

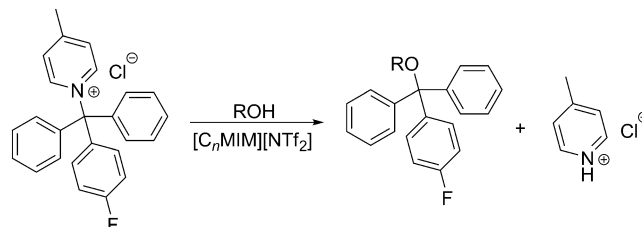
Pseudo-Encapsulation—Nanodomains for Enhanced Reactivity in Ionic Liquids**

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Ionic liquids (ILs) have attracted intense scientific interest in recent years owing to their unique chemical and physical properties as well as their potential to replace volatile organic compounds (VOCs).^[1] One of the major questions investigated has been whether ILs, when used as solvents, display any unique characteristics that may lead to unusual reaction outcomes unattainable with neutral solvents of comparable polarity.^[1a,2] Results thus far suggest that, due to the strong Coulombic interactions present within ILs which are absent within neutral solvents, ILs have the greatest effect on reactions featuring either charged reactants or at least considerable charge development over the course of the reaction. However, investigations into such phenomena have not focussed on the direct consequences of unique structural features of ILs on reaction outcomes.

ILs, particularly those based on the imidazolium cation, show significant structural heterogeneity resulting from the hydrophobic nature of the alkyl side chains when the side chain is propyl or longer, leading to the formation of separate polar and nonpolar domains.^[3] These domains have been implicated in the use of ILs for separations and the size control of nanoparticles and polymers;^[4] however, their potential role in providing unique reaction spaces that could lead to unprecedented precision in the control of organic reactions has not been examined to date. Whether in chemical or biological systems, highly charged structured nanodomains could play a significant and profound role across a vast range of reactions, akin to transitory liquid zeolites.

Thus, to examine the effect of these domains on reactivity from a fundamental point of view, the bimolecular nucleophilic substitution of *N*-(*p*-fluorophenyldiphenylmethyl)-4-picolinium chloride ([Ar₃Pic][Cl]) has been chosen as a model reaction (Scheme 1). Previously, this system has been shown to be sensitive to the solvation environment of the nucleophile, ROH, primarily on account of the similar charge of the electrophile in its initial and transition states, an effect that has also been found for other *N*-*tert*-alkyl pyridinium systems.^[5] As [Ar₃Pic][Cl] is ionic in both initial and transition



Scheme 1. General representation of the nucleophilic substitution of [Ar₃Pic][Cl]. Reactions were conducted at 294.3 K and monitored using ¹⁹F{¹H} NMR spectroscopy.

states, it would be anticipated that the constituents of this salt would reside preferentially within the polar domains of the IL. Through variation of the alkyl side chains of the IL and the R group on the nucleophile, any effects arising from interactions of the alcohol, ROH, with the polar and nonpolar domains can be delineated. To this end, the primary aliphatic alcohols methanol, ethanol, 1-propanol, and 1-butanol as well as water and benzyl alcohol have been examined as nucleophiles in the present work. The ILs investigated as solvents for this reaction were 1-alkyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide salts ([C_nMIM][NTf₂]) where *n* = 2, 4, 6, 8, and 10). The mole fraction of IL employed in these experiments varied from 0.68–0.77, depending primarily on the length of the alkyl side chain, demonstrating that the IL solvent represents the bulk of the reaction medium (see the Supporting Information for precise mole fractions for each system).

As stated previously,^[5c] we chose 4-picoline as a leaving group for experimental convenience, to enable data collection over a reasonable time scale at a moderate temperature. The second-order rate constants obtained from these investigations are summarized in Table 1. While previous investigations of these systems have reported pseudo-first-order rate constants,^[5b,c] second-order rate constants are required to fit the kinetic model discussed below and consequently are used for all discussions herein. As is evident from the results in Table 1, for every nucleophile examined significant rate enhancements were observed when the length of the alkyl side chain of the IL was increased. However, even though a rate enhancement is seen in every case, it is evident that the extent of the increase is not uniform across all substrates. For example, the rate constant observed for water increased by 167% in [C₁₀MIM][NTf₂] relative to that in [C₂MIM][NTf₂], while the corresponding rate increase for 1-butanol between these two solvents was only 84%.

As the variation of the alkyl side chain of the IL is unlikely to directly affect any solvent–transition-state interactions, this rate enhancement must arise from a structural effect within the IL itself. By way of comparison, a significant reduction in

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[**] We thank Dr. Jason Harper and Prof. Greg Warr for helpful discussions, Dr. Ian Luck for his assistance with NMR experiments, and the University of Sydney for funding. C.C.W. thanks the University of Sydney for a Vice Chancellor's Research Scholarship.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201206113>.

Table 1: Second-order rate constants for the nucleophilic substitution of [Ar₃Pic][Cl] at 294.3 K in a range of 1-alkyl-3-methylimidazolium ILs.

IL	Water	Rate constants [$\times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$] ^[a]				
		Methanol	Ethanol	1-Propanol	1-Butanol	Benzyl alcohol
[C ₂ MIM][NTf ₂]	17.0 ± 0.5	33.8 ± 0.4	12.5 ± 0.4	12.7 ± 0.3	14.1 ± 0.8	5.8 ± 0.2
[C ₄ MIM][NTf ₂]	20.6 ± 0.3	46.5 ± 1.9	16.6 ± 0.1	16.7 ± 1.4	17.3 ± 1.2	8.0 ± 0.6
[C ₆ MIM][NTf ₂]	31.9 ± 1.1	57.5 ± 1.3	20.5 ± 0.9	20.2 ± 0.8	22.4 ± 0.5	8.7 ± 0.2
[C ₈ MIM][NTf ₂]	43.3 ± 0.5	68.6 ± 7.6	24.7 ± 0.5	23.2 ± 0.8	24.2 ± 1.9	11.2 ± 0.3
[C ₁₀ MIM][NTf ₂]	45.5 ± 0.9	70.5 ± 3.6	24.3 ± 1.4	25.4 ± 0.3	26.0 ± 1.3	12.1 ± 1.1

[a] Rate constants were obtained by dividing the pseudo-first-order rate constants by the initial concentration of nucleophile (0.515 M for all reactions). Reported errors are standard deviations of at least three replicate experiments.

the hydrogen bond strength caused by utilizing 1-butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imide ([C₄MMIM][NTf₂]) as a solvent rather than [C₄MIM][NTf₂] has been found to yield a reaction rate constant for hydrolysis of $(36.5 \pm 0.8) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$.^[6,5c] This means that the rate increase observed when the alkyl side chain is changed from butyl to octyl is larger than that obtained when the hydrogen-bond acidity of the medium is significantly reduced.^[5c]

Furthermore, the larger rate enhancement for water relative to the aliphatic alcohols or benzyl alcohol suggests that the effect is more pronounced for more polar molecules. The most logical explanation for such behavior arises from the nanostructural heterogeneity of the solvent, that is, the reactants concentrate in the polar domains which are relatively smaller in volume as the alkyl side chain of the IL increases. This phenomenon, that is, the pseudo-encapsulation of reactants in the polar domains of the IL, changes the effective concentrations of the reagents. Such effects have been observed in micellar kinetics,^[7] where the concentration of reagents within the micelle can significantly affect reaction rates. The aforementioned rate effects in micellar systems led to the development of a pseudophase model for the interpretation of kinetic data, where the two phases were defined as the aqueous phase and the interior of the micelle.^[8]

Applying such a pseudophase treatment to this non-micellar, but domain-based reaction system involves separating the rate law into the rates within both the polar and nonpolar domains, as shown in Equation (1), where [ROH]_p

$$r = k_p[\text{ROH}]_p[\text{Ar}_3\text{Pic}]^+_{\text{p}} + k_{\text{np}}[\text{ROH}]_{\text{np}}[\text{Ar}_3\text{Pic}]^+_{\text{np}} \quad (1)$$

and [Ar₃Pic]⁺_p refer to the concentrations of alcohol or water and substrate in the polar domains, respectively, and [ROH]_{np} and [Ar₃Pic]⁺_{np} refer to the corresponding concentrations in the nonpolar domains.

Given the proposition above that [Ar₃Pic]⁺ partitions exclusively into the polar domains, then [Ar₃Pic]⁺_{np} ≈ 0 and the contribution of the nonpolar domain to the rate can therefore be ignored. However, this assumption is not necessarily true for the nucleophile, so it is necessary to define a partition coefficient, *K*, to describe the proportion of nucleophile, ROH, in the nonpolar relative to polar domains and this is formalized in Equation (2).

$$K = \frac{[\text{ROH}]_{\text{np}}}{[\text{ROH}]_{\text{p}}} \quad (2)$$

This can then be combined to give Equation (3), where *V_p* is the volume of the polar domain and *V_{tot}* is the total volume of the system. The full derivation of this expression and the underlying assumptions made can be found in the Supporting Information.

$$r = \frac{k_p(V_{\text{tot}})^2[\text{ROH}]_{\text{tot}}[\text{Ar}_3\text{Pic}]^+_{\text{tot}}}{V_p(KV_{\text{tot}} + V_p(1 - K))} \quad (3)$$

As the total volume of the system was maintained at 1.05 mL for all reactions, only the volume of the polar domains is required in order to fit this model to the observed bimolecular rate constants. The volume of the nonpolar domains was estimated by a group contribution method where the volume of a CH₂ group was treated as 17.2 mL mol⁻¹, a value that has previously been found for imidazolium ILs,^[9] and the CH₃ group was assigned a volume of 25.49 mL mol⁻¹ based on the findings of Plyasunov et al. regarding aliphatic esters.^[10]

Fitting these data to the *V_p* values estimated by this method led to the plots in Figure 1. As can be observed, *R*² values greater than 0.92 were obtained for all nucleophiles in Figure 1 with excellent fits obtained in most cases, particularly given the relative simplicity of the model. In addition, the fitted *K* parameters obtained were consistent with values that could be anticipated in light of literature precedence. The fitted *K* value for water was zero (within error), indicating it does not partition into the nonpolar domains, as has been predicted through molecular dynamics (MD) simulations and determined spectroscopically.^[11]

The value of *K* increased with the length of the side chain for the aliphatic alcohols, consistent with the increased hydrophobicity leading to more favorable partitioning into the nonpolar domains. The *K* values for the alcohols also suggest significant interactions with both domains, as have been predicted by MD.^[11a] The *K* value obtained for benzyl alcohol was similar to that for methanol rather than for a longer chain alcohol and might arise from the quadrupolar interactions between the polar domain of the IL and the aromatic ring, as has been found for other aromatic systems in ILs, thereby favoring benzyl alcohol's solvation in the polar domain.^[12]

It is worth discussing that the rate constant obtained in [C₄MIM][NTf₂] with water as a nucleophile (*V_p* = 0.85 mL) lies significantly below that predicted by the fitted model. [C₄MIM][NTf₂] has been found to possess a nonpolar domain; however, owing to the bulk of the [NTf₂]⁻ anion, this domain is not a continuous microphase like that found for imidazolium ILs with longer alkyl side chains.^[3c] In addition, water has been found to reduce the cohesion of [C₄MIM][NTf₂] even at very low mole fractions^[13] which suggests that the anomalous result for [C₄MIM][NTf₂] with water employed as the nucleophile may arise from the reduced cohesion of the IL which already possesses weakly aggregated nonpolar domains. The reduced dissociating power of the aliphatic

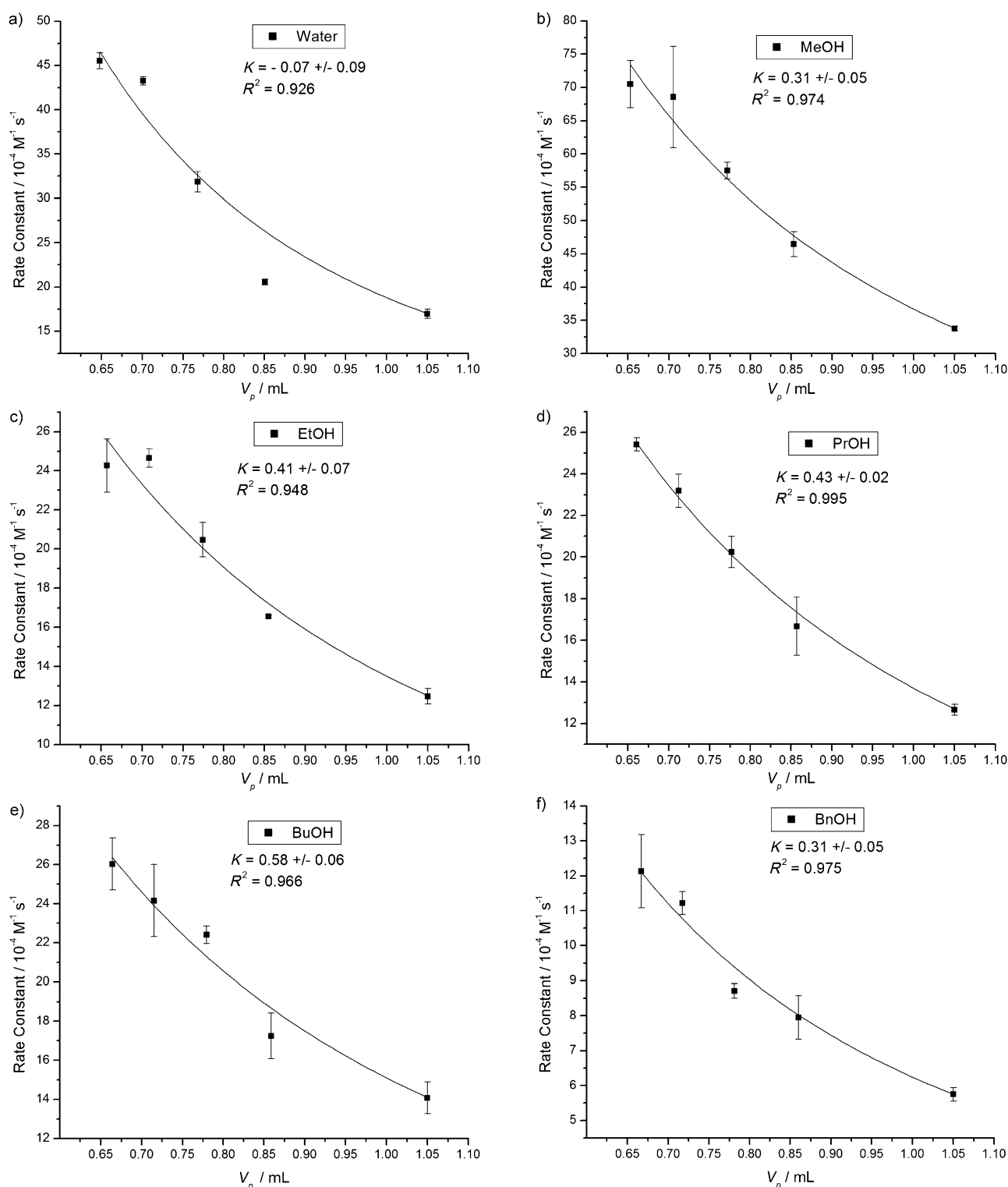


Figure 1. Rate data were fitted to the pseudophase kinetic model using values of V_p estimated from a group-contribution method.

alcohols could account for the significantly better fits obtained for these systems.

It is interesting to note a recent report that has mentioned the inhibition of a dehydration reaction when long alkyl side chains were used on the IL solvent.^[14] The “pseudo-encapsulation” effect outlined herein could be used to account for

these results as the effective water concentration in the polar domains of $[\text{C}_{10}\text{MIM}][\text{Cl}]$ would be much higher than is the case in $[\text{C}_2\text{MIM}][\text{Cl}]$. The difference in the effective water concentration would lead to a significant increase in the rate of the reverse reaction and hence a lower overall yield, as was observed in that system.

In conclusion, a significant rate enhancement, up to 167%, has been observed for a nucleophilic substitution reaction simply through variation of the length of the alkyl side chain of imidazolium ILs. This rate increase has been attributed to the pseudo-encapsulation of reactants in the polar domain of the IL, which changes the effective concentrations of the reagents, and a kinetic model based on this interpretation has been found to accurately represent the observed data.

This pseudo-encapsulation effect suggests that ILs may have the potential to facilitate cascade reactions where, for example, the rate of reaction of a set of polar reagents is accelerated leading to the formation of a nonpolar product that may then react more quickly with an added nonpolar reagent, resulting in significant acceleration of the overall reaction/process. It may also be possible to conduct reactions in the presence of traditionally incompatible compounds, so long as there is a preference for these components to be solvated in separate domains. This would be comparable to the use of nanoencapsulated systems, without the need for the extensive synthetic procedures often associated with such systems.^[15] Furthermore, the use of mixtures of ILs and nonpolar solvents may enhance the rate of reaction of polar reagents through the relative decrease in volume of the polar domains of these ILs for a given reaction volume. Consideration of these effects may therefore further aid the rational selection of ILs as solvents to facilitate favorable chemical outcomes. The consequences of structural heterogeneity may also account for some previously unexplained IL-mediated phenomena, such as the inhibition of dehydration reactions discussed above.

Experimental Section

For the general kinetics protocol, an NMR tube equipped with a Young's valve was charged with *p*-fluorophenyldiphenylmethyl chloride (15–25 mg, 0.05–0.08 mmol) under a flow of nitrogen. 4-Picoline (50 μ L) was added to dissolve the substrate. Approximately 5 min before the reaction was to be monitored, the solution was diluted with the IL containing ROH (0.98 mL of 0.55 M ROH) and cooled in an ice bath. The sample was then mixed using a Vortex mixer and the reference capillary (1-bromo-4-fluorobenzene in D_6 acetone (0.50 M)) inserted co-axially. The tube was immediately inserted into the NMR probe which had been precooled to 294.3 K, the temperature of the NMR tube was allowed to equilibrate, and $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were subsequently obtained at that temperature every 65 seconds. For additional details on synthesis, characterization, and calculation, see the Supporting Information.

Received: July 31, 2012

Published online: October 12, 2012

Keywords: ionic liquids · kinetics · nucleophilic substitution · solvent effects · structural heterogeneity

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