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Kinetics of Selective Formation of Ibuprofenamide by Phase Transfer Catalyzed Oxidation of 2-(4-Isobutylphenyl)propionitrile with Basic Hydrogen Peroxide

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Abstract:

Ibuprofenamide (benzeneacetamide-α-methyl-4-(2-methylpropyl)) is an ibuprofen analogue having anti-inflammatory activity itself and a precursor of many *N*-derivatives, all of which have good anti-inflammatory activities. The conventional process to prepare this amide is by the conversion of ibuprofen to acid chloride by thionyl chloride followed by ammonolysis or careful hydrolysis of the nitrile with H_2SO_4/CH_3COOH mixture. In this paper, the preparation of ibuprofenamide was achieved by the hydrolysis of 2-(4-isobutylphenyl)propionitrile with basic hydrogen peroxide under liquid−liquid phase transfer catalysis, under safe conditions with high conversion and selectivity. A systematic study was conducted to study the effects of various parameters such as different phase transfer catalysts, catalyst loading, substrate loading, and temperature on the conversion and rates of reaction. A kinetic model has been developed and validated against experimental data. With the 2-(4-isobutylphenyl)propionitrile to hydrogen peroxide mole ratio 1:4 at 60 °C, the conversion and selectivity were found to be 70% and 90%, respectively, in 2 h. This is a first report of its kind on mechanism and kinetics of PTC hydrolysis of nitriles. The results are novel.

1. Introduction

Phase transfer catalysis (PTC) has attained an incredible maturity with several interesting applications in the last 35 years, ever since Charles Starks coined the terminology.[1–6] PTC has been extensively applied for the synthesis of organic chemicals useful in agrochemical, dyestuff, pharmaceutical, polymer, perfumes, flavor, and other fine chemical industries.[1–8] However, the literature on the use of PTC for amide synthesis is rather scarce, and nothing is so far reported on kinetic modeling. Amides are industrially very important, and several methods are used to prepare them on a laboratory scale.[9–11] The general method of preparing amides involves either the conversion of acid to acid chloride followed by ammonolysis[12,13] or the hydrolysis of nitriles to amides and carboxylic acids, which is one of the best methods.[14] Some of the industrial examples cover the hydrolysis of amino nitriles to amino acids,[15] acrylonitrile to acrylamide and acetone cyanohydrin to the corresponding amide,[16] en route to methyl methacrylate.

Selective hydrolysis of nitrile to amide is complicated to achieve because the amide is often more easily hydrolyzed than the nitrile from which it is formed and it requires stringent conditions.[11,14] Commonly used methods for nitrile hydrolysis to amides use strong acid (96% H_2SO_4)[17] or base (50% KOH /*t*-BuOH).[18] In order to activate nitrile groups, strong inorganic acid/alkaline base and high temperatures are usually required. Yields range typically from poor to good, depending on the substrates and conditions. As stoichiometric amounts of acid or base are used, large amounts of salts are formed after workup, which is neither economic nor environmental friendly. In general, selective hydrolysis of nitriles to amides is fraught with problems, and yields are reasonable at best due to two reasons: (1) It is hard to stop the hydrolysis at the amide stage, and (2) consecutive hydrolysis to the carboxylic acid often proceeds because the rate constant of amide hydrolysis is usually larger than that for nitrile hydrolysis, especially under dilute acidic or basic conditions. Conversely, in concentrated acid or base the relationship is inverted. [19] Since the nitrile group is not very reactive, harsh conditions using strong acids or bases at high

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temperatures are generally required, which precludes the presence of acid- or base-sensitive functional groups in the substrate.

The hydrogen halides in alcohol, mineral acids, sodium superoxide in DMSO, manganese dioxide, potassium fluoride supported on alumina and metals such as copper have been employed for hydrolysis of nitriles to amides.[20–24] In addition to strong base or acid, enzymes and transition metal catalysts are also used to convert a variety of nitriles to amides. With enzymes, asymmetric hydrolysis or dynamic kinetic resolution of nitriles is possible. Transition metal coordination compounds are reported as catalysts for nitrile hydrolysis leading to good selectivity to amide.[25,26] Certain platinum complexes have also been shown to catalyze this reaction.[27] Among these, the hydration of nitrile with metallic and ionic copper as well as copper oxide have been found very effective to catalyze the hydration of aromatic nitriles.[28,29]

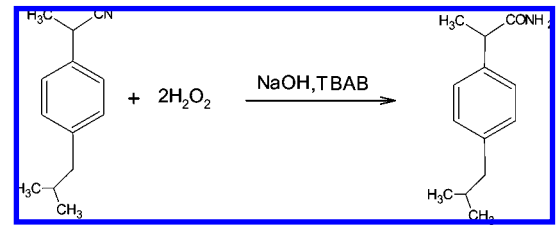
Hydrogen peroxide is a very good oxidation−reduction agent. Basic hydrogen peroxide is used for hydrolysis by using suitable mixtures of solvents.[30–32] H_2O_2 in dilute aqueous alkali can also be used to hydrolyze nitriles to the amides and finally to the acids. This procedure can be stopped at the amide stage by using different alkaline conditions with H_2O_2 in aqueous ethanol.[32a] Compared to the method using 50% KOH in refluxing *t*-BuOH, the reaction conditions are much milder. The effective species is thought to be HO_2^-, which is a much stronger nucleophile than hydroxide ion (α-effect nucleophile).[32a] A method based on a combination of urea/H_2O_2/K_2CO_3 was also reported providing reasonable yields of amides (50−60%).[30] It was found that the hydrolysis with basic hydrogen peroxide may be conveniently carried out under phase transfer catalyzed conditions in dichloromethane, tetra-*n*-butylhydrogen sulfate and excess H_2O_2.[33]

In this work, 2-(4-isobutylphenyl)propionitrile was oxidized with basic hydrogen peroxide under phase transfer conditions to synthesize ibuprofenamide. There is literature available on this reaction. Ibuprofenamide is an analogue of ibuprofen, having a very good anti-inflammatory activity.[34] Its *N*-derivatives such as *N*-pyridinyl, *N*-methyl pyridinyl, *N*-methyl-phenyl, *N*-pyrroline, *N*-morpholine, etc. also show good anti-inflammatory and ulcerogenic activity.[12,13] Another derivative *N*-(2-aryl propionyl)sulfonamides is an inhibitor of neutrophil chemotaxis.[35] With enzymes, asymmetric hydrolysis or dynamic kinetic resolution of nitriles is possible.[36] Enzyme hydrolysis using nitrile hydatases is the best industrial method for conversion of nitriles to amides (e.g., nitro process for acrylamide).[37] Thus, the preparation of ibuprofenamide by using PTC under mild conditions was considered to be an interesting and contemporary topic for research. Different parameters have been studied, and a suitable kinetic model has been proposed to explain the collected data.

2. Experimental Section

2.1. Chemicals and Catalysts. 2-(4-Isobutylphenyl)propionitrile was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad, India. Hydrogen peroxide (30% w/v) and toluene of AR grade were obtained from M/s. s.d. Fine Chem. Pvt. Ltd., Mumbai, India. Tetrabutylammonium bromide (TBAB), tetrabutylammonium iodide (TBAI), ethyltriphenylphosphonium bromide (ETPPB), and tetrabutylammonium hydrogen sulfate (TBAHS), of pure grade, were procured as gift samples from M/s. Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India. All other chemicals were analytical grade obtained from M/s s.d. Fine Chem. Pvt. Ltd.

2.2. Setup and Reaction Procedure. The experimental setup consisted of a 3 cm i.d. fully baffled mechanically agitated reactor of 50 mL capacity, equipped with four baffles and a six-bladed turbine impeller and a reflux condenser. The stirrer was centrally located, and the dimensions of the impeller were as follows: disc turbine impeller of 1.0 cm o.d., made of stainless steel 316, located at a distance of 0.8 cm from the bottom. The entire reactor assembly was immersed in a thermostatic water bath, which was maintained at the desired temperature with an accuracy of ±1 °C. Standard runs were conducted with 0.02 mol 2-(4-isobutylphenyl)propionitrile dissolved in toluene to make up 7 cm^3 volume of organic phase. To the organic phase was added a 10% solution of NaOH (0.005 mol) with 10 mol % of catalyst based on the nitrile. For a standard reaction, 0.08 mol of 30% w/v aqueous H_2O_2 was added with an addition rate of 0.1 mL/min at 1000 rpm at 60 °C. The reaction scheme is given below.



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2.3. Method of Analysis. Samples of the organic phase were withdrawn periodically and analyzed by gas chromatography (Chemito model 8510). A 2.0 m × 3.2 mm i.d. stainless steel column packed with Chromosorb WHP, which was impregnated with 5% SE-30, was used for analysis in conjunction with a FID. Synthetic mixtures were prepared for calibration and used to calculate the concentrations of 2-(4-isobutylphenyl)propionitrile and ibuprofenamide quantitatively. The rates of reaction were based on the disappearance of 1-(4-isobutylphenyl)propionitrile. After the reaction, the toluene layer was separated and cooled to precipitate the solid product. The solid product was filtered and purified by crystallization with methanol. The melting point was found to be 112−114 °C, which matches with the literature value 114−116 °C.[12] The product was also confirmed by GC−MS.

3. Results and Discussion

3.1. Reaction Mechanism. Hydrogen peroxide behaves as an unusual reagent, with both oxidation and reduction properties and in the case of reaction of aromatic nitrile in weakly basic solution, it involves an oxidation−reduction of hydrogen peroxide with simultaneous hydration of the nitrile. A clue for the reaction mechanism was obtained from the work of Wiberg,[37] according to whom in a homogeneous reaction containing nitrile and basic hydrogen peroxide in acetone or ethanol, the rate of reaction is first order in the nitrile, hydrogen peroxide, and hydroxyl ion.

$$RC\equiv N_{(org)} + 2H_2O_{2(aq)} \xrightarrow{k_{obs}} RCONH_{2(org)} + O_{2(g)} + H_2O_{(aq)} \quad \text{(a)}$$

Experiments were done in such a manner as to provide additional support for the mechanism and the kinetic model. Aqueous NaOH solution with the phase transfer agent was taken along with the organic phase containing the nitrile RCN in the batch reactor. Initially experiments were done with aqueous H_2O_2 by taking in a molar ratio of RCN/H_2O_2 of 1:4. It was observed that there was too much frothing due to the oxygen generated in situ and the exothermicity would lead to further hydrolysis to the acid, along with ammonia, thereby affecting the selectivity.

$$RCONH_{2(org)} + 2H_2O_{2(aq)} \xrightarrow{k_{obs}} RCOOH_{(org)} + O_{2(g)} + NH_{3(g)} + H_2O_{(aq)} \quad \text{(b)}$$

Under the liquid−liquid PTC, it was also necessary to ascertain the locale of the reaction and whether kinetic information could be extracted from the collected data. Under basic conditions, typically the OH^- and HOO^- ions will coexist in the aqueous phase, and for the hydrolysis reaction to occur, preferential transfer of HOO^- to the organic phase should occur (normal L−L PTC mechanism) or RCN must diffuse across the interface into the aqueous phase to react with HOO^-.

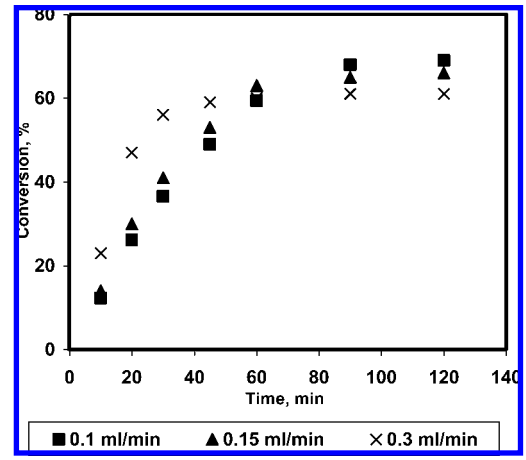

Figure 1. **Effect of rate of addition of H_2O_2, 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), TBAB 0.002 mol, temperature 60 °C, speed of agitation 1000 rpm.**

There are four different reaction regimes possible for L−L PTC as has been discussed by us earlier.[7,39] These are (i) slow reaction (kinetically controlled, rate of diffusion is very high), (ii) diffusion controlled (reaction rate is high), (iii) pseudofast reaction (diffusion and reaction simultaneously occur in the film next to L−L interface), and (iv) instantaneous reaction in the film (diffusion controlled). The details are avoided and can be seen in our work.[7,38] If the concentration of the diffusing species HOO^- in the organic phase remains constant, which is equal to its saturation concentration, then the rate of addition of hydrogen peroxide beyond a certain rate will not affect the conversion and selectivity. As against a homogeneous reaction, the diffusing species will be an ion-pair Q^+HOO^-. If on the contrary RCN diffuses from the organic phase to the aqueous phase, then the aqueous phase will be always saturated with RCN, due to its limited solubility, and the reaction kinetics would show apparent zero order in RCN.

Therefore, a semibatch mode of operation was adopted, and the effect of rate of addition on conversion and selectivity was studied. The speed of agitation was maintained at 1000 rpm to ensure absence of mass transfer resistance, which will be discussed later. Several experiments were done, and a window of operation for the flow rate of hydrogen peroxide was selected. Aqueous hydrogen peroxide was added continuously to the batch of the nitrile in toluene, aqueous base OH^- and phase transfer agent Q^+X^- as a biphasic mixture. The rate of addition of hydrogen peroxide to the reaction mass was varied from 0.1 to 0.3 cm^3/min (Figure 1). The conversions and selectivity were found to be practically the same at 0.1 and 0.15 cm^3/min for 2 h. With the higher rate of addition of 0.3 cm^3/min, the initial rate is faster, and frothing was seen to some extent, indicating the onset of reaction b above. Thus, a rate of 0.1 cm^3/min was used for further reaction to study the effects of various other parameters. The conversion in 2 h was 70%, and selectivity to the product was 90%. The selectivity up to 90 min was closer to 98%. It indicates that the concentration of the ion-pair Q^+HOO^- in the organic phase was always finite and at its

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saturation value and the reaction locale was the organic phase. This allowed the development of the kinetic model.

Thus, steps 1 and 2 produce the ion-pair with peroxo species, and it is transferred to the organic phase.

$$H_2O_{2(aq)} + OH^-_{(aq)} \rightleftarrows HOO^-_{(aq)} + H_2O\,(aq) \quad (1)$$

$$HOO^-_{(aq)} + Q^+_{(aq)} \rightleftarrows Q^+HOO^-_{(aq)} \quad (2)$$

$$Q^+HOO^-_{(aq)} \rightleftharpoons Q^+HOO^-_{(aq)} \quad (3)$$

$$K_1 = \frac{[Q^+HOO^-]_{org}}{[Q^+HOO^-]_{aq}} \quad (4)$$

$$RC \equiv N_{(org)} + Q^+HOO^- \xrightarrow{k_{org}} \quad \text{(RDS)} \quad (5)$$

$$RC = (OOH)N^-Q^+(org)$$

Assuming this step 5 is rate determining (RDS) and all subsequent steps are fast and have no influence on the rate of the reaction, these are as follows:

$$RC = (OOH)N^-Q^+ \leftrightarrows RC(OOH)NH_{(aq)} \quad (6)$$

$$RC = (OOH)N^-Q^+ + H_2O_{(aq)} \rightarrow RC(OOH)NH_{(aq)} + Q^+OH^-_{(aq)} \quad (7)$$

The formation of peroxyimidic acid in step 6 above is important. The homogeneous reaction using ethanol and acetone[37] also mentions the reaction 5 as RDS.

$$RC(OOH) = NH_{(aq)} + H_2O_2 \rightarrow RCONH_2 + O_{2(aq)} + H^+ + OH^-_{(aq)} \quad (8)$$

$$O_{2(aq)} \rightarrow O_{2(g)} \quad (9)$$

$$RCONH_{2(aq)} \rightarrow RCONH_{2(aq)} \quad (10)$$

$$Q^+OH^-_{(aq)} \rightleftarrows Q^+OH^-_{(aq)} \quad (11)$$

$$K_2 = \frac{[Q^+OH^-]_{(org)}}{[Q^+OH^-]_{(aq)}} \quad (12)$$

The overall or observed rate of reaction is equal to that of the RDS:

$$\frac{-\mathrm{d}[A]_{org}}{\mathrm{d}t} = k_{org}[A]_{org}[Q^+HOO^-]_{org} \quad (13)$$

Let $RC = (OOH)N^-Q^+_{(org)}$ be denoted by species A with corresponding factional conversion X_A. The above equation can be integrated provided the term $[Q^+HOO^-]_{org}$ remains constant throughout the reaction phase; that is, the rate of addition of hydrogen peroxide is such that it would render this term a constant, as was discussed earlier. Thus,

$$\frac{-\mathrm{d}[A]_{org}}{\mathrm{d}t} = k_p[A]_{org} \quad (14)$$

This is a typical first-order reaction, giving the following integrated form:

$$-\ln(1 - X_A) = k_p t \quad (15)$$

where k_p is a pseudo-first-order rate constant. On the contrary, if there is a lot of dilution of the aqueous phase and the equilibrium constant is affected, then it is necessary to account for it.

From eqs 1, 2, and 4:

$$K_3 = \frac{[HOO^-]_{aq}[H_2O]_{aq}}{[H_2O_2]_{aq}[OH^-]_{aq}} \quad (16)$$

$$K_4 = \frac{[Q^+HOO^-]_{aq}}{[HOO^-]_{aq}[Q^+]_{aq}} \quad (17)$$

$$[Q^+HOO^-]_{aq} = K_4[HOO^-]_{aq}[Q^+]_{aq} = K_4[Q^+]_{aq}K_3\frac{[H_2O_2]_{aq}[OH^-]_{aq}}{[H_2O]_{aq}} \quad (18)$$

$$[Q^+HOO^-]_{org} = K_1K_3K_4[Q^+]_{aq}\frac{[H_2O_2]_{aq}[OH^-]_{aq}}{[H_2O]_{aq}} = K_e[Q^+]_{aq}[H_2O_2]_{aq}[OH^-]_{aq} \quad (19)$$

$$\frac{-\mathrm{d}[A]_{org}}{\mathrm{d}t} = k_{org}K_e[A]_{org}[Q^+]_{aq}[H_2O_2]_{aq}[OH^-]_{aq} \quad (20)$$

The catalyst amount in moles (N_Q) is distributed between the two phases.

$$N_Q = [Q^+]_{aq}V_{aq} + [Q^+]_{org}V_{org} \quad (21a)$$

$$[Q^+]_{aq} = [Q^+HOO^-]_{aq} + [Q^+OH^-]_{aq} \quad (22a)$$

$$[Q^+]_{org} = [Q^+HOO^-]_{org} + [Q^+OH^-]_{org} \quad (22b)$$

$$N_Q = (V_{aq} + K_1V_{org})[Q^+HOO^-]_{aq} + (V_{aq} + K_2V_{org})[Q^+OH^-]_{aq} \quad (22c)$$

$$[Q^+]_{aq} = \frac{N_Q - [Q^+]_{org}V_{org}}{V_{aq}} \quad (21b)$$

Here

$$V_{aq} = V_{aq-0} + q_{H_2O_2} \cdot t \quad (23)$$

V_{aq-0} is the initial volume of the aqueous phase, $q_{H_2O_2}$ the volumetric rate of addition of aqueous hydrogen peroxide, and t is the time of addition.

$$\frac{-\mathrm{d}[A]_{org}}{\mathrm{d}t} = k_{org} K_e [A]_{org} [H_2O_2]_{aq} [OH^-]_{aq} \times \left(\frac{N_Q - [Q^+]_{org} V_{org}}{V_{aq-0} + q_{H_2O_2} \cdot t} \right) \quad (24)$$

Equation 24 needs a numerical method of analysis and can also be integrated under certain conditions.

If the term in the large brackets on the right-hand side of eq 24 remains constant, then an analytical solution is possible. This can be argued from the following perspective.

$$[Q^+]_{aq} = [Q^+HOO^-]_{aq} + [Q^+OH^-]_{aq} \quad (25)$$

$$[Q^+]_{org} = [Q^+HOO^-]_{org} + [Q^+OH^-]_{org} \quad (26)$$

$$N_Q = (V_{aq} + K_1 V_{org})[Q^+HOO^-]_{aq} + (V_{aq} + K_2 V_{org})[Q^+OH^-]_{aq} \quad (27)$$

It is well-known that hydroxyls are preferentially partitioned in aqueous phase when the organic phase is nonpolar and the ion pairs are lose. So most of the quaternary cation is available to make ion pairs with peroxy ions. Further, the peroxy ion-pair $[Q^+HOO^-]_{org}$ concentration in organic phase also remains constant and is not affected by the slow rate of addition of hydrogen peroxide. Thus, 15 can be written as follows:

$$-\ln(1 - X_A) = k_p' N_Q t \quad (28)$$

or

$$-\ln(1 - X_A) = k_{obs} t \quad (29)$$

where k_{obs} is the observed (pseudo-first-order) rate constant in time^{-1}.

Now the model could be validated by conducting different sets of experiments.

3.2. Effect of Different Catalysts. Various catalysts with different cationic as well as anionic structures, such as TBAB, ETPPB, TBAHS, and TBAI were employed under otherwise similar experimental conditions (Figure.2). Out of these, TBAB gave the maximum rates of reaction and conversion. The order of activity of these catalysts was as follows:

$$TBAI \cong TBAB > ETPPB > TBAHS$$

TBAI is marginally better than TBAB (5.1% as the slopes, k_{obs}, indicate). However, TBAI is almost 3 times more expensive on a commercial scale. Indeed, in many cases KI is added along with Q^+X^- to enhance the rate, where Q^+I^- is generated in situ.[1,39]

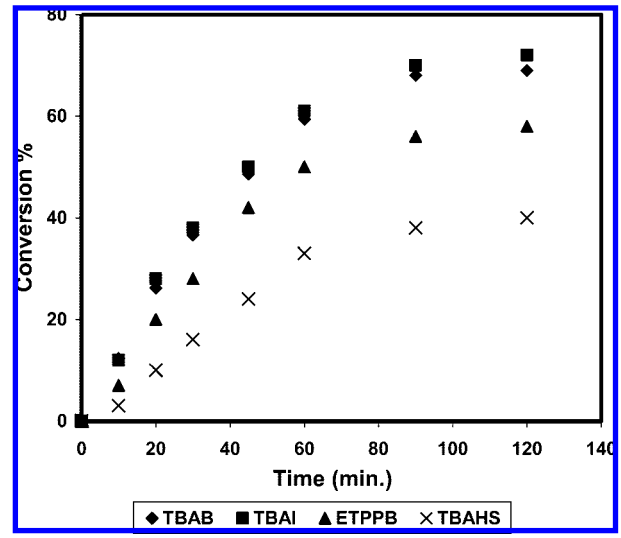

Figure 2. **Effect of different catalysts 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), catalyst 0.002 mol, temperature 60 °C, rate of addition of H_2O_2 0.1 mL/min.**

I^- is a much bulkier anion than Br^- and better partitioned in organic phase. Thus, the model was tested for these catalysts (Figure 3) to find that the data fit very well, and in all cases, the concentration of the ion-pair Q^+HOO^- in the organic phase is constant in each case during the course of the reaction, and the rate is controlled by the intrinsic kinetics. Thus, further experiments were conducted with TBAB, since it is inexpensive and commercially available in high purity.

3.3. Effect of Speed of Agitation. To ascertain the influence of external mass transfer resistance on the transfer of reactants to the reaction phase, the speed of agitation was varied in the range of 600 to 1200 rpm under otherwise similar conditions in the presence of TBAB as the catalyst. Figure 4 shows that conversion is practically the same as the increase in speed of agitation from 600 to 1200 rpm. This shows that there is no external mass-transfer resistance above 600 rpm. Therefore, a speed of agitation of around 1000 rpm was employed in all further experiments. The model also fits the data at and beyond 1000 rpm; this data point is already shown in Figure 3 for TBAB.

3.4. Effect of Catalyst Concentration. The quantity of catalyst (TBAB) was varied from 3×10^{-4} to 6×10^{-3} mol under otherwise similar experimental conditions. The conversion of 2-(4-isobutylphenyl) propionitrile is plotted against time for different catalyst concentrations (Figure.5). As the catalyst loading is increased, the conversion also increased, due to the fact that the concentration of Q^+OOH^- extracted into the organic phase increases with increasing catalyst concentration. The validity of the model was tested to find that it fits the data well up to 10 mol % catalyst loading (=0.0002 mol) (Figure 6) and beyond it the fit is not as good since mass transfer effects are set in due to excessive reaction rate (e.g., 20 mol%).

3.5. Effect of molar ratio. The effect of change in molar ratio of 2-(4-isobutylphenyl) propionitrile: H_2O_2 was studied by varying in the range of 1:1 to 1:6, with reference to the total quantity added, under otherwise similar conditions (Figure 7). At a given time, the concentration of $[Q^+HOO^-]_{org}$ is maintained constant because of the adequate rate of addition of the

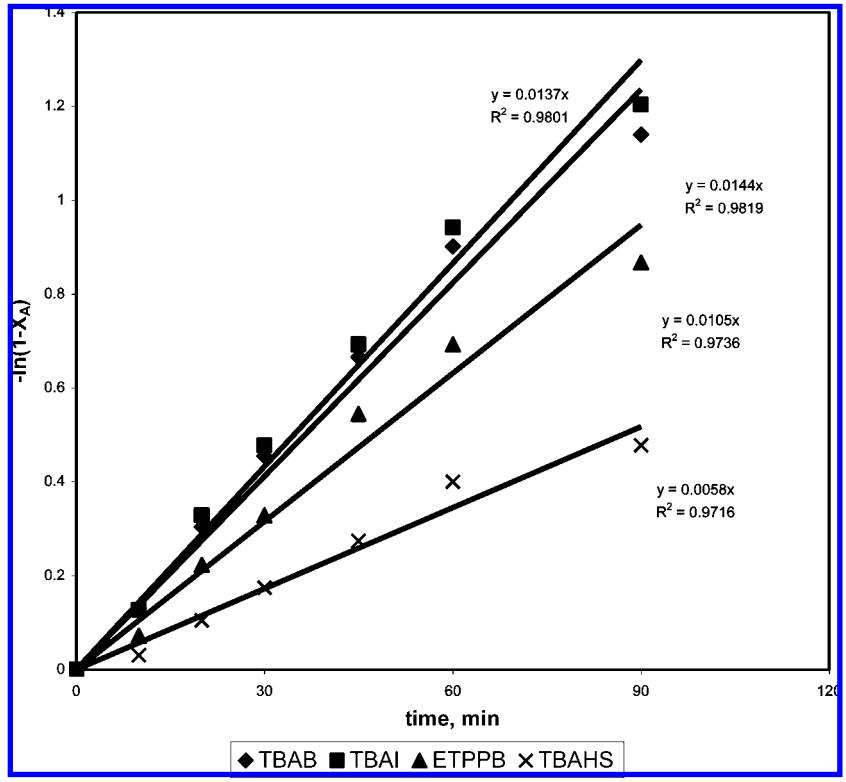

Figure 3. **Validity of model against experimental data for different catalysts 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), catalyst 0.002 mol, temperature 60 °C, rate of addition of H_2O_2 0.1 mL/min.**

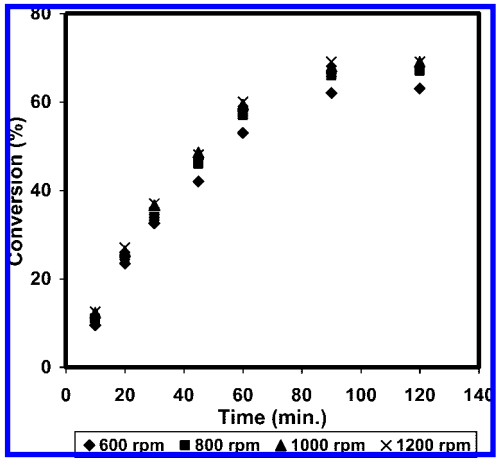

Figure 4. **Effect of speed of agitation 2-(4-isobutylphenyl) propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), TBAB 0.002 mol, temperature 60 °C rate of addition of H_2O_2 0.1 mL/min.**

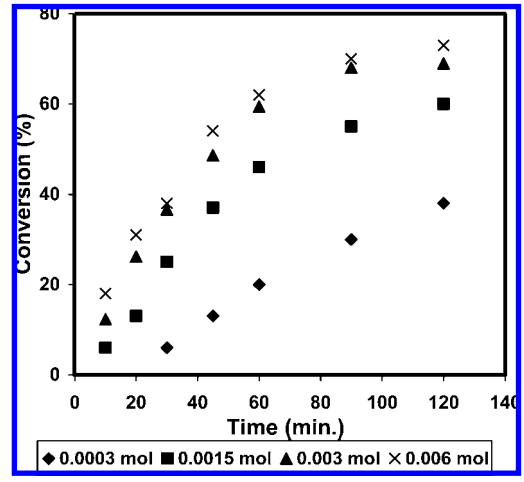

Figure 5. **Effect of catalyst concentration 2-(4-isobutylphenyl) propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), temperature 60 °C, speed of agitation 1000, rate of addition of H_2O_2 0.1 mL/min.**

peroxide, then the substrate to $[Q^+HOO^-]_{org}$, the molar ratio of the substrate with reference to hydrogen peroxide in the reactor is very large, because $[Q^+HOO^-]_{org}$ is very small. Up to 30 min, the conversions are not affected in all cases and remain practically the same for all mole ratios. At mole ratios 1:4 and 1:6, at all times the conversions are the same. $[Q^+HOO^-]_{org}$ is a saturation (constant) value and all transferred $[Q^+HOO^-]_{org}$ reacts with RCN. For lower values of 1:1 and 1:2, based on the stoichiometry of the reaction, the maximum conversion would be 50% and 100%, provided all peroxo ion pair generated in situ is transferred from the aqueous to organic phase. However, as the reaction proceeds, the equilibrium constant K_1 is affected at lower mole ratios and the saturation concentration for $[Q^+HOO^-]_{org}$ is not achieved and therefore lower conversions are obtained after 2 h.

3.6. Effect of NaOH Concentration. The sodium hydroxide concentration was varied from 0.005 to 0.03 mol under otherwise similar conditions (Figure 8). As the concentration of sodium hydroxide increased, the conversion decreased due to the fact that the decomposition of hydrogen peroxide is greater with higher concentration of sodium hydroxide. This is also known from published literature.[17] So 0.005 mol of sodium hydroxide was used for further reactions.

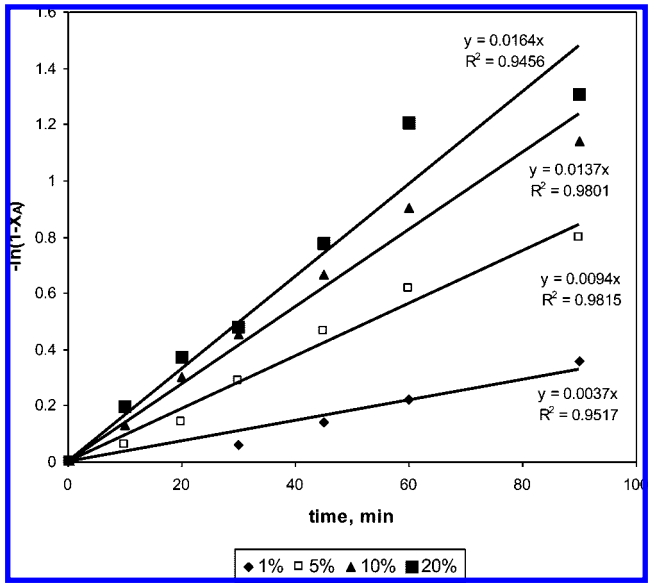

Figure 6. **Validity of model for different catalyst loadings in mol % of substrate 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution), temperature 60 °C, speed of agitation 1000, rate of addition of H_2O_2 0.1 mL/min.**

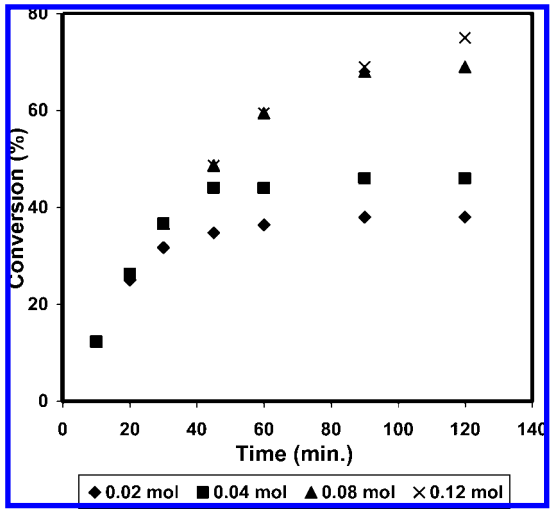

Figure 7. **Effect of mole ratio 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL, NaOH 0.005 mol (10% w/v solution), TBAB 0.002 mol, temperature 60 °C, speed of agitation 1000 rpm rate of addition of H_2O_2 0.1 mL/min.**

3.7. Effect of Temperature. The effect of temperature on the rate of the reaction of 2-(4-isobutylphenyl) propionitrile was studied in the range of 40 to 70 °C under otherwise similar conditions. The conversion of 2-(4-isobutylphenyl) propionitrile was observed to increase with an increase in the reaction temperature from 40 to 60 °C (Figure 9). But at 70 °C it was found that reaction rate decreases since hydrogen peroxide decomposes fast at higher temperature.

Thus, the plots could be made to verify the validity of the above model for three temperatures (Figure 10) to obtain k_{obs}. There is a good fit. Arrhenius plot was made to extract the apparent energy of activation as 5.50 kcal/mol (Figure 11). This value also confirms that the reaction is kinetically controlled under the conditions employed.

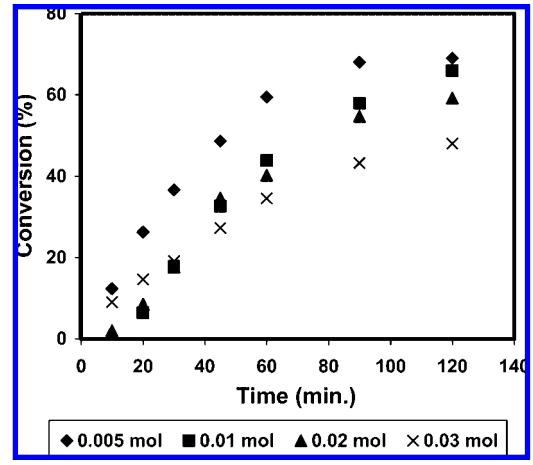

Figure 8. **Effect of NaOH concentration 2-(4-isobutylphenyl)-propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, TBAB 0.002 mol, temperature 60 °C speed of agitation 1000 rpm, rate of addition of H_2O_2 0.1 mL/min.**

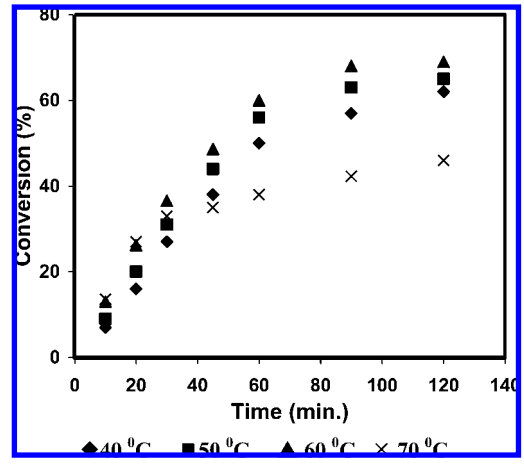

Figure 9. **Effect of temperature 2-(4-isobutylphenyl)propionitrile 0.02 mol, toluene 3.3 mL, H_2O_2 (30%) 0.08 mol, NaOH 0.005 mol (10% w/v solution) TBAB 0.002 mol, speed of agitation 1000 rpm rate of addition of H_2O_2 0.1 mL/min.**

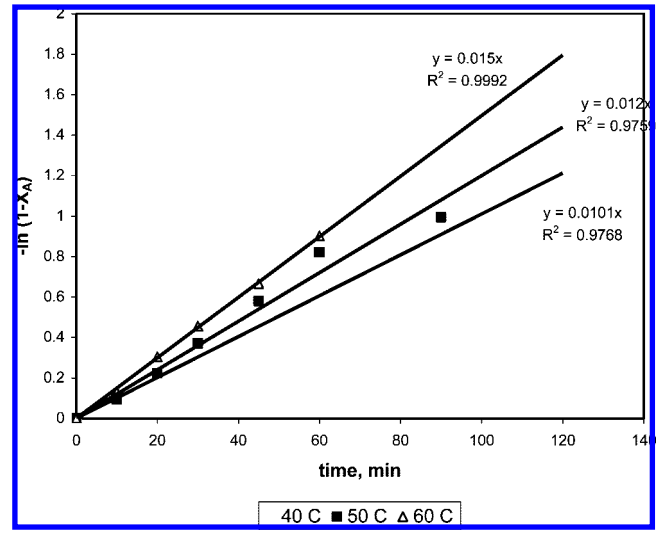

Figure 10. **Validation of model at different temperatures.**

4. Conclusion

The oxidation of 2-(4-isobutylphenyl)propionitrile with basic hydrogen peroxide under phase transfer conditions was studied

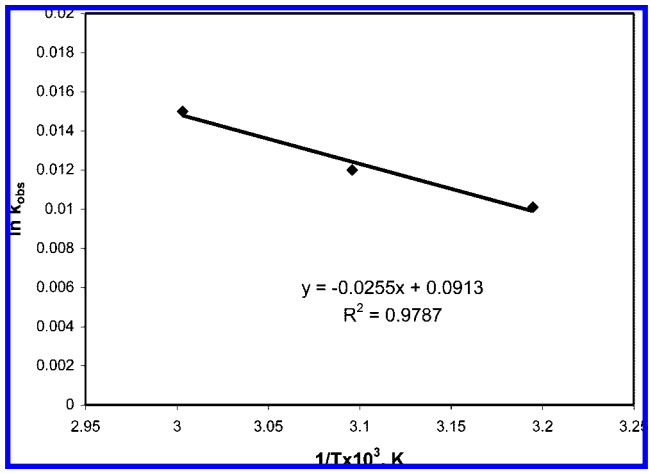

Figure 11. **Arrhenius plot.**

to synthesize ibuprofenamide. A mechanistic model was developed to understand the progress of the reaction and selectivity to ibuprofenamide. Semibatch reaction was selected as the batch experiments result in more frothing, loss of the hydrogen peroxide, and less conversion. With the 2-(4-isobutylphenyl)propionitrile to hydrogen peroxide mole ratio 1:4 at 60 °C, the conversion and selectivity were observed to be 70% and 90%, respectively, in 2 h. Effects of various parameters were studied on the rate of reaction and conversion to confirm the validity of the model. The apparent activation energy was found to be 5.05 kcal/mol. This is a first study on mechanism and kinetics of phase transfer catalyzed oxidation of nitriles using basic hydrogen peroxide. The results are novel.

Nomenclature and Symbols

A	2-(4-isobutylphenyl)propionitrile
$[A]_{org}$	concentration of A in the organic phase, mol/cm^3 of organic phase
K_1	$[Q^+HOO^-]_{org}/[Q^+HOO^-]_{aq}$
K_2	$[Q^+OH^-]_{(org)}/[Q^+OH^-]_{(aq)}$
K_3	$\{[HOO^-]_{aq}\,[H_2O]_{aq}\}/\{[H_2O_2]_{aq}\,[OH^-]_{aq}\}$
K_4	$[Q^+HOO^-]_{aq}/\{[HOO^-]_{aq}\,[Q^+]_{aq}\}$
K_e	$K_1\,K_3\,K_4$
k_{obs}	observed first-order reaction rate constant, min^{-1}
k_{org}	second-order reaction rate constant, cm^3/mol/min
k_p	pseudo-first-order rate constant, min^{-1}
N_Q	total moles of catalyst added to the system, mol
$q_{H_2O_2}$	volumetric rate of addition of aqueous hydrogen peroxide, cm^3/min
t	time of reaction, min
V_{aq}	volume of aqueous phase at time t, cm^3
V_{aq-0}	initial volume of aqueous phase in the reactor, cm^3
V_{org}	volume of organic phase taken initially in the reactor, cm$_3$
X_A	$N_{A0} - N_A/N_{A0}$, fractional conversion of A

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