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Ionic Transformations in Extremely Nonpolar Fluorous Media: Phase Transfer Catalysis of Halide Substitution Reactions

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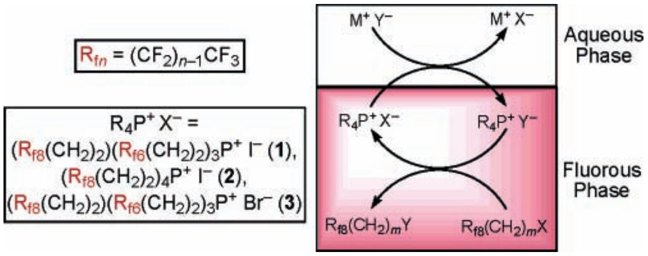
ABSTRACT



Fluorous solutions of alkyl halides $R_{f8}(CH_2)_mX$ (m = 2, 3; X = Cl, Br, I) are inert toward solid or aqueous NaCl, NaBr, and KI, but halide substitution occurs in the presence of fluorous phosphonium salts (10 mol %, 76–100 °C).

Phase transfer catalysis is potentially applicable to any process where two reactants are localized in orthogonal phases. In practice, it has been most extensively employed for organic-solvent-based transformations.[1] Typically one reactant is a poorly soluble salt, the reactive anion of which can be transported from a solid or aqueous phase by a lipophilic and often bulky cation, or by a complex of the salt with a crown ether. However, phase transfer catalysis and related protocols have also been used for reactions in aqueous phases.[2]

Recently, there has been a surge of interest in reactions that involve fluorous reactants, catalysts, and phases.[3] Fluorous solvents—which include perfluoroalkanes but not perfluoroarenes—are both lipophobic and hydrophobic, and are much less polar than alkanes.[4] Hence, appreciable concentrations of only a few non-fluorous solutes can be achieved.[4] As a result, fluorous solvents constitute attractive targets for the deployment of phase transfer catalysts. To date, most transformations involving fluorous reactants or catalysts have been conducted in organic or mixed organic/fluorous solvents. However, scenarios are easily envisaged where it would be desirable to carry out a range of reactions in a fluorous phase. For example, fluorous media represent possible approaches to sequestering toxic compounds or nuclear waste, and it might be necessary to further process material in situ without transfer to a new phase.

In this context, we were curious whether reactions involving ions might be possible in fluorous solvents. We, Stuart,

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(1) (a) *Phase-Transfer Catalysis*; Starks, C. M., Liotta, C. L., Halpern, M., Eds.; Chapman & Hall: New York, 1994. (b) Yadav, G. D. *Top. Catal.* **2004**, *29*, 145.

(2) (a) Okano, T. Counter-phase Transfer Catalysis. In *Aqueous-Phase Organometallic Catalysis*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley/VCH: Weinheim, Germany, 2004; pp 288−300. (b) Reinsborough, V. C. Micellar Catalysis. In *Interfacial Catalysis*; Volkov, A. G., Ed.; Marcel Dekker Inc.: New York, 2003; pp 377−390.

(3) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley/VCH: Weinheim, Germany, 2004.

(4) Gladysz, J. A.; Emnet, C. Fluorous Solvents and Related Media. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley/VCH: Weinheim, Germany, 2004; pp 11−23.

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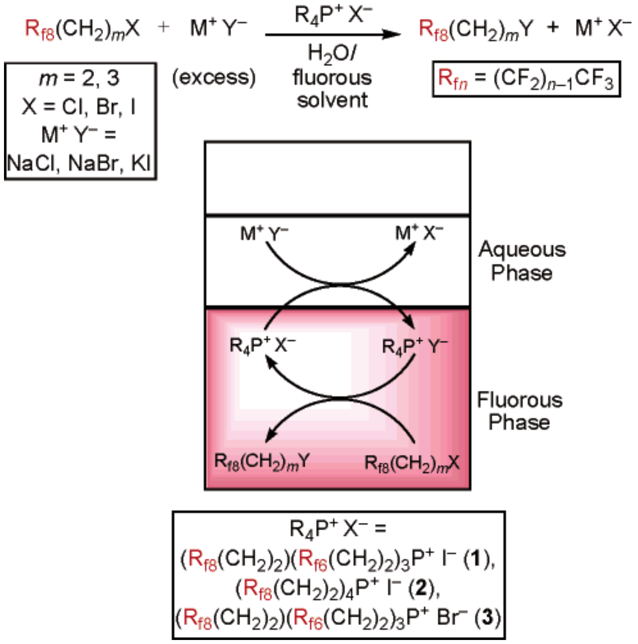
Horváth, and others have recently prepared a number of fluorous aliphatic phosphonium salts with "ponytails" of the formula $CF_3(CF_2)_{n-1}(CH_2)_m$ (abbreviated $R_{fn}(CH_2)_m$).[5−7] Since non-fluorous phosphonium salts are effective phase transfer catalysts for anionic displacement reactions in organic solvents,[1] we thought that fluorous phosphonium salts might catalyze analogous reactions in fluorous solvents. In this Letter, we report that Finkelstein-type reactions[8] of fluorous aliphatic halides can be catalyzed by fluorous phosphonium salts in fluorous solvents at moderate temperatures, and that even non-fluorous phosphonium salts are effective under related conditions. Additional types of fluorous phase transfer catalysts have been developed for other applications, as detailed below.[9]

The fluorous phosphonium iodide and bromide salts $(R_{f8}(CH_2)_2)(R_{f6}(CH_2)_2)_3P^+ I^-$ (**1**), $(R_{f8}(CH_2)_2)_4P^+I^-$ (**2**), and $(R_{f8}(CH_2)_2)(R_{f6}(CH_2)_2)_3P^+ Br^-$ (**3**) shown in Scheme 1 were prepared as described previously.[5] Two types of fluorous alkyl halides—the "three methylene spacer" substrates $R_{f8}(CH_2)_3I$ and $R_{f8}(CH_2)_3Cl$ and "two methylene spacer" substrates $R_{f8}(CH_2)_2I$ and $R_{f8}(CH_2)_2Br$—were obtained as described in the Supporting Information. The $CF_3C_6F_{11}$/toluene partition coefficient of $R_{f8}(CH_2)_3I$ is 50.7:49.3;[10] the other alkyl halides, which feature fewer methylene groups or less polarizable halides, should be somewhat more fluorophilic. None of the alkyl halides exhibit detectable solubility in water.

Scheme 1. Phase Transfer Catalysis of Halide Substitution Reactions in Fluorous Media



In the first series of experiments, a 0.68 M solution of $R_{f8}(CH_2)_3I$ in $CF_3C_6F_{11}$ and excess solid NaCl were stirred at 76 °C. After 24 h, no reaction could be detected, as assayed by ^1H NMR (aliquot with added $CDCl_3$; the CH_2X signals (t) for all of the fluorous alkyl halides are well-separated). A similar experiment was conducted, but using a nearly saturated 5.13 M aqueous solution of NaCl (88:12 NaCl/$R_{f8}(CH_2)_3I$ mol ratio). After 24 h, no reaction could be detected.

Next, analogous liquid/liquid biphase experiments were conducted, but in the presence of 10 mol % of the phosphonium salts **1**, **2**, and **3**. These are insoluble in water, sparingly soluble in fluorous solvents at room temperature, and highly soluble in fluorous solvents at elevated temperatures.[5] The conditions are summarized in Scheme 1. Per entries 1−3 of Table 1, ^1H NMR spectra showed 90−93% conversions to the fluorous alkyl chloride $R_{f8}(CH_2)_3Cl$ after 24 h at 76 °C. For entry 3, no further conversion was noted after three weeks. These data are interpreted as phase transfer catalysis of ionic displacement reactions in the fluorous phase, as supported by additional results below.

Table 1. Data for Halide Substitution Reactions Catalyzed by Fluorous Phosphonium Salts under the Conditions of Scheme 1[a]

entry[b]	substrate	$M^+ Y^-$	$R_4P^+ X^-$	product	temp (°C)	time (h)	convn (%)
1	$R_{f8}(CH_2)_3I$	NaCl	**1**	$R_{f8}(CH_2)_3Cl$	76	72	93
2		NaCl	**2**		76	72	90
3		NaCl	**3**		76	72	91
4[c]		NaCl	**1**		100	24	95
5	$R_{f8}(CH_2)_3Cl$	KI	**1**	$R_{f8}(CH_2)_3I$	100	24	36
						48	61
						120	87
6	$R_{f8}(CH_2)_2I$	NaCl	**1**	$R_{f8}(CH_2)_2Cl$	100	24	26
						48	37
						120	71
7		NaBr	**1**	$R_{f8}(CH_2)_2Br$	100	24	42
						48	53
						120	79
8	$R_{f8}(CH_2)_2Br$	KI	**1**	$R_{f8}(CH_2)_2I$	100	24	43
						48	77
						120	92
9[d]		NaCl	**1**	$R_{f8}(CH_2)_2Cl$	100	120	67

[a] Conditions: $R_{f8}(CH_2)_mX$ (0.34 mmol), $M^+ Y^-$ (2.56 mmol), fluorous solvent (0.5 mL), water (0.5 mL), $R_4P^+ X^-$ (0.034 mmol). [b] The reactions in entries 1−3 were conducted in $CF_3C_6F_{11}$. All others were conducted in perfluoromethyldecalin ($CF_3C_{10}F_{17}$). [c] For the time profile of a duplicate run, see Figure 2. [d] For the time profile, see Figure 1.

Workup of entry 3 gave a 92% yield of a 93:7 $R_{f8}(CH_2)_3Cl/R_{f8}(CH_2)_3I$ mixture, as assayed by NMR. When entries 1−3 were repeated in the absence of water, no reaction occurred. The NaCl remained undissolved. Hence, solid/

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(5) Emnet, C.; Weber, K. M.; Vidal, J. A.; Consorti, C. S.; Stuart, A. M.; Gladysz, J. A. *Adv. Synth. Catal.* **2006**, *348*, 1625.

(6) (a) Vlád, G.; Richter, F.; Horváth, I. T. *Org. Lett.* **2004**, *6*, 4559. (b) Vlád, G.; Richter, F.; Horváth, I. T. *Tetrahedron Lett.* **2005**, *46*, 8605.

(7) See also: Tindale, J. J.; Na, C.; Jennings, M. C.; Ragogna, P. J. *Can. J. Chem.* **2007**, *85*, DOI 10.1139/v07-035.

(8) Smith, M. B.; March, J. *Advanced Organic Chemistry*; Wiley: New York, 2001; p 517.

(9) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429.

(10) Rocaboy, C.; Rutherford, D.; Bennett, B. L.; Gladysz, J. A. *J. Phys. Org. Chem.* **2000**, *13*, 596.

liquid phase transfer catalysis does not take place. Since the boiling point of $CF_3C_6F_{11}$ (76 °C) limits the temperature of these reactions, entry 3 was repeated with perfluoromethyldecalin ($CF_3C_{10}F_{17}$, bp 160 °C) at 100 °C. Now reaction was complete within 24 h (entry 4).

Catalysis of the reverse reaction was investigated. Thus, $R_{f8}(CH_2)_3Cl$ and excess KI (12:88 mol ratio) were similarly combined in perfluoromethyldecalin at 100 °C (entry 5). Substitution occurred, but at a much slower rate (conversion after 24 h, 36%; 120 h, 87%). Since data below suggest the nucleophilicity order $I^- > Br^- > Cl^-$ for Scheme 1, the poorer leaving group ability of chloride likely plays a key role. However, it remains possible that other factors contribute.

To confirm the generality of phase transfer catalysis, analogous reactions were conducted with the "two spacer" fluorous alkyl iodide $R_{f8}(CH_2)_2I$. Such two-spacer electrophiles are known to be much less reactive in S_N2-type processes.[11] As shown in entry 6, reaction with NaCl (perfluoromethyldecalin, 100 °C) gave 26% conversion to $R_{f8}(CH_2)_2Cl$ after 24 h and 71% after 120 h. The reaction with NaBr was somewhat faster (entry 7), with 42% conversion to $R_{f8}(CH_2)_2Br$ after 24 h and 79% after 120 h.

Reactions of the two-spacer fluorous alkyl bromide $R_{f8}(CH_2)_2Br$ with KI and NaCl were also investigated. As shown in entry 8, the first reaction gave as expected $R_{f8}(CH_2)_2I$ (43% and 92% conversion after 24 and 120 h, respectively). It can be extrapolated that the corresponding (degenerate) reaction with $R_{f8}(CH_2)_2I$ would be somewhat faster, which together with entries 6 and 7 establishes the nucleophilicity order given above. The second reaction afforded $R_{f8}(CH_2)_2Cl$ (entry 9). Under these conditions, all three halide ions are present (iodide at 10 mol % from the catalyst). As shown in Figure 1, some of the iodide $R_{f8}(CH_2)_2I$ can also be detected. The $R_{f8}(CH_2)_2I/R_{f8}(CH_2)_2Cl$ ratios at low conversions also support the greater nucleophilicity of the iodide anion.

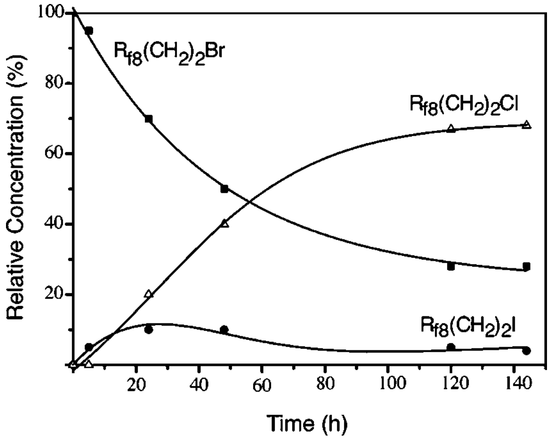

Figure 1. Conversion profile for the reaction of $R_{f8}(CH_2)_2Br$ an NaCl catalyzed by **1** in perfluoromethyldecalin at 100 °C (entry 9, Table 1).

Selected reactions with equimolar amounts of fluorous alkyl halides and phosphonium salts were conducted under homogeneous conditions in perfluoromethyldecalin at 100 °C. As shown in Table 2, substitution occurred, presumably to the equilibrium limit, within the time scales of the reactions in Table 1. This further supports the model in Scheme 1, featuring catalysis in the fluorous phase.

Table 2. Reaction of Fluorous Halides with Equimolar Amounts of Fluorous Phosphonium Salts in Perfluoromethyldecalin[a]

entry	substrate	$R_4P^+X^-$	product	time (h)	convn (%)
1	$R_{f8}(CH_2)_3Cl$	**1**	$R_{f8}(CH_2)_3I$	24	35
				48	36
2	$R_{f8}(CH_2)_2I$	**3**	$R_{f8}(CH_2)_2Br$	24	41
3	$R_{f8}(CH_2)_2Br$	**1**	$R_{f8}(CH_2)_2I$	24	42

[a] Conditions: $R_{f8}(CH_2)_mX$ (0.34 mmol), perfluoromethyldecalin (0.5 mL), $R_4P^+X^-$ (0.34 mmol), 100 °C.

The recycling of the fluorous phosphonium salts after catalysis was investigated. Note that the dominant catalyst rest state will contain the halide ion used for substitution. Thus, hexane was added to the fluorous phase after a reaction analogous to entry 4 of Table 1. The resulting precipitate was washed with hexane and water, and used for a second cycle. As summarized in Table 3, five cycles were conducted. After the fifth cycle, for which the conversion was noticeably lower, 38% of the original catalyst mass remained. Importantly, a ^{31}P NMR spectrum exhibited only a single catalyst signal, suggesting little if any degradation. Separate analyses showed that the dominant mode of catalyst loss was incomplete precipitation.

Table 3. Recovery and Reuse of Fluorous Phosphonium Salt **1** under the Conditions of Scheme 1[a]

cycle	substrate	M^+Y^-	product	time (h)	convn (%)
1	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	24	95
2	$R_{f8}(CH_2)_3Cl$	KI	$R_{f8}(CH_2)_3I$	120	85
3	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	24	91
4	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	24	81
5	$R_{f8}(CH_2)_3I$	NaCl	$R_{f8}(CH_2)_3Cl$	24	66

[a] Conditions: $R_{f8}(CH_2)_3X$ (0.34 mmol), M^+Y^- (2.56 mmol), perfluoromethyldecalin (0.5 mL), water (0.5 mL), **1** (0.034 mmol), 100 °C; see text for recycling details.

Finally, we sought to test the performance of a comparable non-fluorous phosphonium salt. Thus $(CH_3(CH_2)_{11})(CH_3(CH_2)_7)_3P^+I^-$ (**4**), the carbon skeleton of which is similar to that in **1**, was synthesized as described in the Supporting

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[11] Gladysz, J. A. Ponytails: Structural and Electronic Considerations. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley/VCH: Weinheim, Germany, 2004; pp 41−55.

Information. Surprisingly, as indicated by the time profiles in Figure 2, **4** proved to be a superior catalyst. Conditions were triphasic, with solid phosphonium salt occupying the interface between the fluorous and aqueous phases. NMR experiments indicated a very low solubility in perfluoromethyldecalin at room temperature (ca. 0.01 M), increasing somewhat at 100 °C (ca. 0.03 M; water solubility ca. 0.04 M). No reaction took place in the absence of water. This suggests yet another dimension of possibilities for the catalysis of multiphase ionic displacement reactions involving fluorous solvents, and additional investigations will be described in future reports.

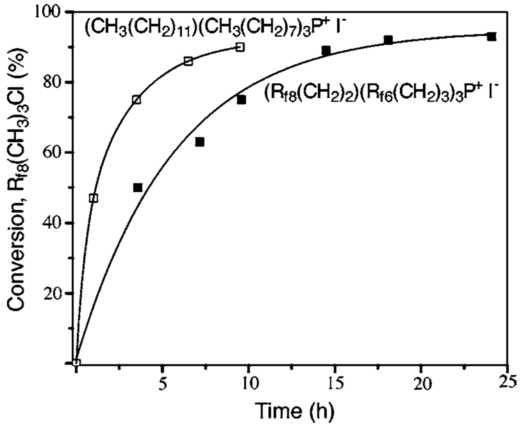
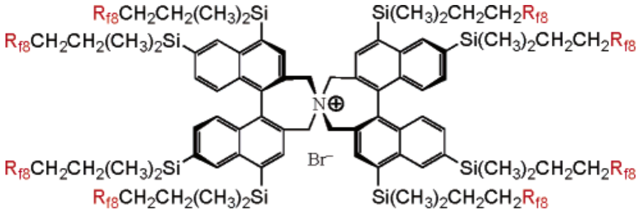


Figure 2. Conversion profile for the reaction of $R_{f8}(CH_2)_3I$ and NaCl catalyzed by **1** (■; duplicate of entry 4, Scheme 1) and **4** (□) in perfluoromethyldecalin at 100 °C.

Some previously reported results deserve emphasis. First, another family of fluorous phase transfer catalysts has been described, as exemplified by **5**.[9] However, these were designed for aqueous/organic biphasic enantioselective reactions, with the primary objective of catalyst recovery. Second, one example of phase transfer catalysis of a halide substitution reaction by a closely related fluorous phosphonium salt, $(R_{f8}(CH_2)_2)_3(R_{f6}(CH_2)_2)P^+ I^-$, has been reported.[5] However, this involved aqueous/organic biphasic conditions, utilizing the perfluoroarene $CF_3C_6F_5$. As noted above, this much more polar substance is not a fluorous solvent,[4] although it does dissolve appreciable quantities of fluorous phosphonium salts.[5]



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In summary, this study has established the feasibility of ionic displacement reactions in one of the least polar solvent families known. These can be effected with stoichiometric quantities of fluorous phosphonium salts under homogeneous conditions in fluorous solvents (Table 2), or with catalytic quantities under aqueous/fluorous biphase conditions (Scheme 1). Interestingly, ionic displacements can also be catalyzed by non-fluorous phosphonium salts under triphasic conditions, but additional experiments are required to clarify the locus of reaction. Further extensions and applications of these potentially useful phenomena will be reported in due course.

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Note Added after ASAP Publication. In the Figure 2 caption $R_{f8}(CH_2CH_2)_3I$ was corrected to $R_{f8}(CH_2)_3I$. The incorrect version was published May 15, 2007; the correct version was published May 16, 2007.

Supporting Information Available: Key experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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