# Phase-Transfer Catalysis. Nucleophilicity of Anions in Aqueous Organic Two-Phase Reactions Catalyzed by Onium Salts. A Comparison with Homogeneous Organic Systems

**Dario Landini,* Angelamaria Maia, and Fernando Montanari***

Contribution from the Centro C.N.R. and Istituto di Chimica Industriale dell'Università', 20133 Milano, Italy. Received September 14, 1977

Abstract: Kinetics of nucleophilic substitutions with inorganic anions in *n*-octyl methanesulfonate, catalyzed by quaternary salts Q^+Y^-, have been measured under conditions of phase-transfer catalysis (PTC) in a chlorobenzene–water two-phase system. Reactions occur in the organic phase and the $MeSO_3^-$ group is irreversibly transferred to the aqueous phase. The observed pseudo-first-order rate constants are linearly related to the effective concentration of the catalyst in the organic phase. The relatively narrow reactivity range and the sequence found in the $PhCl-H_2O$ system ($N_3^- > CN^- > Br^- \sim I^- > Cl^- > SCN^-$) are largely determined by the specific solvation of the anion by a limited number of water molecules. The reaction rates in PTC conditions can be simulated in a homogeneous PhCl solution by adding the amount of water associated to Q^+Y^- and to the substrate. Changing from aqueous to anhydrous PhCl, rates increase up to one power of ten, and the reactivity scale becomes that found in dipolar aprotic solvents ($CN^- > N_3^- > Cl^- > Br^- > I^- > SCN^-$). In PTC and, in an enhanced way, in homogeneous conditions, reactivity of Q^+Y^- increases by diminishing the polarity of the organic solvent. In two-phase systems the observed pseudo-first-order rate constants differ by factors up to two powers of ten by changing the structure of quaternary cation. However, the second-order rate constants, which take into account the actual concentration of the catalyst in the organic phase, differ at most by a factor of 2.5.

Phase-transfer catalysis[1] was introduced in 1965, and then systematically developed, by Makosza. Starks was the first to propose a mechanism which would account for the experimental facts.[2,3] According to Starks' mechanism the catalyst, namely, a lipophilic onium salt, transfers the anion from the aqueous to the organic phase, where the reaction occurs, and then returns the leaving group to the aqueous phase.

$$RX + Q^+Y^- \longrightarrow RY + Q^+X^- \quad \text{(organic phase)}$$

$$X^- + Q^+Y^- \rightleftarrows Y^- + Q^+X^- \quad \text{(aqueous phase)}$$

$$(1)$$
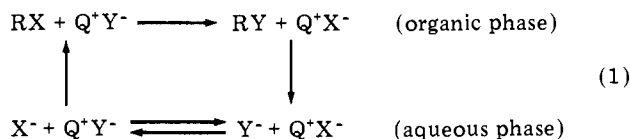
It has been shown that the activity of the onium catalyst depends on its solubility in the organic phase.[3-5] This is also true when crown ethers[6] and cryptands[7] are used as phase-transfer agents. Reaction 1 involves the partitioning of the catalyst between the phases.[8] Using liquid membranes we demonstrated[5] that, at least when the quaternary salt is completely insoluble in water, anions exchange at the interface without the concomitant transfer of the organic cation, with as counterions the quaternary cation Q^+ in the organic phase and the inorganic cation M^+ in the aqueous phase, respectively:

$$RX + Q^+Y^- \longrightarrow RY + Q^+X^- \quad \text{(organic phase)}$$

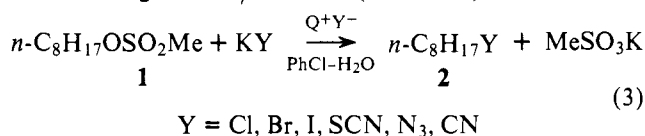$$Y^- + M^+ + X^- \quad \text{(aqueous phase)}$$

$$(2)$$
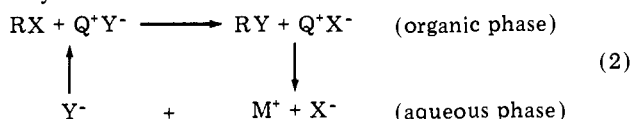
Only a few quantitative studies[3-5,9-11] have been made of these reactions, since most interest has centered on the applicative field.

This paper reports a study of the reactivity of anions as a function of the structure of catalyst, of the organic solvent, and of their hydration shell in the organic phase. A comparison is made between the reaction rates under phase-transfer conditions and those performed under homogeneous classical conditions, in protic or dipolar aprotic solvents.[12]

Results

n-Octyl methanesulfonate (**1**) was chosen as substrate, and

rates of displacement of the methanesulfonic group by anionic nucleophiles (Cl^-, Br^-, I^-, SCN^-, N_3^-, CN^-) were measured at 60 °C in a water–chlorobenzene two-phase system in the presence of catalytic amounts of onium salts Q^+Y^- (0.0167–0.167 mol/mol of substrate) and with a 5:1 molar ratio of inorganic salt/substrate (reaction 3).

$$n\text{-}C_8H_{17}OSO_2Me + KY \xrightarrow[\text{PhCl-H}_2O]{Q^+Y^-} n\text{-}C_8H_{17}Y + MeSO_3K$$
$$\quad\quad\quad 1 \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad 2$$

$$Y = Cl, Br, I, SCN, N_3, CN \tag{3}$$

As already found by other authors,[3,4,13] the reaction rates increase upon increases in the stirring speed up to 300 rpm, and remain constant beyond this value. The reactions were carried out by stirring at 1000 rpm, and the rates were measured by following the disappearance of the substrate by ^{1}H NMR spectroscopy in the presence of an internal standard (benzyl phenyl ether).

The quaternary cations used were phosphonium salts **3** and **4** and ammonium salts **5–15**.
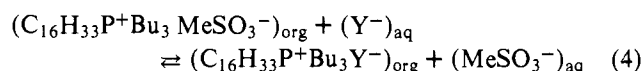
3, $C_{16}H_{33}P^+Bu_3Y^-$	**4**, $Bu_4P^+Br^-$
3a, Y = Cl	**5**, $Pr_4N^+Br^-$
3b, Y = Br	**6**, $PhCH_2N^+Pr_3Br^-$
3c, Y = I	**7**, $Bu_4N^+Br^-$
3d, Y = SCN	**8**, $PhCH_2N^+Bu_3Br^-$
3e, Y = N_3	**9**, $(C_8H_{17})_4N^+Br^-$
3f, Y = CN	**10**, $C_{16}H_{33}N^+Bu_3Br^-$
	11, $C_{16}H_{33}N^+Pr_3Br^-$
	12, $C_{16}H_{33}N^+Et_3Br^-$
	13, $C_{16}H_{33}N^+Me_3Br^-$
	14, $C_{16}H_{33}N^+Me_2EtBr^-$
	15, $C_{16}H_{33}N^+MeEt_2Br^-$

The hexadecyltributylphosphonium cation **3** was used as reference compound for the kinetic screening. A study of the partition coefficient established that in all cases examined the onium salt **3** is entirely in the organic phase associated with the nucleophile, while the methanesulfonate is quantitatively transferred to the aqueous phase. Thus equilibrium 4 is fully shifted to the right.

Table I. Second-Order Rate Constants for the Reaction of *n*-Octyl Methanesulfonate with Various Nucleophiles (Y$^-$)[a] in Chlorobenzene-Water Two-Phase System under Phase-transfer Conditions, and in Anhydrous and Wet Chlorobenzene, at 60 °C

	Phase-transfer conditions (PhCl-H$_2$O)[b]			Homogeneous conditions		
Y$^-$	$k \times 10^3$, M^{-1} s^{-1} [e,f]	k_{rel}	Hydration state n of Q$^+$Y$^-$·nH$_2$O in PhCl[g]	Anhydrous PhCl[c] $k \times 10^3$, M^{-1} s^{-1} [h]	k_{rel}	Wet PhCl[d] $k \times 10^3$, M^{-1} s^{-1} [f,i]
N$_3^-$	19.1	6.8	3.0 ± 0.2	70.4	23.5	19.6
CN$^-$	11.7	4.2	5.0 ± 0.3	86.7	29.0	13.3
Cl$^-$	1.8	0.6	3.4 ± 0.2[j]	19.7	6.6	2.2
Br$^-$	3.2	1.1	2.1 ± 0.2	8.1	2.7	3.3
I$^-$	2.8	1.0	1.0 ± 0.15	3.0	1.0	2.7
SCN$^-$	0.49	0.2	2.0 ± 0.2	0.75	0.3	0.52

[a] From C$_{16}$H$_{33}$P$^+$Bu$_3$Y$^-$(Q$^+$Y$^-$). [b] 20 mL of a chlorobenzene solution of substrate (6 × 10^{-1} M) and of Q$^+$Y$^-$ (1–10 × 10^{-2} M), and 15 mL of an aqueous solution of KY (4.2 M); sodium salt in the case of N$_3^-$. [c] [Substrate] = 2–8 × 10^{-2} M; [Q$^+$Y$^-$] = 3–4 × 10^{-2} M. [d] [Substrate] = 6 × 10^{-1} M; [Q$^+$Y$^-$] = 2–4 × 10^{-2} M; [H$_2$O] = 0.27–0.15 M. [e] k is defined as $k = k_{obsd}/[Q^+Y^-]$. [f] Average of at least three runs. [g] Average from at least four determinations. [h] The rate constants are computer generated using the least-squares analysis and are the average of at least three runs. [i] k is defined as $k = k_{obsd}/[substrate]$. [j] The same value was found in the systems cyclohexane-H$_2$O, toluene-H$_2$O, and o-dichlorobenzene-H$_2$O.

$$(C_{16}H_{33}P^+Bu_3\ MeSO_3^-)_{org} + (Y^-)_{aq}$$
$$\rightleftarrows (C_{16}H_{33}P^+Bu_3Y^-)_{org} + (MeSO_3^-)_{aq} \quad (4)$$

The reactions follow pseudo-first-order kinetics (eq 5) up to at least 80% conversion.

$$\text{rate} = k_{obsd}\ [\text{substrate}] \quad (5)$$

In the same conditions, but in the absence of catalyst, no appreciable conversion was detected after 3 days (more than 20 half-lives with respect to the slowest reaction).[14] The observed rate constants (k_{obsd}, s^{-1}) are linearly dependent on catalyst concentration in the range examined (Figure 1). The second-order rate constants ($k_{obsd}/[Q^+Y^-]$, M^{-1} s^{-1}) are reported in Table I.

Some molecules of water accompany the anion in the process of transfer from the aqueous to the organic phase. The degree of solvation depends on the anion and was measured by titration of water (Karl Fischer analysis) after shaking an aqueous solution of the inorganic salt with an organic solution of the corresponding quaternary salt in the same conditions employed for kinetic measurements (Table I and Experimental Section). *n*-Octyl methanesulfonate is also bonded in the organic phase to a small amount of water (~0.15 mol), determined by the same technique.

For a quantitative evaluation of the influence exerted by the hydration of the anion on its reactivity in two-phase conditions, kinetic measurements were performed in homogeneous systems. In anhydrous chlorobenzene, with comparable concentrations of substrate (2–8 × 10^{-2} M) and phosphonium salt **3** (3–4 × 10^{-2} M) (reaction 6), the reactions followed a second-order kinetic equation 7.

$$n\text{-}C_8H_{17}OSO_2Me + Q^+Y^- \rightarrow n\text{-}C_8H_{17}Y + Q^+MeSO_3^- \quad (6)$$
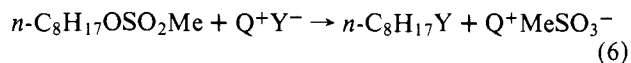
$$\text{rate} = k[\text{substrate}][Q^+Y^-] \quad (7)$$

Kinetic constants, measured by following the disappearance of the nucleophile (potentiometric titration), slightly increased upon decreasing the concentration of the quaternary salt. The values reported in Table I refer to a practically constant concentration of the onium salt.

Kinetic measurements in chlorobenzene were repeated adding to the homogeneous solution an amount of water identical with that associated to the substrate and the quaternary salt under two-phase conditions ([H$_2$O] = 0.27–0.15 M for substrate and quaternary salt concentrations equal to 0.6 and 0.02–0.04 M, respectively). The reactions followed a pseudo-first-order kinetic equation 8.

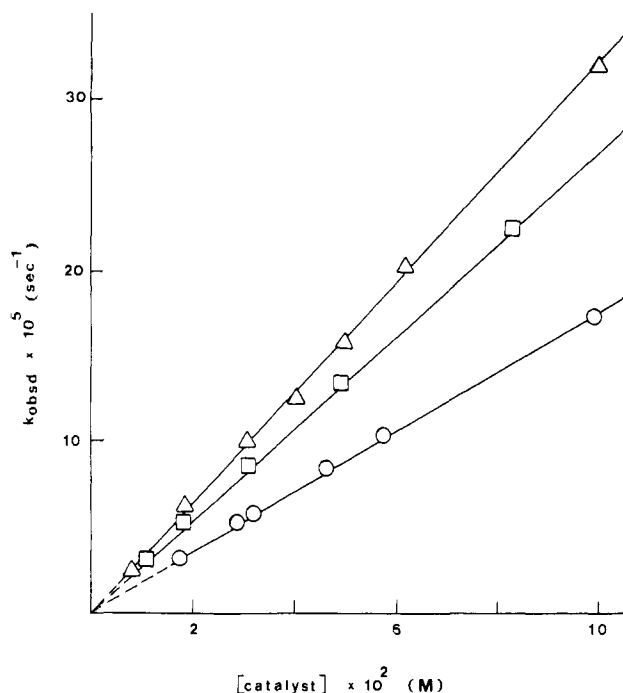$$\text{rate} = k_{obsd}[Q^+Y^-] \quad (8)$$

Figure 1. Dependence of the observed rate constants (k_{obsd}) on catalyst concentration, C$_{16}$H$_{33}$P$^+$Bu$_3$Hal$^-$, for the reaction of *n*-octyl methanesulfonate with various halides in PhCl-H$_2$O two-phase system at 60 °C: Hal = Cl (O), Br (△), I (□). For the reaction conditions see note *b*, Table I.

Second-order rate constants ($k_{obsd}/[\text{substrate}]$) are reported in Table I.

Kinetic measurements were carried out also in anhydrous MeOH and Me$_2$SO and follow eq 7; the data are reported in Table II. The effect of the organic solvent on the reaction rate was studied in the case of Br$^-$ ion for a series of aprotic solvents of different polarity both in anhydrous homogeneous and in two-phase conditions (Table III).

To evaluate the influence of the structure of the quaternary cation, the reactivity of a homogeneous series of ammonium and phosphonium bromides was compared both in the two-phase system (PhCl-H$_2$O) and in anhydrous solvents (PhCl and Me$_2$SO). In Table IV are reported the observed pseudo-first-order rate constants and the second-order rate constants determined by taking into account the actual concentration of catalyst in the organic phase; Table V reports the rate constants measured in anhydrous PhCl and Me$_2$SO. In the latter conditions the observed rate values decrease with an increase

Table II. Second-Order Rate Constants for the Reaction of *n*-Octyl Methanesulfonate ($2\text{-}6 \times 10^{-2}$ M) with Various Nucleophiles (Y^-)[a] in Anhydrous Me$_2$SO and MeOH, at 60 °C

	Me$_2$SO		MeOH	
Y^-	$k \times 10^3$, M^{-1} s^{-1} [b,c]	k_{rel}	$k \times 10^3$, M^{-1} s^{-1} [b,c]	k_{rel}
N$_3$$^-$	13.5	25.5	0.60	1.03
CN$^-$	33.8	63.8	0.40	0.69
Cl$^-$	3.6	6.8	0.09	0.15
Br$^-$	2.3	4.3	0.22	0.38
I$^-$	0.53	1.0	0.58	1.00
SCN$^-$	0.27	0.5	0.17	0.29

[a] From C$_{16}$H$_{33}$P$^+$Bu$_3$Y$^-$. [b] See note *h*, Table I. [c] [C$_{16}$H$_{33}$P$^+$Bu$_3$Y$^-$] = $3\text{-}4 \times 10^{-2}$ M.

Table III. Solvent Effect on the Reaction Rate of *n*-Octyl Methanesulfonate with Bromide Ion[a] under Two-Phase and Anhydrous Homogeneous Conditions, at 60 °C

Organic solvent	Phase-transfer conditions[b] $k \times 10^3$, M^{-1} s^{-1} [d]	Homogeneous conditions[c] $k \times 10^3$, M^{-1} s^{-1} [e]	k_{rel}
Cyclohexane	5.5	40.5	17.6
Toluene	3.7	10.7	4.6
Chlorobenzene	3.2	8.1	3.5
o-Dichlorobenzene	3.2	5.5	2.4
Benzonitrile	1.6	4.5	2.0
Me$_2$SO		2.3	1.0
MeOH		0.22	0.1

[a] From C$_{16}$H$_{33}$P$^+$Bu$_3$Y$^-$. [b] See note *b*, Table I. [c] [Substrate] = $2\text{-}6 \times 10^{-2}$ M; [C$_{16}$H$_{33}$P$^+$Bu$_3$Y$^-$] = $3\text{-}4 \times 10^{-2}$ M. [d] See notes *e* and *f*, Table I. [e] See note *h*, Table I.

in the quaternary salt concentration. Variation depends on structural factors, being higher for ammonium bromides (80% for **12** in a concentration range of $4\text{-}0.5 \times 10^{-2}$ M), smaller for phosphonium bromides where it does not exceed 10%.

Discussion

Reaction Mechanism. The essential aspect of the PTC mechanism proposed by Starks is that the attack of the anionic reagent on the substrate occurs in the organic phase and usually is the rate-determining step of the process, with transport through the interface and reestablishment of equilibria (eq 1 or 2) being fast steps. Substantial evidence for this mechanism was reported by Starks[2,3] and by others.[4,5,9-11]

A first indication that it applies also in these reactions comes from the kinetic behavior: reactions follow regular pseudo-first-order kinetics and the observed rate constants are linearly related to the effective concentration of catalyst in the organic phase (Figure 1, Tables I and IV). This behavior is that expected if transport of anions through the interface is fast[15] and if, as experimentally found, selectivity coefficients in the organic phase ($K^{sel} = [Q^+MeSO_3^-]_{org}/[Q^+Y^-]_{org}$) are about zero,[16] leading to a stationary state in which $[Y^-]_{org} = [Q^+]_{org}$. The independence[17] of the observed rate constants on the stirring speed above 300 rpm shows the unimportance of interfacial phenomena here.

Reactivity of Anions under PTC Conditions. The values reported in Table I show the relative nucleophilicity of a homogeneous series of anions under PTC conditions. The narrow reactivity scale and sequence N$_3$$^-$ > CN$^-$ > Br$^-$ ~ I$^-$ > Cl$^-$ > SCN$^-$ are anomalous with regard to the reactivity of anions, both in protic and dipolar aprotic solvents.

In fact, when quaternary salts **3** react with the same substrate in organic homogeneous solution, the reactivity scales

Table IV. Influence of the Nature of Quaternary Cation (Q$^+$) on the Rate Constant in the Reaction of *n*-Octyl Methanesulfonate with Bromide Ion in a PhCl-H$_2$O Two-Phase System,[a] at 60 °C

Q$^+$ [b]	% catalyst in the organic phase	$k_{obsd} \times 10^5$, s^{-1} [c]	$k \times 10^3$, M^{-1} s^{-1} [d]
3b, C$_{16}$H$_{33}$P$^+$Bu$_3$	100	12.8	3.2
4, Bu$_4$P$^+$	97	10.4	2.7
5, Pr$_4$N$^+$	2.5	0.24	2.4
6, PhCH$_2$N$^+$Pr$_3$	17	1.3	1.9
7, Bu$_4$N$^+$	83	12.0	3.6
8, PhCH$_2$N$^+$Bu$_3$	95	8.2	2.1
9, (C$_8$H$_{17}$)$_4$N$^+$	100	20.4	5.1
10, C$_{16}$H$_{33}$N$^+$Bu$_3$	100	17.3	4.3
11, C$_{16}$H$_{33}$N$^+$Pr$_3$	94	15.9	4.0

[a] 20 mL of a chlorobenzene solution of substrate (6×10^{-1} M) and 15 mL of an aqueous solution of KBr (4.2 M). [b] 0.8 mmol in the system PhCl-H$_2$O. [c] Average of at least two runs. [d] k is defined as $k = k_{obsd}/[Q^+Br^-]_{org}$.

in Me$_2$SO and methanol substantially reflect the well-known reactivity scales of the same anions in dipolar aprotic and protic solvents[18] (CN$^-$ > N$_3$$^-$ > Cl$^-$ > Br$^-$ > I$^-$ > SCN$^-$ and N$_3$$^-$ ~ I$^-$ > CN$^-$ > Br$^-$ > SCN$^-$ > Cl$^-$, respectively, Table II).

The main reason for the behavior of anions under PTC conditions appears to be hydration of quaternary salt and, to a lesser degree, of substrate in the organic phase. As shown in Table I, the state of hydration of quaternary salt in chlorobenzene largely depends on the nature of the anion, which means[3] that water is primarily associated with the latter, and not with the quaternary cation. The hydration number appears to be related[18d] to the size of the anion, as in the sequence Cl$^-$, Br$^-$, I$^-$, and to the charge dispersion, as in the sequence CN$^-$, N$_3$$^-$, SCN$^-$.

At least in the case of phosphonium bromide **3b**, the hydration number (2.1 mol of H$_2$O per mol of Q$^+$Br$^-$) is the same in a series of organic solvents nonmiscible with water.[19] Indeed, the values for Cl$^-$ and CN$^-$ agree with those found independently by Starks in toluene.[3]

In going from PTC conditions to homogeneous solutions in anhydrous chlorobenzene (Table I), the second-order rate constants are practically unchanged for anions with dispersed and/or polarizable charge, but are noticeably enhanced for anions with localized and/or less polarizable charge, as for Cl$^-$, where the rate increase is one power of ten. The reactivity range of anions is remarkably larger, and the sequence CN$^-$ > N$_3$$^-$ > Cl$^-$ > Br$^-$ > I$^-$ > SCN$^-$ essentially reflects that found in Me$_2$SO.

That the reaction rates in PTC conditions can be simulated in homogeneous solution by reproducing the hydration of quaternary salt and substrate (Table I) demonstrates that the specific solvation by a limited number of water molecules in the organic phase is responsible for the particular nucelophilicity scale of anions in PTC conditions. It is also clear, independent proof that in two-phase conditions the reaction takes place in the organic phase.

In homogeneous anhydrous solution the second-order rate constants decrease on changing from chlorobenzene to Me$_2$SO to methanol, with smaller variations for anions with dispersed charge and/or polarizable anions, and larger ones for anions with high charge density and/or less polarizable anions (Tables I and II); for the latter the second-order rate constants in anhydrous chlorobenzene are on the average one and two orders of magnitude faster than those measured in Me$_2$SO and methanol, respectively.

Table V. Influence of the Nature of Quaternary Cation (Q$^+$) on the Rate Constants of the Reaction of *n*-Octyl Methanesulfonate with Bromide Ion in Anhydrous Chlorobenzene and Me$_2$SO, at 60 °C

Q$^+$	[Substrate] $\times 10^{-2}$, M	[Q$^+$Br$^-$] $\times 10^{-2}$, M	PhCl $k \times 10^3$, M^{-1} s^{-1} [a]	Me$_2$SO $k \times 10^3$, M^{-1} s^{-1} [a]
3, C$_{16}$H$_{33}$P$^+$Bu$_3$	2.10	5.98		2.15 ± 0.07
	2.10	3.68	7.61 ± 0.21	2.35 ± 0.07
	2.10	1.10	8.09 ± 0.11	3.29 ± 0.08
	2.10	0.51	8.72 ± 0.11	3.46 ± 0.11
	4.20	2.12	7.94 ± 0.22	
	8.12	4.12	8.20 ± 0.21	
4, Bu$_4$P$^+$	2.10	4.37	8.22 ± 0.21	
	2.10	3.30	8.71 ± 0.13	
	2.10	0.94	8.91 ± 0.09	
	2.10	0.56	9.10 ± 0.15	
7, Bu$_4$N$^+$	2.10	6.52		2.74 ± 0.03
	2.10	4.40	14.0 ± 0.3	
	2.10	0.55	20.2 ± 0.2	3.24 ± 0.08
9, (C$_8$H$_{17}$)$_4$N$^+$	2.10	4.39	13.0 ± 0.3	
	2.10	0.51	19.6 ± 1.0	
10, C$_{16}$H$_{33}$N$^+$Bu$_3$	2.10	6.30		2.39 ± 0.18
	2.10	4.30	12.6 ± 0.2	2.47 ± 0.10
	2.10	1.10	16.6 ± 0.5	3.02 ± 0.07
	2.10	0.55	18.2 ± 0.3	3.20 ± 0.12
	0.81	1.10	17.0 ± 0.2	
	4.05	1.10	16.9 ± 0.2	
11, C$_{16}$H$_{33}$N$^+$Pr$_3$	2.10	4.21	11.4 ± 0.4	
	2.10	0.51	19.2 ± 0.3	3.46 ± 0.28
12, C$_{16}$H$_{33}$N$^+$Et$_3$	2.10	3.93	10.7 ± 0.2	
	2.10	1.00	14.3 ± 0.3	
	2.10	0.51	18.6 ± 0.4	2.91 ± 0.08
15, C$_{16}$H$_{33}$N$^+$Et$_2$Me	2.10	1.06	7.71 ± 0.08	
	2.10	0.58	8.34 ± 0.15	
14, C$_{16}$H$_{33}$N$^+$Me$_2$Et	2.10	1.07	4.19 ± 0.10	
	2.10	0.58	6.51 ± 0.12	
13, C$_{16}$H$_{33}$N$^+$Me$_3$	2.10	1.07	2.76 ± 0.60	
	2.10	0.50	3.88 ± 0.07	3.20 ± 0.7
	1.13	0.50	3.77 ± 0.08	

[a] The rate constants and root mean square deviations are computer-generated values obtained by least squares.

Although in this connection some data were already available,[4] this is the first quantitative comparison, extended to a significant series of anions, between reaction rates under PTC and classical conditions for the same reactions in protic or dipolar aprotic solvents. Table VI summarizes the more significant data of relative reactivities under the various conditions.

State of Association of Quaternary Salt. The possibility that under PTC conditions quaternary salts dissolved in the organic phase are somewhat associated has been discussed by several authors.[3,4,10] Tetraalkylammonium[21,22] and phosphonium[3] salts exist as a quadrupole or as more complex aggregates in weakly polar or apolar anhydrous solvents, whereas they are largely dissociated species in polar solvents.[18a,d,22]

The presence of associated quaternary salts in anhydrous chlorobenzene is shown by the enhancements in second-order rate constants upon diminishing the salt concentration (Table V). This behavior, more pronounced for ammonium salts than for phosphonium salts, contrasts with that found in the same solvent under PTC conditions, where a linear realtionship is found between the observed rate constants and the quaternary salt concentration in the whole range examined (Figure 1). The comparison between the two systems indicates that a limited number of water molecules associated with the quaternary salt in the organic phase are sufficient to suppress the formation of aggregates to a level which has no influence on the reaction rates. Such a conclusion is in agreement with those of other authors,[3,4,10] and, in particular, confirms that invert micelles cannot play any role[3] in phase-transfer catalysis.

As shown in Table III, the reaction rates under PTC conditions decrease with increasing polarity of the organic solvent,

Table VI. Dependence of Relative Reactivities of Anionic Nucleophiles on Solvent, $k_{solv}{}^{Y^-}/k_{MeOH}{}^{Y^-}$, in the Reaction of *n*-Octyl Methanesulfonate with Q$^+$Y$^-$

	k_{rel}			
Y$^-$	MeOH	Me$_2$SO	PhCl–H$_2$O (PTC)	PhCl
N$_3$$^-$	1	22	32	117
CN$^-$	1	84	29	217
Cl$^-$	1	40	20	219
Br$^-$	1	10	14 (25)[a]	37 (176)[b]
I$^-$	1	0.9	4.8	5.2
SCN$^-$	1	1.6	2.9	4.4

[a] Cyclohexane-H$_2$O. [b] Cyclohexane.

with the highest rate in cyclohexane. Differences are modest, but a similar and more striking behavior is found in homogeneous anhydrous solutions: in the latter, rates are two- to eightfold higher then in PTC conditions, with the highest increase in the least polar solvent, cyclohexane.

These results seem to differ from those recently reported by Herriott and Picker.[4] However, the apparent discrepancy is cleared up by considering that the real dependence of reaction rates on the polarity of the solvent is often masked by large variations[3,4] of the partition coefficients of quaternary salts.

A comment is required on the reactivity of quaternary salts in anhydrous solvents. As reported above, it seems reasonable to assume that these salts exist to a large extent as dissociated ions in methanol, as ion pairs in equilibrium with dissociated species in Me$_2$SO, and as ion pairs in equilibrium with associated species in the other solvents. The observed reactivity of

phosphonium bromide **3b** in cyclohexane is 18- and 180-fold higher than in Me₂SO and methanol, respectively (Tables III and VI). The specific solvation of the anion by hydrogen bonding accounts for the lower reactivity in methanol, while a decrease of polarity of the solvent, and hence of solvation, is connected with an increase of nucleophilicity in the other solvents. It may be expected[21,22] that in cyclohexane, at the same concentration, the degree of association of quaternary salt is comparable, or in any case not less, than that in chlorobenzene. Therefore, rates measured in anhydrous cyclohexane should reflect, more than any solvent examined, the intrinsic reactivity of the ion pair Q⁺Br⁻.[23,25]

Influence of the Structure of Quaternary Cation. As shown in Table IV, pseudo-first-order rate constants for Q⁺Br⁻, measured under phase-transfer conditions, differ by factors up to two powers of ten upon variation in the structure of quaternary cation. However the second-order rate constants, which take into account the actual concentration of the catalyst in the organic phase, are in a very narrow range, as the maximum difference is a factor of 2.5. The small variations found within homogeneous series (**4, 3b; 5, 7, 9; 6, 8; 11, 10**) indicate that anionic reactivity slightly increases by increasing the steric hindrance around the cationic center and, with the same alkyl chains, by changing from phosphorus to nitrogen.

This clarifies and quantitatively confirms the already proposed concept[3,4] that the effectiveness of a phase-transfer catalyst depends mainly on its organophilicity, with other structural factors much less important.

By working in anhydrous media, it has been possible to extend the study of the structural effects of quaternary cation to ammonium salts **12–15** containing, besides the hexadecyl chain, only methyl or ethyl groups (Table V). As already shown for methyl derivatives,[2] these compounds cannot be used as phase-transfer catalysts because they promote formation of stable aqueous emulsions. In the homogeneous series **12–15** reaction rates increase by the progressive substitution of methyl with ethyl groups. A fivefold enhancement is seen changing from trimethyl derivative **13** to triethyl derivative **12**, whereas no significant variation is found by substituting ethyl with propyl, butyl, and *n*-octyl groups. This means that the ion pair, at least in the case of ammonium bromides in chlorobenzene, reaches an optimal degree of looseness with three ethyl groups, in addition to the long cetyl chain.

In anhydrous Me₂SO, as already reported for analogous systems,[22] second-order rate constants decrease with the increase in concentration of the salt, likely in connection with changes in the degree of dissociation (Table V). At the same concentration, the reactivity of quaternary bromides remains substantially unchanged in the whole series examined (salts **3, 7, 10–13**, Table V), and appears to be that intrinsic to the free anion ("solvated" by Me₂SO), independent of the structure of the quaternary cation.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as internal standard; potentiometric titrations were carried out with a Metrohm Potentiograph Type E576 using silver and calomel electrodes, the latter isolated with potassium sulfate bridge.

Materials and Solvents. *n*-Octyl methanesulfonate (**1**), bp 112–114 °C (2 mm), *n*²⁰D 1.4398, was obtained according to the literature (lit.[27] bp 110–114 °C (2 mm), *n*²⁰D 1.4392).

Inorganic salts were Analar grade commercial products used without further purification. Quaternary salts **4–9** and **13** were commercially available, purified by crystallization and dried in a vacuum desiccator before use. The ammonium salts **10–12** were prepared according to the literature[28] by refluxing an appropriate trialkylamine with hexadecyl bromide in ethanol. They had the following melting points: **10**, mp 70–72 °C (lit.[28] mp 68–70 °C); **11**, mp 85–87 °C (from ethyl acetate–hexane). Anal. Calcd for C₂₅H₅₄BrN:

C, 66.93; H, 12.69; N, 3.12. Found: C, 67.04; H, 12.67; N, 3.10. **12,** mp 169–171 °C (lit.[28] 145–155 °C). The ammonium salt **15** was obtained in 72% yield by heating at 80 °C for 35 h, in an autoclave, an ethanolic solution of hexadecylethylmethylamine (**16**) with 3 molar equiv of ethyl bromide. After crystallization from acetone it had mp 70–72 °C. Anal. Calcd for C₂₁H₄₆BrN: C, 64.29; H, 11.82; N, 3.57. Found: C, 63.96; H, 11.92; N, 3.46.

The same procedure was used for the preparation of **14** starting from hexadecyldimethylamine **17.**[29] Compound **14** had mp 188–191 °C (from acetone) (lit.[28] mp 178–186 °C). Phosphonium salts **3b** and **3c** were obtained according to Starks' method.[2,30] Phosphonium salts **3a** and **3d–f** were prepared from the corresponding methanesulfonate Q⁺MeSO₃⁻, by exchange with the appropriate anion; experimental details will be reported elsewhere. Many of these salts are hygroscopic and must be stored in a desiccator. Moreover the melting point of long-chain salts is generally dependent on heating speed and shrinkage occurs before the actual melting point.

All the amines, except hexadecylethylmethylamine (**16**), are commercial or known products, used after purification by standard methods. Amine **16** was obtained in 73% yield by N-alkylation of hexadecylethylamine[31] according to Leukart's procedure.[32] It had bp 157–158 °C (4 mm). Anal. Calcd for C₁₉H₄₁N: C, 80.54; H, 14.58; N, 4.94. Found: C, 80.15; H, 14.72; N, 4.87.

Cyclohexane, toluene, chlorobenzene, and *o*-dichlorobenzene were Analar grade chemical solvents, used without further purification in the kinetic measurements under phase-transfer conditions. In the reactions carried on under anhydrous homogeneous conditions they were carefully purified and dried by standard methods,[33] and stored over molecular sieves. Commercial benzonitrile,[34] Me₂SO,[34] and methanol[35] were purified according to literature methods. In all cases Karl Fischer titration showed a water content ≤70 ppm.

Distribution Coefficients. The distribution coefficients for quaternary salts **3a–f, 4, 7,** and **9–11** were determined by stirring 20 mL of a standardized solution of onium salt (4 × 10⁻² M) in the organic solvent with 15 mL of an aqueous solution (4.2 M) of the corresponding inorganic salt in a flask thermostated at 60 °C. Samples of organic phase were withdrawn at various times by stopping the stirrer for 1–5 min, to allow separation of the organic phase sufficient to get a good sample, and titrated on 0.01 N silver nitrate (potentiometric titration). In the case of **5, 6,** and **8,** owing to their low solubility in chlorobenzene, the appropriate amount of quaternary salt (0.8 mmol) was added to the system PhCl–H₂O. Equilibrium 4 was studied in the same conditions described above, adding to the system 12 mmol of potassium methanesulfonate corresponding to the amount formed in reaction 3 at 100% conversion.

Hydration State of Quaternary Salts. The state of hydration of quaternary salts **3a–f, 4,** and **7–11** was determined by stirring 20 mL of a standardized solution of the onium salt (2–4 × 10⁻² M) for 30 min in the organic solvent with 15 mL of an aqueous solution (4.2 M) of the corresponding inorganic salt in a flask thermostated at 60 °C.

Stirring was stopped and aliquots of the organic layer were withdrawn at intervals until a constant content of water was measured (Karl Fischer titration, 1–3 h). Concentration of quaternary salt in the organic layer was measured in parallel by potentiometric titration. The hydration states of salts **3a–f** are reported in Table I. Those for other salts are the following: **4,** 3.0 ± 0.3; **7,** 3.4 ± 0.3; **8,** 3.0 ± 0.2; **9,** 3.1 ± 0.2; **10,** 3.4 ± 0.3; **11,** 3.3 ± 0.2. The values, expressed as moles of water per mole of quaternary salt, are the average from at least four samplings.

Kinetic Measurements. The kinetics under PTC conditions were run in a 100-mL three-neck flask fitted with a flat-bladed stirring paddle, reflux condenser, and sampling port. The stirring speed (1000 ± 50 rpm) was determined using a strobe light and the temperature was controlled at 60 ± 0.1 °C by a LAUDA thermostated bath. The reaction solutions were prepared by weighing the desired amount of reagents in volumetric flasks which were filled to the mark at 60 ± 0.1 °C. In a typical procedure, the reaction flask was charged with 15 mL of an aqueous solution of inorganic salt (4.2 M), 10 mL of chlorobenzene solution of substrate **1** (1.2 M) and benzyl phenyl ether (0.8 M) as internal standard, and 10 mL of chlorobenzene solution of catalyst (2–20 × 10⁻² M). Stirring and timing were started. Samples of organic phase were withdrawn at various times by stopping the stirrer for 20–40 s to allow adequate separation. These were quenched by cooling in an ice bath and analyzed by ¹H NMR. Reaction rates were measured by following the disappearance of the

triplet (CH_2OSO_2Me) centered at δ 4.05 and using the singlet at δ 4.80 ($-OCH_2Ph$) as standard (PhCl as solvent). The pseudo-first-order rate constants (k_{obsd}) were obtained by plotting log [substrate] vs. time and determining the slope of the straight lines. The second-order rate constants, k, were calculated by dividing k_{obsd} by the catalyst concentration.

The quaternary ammonium salts **12–15** gave stable emulsions, which did not allow correct measurements under PTC conditions.

In the kinetic measurements under anhydrous homogeneous conditions 10 mL of a standardized solution of substrate (2.5–10×10^{-2} M) was added to 40 mL of a standardized solution of quaternary salt (4–5×10^{-2} M) in a 100-mL flask, thermostated at 60 ± 0.1 °C. Aliquots of 3 mL, withdrawn periodically, were quenched in 50 mL of ice-cold MeOH and the unreacted nucleophile was determined using 0.01 N silver nitrate (potentiometric titration). From the equation $(1/([B_0] - [A_0])) \ln [BA_0]/[AB_0] = kt$, where [A] = [substrate] and [B] = $[Q^+Y^-]$, or vice versa, the second-order rate constants were calculated using a least-squares computer program. All rates involved at least eight samplings and gave correlation coefficients of 0.995 or better. To avoid the evaporation of the solvent the kinetics in MeOH were run in sealed ampules.

In the reactions in wet chlorobenzene, 40 mL of a standardized solution (A) of the onium salt (4–8×10^{-2} M) and 40 mL of a stock solution (B) of substrate (1.2 M) were separately equilibrated with 30 mL of an aqueous solution (4.2 M) of the corresponding inorganic salt, as described above. At zero time 25 mL of solution B was added to 25 mL of solution A in a 100-mL flask, thermostated at 60 °C. Aliquots of 3 mL, withdrawn periodically, were quenched in 50 mL of ice-cold MeOH, and the unreacted nucleophile was determined using 0.01 N silver nitrate (potentiometric titration). All the experiments were run with large excess of substrate, and the pseudo-first-order rate constants, k_{obsd}, were obtained by plotting log $[Q^+Y^-]$ vs. time and determining the slope of the line. The second-order rate constants, k, were calculated by dividing k_{obsd} by the substrate concentration.

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