



Phase transfer catalysis (PTC): search for alternative organic solvents, even environmentally benign

Dario Landini, Angelamaria Maia*

Istituto di Scienze e Tecnologie Molecolari (ISTM) del CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy

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Dedicated to Professor Renato Ugo on the occasion of his 65th birthday

Abstract

The use of aliphatic esters, ethers and ketones such as dimethyl carbonate (DMC), methyl-*tert*-amyl ether (MTAE), 5-methyl-2-hexanone (MIAK), 4-methyl-2-pentanone (MIBK) as an alternative to traditional solvents (toluene, chlorobenzene, etc.) was explored as a strategy for performing phase transfer catalyzed reactions in organic media, even environmentally benign. Experimental data show that in these media the partition of the catalyst in the organic phase is comparable or higher than that in chlorobenzene, especially in the case of scarcely lipophilic methyltributylammonium (**3**) or tetrabutylammonium (**4**) salts (Eq. (1)). Anion reactivity under PTC conditions increases with decreasing the solvent polarity, in the order: ketone < ester \approx chlorobenzene < ether. Such a trend is even more pronounced in the anhydrous solvent, where in the absence of any solvation it is possible to evaluate the intrinsic reactivity of the ion pair. Results clearly indicate the oxygenated solvents examined (MTAE, DMC, MIAK, MIBK) as a valid alternative to traditional media for PTC.

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1. Introduction

In anion promoted reactions the significant role of the solvent in determining both the solubilization of the salt, source of the nucleophile or base, and the anionic reactivity is well recognized [1,2]. The rate of the process mainly depends on the interaction between the anion and the solvent molecules increasing, even of several orders of magnitude, on going from polar protic media, that specifically solvate the anion

through hydrogen bonds, to solvents where this interaction is minimized (aprotic dipolar solvents) [1,2].

The use of lipophilic quaternary onium salts or complexes of polyether ligands with inorganic salts in anhydrous low polar solvents (toluene, chlorobenzene, 1,2-dichlorobenzene, etc.) revealed particularly effective for studying the reactivity of the anions under conditions that approach those of the gas phase. In such media indeed the reactivity of the anion is remarkably high due to the low interaction with the bulky ion paired cation as well as with the poor solvating medium [3–5].

Anion promoted reactions are extensively used in organic synthesis, particularly under heterogeneous

* Corresponding author. Tel.: +39-02-503-14162;

fax: +39-02-503-14159.

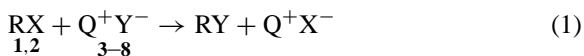
E-mail address: angelamaria.maia@unimi.it (A. Maia).

(liquid–liquid (LL) or solid–liquid (SL)) conditions, such as phase transfer catalysis (PTC). Back to the beginning of 1970s PTC represents the most important innovative methodology in the synthesis of organic products, on a laboratory and industrial scale [4–9]. It allows to realize a number of anionic reactions in high yields and under mild conditions, by using catalytic amounts of quaternary onium salts or polyether ligands (crown ethers, polyethyleneglycols, etc.) and a variety of organic solvents scarcely polar, easily available and recyclable (alifatic and aromatic hydrocarbons, etc.) [4–9]. In addition, as the chemical industry strives to improve not only process efficiency, but also safety and to reduce environmental impact, PTC has become recognized very useful to achieve these goals.

Alternatively, when the substrates and/or products are liquid under reaction conditions the use of solvents may be avoided. PTC reactions without solvents are particularly exploited in industry, due to the advantages of improving yields, rates, product purity and in addition reducing solvent environmental and recovery problems [6,7].

When the above conditions cannot be used the choice of the medium is fundamental in determining: (i) the intrinsic reactivity of the reagents, in particular the ion pair Q^+Y^- ; (ii) the partition equilibria of catalyst and anions (X^- and Y^-) between the two phases [4–9].

In order to find out organic solvents, even environmentally benign, to use as a valid alternative to the traditional media we have carried out a kinetic study of representative S_N2 reactions under PTC (LL and SL) and homogeneous conditions, by systematically changing the substrate RX, quaternary onium cation Q^+ , nucleophile Y^- , and reaction medium (Eq. (1)).



$RX = nC_8H_{17}OSO_2CH_3$ (**1**); nC_4H_9Br (**2**). $Q^+ = MeBu_3N^+$ (**3**); Bu_4N^+ (**4**); $Hexyl_4N^+$ (**5**); $MeOctyl_3N^+$ (**6**); $Octyl_4N^+$ (**7**); $Bu_3C_{16}H_{33}P^+$ (**8**). $Y^- = Cl^-$ (**a**); Br^- (**b**); I^- (**c**); $4NO_2C_6H_4O^-$ (**d**). Solv, methyl-*tert*-amyl ether (MTAE); chlorobenzene (PhCl); dimethylcarbonate (DMC); 5-methyl-2-hexanone (MIAK); 4-methyl-2-pentanone (MIBK).

2. Experimental

2.1. General methods

Potentiometric titrations were carried on with a Metrohm 670 Titroprocessor by using a combined silver electrode isolated with a potassium nitrate bridge or a glass electrode isolated with a potassium chloride bridge. Karl–Fischer determinations were performed with a Metrohm 684 KF coulometer.

1H NMR spectra were performed on a Bruker AC 300 spectrometer using TMS as an external reference. GLC data were obtained with a Hewlett-Packard 6890 by using a HP-5 5% phenylmethylsiloxane column (30 m \times 320 μ m \times 0.25 μ m).

2.2. Materials and solvents

Octyl methanesulphonate (**1**), bp 92–94 °C at 0.003 mmHg, n_D^{20} 1.4392, was prepared according to the literature ([10], bp 98 °C at 1.5 mmHg, n_D^{20} 1.4390).

Butyl bromide (**2**) was a commercial product, utilized as purchased.

Quaternary onium halides **3–8** were Analar grade commercial products, utilized without further purification. Quaternary salts **3–5d** were generated in situ from the commercially available chlorides **3–5a** by exchange with the 4-nitrophenoxide anion, according to the ion pair extraction technique [11,12].

Sodium halides NaHal were AnalaR grade commercial products, kept in a dessiccator under vacuum. Sodium 4-nitrophenoxide was prepared as an orange powder in high yields (>97%) by a literature method [13].

Dry (Fluka) chlorobenzene and dimethyl carbonate ($H_2O \leq 20$ ppm) were used. Methyl-*tert*-amyl ether (MTAE), 4-methyl-2-pentanone (MIBK) and 5-methyl-2-hexanone (MIAK) were dried over molecular sieves (4 Å) and kept under nitrogen. Water determinations were only possible for MTAE ($H_2O \leq 30$ ppm) because ketones react with KF reagent.

2.3. Partition equilibria

The partition of quaternary salts (**3–8**) under LL–PTC conditions was determined by stirring a standardized solution of Q^+Y^- (0.025 M) (20 ml) in the

appropriate organic medium with an aqueous solution of sodium salt (NaY) (2 M) (15 ml) in a flask thermostated at 60 °C. The system was stirred for 10 min, then kept without stirring for an additional 30–40 s to allow good separation of the two phases. Samples (2–3 ml) of the organic phase were withdrawn and potentiometrically titrated with 0.01 N AgNO₃ or 0.01 N HCl. The partition extent was given by the ratio between the concentration of Q⁺Y⁻ in the organic phase before and after contact with the aqueous phase.

2.4. Kinetic measurements

In a typical LL-PTC procedure, the reaction flask thermostated at 60 ± 0.1 °C, was charged with an aqueous solution (15 ml) of sodium salt (NaY) (2 M) and a standardized organic solution (15 ml) of substrate **1** or **2** (0.1 M), catalyst (0.01–0.02 M) and dodecane or tetradecane (0.05 M) as internal standard. The heterogeneous mixture was mechanically stirred at 1000 ± 50 rpm. Samples of the organic phase (0.5 ml) were withdrawn at various times, stopping the stirrer for 40–60 s, dried with Na₂SO₄ and, after centrifugation, analyzed by GLC (see Section 2.1). An analogous procedure was followed under SL-PTC conditions using ground solid NaCl (30 M equiv.) instead of the aqueous solution.

Reaction rates were determined following the appearance of the reaction product RY. The pseudo-first-order rate constants (*k*_{obsd}) were computer generated by plotting log [substrate] versus time and determining the slope of the straight lines. The second-order rate constants *k* (M⁻¹ s⁻¹) were evaluated by dividing *k* by the catalyst concentration in the organic phase.

In the kinetic measurements under homogeneous conditions a standardized organic solution (20 ml) of substrate **1** (0.04–0.06 M) was added to a standardized solution (20 ml) of quaternary salt Q⁺Y⁻ (0.02–0.04 M) in a flask thermostated at 60 ± 0.1 °C. Timing was started. At various times aliquots of the organic phase (2 ml) were withdrawn and titrated with 0.01 N AgNO₃.

The second-order rate constants were evaluated using a least-squares computer program from the equation: $1/([B]_0 - [A]_0) \ln([B][A]_0/[A][B]_0) = kt$, where A is the substrate and B is the quaternary salt or vice versa. All rates involved at least 10 samplings and gave correlation coefficients of 0.995 or better.

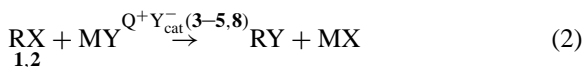
3. Results and discussion

3.1. Partition equilibria

The measurements were performed by contacting under stirring a standardized solution (20 ml) of quaternary onium salt Q⁺Y⁻ (**3–8**) in the appropriate organic medium with an equal volume of an aqueous solution (2 M) of the corresponding sodium salt, at 60 °C. Results show that most of the salts are largely or completely partitioned in the organic phase of the heterogeneous system (80–100%) regardless of the medium (Table 1). By contrast, the polarity of the solvent plays an important role in the case of quaternary salts scarcely lipophilic. As shown in Table 1, the partition of Bu₄N⁺Br⁻ (**4b**) increases from 0% in methyl-*tert*-amyl ether to 20% in chlorobenzene up to about 80% in the more polar 5-methyl-2-hexanone. On the other hand, on changing from Cl⁻ to the more lipophilic 4NO₂-C₆H₄O⁻, the partition of the methyl-tributylammonium salt **3** increases from 8 to 97% in 4-methyl-2-pentanone whereas it is practically unchanged in chlorobenzene.

3.2. Kinetic measurements under LL-PTC conditions

Kinetics have been carried out by stirring at 1000 ± 50 rpm in a flask thermostated at 60 °C an aqueous solution (2 M) (15 ml) of sodium or potassium halide (Cl⁻, Br⁻, I⁻) with an equal volume of a solution of substrate **1**, **2** (0.1 M) and catalyst **5**, **8** (0.01 M) in the appropriate organic medium (MTAE, PhCl, MIBK, MIAK) (Eq. (2)).



RX = *n*C₈H₁₇OMes (**1**); *n*C₄H₉Br (**2**). MY = NaCl, NaBr, NaI, 4NO₂C₆H₄ONa. Q⁺Y⁻ = **3–5**, **8**; org. solv, MTAE, PhCl, MIAK, MIBK.

The rates were measured by following the appearance of the reaction product (the octyl halide or butyl 4-nitrophenylether) evaluated with respect to an internal standard (dodecane and tetradecane, respectively).

The reactions follow regular pseudo-first-order kinetics (Eq. (3)) up to at least 70% conversion and the observed rate constants, *k*_{obsd}, are linearly dependent

Table 1

Partition equilibria^a in the organic phase of Q⁺Y⁻ salts (**3–8**) in organic–aqueous (NaY) two-phase systems, at 60 °C^b

Q ⁺	Y ⁻	Solvent				
		MTAE	PhCl	DMC	MIAC	MIBK
MeBu ₃ N ⁺ (3)	Cl ⁻ (3a)		3			8
	4NO ₂ C ₆ H ₄ O ⁻ (3d)		9			97
Bu ₄ N ⁺ (4)	Cl ⁻ (4a)		16		78	78
	Br ⁻ (4b)	0	20	77	78	50
	4NO ₂ C ₆ H ₄ O ⁻ (4d)		19			100
Hexyl ₄ N ⁺ (5)	Cl ⁻ (5a)	96	98–100	100	87	86–100
	Br ⁻ (5b)	100	89	100	84	85
	4NO ₂ C ₆ H ₄ O ⁻ (5d)		96			100
Octyl ₃ MeN ⁺ (6)	Cl ⁻ (6a)	88	85	97	94	87
Octyl ₄ N ⁺ (7)	Br ⁻ (7b)	89	100	100	100	85
Bu ₃ P ⁺ C ₁₆ H ₃₃ (8)	Br ⁻ (8b)	83	99	100	87	86

^a Defined as [Q⁺Y⁻]_{org}/[Q⁺Y⁻]₀ × 100.^b An organic solution (20 ml) of Q⁺Y⁻ (0.025 M) and an aqueous solution (15 ml) of NaY (2 M).

on the concentration of the catalyst, in the range examined (Eq. (4)).

$$\text{rate} = k_{\text{obsd}} [\text{substrate}] \quad (3)$$

$$k_{\text{obsd}} = k [\text{catalyst}] \quad (4)$$

The second-order rate constants k (M⁻¹s⁻¹), obtained by dividing the observed rate constant, k_{obsd} , for the concentration of the catalyst in the organic phase, are reported in Table 2.

3.2.1. Effect of the specific hydration on the anion reactivity

The rate constant values obtained, in the same solvent, for the series of Hexyl₄N⁺Hal⁻ (**5a–5c**) or

C₁₆H₃₃P⁺Bu₃Hal⁻ (**8a–8c**), span a very narrow range (Cl:Br:I = 1:1.5–2:1.6–3) and the reactivity scales: $k_{\text{I}} > k_{\text{Br}} > k_{\text{Cl}}$ (in MTAE) and $k_{\text{I}} \sim k_{\text{Br}} > k_{\text{Cl}}$ (in the other solvents) are anomalous with respect to the well known sequences of these anions ($k_{\text{Cl}} > k_{\text{Br}} > k_{\text{I}}$) in dipolar aprotic media and in gas phase [1,2]. A similar sequence ($k_{\text{I}} \approx k_{\text{Br}} > k_{\text{Cl}}$) was previously found for the same reaction catalyzed by hexadecyltributylphosphonium salts **8** in chlorobenzene–water two-phase systems (Fig. 1) [14,15]. Such a behavior was attributed to the presence in the organic phase of a limited number n of molecules of water that accompany the anion in its transfer from the aqueous phase, solvating it specifically. The hydration sphere, characteristic of each anion, always reduces the rate

Table 2

Second-order rate constants k (M⁻¹s⁻¹) for the reaction of *n*-octyl methanesulphonate **1** with halides in organic solvent–water two-phase systems under LL–PTC conditions, at 60 °C^a

Q ⁺ Y ⁻	10 ³ × k (M ⁻¹ s ⁻¹)			
	MTAE	PhCl	MIBK	MIAC
Hexyl ₄ N ⁺ Cl ⁻ (5a)	7.0 (1)	4.7 (1)	3.0 (1)	2.7 (1)
Bu ₃ P ⁺ C ₁₆ H ₃₃ Cl ⁻ (8a)	–	1.8	–	–
Hexyl ₄ N ⁺ Br ⁻ (5b)	14.1 (2)	7.8 (1.7)	4.5 (1.5)	4.0 (1.5)
Bu ₃ P ⁺ C ₁₆ H ₃₃ Br ⁻ (8b)	13.8	3.2	4.4	4.0
Hexyl ₄ N ⁺ I ⁻ (5c)	21.7 (3.1)	7.6 (1.6)	5.0 (1.7)	4.2 (1.6)
Bu ₃ P ⁺ C ₁₆ H ₃₃ I ⁻ (8c)	10.0	2.8	4.4	2.5

^a An organic solution (15 ml) of **1** (0.1 M), catalyst Q⁺Y⁻ (0.01–0.02 M) and an aqueous solution (15 ml) of NaY (2 M).

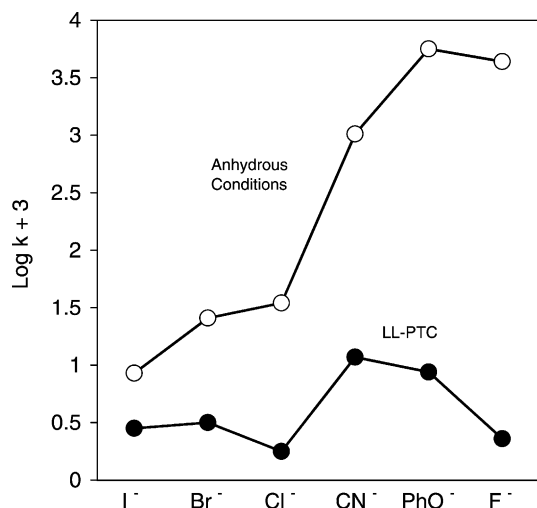


Fig. 1. Comparison of the second-order rate constant k ($M^{-1} s^{-1}$) for the reaction of **1** with different nucleophiles Y^{-} associated with $C_{16}H_{33}P^{+}Bu_3$ (**8**) in anhydrous PhCl (white dots) and in PhCl–H₂O two-phase system (black dots), at 60 °C (data from [14,15]).

of PTC reactions where the reaction in the organic phase is the rate limiting step of the overall process, whereas the exchange of the anions at the interface is relatively fast ($k_{transf} \gg k_{intr}$). This assumption is confirmed by the comparison with the corresponding reactions under anhydrous homogeneous conditions. As shown in Fig. 1, indeed, the nucleophilic reactivity of all the anions Y^{-} increases on switching from chlorobenzene–water two-phase system to anhydrous chlorobenzene (up to about 10^3) as a consequence of the removal of the anion hydration sphere. The

enhancements are particularly pronounced for anions with high charge-to-volume ratios that are also found to have the greatest hydration numbers: F^{-} (8.5), Cl^{-} (3.4), CN^{-} (5), PhO^{-} (4) [11,14,15]. Interestingly, under these conditions the reactivity sequence becomes that typical of these anions in aprotic dipolar solvents ($k_{Cl} > k_{Br} > k_I$) [1,2].

Water determinations in MTAE have shown that this ethereal solvent, after contact with the aqueous phase, retains a quantity of water much higher than that of the chlorobenzene. This quantity does not appreciably change in the presence of a quaternary onium salt. Same results have been obtained with DMC. Hydration determinations of MIAK and MIBK were not possible because ketones react with KF reagent.

3.2.2. Reaction rate as a function of the catalyst lipophilicity

The partition of the catalyst in the organic phase can be a crucial factor in determining the rate of LL–PTC processes.

As shown in Table 3, in the chlorobenzene–water two-phase system the observed rate constant (k_{obsd} , s^{-1}) increases of 100 times on switching from methyltributylammonium chloride (**3a**), mainly partitioned in the aqueous phase (97%), to the lipophilic tetrahexylammonium salt **5a**, completely soluble in the organic phase. The difference drops to only 20 times in the more polar MIBK, where the quaternary onium salts are more soluble, in particular the tetrabutylammonium chloride (**4a**) (78%) (Table 3).

In the case of the much more lipophilic 4-nitrophenoxide, the solubility of the quaternary salts **3–5d** is noticeably different in chlorobenzene, whereas

Table 3
Effect of the catalyst lipophilicity on the second-order rate constant k ($M^{-1} s^{-1}$) of S_N2 reactions under LL–PTC conditions^a

RX	Q ⁺ Y ⁻	PhCl–H ₂ O			4-Methyl-2-pentanone–H ₂ O		
		Partition in the organic phase (%)	$10^5 \times k_{obsd}$ (s^{-1})	$10^3 \times k$ ($M^{-1} s^{-1}$)	Partition in the organic phase (%)	$10^5 \times k_{obsd}$ (s^{-1})	$10^3 \times k$ ($M^{-1} s^{-1}$)
<i>n</i> C ₈ H ₁₇ OMs	MeBu ₃ N ⁺ Cl ⁻	3	0.1	1.8	8	0.33	2.5
	Bu ₄ N ⁺ Cl ⁻	16	2.3	4.3	78	4	2.2
	Hexyl ₄ N ⁺ Cl ⁻	100	10	4.7	100	6.8	3
<i>n</i> C ₄ H ₉ Br	MeBu ₃ N ⁺ Y ⁻	9	0.06	0.30	97	0.91	0.42
	Bu ₄ N ⁺ Y ⁻	19	0.13	0.32	100	0.98	0.43
	Hexyl ₄ N ⁺ Y ⁻	96	0.82	0.36	100	0.92	0.41

Y⁻ = 4NO₂C₆H₄O⁻.

^a See Table 2 for reaction conditions.

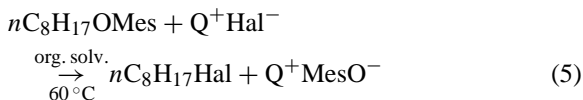
it is almost complete for all the salts in the more polar MIBK (Table 3). As a consequence, in the MIBK–water two-phase system the observed rate constant is unchanged whatever the catalyst may be, whereas it increases (14 times) with the lipophilicity of the catalyst in the PhCl–water two-phase system.

3.3. Kinetics under anhydrous conditions

For a quantitative evaluation of the effect of the specific hydration of the anion on its reactivity under LL–PTC conditions, kinetic measurements were also performed under both SL–PTC and homogeneous anhydrous conditions.

3.3.1. Anionic reactivity in the homogeneous medium

In the homogeneous phase the substrate **1** was reacted with comparable amounts (0.01–0.02 M) of the quaternary onium halide Q^+Hal^- **3–5** in the appropriate anhydrous organic solvent (MTAE, PhCl, DMC, MIBK, CH_3CN) (Eq. (5)).



Reactions follow regular second-order kinetics up to almost 70% conversion (Eq. (6)). The kinetic constants were determined evaluating the disappearance of the halide anion by potentiometric titration.

$$rate = k [substrate] [Q^+Hal^-] \quad (6)$$

As previously found in the chlorobenzene–water two-phase system, on passing from LL–PTC to homogeneous anhydrous conditions the rate constants increase, even remarkably, with enhancements $\Delta k(k_{\text{homogeneous phase}}/k_{\text{LL-PTC}})$ from 1.7 up to about 30

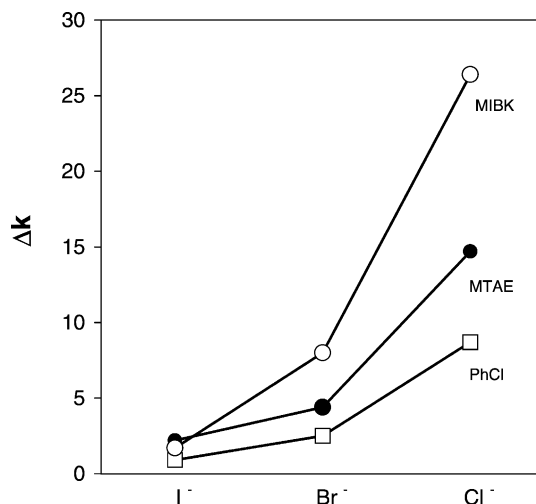


Fig. 2. Reactivity variation $\Delta k(k_{\text{homogeneous phase}}/k_{\text{LL-PTC}})$ of **1** with tetrahexylammonium halides (I^- , Br^- , Cl^-) in different solvents (PhCl, MIBK, MTAE), at $60^\circ C$.

times depending on the nucleophile and the medium (Fig. 2). In addition, the reactivity range in the anhydrous solvent is generally wider than that in the two-phase system ($Cl:Br:I = 2.1:1.3:1$ in the low polar MTAE; $9.3:4.2:1$ in the more polar ketone) and the sequence $Cl > Br > I$ becomes that typical for these anions in aprotic dipolar solvents and gas phase [1,2].

3.3.2. Effect of the structure of the quaternary cation

As reported in Table 4, the second order rate constant k ($M^{-1} s^{-1}$) increases two to three times in going from methyltributylammonium chloride (**3a**) to the bulky tetrahexylammonium chloride (**5a**), whereas it is independent on quaternary cation and much lower in the more polar acetonitrile. An analogous behavior

Table 4

Effect of the quaternary salt (**3–5a**) structure on the second-order rate constant k ($M^{-1} s^{-1}$) of reaction (2) in various solvents, at $60^\circ C^a$

	$10^3 \times k$ ($M^{-1} s^{-1}$)				
	MTAE	PhCl	DMC	MIBK	CH_3CN
MeBu ₃ N ⁺ Cl ⁻ (3a)	–	18.8 (1)	13.1 (1)	30.6 (1)	4.7
Bu ₄ N ⁺ Cl ⁻ (4a)	–	31.1 (1.6)	30.3 (2.3)	55.3 (1.8)	5.2
Hexyl ₄ N ⁺ Cl ⁻ (5a)	99.9	40.9 (2.2)	37.9 (2.9)	82.9 (2.7)	5.4

^a See Table 2 for reaction conditions.

was previously found with the series of hexadecyl-trialkylammonium bromides $C_{16}H_{33}N^+R_3Br^-$ ($R = Me, Et, Pr, Bu$) in chlorobenzene [14,15]. Also in that case the rate constants increase, about five times, changing from the trimethyl to the triethyl derivative, whereas no significant variation is found after further increasing of the alkyl chain length ($R = Pr, Bu$).

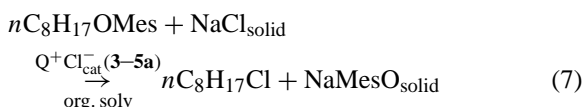
The quaternary salt being the same, the rate constants remarkably depend on the solvent, increasing in the order: $CH_3CN \ll DMC \leq PhCl < MIBK < MTAE$ (Table 4). Such a trend reflects that previously found for the tetrahexylammonium halides **5a–5c** and can be explained in the same way. In anion promoted reactions the solvent plays a major role on the anionic reactivity. The sequence found (Table 4) is strictly determined by the extent of solvation of the entering nucleophile that progressively decreases by diminishing the polarity of the medium, so activating the anion Y^- . It is worth noting the lower reactivity of the free chloride anion in acetonitrile if compared with the reactivity of the scarcely solvated ion pair in MTAE (Table 4). In low polarity media (toluene, cyclohexane) quaternary onium salts are known to be present as ion pairs and ion pair aggregates [5]. The remarkable reactivity of these loose ion pairs in scarcely solvating media largely overcomes the unfavorable effects of the ion pairing [5].

3.3.3. Comparison with LL-PTC conditions

The change from LL-PTC to homogeneous anhydrous conditions noticeably modifies the reactivity of all the quaternary salts whatever the solvent may be. As shown in Fig. 2 for the series of tetrahexylammonium halides **5a–5c**, the highest variation of reactivity Δk is observed for the anion with the highest charge density, the chloride. With this anion the rate constant k ($M^{-1} s^{-1}$), very similar in the three organic media under LL-PTC conditions, increases, up to about 30 times, in MIBK. By contrast, the enhancements of reactivity are less relevant with anions of lower charge density such as Br^- and I^- (up to eight and two times, respectively). Unlike the homogeneous phase where the anion reactivity increases, in the order: $PhCl < MIBK < MTAE$, under LL-PTC conditions the low polar MTAE is always the best solvent, whereas $PhCl$ -water and $MIBK$ -water systems have a reactivity very similar.

3.3.4. Kinetic measurements under SL-PTC conditions

In order to reduce or totally eliminate the specific hydration of the anion extracted in the organic phase associated with the quaternary onium cation the reactions were carried out in organic solvent–solid salt two-phase systems under SL-PTC conditions. Measurements were performed by stirring at 1000 rpm, in a flask thermostated at $60^\circ C$, a heterogeneous mixture of organic solution (15 ml) of substrate **1** and catalyst **3–5a** and sodium chloride as a solid phase (Eq. (7)).



The reaction progress has been monitored by gas chromatography, evaluating the appearance of the reaction product (the *n*-octyl chloride) with the internal standard method (dodecane) (Eq. (7)).

Unlike classic LL-PTC conditions, where the nucleophilic substitution reaction in the organic phase usually represents the rate determining step of the overall process ($k_{intr} \ll k_{transf}$), in these systems the rate of the reaction is often remarkably reduced by the difficulty to regenerate the anion nucleophile from the solid phase ($k_{transf} \ll k_{intr}$). Accordingly, under SL-PTC conditions only the half-life times ($t_{1/2}$) were determined.

As reported in Table 5 for the series of quaternary onium chlorides **3–5a**, the rate of the reaction (Eq. (7)) increases ($t_{1/2}$ decreases of about two times) switching from methyltributylammonium (**3a**) to tetrahexylammonium (**5a**) salt, whatever the solvent may be. Also in this case the reactions in acetonitrile are the slowest (highest half-live times) and do not depend, within the experimental errors, on the steric hindrance around the quaternary cation, in agreement with the fact that in this medium of relatively high dielectric constant ($\epsilon = 39$), all the quaternary salts are dissociated species [3].

3.3.5. Comparison with the homogeneous and LL-PTC conditions

Results of Table 5 show that, as expected, $t_{1/2}$ noticeably increases, up to about 200 times, in going from homogeneous to two-phase (LL-PTC or SL-PTC) systems. It is worth noting that, for all the

Table 5

Half-life times ($t_{1/2}$, m) for the reaction of *n*-octyl methanesulphonate **1** with quaternary onium chlorides **3–5a** in various solvents under SL–PTC conditions, at 60 °C^a

	$t_{1/2}$ (m)			
	Chlorobenzene	DMC	MIBK	CH ₃ CN
MeBu ₃ N ⁺ Cl ⁻ (3a)	279	331	131	697
Bu ₄ N ⁺ Cl ⁻ (4a)	114	186	117	740
Hexyl ₄ N ⁺ Cl ⁻ (5a)	132 (81) ^b (3) ^c	169 (489) ^b (3) ^c	87 (111) ^b (2) ^c	687

^a An organic solution (15 ml) of **1** (0.1 M), catalyst Q⁺Cl⁻ (0.01–0.02 M) and solid NaCl (30 M equiv.).

^b See Table 2 for LL–PTC conditions.

^c Homogeneous phase: [substrate] = 0.02–0.03 M; [Q⁺Cl⁻] = 0.01–0.02 M.

solvents, the $t_{1/2}$ values are very similar in the SL and LL two-phase system except for DMC where the reaction in the liquid–liquid system is slower ($t_{1/2}$ about three times higher) than that in the solid–liquid system (Table 5). Such a difference is most likely due to the high quantity of water retained by this solvent after contact with the aqueous phase that reduces the reactivity of the anion (chloride).

4. Conclusions

The results as a whole show that solvents such as aliphatic esters (DMC), aliphatic ethers (MTAE) and aliphatic ketones (MIAK, MIBK), represent a valid alternative to the traditional solvents for PTC, both for LL and SL two-phase processes.

The partition of the catalyst Q⁺Y⁻ in the organic phase, indeed, is comparable with or even higher than that in chlorobenzene, as in the case of the least lipophilic quaternary salts (Table 1). The catalyst being the same, the rate constant increases with decreasing the solvent polarity and, in the low polar MTAE, it is four to five times higher than that found in chlorobenzene, in spite of the higher quantity of water dissolved in the ether. The trend is even more pronounced in the anhydrous solvent where, in the absence of any solvation, it is possible to measure the intrinsic reactivity of the ion pair Q⁺Y⁻. In this case the rate constants are always higher, up to one order of magnitude, than in chlorobenzene.

Interestingly, the study of reactivity in these media is also of great topicality due to the increasing interest in oxygenated solvents (esters, ketones) for their relatively low toxicity and reduced environmental impact

[16,17]. The toxicity values from material safety data sheets (MSDS) [18] of these solvents are remarkably lower than those of common PTC solvents, even of the most environmentally acceptable toluene [6,18].

DMC, in particular, besides its well known applications as chemical intermediate, has widely been utilized as reaction medium, for cleaner and more sustainable processes [16]. In this line our results highlight that the reactivity in DMC is comparable with that in chlorobenzene under both homogeneous and heterogeneous conditions and hence DMC represents a valid ecosafe alternative to the solvents traditionally used in PTC processes.

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