Polymer-Supported Phase-Transfer Catalysts. High Catalytic Activity of Ammonium and Phosphonium Quaternary Salts Bonded to a Polystyrene Matrix

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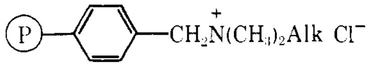
Abstract: The synthesis of tetraalkylammonium and tetraalkylphosphonium salts immobilized on a 2% cross-linked polystyrene matrix is described. Under optimized reaction conditions, the catalytic activity of these salts is comparable with that of the best soluble phase-transfer catalysts. The following factors are significant: (1) high lipophilic character and a topology ensuring enough separation between the anion and the cationic center; (2) a long spacer chain allowing the catalytic site to protrude into the reaction medium; (3) porosity of the resin; (4) highly efficient, turbulent stirring, in order to avoid diffusion control. The relative importance of the latter depends on the amount of cross-linking. Reactions follow pseudo-first-order kinetics, and rates are linearly dependent on molar equivalents of the polymer-supported catalyst. The kinetic behavior, the almost exclusive O-alkylation of phenols, and the hydration numbers of halides bonded to quaternary groups strongly support the hypothesis that reactions occur in an organic shell surrounding the catalytic site. Some examples of applications of polymer-supported phase-transfer catalysts to organic syntheses are also reported.

The attachment of phase-transfer catalysts to insoluble polymer supports greatly simplifies their use in many anion-promoted organic reactions. As in classical phase-transfer catalysis,[2] reactions are run in an aqueous organic two-phase system, but in this case the catalyst is bonded to a polymeric matrix: it forms a third, immiscible solid phase, which may be isolated at the end of the reaction by simple filtration, and recycled for another run, avoiding tedious processes of distillation, chromatographic separation, etc. Herein lies the potential importance of such a technique in industry, since both discontinuous processes with dispersed catalyst and continuous processes on a fixed-bed catalyst are feasible.

Phase-transfer catalysts linked to a polymer matrix were first described by Regen, who pioneered in this field, using tetraalkylammonium salts **1** derived from 2% cross-linked polystyrene to catalyze a wide series of anion-promoted reactions.[3] Polymer-supported catalysts with similar properties were also described by other authors, for example, cationic surfactants (resins **2**), prepared with the aim of simulating on the polymer the phase-boundary conditions of a micelle,[4] and chiral quaternary salts capable of effecting asymmetric syntheses.[5]



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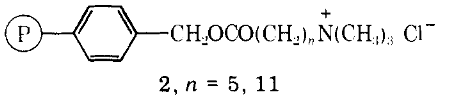


2, n = 5, 11

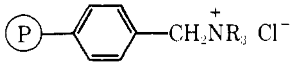
Unfortunately, catalytic activity of quaternary salts **1** and **2** bonded to the polymer is greatly reduced in comparison with that of soluble quaternary salts employed in classical phase-transfer catalysis. A decrease of catalytic activity is commonly observed for polymer-supported catalysts,[6] but in this case the low catalytic efficiency requires[3-5,7] such amounts of resin and reaction conditions that strongly limit the application of this technique. Therefore, it was necessary to know if more efficient catalysts could be prepared.

Our study of this problem[8,9] was based on the heuristic concept that efficient immobilized phase-transfer catalysts should satisfy the same structural requirements[10,11] as efficient soluble catalysts, i.e., high lipophilic character to ensure that reaction proceeds in the organic phase and a topology allowing sufficient separation between the anion and the cationic center. This idea was supported by the principle[5a] that, when a homogeneous catalyst is linked to an insoluble polymeric support, it should be allowed to protrude into the solution in order to be more solvated and, in a sense, "dissolved" in the reaction medium.

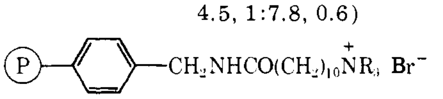
Some preliminary results have been published.[8,9] In the present work we report the preparation, reaction mechanism studies, and applications to organic syntheses of a series of tetraalkylammonium and tetraalkylphosphonium salts bonded to a polystyrene matrix, whose catalytic activity approaches that of efficient homogeneous phase-transfer catalysts. The influence on catalytic activity of diffusion phenomena and of a spacer chain interposed between the quaternary salt and the polymer matrix has also been examined.

Results

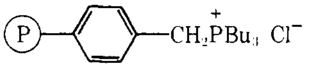
The systems studied were tetraalkylammonium salts **3–6**



3, R = Me (2, 1:1.7, 3.5)
4, R = n-Bu (2, 1:4.6, 1.1; 4.5, 1:7.8, 0.6)



5, R = Me (2, 1:3.3, 1.2)
6, R = n-Bu (2, 1:2.9, 1.1)



7 (2, 1:2.3, 2.0; 4.5, 1:2.1, 2.1; 1, 1:7.0, 1.0)

and tetraalkylphosphonium salts **7–9**, bonded either directly or by long spacer chains to chloromethylated polystyrene (% cross-linking by p-divinylbenzene, frequencies of functionalized monomeric units and mequiv Hal^-/g, respectively, are reported in parentheses).

Condensation of chloromethylated polystyrene with tributylamine and tributylphosphine gave catalysts **4** and **5**, respectively. Catalyst **3** was a commercial product. Long linear chains of 13 or 25 atoms between the cationic center and the benzene ring of polystyrene (catalysts **5**, **6**, **8**, and **9**) were in-

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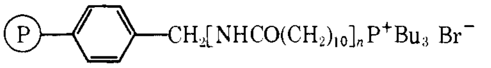
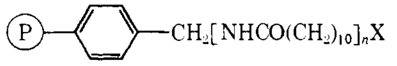
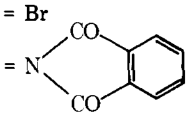


8, n = 1 (2, 1:2.3, 1.4)
9, n = 2 (2, 1:2.3, 1.0)



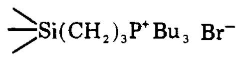
10, n = 1, X = Br
11, n = 2, X = Br
12, n = 1, X =



13, n = 1, X = NH_2

$n\text{-}C_{16}H_{33}P^+Bu_3\ Br^-$ **17**　$n\text{-}C_{16}H_{33}N^+Me_3\ Cl^-$ **18**　$n\text{-}C_{16}H_{33}N^+Bu_3\ Br^-$ **19**

$Bu_4N^+\ Br^-$ **20**



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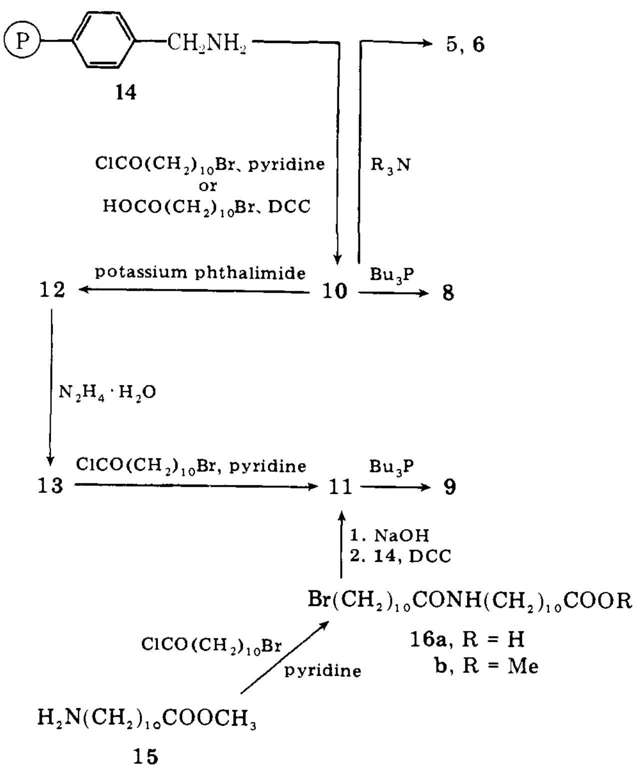
serted as indicated in Scheme I. Some catalysts were also prepared from chloromethylpolystyrene, 4.5% (**4** and **7**) and 1% (**7**) cross-linked by p-divinylbenzene.

Condensation of aminomethylpolystyrene **14** with 11-bromoundecanoyl chloride in pyridine or, alternatively, with 11-bromoundecanoic acid in the presence of dicyclohexylcarbodiimide (DCC) afforded bromo derivative **10**, which when treated with trimethyl- and tributylamine gave ammonium salts **5** and **6**, and, with tributylphosphine, tributylphosphonium salt **8**. Reaction of **10** with potassium phthalimide in dimethylformamide (DMF) followed by hydrazinolysis of phthalimido derivative **12** gave 11-aminoundecanamidomethylpolystyrene **13**. The latter, upon reaction with 11-bromoundecanoyl chloride and then with tributylphosphine, gave catalyst **9**. Alternatively, bromo derivative **11** was prepared by condensing aminomethylpolystyrene **14** with 11-bromoundecanamido-11-undecanoic acid (**16a**) prepared separately from methyl 11-aminoundecanoate (**15**) and 11-bromoundecanoyl chloride.

Scheme I



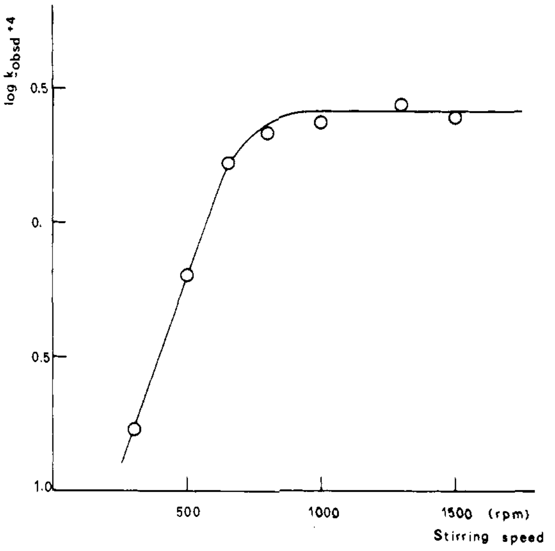


Figure 1. Dependence of the observed pseudo-first-order rate constants (k_{obsd}) on the stirring speed, for Br-I exchange reaction in 1-bromooctane: toluene-water, 90 °C, 0.01 molar equiv of 2% cross-linked catalyst **8**.

Reactions on the resins were almost quantitative at each step, except for condensation of chloromethylpolystyrene with tributylamine and of resin **10** with trimethyl- and tributylamine, which occurred with about 50 and 70-80% yield, respectively. For this reason, the frequency of functionalized monomeric units in **7-9** and **4** was substantially equal to and half of, respectively, the original frequency of chloroalkyl and bromoalkyl groups (generally 1:3).

Frequencies were determined by titration[12] of ionic and/or covalent halogen in compounds **4-11**, and results were confirmed by the observed variations in weight at each step and by elemental analyses.

$$n\text{-}C_8H_{17}Br + X^- \xrightarrow[H_2O]{\text{cat.}} n\text{-}C_8H_{17}X + Br^- \qquad X = I \quad (1)$$

$$X = CN \quad (2)$$

$$X = PhS \quad (3)$$

$$PhCH_2COCH_3 + n\text{-}C_4H_9Br \xrightarrow[\text{50\% aq NaOH}]{\text{cat.}} PhCH(C_4H_9\text{-}n)COCH_3 + Br^- \quad (4)$$

The catalytic activity of polymer-supported catalysts **3-9** was evaluated by reaction 1 (Br-I exchange in n-octyl bromide). The resin was first conditioned for 3-15 h at the required temperature in the presence of the aqueous solution of alkali salt and the organic solvent; substrate was added at zero time. Reaction rates increased upon increasing the stirring speed up to about 800 rpm, and remained constant beyond this value (Figure 1); therefore reactions were carried out by stirring at 1000-1300 rpm. Rates, measured by GLC analysis, were compared with those obtained with similar homogeneous catalysts, **17** and **19**. For all catalysts used, the reactions followed the pseudo-first-order equation

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

up to a conversion of at least 80%. Under the same conditions, but in the presence of nonfunctionalized polystyrene, no appreciable conversion was detected after 20 half-lives. The observed rate constants (k_{obsd}, s^{-1}) for all catalysts used were linearly dependent on the molar equivalents of the polymer-bound quaternary groups. A few examples are reported in

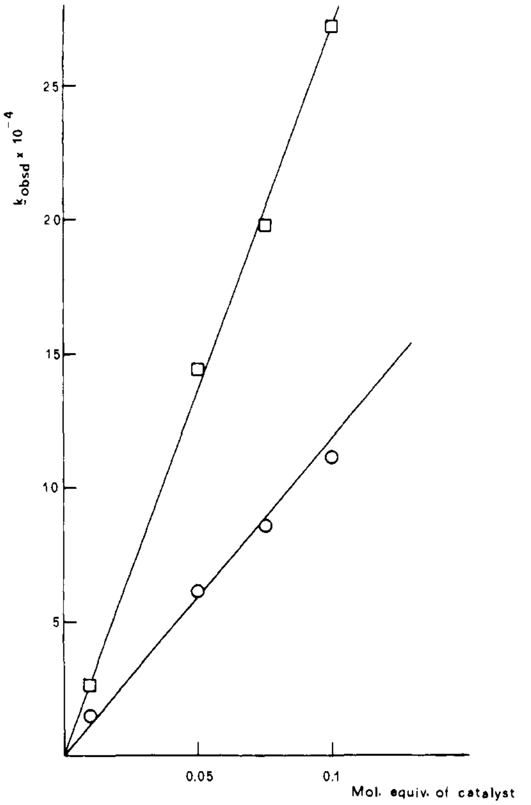


Figure 2. Dependence of the observed pseudo-first-order rate constants (k_{obsd}) on molar equivalents of heterogeneized phosphonium groups, for Br-I exchange reaction in 1-bromooctane: toluene-water, 90 °C, 2% cross-linked catalysts 7 (○) and 8 (□).

Figure 2. The pseudo-first-order rate constants, in the presence of 0.01 molar equiv of catalyst, are shown in Table I.

Reaction rates were also highly dependent on fluidodynamic factors: if optimized turbulence conditions within the stirred mass were not secured, cavitation phenomena could not be avoided, and lower rate constants were observed. Rates were still linearly dependent on the molar equivalents of the immobilized quaternary groups and independent of the stirring speed above 800 rpm. By increasing the size of the stirrer in comparison with the volume of the reaction medium, and/or introducing barriers capable of producing turbulence phenomena within the stirred mass, rates increased significantly from the values reported in Table I (see Discussion and Experimental Section).

For a better evaluation of diffusion phenomena, reactions were also studied under nonoptimized conditions, as a function of the catalyst, the organic solvent (*n*-decane, toluene, *o*-dichlorobenzene), and the temperature. Table II reports the apparent pseudo-first-order rate constants, under nonoptimized conditions, for catalysts 7-9 (0.01 molar equiv) at 90 °C as a function of the organic solvent. The influence of the three parameters under these conditions is best shown in Figure 3.

As an indication of the specific solvation of the catalytic site in quaternary salts bonded to the polymer, the percentage of O- vs. C-alkylation was determined in reaction 6 between alkali phenoxide and benzyl chloride,[13,14] carried out under phase-transfer conditions in the presence of catalysts 7-9. Results were compared with those obtained with soluble phase-transfer catalysts and with quaternary salts supported on silica (Table III).

$$PhO^- + PhCH_2Br \xrightarrow[\text{organic solvent, } H_2O]{\text{cat.}} PhOCH_2Ph + PhCH_2C_6H_4O^- \quad (6)$$

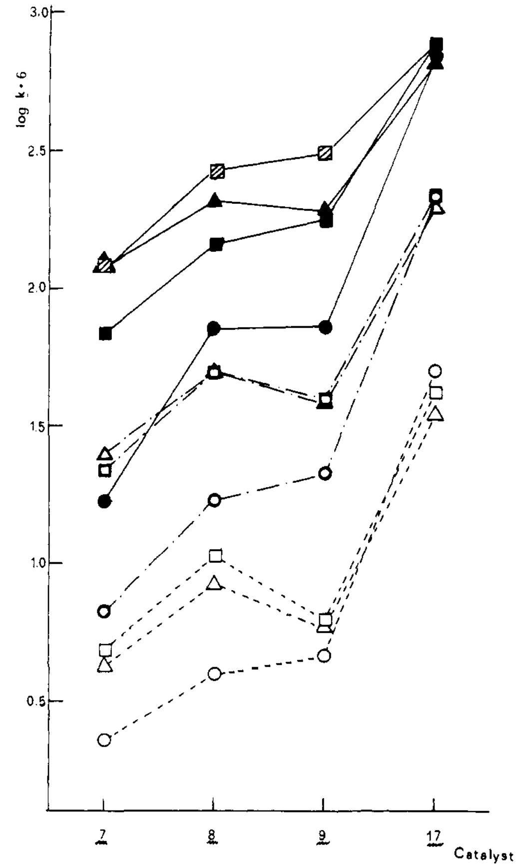


Figure 3. Dependence of the observed pseudo-first-order rate constants (k_{obsd}) on length of the spacer chain, temperature, and organic solvent, for Br-I exchange reaction in 1-bromooctane in the presence of 0.01 molar equiv of catalyst, under nonoptimized conditions. Toluene: ■ (90 °C), □ (70 °C), □ (50 °C), ▨ (90 °C, optimized conditions). *o*-Dichlorobenzene: ▲ (90 °C), △ (70 °C), △ (50 °C). *n*-Decane: ● (90 °C), ○ (70 °C), ○ (50 °C).

To the same end, hydration of anions (Cl^-, Br^-, I^-) bonded to the quaternary cation in resins 7-9 was determined by equilibrating the catalyst at the reaction temperature in the presence of toluene and of an aqueous solution of potassium halide, filtering, and holding the resin at 25 °C until constant weight was obtained (about 3 h). The resin was then suspended in anhydrous methanol, and water was determined by a Karl Fischer titration (Table IV). The degree of swelling of resins 7-9 in the different solvents used for kinetic measurements is reported in Table V.

In addition to the kinetic measurements, catalysts 7 and 8, from 1 and 2% cross-linked polystyrene, respectively, were used in the preparative-scale syntheses of octyl iodide, octyl cyanide, and phenyl octyl sulfide, and for alkylation of benzyl methyl ketone with *n*-butyl bromide (reactions 1-4), as examples of anion-promoted reactions.

Only 0.01 molar equiv of the catalyst was used and, after filtration from the reaction medium, the catalyst could be used directly for another reaction. For a direct evaluation of the reactivity of the polymer-bound catalysts, the syntheses were repeated under the same conditions using the same molar equivalents of hexadecyltributylphosphonium bromide (**17**), instead of 7 or 8 (see Experimental Section).

Discussion

Structure of Polymer-Supported Quaternary Salts. In agreement with the preliminary remarks, results indicate that polymer-anchored quaternary salts must have a structure similar to that of soluble quaternary salts Q^+Y^-, in order to function as efficient phase-transfer catalysts. This is well il-

Table I. Observed Pseudo-First-Order Kinetic Constants (k_{obsd}) for the Reaction of *n*-Octyl Bromide with KI under Phase-Transfer Conditions in the Presence of Polymer-Supported Catalysts[a]

catalyst[b]-$N^+R_3X^-$	% cross-linking	$k_{\mathrm{obsd}} \times 10^6$, s^{-1}	$t^{1/2}$, min	catalyst[b]-$P^+R_3X^-$	% cross-linking	$k_{\mathrm{obsd}} \times 10^6$, s^{-1}	$t^{1/2}$, min
3[c]	2	0.6	19 250				
4	2	157	73	**7**[d]	2	118 (30[e])	97 (390[e])
	4.5	66	175		4.5	30.6	375
					1	340 (122[e])	34 (95[e])
5	2	20.4	565				
6	2	330	35	**8**[f,g]	2	272	44
				9[h]	2	308	37
19		950	12	**17**		783 (11[i])	15 (1050[i])

[a] Toluene, 90 °C; substrate toluene, 1:3 (v/v); 2.5 molar equiv of KI in saturated aqueous solution (see Experimental Section). [b] 0.01 molar equiv; conditioning time 15 h; stirring speed 1300 rpm. [c] For reaction 2 (Br/CN exchange in *n*-octyl bromide) at 90 °C under identical kinetic conditions, $k_{\mathrm{obsd}} = 2.4 \times 10^{-6}\ s^{-1}$; $t^{1/2} = 4800$ min. [d] For the same cation bonded to macroporous polystyrene cross-linked with long chains,[22] $k_{\mathrm{obsd}} = 750 \times 10^{-6}\ s^{-1}$; $t^{1/2} = 15$ min. [e] No stirring; conditioning time 15 h. [f] At 50 °C: $k_{\mathrm{obsd}} = 12.8 \times 10^{-6}\ s^{-1}$; $t^{1/2} = 900$ min. [g] Catalyst, left under stirring in the reaction medium for 24 h (33 half-lives) at 90 °C, then reused after filtration, gave $k_{\mathrm{obsd}} = 263 \times 10^{-6}\ s^{-1}$. [h] At 50 °C: $k_{\mathrm{obsd}} = 17.2 \times 10^{-6}\ s^{-1}$; $t^{1/2} = 675$ min. [i] No stirring.

Table II. Influence of Solvent and Temperature on the Apparent Pseudo-First-Order Kinetic Constants (k_{obsd}) Measured under Nonoptimized Conditions for the Reaction of *n*-Octyl Bromide with KI at 90 °C[a]

	n-decane			toluene			*o*-dichlorobenzene		
catalyst[b]	$k_{\mathrm{obsd}} \times 10^6$, s^{-1}	E_a,[c] kcal/mol	$\Delta S^{\ddagger}$,[c,d] eu	$k_{\mathrm{obsd}} \times 10^6$, s^{-1}	E_a,[c] kcal/mol	$\Delta S^{\ddagger}$,[c,d] eu	$k_{\mathrm{obsd}} \times 10^6$, s^{-1}	E_a,[c] kcal/mol	$\Delta S^{\ddagger}$,[c,d] eu
7	17.1	11.7 ± 0.2	−50.3 ± 0.5	69.5	15.6 ± 0.6	−36.7 ± 1.7	120.9	19.4 ± 0.1	−25.3 ± 0.2
8	70.4	16.6 ± 0.4	−34.1 ± 1.2	145.0	14.8 ± 1.2	−37.3 ± 3.4	211.1	18.9 ± 0.5	−25.3 ± 1.6
9	72.9	16.1 ± 0.4	−35.3 ± 1.4	179.6	19.6 ± 0.5	−23.6 ± 1.6	194.5	20.4 ± 0.2	−21.5 ± 0.6
17	679.9	15.4 ± 0.5	−32.8 ± 1.5	783.0	17.4 ± 0.7	−26.8 ± 2.1	669.0	17.3 ± 0.7	−27.3 ± 3.0

[a] Substrate: solvent = 1:3 (v/v); 2.5 molar equiv of KI in saturated aqueous solution (see Experimental Section). [b] 0.01 molar equiv; conditioning time 3 h; stirring speed 1000 rpm. [c] From measurements at 50, 70, and 90 °C. [d] At 70 °C.

lustrated by tributylammonium resins **4** and **6** from 2% cross-linked polystyrene (Table I), which are 250 and 15 times, respectively, more reactive than the corresponding trimethylammonium resins **3** and **5**, owing to the interionic distance imposed by butyl chains (reaction 1, toluene-water at 90 °C). Their behavior parallels that of homogeneous catalysts. Indeed, although soluble alkyltrimethylammonium salts (e.g., **18**) cannot be used as phase-transfer catalysts since they promote formation of stable aqueous emulsions,[10,15] they are approximately five times less reactive in anhydrous homogeneous media than alkyltributylammonium salts (e.g., **19**).[10]

Tributylammonium resins **4** and **6** are slightly more reactive (1.2–1.3 times) than the corresponding tributylphosphonium resins **7** and **8**, as are soluble tetraalkylammonium catalysts compared to the corresponding phosphonium derivatives.[10]

There are indications in several recent reports that the longer the spacer chain the easier would be the contact between the immobilized quaternary salt and the reaction medium. It was shown by Brown[4] that insertion of an 11-atom instead of a 5-atom linear alkyl chain between the trimethylammonium and carboxylate groups in immobilized catalysts **2** appreciably increases the catalytic activity. Improvement in the Merrifield synthesis of polypeptides was observed[16] by placing a chain of about 30 atoms between the polystyrene support and the point of attachment of the first amino acid. Similar favorable effects were seen[17] in the aminolysis of peptides with sterically hindered C-terminal amino acids by introducing a six-carbon-atom anchoring chain.

The influence of the length of the spacer chain on the reactivity of polymer-supported quaternary salts is illustrated by comparisons within the pairs of ammonium resins **3, 5** and **4, 6** and within the series of phosphonium resins **7–9.** In the three groups of resins, reactivity is more than doubled by introducing a 12-atom linear spacer chain (resins **6** and **8**). Insertion of a second 12-atom chain (resin **9**) leads to another small reactivity increase. The resulting reaction rates approach those with analogous soluble quaternary salts, such as **17** or **19.**

Table III. C-/O-Alkylation in the Reaction of Sodium Phenoxide with Benzyl Bromide under Phase-Transfer Conditions

catalyst	O-alkylation % (in CH_2Cl_2-H_2O)[a]	catalyst	O-alkylation % (in CH_2Cl_2-H_2O)[a]
7	95.2	**17**	100
8	97.0	**20**	100[b]
9	98.4	**21**	73.7[c]

[a] By ^1H NMR spectroscopy in $CDCl_3$; values after 3 h at 25 °C, corrected for C-dialkylation, not for small amounts of O,C-dialkylation products; average of two runs. [b] After 20 h at 27 °C; from ref 14. [c] P. Tundo and P. Venturello, submitted for publication.

Table IV. Hydration State *n* of Halides Bonded to Soluble and Polymer-Supported Quaternary Salts in Toluene-Water Two-Phase System

	hydration state *n*[a]		
catalyst	Cl^-	Br^-	I^-
7	3.5 ± 0.4	2.0 ± 0.2	1.5 ± 0.3
8	3.0 ± 0.4	2.1 ± 0.2	1.1 ± 0.1
9	3.8 ± 0.4	2.0 ± 0.2	1.4 ± 0.3
17[b]	3.4 ± 0.2	2.1 ± 0.2	1.0 ± 0.15

[a] Average from at least three determinations. [b] Values from ref 10a.

Table V. Swelling of Polymer-Supported Catalysts[a,b]

catalyst	water	*o*-dichlorobenzene	toluene	*n*-decane
7	1.5	4.3	1.4	0.7
8	1.2	2.0	0.8	0.5
9	1.4	2.5	1.1	0.8

[a] Solvent: resin (w/w), at 90° C. Estimated accuracy[32] within ±10%. [b] Substantially identical results at 20 and 50 °C, respectively.

Swelling of the Resin and Diffusive Factors. The polymer-supported catalyst requires a preliminary conditioning time, during which the resin is swelled by absorption of solvent to allow better accessibility of substrate and reagents to the catalytic site. Swelling depends on the organic phase, increasing with its polarity, and on the catalyst: in relatively polar or polarizable solvents, it is the greatest for quaternary groups directly bonded to the polystyrene matrix (Table V). In this case, the time required for best conditioning is also quite long (up to 10-15 h for reaction 1 in toluene at 90 °C) and gradually decreases (to 3-6 h) on lengthening the spacer chain.

In the presence of the conditioned catalyst, with all other parameters equal, reaction rates increase upon increasing the stirring speed up to about 800 rpm, and then remain constant beyond this value. This behavior may be compared with that observed in aqueous-organic two-phase systems in the presence of soluble phase-transfer catalysts, where a progressive increase of reaction rates is observed up to about 250-300 rpm, while rates remain constant thereafter.[10,15,18]

Unfortunately, in the case of polymer-supported catalysts, the plateau above 800 rpm does not mean that reaction conditions have been optimized, since dependence of the observed rates on the stirring speed is quite similar for both turbulent (Figure 1) and standard stirring conditions. In the latter case cavitation phenomena may occur, leading to a stationary state of diffusion within the three phases: well-known phenomena in the field of heterogeneous reactions.[19]

The data reported in Table I correspond to our optimal conditions, and probably represent the highest rates obtainable. The difficulties in realizing ideal stirring conditions in the presence of immobilized phase-transfer catalysts, i.e., a violent whirling motion (see below), are seen in their application in syntheses on a preparative scale. For example, in the case of 2% cross-linked resin **8**, a tenfold increase of the reaction volume gives much lower rates than those obtained under the best kinetic conditions.

Therefore the importance of diffusion, most likely internal diffusion,[20,21] requires further efforts to obtain catalysts anchored to macroporous polymers in which this phenomenon is likely minimized. Measurements carried out by one of us with phase-transfer catalysts anchored to specifically synthesized macroporous polystyrene cross-linked with long chains, seem to fully support this view.[22] Also, catalysts bonded to 1% cross-linked polystyrene (Table I) are much less susceptible to these problems of initial conditioning and stirring efficiency.[23]

In this connection, it must be mentioned that increasing the cross-linking from 2 to 4.5% cuts catalytic activity approximately in half.[24] Reactions proceed even in the absence of stirring, although at lower rates. This phenomenon, very limited in the case of classical phase-transfer catalysis,[10] depends on the nature of the immobilized catalyst[23] and the percent of cross-linking (Table I).

Table II reports the rate constants observed under nonoptimized standard conditions for immobilized tributylalkylphosphonium salts **7**-**9** as a function of the spacer chain and the organic solvent. Under standard stirring conditions (see above and Experimental Section) with a 3-h conditioning time, the observed rate constants for each catalyst in toluene-water at 90 °C are about one-half of those measured (Table I) under the optimized turbulence conditions. This occurs despite a stirring speed of 1000 rpm, i.e., in the range in which reaction rates are independent of stirring speed. Very good Arrhenius relationships are obtained in the 50, 70, 90 °C range in the different solvents used.

Figure 3 strikingly shows that, under nonoptimized standard conditions, the effect of diffusion phenomena differs for each catalyst, depending on the chain length, the organic solvent, and the temperature. For example, lowering the reaction temperature progressively decreases the reactivity of catalyst **9** as compared with that of catalyst **8**, and this trend is more pronounced for more polar and/or polarizable solvents. The leveling of activation parameters, observed in *o*-dichlorobenzene for resins **7**-**9**, means that swelling is sufficient in all cases, allowing a relatively easy approach of reagents to the catalytic site even in the least favored resin **7**. On the other hand, the very low apparent activation energy and the exceptionally high, negative apparent activation entropy observed for the latter resin in *n*-decane are probably connected to a poorly solvated and very rigid transition state. An intermediate situation is found in toluene. Swelling values in the various solvents (Table V) are reasonably consistent with these views.

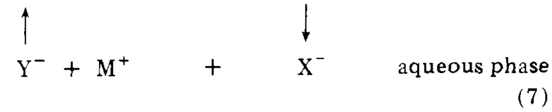
Reaction Mechanism. As shown in Figure 3, reaction rates depend on the amount of anions bonded to the resin, rather than the amount of anions dissolved in the aqueous phase.

This behavior is strictly similar to that observed with soluble quaternary salts:[10,15] under phase-transfer conditions, reactions occur in the organic phase following second-order kinetics (first order in substrate and first order in quaternary salt). It therefore seems implicit that also in the case of polymer-supported quaternary salts reaction between substrate and anion bonded to quaternary cation occurs within an organic solvation shell surrounding the catalytic site, rather than in an aqueous solvation shell or in both. Two independent experiments support this view.

As shown long ago by Kornblum,[13] phenolic systems give high proportions of C-alkylation in polar, protic solvents that strongly solvate the anionic oxygen, whereas in dipolar aprotic solvents the absence of oxygen solvation favors O-alkylation. Accordingly, alkylation of phenol with benzyl bromide (reaction 6) gives phenyl benzyl ether only when it is carried out in methylene chloride-water in the presence of tetraalkylammonium[14] or phosphonium salts. Polymer-supported catalysts give similar results (Table III), implying that under these conditions anionic oxygen is not solvated by water but by the less polar methylene chloride. Comparable results have been found[4] in the alkylation of β-naphthol with resins **2**. The small amounts of C-alkylation (1.8% for resin **9** up to 4.8% for resin **7**) are probably connected to local concentrations of supported polar quaternary groups inside resins. These are confined to the much reduced volume of the solvent-swollen polymer beads, whereas in the homogeneous systems the catalyst molecules can move throughout the whole solution. One may notice that quaternary phosphonium salts bonded to a polar silica support, where surface absorption is important and hydration extensively occurs,[26] give high proportions of C-alkylation of phenol under the same reaction conditions.

Anions of lipophilic quaternary salts dissolved in nonpolar organic media in the presence of an immiscible aqueous solution of the corresponding mineral salt are associated with a limited number of water molecules.[10] This number depends on the anion but is independent of the cation, since very similar values were found for quaternary salts[10] and complexed lipophilic crown ethers[27] and cryptands.[11] As shown in Table IV, the same hydration numbers are found for the three halides bonded to the immobilized salts (**7**-**9**) equilibrated with aqueous and organic phases under the reaction conditions. This implies that the organic phase firmly surrounds polymer-bound quaternary salts.

On the basis of these data, the mechanism of reactions in aqueous-organic media in the presence of polymer-supported quaternary salts may be represented as follows (eq 7).



$$\begin{array}{ccccl} \textcircled{P}\!\sim\!Q^+Y^- + RX & \longrightarrow & \textcircled{P}\!\sim\!Q^+X^- + RY & & \text{organic phase} \\ \uparrow & & \downarrow & & \\ Y^- + M^+ & + & X^- & & \text{aqueous phase} \end{array} \qquad (7)$$

Mechanism 7 is analogous to that shown[10,15] for classical phase-transfer catalysis. As discussed above, reaction should occur in the organic shell surrounding the catalytic site. Anions exchange at the water–organic solvent interface, with the inorganic cation M^+ and the polymer-supported quaternary cation Ⓟ〰Q^+ as counterions in the aqueous and the organic phase.

Applications to Organic Synthesis. Owing to the limits imposed by stirring efficiency, the catalysts described here do not realize yet the ideal situation of a polymer-bound system whose catalytic activity is identical, under a wide range of conditions, with that of comparable soluble catalysts. However, by choosing suitable reaction conditions it is possible to approach the reactivities of efficient soluble catalysts; an example is given by 1% cross-linked catalyst **7**. Catalysts bonded to 2% cross-linked polystyrene (e.g., **8**), in which diffusive factors are more relevant, require longer reaction times.

Conclusions drawn from kinetic measurements in the Br–I exchange reaction can be extended to a wide series (1–4) of anion-promoted reactions. On a preparative scale, very simple reaction conditions are effectively achieved: small amounts of polymer-supported catalyst (0.01 molar equiv) are added to the mutually immiscible aqueous and organic phases, with efficient stirring until the end of the reaction. Then, filtration of the catalyst, separation of the aqueous phase and, if present, evaporation of the solvent allow direct isolation of the product, often very pure.

Continuous recycling of the catalyst is of particular interest if sophisticated systems, such as cryptates or chiral catalysts, are used. The possibility of using immobilized phase-transfer catalysts in a continuous process in fixed-bed reactors[25] makes them very attractive from the industrial point of view.

Work in progress with highly porous polymeric supports indicates that difficulties associated with diffusive and fluidodynamic factors can be greatly reduced. In this way, it will be possible to investigate other aspects that cannot be studied with the present catalysts, such as the influence of frequency of functionalization of the polystyrene chains and the related saturation[3b] and local concentration phenomena.[28]

Experimental Section

o-Dichlorobenzene, toluene, and decane were Analar grade chemical solvents, used without further purification in the kinetic measurements. Chloromethylpolystyrene cross-linked with 1% divinylbenzene (Bio-Beads S-X1, 1.29 mequiv Cl/g) and trimethylammonium resin **3** (2% divinylbenzene, AG 1-X2) were purchased from Bio-Rad Laboratories. Chloromethylpolystyrenes cross-linked with 2% divinylbenzene (Merrifield Polymer, 3.5 mequiv Cl/g) and with 4.5% divinylbenzene (3.7 mequiv Cl/g) were from Fluka AG and from Euteco Research Laboratories, respectively.

Methyl 11-Bromoundecanamido-11-undecanoate (16b). A solution of 1.59 g (7.4 mmol) of methyl 11-aminoundecanoate (**15**),[29] 2.1 g (7.4 mmol) of 11-bromoundecanoyl chloride,[30] and 0.88 g (11.2 mmol) of anhydrous pyridine in 70 mL of anhydrous benzene was stirred for 12 h at room temperature. The mixture was washed with 10% aqueous sulfuric acid, aqueous sodium carbonate, and water, dried, and evaporated to dryness to afford 3.0 g (88%) of **16b**, mp 74–75 °C from cyclohexane. Anal. Calcd for $C_{23}H_{44}BrNO_3$: C, 59.73; H, 9.59; N, 3.03. Found: C, 59.75; H, 9.60; N, 3.05.

11-Bromoundecanamido-11-undecanoic Acid (16a). A solution of 6 g of ester **16b** and 3 g of potassium hydroxide in 100 mL of ethanol was stirred for 12 h at room temperature. The insoluble potassium salt of acid **16a** was filtered and poured into 10% aqueous hydrochloric acid to afford 4.5 g (77%) of acid **16a**, mp 85–88 °C. Crystallization from methanol gave mp 87–89 °C. Anal. Calcd for $C_{22}H_{42}BrNO_3$: C, 58.92; H, 9.44; N, 3.12. Found: C, 59.00; H, 9.60; N, 3.38.

Aminomethylpolystyrene (14). It was prepared by modifying a recently described procedure.[16] A mixture of 10 g of chloromethylpolystyrene (3.5 mequiv Cl/g) and 16.5 g (2.5 molar equiv) of potassium phthalimide in 80 mL of anhydrous dimethylformamide (DMF) was stirred for 5 h at 100 °C. The resin was filtered, washed with water and 95% ethanol, and then added directly to a solution of 25 mL of hydrazine hydrate in 100 mL of 95% ethanol. The mixture was refluxed for 6 h, filtered from the hot ethanol, and washed successively with ethanol, water, ethanol, and three times, alternately, with methylene chloride and ethyl ether. After drying under vacuum, 8.85 g (95%) of resin **14** was obtained. An active chloride titration[12] indicated 100% amination. The IR phthalimide bands at 1710 and 1775 cm^{-1} were absent.

11-Bromoundecanamidomethylpolystyrene (10). Method A. 11-Bromoundecanoyl chloride (15.0 g, 2 molar equiv) was added to a suspension of 7.0 g of resin **14** (26.3 mequiv of NH_2) and 10.6 mL (5 molar equiv) of anhydrous pyridine in 50 mL of anhydrous benzene and the mixture was stirred for 5 h at room temperature. Filtration and washings with methanol, ethyl ether, ethanol, water, ethanol, and three times, alternately, with methylene chloride and ethanol afforded 12.4 g (92%) of isolated resin **10**, with a titer of 1.88 mequiv Br/g (96.5% conversion).

Method B. A mixture of 7.0 g of resin **14**, 19.6 g (3 molar equiv) of 11-bromoundecanoic acid, and 15.4 g (3 molar equiv) of dicyclohexylcarbodiimide (DCC) in 200 mL of anhydrous methylene chloride was stirred for 12 h at room temperature. Filtration and successive washings with hot DMF, 10% ethanol-methylene chloride, methylene chloride, *tert*-butyl alcohol, and methylene chloride afforded 11.2 g (90%) of isolated resin **10**, with a titer of 1.88 mequiv Br/g (96.5% conversion). Anal. Calcd for resin **10**:[31] C, 70.72; H, 7.84; N, 2.73. Found: C, 70.85; H, 7.99; N, 2.86.

11-Bromoundecanamido-11-undecanamidomethylpolystyrene (11). Method A. A mixture of 6.0 g of resin **10** and 21 g (10 molar equiv) of potassium phthalimide in 45 mL of anhydrous DMF was stirred for 5 h at 100 °C. Following the same procedure described for resin **14**, the phthalimidic resin **12** was added to a solution of 15 mL of hydrazine hydrate in 60 mL of ethanol and refluxed for 6 h to afford 4.75 g (90%) of isolated resin **13**. Active bromide determination[12] indicated 100% conversion (2.14 mequiv NH_2/g). Resin **13** (4.0 g), 6.0 g (2.5 molar equiv) of 11-bromoundecanoyl chloride, and 4 mL of anhydrous pyridine in 30 mL of anhydrous benzene, after 5 h stirring at room temperature, afforded 5.9 g (97%) of resin **11** with 1.4 mequiv Br/g (100% conversion). Anal. Calcd for resin **11**: C, 71.08; H, 8.80; N, 4.02. Found: C, 71.30; H, 8.61; N, 3.80.

Method B. A mixture of 1.0 g of resin **14**, 4.9 g (3 molar equiv) of acid **16a**, and 2.3 g (3 molar equiv) of DCC in 70 mL of anhydrous methylene chloride and 50 mL of anhydrous tetrahydrofuran was stirred for 12 h at room temperature. Following the same procedure described for resin **10** (method B), 2 g (80%) of resin **11** was isolated, with a titer of 1.28 mequiv Br/g (90% conversion).

Quaternizations of Tributylamine with Chloromethylpolystyrene and Resin 10 to Resins 4 and 6. A mixture of 6.0 g of chloromethylpolystyrene (3.5 mequiv Cl/g) and 12 g of tributylamine was deaerated under vacuum and heated at 65 °C for 5 days. The resin was filtered and successively washed with water, 1 N hydrochloric acid, water, ethanol, water, ethanol, methylene chloride, ethanol, methylene chloride, and methanol. After drying under vacuum at 60 °C for 3 h, 8.0 g of resin **4** was obtained; active chloride determination[12] indicated 1.07 mequiv Cl$^-$/g (50% quaternization). Chloromethylpolystyrene with 3.7 mequiv Cl/g and 4.5% of cross-linking with *p*-divinylbenzene afforded a resin **4** containing 0.59 mequiv Cl$^-$/g (27% quaternization).

Under the same reaction conditions, resin **10** afforded tributylammonium resin **6**, with a titer of 1.14 mequiv Br$^-$/g (79.5% conversion).

Quaternization of Trimethylamine with Resin 10 to Resin 5. A suspension of resin **10** (1.0 g) in 10 mL of 33% aqueous trimethylamine and 10 mL of acetonitrile was refluxed for 2.5 h; 5 mL of aqueous trimethylamine was added and heating was continued for a further 2.5 h. One gram of resin **5** was isolated, with a titer of 1.20 mequiv Br$^-$/g (69% conversion).

Quaternization of Tributylphosphine with Chloromethylpolystyrene and with Resins 10 and 11 to Resins 7–9. Method A. Chloromethylpolystyrene (3.5 mequiv Cl/g, 1.2 g, 4.2 mmol of chlorine), tributylphosphine (1.69 g, 8.4 mmol), and 30 mL of anhydrous DMF were stirred at 110 °C (external bath) for 4 days. Resin **7** (X = Cl) was filtered, washed with ethanol, water, ethanol, and then three times alternately with methylene chloride and ethyl ether, and dried under vacuum at 60 °C for 3 h. It had a titer of 2.0 mequiv Cl$^-$/g (98% quaternization).

Method B. A flask containing a mixture of chloromethylpolystyrene or resins **10** and **11** and 5 molar equiv of tributylphosphine was deaerated under vacuum, to facilitate penetration of tributylphosphine into the resin, and kept at 65 °C for 7 days (110 °C and 4 days in the case of resin **7**). Resins **7–9** were washed and dried as described in method A, and halide-ion analysis indicated 90–100% quaternization. Anal. Calcd for resin **7** (X = Cl): C, 76.92; H, 9.55. Found: C, 77.05; H, 9.50. Calcd for resin **8** (X = Br): C, 70.88; H, 9.40; N, 1.96. Found: C, 70.66; H, 9.00; N, 1.80. Calcd for resin **9** (X = Br): C, 71.13; H, 9.83; N, 3.12. Found: C, 71.18; H, 9.49; N, 2.98.

Kinetic Measurements. Kinetics under PTC conditions were run in a 4-mL flask, thermostated at the appropriate temperature with circulating butyl phthalate, and a magnetic stirrer. The temperature was controlled within ±0.02 °C by a Colora K-5 ultrathermostat. The stirring speed (±50 rpm) was controlled using a strobe light.

As an example of the procedure generally followed (nonoptimized standard conditions), the flask was charged with 830 mg (5 mmol) of potassium iodide, 0.65 mL of water, 1.04 mL of toluene, and 15 mg (0.02 mequiv) of resin **8**. The mixture was stirred (1000 rpm, 1.2 cm long magnetic bar) at the reaction temperature for 3 h in order to condition the catalyst. Under optimized conditions, a special flask having vertical creases and a 2.0 cm long magnetic bar (i.e., of size comparable with that of the flask bottom) were used, in order to produce a turbulence within the stirred mass; the conditioning time was extended to 15 h.

n-Octyl bromide (386 mg, 2 mmol) was added at zero time. The reaction was followed by GLC analysis (SE-30, 3% over Chromosorb at 120 °C), and results were corrected by calibration with standard mixtures. The pseudo-first-order rate constants (k_{obsd}) were obtained by plotting log [substrate] vs. time and determining the slope of the straight lines. Activation parameters and root mean square deviations were obtained from measurements at 50, 70, and 90 ± 0.1 °C, and values were computer generated (CII 100800) by the least-squares method.

Hydration State of Halides Bonded to Immobilized Quaternary Cations. Catalyst **8** (X = Br), with a titer of 1.35 mequiv Br^-/g (0.148 g, 0.2 mequiv), was suspended in 2.1 mL of toluene and a solution of 1.66 g (10 mmol) of potassium iodide in 1.3 mL of water, and the mixture was stirred for 3 h at 90 °C. The aqueous phase was separated, substituted by a new aqueous solution of potassium iodide (same amounts), and stirred again for 3 h at 90 °C. The resin was filtered under vacuum, washed with water, and left at room temperature until constant weight. A portion was suspended in anhydrous methanol, and the amount of water was measured by Karl Fischer titration. Another portion was suspended in methanol and iodide ion was titrated potentiometrically (>98% exchanged) with a Metrohm Potentiograph Type E 576 using silver and calomel electrodes, the latter isolated with potassium sulfate bridge. The ratio mmol H_2O/mmol I^- was 1.1 ± 0.1. Hydration states of chloride and bromide ions bonded to the same catalyst **8** (X = Cl, Br) were determined in the same way. In order to be sure that the results do not depend on the workup, specimens of the resin were filtered, not washed with water, and held at room temperature till constant weight. Substantially identical values for the hydration state were found, while noticeable amounts of potassium halides were retained by the resin. Ancillary experiments established that a negligible amount of water is retained by the inorganic salt as such under these conditions. The values for resins **7–9** (X = Cl, Br, I) are reported in Table IV.

Reactions of Sodium Phenoxide with Benzyl Bromide. A mixture of 0.34 g (2.0 mmol) of benzyl bromide, 0.80 mL of a 3 M aqueous solution of sodium phenoxide (2.4 mmol), 1 mL of methylene chloride, and 5 molar equiv of the catalyst was magnetically stirred for 3 h at 25 °C. After acidification with aqueous sulfuric acid, resin was filtered and the solution extracted with ethyl ether. Solvent was evaporated in vacuo and products were analyzed by ^1H NMR spectroscopy in $CDCl_3$ [δ 4.95 ($PhCH_2OPh$), 4.40 ($PhCH_2Br$), 4.05–3.80 [$HOC_6H_4CH_2Ph$. $HOC_6H_3(CH_2Ph)_2$] and their O-alkylation products. The results are reported in Table III.

Swelling of Resins. A known weight (about 1 g) of dry resin was suspended in 5 mL of solvent, kept for 12 h at 20 °C, and then filtered in a preweighed sintered glass crucible, following the established procedure.[32] Measurements were also carried out holding the resins for 3 h at 50 and 90 °C, respectively, i.e., under conditions similar to those used for kinetics, then filtering through a preheated glass crucible. Results were substantially identical with those obtained at 20 °C. The results at 90 °C are reported in Table V.

Use of Resins 3–9 as Phase-Transfer Catalysts in Organic Syntheses. The following syntheses are reported as examples of general procedures, using 50 mmol of substrate and 0.5 mequiv of catalysts **7** and **8** (*n* = 6.0 and 1.28, respectively (see ref 31); 1% and 2% cross-linking, respectively). For the sake of comparison with classical phase-transfer catalysis, the syntheses were repeated under the same conditions using 0.5 mmol (0.25 g) of $C_{16}H_{33}P^+Bu_3Br$ (**17**) as soluble phase-transfer catalyst. Catalysts **7** and **8** (0.49 and 0.40 g, respectively) were first conditioned by stirring for 15 h at 90 °C in a mixture of toluene (1.5 mL) and water (4.0 mL) and then added to the reagents. At the end of the reaction, the filtered catalysts **7** and **8** could be reused immediately with no further treatment.

1-Iodooctane. A mixture of 9.65 g (50 mmol) of 1-bromooctane in 26 mL of toluene, 20.7 g (125 mmol) of potassium iodide in 16 mL of water, and 0.49 g of conditioned catalyst **7** was stirred at 90 °C for 3.5 h, giving 95% conversion to 1-iodooctane (GLC analysis, SE-30, 3% over Chromosorb at 120 °C). By continuing the reaction for a further 0.5 h, GLC analysis indicated a practically quantitative conversion. Indeed, filtration from the catalyst, separation of the aqueous phase, washing with water, and fractional distillation of solvent afforded 11.4 g (95%) of 1-iodooctane (≥99% pure). It had bp 106–107 °C (19 Torr), n^{20}_D 1.4886 (lit.[33] bp 86.5 °C (5 Torr), n^{20}_D 1.4889). Reusing of catalyst **7** in a further preparative run, after filtration from the reaction medium, afforded identical results. Repeating the reaction with the same amounts of reagents in the presence of **8**, a 70% conversion was obtained after 24 h at 90 °C. In the presence of the soluble catalyst **17**, a 98% conversion was obtained after 1.5 h under the same reaction conditions.

1-Octanonitrile. A mixture of 9.65 g of 1-bromooctane in 26 mL of toluene, 8.1 g (125 mmol) of potassium cyanide in 16 mL of water, and 0.49 g of conditioned catalyst **7**, stirred at 90 °C, afforded 95 and 100% yields of 1-octanonitrile after 1.5 and 2 h, respectively (GLC analysis, FFAP, 5% over Varaport at 130 °C). 1-Octanonitrile (6.33 g, 91% yield) had bp 107–108 °C (18 Torr) (lit.[34] bp 98.4–98.6 °C (10 Torr), n^{20}_D 1.4285 (lit.[35] 1.42522). Use of **8** under the same conditions but in the absence of toluene afforded 86 and 100% yields after 7 and 9 h at 90 °C, respectively. In the presence of soluble catalyst **17**, a 100% yield was obtained after 1 h at 90 °C.

1-Octyl Phenyl Sulfide. A mixture of 9.65 g of 1-bromooctane, 25 mL of a 3 M aqueous solution of potassium thiophenate (75 mmol), 26 mL of toluene, and 0.49 g of conditioned catalyst **7** was stirred at 25 °C, giving 90 and 100% conversions to octyl phenyl sulfide after 60 and 80 min, respectively (GLC analysis, SE-30 over Chromosorb at 170–240 °C). The product (22 g, 97% yield) had bp 116–117 °C (0.3 Torr), n^{20}_D 1.5302 (lit.[36] bp 168–170 °C (16 Torr), n^{20}_D 1.5174). Catalyst **8** under the same reaction conditions afforded a 97% yield after 1.5 h, whereas, with the soluble catalyst **17**, a 100% yield was obtained after 20 min at 25 °C or[37] after 10 min at 40 °C in the presence of 1.65 mmol of **17**. Reusing of catalyst **8** afforded identical results in two further preparative runs.

3-Phenyl-2-heptanone. A mixture of 6.70 g (50 mmol) of benzyl methyl ketone, 8.56 g (62.5 mmol) of 1-bromobutane, 50 mL of 50% aqueous sodium hydroxide, and 0.49 g of conditioned catalyst **7** was stirred at 20 °C, giving 40 and 68% conversions after 10 and 15 h, respectively (GLC analysis, SE-30, 3% over Chromosorb at 110 °C). Use of catalyst **8** afforded 75 and 100% yields after 12 and 30 h, respectively. At the end of the reaction water and diethyl ether were added, the resin was filtered, and the organic phase was distilled. 3-Phenyl-2-heptanone (9.0 g, 94.7% yield) had bp 136–137 °C (18 Torr), n^{20}_D 1.4999 (lit.[38] bp 92–94 °C (1.8 Torr), n^{25}_D 1.4997). The soluble catalyst **17** and tributylphosphonium catalyst immobilized on macroporous polystyrene cross-linked with long chains[22] gave 95% conversion after 2 h and 98% conversion[22] after 2.5 h at 20 °C, respectively.

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Stereoelectronic Control in the Electrochemical and Mercury-Promoted Reductive Acetoxylation of α,α'-Dibromobicycloalkanones

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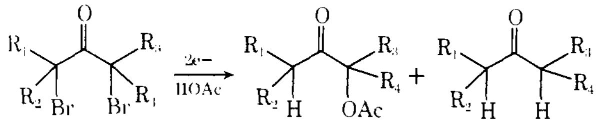
Abstract: Reductions in acetic acid of the stereochemically well-defined α,α'-dibromo ketones *cis*-2,6-dibromo-3,3,5,5-tetramethylcyclohexanone, *cis*-2,6-dibromo-4-*tert*-butylcyclohexanone, 2,4-dibromobicyclo[3.2.1]octan-3-one (and its 2,4-dimethyl derivative), and dibromoisopinocamphone were carried out both electrochemically and by finely dispersed mercury. The results are consistent with a previously proposed mechanism for such reactions involving as its key step the ionization of an enol allylic bromide to a 2-hydroxyallyl cation.

We have previously reported[2] that electrochemical reduction of α,α'-dibromo ketones (**1**) in acetic acid affords α-acetoxy ketones (**2**) in good yield when at least three of the alkyl groups flanking the carbonyl group are alkyl, and that otherwise the principal products are the so-called "parent" ketones (**3**) (eq 1). More recently, we found that dibromo ketones **1** are also converted to **2** and **3** by ultrasonically dispersed mercury in acetic acid.[3] The mercury reaction appears to be mechanistically similar to the electrochemical process, in that increasing α-alkyl substitution favors formation of **2** over **3**, but there are differences between the two processes: (a) for a given dibromo ketone, the ratio of **2** to **3** is generally higher in the mercury reaction; (b) total yields are lower in the mercury reaction; (c) with unsymmetrical dibromo ketones the ratio of isomeric α-acetoxy ketones is generally somewhat different between the two processes.[3-5] We have outlined our reasons for believing the reductive substitution process embodied in the conversion **1** → **2** to be of synthetic utility.[2,3,5]



(1)

1 **2** **3**

Our attention has recently turned to consideration of the mechanism of formation of **2** from **1**. We had originally suggested[2] that electron transfer to **1** results in formation of enolate **4**, which is immediately protonated to enol allylic bromide