloride to sodium salt of OHAP. Diphenyl ether (internal standard) 2.0 mL, toluene to make 30 mL, TBAB 0.002 mol, 1000 rpm, temperature 80 °C.

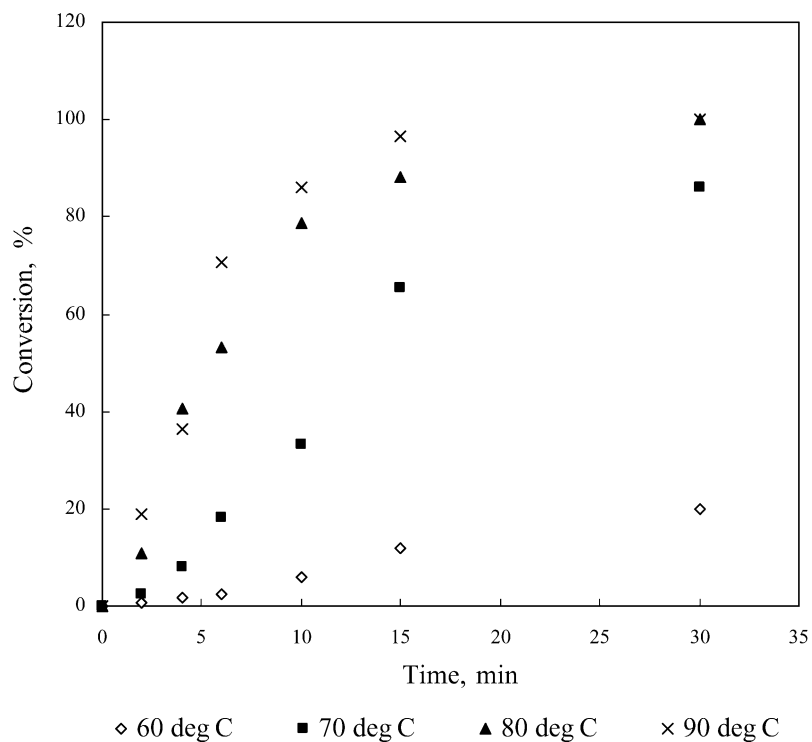


Fig. 7. Effect of temperature. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene to make 30 mL, TBAB 0.002 mol, 1000 rpm.

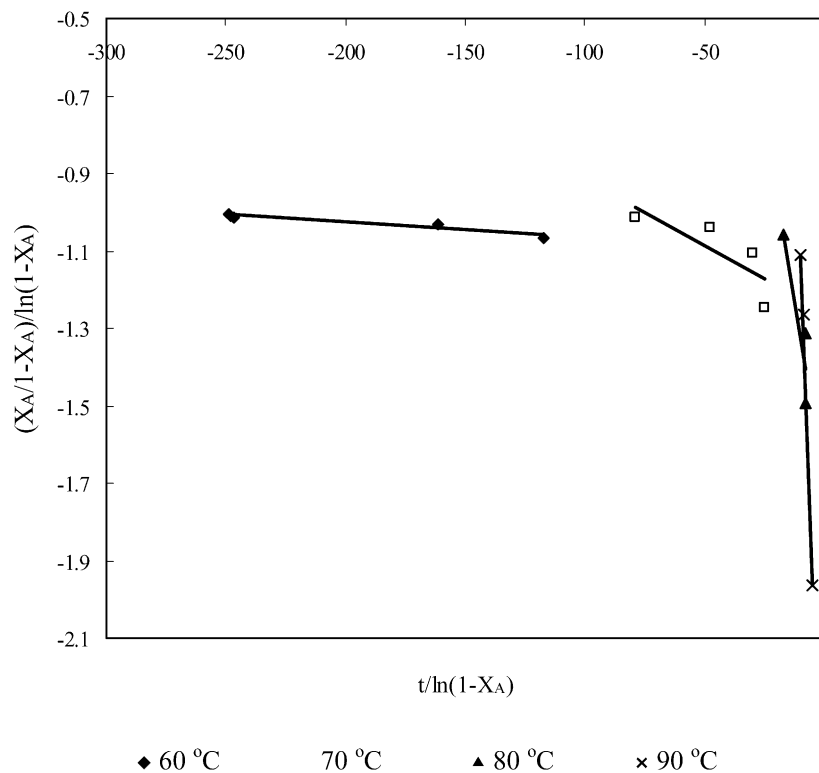


Fig. 8. Validation of model at different temperatures. OHAP 0.01 mol, NaOH 0.012 mol, benzyl chloride 0.01 mol, diphenyl ether (internal standard) 2.0 mL, toluene 30 mL, TBAB 0.002 mol, 1000 rpm. $k_r = 5.97 \text{ cm}^3 \text{ mol}^{-1} \text{ min}^{-1}$; $K_e = 2.1072$ for 60 °C; $k_r = 52.23 \text{ cm}^3 \text{ mol}^{-1} \text{ min}^{-1}$; $K_e = 2.2596$ for 70 °C; $k_r = 541.79 \text{ cm}^3 \text{ mol}^{-1} \text{ min}^{-1}$; $K_e = 2.6864$ for 80 °C; $k_r = 2664.18 \text{ cm}^3 \text{ mol}^{-1} \text{ min}^{-1}$; $K_e = 3.8332$ for 90 °C.

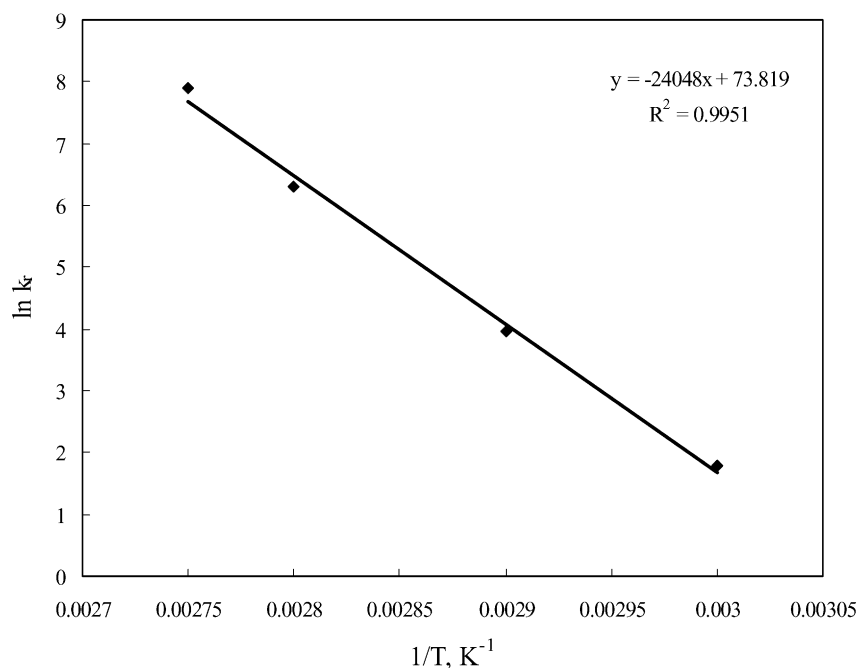


Fig. 9. Arrhenius plot.

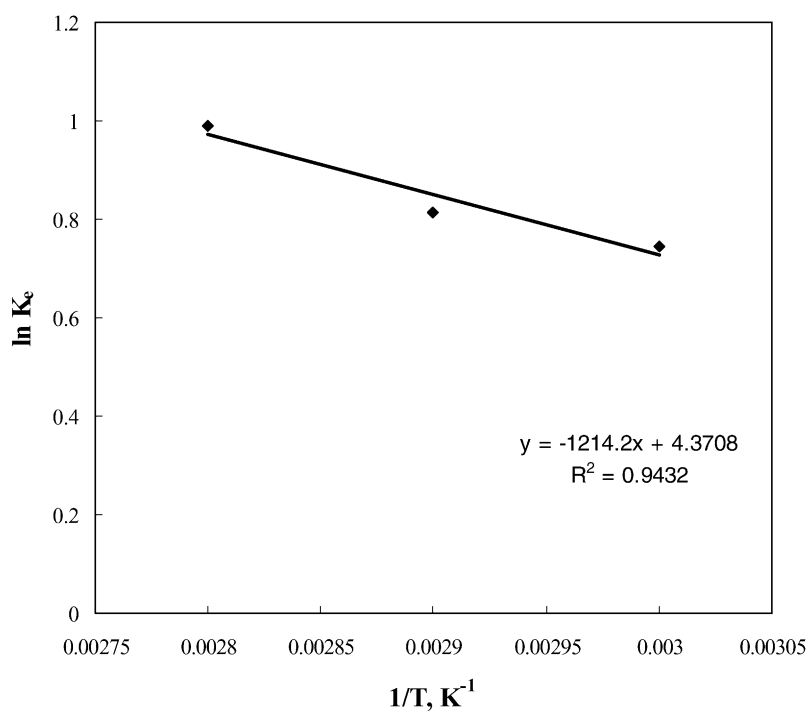


Fig. 10. Gibbs free energy plot.

4. Conclusions

There is a plethora of papers on solid–liquid phase transfer catalysis and a few papers have appeared on the use of microwaves to synergistically enhance the rates of S–L PTC, but all of which are at very high energy input which mask the true effect of the phase transfer agent. The current work addresses

a low energy input microwave irradiated S–L PTC (MISL-PTC) in the synthesis of 2'-benzyloxyacetophenone which is an important pharmaceutical intermediate for the manufacture of several drugs. We have shown for the first time the novelties of low power microwave irradiated solid–liquid phase transfer catalysis in enhancements of the rate of selective O-alkylation of sodium salt of *o*-hydroxyacetophenone

with benzyl chloride by using a variety of catalysts amongst which tetra-*n*-butylammonium bromide was found the best catalyst at 80 °C. There was an enhancement of 30 times over the corresponding S–L PTC with 100% selectivity. The mechanism based on homogeneous solubilization of solid resulting in the formation of an active ion pair with the nucleophile was found to prevail in the system. A complete theoretical analysis is done to determine both the rate constant and equilibrium constant from the same set of data. The reaction is intrinsically kinetically controlled. The Gibbs free energy for the solid dissolution with anion exchange reaction in the organic phase was also calculated.

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