

Effective Darzen's condensation of 4-nonanolide with 1,6-dibromohexan-2-one using new bead-shaped insoluble multi-site (six-site) phase transfer catalyst and low concentration of aqueous NaOH

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Received 19 September 2006; received in revised form 6 July 2007; accepted 9 July 2007
Available online 19 July 2007

Abstract

New bead-shaped insoluble polymer-supported multi-site (six-site) phase transfer catalyst (BSIMPTC) was synthesized from mesitylene as a starting material and its catalytic efficiency was studied with the kinetics of Darzen's condensation of 4-nonanolide with 1,6-dibromohexan-2-one. The presence of six active-sites in the newly synthesized BSIMPTC, viz., 2,4,6-tris[(4-(2,2'-bis(*N*-triethylammoniummethylene chloride) eth-1-ene) phenoxy)benzene] was characterized through FT-IR, solid ¹H NMR, ¹³C NMR, SEM and [chloride ion] analyses and found that the BSIMPTC contains ≈6 active-site centers. The Darzen's condensation reaction of 4-nonanolide was performed at lower temperature (40 °C) under pseudo-first order rate conditions by taking lower concentration of aqueous NaOH (15%, w/v, 3.75 M) and excess of 1,6-dibromohexan-2-one. The disappearance of 4-nonanolide was quantitatively monitored by a gas chromatograph for the calculation of the pseudo-first order rate constant. The presence of more number of active-sites in BSIMPTC was further confirmed from the comparative study of pseudo-first order rate constant with the rate constants of single-site polymer-supported phase transfer catalyst. The comparative rate constant results reveal that the BSIMPTC is highly active-than the corresponding soluble six-active-site and almost ≈4 times higher active-than with insoluble/soluble single-site PTCs. The effect of various experimental parameters such as [substrate], [catalyst], [NaOH], stirring speed, and temperature on the rate of the reaction have also been studied and found that each variables are influenced the rate of reaction. Based on the obtained kinetic results, a suitable mechanism is proposed.

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Keywords: Phase transfer catalyst; 4-Nonanolide; Oxirane; Multi-site; Interfacial; Polymer supported; Triphase catalysts; Darzen's condensation

1. Introduction

Phase transfer catalysis (PTC) has been recognized as an effective practical methodology for organic synthesis due to its operational simplicity, mild reaction conditions, safety considerations, and environmental concerns. Because of these salient features, the research and the developments of novel PTC especially to carry out rare organic reactions have received considerable industrial interest [1,2]. So far, many reviews on synthetic methods using different phase transfer catalysts have

appeared [3–5]. However, most of the researchers are more reluctant to employ soluble PTCs for any organic reactions owing to its inseparability of the catalyst from the PTC reaction mixture. Therefore, preparation techniques involving development of various insoluble single-site PTC has had much importance, since its introduction by Regan [6] due to their easy isolation and product purification. Particularly, bead-shaped polymer-supported PTC (PS-PTC), also known as triphase catalysts (TC), provides an attractive means of recycling the catalysts after completion of reaction. One of the main advantages of the recycling of the catalyst is that it enables reactions to be carried out in the continuous mode of addition and also reduction of cost of the catalyst. There are many types of single-site PT catalysts

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such as quaternary ammonium [6], phosphonium salts [7], crown ethers [8], cryptands [9], etc. are immensely popular due to their availability and easy reaction work-up. The copolymer of poly(styrene) cross-linked with divinylbenzene is the most common support used for the preparation of tri-phase catalysts. The study involving various single-site PSPTC reported by Montanari and Tundo [10] Brown and Jenkins [11], Ohtani et al. [12], Chaudhari and Ramachandran [13], Ford and Balakrishnan [14] and Balakrishnan and Murugan [15] had created a remarkable record in the synthesis of various organic compounds. However, the prime consideration in the selection of the catalyst is economy of scale and efficiency of the PTC, specifically on the industrial-scale preparation of organic compounds. In order to cater these needs, “multi-site” phase-transfer catalysts (MPTCs) has been developed and employed to large-scale reactions. Idoux et al. [16] first reported the soluble and insoluble MPTCs containing three phosphonium active-sites. Subsequently, Balakrishnan and Jeyachandran [17] have also studied the soluble quaternary ammonium ion containing two active-sites. Benaglia et al. [18] have studied the insoluble poly(ethylene glycol) supported tetrakis quaternary ammonium catalyst that is recyclable in nature. Wang and Hsieh [19] carried out the dihalocyclopropanation of 4-vinyl-1-cyclohexene reaction using novel soluble di-site PTC. Recently, dimeric [20,21] and trimeric [22] chiral phase transfer catalysts (CPTCs) in the form of quaternary ammonium ion were also synthesized from *o*-, *m*- or *p*-xylene dibromide, bis(bromomethyl)naphthalenes and mesitylene tribromide. The catalytic efficiency of these CPTC’s has been studied for the C-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with benzyl bromide and good chemical yield and ees have been found. In our laboratory, earlier, we also developed and reported various chiral and non-chiral forms of phase-transfer catalysts such as six-site [23–25], single-site [26], dimeric [27] and trimeric [28,29] ones for the application of various organic reactions. In general, MPTCs have the potential for offering greater PTC activity and effecting a particular synthetic transformation under mild reaction conditions.

The Darzen’s reaction is one of the more important carbon–carbon bond forming reactions in synthetic organic chemistry because of the multifunctionality and utility of the α,β -epoxy carbonyl products. Although many examples are known for diastereoselective control in the Darzen’s reaction [30], few successful results involving achiral catalysts or reagents have been reported [31–33]. Ohtomi et al. [34] studied the synthesis of nitriles from the reaction of alkyl halide and sodium cyanide in presence of PT catalysts. They also reported [35] a convenient and effective Darzen’s condensation of ketones with chloroacetonitriles catalyzed by octopus-structured catalyst. Colonna et al. [36] performed the Darzen’s reactions in aqueous/organic biphasic system in the presence of chiral catalysts, viz. (–)-*N*-alkyl-*N*-methyl ephedrium halides, supported or non-supported polymeric matrix and produced optically active α,β -epoxy-sulfones and nitriles.

By considering the significance of all the earlier studies in general and development of insoluble multi-site PTC in particu-

lar, we have decided to synthesize a novel bead-shaped insoluble polymer-supported MPTC (BSIMPTC) containing maximum number of possible active-sites (≈ 6). The catalytic efficiency of this new BSIMPTC was examined by conducting the study of Darzen’s condensation reaction between the 1,6-dibromohexan-2-one with 4-nonanolide under pseudo-first order conditions. The efficiencies of the BSIMPTC were compared with other reported soluble six-site [24] and insoluble/soluble single-site PTC in order to know to the superiority of the catalyst.

2. Experimental

2.1. Mesityldehyde (2)

Mesitylene **1** (5 g, 41.6 mM) was taken in a two-necked RB flask fitted with a reflux condenser and an addition funnel, and 25 ml of conc. HCl and Zn(CN)₂ (1.6 g, 14.19 mM) were added to the above solution. After adding a catalytic amount of aluminium chloride, the whole solution was kept in an oil bath for about 18 h at 60 °C. As a result of the reaction, pale yellow solution of mesitaldehyde **2** was formed. It was purified by column chromatography using hexane:ethyl acetate (80:20) as eluent.

Yield: 94%.

bp: 143–144 °C.

FT-IR (KBr): 1735.8 (C=O).

¹H NMR (200 MHz, CDCl₃) δ : 2.38 (s, 9H, –CH₃), 6.56–6.75 (m, 3H, aromatic) 10.24 (s, 1H, aldehyde).

2.2. 2,4,6-Tris(chloromethyl)benzaldehyde (3)

Mesityldehyde **2** (3.0 g, 20.24 mM), carbon tetrachloride (50 ml) and *N*-chloro succinimide (13.71 g, 91.09 mM) were taken in a 150 ml RB flask. The solution was kept in a water bath for 12 h at 80 °C; benzoylperoxide (3 g) was added slowly to the reaction mixture. After completion of the reaction, the solvent was removed by evaporation and a crude yellow colour chlorinated solid compound, viz., 2,4,6-tris(chloromethyl)benzaldehyde **3** was formed and it was recrystallized in ethanol.

Yield: 92%.

mp: 134–135 °C.

FT-IR (KBr) cm^{–1}: 1654.6 (C=O), 721.3 (C–Cl).

¹H NMR (200 MHz, CDCl₃) δ : 4.55 (s, 6H, methylene), 7.34 (s, 3H, aromatic), 10.23 (s, 1H, aldehyde).

The compound **3**, viz., 2,4,6-tris(chloromethyl)benzaldehyde (2.5 g, 9.94 mM) was reduced with isopropyl alcohol (0.61 ml, 9.94 mM) and aluminum chloride (1.33 g, 9.94 mM) in the presence of CCl₄ (30 ml) (Meerwein–Ponndorf–Verley reduction). The RB flask (150 ml) containing the reaction mixture was refluxed for 24 h at 70 °C in the oil bath. After the solvent was removed from the mixture by vacuum distillation, a deep yellow coloured crude product of 2,4,6-tris-(chloromethyl)benzyl

alcohol was formed. The crude product was purified by column chromatography using benzene-ethyl acetate as eluent.

Yield: 83%.

mp: 184 °C.

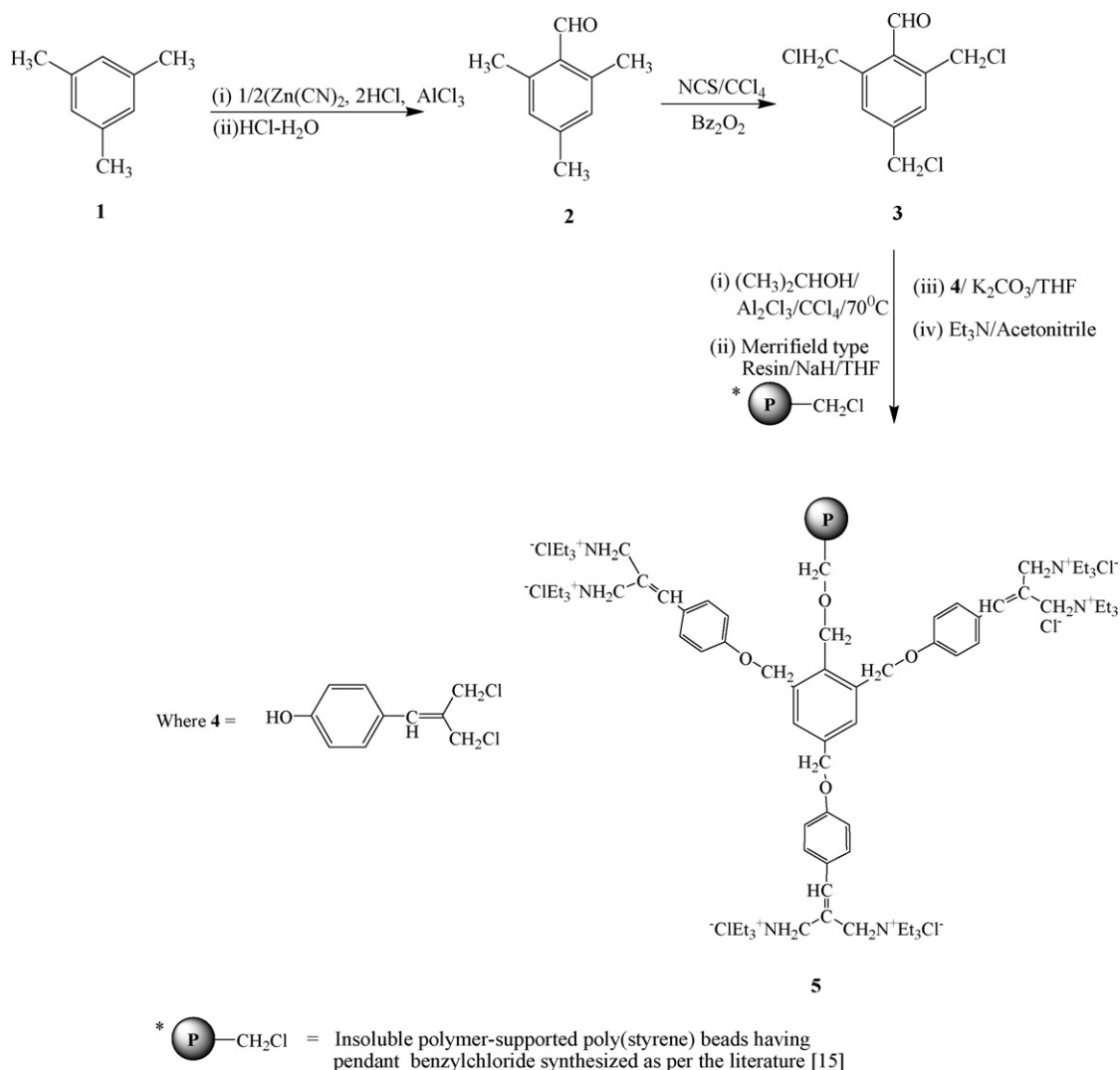
FT-IR (KBr): 725 (C–Cl), 3553 (broad, –OH); ¹H NMR (200 MHz, CDCl₃) δ: 4.03 (s, 2H, methylene), 4.32 (s, 6H, methylene), 5.61 (bs, 1H, hydroxyl), 7.25 (s, 3H, aromatic).

2.3. Preparation of bead-shaped insoluble polymer-supported 2,4,6-tris[(4-(2,2'-bis(*N*-triethyl ammonium methylene chloride)eth-1-ene)phenoxy)benzene [BSIMPTC] (Scheme 1)

The cross-linked poly(styrene) beads was prepared by following the known procedure [15], i.e. by conducting the copolymerization of vinylbenzylchloride (25%, functional monomer) divinylbenzene (2%, cross-linking) and styrene (77%) through the suspension polymerization method. The resulting cross-linked poly(styrene) terpolymer beads was dried

and sieved into different mesh sizes using Testing Sieve Shaker (RO-TAP, W.S. Tyler Company, OH). Two grams of beads having mesh size +140–170 was swelled in THF (50 ml) for 24 h, then 2,4,6-tris-(chloromethyl)benzyl alcohol (2 g, 7.89 mM) and sodium hydride (0.7 g, 29.17 mM) were added to the swelled poly(styrene) beads, and the solution containing beads was refluxed for 24 h at 60 °C, thus producing the condensed product of polymer-supported 2,4,6-tris-(chloromethyl)benzyl ether. It was filtered and washed with methanol (20 ml) and acetone (15 ml). The condensed product of polymer-supported beads was further treated with 2,2-bis(chloromethyl-3-(4-hydroxybenzene)-2-ethene **4** (1.8 g) and K₂CO₃ (2 g) in THF (40 ml). The reaction mixture was refluxed in an oil bath for 24 h at 80 °C. The solvent was removed by filtration to yield yellow coloured beads. The beads was further washed with methanol (20 ml) and acetone (15 ml) and then dried (yield, 84%).

Finally, the polymer-supported 2,4,6-tris[(4-(2,2'-chloromethyl-eth-1-ene) phenoxy) benzene (2 g) beads was swelled in acetonitrile (50 ml) medium for about 24 h along with an excess of triethylamine (25 ml) for quaternization



Scheme 1. A schematic diagram for the synthesis of BSIMPT catalyst.

reaction in an inert atmosphere (N_2 gas). The whole setup was placed in an oil bath and the reaction mixture was stirred for 48 h at $80^\circ C$. After quaternization, the solvent was removed by distillation and the yellowish bead-shaped insoluble polymer-supported multi-site phase transfer catalyst (BSIMPTC) **5** was washed continuously with methanol (3×15 ml) and acetone (3×15 ml). The dried BSIMPTC **5** (yield 92%) was used to estimate the chloride ion concentration by the Volhard's method [37], to measure the extent of quaternization.

FT-IR (KBr) cm^{-1} : 1654.8 (C–O–C), 1087.8 (C–N); 1H NMR (solid 300 MHz) δ : 1.25–2.5 (broad, 54H, methyl, $-N^+CH_2CH_3$), 3.13–4.25 (broad, 36H, methylene, $N^+CH_2CH_3$), 4.3–5.75 (s, 10H, $-CH_2$, benzyl proton), 5.75–6.38 (broad, 3H, vinyl proton), 6.50–9.0 (broad, aromatic proton); ^{13}C NMR (75 MHz): 11.9, 43.3, 64.1, 71.8, 75.7, 131.0, 144.7, 147.9. [Chloride ion]: calculated value 4.16 meq g^{-1} , found 3.72 meq g^{-1} .

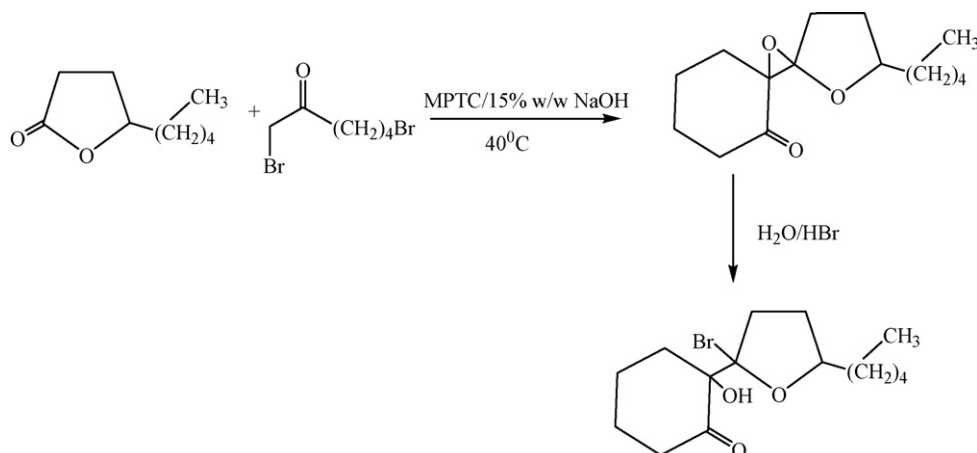
Similarly, in order to compare the chloride ion concentration of this insoluble BSIMPTC with insoluble single-site PS-PTC, the same polymer-supported poly(styrene) beads (obtained by the known procedure [15] but without condensation of **3**) was quaternized and then the concentration of chloride ion was estimated by the Volhard method. The estimated [chloride ion] was found to be 1.15 meq g^{-1} .

2.4. Typical kinetic measurements of Darzen's condensation of 4-nonanolide to 1,6-dibromohexan-2-one (Scheme 2)

The comparative kinetic experiments were performed in an 150 ml RB two-necked flask fitted with a flat-bladed stirring paddle under identical reaction conditions taking all the four different test catalysts such as reported soluble six-site PTC [24], commercially available soluble single-site (TEBAC), insoluble single-site [15] and newly synthesized insoluble BSIMPTCs. Initially, in order to examine the presence of six-active-sites in BSIMPTC, similar quantities of (0.2 g, +140–170 mesh) BSIMPTC and insoluble bead-shaped single-site polymer-supported PTC were taken individually and employed

to carry out the model reaction, viz., Darzen's condensation to 4-nonanolide with 1,6-dibromohexan-2-one (Scheme 1). The reaction was carried out by the reverse addition method (delayed addition of substrate). The 1,6-dibromo-pentan-2-one (20 ml), aqueous NaOH 15% (w/v), 3.75 M (20 ml), hexadecane (1 ml) and the respective bead-shaped insoluble PTCs were added and the mixture was stirred at 200 rpm for 5 min at $40^\circ C$ to stabilize the catalyst. Then the stirring speed was increased to 500 rpm and 4-nonanolide (2 mol) was added to the reaction mixture at zero time. Samples of each reaction catalyzed by these two catalysts were collected from the organic layer of the mixture (by stopping the stirring for 10–15 s in each time) at regular intervals. The kinetics of the reaction was studied by estimating the amount of 4-nonanolide consumed through gas chromatography. The column (5% SE-30 chrom WHP 80/100, 3 m \times $1/8$ in. stainless steel paced column) temperature was maintained $80^\circ C$. For every sample 0.5 μ l of reaction mixture was injected to the column and the products were analyzed; the retention time was 2.78 min for 4-nonanolide, 3.02 min for 1,6-dibromohexan-2-one, 2.91 min for epoxide product, and 5.07 min for 2-(2-bromo-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-2-hydroxy-cyclopentanone product.

Similarly, in order to compare the catalytic efficiency of soluble and insoluble catalysts, the pairs such as soluble six-site, viz., 1,3,5-tris(4-(2,2-bis(*N*-triethylammoniummethylene chloride)eth-1-ene)-phenoxy)methyl benzene (TBTEAPB) [24] with corresponding newly synthesized bead-shaped insoluble six-site PTC, viz., BSIMPTCs and soluble single-site (TEBAC) with bead-shaped single-site PS-PTC were taken individually and the Darzen's condensation reaction was carried out under identical reaction conditions. In order to compare the efficiency of these catalysts, the concentration of active-site (i.e. [chloride ion]) of soluble and insoluble six-site pair has been fixed with equimoles, i.e. 3.72 meq g^{-1} ; and for soluble and insoluble single-site PTCs, the [chloride ion] was maintained as 1.15 meq g^{-1} . Otherwise, the substrate concentration, reaction conditions and other analysis parameters are maintained as mentioned in the previous insoluble catalyzed reaction system. The



Scheme 2. Darzen's condensation of 4-nonanolide with 1,6-dibromohexan-2-one under PTC condition.

pseudo-first order rate constants were evaluated from the plots of $\log(a-x)$ versus time.

The proved superior catalyst, viz., BSIMPTC has been employed for thorough kinetics of the same reaction by varying the kinetic variables include stirring speed, [substrate], [catalyst] and temperature. To isolate the product from the cold reaction mixture, 50 ml of ether was added and the ethereal layer was decanted using separating funnel and evaporated. A pale yellowish oily product formed was further purified using silica gel column chromatography using benzene:ethanol (80:30) as eluent. The spectral data for the formation of epoxide and 2-(2-bromo-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-2-hydroxy-cyclopentanone derivatives were confirmed by various spectral studies, viz., FT-IR, ^1H NMR and ^{13}C NMR and mass spectra.

At high $[\text{NaOH}]$, the observed oxirane product was further cleaved due to ring strain and produced 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl) cyclohexanone.

2.4.1. 2-Pentyl-1,12-dioxo-dispiro[4.0.5.1]dodecane (Oxirane product)

FT-IR (KBr) cm^{-1} : 1228 (C–O).

^1H NMR (200 MHz, CDCl_3) δ : 1.05–1.10 (t, 3H, $J=5.0$ Hz, methyl), 1.29–1.40 (m, 8H, furan side chain alkane methylene), 1.45–2.0 (m, 8H, methylene (cyclohexanone moiety)), 2.05–2.20 (m, 4H, methylene (furan moiety)), 3.77 (m, 1H, methyne (Furan)).

^{13}C NMR (50 MHz, CDCl_3) δ : 14.2, 21.1, 23.1, 24.2, 25.4, 25.7, 27.2, 28.8, 32.8, 69.8, 72.7, 95.6 176.2.

Mass (m/z): 257.9 (M^+).

2.4.2. 2-Bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)cyclohexanone

FT-IR (KBr) cm^{-1} : 3456 (–OH), 1725 (C=O), 685 (C–Br).

^1H NMR (200 MHz, CDCl_3) δ : 1.08–1.24 (t, 3H, $J=6.0$, methyl), 1.25–1.42 (m, 8H, furan side chain methylene), 1.55–1.75 (m, 12H, methylene), 2.5 (bs, 2H, –OH) 4.03–4.11 (m, 1H, furan methyne).

Mass (m/z): 333.07 (M^+).

3. Result and discussion

3.1. Characterization of bead-shaped insoluble polymer-supported

2,4,6-tris[(4-(2,2-bis(*N*-triethylammoniummethylene chloride)eth-1-ene) phenoxy methyl] benzene (i.e. BSIMPTC)

Bead-shaped insoluble polymer-supported MPTC is definitely a viable and attractive catalyst due to its efficiency, convenient shape to fill/pack into various reactors which include column, fixed bed, etc. and easy reusability. In the synthesis of BSIMPTC, initially mesitylene **1** was first converted into mesitaldehyde **2** by the method of Gattermann Koch formylation. The formation of aldehyde compound **2** was confirmed through appearance of C=O peak at 1725 cm^{-1} in the FT-IR spectrum.

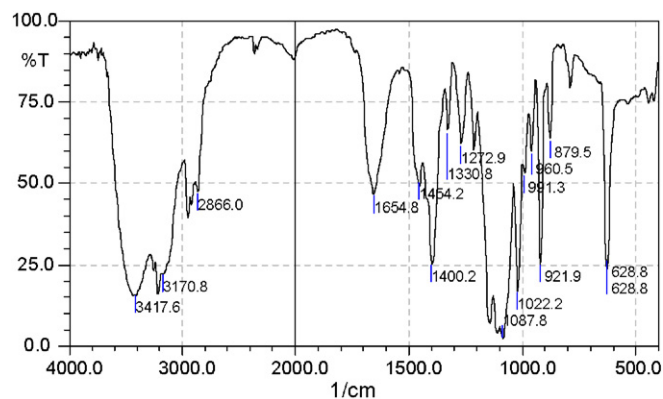
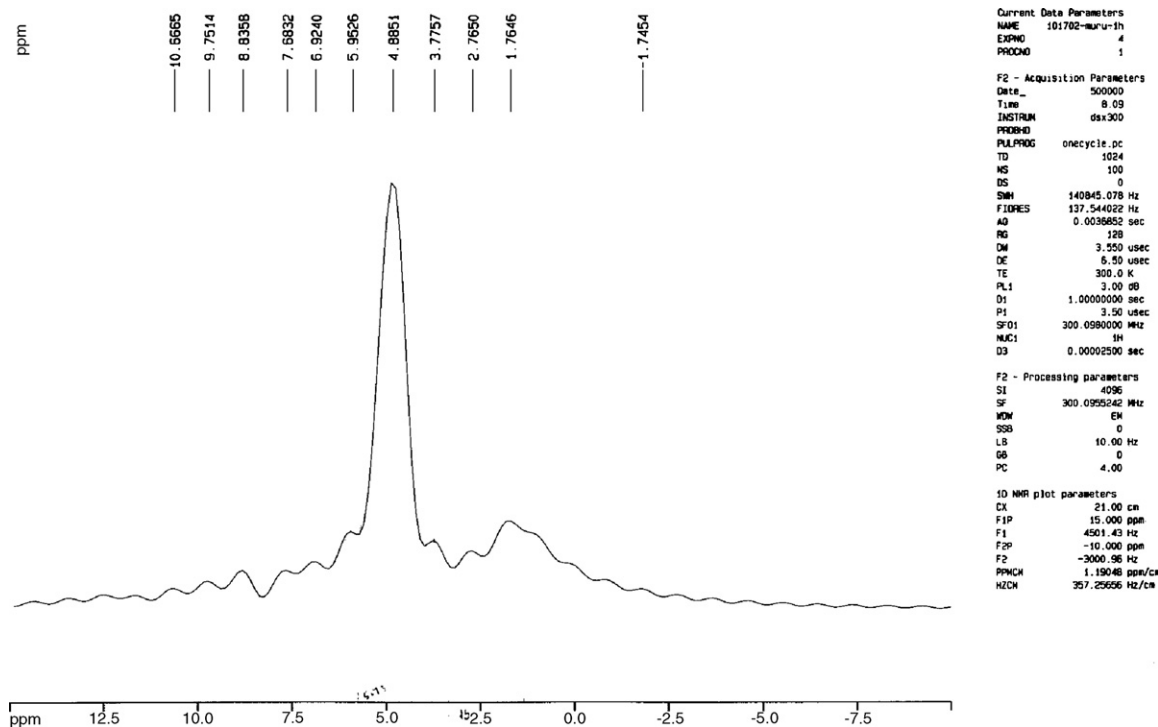


Fig. 1. FT-IR spectrum of BSIMPTC 5.

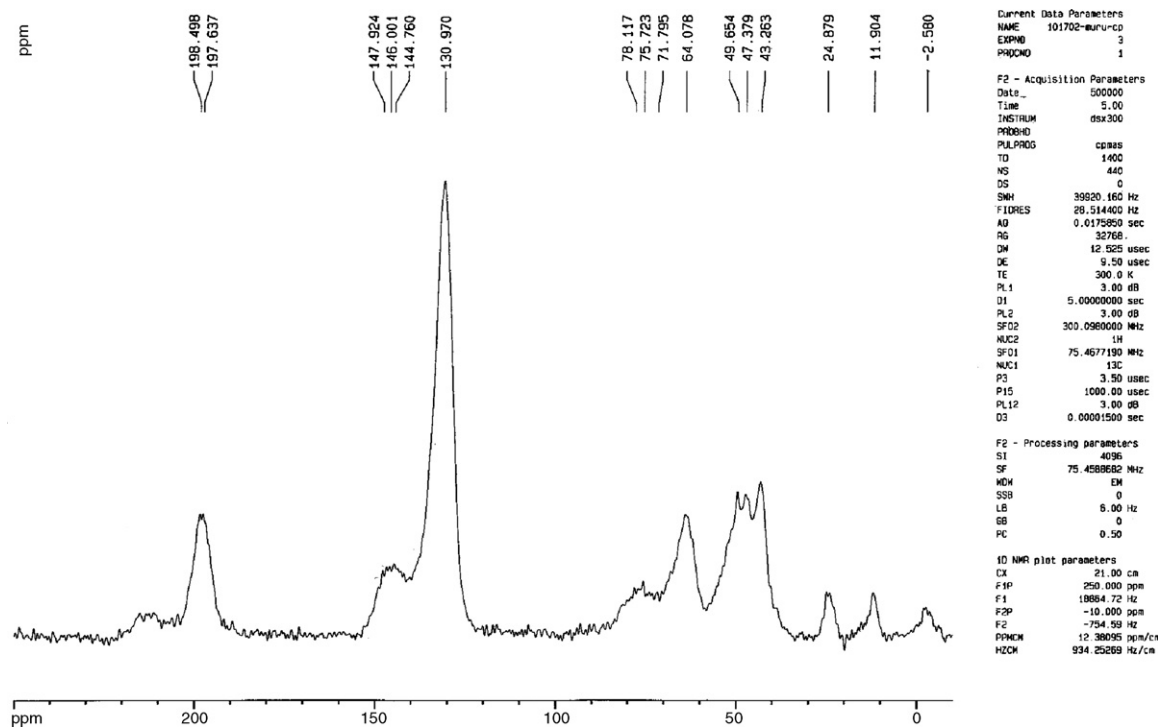
Further, the aldehyde compound **2** was converted into trichloro derivative in the presence of *N*-chlorosuccinamide/ CCl_4 to produce the trichloro compound **3**. Then the reduction of aldehyde group in **3** into alcohol was confirmed through FT-IR and ^1H NMR as described in Section 2. Furthermore, the obtained alcohol compound **3** was condensed with polymer-supported poly(styrene) co-polymer beads [15] (Merrifield type resin) enriched with 25% active-site [(VBC), +140–170 mesh]; the condensation was confirmed through the disappearance of the –OH stretching frequency peaks at $3400\text{--}3600\text{ cm}^{-1}$ and the appearance of the C–O–C stretching peak at 1654 cm^{-1} in FT-IR. Then the bead-shaped insoluble polymer-supported chloride compound was converted into polymer-supported 2,4,6-tris[(4-(2,2'-chloromethyl-eth-1-ene)phenoxy) benzene by treatment with 2,2-bis(chloromethyl-3-(4-hydroxybenzene)-2-ethene **4** which was confirmed from the appearance of the intense C–Cl stretching band at 720 cm^{-1} in the FT-IR spectrum. Finally, the resulting beads product was made into catalyst, i.e. BSIMPTC via quaternization reaction; the formation of quaternary site was confirmed from the appearance of C–N stretching frequency at 1087.8 cm^{-1} and the disappearance of C–Cl stretching frequency at 720 cm^{-1} in the FT-IR spectrum (Fig. 1) and also in the solid ^1H NMR spectrum (Fig. 2), the ethyl group moiety containing 54 methyl protons appeared as a broad peak (signal) at 1.25–2.5 ppm and 36 methylene protons appeared at 3.13–4.25 ppm, which is indicative of the quaternization of **5**. Similarly, in the ^{13}C NMR spectrum (Fig. 3), the presence of *N*-ethyl group containing methyl and methylene carbons was confirmed through the intense bands at 11.9 and 43.3 ppm, respectively, evidencing the presence of six active-sites. Finally, the formation of six quaternised ammonium cation sites was also confirmed from the results of [chloride ion] analysis through the Volhard method. That is, based on the structure of BSIMPTC, the theoretical calculation with respect to Cl^- gives the value of 4.12 meq g^{-1} . The experimental value of $[\text{Cl}^-]$ was found to be 3.72 meq g^{-1} , being close to the theoretical value thus confirming the presence of six Cl^- in the BSIMPTC molecule. The SEM figures show that the newly prepared copolymer catalyst, viz., BSIMPTC exhibits bead-shape in nature with heterogeneous surface morphology (Fig. 4a and b) and it is an evidence for the availability of more active-sites.

Fig. 2. ^1H NMR spectrum of BSIMPTC 5.

3.2. Comparative study for the efficiency of soluble and insoluble catalysts

The pseudo first-order rate constants for the Darzen's condensation between the 4-nonanolide with 1,6-dibromohexan-2-one has been determined to investigate the relative catalytic

efficiency of soluble and insoluble single-site PTC's pairs such as triethylbenzylammonium chloride (TEBAC) with insoluble bead-shaped polymer-supported benzyltriethylammonium chloride (PS-PTC) and high-numbered active-site pairs, i.e. reported [24] soluble six-site MPTC, viz., 1,3,5-tris(4-(2,2-bis(*N*-triethylammoniummethylene chloride)eth-1-

Fig. 3. ^{13}C NMR spectrum of BSIMPTC 5.

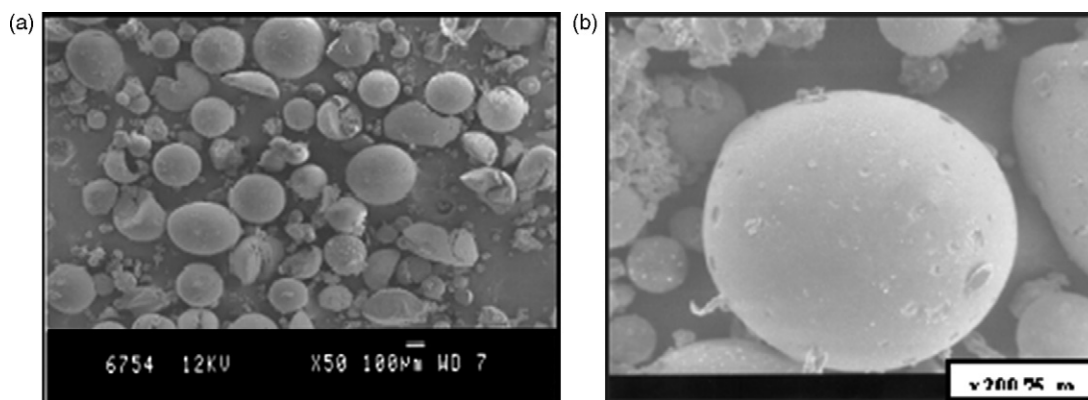


Fig. 4. SEM images for BSIMPTC: (a) pictorial view and (b) magnified single-bead view.

ene)-phenoxy)methyl) benzene (TBTEAPB) [24] with newly synthesized insoluble BSIMPTC, viz., 2,4,6-tris[(4-(2,2'-bis(*N*-triethylammoniummethylene chloride)eth-1-ene)phenoxy) benzene. It is necessary to mention here that each of pair of MPTC's contains N^+ and Cl^- ions as a catalytic moiety irrespective of soluble and insoluble nature so as to conduct the comparative studies with the same experimental condition/catalytic environment. Similarly, as mentioned in Section 2, the same quantity of [chloride ion] of the soluble and insoluble pair has been maintained for reasonable comparison. The observed results reveals that (Table 1) the enhancement in rate constants observed in six-site soluble/insoluble are found to be a multitude of increment based on the number of active-site of MPTC's as compared with their corresponding soluble/insoluble single-site PTCs.

Although the reactions were carried out under identical experimental conditions using all the catalysts individually, the pseudo-first order rate constants for six-site soluble/insoluble catalysts are approximately four times as active as their respective soluble/insoluble single-site catalysts (entries 2–5, Table 1). Particularly, this trend of observation is the proven evidence for the presence of more number of active-sites (≈ 6 site) in the newly synthesized bead-shaped BSIMPTC. From the earlier studies it is understood that the number of catalytic site usually decided the catalytic efficiency of that particular catalyst. But, the structure of the catalyst and substrates and their proper orientation towards catalytic sites may also play significant role in promoting the rate constant of Darzen's reaction. Further, the observed catalytic efficiency of BSIMPTC is found to be higher than the corresponding soluble six-site due to the fact that the polymer-bound MPTCs have more organophilic

attraction due to its presence of nonpolar polymer backbone [39] and also the presence of microphase effect of the catalyst. These kinds of studies are already reported by Hammett and Bernard [38] and Desikan and Doraisamy [39]. Normally, the possibility of diffusion scenario is complicated in the system with porous catalyst particles and two liquid phases. The droplets of the dispersed phase have to diffuse into the pores of the catalyst to active-sites for the reaction to occur. The more lipophilic character of these droplets has higher affinity with the bead-shaped insoluble six-site MPTC catalyst. Similar observation was already reported by various researchers, viz., Regen et al. [40] and Sherington and co-workers [37] on the single-site insoluble polymer catalysts; they have proved that supported poly(ethylene glycols) and crown ethers have higher reactivity than their respective soluble single-site analogues. Therefore, since insoluble six-site BSIMPTC has found to be superior than the corresponding reported soluble six-site and single-site PTCs, we have chosen this BSIMPTC to study the thorough kinetics of Darzen's condensation between the 4-nonanolide with 1,6-dibromohexan-2-one.

3.3. The Darzen's condensation reaction studied by different carbonyl compounds with chloroacetonitrile under various MPTCs

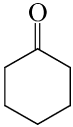
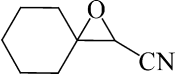
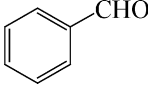
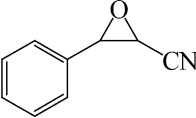
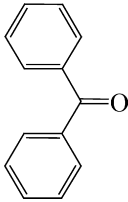
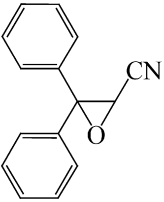
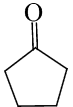

In order to confirm the reactivity of BSIMPTCs with other PTCs, all the chosen catalysts were employed for the same Darzen's condensation reaction but taking different carbonyl compounds, viz., cyclohexanone, benzaldehyde, benzophenone and cyclopentanone with chloroacetonitrile under identical reaction conditions (Table 2). The disappearance of substrates (respective carbonyl compound) were measured by gas chromatography. Here the observed results (in terms of % of yield) shows that BSIMPTC **5** is found to be also more active than the soluble six-site MPTC and single-site PTCs. Therefore, it is understand that irrespective of substrate, the BSIMPTC is superior since it contains more number of active-sites (≈ 6), that further all the active-sites are immobilized with the polymer-support and that the catalytic distribution in the reaction system is more restricted. Hence, the reactants from both the organic and aqueous phases must migrate from their respective bulk

Table 1
Comparison of reaction rate using single-site and multi-site PTCs

Entry	Name of the PTCs	$k_{\text{obs}} \times 10^{-3}, S^{-1}$
1	Control experiment (with out catalyst)	Nil
2	PS-PTC (insoluble single-site)	1.50
3	TEBAC (soluble single-site)	1.15
4	Six-site ^a (soluble)	3.85
5	BSIMPTC (six-site insoluble)	4.77

^a This catalyst is already reported from our laboratory [24].

Table 2
Catalytic efficiency of various soluble/insoluble SPTCs and MPTCs under identical reaction conditions for the study of Darzen's condensation of different carbonyl compounds

Entry	Ketones	Catalyst as per the Entry No.	Product	Yield (%)	Spectral Data
1		TEBAC PSPTC 4 5		31 35 72 96	FT-IR (KBr) cm^{-1} : 1256 (C–O–C), 2243 (C \equiv N); ^1H NMR (200 MHz, CDCl_3) δ : 1.27 (p, 6H, methyne), 2.78 (t, 4H, $J=8.2$ Hz, methyne), 3.45 (s, 1H, methyne); ^{13}C NMR (50 MHz): 20.3, 27.4, 35.6, 49.3, 67.8, 132.1; m/e [M^+] = 137.89
2		TEBAC PSPTC 4 5		38 46 84 100	FT-IR (KBr) cm^{-1} : 1248 (C–O–C), 2255 (C \equiv N); ^1H NMR (200 MHz, CDCl_3) δ : 3.56 (d, 1H, $J=4.2$ Hz, methyne), 4.02 (d, 1H, $J=3.7$ Hz, methyne), 7.23–7.46 (m, 5H, aromatic); ^{13}C NMR (50 MHz): 42.3, 58.7, 117.2, 124.3, 128.5, 129.7, 146.0, m/e [M^+] = 145.76
3		TEBAC PSPTC 4 5		– 36 86 98	FT-IR (KBr) cm^{-1} : 1250 (C–O–C), 2240 (C \equiv N); ^1H NMR (200 MHz, CDCl_3) δ : 4.21 (s, 1H, methyne), 6.25–7.45 (m, 10H, aromatic); NMR (50 MHz): 48.2, 67.8, 115.4, 126.2, 128.3, 131.5, 146.7; m/e [M^+] = 220.63.
4		TEBAC PSPTC 4 5		14 31 79 99	FT-IR (KBr) cm^{-1} : 1260 (C–O–C), 2245 (C \equiv N); ^1H NMR (200 MHz, CDCl_3) δ : 1.24 (t, 4H, $J=4.56$ Hz, methylene), 1.64 (m, 4H, methylene), 3.25 (s, 1H, methyne), [M^+] = 120.01.

phases to the catalyst surface to contact the catalytic sites. In addition, the reactants also must diffuse within the polymer support in order to meet the active-sites present inside the matrix which in turn may promote the reaction. Earlier, it is commonly believed that triphase catalysts have lower reactivity than their soluble analogs in the two-phase reaction system. But, in our observation, it is not true and we strongly believe that the presence of more number of active-sites (six active-sites), organophilicity character, and external and intraparticle mass transfer could co-operatively accelerate the reaction rate compared to their corresponding soluble analogues. Recently, Desikan and Doraiswamy [39] and Glatzer and co-workers [41] have performed a comparative assessment of heterogeneous and homogeneous PT catalysts with different categories of PTC systems/substrate and proved that the polymer-supported catalyst performed distinctly better than the soluble counterpart.

3.4. Kinetic study for Darzen's condensation reaction using newly synthesized six-site BSIMPTC

3.4.1. Effect of stirring speed

The effect of varying the stirring speed on the rate of Darzen's reaction of 4-nonanolide with 1,6-dibromo-hexan-2-one in the

presence of BSIMPTC was studied in the range of 100–700 rpm and keeping the other parameters constant. The observed pseudo-first order rate constant suddenly increased with an increase in the agitation rate from 100 to 200 rpm, and then there is a linear increase in the rate of the reaction at 200–700 rpm. Further increase in the agitation speed does not alter the reaction rate (Fig. 5); this may be due to the fact that the reaction kinetics may be controlled by the chemical reaction in the organic phase for the stirring speed greater than 700 rpm. Furthermore, in our study at stirring speed level of 700 rpm anion exchange equilibrium is very fast from the aqueous phase to the organic phase,

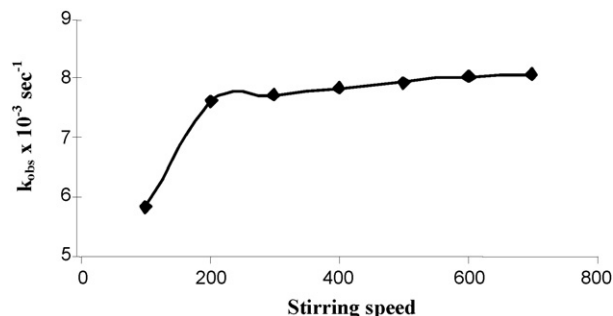


Fig. 5. Effect of variation of stirring speed on observed reaction rate.

and also the substrate consumption is dependent of the agitation speed. At below 700 rpm, there is no rapid mass transfer and hence low reaction rates and also diffusion-controlled kinetics are observed. In the case of stirring speed above 700 rpm, the rate constant is almost constant. Similar observation was reported by Landini et al. [42], Starks and Owens [43], Herriott and Picker [44] and Freedman et al. [45], which reflects kinetic control by mass transfer of the chemical reaction $[Q^+X^-]$ is at a steady state concentration. Hence, the dependence of the reaction rate constants on the lowest stirring speed, i.e. 200 rpm observed in the present study is indicative of presence of more number of active-site and also the reaction proceeding via an interfacial mechanism. Moreover, the conversion rate increases with an increase in the agitation speed up to 100 rpm, which agrees with the interfacial mechanism rather than Stark's extraction reaction mechanism [41]. From the previous discussions, we suggest that the Darzen's reaction must also proceed via interfacial mechanism.

3.4.2. Effect of varying substrate amount

Kinetic experiments were conducted by varying the amount of 4-nonanolide from 6.17 to 18.52 mM keeping the remaining parameters constant. The observed pseudo-first order rate constant of the reaction increased with increasing substrate concentration (Table 3), suggesting that the increase in the rate constant even at higher concentration of substrate may be attributed to the proportionate increase in the number of catalytic active-sites available in the BSIMPTC and also proving the strong evidence for the presence of multi-catalytic sites. Though we have fixed the large molar ratio of the substrate (12.34 mM) and catalyst (0.2 g), the rate constant increases remarkably even with very low amount of BSMPTCs, which confirms the presence of multi-catalytic site.

3.4.3. Effect of varying the sodium hydroxide concentration

Kinetic experiments were conducted by varying the concentration of aqueous sodium hydroxide (4.41–9.25 M) and keeping the other parameters constant. The observed rate constant (Fig. 6) shows that the rate of the reaction strongly depended on the strength of sodium hydroxide. A similar observation was reported by Wu and Lai [46] in the study of allylation of phenoxide under PTC conditions. Wang and Yang [47] also studied the kinetics of 4-bromophenylallyl ether using PTC and KOH instead of NaOH and found that the rate of the reaction initially increased and then decreased gradually when the concentration of KOH increased.

Table 3
Effect of variation of [substrate]

Substrate amount (mM)	$k_{\text{obs}} \times 10^{-3}, \text{S}^{-1}$
6.17	2.50
9.26	4.24
12.35	5.51
15.43	6.60
18.52	8.45

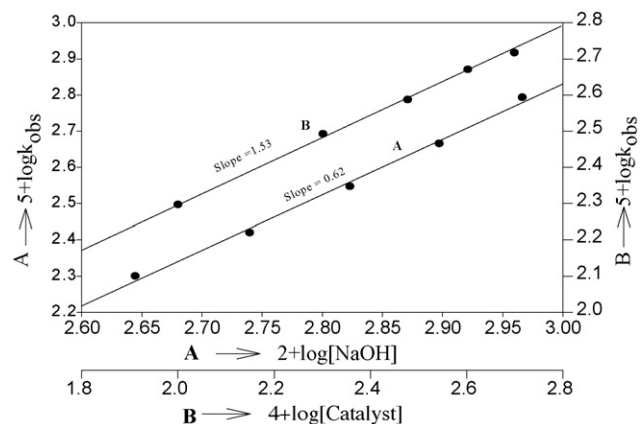


Fig. 6. (A) Effect of [NaOH] and (B) effect of [catalyst] on observed reaction rates.

The increase in the rate constant in the present study may be due to the presence of excess of OH^- ions as well as a large OH^- ion activity due to less solvation by H_2O . Thus, the observed rate constants were found to increase with an increase in the concentration of hydroxide ions. A bilogarithmic plot of the reaction rate against [NaOH] gives a straight line having a slope of 0.62 for BSIMPTC. Similar observation was reported in the C-alkylation of phenylacetone with *n*-butylbromide using di-site PTC [47], the kinetic order with respect to the aqueous sodium hydroxide concentration being 2.0. Further, it may be noted that the BSIMPTC is more active even in low concentration of NaOH (15%, w/v, 3.75 M); such observations are rare in literature. The use of small quantities of NaOH for any chemical reaction would definitely reduce the pollution and enhance the economy.

3.4.4. Effect of varying catalyst concentration

Kinetic experiments were conducted by varying the amount of BSIMPTC from 0.1 to 0.5 g with the other parameters, viz., stirring speed, [NaOH], [substrate] and temperature kept constant. The observed rate constants (Fig. 6) linearly increased with an increase in the concentration of catalyst. Controlled reactions were also carried out for the Darzen's reactions under specified conditions and there is no product formed even after 3 h. Jonczyk et al. [48] reported similar observations in the Darzen's condensation of α -chlorophenyl acetonitrile with benzaldehyde under PTC conditions. In the study of Br-I exchange reaction of 1-bromooctane, Molinari et al. [49] observed a similar trend in pseudo-first order rate constants as a function of the amount of heterogenised phosphonium containing PTC catalyst. Wang et al. [47] also reported similar observations in the kinetic study of the synthesis of 4-bromophenyl allyl ether under PTC conditions.

A bilogarithmic plot of the reaction rate versus catalyst concentrations gives a straight line with a slope of 1.53 for BSIMPTC. The increased rates are due to the increase in the number of catalytic sites in BSIMPTC and also to the adjacent availability of two cationic sites (catalytic site) in each styrene unit of the catalyst, which strongly influence the co-operative

interaction with the substrate thus enabling efficient binding of nucleophiles as well as electrophiles leading to an acceleration of the Darzen's condensation. The observation of linear dependence of the reaction rate on the catalyst concentration shows that the reaction may proceed through an interfacial mechanism. In the study of dehydrobromination of phenethylbromide [50], zero order kinetics with respect to the catalyst concentration was observed. Chiellini et al. [51] reported a linear dependence of the reaction rate constant on the catalyst in the study of ethylation of phenylacetonitrile. Halpern et al. [52] also reported an increase in the rate of the reactions strongly influenced by the structure of the catalyst during the reaction of deoxybenzoin and dimethyl sulphate in the presence of aqueous sodium hydroxide.

3.4.5. Effect of temperature variation

The effect of varying temperature on the rate of Darzen's condensation of 4-nonanolide with 1,6-dibromo-hexan-2-one was studied in the temperature range 30–50 °C with other parameters kept constant. The observed rate constants increased with an increase in temperature. The energy of activation calculated from Arrhenius plot (Fig. 7) was $E_a = 29.30 \text{ kcal mol}^{-1}$. The other thermodynamic parameters, viz., ΔG^\ddagger , ΔS^\ddagger and ΔH^\ddagger were $10.55 \text{ kJ mol}^{-1}$, -33.84 eu and $-45.90 \text{ J mol}^{-1}$, respectively.

The activation energy for the ethylation of pyrrolidin-2-one was reported to be $12.4 \text{ kcal mol}^{-1}$ under PTC conditions and for this an interfacial mechanism was proposed [52]. In a comprehensive study [46] of the synthesis of 4-bromophenylallyl bromide, the rate constant increased with an increase in temperature and the E_a value was found to be $12.5 \text{ kcal mol}^{-1}$. Do and Chou [53] also observed a similar result in the oxidation of benzyl alcohol using tetrabutylammonium hypochlorite as PTC. In the study of dehydrobromination of phenethyl bromide [50], the reaction proceeded more rapidly in the presence of tetraoctylammonium bromide (PTC) and followed zero order kinetics. The low activation energy, i.e., 8 kcal mol^{-1} suggested a hydroxide ion extraction mechanism and it was governed by

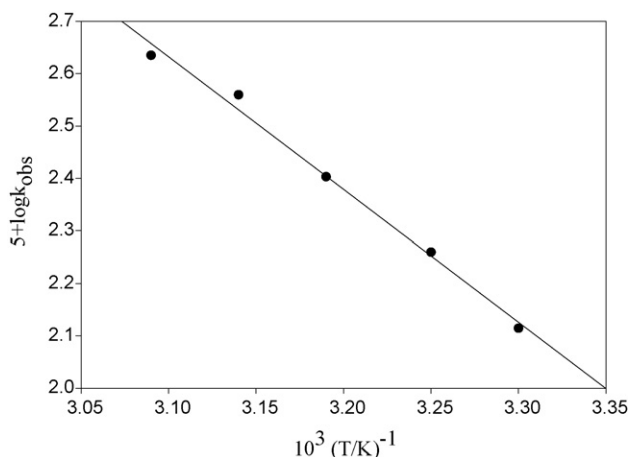


Fig. 7. Arrhenius plot.

diffusion. The E_a for intraparticle diffusion in anion exchange resin [54] in aqueous solution is of the order of $5\text{--}10 \text{ kcal mol}^{-1}$. Lee et al. [55] also reported a similar effect of temperature on the reaction rate for the formation of phenyl benzoate using tetrabutylammonium bisulfate as PTC and without PTC.

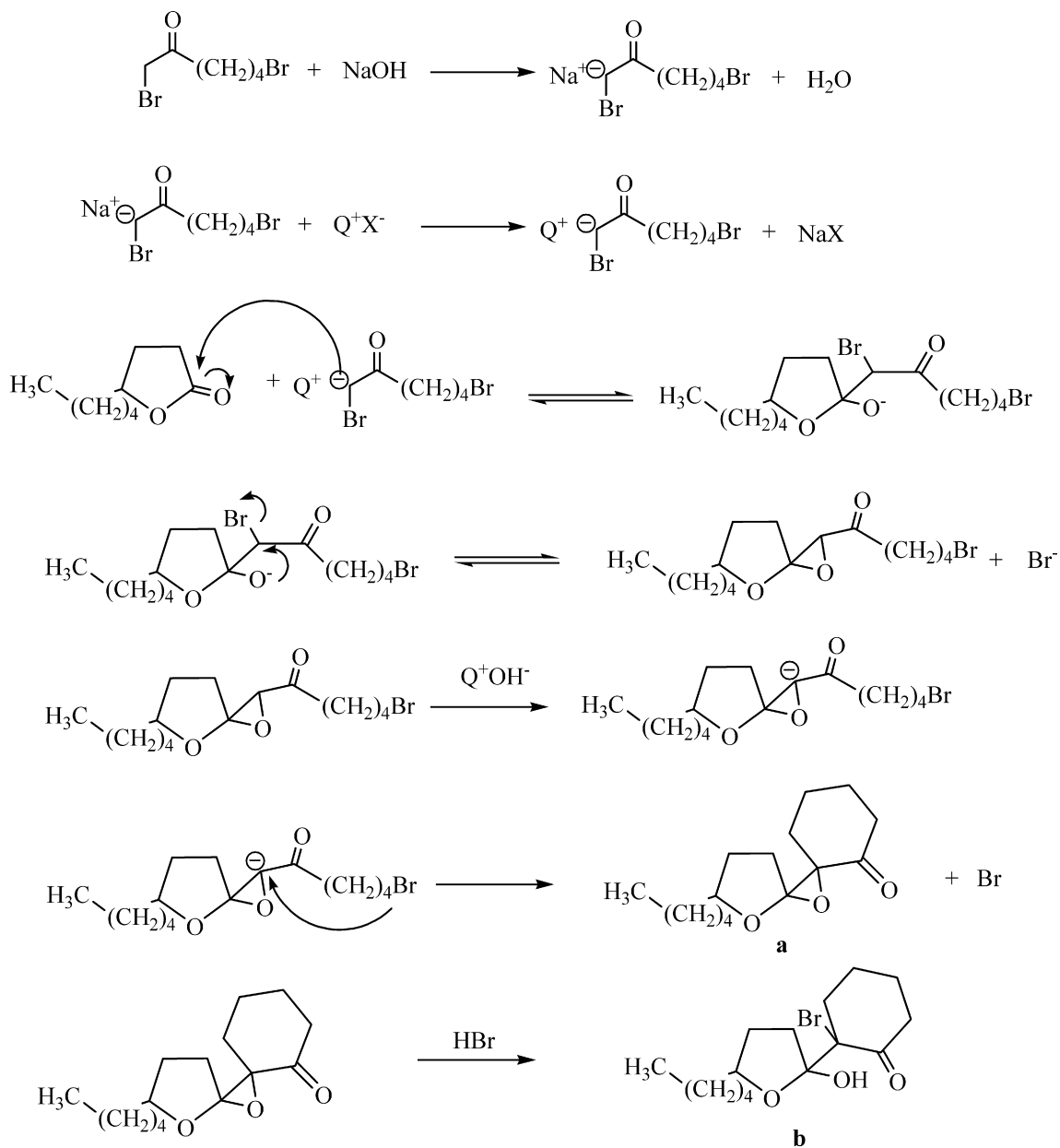
Considering all the earlier studies, it may be inferred that the reaction having higher E_a value may proceed via an interfacial mechanism. In our study, the activation energy for the Darzen's condensation of 4-nonanolide is found to be more than 10 kcal mol^{-1} and hence we also propose an interfacial mechanism for this reaction. Further, it was also proved earlier that this magnitude of E_a values is an indication of diffusion-controlled reaction.

3.4.6. Reaction mechanism

Based on the results and observations, it is suggested that the Darzen's condensation reaction may proceed by the following steps. Initially, deprotonation of an active hydrogen in 1,6-dibromo-hexan-2-one takes place and then the addition of the carbanion to the carbonyl of 4-nonanolide has occurred. Then the intramolecular rearrangement of the tetrahedral intermediate O^- anion to dehalogenation of the bromide anion and finally an oxirane compound is formed, viz., 2-Pentyl-1,12-dioxa-dispiro[4.0.5.1]dodecane. Further, the hydroxylated MPTC catalyst ($Q^+ OH^-$) is able to abstract another proton from the active methylene bromo compound to give the cyclic oxirane compound, viz., 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)cyclohexanone. At high $[OH^-]$, the transfer of MPTC/ OH^- ($Q^+ OH^-$) from the aqueous phase to the organic phase increases and as a result, the formation of water molecule/HBr increases; hence, the oxirane is easily hydrolyzed and produces 2-bromo-2-(2-hydroxy-5-pentyl-tetrahydro-furan-2-yl)cyclohexanone as the final product.

Normally, the direction of epoxide opening in acid or base catalyzed reactions was deduced by the products formed from the reaction of unsymmetrical substituted epoxides with nucleophiles such as alkoxide or OH^- ions. The reaction of 2-pentyl-1,12-dioxadispiro[4.0.5.1]dodecane with sodium hydroxide yields sodium salts that can be easily hydrolyzed in the presence of hydrobromide to form 2-bromo-2-(2-hydroxy-5-pentyltetrahydrofuran-2-yl)cyclohexanone as final product; the nucleophile has easily attacked on the less substituted carbon atom. This is expected for any simple bimolecular reaction, as steric hindrance to the approach of the reagent is less at this atom. Thus, the base/acid catalyzed ring opening of an epoxide or oxiranes is an S_N2 displacement reaction with a hydroxide ion containing MPTCs as the leaving group and has no counterpart with the normal ethers. It occurs with epoxides only because the relief in ring strain provides a potent driving force for the Darzen's condensation reaction.

From the observed results, we have concluded that the rate constants are dependent on the stirring speed up to 500 rpm, the rate of the reaction is strongly dependent on the concentration of the catalyst and aqueous sodium hydroxide and that the higher E_a value is consistent with the interfacial mechanism.



4. Conclusion

For the first time, we have synthesized and characterized a new bead-shaped insoluble polymer-supported multi-site phase transfer catalyst containing six-active-sites (BSIMPTCs) and its catalytic ability has been proved thoroughly based on the enhanced (≈ 4 times as compared with single-site insoluble catalyst) pseudo-first order rate constant of Darzen's condensation of 4-nonanolide with 1,6-dibromohexan-2-one reaction in the presence of a low amount of aqueous sodium hydroxide (15%, w/v). It is further confirmed that this BSIMPTC is found to be more active than the corresponding soluble six-site MPTC and single-site PTCs owing to its higher degree of organophilicity due to the presence of the nonpolar polymeric backbone. The effect of various experimental parameters, viz., stirring speed, [substrate], [catalyst], [hydroxide ion] and temperature are found to influence the observed rate constants in the Darzen's condensa-

tion reaction even under lower [MPTC] and [NaOH] conditons. Furthermore, we have also evaluated E_a and other thermodynamic parameters like ΔG^\ddagger , ΔS^\ddagger and ΔH^\ddagger as $29.30 \text{ kcal mol}^{-1}$, $10.55 \text{ kJ mol}^{-1}$, -33.84 eu and $-45.90 \text{ J mol}^{-1}$, respectively. The observed higher E_a value has confirmed that the Darzen's condensation of 4-nonanolide should proceed via an interfacial mechanism and also diffusion controlled reaction.

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