Ultrasound and Two Active Site Phase-Transfer Catalyst Effect in Asymmetry Synthesis: A Kinetic Study

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The phase transfer catalyst 1-benzyl-1,4-diazoniabicyclo[2.2.1]hepta-2,4(7)-dienedichloride (BDHDC) in organic chiral synthesis was used in this study. Kinetic parameters such as ultrasonication effect, phase transfer catalyst dose, solvents, butyl chloride volume, stirring speed and weight of KOH were examined for the phase transfer catalytic reactions. The reaction between phenyl acetonitrile and butyl chloride was carried out under basic conditions and ultrasonic irradiation (300 W, 40 kHz) using BDHDC as a phase transfer catalyst. The introduction of BDHDC catalyst significantly improved the overall reaction, resulting in a high yield of the chiral combination. The product formation has been optimized by modifying the kinetic parameters.

Keywords: Substitution reaction, Phase transfer catalyst, Kinetic study.

INTRODUCTION

In many research fields including medicinal field, organic reactions are facing different issues because of the solubility and yield. To speed up or enable reactions between chemical species dwelling in mutually insoluble phases is the focus of phase transfer catalysis [1,2]. When two reacting species are positioned in immiscible phases, heterogeneous chemical reactions can frequently be suppressed by several factors [3,4]. The most important challenge lies in bringing together nucleophilic reagents that are water soluble. Due to this, the reaction yield will be affected. Phase-transfer catalysis, often known as PTC, is a helpful technique that can be used to create organic molecules from two reactants that cannot mix together [5]. Excessive solvation of the nucleophile, however, causes only modest rate acceleration. Alternatives include the use of costly dipolar aprotic solvents, which provide challenges in post-reaction recovery due to their difficulty to isolate from the reaction mixture.

Catalytic quantities of phase transfer agents are used in phase transfer catalysts to enable reactions between reagents in two immiscible phases. This is an effective way for over-coming such a challenge. Quaternary ammonium salts immobilized on clays, either by adsorption on or intercalation within such inorganic matrices, have been the focus of substantial research and development as triphase catalysts [6]. The intrinsic disadvantages of these catalysts, such as their restricted swelling capability in organic solvents, make them unsuitable for many reactions and prohibit their widespread adoption. The use of these intercalated ammonium salts as phase transfer catalysts (PTC) was limited to a few processes. For example, benzyltri-*n*-butylammonium ion supported by montmorillonite was used as a catalyst in the reaction of phenol with *n*-butyl bromide or in the synthesis of symmetrical formaldehyde acetals [7]. The phenomenon of phase-transfer catalysis occurs when the rate of a reaction between the chemical species in different phases is increased by adding a small amount of an agent that extracts one of the reactants, most commonly an anion, across the interface into the other phase so that the reaction can proceed. The resulting anion is transferred from the organic phase back into the aqueous or solid phase, completing the reaction and the transfer step.

The efficiency of phase transfer catalysts (PTC) is also affected by catalyst hydrophobicity and counter ion strength. Phase transfer catalysis reactions are far more enticing than approaches that rely on polar, water-miscible solvents. These advantages have led to the widespread use of phase transfer reactions in synthetic organic chemistry, with the reactions being praised as "green" alternatives to various homogeneous reaction approaches. In recent years, broad categories for asymmetric catalysis have emerged. Three fields that are now complementary to one another are organocatalysis, metal catalysis and enzymatic transformations; however, in this study, greater attention is placed on organoasymmetric synthesis using disite phase transfer catalyst in basic condition [8-10]. 2-Phenyl-hexanitrile may be an important chemical that has a wide range of synthetic uses. The most prominent use is as a chiral acid intermediate [11,12]. Alkyl halide compounds have high reactivity, which enhances their significance in organic synthesis procedures [13]. Organic chemists have been working toward the objective of speeding up and running such processes under mild conditions for quite some time. A phase transfer catalyst enables the passage of a reactant between phases during a reaction in a heterogeneous system. Also, these kinds of reactions can be conducted in presence of ultrasonication to enhance the reaction rate and yield [14]. Hence, this work presents the chiral synthesis reaction in presence of our reported phase transfer catalyst 1-benzyl-1,4-diazoniabicyclo[2.2.1]hepta-2,4(7)-dienedi-chloride (BDHDC) [15]. Additionally, the potential future applications such as the kinetic parameters including ultrasonication effect, PTC dose, solvents effect, butyl chloride volume, RPM effect and KOH weight are also explored [16-19].

EXPERIMENTAL

All the reactants and reagents were purchased from Sigma Aldrich-India. SRL chemicals, Mumbai, India supplied both the solvents and the base. All the purchased chemicals used as such without any purification. The reaction was tracked using a Merck India- silica gel TLC plate using 2:8 ethyl acetate/hexane solvent mixture. This study used 5 L ultrasonic cleaner tanks with interior dimensions of 48 cm × 28 cm × 20 cm and the specifications of Ultrasonic water bath, Equitron, Media Instrument Manufacturing Company, Chennai, India. The Perkin-Elmer LS25 was used to record the ultraviolet spectrum in ethanol. The Jasco-6300 spectrometer was used to record the FT-IR spectra between 400 and 4000 cm^{-1}. The Bruker NMR-400 spectrometer was used to acquire ^{1}H NMR and ^{13}C NMR spectra in CDCl$_3$. Using capillary column (30 m × 0.525 mm i.d), 100% poly(dimethyl siloxane), GC-Varian 3700 model the product and reactants were monitored at the injection temperature 250 ℃, FID detectors 300 ℃. The yields were calculated using a standard curve using biphenyl.

Ultrasonication: Ultrasound liquid bath with double-layer stainless steel sonochemical reactor and aqueous medium to limit ultrasound to reactor vessel was used to study the reaction rate. A flat transducer positioned at the bottom of the tank generated two operational frequencies (28 and 40 kHz) with an output power of 300 W. A 250 mL three-necked Pyrex round bottom flask was fitted in the ultrasonic bath and 2 cm above the transducer at the bottom to optimize ultrasonic energy. All experiments were carried out at a frequency of 40 kHz (300 W).

Phase transfer catalyst: As per the reported methods, this work prepared the phase transfer catalyst BDHDC (Fig. 1) and used for the asymmetric synthesis [15].
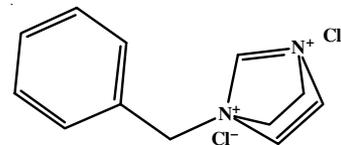
Fig. 1. Cheimcal structure of 1-benzyl-1,4-diazoniabicyclo[2.2.1]hepta-2,4(7)-dienedichloride (BDHDC)

Synthesis of 2-phenylhexanenitrile (PHN): To generate the anion, 10 g of KOH, 1 mL of water and 5.7 mmol of phenyl acetonitrile were introduced in to the reaction vessel and well powdered for few minutes with overhead stirring. Then 0.74 g (8 mmol) of 1-chlorobutane and the newly synthesized BDHDC (0.3 g) were gently added over 5 min in 30 mL chlorobenzene. The reaction mixture was vigorously stirred for 2 h at 60 ℃. TLC confirmed the formation of the product. Simple extraction with 5 mL of ethyl acetate yielded the crude product. Under reduced pressure, the collected organic layer was concentrated and product was isolated. In order to obtain a completely pure chiral product, specifically 2-phenylhexanenitrile, in the form of a colourless semi-solid, the impure product underwent thin-layer chromatography (TLC) using a mixture of hexane and ethyl acetate (8:2, v/v) as eluent. Similar reactions were carried out under varied conditions, such as the presence of ultrasonication and kinetic parameters as specified in **Scheme-I**. Semi-solid; UV-λ_{max}: 209 nm, 263 nm, 323 nm, FTIR (KBr, ν_{max}, cm^{-1}): 3005, 2724, 2324, 1793, 1427, 1237, 490, 463, ^{1}H NMR (500 MHz, CHCl$_3$-d_6) δ ppm: 7.52-7.41 (m, 2H), 7.37-7.36 (m, 1H), 7.34 (dd, J = 7.7, 1.7 Hz, 2H), 3.88 (t, J = 6.0 Hz, 1H), 2.03-2.01 (dt, J = 12.8, 6.3 Hz, 1H), 1.99-1.89 (dq, J = 12.8, 6.4 Hz, 1H), 1.36-1.12 (m, 2H), 0.79 (t, J = 6.4 Hz, 3H).
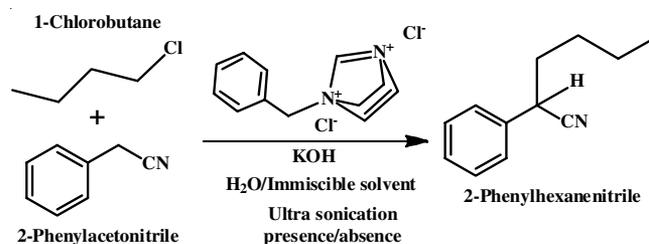
Scheme-I: Synthesis of 2-phenylhexanenitrile (PHN)

Kinetic model of PTC based asymmetric synthesis: A phase-transfer catalyst BDHDC catalyzed the reaction between 2-phenylacetonitrile and butyl chloride to prepare the chemical in aqueous alkaline (KOH) biphase medium under ultrasonic irradiation. The kinetics was monitored with excess reactants as a limiting agent. The reaction investigates how radiation frequency (40 kHz, 300 W) and stirring speed (400 rpm) affect the rate constant (k_{app}) [20]. The conversion (X) of butyl chloride is defined as follows:

$$X = 1 - \left(\frac{[\text{ButCl}]_o}{[\text{ButCl}]_t} \right) \qquad (1)$$

where $[\text{ButCl}]_o$ and $[\text{ButCl}]_t$ are the concentration of butyl chloride at time $t = 0$ and $t > 0$, respectively. The rate expression for this reaction may be expressed as:

$$-r\text{PHN} = k_{app} [\text{ButCl}]_o \qquad (2)$$

where, k_{app} is the apparent reaction rate constant. This reaction was carried out in a batch reactor, so the disappearance rate of ButCl with time (t) can be expressed as:

$$\frac{-d[\text{ButCl}]_o}{dt} = -r\text{PHN} = k_{app}[\text{ButCl}]_o \qquad (3)$$

On integrating eqn. 3 yields:

$$-\ln \left(\frac{[\text{ButCl}]_o}{[\text{ButCl}]_{o,i}} \right) = -\ln(1-X) = k_{app} \qquad (4)$$

By plotting $-\ln(1-X)$ *vs.* time, (t), we get the K_{app} value. This pseudo first-order equation was used to calculate the k_{app} value for the present study.

Effect of solvents: Experiment was conducted to examine the influence of several organic solvents on the rate of butylation, under typical reaction conditions. Toluene, anisole, cyclohexane, chlorobenzene and benzene are the five organic solvents employed for their solvent properties.

Effect of ultrasound: Using the newly synthesized two-site phase-transfer catalyst BDHDC, stirring speed was kept constant at 400 rpm and varied ultrasonic irradiation 0 to 40 kHz, 300 W was used to evaluate the rate of butylation. The stirring speed for reaction kinetics was fixed at 400 rpm, as it has been found to be the point of maximum rate and the limiting rate [21].

Effect of BDHDC dose: The influence of catalyst quantities on the reaction rate of butylation was investigated by increasing the amount of BDHDC from 0.1 g to 0.9 g under ultrasonic irradiation (40 kHz, 400 W). The linear plot of $-\ln(1-X)$ with time revealed pseudo first-order kinetics. The reaction rate increased as the amount of BDHDC increased. This is due to the simultaneous effect of the catalyst and ultrasound. The k_{app} values are proportional to phase-transfer catalyst weight. The increase in k_{app} value is related to the favourable effect of ultrasound as well as stirring speed (400 rpm). The reaction was conducted in presence of different doses of BDHDC by keeping the reactants and conditions such as 3 g of KOH, 30 mL of H_2O, 2.0 mL of butyl chloride and 30 mL of chlorobenzene at 40 ºC.

Effect of KOH and RPM: The concentration of alkaline chemicals has a significant impact on the frequency of reactions. Butylation of phenyl acetonitrile is highly dependent on the concentration of KOH. The pseudo first-order kinetic tests used 20-40 g of KOH under identical reaction conditions. The basicity of hydroxide ion greatly increased k_{app} values. Similarly, the reaction rate was investigated by varying rotation speed from 100 to 800 RPM at standard conditions.

RESULTS AND DISCUSSION

During the course of this research, a phase transfer catalyst with two active sites was developed for use in organic conversion processes. The butylation procedure and kinetic properties of phenyl acetonitrile were also investigated. The butylation procedure, which this study used to its maximum potential, was both cost-effective and yield-enhancing because of the synthesized PTC-BDHDC. The outcomes of the reactions were examined in presence and absence of ultrasonication energy. At first, the reaction conducted in different solvents based on their dielectric constants (Table-1). Chlorinated solvent showed good results for 1 g dose of BDHDC in absence of ULS ($10.5 \times 10^3\,\text{min}^{-1}$) and presence of ultrasonication ($42.2 \times 10^3\,\text{min}^{-1}$). When compare the results, cyclohexane exposed lowest rate of formation (17.8 and $4.8 \times 10^3\,\text{min}^{-1}$). Ultrasonic waves may also penetrate more deeply into more polar liquids, resulting in more effective collisions between the reactants. Because of this, chlorobenzene has a greater k_{app} value than other compounds. Hence, further reactions were carried in chlorobenzene solvent and examined the kinetic parameters.

TABLE-1
EFFECT OF PTC-BDHDC DOSE AND ULTRASONIC
POWER (40 kHz, 300 W) ON RATE CONSTANT

Solvents	Effect of organic solvents ($k_{app} \times 10^3\,\text{min}^{-1}$)		
	Dielectric constant	Ultrasonication	
		With	Without
Cyclohexane	2.06	17.8	4.8
Benzene	2.25	24.2	6.9
Toluene	2.31	28.9	7.8
Anisole	4.3	37.6	9.2
Chlorobenzene	5.5	42.2	10.5

At constant stirring in chlorobenzene, reactions were conducted by varying the PTC dose gradually from 0.1 to 0.9 and the reaction rates were calculated for each reaction (Table-2). Without ultrasonication, the results showed a rate ranging from 4.02×10^1 to $10.53 \times 10^3\,\text{min}^{-1}$. The reaction rate increased

TABLE-2
EFFECT OF PTC-BDHDC DOSE AND ULTRASONIC POWER (40 kHz, 300 W) ON RATE CONSTANT

Amount of BDHDC (g)	Effect of BDHDC		Effect of ultrasonication (ULS)	
	$k_{app} \times 10^3\,(\text{min}^{-1})$	$k_{app} \times 10^3\,(\text{min}^{-1})$ (Without ultrasonication)	Ultrasonication	$k_{app} \times 10^3\,(\text{min}^{-1})$
0.1	4.02	16.03	0	6.02
0.3	5.01	25.33	28	15.85
0.5	6.14	27.54	40	27.82
0.7	8.36	35.68	–	–
0.9	10.53	41.03	–	–
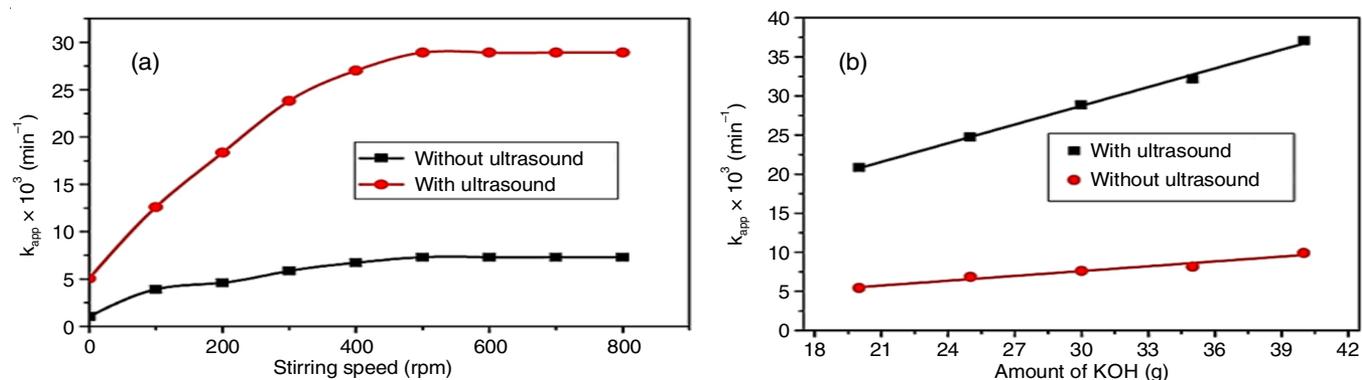
Fig. 2. (a) RPM *versus* rate constant graph (b) Amount of KOH *vs.* rate constant graph in presence and absence of ultra-sonication

4 times in presence of ultrasonication and observed gradual increase. Similarly, this research extended by modifying the supplied ultrasonication power with 0.5 g of PTC in chlorobenzene solvent.

It implies that at higher KOH concentrations, hydroxide ions are less solvated by water molecules, enhancing their activity. The hydroxide ion concentration considerably enhanced the rate constant in the PTC kinetic study of alkylation of benzyl cyanide with *n*-chlorobutane [22]. The reaction kinetics was studied under two different conditions, such as RPM and KOH quantity. The graphs of the parameters speed *vs.* rate and amount of KOH *vs.* rate are shown in Fig. 2a-b.

As the rotation speed increases the fast transformation of ions and the good yield. Likely, the amount of KOH increases the rate of the butylation reaction and the yield. Both graphs expressed the gradual increase and kinetics followed the pseudo first-order reaction with respect of butyl chloride. Synthesized product (PHN) exhibited three peaks at 209 ($\pi \rightarrow \pi^*$), 263 ($n \rightarrow \sigma^*$) and 323 ($n \rightarrow \pi^*$) for the functional group -CN attached with aromatic asymmetry carbon. The vibrational spectra, similar to the ultraviolet spectra, confirmed the various stretching and bending modes of vibrational frequencies for the major functional groups of the product. The product showed the peaks for aliphatic C-H stretching (3005-2724 cm^{-1}) and –CN (2324 & 1237 cm^{-1}). ^{1}H NMR also confirmed the single peak at 3.88 ppm, which may the relevant peak for asymmetry carbon.

Conclusion

The kinetics study of phase transfer catalyst 1-benzyl-1,4-diazoniabicyclo[2.2.1]hepta-2,4(7)-dienedichloride (BDHDC) in the synthesis of 2-phenylhexanenitrile (PHN) from benzyl cyanide and butyl chloride was investigated. The reaction followed the pseudo first-order kinetics and the k_{app} values were depends on various kinetic variables. An interfacial mechanism in presence of BDHDC-PTC catalyzed reaction along with ultrasound irradiation showed better efficacy as compared to the reactor operated under phase transfer catalyst without ultrasound irradiations. The results of this study indicated that the BDHDC may be used as a phase transfer catalyst under ultrasonication, which results in a high yield.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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