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Fundamental analysis of microwave irradiated liquid–liquid phase transfer catalysis (MILL-PTC): Simultaneous measurement of rate and exchange equilibrium constants in selective *O*-alkylation of *p*-*tert*-butylphenol with benzyl chloride

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Abstract

Fundamentals of low power microwave irradiated liquid–liquid phase transfer catalysis (MILL-PTC) have been brought out in enhancements in the rates of alkylation of *p*-*tert*-butylphenol with benzyl chloride and selectivity towards *O*-alkylated product. Further, a method was proposed for measuring simultaneously the reaction rate constant and anion exchange equilibrium constant from the same set of data. The reaction was studied with a variety of phase transfer catalysts using conventional heating (CH) as well as low power (40 W) microwave irradiation (MW). The *O*-alkylated product 1-(1,1-dimethylethyl)-4-phenylmethoxybenzene was selectively formed with tetra-*n*-butylammonium bromide (TBAB) as the catalyst under both CH and MW conditions. The rates of PTC reaction were greatly accelerated under MW. The activation energy of the reaction under CH and MW was nearly the same but the pre-exponential factor in the Arrhenius equation was increased by orders of magnitude under MW. The Gibbs free energy calculated for the exchange reactions suggested that the entropy of MILL-PTC reaction was greater than that of conventionally heated liquid–liquid PTC reaction.

Keywords: Microwave irradiated liquid–liquid phase transfer catalysis (MILL-PTC); Intensification of rates; Reaction kinetics; Modeling; *p*-*tert*-Butylphenol; Benzyl chloride; *O*-Alkylation; Rate constant; Equilibrium constant

1. Introduction

Substituted aromatic ethers are valuable as perfume and flavour compounds. Synthesis of such ethers is amenable to phase transfer catalysis (PTC) [1–3]. Ethers are synthesized by alkylation reactions using different catalysts such as phase transfer catalysts in two liquid phases [4] and in three liquid phases [5,6], cation-exchange resins [7], bases [8,9] and clays [10]. Isomerization is also used to make ethers [11]. The novelties of liquid–liquid (L–L) [12–14], solid–liquid (S–L) [15–17], solid–liquid–omega–liquid (S–L–ω–L) [18,19] and liquid–liquid–liquid (L–L–L) PTC [9,10,20] reactions have been conducted in our laboratory for reactions employed in perfumery, pharmaceutical and agrochemical industries including kinetic modeling. Of late, microwave irradiation has been increasingly used as a synthetic tool in a large number of studies. Microwave technology is a novel approach towards clean and green chemistry and it is 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 [21]. The microwave-assisted organic synthesis (MAOS) technology has moved to the forefront of chemical research today and several reviews, monographs, books, etc. have appeared from all parts of the

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Nomenclature

$[A]_{\text{org}}$	concentration of benzyl chloride in the organic phase (mol/cm^3)
ΔG	Gibb’s free energy (kcal/mol)
ΔH	enthalpy (kcal/mol)
k_{org}	second order rate constant of forward reaction in organic phase (cm^3/(mol s))
K_{e}	overall ion exchange reaction equilibrium constant
N_{Q}	total moles of catalyst added to the system at time $t = 0$ (mol)
$[N_{\text{Q}}]_{\text{org}}$	moles of the catalyst per unit volume of organic phase (mol/cm^3)
$[\text{Q}^+\text{X}^-]_{\text{org}}$	concentration of quaternary salt in the organic phase (mol/cm^3)
$[\text{Q}^+\text{X}^-]_{\text{aq}}$	concentration of quaternary salt in the aqueous phase (mol/cm^3)
$[\text{RO}^-\text{Q}^+]_{\text{aq}}$	concentration of nucleohile ion-pair in the aqueous phase (mol/cm^3)
$[\text{RO}^-\text{Q}^+]_{\text{org}}$	concentration of nucleohile ion-pair with quat in the organic phase (mol/cm^3)
ΔS	entropy (kcal/(mol K))
T	temperature (K)
V_{org}	volume of the organic phase (cm^3)
X^-	leaving group
X_{A}	fractional conversion of reactant A
Y^-	nucleophile

Greek symbols

ϕ	fraction of quaternary cation in the organic phase

world [22–30]. Microwave assisted heating has been shown to be an invaluable method, since it reduces the reaction times dramatically, typically from days or hours to minutes or seconds. When multi-mode power input at higher rates is used, it leads to evaporation of the solvent. A large number of papers, which appeared in several journals, are based on 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. 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. Obviously, no kinetic studies have been reported and such data essential for scale-up are missing from published literature [24–26].

The rates of the PTC reactions can be synergistically enhanced by using microwave irradiation including selectivity of the desired product. The microwave irradiation (MW) assisted solid–liquid phase transfer catalyzed synthesis of *o*-ethoxyphenol has been reported [27]. The solid composite copper–copper chloride assisted alkylation of naphthols promoted by microwave irradiation has been developed [28]. Loupy et al. [29] have given a detailed account of the microwave activation in various solid–liquid phase transfer catalyzed reactions [30]. Several large pharmaceutical companies have reported dramatic productivity increases in switching from conventional synthesis to MAOS [30]. Organic syntheses of various ethers employing solid–liquid phase transfer catalyst under microwave conditions have been reported by quite a few researchers [31–36].

The literature published on microwave assisted PTC reactions so far deals with only S–L PTC at very high input energy (typically of the order of 600 W) which leads to a final temperature of over 140–180 °C depending on the polarity of the reaction medium. The solubility of the solid reagent increases substantially in the medium at these temperatures thereby masking the effect of the phase transfer catalyst. Furthermore, since most of the quaternary salts used, as catalysts are thermally unstable at high temperatures and at temperatures beyond 120–130 °C, they may become totally ineffective due to decomposition; for instance, in the presence of bases, the degradation will start from 60 °C onwards and is a strong function of concentration of the base [1]. The published literature is totally devoid of studies in kinetics of MW assisted PTC. One of the reasons is that the reaction times for small quantities of reagents using a multi-mode microwave irradiation range from a few seconds to a few minutes and sampling has been difficult. Secondly, the purpose of most of the studies was to demonstrate the versatility of MAOS in intensifying rates of reactions and selectivites, and the “greenness” of the technique. However, there is no report on microwave assisted L–L PTC reactions, which are typically conducted at milder temperatures less than 100 °C.

After studying these lacunae, we have been convinced that to study L–L PTC reaction of industrial importance under milder conditions would throw light on enhancement in rates and selectivities under microwave irradiation. Alkylation reactions are one of the most widely studied PTC reactions. Thus, the selectivity of *O*-alkylation over *C*-alkylation in reaction between *p*-*tert*-butylphenol and benzyl chloride was taken as a model reaction for low energy mono-mode microwave irradiation. The *O*-alkylated product 1-(1,1-dimethylethyl)-4-phenylmethoxybenzene is an important intermediate, which is specifically used in the preparation of heat resistant paper of improved sensitivity and stability. Thus, the current work has an academic impact and industrial applicability, demonstrating the prowess of low energy microwave irradiated liquid–liquid phase transfer catalysis (MILL-PTC). Further, a general modeling method is devised, which would enable us to determine the rate constant and also the overall equilibrium constant for exchange of anions, using the same set of data. The subtle differences in the two modes of heating are clearly due to differences in energy of activation and Gibbs free energy for the system.