spectively, as determined by EPR spectroscopy (vide supra). The sample was immediately immersed in liquid nitrogen, freeze–pump–thaw degassed as described through five cycles and sealed at 2 × 10^{-5} torr. The sample was heated at 72 ± 1 °C for 3 h. During this time 17% disproportionation of starting materials occurred. After the 3 h, five successive ^{1}H NMR spectra at expanded sweep width were recorded. The relative amounts of reduction products were determined by comparison of the area for the methylene protons with the area for the methine protons. The areas of the ^{1}H NMR absorptions were measured by cutting out the expanded peaks and weighing. The k_H/k_D from the five spectra, uncorrected for the difference between the radical ratio and 50:50, was 1.03 ± 0.09.

EPR Measurement of the Ratio of *N*-Deuterio-3,5,5-trimethyl-2-morpholinon-3-yl (1a) to 3,5,5-Trimethyl-2-morpholinon-3-yl (1) in the Deuterium Kinetic Isotope Experiment. An identical sample with the one described above was analyzed by EPR spectroscopy to determine the relative concentrations of 1 and 1a. The radical ratio was measured by double integration of a region of the EPR spectrum of the mixture in which the absorptions of 1 and 1a were distinct and equally intense. The double integration was accomplished by cutting out and weighing the appropriate peaks. The EPR measurement at 72 °C prior to reaction gave a ratio of **1a** to **1** of 49.8 ± 0.4:50.2 ± 0.4. After 17% disproportionation, another EPR measurement was made at 72 °C, and the ratio of **1a** to 1 was 53.3 ± 2.0:46.7 ± 2.0. Although the ratio at termination was close to the initial ratio, the change introduced a small error in the k_H/k_D measurement. The k_H/k_D for the disproportionation calculated as 1.03 × (51.5/48.5) = 1.10 ± 0.09, where 51.5/48.5 was the average radical ratio.

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Catalysis Mechanism of Phosphonium Salts Supported on Silica Gel in Organic–Aqueous Two-Phase Systems

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Abstract: The mechanism of phase-transfer catalysis by phosphonium salts supported on silica gel in organic-aqueous two-phase systems has been studied in the kinetically convenient reaction *n*-BuBr → *n*-BuI without solvent. This catalysis is not controlled by the diffusion but, as with homogeneous catalysts, by the regeneration of the catalytic centers. However, unlike with soluble catalysts, with such systems the reaction proceeds rapidly even in the absence of stirring. The longer the alkyl chain between the catalytic centers and the matrix, the larger the ratio of the activity without stirring to the optimal activity (ranging from 0.3 to 0.7). The long alkyl chain acts as an anion pump between the aqueous and organic phases, both of which are present in the third solid phase.

In the classical mechanism of phase-transfer (PT) catalysis,[1] the nucleophilic substitution reaction (eq 1) occurs in the organic

$$\mathrm{RX(org)} + \mathrm{Y^-(org)} \xrightleftharpoons{k,\ [\mathrm{Q^+}]} \mathrm{RY(org)} + \mathrm{X^-(org)} \tag{1}$$

$$\mathrm{X^-(org)} + \mathrm{Y^-(aq)} \xrightleftharpoons{K_a,\ [\mathrm{Q^+}]} \mathrm{X^-(aq)} + \mathrm{Y^-(org)} \tag{2}$$

phase and is the rate-determining step. For most entering and leaving groups, catalyst regeneration by exchange between the aqueous (aq) and organic (org) phases (eq 2) is so rapid that it has no effect on reaction rates.

Starks[2] has shown that in exchange reactions between 1-chlorooctane and sodium cyanide catalyzed by hexadecyltributylphosphonium bromide (**5**), equilibrium a, with equilibrium constant K_a, becomes the fastest step at quite low stirring speeds (approximately 250 rpm). Therefore, since the nucleophile concentration in the organic phase remains constant, pseudo-first-order kinetics are always observed with k as the rate constant.

Moreover in all the studies reported in the literature of PT catalysts supported on polystyrene[3] or silica[4] resins, pseudo-first-order kinetics have been observed for S_N2 displacement and reduction reactions.

In the case of polymeric silica support, it has been shown that the first step is the adsorption of the organic substrate on the matrix, to which the nucleophile-containing aqueous phase is also present. On the other hand, for nonconditioned polystyrene matrices, Regen[5] has shown that the reaction rate is independent of the stirring speed. The observed data suggested that a diffusion-limited chemical reaction was the rate-controlling step.

With the aim of elucidating the factors controlling the catalysis and the nature of catalytic environment of phosphonium salts chemically bonded to silica gel, catalysts **1–4** were studied in a simple and kinetically convenient reaction: bromine–iodine exchange on an alkyl halide, run in a two-phase organic–aqueous KI system. This reaction proceeds to the iodo derivative within the limits of detectability of the bromide, and thus eq 1 is completely shifted to the right. Moreover, because of the nucleophile selected (I^-) and because of the analogy with free catalysts, equilibrium 2 decidedly favors the uptake of I^- by the polymer.[6]

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(1) (a) Weber, W. P.; Gokel, G. W. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: West Berlin, 1977. (b) Starks, C. M.; Liotta, C. "Phase Transfer Catalysis"; Academic Press: New York, 1978. (c) Dehmlow, E. V.; Dehmlow, S. S. "Phase Transfer Catalysis"; Verlag Chemie: Weinhein, 1980.

(2) Starks, C. M.; Owens, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3613.

(3) (a) Regen, S. L. *J. Am. Chem. Soc.* **1975**, *97*, 5956. (b) Cinquini, M.; Colonna, S.; Molinari, M.; Montanari, F.; Tundo, P. *J. Chem. Soc., Chem. Commun.* **1976**, 394. (c) Molinari, M.; Montanari, F.; Tundo, P. *Ibid.* **1977**, 639. (d) Molinari, M.; Montanari, F.; Quici, S.; Tundo, P. *J. Am. Chem. Soc.* **1979**, *101*, 3920. (e) Tundo, P. *Synthesis* 1978, 315. (f) Review: Regen, S. L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 421.

(4) (a) Tundo, P. *J. Chem. Soc., Chem. Commun.* **1977**, 641. (b) Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1979**, *101*, 6606.

(5) Regen, S. L.; Besse, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4059.

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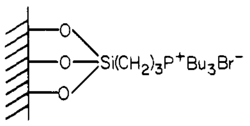

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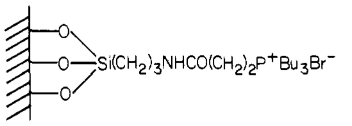

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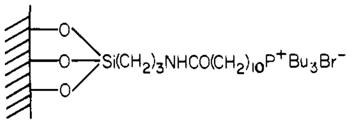

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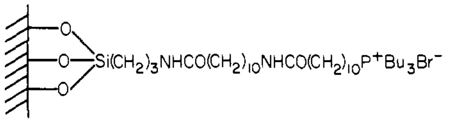

4

$C_{16}H_{33}P^+Bu_3Br^-$

5

Results

Since solvent polarity has no effect on pore diameter in silica gel, no solvent is needed and catalysts **1**–**4** were used in the reactions run in an aqueous-organic substrate system.

$$n\text{-}C_4H_9Br + KI \xrightarrow[H_2O]{\text{cat}} n\text{-}C_4H_9I + KBr \qquad (3)$$

The concentration of inorganic salt in the aqueous solution was such that the supported catalysts were positioned at the interface between the upper organic phase and the lower aqueous one.

Since the reaction rate varies considerably as a function of the organic–water interfacial area and of the rate and type of stirring, these reactions were run by using a system designed (see Experimental Section) to ensure that the stirring was constant, uniform without jolts, and measurable.

Visual observations revealed that **1**–**4** are completely wettable even in nonpolar organic phases (heptane) and also in water if the air on the support is removed with stirring or under vacuum.

The activity of **1**–**4** did not vary consistently with the mesh of the silica gel (Table II). However, catalyst activity was directly proportional to the quantity of the catalyst used both in the reactions run with stirring and in those run without using small quantities of catalyst, that is, in cases where the grains of functionalized silica were completely accessible to the two phases (Figure 3). Both of these observations agree with results[5] for nonconditioned polystyrene resins containing tributylphosphonium groups directly bonded to the matrix: $\textcircled{P}\text{-}C_6H_4CH_2P^+Bu_3Cl^-$.

Figure 1 shows the course of reaction 3 catalyzed by **1** and **3** (0.05 mol of catalyst/mol of substrate) without stirring at 80 °C. Both had previously been conditioned for 0.5 h to allow the Br^- polymer to change to I^- (see paragraph on Exchange with $^{131}I^-$).

The reaction began as soon as the organic substrate was added with catalyst **1** more active than **3**. As the reaction proceeded, the first fast step was followed by a second slower one (pseudo-first-order), in which these activities were reversed.

Figure 2 shows the activities of **1** and **3** as a function of the stirring speed (rpm). Without stirring and for a stirring speed below 200 rpm, the activities of **1** and **3** reversed so that $k_{obsd}(\mathbf{1}) < k_{obsd}(\mathbf{3})$, to reach a plateau above approximately 1000 rpm ($k_{obsd}(\mathbf{1})$ is k_{obsd} for catalyst **1**).

Table I reports the effects of varying KI concentrations (with or without KBr and KCl addition) on the activities of **1** and **3**. This was designed to study the effect on k_{obsd} of any diffusion phenomena of the nucleophile.

Table II reports the ΔH^{**}, ΔS^{**}, and ΔG^{**} for **1**–**4** without stirring and **1**–**5** with stirring, measured by running reaction 3 at 70, 80, and 90 °C. All the catalysts gave a good Arrhenius plot (correlation coefficient ≥ 0.98).

Table I. Observed Pseudo-First-Order Rate Constants (k_{obsd}) for the Reaction of 1-Bromobutane with Aqueous KI, Catalyzed by 3 (0.01 mol equiv) at 80 °C, in the Presence and in the Absence of KCl and KBr as an Unstirred Process[a]

mol of salts × 10^2			
KI	KBr	KCl	10^6k_{obsd}, s^{-1}
4.0			27.6
3.0[b]			28.9
2.0			36.7
2.0	1.0		22.2
2.0		1.0	25.5
1.5	1.5		19.8
1.5		1.5	20.6
1.0	2.0		18.7
1.0		2.0	21.6

[a] 1-Bromobutane, 10 mmol; H_2O, 3.25 mL; 3, 0.08 g, 100–140 mesh. Average of at least two runs. [b] Standard conditions.

Table III reports for **1**–**4** the values and the ratio between k_{obsd} with stirring (0.01 mol equiv of catalyst brought to 0.001) and k_{obsd} without (0.001 mol equiv of catalyst).

The rate of exchange of parent Br^- ion on functionalized silica gel with the I^- was determined at 25 °C by using an aqueous KI solution containing small amounts of $^{131}I^-$ as a radioactive source.

Heptane was used instead of 1-bromobutane since reaction 3 occurs even at room temperature (approximately 60% of 1-iodobutane after 15 h, with 0.05 mol equiv of catalyst **1**).

The results are reported in Figure 4. The exchange was very fast, even without stirring for **2**–**4**, while the exchange for **1** was slower.

Discussion

Undoubtedly, in the case of -onium salts on polymer supports, equations more complex than (1) and (2) must be considered, taking into account any processes of adsorption and/or diffusion

$$RX(org) + \textcircled{P}(Y^-) \overset{K_b}{\rightleftharpoons} RX\cdot\textcircled{P}(Y^-) \overset{k}{\rightleftharpoons} RY\cdot\textcircled{P}(X^-) \overset{K_c}{\rightleftharpoons} RY(org) + \textcircled{P}(X^-) \qquad (4)$$

$$Y^-(aq) + \textcircled{P}(X^-) \overset{K_d}{\rightleftharpoons} Y^-\cdot\textcircled{P}(X^-) \overset{K_e}{\rightleftharpoons} X^-\cdot\textcircled{P}(Y^-) \overset{K_f}{\rightleftharpoons} X^-(aq) + \textcircled{P}(Y^-) \qquad (5)$$

where $\textcircled{P}(X^-)$ and $\textcircled{P}(Y^-)$ represent the supported phosphonium salt in the X^- and Y^- forms, respectively; $RX\cdot\textcircled{P}$, $RY\cdot\textcircled{P}$, $Y^-\cdot\textcircled{P}$ and $X^-\cdot\textcircled{P}$ represent RX, RY, Y^-, and X^- in the environment of the third solid phase.

Processes b, c, d, and f are controlled by adsorption (through their respective constants K_{b-f}), by diffusion, or by both. Equilibrium e however is controlled by the affinity of the nucleophile for the immobilized -onium group.

In reality, the situation may be even more complex if in (4) and (5) the continuity of the two liquid phases up to the catalytic center is not guaranteed. When only one of the phases is present during catalysis, without solution continuity, along the entire polymer, the second phase presents itself in the form of small streams which may be blocked by the first competitive phase and thus may form globules within the polymer.

In this case eq 4 and 5 control the reaction, with regard to the less similar phase limited to the part which can exchange freely with the mother phase. The trapped portion will exchange only by very slow processes.

It is difficult however to determine the fraction of the polymer involved in these physical entrapment phenomena compared to the accessible region in which adsorption and/or diffusion phenomena may freely occur. Therefore, an enumeration of the kinetic laws which must be observed in the various cases is of necessity long and complex. It is preferable to use an analysis of the experimental data to discard certain hypotheses and thus

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(6) We could not quantitatively measure the iodide in **1**–**4** in the presence of bromide, since the inorganic support strongly interferes with the analysis (nitrous acid, aqueous bromine, and potassium iodate). The affinity of phosphonium salts for I^- in competition with Br^- has been documented by many authors, in both phase-transfer catalysis and extractive alkylation (Brändstron, A. "Preparative Ion-Pair Extraction, an Introduction to Theory and Practice"; Apotekarsocietaten/Hässle Läkemedel: Stockholm, 1974).

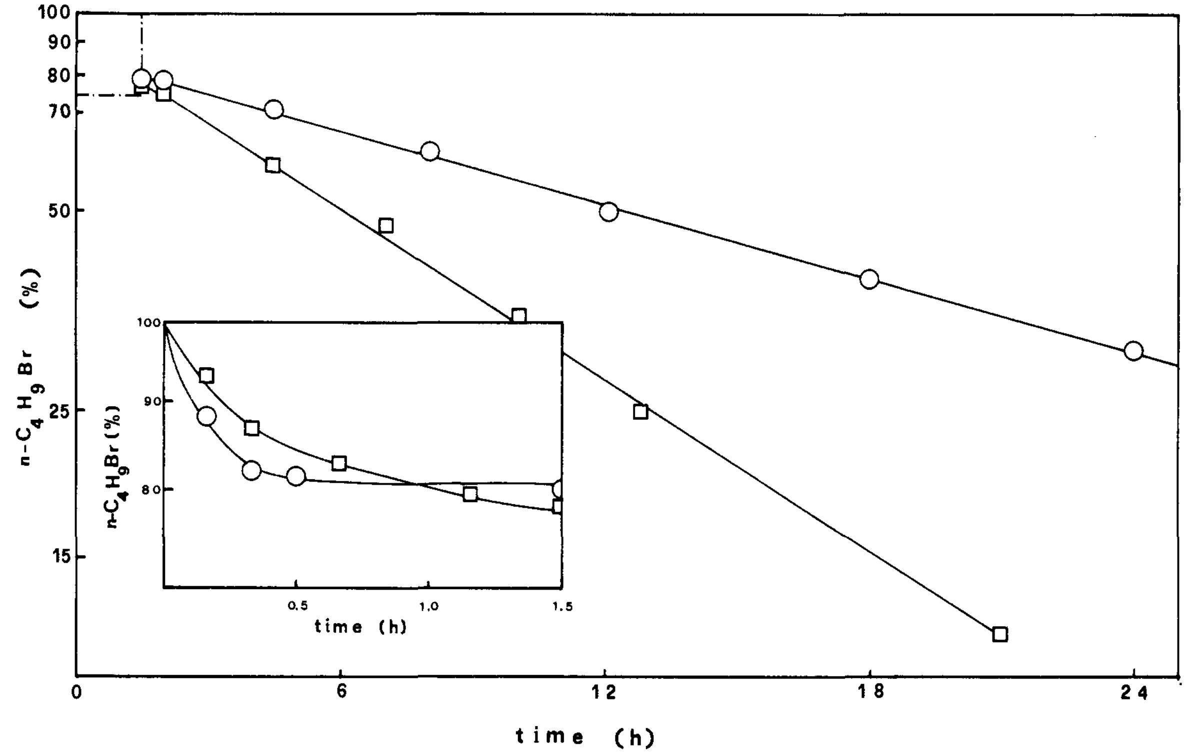

Figure 1. Disappearance of 1-bromobutane in the reaction with aqueous potassium iodide in two-phase system with 0.05 molar equivalents of catalysts 1 (○) and **3** (□), without stirring at 80 °C. Insert shows plots in upper left corner. For the reaction conditions see Table I, footnote *b*.

Table II. Observed Pseudo-First-Order Rate Constants (k_{obsd}) and Activation Parameters in Stirred (st) and Undstirred (unst) Experiment[a]

catalyst	T, °C	$10^6 k_{obsd}$(st), s^{-1}	$10^6 k_{obsd}$(unst), s^{-1}	ΔH^{**}(st), kcal mol^{-1}	ΔH^{**}(unst), kcal mol^{-1}	ΔS^{**}(st), eu	ΔS^{**}(unst), eu	ΔG^{**}(st), kcal mol^{-1} (80 °C)	ΔG^{**}(unst), kcal mol^{-1} (80 °C)
1	70	137.0	6.9	14.04	16.24	−35.6	−35.1	26.6	28.6
	80	225.0	13.0 (13.4,[b] 12.7[c])						
	90	452.0	27.2						
2	70	132.0	15.7	6.38	7.67	−57.9	−58.3	26.8	28.3
	80	178.0	25.7						
	90	234.0	30.8						
3	70	82.0	19.9	6.52	5.47	−58.4	−64.3	27.2	28.2
	80	120.0	28.9 (27.3,[b] 31.1[c])						
	90	146.0	32.7						
4	70	78.8	29.7	18.58	16.75	−23.4	−30.8	26.8	27.6
	80	179.0	53.9						
	90	374.0	122.0						
5	70	1288		10.61		−41.1		25.1	
	80	2125							
	90	3210							

[a] 1-Bromobutane, 10 mmol; KI, 5.0 g; H_2O, 3.25 mL; catalyst, 0.01 mol equivalents, 100–140 mesh. Average of at least two runs. [b] Catalyst, 70–100 mesh. [c] Catalyst, 140–270 mesh.

Table III. Effect of the Stirring on the Activities of 1–4 in the Reaction of 1-Bromobutane with Aqueous KI[a]

catalyst	$10^5 \times k_{obsd}$(st),[b] s^{-1}	$10^6 \times k_{obsd}$(unst),[c] s^{-1}	k_{obsd}(unst)/k_{obsd}(st)10
1	22.5	7.7	0.33
2	17.8	4.4	0.25
3	12.0	8.5	0.71
4	17.9	12.2	0.68

[a] 1-Bromobutane, 10 mmol; H_2O, 3.25 mL; KI, 5.0 g; $T = 80$ °C; catalysts, 100–140 mesh. [b] Catalyst, 0.01 mol equiv. [c] Catalyst, 0.001 mol equiv.

simplify interpretation of the data.

The data in Figures 1–3 show that eq 4 and 5 do not apply completely and contemporaneously. In this case, indeed, in the absence of stirring, the reaction should proceed with the same rate at both beginning and end. Moreover, since as soon as the substrate is added the reaction begins quickly, the diffusion of substrate toward polymer cannot affect the reaction rate. In agreement with the visual observations of the polymer's organic accessibility, it follows that in eq 4 processes b and c may be controlled by adsorption (a very rapid process) but not diffusion.

The subsequent slowdown shows how difficult it is for the aqueous KI solution to be present along the entire polymer. This is seen in other ways for catalysts **1** and **3**.

For homogeneous catalysts eq 2 controls catalyst regeneration and is the rate-determining step, in the absence of stirring; the corresponding equation (5) is equally important in the case of catalysts on polymer supports.

The concentration of nucleophile in the aqueous phase, in the presence or absence of other ions (Table I), does not affect the

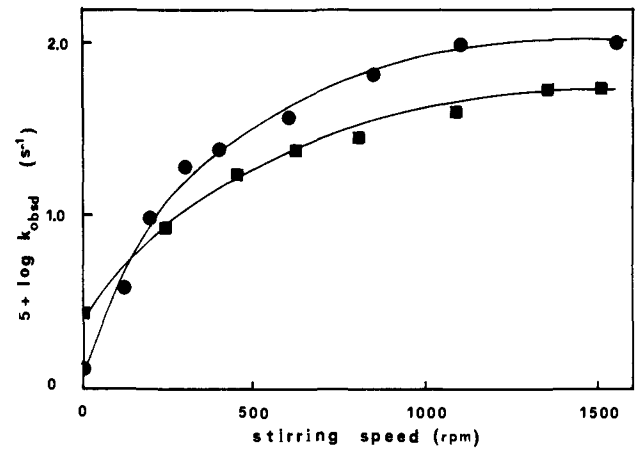

Figure 2. Dependence of the observed pseudo-first-order rate constants (k_{obsd}) on the stirring speed, for Br–I exchange reaction in 1-bromobutane with aqueous potassium iodide, at 80 °C, and 0.05 molar equivalents of catalysts 1 (●) and 3 (■). For the reaction conditions see Table I, footnote *b*.

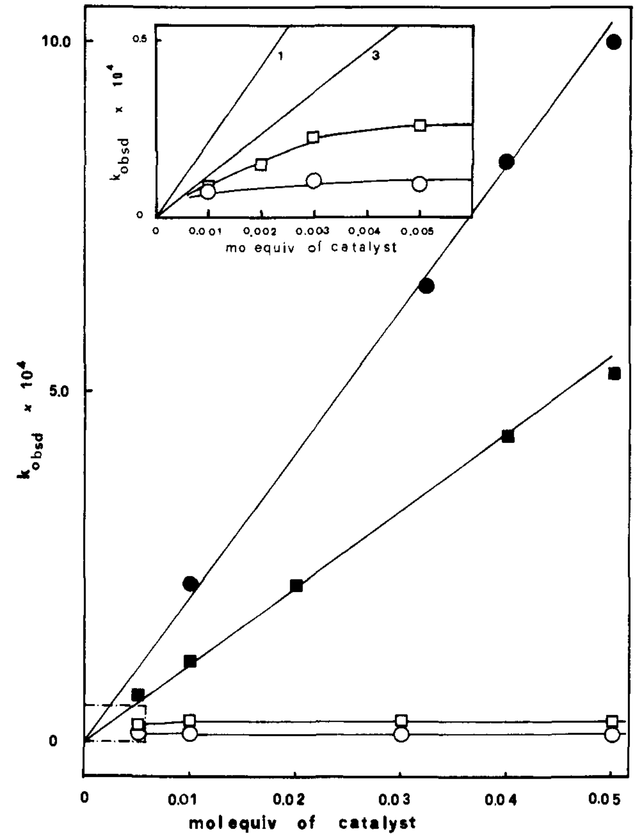

Figure 3. Dependence of the observed pseudo-first-order rate constants (k_{obsd}) on molar equivalents of immobilized phosphonium salts, 1 (○, ●) and 3 (□, ■), for Br-I exchange reaction in 1-bromobutane with aqueous potassium iodide, at 80 °C, as a stirred (●, ■) and unstirred (○, □) experiment. Inset shows plots in lower left corner.

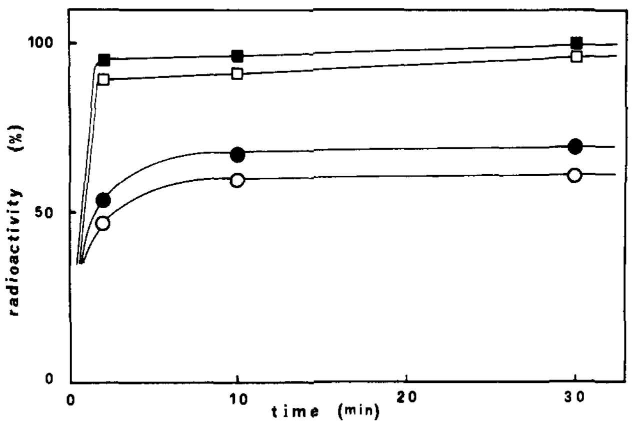

Figure 4. Plot of the induced radioactivity in 1 (○, ●) and 3 (□, ■) by means of aqueous $^{131}I^-$ as a function of time, in stirred (●, ■) and unstirred (○, □) experiment, at 25 °C. Catalysts 2 and 4 behaved like 3 and have been omitted for clarity. Since 1–4 differ in their ability to quench β^- radiation, the induced radioactivity is compared with the radioactivity of the corresponding systems after 15 h of stirring. Average of double measurements of two different runs.

reaction rate as dramatically as it would if the diffusion of the nucleophile toward the polymer was the step controlling the regeneration of catalytic centers. The coefficients of diffusion of 1 M KCl, KBr, and KI in H_2O at 25 °C are 1.892, 1.975, and 2.065 × 10^5 D/μ^2 s^{-1}, respectively.[7]

Rather, these data might show that in equilibrium e the Ⓟ(I$^-$)/Ⓟ(Br$^-$) and Ⓟ(I$^-$)/Ⓟ(Cl$^-$) ratio is very high since the functionalized silica polymer, like homogeneous catalysts, has much greater affinity for I$^-$ than for Br$^-$ and Cl$^-$. Furthermore, the smaller decrease of catalytic activity in the presence of Cl$^-$ shows Ⓟ(I$^-$)/Ⓟ(Cl$^-$) > Ⓟ(I$^-$)/Ⓟ(Br$^-$). Analogously, under aqueous-organic two-phase condition, homogeneous catalysts have partition coefficients in the following order I$^-$ > Br$^-$ > Cl$^-$.

Inorganic salts are poorly adsorbed on silica gel when the aqueous phase is present, as shown by the fact that nonfunctionalized silica gel does not catalyze bromine–iodine exchange reactions in an aqueous–organic system. Only when the aqueous phase is excluded and the solid salts are finely dispersed on the silica gel, as a "solid solution", are they reactive toward nucleophilic substitution, whether the halide is in the gas[8] or liquid phase.[9]

Equilibrium e is finely controlled by the presence and position of catalytic centers in the matrix.

Some catalytic centers may exchange their Br$^-$ ions with I$^-$, according to eq 5, while others deeper in the polymer, after exhausting the nearby reserve of I$^-$(aq) in globules, remain in the form of Br$^-$ and are thus ineffective in terms of catalysis.

If there is some kind of exchange between the internal produced Br$^-$ and the aqueous stock I$^-$ solution, this must necessarily be very slow. If the entire polymer were this way, the kinetics would be zero order with respect to the organic substrate since the substitution reaction would be the faster process in comparison.

Therefore, the only possibility is that only the catalytic centers directly accessible to the aqueous phase function according to eq 5, in which the importance of processes d and f is tied to the rate of diffusion of saline solution on the matrix near the active catalytic centers.

Activation Energy Measurements. The data in Table II show the following. (1) The way that the reaction is run (with or without stirring) has little effect on activation parameters for each catalyst: all the catalytic centers have the same microenvironment and the only function of the stirring is to increase the active molar fraction. (2) The ratio of the k_{obsd} with **5** to that with the supported catalysts ranges from 0.14 to 0.045, with stirring at 90 °C. This low activity may be attributed to the presence of water on the polymeric support which leads to a protic polar microenvironment less favorable to aliphatic S_N2[10] and to the inaccessible and unworking phosphonium groups. (3) For **1** and **4** the reaction is entropically favored with respect to **5**; for **2** and **3** however it is disfavored. This is the effect of the lipophilic covering of the matrix, the form of which may be different due to the different chemical structure of the multilayer covering of catalysts **1**–**4**.

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[7] "Handbook of Chemistry and Physic", 56th ed.; CRC Press: Cleveland, Ohio, 1975–1976; Table F-60.

[8] Tundo, P. *J. Org. Chem.* **1979**, *44*, 2048. (b) Tundo, P.; Venturello, P. *Synthesis* **1979**, 952.

[9] Regen, S. L.; Koted, C. *J. Am. Chem. Soc.* **1977**, *99*, 3837.

[10] (a) Parker, A. J. *Q. Rev., Chem. Soc.* **1962**, *16*, 163. (b) Illuminati, G. "Solution and Solubilities; Chemistry"; Wiley: New York, 1976; Vol. 8, Part 2, Chapter XII.

Exchange with $^{131}I^-$. Even in the absence of stirring, catalysts **2**, **3**, and **4** exchange their parent Br^- with I^- very rapidly and at room temperature.

The greater difficulty of catalyst **1** in exchanging with the aqueous phase may be related to the different type of covering on the silica which makes **1** different from the other catalysts with amide functions.[11]

However, this fast exchange shows that the steps d and f are not important in determining the reaction rate and shows indirectly that in the solid phase aqueous globules are present, in which Br^- collects when it is generated in a substitution reaction occurring within the polymer. This filling up with $Br^-(aq)$ then makes catalyst regeneration problematical.[12]

It may be concluded that, like soluble catalysts, the pseudo-first-order rate constant observed is the display only of the S_N2 reaction[13] in the organic phase.

Unlike soluble, -onium salts immobilized on silica gel are active even in the absence of stirring: on the one hand, the particular porous structure of the matrix multiplies by many orders of magnitude the contact surface between the two phases; on the other, the catalytic centers must remain near the aqueous phase and not far in the organic one, where regeneration would be impossible, as is the case with homogeneous catalysts.

Chain Length. With stirring, when the regeneration of the internal globules leads to optimal activity, the efficiency of **1**–**4** is of the order **1** > **4** ≃ **2** > **3**, the same as that previously found for ketone reduction.[4b]

In the absence of stirring, on the other hand, the activity of **1**–**4** is related to the molar fraction of the catalytic centers which remain active constantly and function continuously. The ratio k_{obsd}(stirring)/k_{obsd}(no stirring) (Table III) shows that in **3** and **4** only 30% of the -onium groups working in the presence of stirring are inactive in the absence of stirring.[14]

The most recent results of Murray et al.[15] on electrode surface modified through silanation indicate that the electron transport to the surface is more efficient if the covering is multilayered rather than single layered. They suggest this is probably due to a more flexible two-dimensional structure of the silane layer: the functionalized layer appears to be "porous" enough to allow the diffusion of species to the electrode surface, and a sufficiently long chain silane allows attached electroactive centers to approach the surface closely for the electrochemical process to occur.

Martini et al.[16] have recently shown that nonfunctionalized silica gel holds water in two continuous layers of different natures: a noncrystallizable internal one oriented with hydrogen bond to the silanolic and siloxanic groups of the matrix (approximately 10 layers of water molecules) and a second one adhering to the first in the form of a meniscus.

The complexity of catalytic systems **1**–**4** precludes us from providing a picture of the microenvironment of the catalytic system.

However, the stated situation for surface modified electrodes and nonfunctionalized silica gel must be similar in **1**–**4** where the silicon frame is the carrier of the aqueous solution. The nature of the functionalization affects the number and arrangement of the aqueous globules in the covering, and/or the longer alkyl chains, with their higher motional freedom, are able to exchange the anion with more removed reserves of nucleophile.

The long alkyl chains favor anion exchange, somewhat as occurs in exchange in biological systems; this similarity was suggested by the high activity of these systems in micelle-promoted reactions.[17]

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[11] (3-Glycidoxypropyl)triethoxysilane does not functionalize silica gel satisfactorily, under the same conditions used to prepare catalysts 1–4 (in toluene at reflux), despite having the same active groups. Evidently the alkyl residue plays an important role in the incomplete covering of the surface structure of the silica gel and probably also in the structures of the covering obtained. Therefore, **2**, **3**, and **4** may be more closely compared given their common starting material.

[12] Analytical tests carried out on another substitution reaction confirmed that the catalysis, in the absence of stirring, is controlled by the regeneration of the catalyst: $n\text{-}C_8H_{17}OSO_2CH_3 + KBr \rightarrow n\text{-}C_8H_{17}Br + CH_3SO_3K$. Such a reaction, carried out according to Table II footnote *a* (T = 80 °C; catalyst = 0.05 mol quiv; KBr = 3.0 g), was suitable for the determination with Ag^+ of the bromide loading the phosphonium groups with respect to the total anions. The reaction was stopped and the catalyst filtered without further agitation and washed several times with water, ethanol, water, ethanol, and ethyl ether; after evaporation of the solvent, bromide present in the recovered catalysts **1** and **3** was volumetrically determined according to Volhard (see ref 4b). Results [catalyst (stirred, ca. 1500 rpm, or not stirred), time (min), conversion (% by GLC) into 1-bromooctane, titer (% referred to the primitive titer)]: **1** (stirred), 15, 23, 94; **3** (stirred), 15, 17, 100; **1** (not stirred), 75, 15, 28; **3** (not stirred), 75, 18, 68. Such a behavior, also reported for polystyrene resins (see ref 5) in a similar reaction, moreover attests the reversed activities of **1** and **3** when the reaction is carried out with or without stirring.

[13] Assuming that continuity of the organic substrate is guaranteed up to the matrix catalytic centers and supposing that the polymer is constantly kept in the I^- form during the course of the reaction, we may simplify eq 4 as

$$A \underset{k_{-1A}}{\overset{k_{1A}}{\rightleftharpoons}} A^* \xrightarrow{k} B^* \underset{k_{1B}}{\overset{k_{-1B}}{\rightleftharpoons}} B \qquad (4')$$

where A and B refer respectively to the concentration of alkyl bromide and iodide and the asterisk represents the respective adsorbed compounds. If k_1 and k_{-1} are rapid processes compared to k (nondiffusion-controlled reactions), then

$$K_A = \frac{k_{1A}}{k_{-1A}} = \frac{A^*}{A} \qquad K_B = \frac{k_{1B}}{k_{-1B}} = \frac{B^*}{B} \qquad (6)$$

where the K values refer to the corresponding partition constants. If

$$A^* = K_A A \qquad B^* = K_B B \qquad \frac{dB^*}{dt} = kA^* + k_{1B}B + k_{-1B}B^* \qquad (7)$$

then by substitution $K_B dB/dt = kK_A A + k_{1B}B - k_{1B}B$; that is

$$dB/dt = (K_A/K_B)kA \qquad (8)$$

Since it is reasonable to assume in this case that $K_A = K_B$, then

$$dB/dt = kA \qquad (8')$$

and so

$$A = A_0 e^{-kt} \qquad (9)$$

If on the other hand the hypothesis leading to eq 6 does not apply and so the reaction is diffusion controlled, with the assumption that $k_{1A} = k_{-1A} = k_{1B} = k_{-1B} = k_d$ in eq 4′ (since A and B have about the same size and the diffusion rate is a constant for a given polymer), then the following equation similar to eq 9 is obtained (see supplementary material)

$$A = A_0 e^{-mt} \qquad (10)$$

where $m = [2k_d + k - (4k_d^2 + k^2)^{1/2}]/2$. Whether the reaction is controlled by adsorption or diffusion, pseudo-first-order kinetics are followed. In reality, though, first-order kinetics can conceal complex and different mechanisms. Diffusion, however, strikingly slows down the reaction (for example, in eq 10, if $k_d = k$, $k_{obsd} = 0.38k$). In the $NaBH_4$ reduction of ketones catalyzed by **1**–**4**, if diffusive processes were important, it would be difficult to justify the observed reaction rate, which is higher than that found with homogeneous catalysts.

[14] The difference between phase-transfer catalysts supported on silica gel and those supported on polystyrene is given by some of our unpublished results (Tundo, P.; Montanari, F.). If the catalytic center is very close to the skeleton, as in Ⓟ-$C_6H_4CH_2P^+Bu_3Cl^-$ (Ⓟ = polystyrene 2% cross-linking), it is able to catalyze exchange reaction even in the absence of stirring, since the polystyrene resin is wettable due to the proximity of the polar -onium groups. On the other hand, when a long alkyl chain intervenes, as in Ⓟ-$C_6H_4NHCO(CH_2)_{10}P^+Bu_3Br^-$, their activity is greater in the presence of stirring but falls practically to zero in its absence. Once the catalyst is regenerated, as is guaranteed by the stirring, the reaction proceeds in a decidedly organic environment and their efficiency approaches that of homogeneous catalysts. In the absence of stirring, the catalytic centers are projected in the organic phase with no possibility of regeneration due to the apolarity of the matrix. The latter contains no reserve and may not be the carrier of the nucleophile present in the aqueous solution. Macroporous functionalized polystyrene resins (ref 3e) represent an intermediate between these two extremes. When conditioned, these catalyze the reactions, although more slowly, even in the absence of stirring. However, in these systems the type of mechanism may be different. In some reactions (like the alkylation of benzyl methyl ketone by 1-bromobutane in 50% NaOH), the resin completely infiltrates the two phases to visually form a single phase the consistency of cream. Probably both phases are trapped in distinct globules in the broad mesh of polymer.

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Experimental Section

Nuclear magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R-24B 60-MHz ^{1}H NMR spectrometer.

Radioactivity measurements were performed on a Beckmann LS-100 liquid scintillation system.

Materials. The starting material silica gel was Merck Kieselgel 60 (Art. No. 7734), 70–230 mesh, pore diameter 60 Å, specific surface area = 500 m^2/g.

Catalysts 1–**4** supported on silica gel were synthesized and analyzed as described previously.[4b] They were then sifted to give mesh intervals of 70–100, 100–140, and 170–230, respectively. Catalysts **1**–**4** had titers of 0.68, 0.94, 1.24, and 0.66 mequiv of Br$^-$/g, respectively.

Hexadecyltributylphosphonium bromide **5** was prepared according to Starks,[18] mp 54 °C.

n-Butyl bromide and inorganic reagents were ACS reagent grade. Na^{131}I was supplied by New England Nuclear, Massachusetts, U.S.A.

Kinetic Methods. All the kinetic experiments were run at the desired temperature (70, 80, 90 ± 0.5 °C) in a 10-mL flask with a Teflon top connected with a circulating paraffin thermostat (Colora K-5 Ultrathermostat).

In a typical experiment without stirring, the flask was charged with water (3.25 mL), potassium iodide (5.0 g, 30.0 mmol), and catalyst (0.05 molar equivalents, corresponding to 0.74, 0.53, 0.40, and 0.76 g of **1**, **2**, **3**, and **4**, respectively) and equilibrated for 0.5 h. 1-Bromobutane (1.74 mL, 10.0 mmol) was then added. The interfacial area between organic and aqueous phase was 3.0 cm^2.

The reaction procedure was to take samples of the upper organic layer at suitable time intervals and to follow with NMR the disappearance of reagent and appearance of 1-iodobutane. The relative concentrations of the two were determined from the areas (a_{Br} and a_{I}) of the central peaks of the partially overlapping triplets centrated at 3.38 and 3.18 ppm, respectively (CCl$_4$; internal Me$_4$Si), after calibration with known mixtures of authentic samples. The pseudo-first-order rate constants were obtained from the slope of the plots of ln ($a_{\mathrm{Br}}/a_{\mathrm{Br}} + a_{\mathrm{I}}$) vs. time, after the rapid first period was rejected, by the least-squares method (correlation coefficient > 0.98). All the kinetic runs were followed to more than 70% conversion.

Experiments with stirring were conducted under the same conditions by using a Teflon-coated stirring bar (2.0 cm × 0.7 cm) placed in the reaction vessel first. Its length was selected as slightly less than the diameter of the bottom of the flask so that the type of stirring would be the same in all experiments. The magnetic stirrer was connected with a mechanical revolution counter in order to determine the precise stirring speed. All the kinetic runs were performed at least twice and gave good reproducibility of the observed kinetic constants (approximately ±5% for the unstirred and ±10% for the stirred experiments).

Iodine contents of 1 and **3** were evaluated before and after catalysis; the catalyst was previously converted into I$^-$ form by treatment with KI(aq)/heptane, according to the results of the radioactivity measurements, and then placed in the reaction with stirring. After usual washing the dried catalyst was analyzed according to Volhard. Results: catalyst **1**, 0.61 before and 0.63 mequiv of I$^-$/g after the catalysis; catalyst **3**, 1.15 before and 1.15 mequiv I$^-$/g after the catalysis.

Radioactivity Measurements. The stock solution was prepared from 0.1 mL of a solution of Na^{131}I in 0.1 N NaOH (5 mCi) with 100 g of KI, bringing the volume to 150 mL with water. The flask was charged with 0.50 mol equiv of immobilized phosphonium salts (catalysts **1**–4), 0.8 mL of heptane, and 1.0 mL of water. The resulting mixture was stirred for approximately 5 min and 5.0 mL of radioactive solution was added. Concentration gradients in the aqueous phase were eliminated with a few rotations of the suspension.

In the experiments without stirring, the flask was left to rest away from vibrations. At suitable intervals samples were drawn from the solid phase, washed with water until radioactivity disappeared in the aqueous phase and with acetone, and allowed to air-dry. In experiments with stirring, rate of 1000 rpm was ensured.

The 20–60-mg samples of radioactive silica in strips were placed in scintillation flasks with 10.0 mL of a 0.05 M solution of 2,5-diphenyloxazole (PPO, Beckmann) in toluene and analyzed.

Since catalysts 1–**4** and nonfunctionalized silica gel differ in radiation quenching properties (**1** > **2** ≥ **3**, **4**), a common reference could not be taken.

It was therefore assumed that Br$^-$–I$^-$ exchange was complete after 15 h with stirring for each catalyst. The different values of observed radioactivity were thus referred to this.

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Supplementary Material Available: A listing of additional equations (1 page). Ordering information is given on any current masthead page.

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Synthesis of Crobarbatine Acetate. A Macrocyclic Pyrrolizidine Alkaloid Ester

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Abstract: A synthesis of the 11-membered lactonic pyrrolizidine alkaloid ester, crobarbatine acetate, and a diastereomer (**26** and **27**) has been achieved, starting from (+)-retronecine (**1**) and (±)-*trans*-β-methyl-γ-carboxy-γ-valerolactone (**3**). The highly functionalized intermediate **22** was coupled with **1** to give the allylic ester **23** in 62% yield. Cyclization to give lactones **26** and **27** was brought about by treating **23** with copper(I) triflate in toluene–THF.

The pyrrolizidine alkaloids have attracted the attention of organic chemists with increasing frequency in recent years.[1-10] The large number of these alkaloids and their wide range of biological activities have made them particularly attractive syn-

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