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Kinetics of the Reaction between 2-Phenylpropionitrile and 2-Chloro-5-nitrotrifluoromethylbenzene under Phase-Transfer Catalysis

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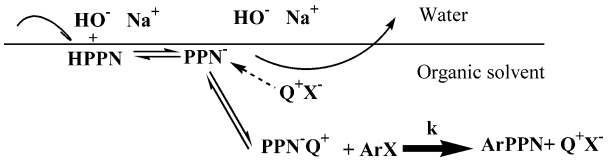

Phase-transfer catalysis (PTC) is a widely accepted methodology in organic synthesis. Although a great number of organic syntheses were reported in PTC conditions, systematic kinetic studies are scarce. In the present report, a detailed study of the kinetics of the reaction between 2-chloro-5-nitrotrifluoromethylbenzene (CNTFB) and 2-phenylpropionitrile anion (HPP^-), under PTC, was performed under several conditions. The reaction was carried out either in toluene or chlorobenzene as the organic phase, in the presence of a concentrated aqueous solution of NaOH using tetraalkylammonium (Q^+X^-) salts as phase-transfer catalysts. The major product was 2-(4-nitro-2-trifluoromethylphenyl)-2-phenylpropionitrile, and its yield depends on the experimental conditions. Different aspects of the mechanism are discussed and quantified. Kinetic data were explained by means of an interfacial mechanism that involves the deprotonation of the adsorbed nucleophile precursor followed by its catalyst-mediated extraction to the organic phase. A multicomponent Langmuir-type interface was assumed. Although the extraction of OH^- by catalyst to the organic phase is usually disregarded, the formation of the substrate hydrolysis product that leads to catalyst poisoning was also investigated. The influence of this side reaction on the yield of the main product was established. A discussion about the influence of this side process on the main reaction and the operating mechanism is presented.

Introduction

Phase-transfer catalysis (PTC) is a widely accepted methodology in organic synthesis, where reagents in different phases come in contact by means of a phase-transfer catalyst. This catalyst is capable of dissolving or extracting the reagent into the organic phase, in the form of an ion pair, where the reaction with the substrate takes place. In the present report, the practical and phenomenological Dehmlow's definition for the term phase-transfer catalysis is used irrespective of the operating mechanism.[1]

A great number of different organic reactions are carried out under PTC conditions[2] because this methodology allows the synthesis of many compounds not only from poorly reactive starting materials but also with an increase in yield or selectivity. Irrespective of the mechanistic details, these processes offer a number of advantages over homogeneous alternatives, and most of these have been recognized as "green" alternatives in synthetic organic chemistry.[3−5] Moreover, the use of chiral PTC to satisfy the increasing demand of enanteomerically enriched compounds has been thoroughly demonstrated.[4,6]

The reactivity of in situ generated anionic nucleophiles under PTC conditions is usually enhanced since they result unsolvated and therefore strongly activated for the substitution reactions.[1,7,8] The reaction of carbanions with haloaromatic compounds offers important synthetic pos-

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sibilities as it provides a way to introduce a carbon skeleton in an aromatic ring, which is often accompanied by the introduction or change in functionality.[9,10] The reactions of α-phenyl alkylacetonitriles with chloronitrobenzenes were reported to proceed with yields ranging from 59 to 92%.[1,11,12] An interfacial mechanism, which involves the carbanion formation by proton abstraction from the CH acid dissolved in a nonpolar solvent by a concentrated aqueous NaOH phase boundary, is usually accepted for this type of reaction.[12,13] Thus, in situ generated carbanions are ion-exchanged and extracted to the organic phase as fully lipophilic ion pairs with the PT cation and further reacted with the substrate, even though a mechanistic picture of the way these reactions take place was proposed in the early 1970s.[14] In this work, the kinetics of the reaction between 2-chloro-5-nitrotrifluoromethylbenzene (CNTFB) and 2-phenylpropionitrile anion (HPP^-) under PTC to yield 2-(4-nitro-2-trifluoromethylphenyl)-2-phenylpropionitrile has been studied. To the best of our knowledge, no kinetic data have been reported for this reaction. This type of data can provide the basis for future process design simulations to assess possible industrial applications.[15−17]

The reaction was performed either in toluene or chlorobenzene as the organic phase in the presence of a concentrated aqueous solution of NaOH using tetraalkylammonium (Q^+X^-) salts as PT catalyst. The effect of variables such as base concentration, type, and concentration of catalyst were explored. Different aspects of the mechanism are discussed and quantified. Since catalyst-mediated OH^- extraction to the organic phase can occur under certain conditions, the substrate hydrolysis in the reaction media was also investigated. To find the influence of this side reaction on the yield of the main reaction, the rate of formation of the phenol derivative was investigated under certain experimental conditions. A discussion about the influence of this side process on the main reaction and the operating mechanism is presented.

Experimental Section

General Methods. GC columns 30 m × 0.32 mm, phase thickness 0.25 mm and 25 m × 0.25 mm, phase thickness 0.25 mm, were used. NMR spectra were acquired on a 200 MHz spectrometer. Normal-phase chromatography was performed with 99% hexane-2-propanol as eluent.

Materials. 2-Chloro-5-nitro-trifluoromethylbenzene (CNTFB), 2-phenylpropionitrile (HPPN), 1-methylnaphthalene (MN), tetrabutylammonium bromide (TBAB), benzyltriethylammonium bromide (BTAB), tetrahexylammonium chloride (THAC), tetraethylammonium chloride (TEAC), tetrabutylammonium chloride (TBAC), tetrabutylammonium hydrosulfate (TBAHS), and benzyldodecyldimethylammonium bromide were used without further purification. Chlorobenzene, toluene, acetonitrile, *n*-hexane, 2-propanol, and dichloromethane (HPLC quality) were used as received. Pure water, conductivity 0.3−0.5 μΩ at 298 K, was obtained in a WaterPro Mobile for HPLC system.

Procedures. The kinetic experiments were carried out in a 20 mL three-necked flask equipped with a condenser and a mechanical stirrer. The stirrer contains a mixing shaft of 6 mm diameter equipped with three six-bladed turbine-type impellers. The reactor was immersed in a water-bath at 40.0 ± 0.1 °C unless otherwise specified. All of the concentrations given apply to a single phase.

To start a kinetic run, known quantities of HPPN, CNTFB, and tetraalkylammonium salt (Q^+X^-), dissolved in 5 mL of toluene or chlorobenzene, were introduced into the reactor at the desired temperature. The stirring rate was adjusted by a rotor revolution counter to 1400 rpm unless otherwise specified. At zero time, a measured quantity of a thermostated aqueous NaOH solution was added to the reactor. At given times, the stirring was stopped, the two phases were allowed to separate, and 50 μL of the organic phase was withdrawn from the reaction mixture, diluted to 5 mL, and quenched with 0.2 mL of hydrochloric acid (30% v/v). The content of the organic phase was quantitatively analyzed either by GC, using 1-methyl naphthalene (MN) as an internal standard, or by HPLC.

Reaction kinetics was studied by following the disappearance of the substrate by GC using MN as internal standard. The chromatographic area of the product, 2-(4-nitro-2-trifluoromethylphenyl)-2-phenylpropionitrile, was not quite reproducible by GC. Thermal discrimination or partial thermal decomposition in GC split/splitless injector was thought to be the cause of the lack of reproducibility in the product areas. Thus, the rate of product formation was followed by HPLC. The amount of the product was obtained through direct comparison of the peak areas against a calibration curve. The pseudo-first-order rate constants (k_{obs}) were obtained by a nonlinear least-squares fit of the experimental concentration vs time data.

Calculation of Φ. To evaluate Φ (eq 17), experiments were carried out the same way as described before but with no CNTFB added.[18] Under such experimental conditions, only eqs 3−5 are applicable. The value of Φ was determined taking into account the mass balance for the catalyst and the value of the Q^+PPN^- concentration in the organic phase. The later was determined by titration of the bromide anion in the organic phase, according to Mohr's methodology, keeping all of the experimental conditions constant except Q_o. A constant value of 0.70 ± 0.05 was obtained within the range 5×10^{-3} to 25×10^{-3} M for TBAB concentrations.

Preparative Synthesis of 2-(4′-Nitro-2′-trifluoromethylphenyl)-2-phenylpropionitrile. A mixture of CNTFB (3.38 mmol), HPPN (4.05 mmol), and TBAB (1.01 mmol) dissolved in 3 mL of chlorobenzene was placed in a three-necked flask equipped with a vertical condenser and a thermometer. After a short period of efficient magnetic stirring, 4 mL of a 50% w/w aqueous NaOH solution was added. The mixture was kept at 40.0 ± 0.1 °C for 24 h. The crude mixture was extracted with dichloromethane and filtered on Florisil. Removal of the solvent and flash chromatography (silica gel, 60 mesh, eluent: petroleum ether−dichloromethane gradient) provided the pure compound. The purity was confirmed by HPLC and GC−MS.

The product was characterized by FT-IR, GC−MS, ^{1}HNMR, and ^{13}C NMR. FT-IR: ν (cm^{-1}, KBr) = 3095.6, 3056.5, 2411.2, 1618.7, 1534.3, and 1360.8 (NO_2), 1483.1, 1418.8, 1400.1,

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1317.1 (CF_3), 1295.2, 1177.8, 1141.6, 1123.1, 650−800. GC−MS (EI, 70 eV): *m/z* (relative intensity) 320 (84, M^+), 305 (100, M − CH_3), 259 (24, 305 − NO_2) 239 (14, 259 − FH), 190 (68, $C_6H_3NO_2CF_3^+$), 130 (84, $C_6H_5CCNCH_3^+$), 103 (46, 130 − CNH), 77 (44, $C_6H_5^+$). ^{1}H NMR (200.13 MHz, $CDCl_3$, TMS): δ (ppm) = 2.23 (s, 3H), 7.20 (d, J = 7.8, 2H), 7.34 (m, 3H), 8.63 (d, J = 2.56, 1H), 8.49 (dd, J = 2.56, J = 8.95, 1H), 8.05 (d, J = 8.95, 1 H). ^{13}C NMR (50.32 MHz, $CDCl_3$, TMS): δ (ppm) = 31.1, 45.7, 120.3 (CN), 124.5, 124.7 (CF_3), 125.7, 126.5, 128.4, 129.0, 130.8, 131.4, 140.2, 144.3, 148,2.

Preparative Synthesis of 4-Nitro-2-trifluoromethylphenol. A standard procedure for the synthesis of phenol derivatives was used.[19] Thus, a mixture of 8 mmol (1.8 g) of CNTFB, 0.5 mmol (0.2 g) of benzyldodecyldimethylammonium bromide in 4 mL of methanol, and 4 g of a 50% w/w NaOH solution were thoroughly stirred by means of a mechanic stirrer. The reaction was followed by TLC (silica F254, dichloromethane−petroleum ether 1:1) until complete CNTFB disappearance. The reaction mixture was extracted with dichloromethane with a previous adjustment of the pH to 5 with a 50% v/v aqueous hydrochloric acid solution. Staining of the phase was observed upon acidification. Thin-layer chromatography (silica F254, diethyl ether−dichloromethane, 1:1) of the organic phase shows two spots; the largest one was the phenol derivative, which remained at the origin of the TLC run. The organic solvent was evaporated under vacuum. The residue dissolved in water−acetonitrile shows that the characteristic pH dependence of the absorption bands of the phenol derivatives was also observed.[20,21] The product was reacted with bis(trimethylsilyl)trifluoracetamide to obtain trimethyl(4-nitro-2-trifluoromethylphenoxy)silane which was analyzed by GC−MS. GC−MS (EI, 70 eV): *m/z* (relative intensity) 279 (5, M^+), 264 (100,M − 15), 218 (14, 264 − NO_2), 77 (36, M − 15 − $OSi(CH_3)_2NO_2$-CF_3), 71 (18, $Si(CH_3)_3^+$), 69 (2, CF_3^+).

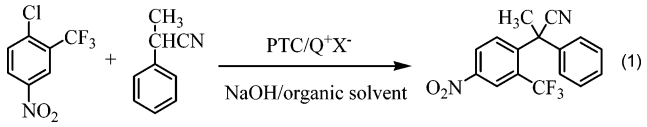
Kinetics. The reaction rates were measured by the initial rate method in order to avoid longer time complications. The sampling time could not be smaller than 1 min. Therefore, a pseudo-first-order rate constant of ca. 5×10^{-3} s^{-1} is approximately the highest value that could be measured by this methodology with a percentage of error below 10%.

Catalyst Stability. The catalyst in the organic phase, in either the presence or absence of the nucleophile, was stirred at a controlled temperature with the basic aqueous phase. According to the methodology suggested by Dehmlow[22] for chloride, aliquots were analyzed at different times by Mohr's titration of bromide in the organic phase. An attempt to perform the experiment under the same experimental conditions as the kinetics runs failed because the concentrations were below the limit of sensitivity of the method. Therefore, a concentration of ammonium salt at least 10 times greater than that of the kinetic runs was used. Chlorobenzene was used as solvent to avoid solubility problems.

Results and Discussion

The reaction of CNTFB with HPPN under PTC conditions afforded 2-(4-nitro-2-trifluoromethyl-phenyl)-2-phenylpropionitrile (eq 1) as the main product, as shown by TLC, GC, and HPLC analysis of the reaction mixtures at infinite time.

The organic solvents used were either toluene or chlorobenzene as described. This solvent proved to be the most versatile to solubilize the reactants and catalyst used in this study.



(1)

Different salts were evaluated as catalyst such as THAC, TBAC, TEAC, TBAB, TBAHS, and BTAB. The salt counteranion seemed to be very important to achieve the desire solubility in the organic phase. Chlorides and bisulfate salts are scarcely soluble in the organic phase; in fact, the chloride salt of the most organophilic assayed cation, which is THAC, is almost at the solubility edge of the catalyst. Therefore, although the use of highly hydrophilic anions, such as chloride or bisulfate, is preferable to avoid catalyst poisoning, they were rejected due to their low solubility. Moreover, it has been reported that PT-catalyst bearing alkyl groups with 16 or more carbon atoms are very effective due to their high lipophilicity.[23] Consequently, taking into account the greater lipophilicity and therefore the higher solubility of TBAB in the organic phase, the kinetic studies were conducted using this catalyst.

Preliminary kinetic experiments were conducted by mechanically stirring different concentrations of TBAB in 5 mL of a toluene solution (0.1 M of CNTFB and 0.526 M HPPN) with 5 mL of NaOH aqueous solution (50% w/w). The plot of the pseudo-first-order rate constants (k_{obs}) vs TBAB concentration is shown in Figure 1. At TBAB concentrations higher than 0.025 M, the reaction becomes excessively fast to be measured. Below 0.005 M, the reaction goes to a halt with a rather low percentage of conversion.

To investigate the reason for the observed low conversion, different experimental conditions were assayed. A 33% conversion was obtained after 24 h when 5 mL of a toluene solution (0.103×10^{-3}, 0.0425×10^{-3}, and 3.93×10^{-3} M of HPPN, CNTFB, and TBAB, respectively) was stirred with 5 mL of a 50% w/w aqueous NaOH. Then, experiments with a higher TBAB/CNTFB ratio were performed keeping the other experimental conditions constant. Enhancing the ratio by a factor of 3 increases the conversion almost 2-fold. In every case, the reaction reaches 100% conversion if an excess of the fresh catalyst is added to the reaction medium. Similar results were obtained if BTAB was used as catalyst.

Since the catalyst decomposition[1] is one of the most frequent causes of observed inhibition, studies were conducted in order to test catalyst stability under the experimental conditions.

Catalyst Stability. Quaternary onium salts decompose by two major mechanisms, Hoffman elimination and nucleophilic displacement.[1] Both reactions could be promoted by either high-temperature exposure or the presence of strong alkaline medium or powerful nucleophilic compounds. The results obtained for TBAB in the presence of NaOH (50% w/w) are collected in Table 1. As can be observed, negligible decomposition seems to be operating within the first hour of reaction. Moreover, it can be assumed that the organophilic catalyst remains in the organic phase, since the amount of bromide in this phase before phase contact equals the amount found after contact.

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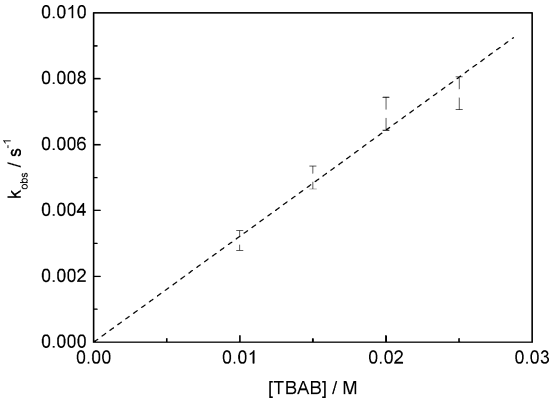
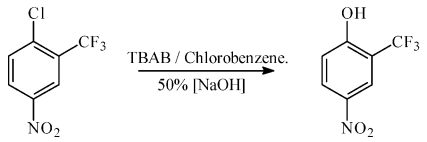


FIGURE 1. Effect of the TBAB concentration on the kinetics of the reaction: 5 mL of a toluene solution (CNTFB 0.1 M and HPPN 0.526 M) with 5 mL of NaOH aqueous solution (50% w/w).

The effect of the nucleophile on the catalyst stability is shown in Table 2. As can be observed, the amount of catalyst remains constant during the experiment, although part of it should be forming ion pairs with PPN anions. Previous studies showed that TBAB was also stable in the presence of the related phenylacetonitrile anion.[18] Since these results demonstrated that the catalyst is stable under the present experimental conditions, other factors should therefore be responsible for the observed inhibition. When phenylacetonitrile was reacted with CNTFB under PTC conditions,[24] catalyst poisoning was observed. Makosza et al.[24] pointed out that the *ipso*-substitution product, 2-(4-nitro-2-trifluoromethylphenyl)-2-phenylacetonitrile, is more acidic and lipophilic than the nucleophile itself and causes displacement from the lipophilic ion pair with tetrabutylammonium cation. In this case, the reaction comes to a halt with low conversion. 5-Chloro-3-phenyl-6-trifluoromethylbenzo[*c*]isoxazole is formed instead of the *ipso*-dechlorination substitution product in a faster phase-transfer-catalyzed reaction. However, in the present case, the nonionizable nature of the *ipso*-substitution product prevents the product mediate inhibition. The presence of side products which could be both strong acids and lipophilic enough to poison the catalyst was therefore investigated.

Catalyst Poisoning. The presence of a noticeable amount of precipitate was observed and isolated from the reaction medium when 5 mL of a toluene solution (3 M in HPPN, 0.1 M in CNTFB, and 0.005 M in TBAB) was stirred with 5 mL of 41% w/w of aqueous NaOH. Under these experimental conditions, which amount to high HPPN concentration but low concentration of catalyst and NaOH, in the presence of less polar organic solvent, a rapid but not complete disappearance of the substrate took place. The isolated precipitate was identified as a sodium salt of 4-nitro-2-trifluoromethylphenol. The structure of the phenol was confirmed by comparison with the compound synthesized by an independent procedure.[19] The highly acidic phenolic derivative can be deprotonated at the phase boundary and efficiently compete with the nucleophile poisoning the catalyst. The phenol formation was also found in the PTC reaction involving 1,2,3,4-tetrafluorobenzene with base.[25] A precipitate of 2,4,6-tribromophenolate was also observed under similar experimental conditions in a related system.[26]

Kinetic of the Reaction of CNTFB with the Base. To establish the importance of the side reaction represented in eq 2, a kinetic study was performed.



(2)

Equimolecular amounts of CNFTB/TBAB were used in order to avoid catalyst poisoning. The kinetic studies were performed in the absence of HPPN using chlorobenzene as solvent in order to improve catalyst solubility. Thus, 5 mL of chlorobenzene solution (0.1 M in CNTFB and TBAB) was mechanically stirred with 5 mL of 50% w/w aqueous NaOH. The kinetics was followed by monitoring the disappearance of CNTFB by GC−MS.

The reaction is slow and the initial rate method had to be applied. Assuming a pseudo-first-order dependence on the substrate, an observed rate constant of $(6.0 \pm 0.3) \times 10^{-5}$ s^{-1} was calculated. It should be pointed out that, despite the more favorable conditions of this experiment compared to the ones of the results displayed in Figure 1, that is equimolecular amounts of catalyst and the use of a better solvent, the estimated k_{obs} value is 2 orders of magnitude lower than the values reported in the former experiment. Therefore, the formation of the phenol derivative only can be a problem at long reaction times or under experimental conditions that makes the main reaction slow, such as low concentration of either catalyst and/or base.

Effect of Different Experimental Variables on Substrate Consumption. The effects of different variables in the percentages of conversion, defined as the percentage of CNTFB reacted to give products, were determined by varying the solvent, the base, and substrate concentration.The results are shown in Table 3. As can be observed, runs 1−6, the percentage of conversion decreases with the concentration of base in the aqueous phase. It is known that hydroxide ion extraction to the organic phase is favored at low base concentration because of its greater degree of hydration of the extracted ion pair.[25] In addition, due to lower acidity of HPPN related to water, a more hydrated organic phase brings about a decrease in the PPN^- concentration in the phase. Therefore, the lower percentage of conversion observed at low base concentration could be the contribution of both catalyst poisoning and a slower phenylpropionitrile nitroarylation reaction.

The solvent also seems to have a great influence on the percentage of conversion. Thus, a lower percentage of conversion was found when toluene was used (run 7) instead of chlorobenzene (run 1).[3] Wang et al. reported the influence of solvent polarity on the PTC reaction of dibromo-*o*-xylene with *n*-butanol under basic conditions.[27]

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TABLE 1. Effect of Strong Basic Medium on TBAB Stability

time (min)	0	15	24	49	60
TBAB (mmol)[a]	0.525 ± 0.005[b]	0.521 ± 0.005	0.526 ± 0.005	0.528 ± 0.005	0.522 ± 0.005

[a] 5 mL of 0.105 M TBAB in chlorobenzene was stirred at 40 °C and 1000 rpm with 5 mL of 50 wt % aqueous NaOH. [b] Before contact among the organic and aqueous phases.

TABLE 2. Influence of the HPPN on the TBAB Stability

time (min)	0	5	15	25	78
TBAB (mmol)	0.495 ± 0.005[b]	0.465 ± 0.005	0.470 ± 0.005	0.468 ± 0.005	0.470 ± 0.005

[a] 5 mL of chlorobenzene solution, 0.105 M TBAB, and 0.155 M PPN were stirred at 40 °C and 1000 rpm with 5 mL of 50 wt % aqueous NaOH. [b] Before contact among phases.

TABLE 3. Effect of Different Experimental Conditions on the Percentage of Conversion[a]

run	$[OH^-]$ (w/w, %)	conversion[b] (%)
1	40	100
2	35	100
3	30	90
4	28	80
5	27	40
6	25	35
7	40[c]	50
8	35[d]	46

[a] 5 mL of organic phase, 0.1 M CNTFB, 3 M HPPN unless specified, and 5×10^{-3} M in TBAB were mechanically stirred at 1000 rpm with 5 mL of aqueous NaOH. Chlorobenzene was used as solvent unless specified. [b] At 24 h of reaction. [c] Toluene. [d] 0.97 M HPPN.

These authors found that the reaction in chlorobenzene is faster than in toluene. In light of our results, the lower conversion found in toluene could hence be due to the slower rate of the *ipso*-substitution reaction compared with the reaction which leads to catalyst poisoning.

Keeping constant the other experimental conditions, a decrease in the HPPN concentration also decreases the percentage of conversion (runs 2 and 8 in Table 3). The observed results are probably due to the differential rate of the competitive reactions under the different experimental conditions, i.e., the slow phenol formation leading to catalyst poisoning and the HPPN substitution. Thus, when the main reaction becomes slow enough, the side reaction progressively poisons the catalyst until the reaction comes to a halt. The present results seem to be in agreement with the peculiar dependence of the concentration of tetrabutylammonium 2,4,6-tribromophenolate with the concentration of the potassium hydroxide observed by Wang et al.[26] These authors suggested that the true concentration of tetrabutylphenolate in the organic phase is highly dependent on the phenol dissociation and salting-out effect.

The best experimental conditions to carry out the kinetic study should be a compromise between a high conversion and a measurable rate. Therefore, to choose the best experimental conditions for performing a thorough kinetic study, the effect of the base concentration upon reactivity were further investigated.

Effect of the NaOH Concentration in the Aqueous Phase upon Reactivity. This studies were performed using 5 mL of a toluene solution, 0.1 M in CNTFB, 0.02 M TBAB, 0.06 M of methylnaphthalene, and 0.526 M of HPPN were stirred with 5 mL of different concentrations of aqueous NaOH.

At 15% w/w of NaOH, the reaction rate was negligible. At 30% w/w a k_{obs} of $(3.7 \pm 0.3) \times 10^{-3}$ s^{-1} was obtained. Over 30% of NaOH the rate is too fast to be measured by the initial rate method, and a roughly lower limit of its value could be estimated, as discussed in the Experimental Section. A rather similar effect was previously observed for a related system, and it was attributed to the amount of water present in the organic phase.[18] At high base concentration, the organic phase dehydration by the hydroxide ions and the increase in the rate of the deprotonation−extraction steps might occur.[29] Both effects in turn allow an explanation of the increase in the observed rate coefficient with the base concentration.

A competition between both substitution reactions, the main and the side reactions, occurs at each base concentration; the faster the main reaction, the higher the percentage of conversion that is achieved. At small base concentration poor deprotonation and a small selectivity constant, K_s, (see eq 5) could be expected.[25,28] Actually, at 15% w/w of NaOH the catalyst-promoted extraction of solvated hydroxide to the organic phase might occur but, taking into account that the more hydrated hydroxide anion is a poorer nucleophile than the necked one, the phenol derivative formation is almost negligible. This side reaction seems to be slightly more significant when the percentage of base is increased to 30% w/w. However, as previously discussed, the rate of the hydrolysis reaction is slower than the corresponding main reaction and did not proceed to complete conversion even when stoichiometric amount of TBAB is used.On the basis of the previous results, the kinetic studies were performed in 30% w/w base solution to obtain a cleaner and most complete reaction.

Effect of Substrate Concentration in the Reaction Rate. Kinetic runs were performed by stirring 5 mL of a toluene solutions of HPPN 0.526 M, TBAB 0.02 M, and varying concentrations CNTFB (between 0.04 and 0.16 M) with 5 mL of 30% w/w aqueous sodium hydroxide. A first-order kinetics on substrate, characteristic of a chemical-controlled rate, was obtained with a pseudo-first-order rate constant of $(3.75 \pm 0.05) \times 10^{-3}$ s^{-1} for all the CNTFB concentrations studied. These results imply that the protonation−extraction equilibriums are faster than the rate of the S_NAr reaction in the organic phase.[29,30]

Effect of the TBAB Concentration on the Reaction Kinetics. The kinetics of the reaction was studied

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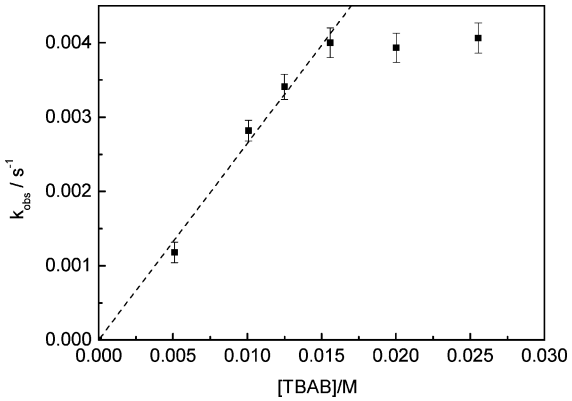

FIGURE 2. Effect of the catalyst concentration on the kinetics of the reaction between CNTFB and HPPN under basic PTC conditions: 5 mL of toluene solution, 0.526 M HPPN, 0.1 M CNTFB; 5 mL of 30% wt % of aqueous NaOH.

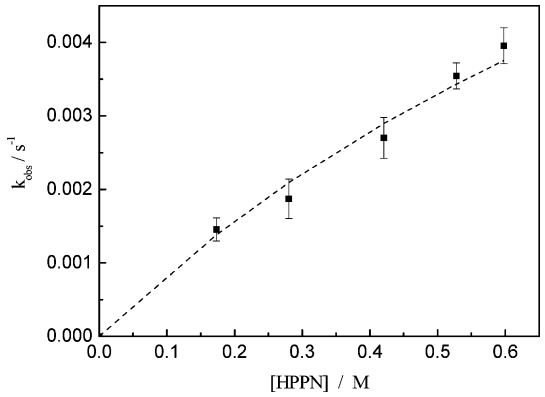

FIGURE 3. Effect of the 2-phenylpropionitrile concentrations upon the reactivity: 5 mL of toluene solution, 0.1 M CNTFB and 0.015 M TBAB, and 5 mL of 30 wt % NaOH as aqueous phase.

varying the TBAB concentration and keeping the other experimental conditions constant. The results are shown in Figure 2. Two different behaviors become apparent. At low initial concentrations of catalyst, a linear dependence on k_{obs} is observed. Such linear tendency is characteristic when the nucleophile deprotonation occurs at the interface and the rate-limiting step is the nucleophilic substitution.[31] The intercept of the plot is negligible, and it would correspond to an undetectable rate of the noncatalyzed reaction. Over certain concentration of catalyst, ca. 0.015 M, the reaction rate becomes constant. This could be attributed to interface saturation, which means that the mass transfer of the active species into the organic phase reaches a maximum value. At this point, the addition of more catalyst will not help the reaction to proceed faster. However, since the reaction in the organic phase becomes too fast to be measured by the initial rate method (see the Experimental Section), the possibility of an underestimated observed rate constant should also be considered. Nevertheless, as expected, the slope of the linear part of the plot in Figure 2 (0.26 ± 0.01 M^{-1} s^{-1}) is lower than the one obtained at 50% w/w NaOH in Figure 1 (0.40 ± 0.02 s^{-1} M^{-1}).

Effect of the HPPN Concentration upon Reactivity. The kinetics of the reaction was studied at different HPPN concentrations, keeping the other experimental conditions fixed. The experimental results are shown in Figure 3. Under these conditions, the observed rate constant increases with the nucleophile concentration.

Mechanism. When "in situ" generated nucleophiles, by deprotonation a lipophilic weak acid precursor (HPPN), are involved in PTC reactions, both the unchanged nucleophile and its anion are extracted to the organic medium due to the strong salting out effect of the aqueous phase. The extraction should be accomplished with the aid of the PT-catalyst; otherwise, a bilayer-like arrangement of alkali metal cations on the aqueous side and deprotonated nucleophiles on the organic side of the phase boundary is formed instead.[1] In such cases, and according to the hitherto presented data, an interfacial mechanism has been postulated.[13,14] At first, the nucleophile precursor is adsorbed at the interface where it is deprotonated by the strong base and is further extracted, as a fully lipophilic ion pair with the PT-cation, to the organic phase. The following mechanistic steps can be written:

$$\mathrm{HPPN} + \Theta_s \overset{\beta}{\rightleftharpoons} \Theta_{\mathrm{HPPN}} \tag{3}$$

$$\Theta_{\mathrm{HPPN}} + \mathrm{HO^-} \overset{K_a}{\rightleftharpoons} \Theta_{\mathrm{PPN^-}} + \mathrm{H_2O} \tag{4}$$

$$\Theta_{\mathrm{PPN^-}} + \mathrm{Q^+X^-_{org}} \overset{K_s}{\rightleftharpoons} \mathrm{Q^+PPN^-_{org}} + \Theta_{\mathrm{X^-}} \tag{5}$$

$$\mathrm{Q^+PPN^-_{org}} + \mathrm{ArX} \overset{k}{\rightleftharpoons} \mathrm{ArPPN} + \mathrm{Q^+X^-_{org}} \tag{6}$$

where Θ_s, Θ_{HPPN}, $\Theta_{\mathrm{PPN^-}}$, and $\Theta_{\mathrm{X^-}}$ are the fractions of the interface cover by solvent, HPPN, PPN^-, and X^-, respectively. The subscript "org" is used to denote ion pairs in the organic phase.

Assuming the interfacial excesses of HPPN and PPN^- and the corresponding fractions coverage can be expressed by the Langmuir monolayer isotherm of a multicomponent system,[32] the constant for eq 1 can be expressed as follows:

$$\beta = \frac{\Theta_{\mathrm{HPPN}}}{[\mathrm{HPPN}]\,\Theta_s} \tag{7}$$

Taking into account all surface-active compounds

$$\Theta_s = 1 - \sum_i \Theta_i \tag{8}$$

The acidity constant for HPPN deprotonation at the phase boundary, K_a (in eq 4), is defined as

$$K_a = \frac{\Theta_{\mathrm{PPN^-}}[\mathrm{H_2O}]}{\Theta_{\mathrm{HPPN}}[\mathrm{HO^-}]} \tag{9}$$

As already discussed, the generated carbanion, as a Na^+ salt, can neither migrate into the organic phase, because the highly hydrophilic counterion, nor move with carbanions into the aqueous phase, due to the strong

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salting out effect.[33] The selectivity equilibrium constant, K_s (in eq 5) for the extraction of PPN^- with respect to that of X^-, entails the nucleophile extraction to the organic phase as a fully lipophilic ion pair with the onium ion. Its mathematic expression is shown in eq 10.

$$K_s = \frac{[Q^+ PPN^-]_{org}\Theta_{X^-}}{\Theta_{PPN^-}[Q^+X^-]_{org}} \quad (10)$$

The intrinsic second-order rate coefficient for the main substitution reaction in the organic phase is represented by k (eq 6).

Processes depicted in eqs 11−13 could also be taking place.

$$OH^- + Q^+X^-_{org} \rightleftharpoons Q^+OH^-_{org} + X^- \quad (11)$$

$$Q^+OH^-_{org} + ArX \xrightarrow{k'} Q^+X^-_{org} + ArOH \quad (12)$$

$$Q^+OH^-_{org} + HPPN \rightleftharpoons Q^+PPN^-_{org} + H_2O \quad (13)$$

Even though X^- are more lipophilic than the very hydrophilic OH^-, and eq 11 should be shifted to the left,[1,7,33] the importance these equation is stressed since the phenol derivative is found as side product in the reaction medium. Although it has been pointed out that the hydroxide ion transfer to the organic phase only occurs when both very weak acids and highly hydrophilic catalyst counterion HSO_4^- are involved,[34−36] it seems that, at least under experimental conditions that make reaction 6 slow enough, eq 12 yields the surface-active phenol derivative, whose deprotonated form finally leads to catalyst poisoning. Taking into account the lower acid strength of HPPN compared to water, the equilibrium (13) would be almost completely displaced to the left side, and therefore, it would not be a source of nucleophile in the reaction medium.

The kinetic rate (r) for ArX disappearance, eq 14, should therefore be the contribution of two reactions, one that leads to the arylation of the HPPN (eq 6) and other that produces the phenol derivative (eq 12). It is important to note that the reactions at the phase boundary were ignored in view of the fact that no reaction at all was observed in the absence of catalyst.

$$r = -d[ArX]/dt = (k[Q^+PPN^-]_{org} + k'[Q^+OH^-]_{org})[ArX] \quad (14)$$

However, as described previosly, the rate of phenol formation measured in the absence of HPPN and using equimolecular amounts of catalyst and substrate has a value of $(6.0 \pm 0.3) \times 10^{-5}$ s^{-1}. This is at least 2 orders of magnitude slower than the one obtained (i.e., $(7.5 \pm 0.4) \times 10^{-3}$ s^{-1}) under the same conditions but using four timesless catalyst (Figure 1). Thus, this side reaction could be neglected in eq 14. Besides, at short reaction times, when both nucleophile precursor and the base are in great excess over the catalyst, $[Q^+ PPN^-]_{org}$ remains constant and eq 14 can be rewritten as follows

$$r = k[Q^+PPN^-]_{org}[ArX] = k_{obs}[ArX] \quad (15)$$

where k_{obs} is the observed pseudo-first-order rate coefficient.

Assuming a fast equilibrium previous to the determining step, the substitution reaction in the organic phase, and taking into account the mass balance for the catalyst, $Q_o = [Q^+X^-]_{org} + [Q^+PPN^-]_{org}$, eq 16 can be obtained.

$$k_{obs} = \frac{k\beta K_a K_s Q_o \Theta_s [OH^-][HPPN]}{[H_2O]\Theta_{x^-} + \beta K_a K_s \Theta_s [OH^-][HPPN]} \quad (16)$$

For the sake of simplicity, eq 16 can be written in the form of eq 17

$$k_{obs} = \frac{kQ_o[HPPN]}{\phi^{-1} + [HPPN]} \quad (17)$$

where $\Phi = (\beta K_a K_s [HO^-]\Theta_s)/([H_2O]\Theta_{x^-})$

Estimation of the Intrinsic Second-Order Rate Coefficient. At short reaction times, it can be assumed that the coverage of the interface remains almost unchanged and, hence, Θ_s and Θ_{x^-} as well. Data adjustment requires evaluating Φ at the working conditions. To accomplish the task, the experiments described in the Experimental Section were carried out. Under these circumstances, only steps 3−5 of the mechanism can occur and Φ can be evaluated from eq 18.

$$\Phi = \frac{[Q^+PPN^-]_{org}}{(Q_o - [Q^+PPN^-]_{org})[HPPN]} \quad (18)$$

Thus, by the introduction of the proper value of Φ (0.7 M^{-1} under the present conditions) in eq 17, the value of k can be estimated from the slope of the linear portion of the k_{obs} vs Q_o plot (Figure 3). A value of $k = 0.95 \pm 0.07$ s^{-1} M^{-1} for [NaOH] = 30% w/w was obtained.

Other estimations could be performed provided the Φ value is almost independent of the HPPN concentration operating range. Nonlinear least-squares fitting of data in Figure 3 by means of eq 16 gave a k value of 0.85 ± 0.08 s^{-1} M^{-1}. As can be appreciated, good estimates for k within experimental error were obtained by two different data sets.

Effect of Stirring Rate upon the Reactivity. The results are shown in Figure 4. As can be noticed, a rise in the stirring rate produce a typical increase in the pseudo-first-order rate constant. This behavior is characteristic of reaction believed to proceed through an interfacial mechanism.[37] This effect can be attributed to the related enhance in the interfacial surface area.[17,38−40]

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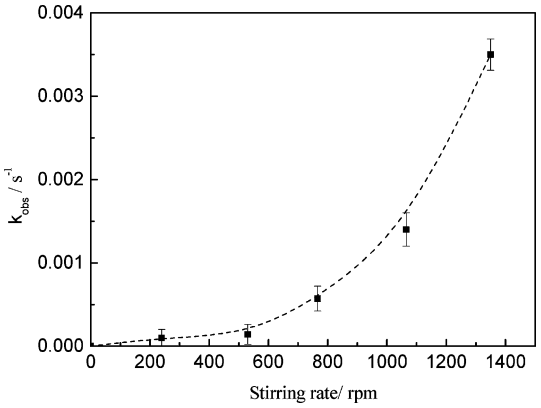

FIGURE 4. Effect of stirring rate on the pseudo-first-order reaction rate: 5 mL of toluene solution, 0.526 M MBC, 0.1 M 2CNTFB, 0.02 M TBAB, were mechanically stirred with 5 mL of 30 wt % NaOH.

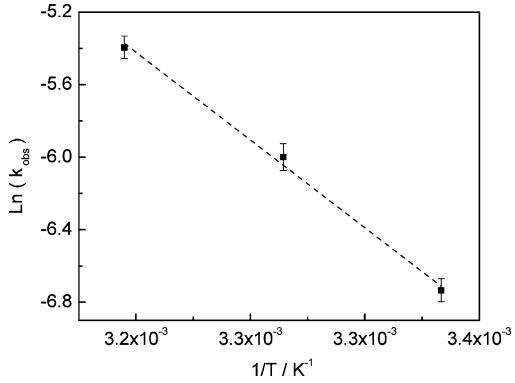

FIGURE 5. Effect of the temperature upon the reactivity of CNTFB and HPPN under PTC conditions: 5 mL of toluene solution, 0.526 M HPPN, 0.1 M CTFNB, 0.015 M TBAB, 5 mL of 30% wt % aqueous NaOH.

At stirring rates higher than 1450 rpm the reaction is too fast to be followed by the initial rate method.

Temperature Effect on the Observed Rate Constant. An Arrhenius plot of the data at different temperatures is shown in Figure 5. From this plot, the activation parameters $\Delta H^{\ddagger} = 80 \pm 5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -212 \pm 20$ J mol^{-1} K^{-1} were calculated in the range of temperature used. These values are consistent with the complexity of proposed mechanism, where carbanions are the nucleophiles.[41−44] The GC analysis of the reaction mixture at 40 °C shows a clean reaction, and the *ipso*-substitution product is the only one observed. The rates of product formation and CNTFB disappearance agree within the experimental error with values of $(4.3 \pm 0.3) \times 10^{-3}$ and $(3.9 \pm 0.3) \times 10^{-3}$ s^{-1}, respectively.

Conclusions

HPPN and CNTFB react under basic phase-transfer-catalysis conditions to give mainly the chloro-*ipso*-substitution product. Even though the phase-transfer catalyst is stable to experimental conditions, the deprotonated phenol side product slowly poisons it. This side reaction becomes important at rather low catalyst concentration, i.e., under experimental conditions where the main reaction is excessively slow. The system is very sensitive to the base concentration that mainly changes the degree of nucleophile hydration in the organic phase and consequently strongly affects the rate of reaction. The reaction is sped up by an increase in the concentration of catalyst or nuclephile precursor and by the stirring rate. An interfacial mechanism was assumed, and the data were adjusted taking into account a Langmuir monolayer isotherm of a multicomponent system at the phase boundary. The intrinsic second-order rate coefficients estimated from two different sets of data agree within the experimental error. As a final remark, one can state that the reported data allowed us to draw a complete kinetic formulation of the reaction mechanism and the main hints that should be considered while using it as a synthetic tool.

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