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Understanding the effects of solvate ionic liquids as solvents on substitution processes†

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The effects of solvate ionic liquids as solvents have been considered for two substitution processes where the solvent effects of typical ionic liquids have been extensively investigated previously; the bimolecular nucleophilic substitution (S_N2) reaction between pyridine and benzyl bromide and the nucleophilic aromatic substitution (S_NAr) reaction between ethanol and 1-fluoro-2,4-dinitrobenzene. It was found that use of solvate ionic liquids gave rise to similar trends in the activation parameters for both substitution processes as typical ionic liquids, implying the microscopic interactions responsible for the effects were the same. However, different effects on the rate constants compared to typical ionic liquids were observed due to the changes in the balance of enthalpic and entropic contributions to the observed rate constants. From these data it is clear that the reaction outcome for both of these substitution reactions fall within the 'predictive framework' established in previous studies with a cautionary tale or two of their own to add to the general knowledge of ionic liquid solvent effects for these processes, particularly with respect to potential reactivity of the solvate ionic liquids themselves.

Ionic liquids are typically defined as salts with melting points below 100 °C [1–3] and usually consist of a bulky, asymmetric organic cation accompanied by either an organic or inorganic anion.[2,4] Ionic liquids have garnered interest in a number of fields due to their often favourable properties compared to conventional molecular solvents. Properties such as low flammability and volatility,[3,5] as well as considerable thermal stability make the use of ionic liquids as solvents for synthesis[6,7] and selective extraction,[8,9] and as electrolytes in batteries[10–12] safer and prospectively 'greener'.[13–15] Modification of the physicochemical properties of ionic liquids is possible through variation of the constituent ions,[2,16,17] thus through rational choice of the components of the ionic liquid these salts have often been deemed as 'task-specific', or 'designer', solvents.[16,18]

Solvate ionic liquids are a subclass of ionic liquids that contain at least one complex ion.[19] As solvents, these substances might be considered to allow simple, rapid yet effective modification of the components of the ionic liquid. The lithium glyme solvate ionic liquids are one example of this class of ionic liquids; they contain a lithium ion solvated by a polyether (glyme) as the cation.[20] Lithium glyme salts made in equimolar ratios of lithium bis(trifluoromethanesulfonyl)imide and glyme[21] have properties akin to those of ionic liquids[20] and the formation of a stable complex cation has been determined through self-diffusion coefficients,[21] molecular dynamics simulations[22] and Kamlet–Taft solvent parameters.[23,24] A simplified depiction of two such lithium glyme solvate ionic liquids (lithium triethylene glycol dimethyl ether bis(trifluoromethanesulfonyl)imide ($[Li(G3)][N(SO_2CF_3)_2]$, **1**) and lithium tetraethylene glycol dimethyl ether bis(trifluoromethanesulfonyl)imide ($[Li(G4)][N(SO_2CF_3)_2]$, **2**)) is shown in Fig. 1.‡

The Kamlet–Taft solvent parameters also indicated that the hydrogen bond donating ability of each of the lithium glyme ionic liquids **1** and **2** was greater than that of the parent glyme[23] as well as other typical ionic liquids (such as 1-butyl-bis(trifluoromethanesulfonyl)imide $[Bmim][N(SO_2CF_3)_2]$, **3**).[25] The lithium glyme salts **1** and **2** lack acidic protons suggesting that the higher hydrogen bond donating ability was due to strong interactions between the lithium centre of the cation and the probe molecule.[23] This strong coordination might be

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† Electronic supplementary information (ESI) available: Preparation of the solvate ionic liquids **1** and **2**, further details of the kinetics analyses including rate equations, stock solution composition and rate constant data for substitution reactions examined, further experimental details on the experiments undertaken to identify the 'alternate' product including ^1H NMR and high resolution mass spectra along with experiments supporting the mechanism of its formation. See DOI: 10.1039/c9ob01753d

‡ Whilst the glyme solvate ionic liquids are commonly depicted as shown in Fig. 1 they can also exist either as complexes where multiple glymes complex to multiple lithium centres or as larger clusters.[22]

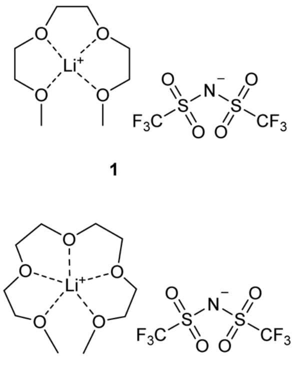
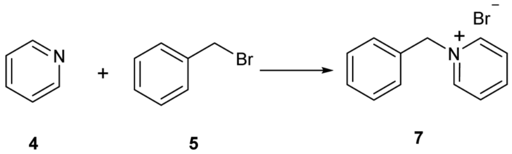
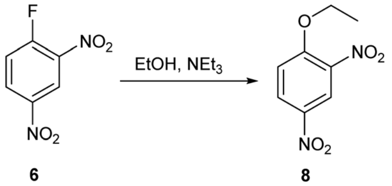


Fig. 1 A simplified representation of the solvate ionic liquids [Li(G3)][N(SO_2CF_3)$_2$] **1** and [Li(G4)][N(SO_2CF_3)$_2$] **2**.



Scheme 1 The bimolecular nucleophilic substitution (S_N2) reaction between pyridine **4** and benzyl bromide **5** to give the pyridinium salt **7**.



Scheme 2 The nucleophilic aromatic substitution (S_NAr) reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** to give the phenetole **8**.

of interest in systems where interaction of the cation of an ionic liquid is favourable.

A number of studies have attempted to understand and rationalise the effect ionic liquids have when used as solvents for synthetic processes compared to the reaction outcomes observed in conventional molecular solvents.[26,27] The effects of using solvate ionic liquids for preparative chemistry is, by comparison, extremely limited – there have only been three reports in the literature. One case is an organocatalytic asymmetric aldol reaction; however, the solvate ionic liquid is only present in catalytic quantities and as such is not acting as a solvent.[28] Two examples where lithium glyme solvate ionic liquids were used in much greater proportions were for a series of electrocyclic transformations[29] and the synthesis of α-aminophosphonates.[30] These studies demonstrated higher yields in shorter reaction times for reactions in solvate ionic liquids, compared to a molecular solvent. However, the reactions were only performed at one solvent composition for each type of reaction and solvent effects of ionic liquids are known to vary with composition.[27] Importantly, the authors provided some explanation for the reaction outcomes (in terms of the relatively high Lewis acidity of the lithium glyme solvate ionic liquids).

If solvate ionic liquids are to be used in preparative chemistry, a rational understanding of their solvent effects is needed. Ideally, comparisons to ‘typical’ ionic liquids could be made. As such, it is of interest to consider the effects of solvate ionic liquids on processes which have previously been extensively examined in other ionic liquids. Two such processes are the bimolecular nucleophilic substitution (S_N2) reaction between pyridine **4** and benzyl bromide **5** (Scheme 1)[31–36] and the nucleophilic aromatic substitution (S_NAr) reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** (Scheme 2).[37–40]

Rate constant enhancements observed on moving to an ionic liquid for the S_N2 reaction (Scheme 1) were found to be due to an entropic effect, arising from a key interaction between the cation of the ionic liquid and the nucleophilic lone pair of pyridine **4**.[32,33] Greater rate constant enhancement was observed when using ionic liquids with greater charge density and accessibility to the charged centre of the cation.[34,35] For the S_NAr reaction (Scheme 2), it was found that the greatest rate enhancement was observed when the charged centre of the cation of the ionic liquid was most hindered.[38] At the same time, the more available the anion of the ionic liquid was to interact with the electrophile **6**, the greater the rate constant enhancement observed.[39] However, it was noted that using the traditional salt lithium bis(trifluoromethanesulfonyl) imide (Li[N(SO_2CF_3)$_2$]) resulted in a greater rate constant enhancement than any of the ionic liquids considered; this was proposed to be due to favourable interaction between the small, charge dense lithium cation and the nucleophile, ethanol.[38]

Each of these reactions provides an opportunity to consider the effects of solvate ionic liquids and how such effects might be considered in terms of the solvent effects typically observed in ionic liquids. As such, each of the processes shown in Schemes 1 and 2 was examined in the representative lithium glyme ionic liquids **1** and **2**.

Results and discussion

Solvent effects of solvate ionic liquids on a bimolecular nucleophilic substitution reaction

Initially considered were the effects of the solvate ionic liquids **1** and **2** on the bimolecular nucleophilic substitution reaction between pyridine **4** and benzyl bromide **5** (Scheme 1). As mentioned above, previous studies have shown that the greater the charge density and accessibility to the charge centre of the cation of an ionic liquid, the greater the rate constant enhancement, relative to acetonitrile,[35] due to a key interaction between the nucleophilic lone pair of pyridine **4** and the cation of the ionic liquid.[33,35] It was anticipated that greater control of these microscopic interactions, and thus reaction outcome, may be achieved with the lithium glyme solvate ionic

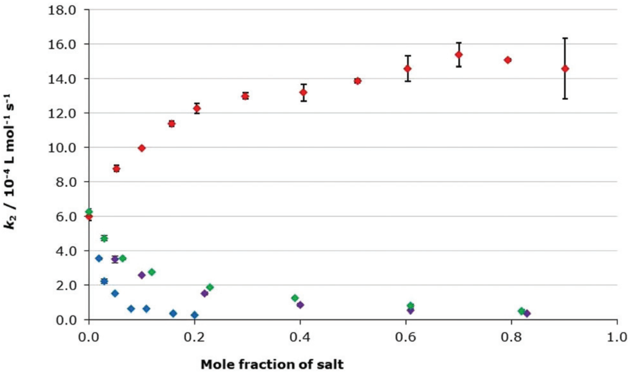


Fig. 2 The bimolecular rate constants for the S_N2 reaction between pyridine **4** and benzyl bromide **5** across a range of different solvent compositions of either the ionic liquid [Bmim][$N(SO_2CF_3)_2$] **3** (red),[31] one of the solvate ionic liquids [Li(G3)][$N(SO_2CF_3)_2$] **1** (purple) and [Li(G4)][$N(SO_2CF_3)_2$] **2** (green), or the 'traditional' salt Li[$N(SO_2CF_3)_2$] (blue) in acetonitrile at 22.2 °C. Uncertainties are the standard deviation of triplicate results; a large number of the error bars fall within the size of the markers used.

liquids [Li(G3)][$N(SO_2CF_3)_2$] **1** and [Li(G4)][$N(SO_2CF_3)_2$] **2** given the highly accessible, charge dense cations[23] and the weak coordinating ability of the bis(trifluoromethanesulfonyl)imide anion.

The effect on the bimolecular rate constant of the reaction between pyridine **4** and benzyl bromide **5** (Scheme 1) on the proportion of either of the solvate ionic liquids **1** and **2** in the reaction mixture was considered. The importance of the complexed lithium cation in the glyme solvate ionic liquids **1** and **2** was also considered by investigating the trend in the rate constant when using the 'traditional' salt Li[$N(SO_2CF_3)_2$]. These data are shown in Fig. 2 with the data obtained in previous studies for a representative typical ionic liquid [Bmim][$N(SO_2CF_3)_2$] **3** [31] included for comparison.

For each of the lithium glyme solvate ionic liquids **1** and **2**, as well as the 'traditional' lithium salt, there is a distinct decrease in the rate constant as the proportion of these lithium salts increase in the reaction mixture, relative to the molecular solvent acetonitrile.§ There is little difference in the magnitude of the rate constant decrease observed between the two solvate ionic liquids, though generally the triglyme case **1** was slower, whilst the 'traditional' lithium salt exhibits a significantly greater decrease in the rate constant. The majority of these decreases in the rate constant have occurred by low proportions of these salts in the reaction mixture; by $\chi_{\text{salt}} \approx 0.1$ for Li[$N(SO_2CF_3)_2$] there is an approximately 20-fold decrease in the rate constant and by $\chi_{\text{salt}} \approx 0.2$ for the solvate ionic liquids **1** and **2** there is a 6-fold decrease in the rate constant. It is interesting to note that the trend in the rate constant as the proportion of the solvate ionic liquids **1** and **2** in the reaction mixture is varied 'mirrors' that observed for [Bmim][$N(SO_2CF_3)_2$] **3**.[31] This observation could suggest that the microscopic origin resulting in the change in the rate constant observed (regardless of the direction) is likely the same.

The order of the rate constant decreases implies that coordination of the lithium by a glyme has an effect on the interaction responsible for the rate constant changes with non-coordinated lithium having the greatest effect on rate constant. The small difference between the ionic liquids **1** and **2** is consistent with greater coordination of the lithium centre in the tetraglyme case **2**.

In order to further investigate these suppositions regarding the microscopic origins behind the changes in the rate constant observed, temperature dependent kinetic studies were undertaken. The rate constants were measured across a range of temperatures and the data was analysed using the bimolecular form of the Eyring equation (see Fig. S1 in the ESI†) to determine the activation parameters at select solvent compositions (Table 1). The solvent compositions chosen were the cases where the solvate ionic liquids **1** and **2** were diluted by reagents only ($\chi_{\text{salt}} \approx 0.8$) and the point of greatest solubility for the Li[$N(SO_2CF_3)_2$] in acetonitrile ($\chi \approx 0.2$). The activation parameters for the molecular solvent, acetonitrile, and the ionic liquid [Bmim][$N(SO_2CF_3)_2$] **3** ($\chi_{\text{salt}} \approx 0.9$) have been included for comparison.[32]

An increase in both the enthalpy and entropy of activation was observed for the two solvate ionic liquids **1** and **2** as well as the 'traditional' salt Li[$N(SO_2CF_3)_2$] relative to the molecular solvent acetonitrile. The trends in the activation parameter changes are similar to those observed on changing solvent from acetonitrile to the ionic liquid [Bmim][$N(SO_2CF_3)_2$] **3**,[32] though the magnitude of the difference in the activation parameters is greater for the lithium salts. These similarities suggest that the same microscopic interactions (between the cation of the salt and the nucleophilic lone pair on pyridine **4**) might be responsible for the rate changes.

Whilst the changes in the activation parameters on moving from acetonitrile are in the same direction for all the salts considered, the magnitudes of these changes are significantly different. The enthalpy of activation for the process in each of the solvate ionic liquids **1** and **2** and in the mixture containing the parent lithium salt is significantly greater than in

Table 1 Activation parameters for the S_N2 reaction between pyridine **4** and benzyl bromide **5** in solvent mixtures of either [Bmim][$N(SO_2CF_3)_2$] **3** ($\chi_3 \approx 0.9$), Li[$N(SO_2CF_3)_2$] ($\chi_{\text{salt}} \approx 0.2$), [Li(G3)][$N(SO_2CF_3)_2$] **1** ($\chi_1 \approx 0.8$) or [Li(G4][$N(SO_2CF_3)_2$] **2** ($\chi_2 \approx 0.8$) in acetonitrile

Solvent	χ_{salt}	$\Delta H^{\ddagger a}$/kJ mol^{-1}	$\Delta S^{\ddagger a}$/J K^{-1} mol^{-1}
Acetonitrile[b]	0	43.4 ± 0.8	−224 ± 3
[Bmim][$N(SO_2CF_3)_2$] **3**[b]	0.86	49.9 ± 0.8	−195 ± 3
Li[$N(SO_2CF_3)_2$]	0.20	63.2 ± 2.2	−186 ± 7
[Li(G3)][$N(SO_2CF_3)_2$] **1**	0.82	58.8 ± 1.9	−194 ± 6
[Li(G4][$N(SO_2CF_3)_2$] **2**	0.83	58.6 ± 1.1	−190 ± 3

[a] Uncertainties reported are propagated from the linear regression. [b] Reproduced from Yau *et al.*[32]

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§ This decrease in the rate constant has been noted previously in the presence of lithium bis(trifluoromethanesulfonyl)imide for a related S_N2 reaction (4-methylbenzyl bromide instead of the protio case **5** examined here).[47]

[Bmim][$N(SO_2CF_3)_2$] **3**¶ while the entropies of activation are the same. These data indicate a different balance of entropic and enthalpic effects; whereas in the previously considered salt **3** the entropic term dominated resulting in a rate constant increase, the enthalpic contribution was most significant for each of the lithium salts considered, resulting in a rate constant decrease. This detrimental balance of enthalpic and entropic contributions based on interactions between the starting materials and components of the ionic liquid has been observed in another bimolecular nucleophilic substitution process involving a charged nucleophile where the rate constant was also negatively affected relative to the molecular solvent.[41–43] Such ionic liquid solvent effects for solvate ionic liquids might mean that they cannot be used to facilitate an S_N2 process, however they should be kept in mind when it might be desirable to manipulate reaction outcome for such a process. It would be expected that in cases where coordination of the lithium by the nucleophile predominates (such as that presented here), then suppression of a competing S_N2 process might be possible.

This example demonstrates that the arguments presented previously for the microscopic origins of solvent effects of 'typical' ionic liquids can be extended to solvate ionic liquids (and, in fact, salts that are solid at room temperature). The cautionary tale in this case is that the balance of enthalpic and entropic effects may be difficult to assign, and hence the changes in reaction outcome different between the types of ionic liquid considered.

Solvent effects of solvate ionic liquids on a nucleophilic aromatic substitution reaction

Given the significant interactions seen in solution involving the cations of the lithium glyme solvates **1** and **2**, it was of interest to see the effects of these salts on the outcome of the reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** (Scheme 2). Previous work has shown that for this reaction addition of Li[$N(SO_2CF_3)_2$] to the reaction mixture resulted in increases in the rate constant due to favourable interaction between the oxygen of ethanol and the lithium cation.[38] The effect of the lithium salt on the rate constant was greater than that of the wide range of ionic liquids considered,[38] though limited by the solubility of the lithium salt. It was therefore of interest to determine whether the lithium glyme solvate ionic liquids **1** and **2** might be used to increase the proportion of lithium in the reaction mixture without decreasing the efficacy of the microscopic interactions.

Initial investigations focused on understanding the dependence of the rate constant on the proportion of solvate ionic liquid in the reaction mixture, the results of which are shown in Fig. 3 below with comparison to the ionic liquid **3** and Li[$N(SO_2CF_3)_2$].[38] Whilst undertaking these studies it became apparent that at $\chi_{\text{solvates}} > 0.4$ an additional product was forming alongside the expected phenetole **8**; this will be discussed further below. As such, the discussion will start with the effects of solvate ionic liquids on the reaction shown in Scheme 2 at solvent compositions $\chi_{\text{solvates}} \leq 0.4$.

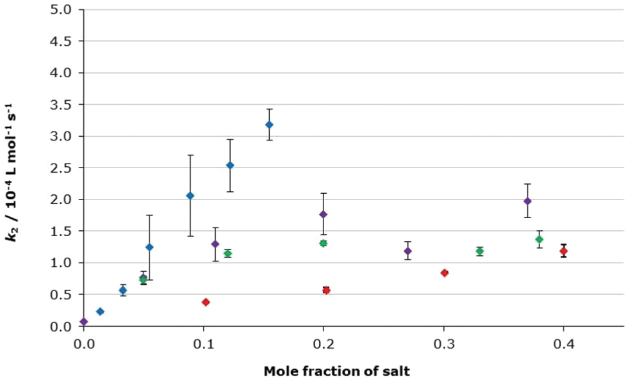

Fig. 3 The bimolecular rate constants for the S_NAr reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** across a range of different solvent compositions of either the ionic liquid [Bmim][$N(SO_2CF_3)_2$] **3** (red),[38] one of the solvate ionic liquids [Li(G3)][$N(SO_2CF_3)_2$] **1** (purple) and [Li(G4)][$N(SO_2CF_3)_2$] **2** (green), or the 'traditional' salt Li[$N(SO_2CF_3)_2$] (blue)[38] in ethanol at 51.0 °C. Uncertainties are the standard deviation of triplicate results; some uncertainties fall within the size of the markers used.

For both of the solvate ionic liquids **1** and **2** there is an increase in the rate constant relative to ethanol upon addition of any amount of the salts **1** and **2** to the reaction mixture. The trend in the rate constants observed as the proportion of the solvate ionic liquids **1** and **2** in the reaction mixture increases is similar to that observed in both the 'typical' ionic liquid **3** and the salt Li[$N(SO_2CF_3)_2$];[38] the rate constant generally increases as the amount of salt in the reaction mixture increases. The effect of the two solvate ionic liquids **1** and **2** is generally intermediate between the other cases presented, with the triglyme salt **1** having a slightly greater effect on the rate constant; for [Li(G3)][$N(SO_2CF_3)_2$] **1** there is an approximately 30-fold increase in the rate constant at $\chi_{\text{solvates}} \approx 0.4$ whereas the rate constant enhancement in [Li(G4)][$N(SO_2CF_3)_2$] **2** is approximately 20-fold at a similar solvent composition, both relative to ethanol.

To better understand the microscopic origins of these solvent effects, the activation parameters were determined for the solvate ionic liquids **1** and **2** and compared to those previously determined for [Bmim][$N(SO_2CF_3)_2$] **3** and Li[$N(SO_2CF_3)_2$].[38] A solvent composition of $\chi_{\text{solvates}} \approx 0.2$ was considered for the two solvate ionic liquids **1** and **2** to allow more direct comparison to the Li[$N(SO_2CF_3)_2$] data determined previously.[38] These data were determined in an analogous manner to that described for the S_N2 processes discussed above and are presented in Table 2 below.

For reaction mixtures containing each of the solvate ionic liquids **1** and **2**, there is an increase in the entropy of activation

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¶There is a small difference in the enthalpies of activation between the two solvate ionic liquids **1** and **2** and lithium bis(trifluoromethanesulfonyl)imide case, however, given the marginal differences in magnitude as well as the different mole fractions of these salts it is difficult to draw any definite conclusions from the enthalpy of activation data alone.

Table 2 Activation parameters for the S$_N$Ar reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** in solvent mixtures of either [Bmim][N(SO$_2$CF$_3$)$_2$] **3** ($\chi_3 \approx 0.5$), Li[N(SO$_2$CF$_3$)$_2$] ($\chi_{\text{salt}} \approx 0.2$), [Li(G3)][N(SO$_2CF_3$)$_2$] **1** ($\chi_1 \approx 0.2$) or [Li(G4)][N(SO$_2CF_3$)$_2$] **2** ($\chi_2 \approx 0.2$) in acetonitrile

Solvent	χ_{salt}	$\Delta H^{\ddagger a}$/kJ mol^{-1}	$\Delta S^{\ddagger a}$/J K^{-1} mol^{-1}
Ethanol[b]	0	49.0 ± 0.5	−259 ± 2
[Bmim][N(SO$_2$CF$_3$)$_2$] **3**[b]	0.54	49.6 ± 0.5	−229 ± 2
Li[N(SO$_2$CF$_3$)$_2$][b]	0.16	57.2 ± 2.2	−202 ± 7
[Li(G3)][N(SO$_2$CF$_3$)$_2$] **1**	0.21	55.7 ± 1.8	−213 ± 6
[Li(G4][N(SO$_2$CF$_3$)$_2$] **2**	0.22	51.5 ± 4.0	−225 ± 12

[a] Uncertainties reported are propagated from the linear regression. [b] Reproduced from Hawker *et al.*[38]

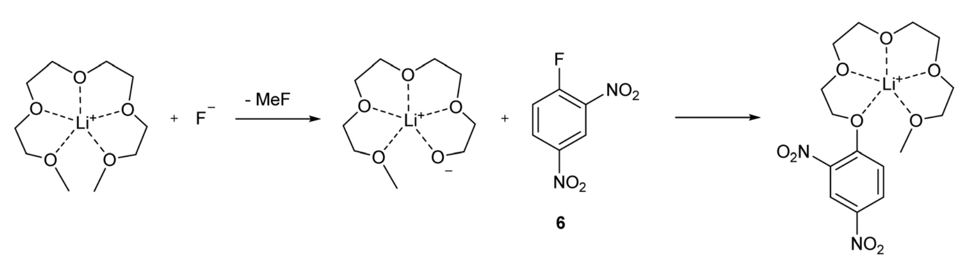
relative to the ethanol case; the enthalpy of activation is either the same or slightly larger. As such, the rate constant increase observed is due to an entropic effect; this outcome is consistent with previous results for other ionic liquids at low mole fractions in the reaction mixture.[38,39]

These trends in the activation parameters suggest an increase in interaction with, and organisation about, the starting materials by the solvate ionic liquids **1** and **2** relative to ethanol. Previous studies have correlated such trends in the activation parameters with interactions between ethanol and the lithium centre (in the Li[N(SO$_2$CF$_3$)$_2$] case[38]) and between the electrophile **6** and the anion of an ionic liquid (for ionic liquid cases such as [Bmim][N(SO$_2$CF$_3$)$_2$] **3** [40]). In the cases discussed here, it is likely that there is a balance of both of these microscopic interactions present when the solvate ionic liquids **1** and **2** are in the reaction mixture. Interpreting this balance further would be of interest, given the different coordination environments of the lithium centre in each case, but is complicated by the uncertainties in the activation parameter data. However, importantly, the understanding of ionic liquid solvent effects developed previously[38,39] for this reaction can be applied to predict the effects (and their microscopic origin) for solvate ionic liquids.

As indicated above, additional signals were observed in the ^{1}H NMR spectra of reaction mixtures in the solvate ionic liquids at $\chi_{\text{solvate}} > 0.4$ (see Fig. S5†); these signals suggested an additional product other than the phenetole **8**. Reaction of the electrophile with either adventitious water or triethylamine was ruled out by preparing authentic samples of the appropriate species and adding the material to the reaction mixtures (see Fig. S7–12†). Dilution of the reaction mixtures with ethanol did not affect the signals (see Fig. S6†), suggesting that they were not due to coordination of the product **8** with lithium. Attempted direct reaction of the benzene **6** with tetraglyme proved, not surprisingly, unsuccessful (Fig. S13–15†). However, reaction of the solvate ionic liquid [Li(G4)][N(SO$_2$CF$_3$)$_2$] **2** with the benzene **6** gave a product with signals in the ^{1}H NMR spectrum consistent with those new signals observed during the kinetic experiments (Fig. S17†), suggesting that the additional product formed during the reactions at high proportions of the solvate ionic liquid was a lithiated form of an aromatic glyme ether, exemplified by species **9**. Isolation of the additional product **9** from the reaction mixtures (through separation and chromatography) proved impossible; this is not unreasonable given that, due to the lithiated polyglyme nature of the species **9**, it likely exists as a component of the solvate ionic liquid. (Likewise, separation of the delithiated form of species **9** from the corresponding glyme proved unsuccessful.) Instead characterisation of the product by using high resolution mass spectrometry was carried out on the reaction mixture and the data corresponded to the lithiated glyme product **9** (see ESI, Fig. S20†).

These experiments show that the polyether of the solvate ionic liquid reacts with the benzene **6** and that the lithium cation is necessary for this reactivity, likely activating the polyether. A plausible mechanism would involve the nucleophilic attack of free fluoride (produced from any S$_N$Ar reaction involving the benzene **6**) onto the glyme, which is activated through coordination to lithium (Scheme 3). The generated alkoxide (or alcohol after reprotonation in the reaction mixture) can then act as the nucleophile in the S$_N$Ar reaction with the electrophile **6**. Support for this mechanism is provided by additional experiments in which a fluoride scavenger was added to the reaction mixture and no such reaction occurred, and when fluoride was added to the salt **2** and similar signals were found in the ^{1}H NMR spectrum of the reaction mixture (see ESI† for experimental details).

The presence of the additional products only at high mole fractions of the solvate ionic liquids **1** and **2** is readily explained. Obviously, at solvent compositions containing greater amounts of solvate ionic liquid, more of the activated polyether nucleophile is present in the reaction mixture.



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Scheme 3 The proposed mechanism for the reaction of [Li(G4)][N(SO$_2$CF$_3$)$_2$] **2** with 1-fluoro-2,4-dinitrobenzene **6** to give the lithiated form of the glyme product **9**; it is anticipated that analogous reactions occur in the salt **1** case.

Further, at these solvent compositions there is less ethanol; along with reducing the amount of competitive nucleophile present, the fluoride anion generated from any reaction of the benzene **6** is less solvated by the protic ethanol than at lower proportions of the solvate ionic liquids, resulting in a greater reactivity of the fluoride present.[44] Interestingly, reactivity of lithium glyme solvate ionic liquids has not been noted in other studies where this subclass of ionic liquids have been used as solvents for preparative chemistry.[28–30] Presumably this lack of reactivity is due to either the use of low mole fractions of solvate ionic liquid ($\chi_{\text{solvates}} \leq 0.4$), the absence of a sufficiently strong nucleophile or a combination of both.

Whilst formation of this additional product as a result of reactivity of the solvate ionic liquid does limit the utility of these ionic liquids above certain proportions in the reaction mixture, it should be noted that the general trend in rates constants at $\chi_{\text{solvates}} > 0.4$ matches what has been seen previously for other ionic liquids (see Fig. S2†).[38,39] This overall predictability of behaviour demonstrates one of the advantages of using solvate ionic liquids as solvents for S_NAr reactions. The rate constant enhancements observed and the microscopic origins behind these enhancements are predictable based on previous studies of ionic liquid solvent effects on this reaction.[37–40] Note, however, that caution is advised in considering the solvent composition and the reaction conditions such that promotion of an undesired side-reaction involving the ionic liquid is prevented.

Conclusions

From the work presented here, the understanding of ionic liquid solvent effects on both S_N2 and S_NAr reactions has been extended to incorporate the solvate subclass of ionic liquids.

For the S_N2 reaction between pyridine **4** and benzyl bromide **5**, the same microscopic interactions were present in solvate ionic liquids and 'typical' ionic liquids, however the balance of enthalpic and entropic contributions resulted in different reaction outcomes. Where rate constant enhancement has been observed previously for 'typical' ionic liquids, the rate constant decreased in the presence of the solvate ionic liquids **1** and **2** relative to the molecular solvent, acetonitrile. This knowledge might be of benefit in instances where disfavouring an S_N2 reaction, such as one that forms an unwanted byproduct, may be desirable.

For the S_NAr reaction between ethanol and 1-fluoro-2,4-dinitrobenzene **6** it was found that whilst both solvent effects of solvate ionic liquids on the rate constant, and microscopic origins of such, were predictable based on previous studies,[37–40] care needs to be taken to avoid reactivity of the solvent. This reactivity is likely to be particularly notable at solvent compositions containing high proportions of the solvate ionic liquid, particularly where strong nucleophiles are present in the reaction mixture. Importantly, given it has been identified, such reactivity may be worked around given proper synthetic design of the reaction conditions. Notably, this study has highlighted the ability of solvate ionic liquids to increase the reactivity of polyethers which generally are treated as inert.

In summary, there is the potential to control reaction outcome for these, and related, substitution reactions with accessibility to simple modification of the cation through variation of the coordinating ligand, thus opening up further avenues for ionic liquid design and manipulation of the microscopic interactions in these systems.

Experimental

Benzyl bromide **5**, pyridine **4** and triethylamine were distilled[45] and stored over activated molecular sieves (3 Å) at 4 °C prior to use. Ethanol and acetonitrile were distilled[45] and stored over activated molecular sieves (3 Å) at room temperature under nitrogen. All other chemicals were purchased and used without further purification. The solvate ionic liquids $[\mathrm{Li(G3)}][\mathrm{N(SO_2CF_3)_2}]$ **1** and $[\mathrm{Li(G4)}][\mathrm{N(SO_2CF_3)_2}]$ **2** were prepared according to a modified literature procedure.[21] The appropriate glyme was rinsed into $\mathrm{Li[N(SO_2CF_3)_2]}$ (which had been dried under reduced pressure until a constant pressure reading was of <0.1 mbar was obtained) with dichloromethane and the resulting mixture was stirred under nitrogen for 2–3 days. The solvate ionic liquids **1** and **2** were dried under reduced pressure (<0.1 mbar) at room temperature until a constant pressure reading was obtained and <300 ppm water was detected *via* Karl-Fischer titrimetry yielding both solvate ionic liquids **1** and **2** as clear, colourless liquids. Full experimental details for the preparation of these solvate ionic liquids **1** and **2** can be found in the ESI.†

All kinetic measurements were obtained by monitoring reaction progress using NMR spectroscopy with either a Bruker Avance III 400, 500 or 600 NMR spectrometer equipped with either a BBO, BBFO or TBI probe; results were shown to be reproducible regardless of either the spectrometer or the probe used. The temperature of the NMR spectrometers and water baths were calibrated using a thermocouple containing ethanol.

For the S_N2 reaction, reaction progress was monitored using ^{1}H NMR spectroscopy either following the depletion of the signal due to the benzylic proton signal of benzyl bromide **5** at δ *ca.* 4.4 (for reaction <18 h which were monitored in the NMR spectrometer) or by following both this benzylic signal as well as that of the product **7** at δ *ca.* 5.5 (for reactions ≥18 h which were incubated in a water bath calibrated to the desired temperature with spectra collected periodically) to determine the extent of conversion to >95% completion. For the S_NAr reaction, reaction progress was monitored in the NMR spectrometer using ^{19}F{^{1}H} NMR spectroscopy by following depletion of the starting material **6** fluorine signal at δ *ca.* −109 over time to >95% completion.

For the kinetic studies of the dependence of the rate constant on the amount of salt present in the reaction mixture for both of the reactions considered, stock solutions were prepared containing different solvent compositions of the salt of choice and the appropriate molecular solvent. These stock solutions also contained at least a 10-fold excess of the nucleophile, relative to the electrophile. For the studies of the S_N2 reaction, the electrophile **5** was included in the stock solution with *ca.* 0.5 mL aliquots being transferred to 5 mm NMR tubes which were kept at −196 °C prior to conducting the kinetic studies. For the S_NAr reaction, an approximately 10-fold excess of triethylamine, relative to the electrophile **6**, was also included in the stock solution and the required amount of the electrophile **6** was added to a 5 mm NMR tube instead of to the stock solution. A 0.5 mL aliquot of the stock solution was added to the prepared NMR tube containing the electrophile **6** and was thoroughly mixed prior to undertaking the kinetic studies. The bimolecular rate constants for both processes were determined by division of the observed pseudo-first order rate constant, obtained by fitting a linear equation to the natural log of the area under the respective NMR signals discussed above with time using LINEST in Microsoft Excel, by the concentration of the nucleophile.

The temperature dependent kinetic studies were undertaken in an analogous manner to those kinetic studies described above at select solvent compositions discussed in the main text. Four temperatures were selected across a range of 30 °C for both substitution reactions. These rate constants were fit to the bimolecular form of the Eyring equation[46] using the LINEST function in Microsoft Excel to determine the activation parameters.

Additional details pertaining to the exact stock solution compositions (including masses, concentrations of reagents and the mole fractions of salt), temperatures, rate constants, rate equations can be found in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083.
2 C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, 2005, **18**, 275–297.
3 F. Endres and S. Z. El Abedin, *Acc. Chem. Res.*, 2007, **40**, 1106–1113.
4 A. Maia, *Mini-Rev. Org. Chem.*, 2011, **8**, 178–185.
5 K. N. Marsh, A. Deev, A. Wu, E. Tran and A. Klamt, *Korean J. Chem. Eng.*, 2002, **19**, 357–362.
6 N. Kaur, *Synth. Commun.*, 2018, **48**, 473–495.
7 J. P. Hallett and T. Welton, *Chem. Rev.*, 2011, **111**, 3508–3576.
8 G. Huddleston, D. Jonathan and R. Rogers, *Chem. Commun.*, 1998, 1765–1766.
9 A. Berthod, M. J. Ruiz-Ángel and S. Carda-Broch, *J. Chromatogr. A*, 2018, **1559**, 2–16.
10 D. R. MacFarlane, M. Forsyth, P. C. Howlett, M. Kar, S. Passerini, J. M. Pringle, H. Ohno, M. Watanabe, F. Yan, W. Zheng, S. Zhang and J. Zhang, *Nat. Rev. Mater.*, 2016, **1**, 15005.
11 I. Osada, H. de Vries, B. Scrosati and S. Passerini, *Angew. Chem., Int. Ed.*, 2016, **55**, 500–513.
12 Q. Yang, Z. Zhang, X.-G. Sun, Y.-S. Hu, H. Xing and S. Dai, *Chem. Soc. Rev.*, 2018, **47**, 2020–2064.
13 R. A. Sheldon, *Green Chem.*, 2005, **7**, 267–278.
14 M. Amde, J.-F. Liu and L. Pang, *Environ. Sci. Technol.*, 2015, **49**, 12611–12627.
15 K. S. Egorova, E. G. Gordeev and V. P. Ananikov, *Chem. Rev.*, 2017, **117**, 7132–7189.
16 M. Freemantle, *Chem. Eng. News*, 1998, **76**, 32–37.
17 M. T. Clough, C. R. Crick, J. Gräsvik, P. A. Hunt, H. Niedermeyer, T. Welton and O. P. Whitaker, *Chem. Sci.*, 2015, **6**, 1101–1114.
18 I. Newington, J. M. Perez-Arlandis and T. Welton, *Org. Lett.*, 2007, **9**, 5247–5250.
19 C. Austen Angell, Y. Ansari and Z. Zhao, *Faraday Discuss.*, 2012, **154**, 9–27.
20 K. Yoshida, M. Nakamura, Y. Kazue, N. Tachikawa, S. Tsuzuki, S. Seki, K. Dokko and M. Watanabe, *J. Am. Chem. Soc.*, 2011, **133**, 13121–13129.
21 K. Ueno, K. Yoshida, M. Tsuchiya, N. Tachikawa, K. Dokko and M. Watanabe, *J. Phys. Chem. B*, 2012, **116**, 11323–11331.
22 W. Shinoda, Y. Hatanaka, M. Hirakawa, S. Okazaki, S. Tsuzuki, K. Ueno and M. Watanabe, *J. Chem. Phys.*, 2018, **148**, 193809.
23 D. A. Dolan, D. A. Sherman, R. Atkin and G. G. Warr, *ChemPhysChem*, 2016, **17**, 3096–3101.
24 D. J. Eyckens, B. Demir, T. R. Walsh, T. Welton and L. C. Henderson, *Phys. Chem. Chem. Phys.*, 2016, **18**, 13153–13157.
25 L. Crowhurst, R. Falcone, N. L. Lancaster, V. Llopis-Mestre and T. Welton, *J. Org. Chem.*, 2006, **71**, 8847–8853.
26 A. Gilbert, R. S. Haines and J. B. Harper, in *Elsevier Reference Modules in Chemistry, Molecular Sciences and Chemical Engineering*, ed. J. Reedijk, Elsevier, Waltham, MA, 2018, DOI: 10.1016/B1978-1010-1012-409547-409542.414212-X.
27 R. R. Hawker, R. S. Haines and J. B. Harper, *Adv. Phys. Org. Chem.*, 2018, **52**, 49–85.

28 A. Obregón-Zúñiga, M. Milán and E. Juaristi, *Org. Lett.*, 2017, **19**, 1108–1111.

29 D. J. Eyckens, M. E. Champion, B. L. Fox, P. Yoganantharajah, Y. Gibert, T. Welton and L. C. Henderson, *Eur. J. Org. Chem.*, 2016, 913–917.

30 D. J. Eyckens and L. C. Henderson, *RSC Adv.*, 2017, **7**, 27900–27904.

31 K. S. Schaffarczyk McHale, R. R. Hawker and J. B. Harper, *New J. Chem.*, 2016, **40**, 7437–7444.

32 H. M. Yau, A. G. Howe, J. M. Hook, A. K. Croft and J. B. Harper, *Org. Biomol. Chem.*, 2009, **7**, 3572–3575.

33 H. M. Yau, A. K. Croft and J. B. Harper, *Faraday Discuss.*, 2012, **154**, 365–371.

34 E. E. L. Tanner, H. M. Yau, R. R. Hawker, A. K. Croft and J. B. Harper, *Org. Biomol. Chem.*, 2013, **11**, 6170–6175.

35 R. R. Hawker, R. S. Haines and J. B. Harper, *Chem. Commun.*, 2018, **54**, 2296–2299.

36 S. T. Keaveney, D. V. Francis, W. Cao, R. S. Haines and J. B. Harper, *Aust. J. Chem.*, 2015, **68**, 31–35.

37 E. E. L. Tanner, R. R. Hawker, H. M. Yau, A. K. Croft and J. B. Harper, *Org. Biomol. Chem.*, 2013, **11**, 7516–7521.

38 R. R. Hawker, M. J. Wong, R. S. Haines and J. B. Harper, *Org. Biomol. Chem.*, 2017, **15**, 6433–6440.

39 R. R. Hawker, R. S. Haines and J. B. Harper, *Org. Biomol. Chem.*, 2018, **16**, 3453–3463.

40 S. G. Jones, H. M. Yau, E. Davies, J. M. Hook, T. G. A. Youngs, J. B. Harper and A. K. Croft, *Phys. Chem. Chem. Phys.*, 2010, **12**, 1873–1878.

41 N. L. Lancaster, T. Welton and G. B. Young, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2267–2270.

42 N. L. Lancaster, P. A. Salter, T. Welton and G. B. Young, *J. Org. Chem.*, 2002, **67**, 8855–8861.

43 N. L. Lancaster and T. Welton, *J. Org. Chem.*, 2004, **69**, 5986–5992.

44 C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, 1974, **96**, 2250–2252.

45 W. L. F. Armarego and C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 7th edn, 2013.

46 H. Eyring, *J. Chem. Phys.*, 1935, **3**, 107–115.

47 H. M. Yau, S. J. Chan, S. R. D. George, J. M. Hook, A. K. Croft and J. B. Harper, *Molecules*, 2009, **14**, 2521–2534.