Ionic Liquid Effects

On

Nucleophilic Substitutions

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Declaration

The work described in this thesis was carried out at Imperial College London between October 2009 and June 2013. The entire body of work is my own unless stated to the contrary and has not previously been submitted for a degree at this or other university.

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Abstract

In this thesis we demonstrate a fundamental difference between nucleophilic substitution reaction mechanisms in ionic liquids versus conventional solvents. Reported herein are the effects of ionic liquid solvents on substitution reactions between a cationic electrophile and the chloride anion of various organic and inorganic salts. We have combined novel quantitative studies of the nucleophilic source [Cat]Cl with our studies of [C₄C₁im]Cl and compared their reactivities, k₂. For the first time, Eyring activation parameters have been calculated for substitution reactions between charged species in ionic liquid solvents and reveal a hitherto unprecedented role of the cation in the transition state. The activation parameters (ΔH° and ΔS°) suggest the reactivity of the chloride anion can be manipulated by varying the size and chemical nature of the cation, and also shed light on cation hydrogen bond donating effects. The superior ability of ionic liquid solvents to fully screen the charges of reactant ions is shown to break down as ions become larger, less charge dense and display a tendency to self-aggregate.
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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Kamlet-Taft hydrogen bond donating ability of a solvent</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Kamlet-Taft hydrogen bond accepting ability of a solvent</td>
</tr>
<tr>
<td>$\pi^*$</td>
<td>Kamlet-Taft dipolarity/polarizibility of a solvent</td>
</tr>
<tr>
<td>$\delta_C$</td>
<td>$^{13}$C chemical shift / ppm</td>
</tr>
<tr>
<td>$\delta_H$</td>
<td>$^1$H chemical shift / ppm</td>
</tr>
<tr>
<td>$\varepsilon_0$</td>
<td>permittivity of free space</td>
</tr>
<tr>
<td>$\varepsilon_r$</td>
<td>dielectric constant</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celsius</td>
</tr>
<tr>
<td>CIP</td>
<td>contact ion pair</td>
</tr>
<tr>
<td>cP</td>
<td>centipoises</td>
</tr>
<tr>
<td>$\lambda_{\text{max}}$</td>
<td>wavelength of maximum absorption / nm</td>
</tr>
<tr>
<td>$\nu_{\text{max}}$</td>
<td>frequency of maximum absorption / cm$^{-1}$</td>
</tr>
<tr>
<td>[C$_4$C$_1$im]$^+$</td>
<td>1-butyl-3-methylimidazolium cation</td>
</tr>
<tr>
<td>[C$_4$C$_1$py]$^+$</td>
<td>N,N-butyldimethylpyrrolidinium cation</td>
</tr>
<tr>
<td>[C$_4$py]$^+$</td>
<td>N-butyldimethylpyrrolidinium cation</td>
</tr>
<tr>
<td>[C$_4$C$_1$C$_1$im]$^+$</td>
<td>1-butyl-2,3-methylimidazolium cation</td>
</tr>
<tr>
<td>[HC$_4$im]$^+$</td>
<td>1-butylimidazolium cation</td>
</tr>
<tr>
<td>[NTf$_2$]$^-$</td>
<td>bis(trifluoromethylsulfonyl)imide anion</td>
</tr>
<tr>
<td>[OTf]$^-$</td>
<td>trifluoromethanesulfonate anion</td>
</tr>
<tr>
<td>Abs</td>
<td>absorbance</td>
</tr>
<tr>
<td>nBu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>BuEtOH</td>
<td>butoxyethanol</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DMSO-d&lt;sub&gt;6&lt;/sub&gt;</td>
<td>deuterated DMSO</td>
</tr>
<tr>
<td>DN</td>
<td>donor number</td>
</tr>
<tr>
<td>Eq.</td>
<td>equation</td>
</tr>
<tr>
<td>Equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray</td>
</tr>
<tr>
<td>$E_T^{(30)}$</td>
<td>Reichardt’s empirical polarity scale / kcal mol&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>$E_T^N$</td>
<td>normalised form of ET(30)</td>
</tr>
<tr>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>HBA</td>
<td>hydrogen bond acceptor</td>
</tr>
<tr>
<td>HBD</td>
<td>hydrogen bond donor</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant / Hz</td>
</tr>
<tr>
<td>$k$</td>
<td>generic rate constant</td>
</tr>
<tr>
<td>$k_{obs}$</td>
<td>observed (extrapolated from experiment) rate constant</td>
</tr>
<tr>
<td>$k_2$</td>
<td>bimolecular reaction rate constant / M&lt;sup&gt;-1&lt;/sup&gt; s&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>LSIMS</td>
<td>liquid secondary ion mass spectrometry</td>
</tr>
<tr>
<td>LSER</td>
<td>linear solvation energy relationship</td>
</tr>
<tr>
<td>M</td>
<td>dipole moment</td>
</tr>
<tr>
<td>$m$</td>
<td>meta</td>
</tr>
<tr>
<td>m/z</td>
<td>mass over charge ratio</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
</tbody>
</table>
n- normal-
NMR nuclear magnetic resonance
o ortho
p para
pK\textsubscript{a} acid dissociation constant
ppm parts per million
PTC phase transfer catalysis
RT room temperature
[R\textsubscript{4}N]\textsuperscript{+} tetraalkylammonium
[R\textsubscript{4}P]\textsuperscript{+} tetraalkylphosphonium
S\textsubscript{N}1 unimolecular nucleophilic substitution
S\textsubscript{N}2 bimolecular nucleophilic substitution
s singlet
SSIP solvent separated ion pair
t triplet
T temperature
THF tetrahydrofuran
UV/vis ultraviolet/visible
Chapter 1: Introduction
Solvents in Chemistry

Developing and understanding solutions could perhaps be considered the fundamental aim of the traditional chemist. Indeed, progress in solvent chemistry provides a timeline by which most disciplines of chemistry may be measured. In the beginning, all liquids were described as “water” (470 BC) after which advances to the discovery of solutions from which solutes could be recovered (1600s) were reasonably slow. The detection of solvent effects on reaction rates (early 1800s) and chemical equilibria (late 1800s) came during a golden century for advancement in chemistry, concurrent with Mendeleev and his discovery of the periodic table. It is arguable that this period marks the transition from the trial and error of alchemy to the discipline of chemistry.

In the present day we find ourselves synthesising novel reaction-specific ionic liquid solvents and challenging conventional solvent behaviour descriptors.

Context

Continuous growth of the world population, currently estimated to be 7 billion,¹ and rapid economic development places increasing pressure on the environment, global food supplies and energy resources. Tackling the immense challenges posed by climate change requires both mitigation and adaption whilst addressing the needs of the population. The ever more apparent effects of climate change have served to highlight the importance of the role of chemistry in society whether for better or for worse. Chemistry provides us a method to advance key emerging technologies including the field of renewable energy and lower carbon development. Additionally, legitimate concerns surrounding emissions by the chemical industry itself require a global effort to develop more efficient, safer and cleaner chemical processes.

One of the greatest contributors to the chemical industry’s environmental footprint is the use of solvents due to the vast quantities in which they are used and the wide range of impacts on air quality they have. There are some sixty commonly used solvents in the field of chemistry of which the vast majority are volatile, toxic compounds. The hazardous handling properties and risks of atmospheric and soil contamination, particularly by chlorinated hydrocarbons, have led to worldwide efforts to reduce the emissions (and use) of volatile organic compounds (“VOCs”).²
The use of VOCs must be minimised and the actual processes employed by the chemical industry made less wasteful if the requirements of new legislation are to be met. At research level a number of methods to reduce solvent waste are being investigated including the use of alternative solvents such as supercritical CO₂, fluorous biphasic systems, solvent-free processes, the use of clean solvents such as water and the use of non-volatile ionic liquid solvents.
**Introduction to ionic liquids**

*Definition*

Ionic liquids, an association of organic cations and anions, are defined as being any salt in the molten state. Of particular interest in this work, due to their ease of handling and application, are room temperature ionic liquids “RTILs”: salts which are molten in ambient conditions. The vast scope of cations and anions available from which to form an ionic liquid has led to the term “designer solvent”, describing an ability to adapt the system to suit the application.³ They are neither flammable nor significantly volatile⁴ and extensive research into the possible applications of such media as solvents in synthetic and catalytic reactions has already been carried out.

*Applications*

There are numerous advantages to the use of ionic liquids in place of conventional solvents beyond the fact that they are often claimed to be more environmentally friendly: ionic liquids can act as a solvent for a great number of organic and inorganic compounds and can accommodate large changes in reaction temperature; the high thermal conductivity of an ionic liquid is a property conducive to complete reactant conversion and shorter reaction times⁵ and most importantly, the physical properties of ionic liquids can all be modified by varying the anions and cations of which the ionic liquid is composed.

This signifies new ground in solvent properties i.e. that it is possible to manipulate the solvent to suit the requirements of a given reaction. The fact that the hydrophobic/hydrophilic properties, viscosity,⁶ and density (1-1.69cm⁻¹)⁷ can be easily tuned in ionic liquids has been crucial to their use in biphasic catalytic reactions.⁸ The electrochemical window i.e. the range over which the ionic liquid is neither oxidised nor reduced at an electrode, is unusually large when compared with aqueous electrolytes and so ionic liquids are seen to exhibit superior electrochemical properties.⁹ Whilst these properties and their corresponding applications are of great interest, they are beyond the scope of this work, which will instead focus on the effects that ionic liquids can have upon solute materials.

A fundamental understanding of this class of solvent’s physical and chemical properties must be achieved to aid the cause for the use of ionic liquids on an industrial scale. Physical properties such as melting point, boiling point, viscosity and density have already been...
established for various ionic liquids. However, chemical properties such as polarisability, dipolarity and hydrogen bond donating/accepting ability are of current interest. Through comprehension of the intermolecular interactions between ionic liquid solvents and potential solutes, we can begin to elucidate observed reaction rates and solute solubilities. In an effort to be able to predict the effect an ionic liquid will have on a given chemical process, we strive to understand more fully their chemical properties and to understand ionic liquids on a molecular level.

Composition of Ionic Liquids

The cation is typically a large organic structure with low symmetry such as substituted forms of phosphonium, sulfonium, imidazolium, pyridinium and pyrrolidinium ions. By far the most commonly studied are the asymmetric N,N’-dialkylimidazolium cations.

![Figure 1 - Typical ionic liquid cations](image)

In the case of imidazolium-based ionic liquids, X-ray spectroscopy demonstrates that the long-range structure is almost entirely dependent on the nature of the cation while the anion determines the strength of hydrogen bond and the cation-cation and cation-anion distances. Moreover it is clear that the presence or not of hydrogen H(2) at the C2 position of the imidazolium ring controls the 3D organisation of ionic liquid due to strong hydrogen bonding with the anion and would determine the availability of imidazolium cation to interact with solutes.
Anions used tend also to be bulky and can be either organic or inorganic in nature. The nature of the anion can therefore be significantly altered according to nucleophilicity/basicity.

![Typical ionic liquid anions](image)

It is necessary to study reactions in ionic liquids in the absence of water (or other impurities such as chlorides) in order to concentrate solely on the effects caused by the solvent and avoid competition from additional hydrogen bonding. Consequently, trifluoromethanesulfonate, $[\text{OTf}]^-$, and $\text{bis(trifluoromethylsulfonyl)imide}$, $[\text{NTf}_2]^-$, are favourable anions when studying solvent effects because the corresponding ionic liquids are relatively hydrophobic, generally liquid at room temperature and their purification can be well controlled.\textsuperscript{14}
Preparation and Purification of Ionic Liquids

Theory

Throughout this work, imidazolium-based ionic liquids have been used exclusively, though pyrrolidinium based ionic liquids were also synthesised for future use. There are two possible synthetic methods for the preparation of these classes of ionic liquid: (i) the two-step alkylation followed by metathesis method and (ii) the one-step direct combination method.

The two-step method involves the alkylation of an imidazole/pyrrolidine derivative followed by an ion exchange with the lithium salt of the desired anion. Alkylation is achieved using an alkyl halide (chloride in this work) of desired chain length.

![Reaction Scheme 1 - Two-step ionic liquid synthesis](image)

The one-step method comprises the direct combination of a molecular species with the imidazole/pyrrolidine derivative.

![Reaction Scheme 2 - One-step ionic liquid synthesis](image)

Whilst the two-step method generates lithium halide impurities which must be washed out and the direct combination method by design does not; ionic liquids of high purity are
achieved by the more intensive two-step method which can be carried out at relatively low temperatures (<50°C). The direct combination method is very exothermic and it is widely known that higher temperatures during ionic liquid synthesis (>50°C) lead to coloration. Bearing in mind that the starting materials are more expensive and also that the precision required during synthesis is much greater for direct combination, only the two-step method has been used in this work. Details of synthetic methods can be found in the experimental section, Chapter 8.
Polarity of Ionic Liquids

*An Introduction to “Polarity”*

It is well understood that solvents are key factors in determining reaction rates and the equilibrium position in a chemical process.\(^{11}\) The properties of solvents are the bases upon which users will choose from a list of potential solvents the most appropriate one in which to carry out their reactions. Amongst the various chemical and physical characteristics of solvents, polarity (as generally described by the dielectric constant) has been the most widely used property by which to classify solvents. The prevalent use of the dielectric constant \((\varepsilon_r)\) as a polarity descriptor has arisen from the seemingly sound correlation between a liquid’s ion solvating properties and its dielectric constant.

If a molecule possesses a permanent dipole moment it is described as being “polar” whereas “non-polar” is the common designation for a molecule in the absence of such a charge. It follows that the terms “polar solvent” and “non-polar solvent” are commonly used in reference to the bulk properties of the liquid with the same expressions being applied according to dielectric constant values also. Solvents with a low value of \(\varepsilon_r\) are typically labelled “non-polar” and those with high values “polar”.

However, the blanket use of these physical constants to characterise a solvent’s polarity is precarious indeed, for dipole moments and dielectric constants are not directly related.

"Polarities"

![Figure 3 - The uncertain relationship between the dipole moments and dielectric constants for some common laboratory solvents\(^{10}\)](image-url)
The previously discussed physical properties do not consider any specific intermolecular interactions which may take place. Solvent/solvent and solute/solvent interactions take place at the microscopic level as well as the non-specific interactions of the bulk solvent. From now on we will understand polarity to mean the sum of all possible interactions, specific and non-specific, between the solute and the solvent but excluding any interactions which lead to clearly defined chemical changes in the solute as defined by IUPAC.

Polarity requires a great many measurements to be taken in order to have any meaningful numerical value. Even the very bare bones of the dielectric constant, the Coulombic forces, involve specific interactions (e.g. hydrogen bonding and charge transfer forces) and also non-specific interactions (e.g. dispersive, inductive and directional forces) between ions. Given that solvophobic interactions and solvent polarizability are yet to be mentioned, it is evident that the task of confining the idea of polarity to one number is impossible.

**Empirical Polarity Parameters**

Empirical solvent polarity parameters provide another way of looking into solvent behaviour and give a better description of the solvent effects than considering single physical constants. Empirical parameters, like single physical constants, can give an idea of the electrostatic properties of a solvent but they additionally include a more complete assay of the intermolecular forces acting in solution.

The limitation of the empirical polarity parameter method is much the same as for any other solvent investigation method: the effects observed are not absolute and they are the comparison between the test solvent and the standard solvent used in some reference process.

Equilibrium measurements\(^1\) and kinetic measurements\(^2\) have been developed to obtain empirical solvent polarity parameters. This work shows the parameters derived from Kamlet-Taft spectroscopic measurements. This type of analysis has been deemed by our group to be the most suitable method when investigating the various ionic liquid solvents, with the rationale being described in the following section.
Kamlet-Taft Polarity Measurements for Ionic Liquids

Ionic liquid polarity measurements have been taken by many groups using various methods including Nile Red measurements, gas chromatography, fluorescent probes, Reichardt’s Dye and Kamlet-Taft measurements.

Although not all data are in agreement, general consensus finds ionic liquids to be highly, though not extremely, polar. Ionic liquid polarity values are analogous to those of short chain alcohols but not as high as water.

Kamlet-Taft parameters have been chosen for this work due to the vast number of molecular solvents with recorded Kamlet-Taft values in the literature. Values have also been published for a few ionic liquids which enable meaningful comparisons and experimental procedures to be easily verified. Additionally, the parameters measured can be used to perform linear solvation energy relationship, LSER, analysis which gives further insight into the solvent environment of the ionic liquid media.

The Kamlet-Taft solvatochromic equation describing the transition energy is:

$$A = A_0 + a\alpha + b\beta + s\pi^*$$

Equation 1 - The Kamlet-Taft solvatochromic equation

where A is the solute property being studied (the position of maximum absorption in the UV spectrum in this work), Ao is the regression value of the solute property, $\alpha$ is the solvent hydrogen bond donor (HBD) ability or acidity parameter, $\beta$ is the hydrogen bond acceptor (HBA) ability or basicity parameter, and $\pi^*$ is the solvent’s polarizability/dipolarity. $\pi^*$ describes the ability of the solvent to stabilise a charge or a dipole. Constants a, b, and s are characteristic of the solute. The magnitudes of a, b and s are relative to the influence of the corresponding solvent-solute interactions ($\alpha$, $\beta$ and $\pi^*$) on A. It should be noted that Equation 1 is a relatively simple variation of the Kamlet-Taft equation and therefore makes for a more mathematically digestible analysis. Additional parameters can be included as necessary for specific processes.
Some typical dyes used to determine Kamlet-Taft parameters are shown below:

![Reichardt's dye](image1.png) ![4-nitroaniline](image2.png) ![N,N-diethyl-4-nitroaniline](image3.png)

**Figure 4 - Typical Kamlet-Taft dyes**

Table 1 shows the Kamlet-Taft parameter values for both molecular and ionic liquid solvents:

<table>
<thead>
<tr>
<th>Molecular Solvents</th>
<th>α</th>
<th>β</th>
<th>π*</th>
<th>Ionic Liquids</th>
<th>α</th>
<th>β</th>
<th>π*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.12</td>
<td>0.14</td>
<td>1.33</td>
<td>[C₄C₁im][NTf₂]</td>
<td>0.617</td>
<td>0.243</td>
<td>0.984</td>
</tr>
<tr>
<td>MeOH</td>
<td>1.05</td>
<td>0.61</td>
<td>0.73</td>
<td>[C₄C₁im][OTf]</td>
<td>0.625</td>
<td>0.464</td>
<td>1.006</td>
</tr>
<tr>
<td>MeCN</td>
<td>0.350</td>
<td>0.370</td>
<td>0.799</td>
<td>[C₄C₁im][BF₄]</td>
<td>0.627</td>
<td>0.376</td>
<td>1.047</td>
</tr>
<tr>
<td>Acetone</td>
<td>0.202</td>
<td>0.539</td>
<td>0.704</td>
<td>[C₄C₁im][PF₆]</td>
<td>0.634</td>
<td>0.207</td>
<td>1.032</td>
</tr>
<tr>
<td>DCM</td>
<td>0.042</td>
<td>0</td>
<td>0.791</td>
<td>[C₄C₁pyrr][NTf₂]</td>
<td>0.427</td>
<td>0.252</td>
<td>0.954</td>
</tr>
<tr>
<td>Toluene</td>
<td>0</td>
<td>0.077</td>
<td>0.532</td>
<td>[C₄C₁C₁im][BF₄]</td>
<td>0.402</td>
<td>0.363</td>
<td>1.083</td>
</tr>
<tr>
<td>Hexane</td>
<td>0.07</td>
<td>0.04</td>
<td>-0.12</td>
<td>[C₄C₁C₁im][NTf₂]</td>
<td>0.381</td>
<td>0.370</td>
<td>1.010</td>
</tr>
</tbody>
</table>

**Ionic Liquid Effects on Stoichiometric Chemical Reactions**

The effects of ionic liquid solvents on chemical processes are central to understanding how ionic liquids behave on a molecular level. It is fair to say that most reactions will proceed in ionic liquids, but the reaction pathways, rates and equilibria are often found to be
fundamentally different to the corresponding reactions in molecular solvents. It is through analysis of well-known reactions in ionic liquids that we can gain insight into the solvent’s polarity, microscopic viscosity, diffusion ability, acidity/basicity, ionising power and solute dissociation faculty.

As one of the most straightforward reactions which can take place, energy transfer reactions were amongst the first to be studied in ionic liquids and provide a good example by which ionic liquids were seen to have a measurable solvent effect. That ionic liquids can be easily purged of oxygen is in fact an attractive quality for solvents in this type of reaction, where oxygen frequently quenches the electronically excited states of the solutes under investigation. Ionic liquid [C₄C₁im][PF₆] was found to prolong the life of the excited triplet state of xanthone and pyrene when compared with acetonitrile and propan-2-ol. In the same study it was found that the reaction in ionic liquids had a much smaller rate constant than in molecular solvents owing to slower diffusion of reacting species.

The subject of this work is to deepen the understanding of ionic liquid effects in the case of substitution reactions, notably those of the S₂2 type.
Nucleophilic Substitutions

\( S_N2 \) Reactions in Molecular Solvents

Reaction Scheme 3 depicts the nucleophilic substitution reaction between chloromethane and the hydroxide anion. This reaction occurs as a bimolecular process with a new bond being formed between the hydroxide group and the carbon atom of the methyl group, whilst the bond between the methyl group and the chlorine atom is broken. The resulting products are methanol and a departing chloride anion referred to as the “leaving group”.

\[
\begin{align*}
\text{H} & \text{O} \quad \text{H} \quad \text{C} \quad \text{Cl} \\
\text{H} & \text{H} \quad \text{H} \\
\end{align*}
\]

Transition state

Bond being made

Bond being broken

In the \( S_N2 \) type substitution, bond breakage and bond formation occur simultaneously and thus there is only one transition state. Unlike reaction intermediates, transition states have no real lifetime and so the change from the transition state to products is, to all experimental purposes, instantaneous. The transition state represents the highest point of energy in the reaction pathway and the formation of the transition state is the rate-determining step.

As for all \( S_N2 \) reactions and in the example shown in reaction scheme 3, two reacting species take part in the rate-determining step (activated complex formation) and therefore the reaction rate is proportional to the concentrations of both species: nucleophile and electrophile.

In this work, \( S_N2 \) reactions have been carried out at constant temperature and with a large excess of the electrophilic species thereby generating \textit{pseudo}-first order reaction kinetics. Running a reaction with one of the species in large excess will mean that its concentration is effectively constant and the rate will become dependent on the concentration of the other species, in this case the nucleophile. Thus the effect that the solvent has upon the nucleophile’s behaviour can be investigated.
Reactions will proceed faster if the nucleophile is stronger or has greater “nucleophilicity” given that the nucleophile is involved in the rate-determining step. In the gas phase there is a direct correlation between the relative basicity and nucleophilicity of the nucleophile, whereas in solution the story gets a little more complicated. Generally speaking, the nucleophilicity increases from right to left across the periodic table and anions are preferable to neutral species.

**Solvent Effects in Nucleophilic Substitutions**

The study of nucleophilic substitution reactions provides a familiar route to examining solvent effects on chemical processes. The correlation between basicity and nucleophilicity that we find in the gas phase is lost in solution as solvent effects become accountable for changing the behaviour of the nucleophile to a greater or lesser extent. Polar protic solvents such as alcohols and water are very good at solvating anions and hence nucleophiles are very highly solvated by these types of solvent, so much so that the nucleophile’s availability to take part in the $S_N2$ reaction is impaired and these substitutions take place at a relatively slow rate. Much faster are nucleophilic substitution reactions which take place in polar aprotic solvents such as acetonitrile and dimethylformamide. This is due to the polar aprotic solvent’s superior ability to solvate cations and poorer capacity to solvate anions. Solvents are capable of changing a nucleophile’s nucleophilicity considerably.

The ability of a solvent to affect a reaction’s rate constant can be described by transition state theory, which states that the Gibbs free energy of activation may be altered if there is a difference between the solvation of the reactants and the activated complex/transition state. The solvent will determine the way in which the reactants and the activated complex are solvated and this in turn will determine the rate of the reaction. Transition state theory is discussed in greater detail at the end of this chapter.

**Hughes-Ingold Theory**

Hughes and Ingold provide a set of rules which describe the effects of molecular solvents on chemical reactions based on the relative solvations of the reactants and activated complexes.
The method comprises a model which considers electrostatic interactions between dipolar molecules and ions in the initial and transition states. The model predicts that high polarity solvents will accelerate reactions in which charge density is created and decelerate reactions in which charge density is removed in the activation step. Where a reaction involves negligible change in charge density in going from reactants to the transition state then there will be either a very small or no effect on the reaction from the solvent. Deviations from the model are attributed to specific interactions such as hydrogen bonding which are not included in this theory.

More specifically, Hughes and Ingold investigated solvent effects on nucleophilic substitution and elimination reactions using a simple qualitative model which reflected only electrostatic interactions between ions or dipolar molecules and solvent molecules in initial and transition states. Based on empirical observations and reasonable assumptions, the rules predict that the extent of solvation in the presence of electric charges adheres to the following:

1. An increase in the magnitude of charge will increase solvation;
2. An increase in dispersal of charge will decrease solvation; and
3. Destruction of charge will decrease solvation more than dispersal of charge.

The reaction rate will be increased or decreased on changing to a more polar solvent depending on whether there is more or less charge density created in the activation process. By way of illustration, the reaction between ions of equal charge results in an increase in charge density during the activation process. Therefore increasing the solvent polarity will increase the rate of reaction. On the other hand, a reaction between oppositely charged ions (in which forming the activated complex reduces the charge) will be slower in polar solvents as polar solvents better solvate the reactants compared to the activated complex.

Qualitative predictions about solvent polarity effects on nucleophilic substitutions are summarised in Table 2.
Table 2 - Predicted solvent effects on rates of nucleophilic substitutions

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Initial reactants</th>
<th>Activated complex</th>
<th>Charge alteration during activation</th>
<th>Effect of increased solvent polarity on rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_N^1$</td>
<td>R-X</td>
<td>$R^\delta^+\cdots X^\delta^-$</td>
<td>Separation of unlike charges</td>
<td>Large increase</td>
</tr>
<tr>
<td>$S_N^1$</td>
<td>R-X+</td>
<td>$R^\delta^+\cdots X^\delta^-$</td>
<td>Dispersal of charge</td>
<td>Small decrease</td>
</tr>
<tr>
<td>$S_N^2$</td>
<td>Y + R-X</td>
<td>$Y^\delta^+\cdots R\cdots X^\delta^-$</td>
<td>Separation of unlike charges</td>
<td>Large increase</td>
</tr>
<tr>
<td>$S_N^2$</td>
<td>Y- + R-X</td>
<td>$Y^\delta^+\cdots R\cdots X^\delta^-$</td>
<td>Dispersal of charge</td>
<td>Small decrease</td>
</tr>
<tr>
<td>$S_N^2$</td>
<td>Y+ R-X</td>
<td>$Y^\delta^+\cdots R\cdots X^\delta^+$</td>
<td>Dispersal of charge</td>
<td>Small decrease</td>
</tr>
<tr>
<td>$S_N^2$</td>
<td>Y- + R-X+</td>
<td>$Y^\delta^+\cdots R\cdots X^\delta^+$</td>
<td>Destruction of charge</td>
<td>Large decrease</td>
</tr>
</tbody>
</table>

**Limitations of the Hughes-Ingold Rules**

Given that the Hughes-Ingold approach treats the solvent as a dielectric continuum and therefore considers the solvent’s polarity to arise only from electrostatic interactions, the theory is insufficient to describe solvent effects on reaction rates where intermolecular interactions are of great importance. For example, as a result of specific solvation effects, anionic nucleophiles become less reactive in protic solvents (this concept is discussed further later in this chapter). This observable fact is not predicted by the Hughes-Ingold principles.

Another limitation of the Hughes-Ingold model is that it is based on static equilibrium transition-state solvation. In other words, it assumes that the reorientational relaxation of solvent molecules during the activation process is sufficiently fast so that the activated complex will be in thermal equilibrium with the surrounding solvent shell. This assumption does not hold true for all cases with an example being reactions which are particularly fast. In such reactions, solvent reorientation rates contribute to the overall reaction rate and transition state theory breaks down. The limitations of transition state theory are discussed further at the end of this chapter.

Although the myriad of successful applications of the Hughes-Ingold theory attest to its efficacy, the model assumes that the contribution of entropy changes to the changes in the Gibbs energy of activation are negligible. This suggests that Gibbs energy expression, $\Delta G^\neq = \Delta H^\neq - T\Delta S^\neq$, is controlled by enthalpy changes. This assumption is reasonable because an increase in solvation is usually accompanied by a decrease in entropy. Increasing enthalpy...
changes are counteracted by decreases in the entropy of activation but these decreases tend to be small for most reactions. So in most cases, the assumption of an enthalpy dominated Gibbs energy of activation holds, but there have been a number of reactions reported where the entropy of activation is the controlling factor. Polar solvents seem to minimise the loss of entropy during the activation process, and this is the main reason that rates increase with solvent polarity.

In a similar vein, the Hughes–Ingold model also disregards changes in solvent structure. Even though solvent–solvent interactions are usually insignificant compared to solute–solvent interactions, when reactions are carried out in highly structured solvents like water or ionic liquids, the effects of solvent association should be given some attention. A purely electrostatic theory discounts such solvent–solvent interactions.

**Nucleophilic Substitution Reaction Rates and Specific Solvation Effects**

Hydrogen bonding and other electron pair donating/accepting abilities constitute specific interactions that can occur between solvent and solute molecules. Understanding how these specific interactions affect the solvation of reactants and activated complexes can help to explain the mechanisms and rates of organic reactions. For example, it is well known that the overall reaction rate can be significantly affected by solvation of the departing anion in nucleophilic substitution.  

Hydrogen bonding plays an important role in the interactions between hydrogen bond donating (or protic) solvents and anions. Protic media are therefore good anion solvators. Due to the small size of the hydrogen atom, smaller anions such as fluoride and chloride are better solvated than larger anions such as thiocyanate and iodide. A protic solvent can apply such a strong electron withdrawing pull on the leaving group that some nucleophilic substitutions found to be bimolecular in alcohols actually become first order in acidic solvents.

\[
\text{SN}_1: \quad \text{R-X} + \text{H-S} \xrightleftharpoons{\text{SN}_1} \text{SN}_2 \quad [\text{R}^\delta--\text{X}^\delta--\text{H-S}]^* \xrightarrow{+\Theta} \text{R} + \text{X}^\Theta--\text{H-S} \\
\text{SN}_2: \quad \text{Y}^\Theta + \text{R-X} + \text{H-S} \xrightleftharpoons{\text{SN}_2} \quad [\text{Y}^\delta--\text{R}--\text{X}^\delta--\text{H-S}]^* \quad \xrightarrow{\Theta} \quad \text{Y-R} + \text{X}^\Theta--\text{H-S}
\]

**Reaction Scheme 4 - Hydrogen bonding between solvent and activated complex in nucleophilic substitution reactions**
In the Reaction Scheme 4, the strength of X…H will determine the energy required for ionization of R-X. When X…H is strong, the ionization energy of R-X is reduced and the rate of reaction increases. Accordingly, substitution reactions tend to be accelerated by protic solvents. It is for this reason that substitution reactions of haloalkanes are carried out in alcohols, carboxylic acids and water. The relative strength of hydrogen bonding in the initial and transition states overcomes the electrostatic effect of solvents on the Gibbs energy of activation. On the contrary, attacking nucleophiles in $S_N2$ reactions can be specifically solvated by protic solvents, thus lowering its ground state energy and reducing its reactivity. As the energy of the activated complex is a fixed value, the energy of activation becomes greater and, therefore, the rate of reaction decreases. An example of an $S_N2$ reaction where the nucleophile is specifically solvated and the rate decreases can be found when the reaction in Reaction Scheme 5 is carried out in methanol. If 1,4-dioxane, a non-protic solvent, is added to the reaction mixture an acceleration of the substitution process results. The presence of dioxane partially prevents methanol from solvating the methoxide ion and enhancement of the nucleophilic reactivity of the methoxide results. Careful consideration of both the deactivation of the nucleophile and the activation of the leaving group caused by the hydrogen bond association with the protic solvent is required when determining solvent selection as these two effects compete and the final outcome depends on the chemical makeup of the reactants.

$$\text{CH}_3\text{O}^- + \text{H}_2\text{C}------\text{I} \xrightarrow{k_2} \text{CH}_3\text{O}------\text{CH}_3 + \text{I}^-$$

Reaction Scheme 5 - Effects of the addition of 1,4-dioxane to the alkaline solvolysis of iodomethane in methanol

<table>
<thead>
<tr>
<th>Solvent (1,4-dioxane in cL/L)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_2^{rel}$</td>
<td>1</td>
<td>1.9</td>
<td>3.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 3 - Rate constants with increasing concentration of 1,4-dioxane

The nucleophile has to displace the surrounding solvent shell whilst a new solvent shell forms around the activated complex during the activation step of a nucleophilic substitution process. We can conclude then that the more strongly the solvent molecules are associated with the
nucleophile, the higher the energy of activation and therefore lower the rate of reaction. Therefore a well solvated nucleophile is less reactive than a poorly solvated nucleophile.

Polar aprotic solvents (solvents that cannot form hydrogen bonds in solution) tend not to solvate the nucleophile but rather surround the accompanying cation, thereby raising the ground state energy of the nucleophile. Because the energy of the activated complex is a fixed value, the energy of activation becomes less and, therefore, the rate of reaction increases.

![Diagram explaining energy level needed for reaction to occur](image)

**Figure 5 - The effect of solvent polarity on the energy of activation and therefore the rate of reaction**

However, on account of their polarisability, polar aprotic solvent behaviour is not always so clear cut. Polar aprotic solvents are able to interact strongly with large, polarisable anions such as iodide and thiocyanate. This concept is also explained by the principle of hard and soft acids and bases (HSAB principle): hard anions are better solvated by hard solvents (hydrogen bond donating), whereas soft anions are solvated to a greater degree by soft solvents (dipolar, non-hydrogen bond donating).³³

*Anion Solvation in Nucleophilic Displacements*

It can be seen in the case of the halide ions that the nature of the solvent can dramatically alter the reactivity of the nucleophiles. While the orders of nucleophilicity and leaving group ability of the halide ions are I⁻ > Br⁻ > C⁻ > F⁻ in protic solvents such as H₂O or alcohols, the halide ion nucleophilicity order is reversed to F⁻ > Cl⁻ > Br⁻ > I⁻ in polar aprotic solvents such as acetone and dimethyl sulfoxide even though their leaving group ability order remains as I⁻ > Br⁻ > Cl⁻ > F⁻. This same order of halide reactivity is also found when a quaternary ammonium salt is used as a solvent. It could therefore be concluded that in the absence of ion solvation the halide ion nucleophilicity order is F⁻ > Cl⁻ > Br⁻ > I⁻ which also applies to
reactions in the gas phase where no solvent is present. Negatively charged nucleophiles are far less solvated in polar aprotic media when compared with protic solvents to the extent that they can be thought of as being “naked” and therefore are much more reactive in polar aprotic solvents than in protic solvents.\(^{34}\) Polar aprotic solvents are particularly useful for S\(\text{N}_2\) reactions as they dissolve salts such as metal halides or metal alkoxides, because they solvate the metal cation (e.g., \(\text{K}^+\) or \(\text{Na}^+\)). However they do not strongly solvate the anionic nucleophile (e.g., \(\text{X}^-\) or \(\text{`OR}\)), because they have no OH group and cannot form hydrogen bonds as previously discussed, leaving the anion free to react. On the other hand, it can be difficult to find a polar aprotic solvent capable of dissolving salts containing very small nucleophiles such as \(\text{K}^+\text{CN}^-\) and \(\text{K}^+\text{F}^-\) which are actually insoluble in dimethyl sulfoxide. The use of protic/polar aprotic solvent mixtures has proved a useful way to mitigate limited solubility issues when carrying out nucleophilic displacements, i.e. a 90:10 mixture of dimethyl sulfoxide and water has been found to effectively dissolve KCN and KF.\(^{35}\) Tetraalkylammonium salts have also been found to provide an alternative solution by acting both as the source of the nucleophile and as the solvent.\(^{36}\)

When the nucleophile is neutral, as for amines, changing the solvent from protic to polar aprotic is not usually accompanied by such a dramatic change in reaction rate when compared with negatively charged nucleophiles.\(^{37}\)

**Cation Solvation in Nucleophilic Displacements**

The extent of an anion’s association with its corresponding cation plays a key role in determining its nucleophilic reactivity as well as any anion specific solvation effects. This concept is most obvious when we consider that free ions are more reactive than ion pairs – association of any kind will deactivate the nucleophile to a greater or lesser extent as modelled in Reaction Scheme 6.
In the presence of \( M^+ \) more energy is required to form the activated complex from the ion pair compared with the dissociated anion model in order to overcome the Coulombic forces between the oppositely charged ions. In weakly dissociating solvents (solvents with low permittivities) the extent of ion pairing is large and the nucleophilicity of the anion will be dependent on the nature of the cation.\(^{38}\)

There are a number of possible steps that can be taken in order to minimize the interactions between cation and anion and therefore increase the nucleophilicity of the anion:

1. Strongly dissociating solvents (solvents with high permittivities) can be used to reduce the number of associated ions;\(^{39}\)
2. Bulky charge diffuse counter cations such as tetraalkylammoniums can be used in place of small, hard alkali metal cations;
3. Lewis bases and other electron pair donating solvents can be used to improve solvation of the small alkali metal cations; or
4. Formation of macrocyclic complexes to for ligand separated ion pairs.

The reaction of \( n \)-butyl 4-bromobenzene sulfonate with lithium- and tetra-\( n \)-butylammonium halides in the weakly dissociating solvent acetone \((\varepsilon_r = 20:6)\)^{40} is an example of step 2 listed above.
Reaction Scheme 7 - Anion activation by means of a tetraalkylammonium cation

Table 4 - Rate constants with changing nucleophile

<table>
<thead>
<tr>
<th></th>
<th>X⁻</th>
<th>I⁻</th>
<th>Br⁻</th>
<th>Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_2^{rel}$ / Li⁺ salt</td>
<td>6.2</td>
<td>5.7</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>$k_2^{rel}$ / (n-C₄H₉)₄N⁺ salt</td>
<td>3.7</td>
<td>18</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

The nucleophilic reactivity of the lithium salts changes in the same order as in protic solvents ($\Gamma > \text{Br}^- > \text{Cl}^-$). However, the order is reversed for the ammonium salts and follows the same order found in polar aprotic solvents ($\text{Cl}^- > \text{Br}^- > \Gamma$). The large tetraalkylammonium forms a relatively weak association with the anion compared to the small, charge dense lithium cation. In acetone solutions, quaternary ammonium salts should be almost fully dissociated and the reactivity order attained with these salts reflects that of the free, non-associated halide ions.

As noted previously, solvents of high Lewis basicity can also be used to dissociate ion pairs and therefore enhance the anion reactivity (recalling that nucleophiles are themselves essentially Lewis bases). The electron-pair donor property of the Lewis base solvent allows for specific solvation of the cation whilst poorly solvating the anion. Presented below is an example of a Lewis base being used to increase nucleophilicity:

Reaction Scheme 8 - The alkylation of diethyl sodio-n-butylmalonate with 1-bromobutane in benzene
Table 5 - Relative rate constants of the alkylation of diethyl sodio-\(n\)-butylmalonate with 1-bromobutane in benzene at 25°C with various additives.\(^{32}\)

<table>
<thead>
<tr>
<th>Added Cation Solvator (0.648 mol / L)</th>
<th>(k_{2}^{\text{rel}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>no additive (benzene only)</td>
<td>1</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>1.1</td>
</tr>
<tr>
<td>Acetone</td>
<td>1.3</td>
</tr>
<tr>
<td>Ethanol</td>
<td>4.4</td>
</tr>
<tr>
<td>Dimethoxyethane</td>
<td>6.4</td>
</tr>
<tr>
<td>1,4-dioxane</td>
<td>18</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>19</td>
</tr>
<tr>
<td>1-methylpyrrolidin-2-one</td>
<td>30</td>
</tr>
<tr>
<td>hexamethylphosphoramide</td>
<td>54</td>
</tr>
</tbody>
</table>

The sodium metal derivatives of CH-acidic compounds, such as diethyl sodio-\(n\)-butylpropanedioate shown above, are usually highly aggregated in benzene due to the solvent’s low relative permittivity. As can be seen in Table 5, an assortment of electron pair donor solvents used as additives produced a dramatic accelerating effect attributed to the specific solvation of the sodium ion which tends to dissociate the high-molecular mass ion pair aggregate that exists in benzene solution.\(^{43}\) Notably, despite their similar relative permittivities, the reaction proceeds at a markedly higher rate in 1,2-dimethoxyethane (\(\varepsilon_r = 7.2\)) than in tetrahydrofuran (\(\varepsilon_r = 7.6\)). It is likely that the additional and less constrained oxygen atom present in the 1,2-dimethoxyethane contributes to better solvation of the cation thereby increasing the anion reactivity.
Nucleophilic Substitutions in Ionic Liquids

Literature Review

Discussed here are kinetic, mechanistic and synthetic studies of nucleophilic substitution reactions that have been studied in ionic liquids. Typically the mechanistic and kinetic studies are concerned with quantitative analysis of reaction rates in ionic liquids and inference of any mechanistic details through comparison with molecular solvents. Additionally, several synthetic routes involving nucleophilic substitution processes have been studied in ionic liquids in an attempt to improve reaction yields compared to molecular solvents, or to try new chemistry which has previously been unsuccessful.

Intensive research into nucleophilic substitutions in ionic liquids began approximately ten years ago with the Wheeler Group’s investigations into the reaction between benzyl chloride and the cyanide anion.\textsuperscript{44}

\begin{center}
\begin{align*}
\text{Ph-Cl} + \text{KCN} & \rightarrow \text{Ph-CN} + \text{KCl} \\
\text{Reaction Scheme 9 - Nucleophilic displacement by cyanide on benzyl chloride}
\end{align*}
\end{center}

This particular substitution is generally quite problematic due to the inorganic cyanide salt being insoluble in most organic solvents. Traditionally, phase-transfer catalysis (PTC) involving tetraalkylammonium salts is used to move the anion between a polar phase containing the reacting salt and the non-polar phase containing the organic substrate.\textsuperscript{45} Wheeler found that the ionic liquid [C\textsubscript{4}C\textsubscript{1}im][PF\textsubscript{6}] could be used as the transfer catalyst and the solvent to excellent effect: complete conversion is achieved in less than 30 minutes. The process is still considered to be biphasic as the solid inorganic cyanide salt is only partially soluble in the ionic liquid and forms a suspension.

Since 2001, there have been numerous publications regarding substitution reactions in ionic liquids, but kinetic and mechanistic studies of these reactions in order to expound the chemical properties of molten salt solvents are among the rarer of these investigations.

The first kinetic studies of substitution reactions in ionic liquids were reported in the 1970s by Ford and co-workers. The substitution studied was between nucleophilic tetraethylammonium halides and methyl-\textit{p}-toluenesulfonate in molten triethyl-\textit{n}-hexylammonium triethyl-\textit{n}-hexylboride.\textsuperscript{46} The authors found that the molten salts, as with
dipolar aprotic solvents, solvate the halides only weakly when compared with protic solvents. It took a further three decades before research of this type was given greater attention during the ionic liquid boom at the turn of the millennium.

Lancaster et al. took up the kinetic studies made originally by Ford, studying the reaction of iodide, bromide and chloride ions with methyl-\(p\)-nitrobenzenesulfonate in the ionic liquid \([\text{C}_4\text{C}_1\text{im}][\text{BF}_4]\).\(^{47}\) Halide sources were of the type \([\text{C}_4\text{C}_1\text{im}]X\) which ensures there is only one type of cation present in the solution and avoids additional electrostatic effects.

![Reaction Scheme 10 - Methylation reactions investigated by Lancaster and co-workers](image)

Via second order rate constant measurements, the authors found the reactivity to be \(\Gamma^- > \text{Cl}^- > \text{Br}^-\). This trend differed from Ford and co-workers’ results \((\text{Cl}^- > \text{Br}^- > \Gamma^-)\) and the Lancaster group concluded that different ionic liquids exhibit different behaviours and therefore further studies must be made into halide nucleophilicity in ionic liquids.

A second study by Lancaster et al.\(^{48}\) followed the same format as shown in Reaction Scheme 10, but involved both molecular solvents and various ionic liquids to make better comparisons. The reaction kinetics of chloride, bromide and iodide ions with methyl-\(p\)-nitrobenzenesulfonate were examined in dichloromethane, hexafluoropropan-2-ol, \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\), \([\text{C}_4\text{C}_1\text{pyrr}][\text{NTf}_2]\), and \([\text{C}_4\text{C}_1\text{C}_1\text{im}][\text{NTf}_2]\). For each reaction carried out in the ionic liquids, the halide was added as the salt of the ionic liquid cation, e.g. \([\text{C}_4\text{C}_1\text{pyrr}][X]\). In this way purely the ionic liquid effects could be studied without possibility of solute cation contributions. In hexafluoropropan-2ol, tetramethylammonium halides were employed as the nucleophile sources and in dichloromethane, \(\text{bis}(\text{triphenylphosphoranylidene})\text{ammonium halides were used. The second order rate constants obtained for the demethylation reaction in each solvent are shown in Table 6.}
Table 6 - Rate constants obtained by Lancaster and co-workers

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T / °C</th>
<th>$k_2$ (Cl$^-$) / M$^{-1}$ s$^{-1}$</th>
<th>$k_2$ (Br$^-$) / M$^{-1}$ s$^{-1}$</th>
<th>$k_2$ (I$^-$) / M$^{-1}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>25</td>
<td>0.0124</td>
<td>0.0195</td>
<td>0.0232</td>
</tr>
<tr>
<td>[C$_4$C$_1$C$_1$im][NTf$_2$]</td>
<td>25</td>
<td>0.0296</td>
<td>0.0221</td>
<td>0.0238</td>
</tr>
<tr>
<td>[C$_4$C$_1$py][NTf$_2$]</td>
<td>25</td>
<td>0.0391</td>
<td>0.0226</td>
<td>0.0188</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$, ion pair</td>
<td>22</td>
<td>0.51</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>CH$_2$Cl$_2$, free ion</td>
<td>22</td>
<td>1.04</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>(CF$_3$)$_2$CHOH</td>
<td>50</td>
<td>0.00011</td>
<td>0.00045</td>
<td>0.00039</td>
</tr>
</tbody>
</table>

As can be seen in Table 6, it was found that reaction rates were significantly faster in dichloromethane and slowest in the highly ionizing and strong hydrogen bond donating hexafluoropropan-2-ol. The rates of reaction in the ionic liquids, whilst of the same order of magnitude, differ with changing cation. We can conclude, therefore, that rates and viscosities do not correlate. If viscosity had been a rate-determining factor then the slowest reactions would have taken place in the ionic liquids.

The authors used the Hughes-Ingold principles to explain the trend observed with the reaction rate decreasing from dichloromethane to ionic liquids to hexafluoropropan-2-ol. Hughes-Ingold theory predicts that the rate of reaction between the ionic nucleophile and the neutral electrophile will be decreased as solvent polarity increases due to the dispersal of charge on formation of the activated complex. Using dielectric constants as the polarity descriptors we can see that polarity increases going from dichloromethane (9.1) to ionic liquids (11-15) to hexafluoropropan-2-ol (16.7) and this is the same order in which the reaction rate decreases.

Taking a closer look at the chloride ion, the reactivity is found to change on changing the ionic liquid. The authors suggest that the hydrogen bond donating ability of the ionic liquid cation determines the nucleophile reactivity with the strongest hydrogen bond donating cation deactivating the Cl$^-$ to the greatest extent and resulting in the slowest reaction rate. This is indeed the trend that is observed: [C$_4$C$_1$py]$^+$ > [C$_4$C$_1$im]$^+$ > [C$_4$C$_1$C$_1$im]$^+$. However, this explanation is only qualitatively extrapolated from the results and has not been demonstrated quantitatively in this work. To do so would require relating the experimental rate constants to a numerical gauge of each solvent’s hydrogen bond donating ability. That which Lancaster et
The authors discuss the nucleophilicities of the halide ions in the commonly used ionic liquid, [C₄C₁im][NTf₂]. They find that the reactivity decreases in the order I⁻ > Br⁻ > Cl⁻ which is in accordance with their previous study into the halide nucleophilicity trend in the ionic liquid [C₄C₁im][BF₄]. The authors note that the trend is reversed in the less strongly hydrogen bond donating ionic liquid [C₄C₁py][NTf₂]. Lancaster and co-workers reasonably suggest that both the ionic liquid cation and anion play a role in the solvation of the reactants. Further investigations into the effects of the ionic liquid anion are required to determine the importance of each contribution.

The study closes by determining the Eyring activation parameters for the demethylation reaction by chloride in each solvent. The authors chose to analyse only the chloride ion due to the higher quality spectra and the fact that the activation parameters were found to be the same as those determined for the reaction using the bromide ion in a previous study. The results are summarised in Table 7.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>ΔH$^\ddagger$ / kJ mol$^{-1}$</th>
<th>TΔS$^\ddagger$ / J K$^{-1}$ mol$^{-1}$</th>
<th>ΔG$_{298}^\ddagger$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C₄C₁im][NTf₂]</td>
<td>71.8</td>
<td>-42.2</td>
<td>84.4</td>
</tr>
<tr>
<td>[C₄C₁im][NTf₂]</td>
<td>71.8</td>
<td>-37.3</td>
<td>82.9</td>
</tr>
<tr>
<td>[C₄C₁py][NTf₂]</td>
<td>68.5</td>
<td>-43.9</td>
<td>81.6</td>
</tr>
<tr>
<td>CH₂Cl₂, ion pair</td>
<td>79.5</td>
<td>7.9</td>
<td>77.2</td>
</tr>
<tr>
<td>CH₂Cl₂, free ion</td>
<td>54.4</td>
<td>-58.6</td>
<td>71.9</td>
</tr>
</tbody>
</table>

It can be seen that the ΔH$^\ddagger$ are similar to those for the ion pair in dichloromethane and it could be determined therefore that ionic liquid effects on activation enthalpy do not arise from differences in polarity between the ionic liquids and the dichloromethane. The differences come from the association of the chloride ion with either the ionic liquid cation or anion. This fact would suggest that the rate limiting step is the same for both the ionic liquid solvents and the dichloromethane, i.e. the enthalpic cost of forming the chlorine-carbon bond and breaking the chloride-cation association on forming the activated complex. When the...
reaction takes place through free ions in the dichloromethane, the chlorine-carbon bond is formed with the simultaneous cleavage of the solvent cation-chlorine association and thus the enthalpy of activation is lower. The idea that all solute ions in an ionic liquid are associated with other oppositely charged ions is hardly surprising. The activation enthalpy for the ion pair reaction in dichloromethane is similar to those in the ionic liquids so we would therefore expect a similar enthalpic cost of ion dissociation to be incurred.

A variance in $\Delta S^{\neq}$ between ionic liquid solvent and dichloromethane is found in Table 7 where the values are fairly large and negative for the ionic liquids but small and positive for the ion pair reaction in dichloromethane. In dichloromethane the ion pair must be broken to form the activated complex and during this process a cation is liberated. This compensates for the entropy lost by association of the reacting species. In the ionic liquid, no matter which ion pair is broken to form the activated complex, the cation is not liberated as it is already associated with the ionic liquid anions. Therefore the large negative $\Delta S^{\neq}$ constitutes the loss of entropy which arises from the associative nature of the $S_N2$ process.

The Gibbs energy of activation varies inversely with the $k_2$ values as expected. The largest $\Delta G^{\neq}$ relates to the slowest reaction and the smallest $\Delta G^{\neq}$ relates to the fastest reaction. Lancaster et al. proposed the reaction shown in Reaction Scheme 11 in light of the work by Hardacre and co-workers$^{50}$ who showed that in [C$_4$C$_1$im]Cl, the chloride ion is surrounded by six cations. The left-hand side of the equilibrium shows the fully coordinated chloride ion which is unavailable for reaction, whereas on the right-hand side one face of the chloride ion is exposed to the substrate following the dissociation of one [C$_4$C$_2$im]$^+$ cation, to produce a chloride that is available for reaction.

![Reaction Scheme 11](image)

Reaction Scheme 11 - The demethylation reaction mechanism proposed by Lancaster and co-workers
At least one cation must dissociate from the chloride ion in order for the chloride to react in the ionic liquid. Given that the reaction is slowest in [C₄C₁im][NTf₂] it can be deduced that the interaction between [C₄C₁im]⁺ and the chloride ion is strongest and weakest between [C₄C₁py]⁺ and the chloride as the pyrrolidinium based ionic liquid proved to support the fastest reaction.

In a subsequent work, Lancaster and Welton studied the effect of the ionic liquid anion on the reaction between methyl-p-nitrobenzenesulfonate and the halides Cl⁻, Br⁻ and I⁻. The reaction shown in Reaction Scheme 12 was carried out in several ionic liquids composed of the same cation and different anions.

\[
\text{O}_{2}N\text{--CH₃ + X} \xrightleftharpoons{} [C₄C₁im][Y⁻] \xrightarrow{} \text{O}_{2}N\text{--CH₃ + CH₃-X}
\]

\[Y⁻ = [\text{BF}_4⁻], [\text{PF}_6⁻], [\text{SbF}_6⁻], [\text{OTf}]⁻, [\text{NTf}_2]⁻\]

**Reaction Scheme 12 - The demethylation of methyl-p-nitrobenzenesulfonate studied by Lancaster and Welton**

Both chloride and bromide ions were introduced as the [C₄C₁im]⁺ salts and iodide was added as the [C₂C₁im]⁺ salt. Lancaster and Welton carried out kinetic analyses of the reactions in each of the [C₄C₁im][Y⁻] ionic liquids and also some conventional solvents for comparison. The results can be seen in Table 8. Note that the results recorded in acetonitrile, dimethyl sulfoxide and methanol are reported relative to bromide.

**Table 8 - Kinetic outcomes of the demethylation reactions**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T / °C</th>
<th>k₂ (Cl⁻) / M⁻¹ s⁻¹</th>
<th>k₂ (Br⁻) / M⁻¹ s⁻¹</th>
<th>k₂ (I⁻) / M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C₄C₁im][BF₄]</td>
<td>25</td>
<td>0.0403</td>
<td>0.0381</td>
<td>0.0538</td>
</tr>
<tr>
<td>[C₄C₁im][PF₆]</td>
<td>25</td>
<td>0.0144</td>
<td>0.0086</td>
<td>0.0278</td>
</tr>
<tr>
<td>[C₄C₁im][SbF₆]</td>
<td>25</td>
<td>0.0115</td>
<td>0.0123</td>
<td>0.0180</td>
</tr>
<tr>
<td>[C₄C₁im][OTf]</td>
<td>25</td>
<td>0.0197</td>
<td>0.0314</td>
<td>0.0619</td>
</tr>
<tr>
<td>[C₄C₁im][NTf₂]</td>
<td>25</td>
<td>0.0124</td>
<td>0.0195</td>
<td>0.0232</td>
</tr>
<tr>
<td>CH₂Cl₂, ion pair</td>
<td>22</td>
<td>0.51</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>CH₂Cl₂, free ion</td>
<td>22</td>
<td>1.04</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>(CF₃)₂CHOH</td>
<td>50</td>
<td>0.00011</td>
<td>0.00045</td>
<td>0.00039</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Comparing the rates of reactions of both chloride and bromide ions in the ionic liquids with the rates in dichloromethane, it is evident that the reaction proceeds at a slower rate in ionic liquids. The Hughes-Ingold approach predicts this result on the basis that on going from ionic reactant to a charge disperse activated complex, the reaction will proceed faster in less polar solvents such as dichloromethane and slower in more polar solvents such as the ionic liquids. Hughes-Ingold theory predicts that more polar solvents will stabilise anionic nucleophiles and reduce their reactivity and hence increase the energy of activation. A schematic diagram of the charge dispersed activated complex can be seen in Figure 6.

![Figure 6 - Schematic representation of the activated complex](image)

Hughes-Ingold theory, however, does not explain the differences in reaction rates found in the ionic liquid. The authors therefore introduce the Kamlet-Taft polarity descriptors as an alternative to dielectric constants as a means to defining solvent polarity. The Kamlet-Taft parameters for the ionic liquids and molecular solvents used in the study are shown in Table 9.
The parameter $\pi^*$ (polarizability) is used to justify the lower polarity of dichloromethane compared to the ionic liquids but does little to explain the differences in reaction rates found in the ionic liquids themselves. Indeed, given that $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ has the highest $\pi^*$ value, this ionic liquid should give the slowest reaction rate amongst the ionic liquids. It is unexpected therefore that the reactions using chloride and bromide are fastest in this ionic liquid and the iodide ion recorded its second highest $k_2$ value. Changing the anion of the ionic liquid is most associated with the hydrogen bond acceptor parameter $\beta$. A high $\beta$ value denoted a strong hydrogen bond between anion and cation and it would be expected that the halide would therefore be less coordinated and more nucleophilic. However, no real correlation between the kinetic data and $\beta$ was found. Slightly better correlation is found between the reaction rates and the ionic liquids’ $\alpha$ values. A higher value of $\alpha$ (hydrogen bond donating ability) means that the ionic liquid cation will be more coordinated to the nucleophile and so the nucleophile becomes deactivated relative to solvents with lower values of $\alpha$. The authors therefore expected to see the fastest reaction in the ionic liquid with the lowest $\alpha$ value and the slowest reaction in the ionic liquid with the highest $\alpha$ value ($[\text{C}_4\text{C}_1\text{im}][\text{SbF}_6]$). This trend is generally observed, albeit with a few outliers. The authors therefore conclude that the Kamlet-Taft parameters along with the Hughes-Ingold principles do not adequately predict or explain the results observed and that hydrogen bonding effects are not the exclusive contributing factor to the reaction rates.
Lancaster and Welton found in their study that the nucleophilicity of all three halides tested were affected by changing the ionic liquid anion. The authors found that when chloride was used as the nucleophile, the ionic liquid cation and anion effects were of the same order. On the other hand, for both bromide and iodide, changing the ionic liquid anion had a more pronounced effect than changing the ionic liquid cation on the halide nucleophilicities. By comparing the relative nucleophilicities of the halides in ionic liquids and molecular solvents with similar $E_T^{N}$ values the authors concluded that chloride is more nucleophilic than bromide in $[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$ and dimethyl sulfoxide. Chloride and bromide nucleophilicities were found to be equivalent in the $[\text{BF}_4]$ and $[\text{SbF}_6]$ ionic liquids and acetonitrile, whereas bromide became more nucleophilic than chloride in methanol and the ionic liquids $[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$ and $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$. In general, the iodide ion was found to be more nucleophilic than bromide but the authors note that some of the rates reported for iodide carry large uncertainties due to poorer quality spectra. The fastest reactions were recorded in $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$ and the slowest in $[\text{C}_4\text{C}_1\text{im}][\text{SbF}_6]$.

Lancaster and Welton’s previous work had shown that the ionic liquid cation affects the nucleophilicity of the chloride ion whilst there is little to no effect on bromide or iodide ions. This subsequent study shows that changing ionic liquid anion affects the nucleophilicity of all the halide ions tested.

As with their previous studies, the authors carried out Eyring activation parameter analysis by studying the reaction kinetics at various temperatures. The results are listed in Table 10.

**Table 10 - Results of the activation parameters analysis of the demethylation reactions**

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Solvent</th>
<th>$\Delta H^\neq$ / kJ mol$^{-1}$</th>
<th>$T\Delta S^\neq$ / J K$^{-1}$ mol$^{-1}$</th>
<th>$\Delta G_{298}^\neq$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$</td>
<td>52.8</td>
<td>-97.3</td>
<td>81.8</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$</td>
<td>56.4</td>
<td>-86.5</td>
<td>82.2</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$</td>
<td>74.2</td>
<td>-27.3</td>
<td>82.4</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{PF}_6]$</td>
<td>79.4</td>
<td>-11.0</td>
<td>82.7</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{SbF}_6]$</td>
<td>78.6</td>
<td>-19.2</td>
<td>84.3</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{OTf}]$</td>
<td>71.8</td>
<td>-33.8</td>
<td>81.9</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>71.8</td>
<td>-42.2</td>
<td>84.4</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>CH$_2$Cl$_2$, ion pair</td>
<td>79.5</td>
<td>7.9</td>
<td>77.2</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>CH$_2$Cl$_2$, free ion</td>
<td>54.4</td>
<td>-58.6</td>
<td>71.9</td>
</tr>
</tbody>
</table>
As expected, the Gibbs energies of activation follow the same trend as the $k_2$ values recorded. The authors note that the $\Delta G^\neq_{298}$ value is much lower in dichloromethane where two reaction mechanisms take place than in any of the ionic liquids. Overall, the activation energies are very similar to those recorded in Lancaster’s previous study into the ionic liquid cation effect. Additionally, with the exception of the reaction in $[C_4C_1im][BF_4]$, the activation enthalpies are similar to those found for the ion pair reaction in dichloromethane. This result is in accordance with the authors’ previous study which proposed that at least one of the six surrounding ionic liquid cations must dissociate from the nucleophile before it can react (Reaction Scheme 11). With the exception of the ion pair reaction in dichloromethane, activation entropies are negative as expected for an associative reaction. Lancaster and Welton explain that the extent to which the $\Delta S^\neq$ values are negative depends on how coordinated the halide ions are in solution which depends on how coordinating the ionic liquid anion is. In $[C_4C_1im][BF_4]$ the halide ions are the least coordinated which gives the system a lower entropy than the halide solutions in other ionic liquids. Therefore the activation entropy is much more negative in $[C_4C_1im][BF_4]$ than in other ionic liquids. The positive activation enthalpy recorded in dichloromethane agrees with the authors’ previous result and is explained by the liberation of the $p$-nitrobenzenesulfonate in the molecular solvent which is not possible in the ionic liquids.

Lancaster’s work into ionic liquid effects continued with a study of the nucleophilic substitution reaction between charge-neutral nucleophiles and the charge-neutral electrophile, methyl-$p$-nitrobenzenesulphonate.53 Three ionic liquids were studied; $[C_4C_1py][NTf_2]$, $[C_4C_1py][OTf]$ and $[C_4C_1im][OTf]$, and several alkylamines were employed as the nucleophile as can be seen in Reaction Scheme 13.

![Reaction Scheme 13](image)

**Reaction Scheme 13 - The demethylation reactions examined**

The authors report quantitative kinetic studies of the substitution reaction by various alkylamines in the ionic liquids mention above and also in the molecular solvents;
acetonitrile, dichloromethane and water, in order to draw comparisons. The second order rate 
constants obtained are listed in Table 11.

Table 11 - Results of the kinetic studies of the methylation reactions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T / °C</th>
<th>$k_2$ ($^n$BuNH$_2$) / M$^{-1}$ s$^{-1}$</th>
<th>$k_2$ ($^n$Bu$_2$NH) / M$^{-1}$ s$^{-1}$</th>
<th>$k_2$ ($^n$Bu$_3$N) / M$^{-1}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C$_4$C$_1$py][NTf$_2$]</td>
<td>25</td>
<td>0.358</td>
<td>0.493</td>
<td>0.103</td>
</tr>
<tr>
<td>[C$_4$C$_1$py][OTf]</td>
<td>25</td>
<td>0.922</td>
<td>1.04</td>
<td>0.523</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][OTf]</td>
<td>25</td>
<td>0.500</td>
<td>0.541</td>
<td>0.0529</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>25</td>
<td>0.155</td>
<td>0.182</td>
<td>0.0257</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>25</td>
<td>0.0165</td>
<td>0.0454</td>
<td>0.0200</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>25</td>
<td>0.0547</td>
<td>0.0665</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

(amine: nPr$_2$NH) (amine: Et$_3$N)

As for their preceding study, both the Hughes-Ingold principles and Kamlet-Taft polarity 
descriptors were used to interpret the kinetic data obtained in the ionic liquids and 
conventional solvents. The Kamlet-Taft parameters used for the study are shown in Table 12.

Table 12 - Kamlet-Taft parameters for the solvents used by Lancaster and co-workers

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\alpha$</th>
<th>B</th>
<th>$\pi^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C$_4$C$_1$py][NTf$_2$]</td>
<td>0.427</td>
<td>0.252</td>
<td>0.954</td>
</tr>
<tr>
<td>[C$_4$C$_1$py][OTf]</td>
<td>0.396</td>
<td>0.461</td>
<td>1.017</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>0.625</td>
<td>0.489</td>
<td>1.006</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>0.042</td>
<td>-0.014</td>
<td>0.791</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>0.350</td>
<td>0.370</td>
<td>0.799</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>1.12</td>
<td>0.14</td>
<td>1.33</td>
</tr>
</tbody>
</table>

The Hughes-Ingold principles correctly predict the results found in Table 12, with the rate of 
reaction decreasing in the order $k_2$(ionic liquids) > $k_2$(acetonitrile) > $k_2$(dichloromethane). 
The polarizability descriptor $\pi^*$ can be seen to quantify the polarity of the solvents and the 
rate will increase with increasing $\pi^*$ when a S$_N$2 reaction takes places between charge-neutral 
species as is observed for this reaction. On the other hand water, which has the highest $\pi^*$
value listed, recorded very slow reaction rates and does not fit the general trend observed. The authors discussed the case of water separately.

Looking specifically to the ionic liquids, however, the $\pi^*$ values do not adequately explain the rates of reaction observed. Given that the $\pi^*$ values are approximately the same for each ionic liquid, it would be expected that the reaction rates would be approximately the same. This is not at all the case as we can see that the rates recorded for each amine vary significantly depending on the ionic liquid solvent used. It is therefore clear that solvent polarizability alone does not determine the reaction rate and that some other specific effects need to be taken into account. Lancaster and co-workers also noted a significant rate increase for the primary and secondary amines on changing the solvent from dichloromethane to the ionic liquids. No such dramatic increase was observed on going from acetonitrile to ionic liquids despite the fact that dichloromethane and acetonitrile have similar values of $\pi^*$. It is clear in this case that hydrogen bonding effects are of great importance.

![Figure 7](image_url)

**Figure 7 - Hydrogen bonding between ionic liquid anion and the emerging ammonium ion in the activated complex**

Hydrogen bond accepting solvents will support the formation of the activated complex as when the amine attacks the electrophile, it begins to develop a positive charge on the nitrogen atom and consequently the N-H protons become stronger hydrogen bond donors. Dichloromethane has a $\beta$ value of zero and therefore cannot hydrogen bond with the activated complex. Thus the rate of reaction is dramatically reduced in this solvent relative to those with higher values of $\beta$.

Lancaster *et al.* described the results recorded in water separately due to the very low reaction rates observed despite Hughes-Ingold theory predicting that the fastest rates should be observed in this solvent due to its high polarity. The authors attributed the low reaction rates observed to water’s very high $\alpha$ value. Water is a much stronger hydrogen bond donor than the other solvents tested, so much so in fact that it hydrogen bonds to the amine via the lone pair on the nitrogen atom and deactivates the nucleophile.
There is also the possibility that the hydrogen bond donor can interact with the emerging p-nitrobenzene sulfonate leaving group and promote the reaction this way. Competition between deactivation of the nucleophile and activation of the leaving group is always possible with a strong hydrogen bond donating solvent such as water. The authors argue that in light of the empirical evidence that the reaction proceeds very slowly in water, the deactivation of the nucleophile must be the dominant effect in this case. Lancaster and co-workers also carried out Eyring activation parameter analysis on the results to better understand the energetic differences between the ionic liquids and molecular solvents. The Eyring activation energies extracted can be found in Table 13.

**Table 13 - The Eyring activation parameters recorded by Lancaster *et al.***

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Nucleophile</th>
<th>$\Delta H^\ddagger$ / kJ mol$^{-1}$</th>
<th>$\Delta S^\ddagger$ / J K$^{-1}$ mol$^{-1}$</th>
<th>$\Delta G_{298}^\ddagger$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{C}_4\text{C}_1\text{py}]\text{NTf}_2]$</td>
<td>$^n\text{Bu}_2\text{NH}$</td>
<td>38.6</td>
<td>-120</td>
<td>74.4</td>
</tr>
<tr>
<td></td>
<td>$^n\text{BuNH}_2$</td>
<td>42.5</td>
<td>-111</td>
<td>75.6</td>
</tr>
<tr>
<td></td>
<td>$^n\text{Bu}_3\text{N}$</td>
<td>34.3</td>
<td>-141</td>
<td>76.3</td>
</tr>
<tr>
<td></td>
<td>$^n\text{Bu}_2\text{NH}$</td>
<td>38.5</td>
<td>-116</td>
<td>73.1</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{py}]\text{OTf}]$</td>
<td>$^n\text{BuNH}_2$</td>
<td>37.2</td>
<td>-120</td>
<td>72.9</td>
</tr>
<tr>
<td></td>
<td>$^n\text{Bu}_3\text{N}$</td>
<td>59.4</td>
<td>-51.5</td>
<td>74.8</td>
</tr>
<tr>
<td></td>
<td>$^n\text{Bu}_2\text{NH}$</td>
<td>41.2</td>
<td>-113</td>
<td>74.8</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}]\text{OTf}]$</td>
<td>$^n\text{BuNH}_2$</td>
<td>43.4</td>
<td>-105</td>
<td>74.6</td>
</tr>
<tr>
<td></td>
<td>$^n\text{Bu}_3\text{N}$</td>
<td>50.4</td>
<td>-100</td>
<td>80.2</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CN}$</td>
<td>$^n\text{Bu}_2\text{NH}$</td>
<td>40.0</td>
<td>-126</td>
<td>77.6</td>
</tr>
<tr>
<td></td>
<td>$^{n}$BuNH$_2$</td>
<td>$^{n}$Bu$_3$N</td>
<td>CH$_2$Cl$_2$</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>---------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>$^{n}$Bu$_2$NH</td>
<td>37.5</td>
<td>-133</td>
<td>77.1</td>
<td></td>
</tr>
<tr>
<td>$^{n}$Bu$_3$N</td>
<td>35.7</td>
<td>-155</td>
<td>81.9</td>
<td></td>
</tr>
<tr>
<td>$^{n}$BuNH$_2$</td>
<td>35.0</td>
<td>-162</td>
<td>83.3</td>
<td></td>
</tr>
<tr>
<td>nBu$_3$N</td>
<td>32.6</td>
<td>-161</td>
<td>80.6</td>
<td></td>
</tr>
<tr>
<td>nBu$_3$N</td>
<td>34.5</td>
<td>-161</td>
<td>82.5</td>
<td></td>
</tr>
</tbody>
</table>

The Gibbs energies of activation follow the expected trends established by the second order rate constants and are lower in the ionic liquids corresponding to the faster reactions and higher for the molecular solvents corresponding to slower reactions. It can be seen that the enthalpy of activation for the primary and secondary amines is not very sensitive to the identity of the solvent used whereas for the tertiary amine there is a large variation in $\Delta H^\neq$. Perhaps counter-intuitively, the $\Delta H^\neq$ values in dichloromethane are lower than in the ionic liquids. We must therefore conclude that the enthalpy of activation is not the dominant factor in determining the reaction rate; otherwise we would expect a faster reaction in dichloromethane. Paying attention therefore to the entropies of activation, the largest $\Delta S^\neq$ values recorded are for the reactions in dichloromethane. Whilst still large and negative, the $\Delta S^\neq$ values in the ionic liquids are somewhat lower than for dichloromethane and Lancaster and co-workers propose that $\Delta S^\neq$ determines the reactivity of the nucleophiles for this reaction in these solvents.

Having observed $S_N2$ type nucleophilic substitution reactions using halides that could be accelerated or decelerated according to choice of ionic liquid solvent, Crowhurst and co-workers continued investigating this area by studying the same reactions using various polyatomic anionic nucleophiles. The authors combined studies of halide reactivities in nucleophilic substitutions with the reactivities of acetate, trifluoroacetate, cyanide and thiocyanide ions in ionic liquids [C$_4$C$_1$py][OTf], [C$_4$C$_1$py][NTf$_2$] and[C$_4$C$_1$im][NTf$_2$]. Crowhurst et al. compared the reactivities measured in ionic liquids with the same reactions in molecular solvents dichloromethane, dimethyl sulfoxide and methanol. Reaction Scheme 14 depicts the reactions examined by the authors.
The second order rate constants, \(k_2\), obtained for the reactions are listed in Table 14 and compared to the results obtained for the halides by Lancaster and co-workers.\textsuperscript{53, 54}

**Table 14 - Results of the kinetic analysis of the demethylation reactions**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>CN(^-)</th>
<th>Ac(^-)</th>
<th>Cl(^-)</th>
<th>Br(^-)</th>
<th>I(^-)</th>
<th>TFA(^-)</th>
<th>SCN(^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C(_4)C(_1)py][NTf(_2)]</td>
<td>1.56</td>
<td>5.40x10(^{-2})</td>
<td>3.9x10(^{-2})</td>
<td>2.2x10(^{-2})</td>
<td>1.88x10(^{-2})</td>
<td>2.50x10(^{-3})</td>
<td>4.61x10(^{-2})</td>
</tr>
<tr>
<td>[C(_4)C(_1)py][OTf]</td>
<td>1.91</td>
<td>9.0x10(^{-2})</td>
<td>9.9x10(^{-2})</td>
<td>6.0x10(^{-2})</td>
<td>4.1x10(^{-2})</td>
<td>6.9x10(^{-3})</td>
<td>6.1x10(^{-2})</td>
</tr>
<tr>
<td>[C(_4)C(_1)im][NTf(_2)]</td>
<td>0.386</td>
<td>9.3x10(^{-3})</td>
<td>1.2x10(^{-2})</td>
<td>1.9x10(^{-2})</td>
<td>2.3x10(^{-2})</td>
<td>8.6x10(^{-4})</td>
<td>3.97x10(^{-2})</td>
</tr>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>2.69</td>
<td>0.271</td>
<td>1.07</td>
<td>0.46</td>
<td>6.6x10(^{-2})</td>
<td>6.4x10(^{-3})</td>
<td>2.27x10(^{-2})</td>
</tr>
<tr>
<td>CH(_3)OH</td>
<td>0.0162</td>
<td>6.8x10(^{-4})</td>
<td>4.0x10(^{-4})</td>
<td>1.62x10(^{-3})</td>
<td>6.0x10(^{-3})</td>
<td>5.14x10(^{-5})</td>
<td>2.29x10(^{-2})</td>
</tr>
<tr>
<td>DMSO</td>
<td>17.7</td>
<td>4.40</td>
<td>0.90</td>
<td>0.391</td>
<td>0.192</td>
<td>4.85x10(^{-2})</td>
<td>2.90x10(^{-2})</td>
</tr>
</tbody>
</table>

It was noted by the authors that although the Hughes-Ingold rules\textsuperscript{25} suggest the reaction should be retarded by more polar solvents, there was no obvious correlation between dielectric constant of the solvent and the reaction rate. Viewing the data as a whole, there is a general trend in the rate constants: DMSO > DCM > [C\(_4\)C\(_1\)py][OTf] > [C\(_4\)C\(_1\)py][NTf\(_2\)] > [C\(_4\)C\(_1\)im][NTf\(_2\)] > MeOH. It is clear that the Hughes-Ingold rules fail to predict the reaction rates in these solvents given that dimethyl sulfoxide has the highest dielectric constant (46.45) of those studied and accounts for the fastest reaction rates. Crowhurst and co-workers therefore included the Kamlet-Taft solvent polarity descriptors which better account for specific effects such as hydrogen bonding to analyse the kinetic data. The Kamlet-Taft parameters \(\alpha\), \(\beta\) and \(\pi^*\) used in this study are listed in Table 15.
Table 15 - Solvent Kamlet-Taft parameters used by Crowhurst and co-workers

<table>
<thead>
<tr>
<th>Solvent</th>
<th>α</th>
<th>B</th>
<th>π*</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C₄C₁py][NTf₂]</td>
<td>0.427</td>
<td>0.252</td>
<td>0.954</td>
</tr>
<tr>
<td>[C₄C₁py][OTf]</td>
<td>0.396</td>
<td>0.461</td>
<td>1.017</td>
</tr>
<tr>
<td>[C₄C₁im][NTf₂]</td>
<td>0.625</td>
<td>0.489</td>
<td>1.006</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>0.042</td>
<td>-0.014</td>
<td>0.791</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>1.05</td>
<td>0.61</td>
<td>0.73</td>
</tr>
<tr>
<td>DMSO</td>
<td>0.00</td>
<td>0.76</td>
<td>1.00</td>
</tr>
</tbody>
</table>

In order to understand the solvent dependencies of the nucleophiles, the authors carried out a linear solvation energy relationship (LSER) analysis. The LSER provides a means to quantitatively understanding solvent dependent data and explains changes in solute properties in terms of the Kamlet-Taft parameters. LSER analysis relates the logarithm of the rate constant to α, β and π* as shown in Equation 3:

\[ \ln k_2 = XYZ_0 + s\pi^* + a\alpha + b\beta \]

Equation 3 - Relationship between Kamlet-Taft parameters and the logarithm of the rate constant

This equation has been used in the analysis of various reaction rate data for many solvent dependent processes. The results of the LSER analysis are summarised in Table 16.

Table 16 - Results of the LSER analysis by Crowhurst et al.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>R²</th>
<th>S value</th>
<th>F value</th>
<th>LSER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>0.99</td>
<td>0.34</td>
<td>369</td>
<td>( \ln k_2 = 0.21 - 7.56\alpha )</td>
</tr>
<tr>
<td>Br⁻</td>
<td>0.97</td>
<td>0.41</td>
<td>131</td>
<td>( \ln k_2 = -0.87 - 5.38\alpha )</td>
</tr>
<tr>
<td>I⁻</td>
<td>0.88</td>
<td>0.4582</td>
<td>29</td>
<td>( \ln k_2 = -2.21 - 2.85\alpha )</td>
</tr>
<tr>
<td></td>
<td>0.95</td>
<td>0.33</td>
<td>30</td>
<td>( \ln k_2 = -2.57 - 3.05\alpha + 1.16\beta )</td>
</tr>
<tr>
<td>Ac⁻</td>
<td>1.00</td>
<td>0.2610</td>
<td>324.69</td>
<td>( \ln k_2 = -0.69 - 7.79\alpha + 2.90\beta )</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.20</td>
<td>373</td>
<td>( \ln k_2 = -2.37 - 7.60\alpha + 2.65\beta + 1.83\pi^* )</td>
</tr>
<tr>
<td>TFA⁻</td>
<td>0.90</td>
<td>0.82</td>
<td>36</td>
<td>( \ln k_2 = -3.62 - 5.66\alpha )</td>
</tr>
<tr>
<td></td>
<td>0.97</td>
<td>0.48</td>
<td>57</td>
<td>( \ln k_2 = -9.18 - 4.94\alpha + 5.76\pi^* )</td>
</tr>
<tr>
<td>SCN⁻</td>
<td>0.89</td>
<td>0.89</td>
<td>31</td>
<td>( \ln k_2 = -3.87 - 2.46\alpha )</td>
</tr>
<tr>
<td>CN⁻</td>
<td>0.86</td>
<td>1.00</td>
<td>25</td>
<td>( \ln k_2 = -2.03 - 5.75\alpha )</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>0.99</td>
<td>128</td>
<td>( \ln k_2 = -3.16 - 5.07\alpha + 5.78\pi^* )</td>
</tr>
</tbody>
</table>
The authors report that “acceptable” correlations were achieved with all of the nucleophiles in the ionic liquids and molecular solvents tested. However, it is unclear what criteria the authors used to define “acceptability” for the correlations. From the LSER analysis it was concluded that for this reaction there is no special “ionic liquid effect”. The Kamlet-Taft parameters adequately describe the solvent-solute interactions. In Table 16 it can be seen that α appears in each of the LSERs and always as a negative value. This result suggests that increasing solvent hydrogen bond donating ability of the solvent decreases the reaction rate. It is well-known that hydrogen bond donating solvents can stabilise anionic nucleophiles and therefore reduce their reactivity. The extent to which this phenomenon will affect a reaction depends on how strong a hydrogen bond donor the solvent and how good a hydrogen bond acceptor the nucleophile is.

Crowhurst and co-workers found that α alone provided the best LSER fit for chloride, bromide and thiocyanide ions. For iodide and acetate, a better fit was found by including both α and β parameters and for cyanide, acetate and trifluoroacetate, π* also appears in the correlation.

The authors explain that π* appears in the correlations of only three nucleophiles due to the relatively narrow range of π* values associated with the solvents studied. A π* effect may have been seen had a broader range of solvents been investigated, but solute solubilities limited the selection of potential solvents. Hughes-Ingold theory predicts a negative coefficient for the π* term which disagrees with the correlations observed by Crowhurst and co-workers. The authors also suggest that the positive values obtained for the π* coefficients are in agreement with the Hughes-Ingold rules. This interpretation is incorrect as the rules suggest that the reaction rate should be decreased by increasing solvent polarity which would be represented by a negative coefficient for π*.

For both iodide and acetate, the β coefficients have positive values which mean that larger values of β lead to faster reaction rates. The authors suggest that solvents with high β values have stronger interactions between solvent cation and solvent anion meaning that the cation is less available to interact with the solute anion and therefore less able to deactivate the nucleophile. Thus, the reaction rates increase with higher β values. Figure 9 depicts the competing interactions.
In a previous work, Lancaster and co-workers proposed that for the reaction of methyl-\textit{p}-nitrobenzenesulfonate with bromide and chloride ions, changing the ionic liquid anion had no effect on the reaction rate. The LSER analysis by Crowhurst \textit{et al.} serves to corroborate this conclusion as $\beta$ was found not to correlate for reactions with chloride and bromide. These reactions correlated best with $\alpha$ only. Given that it is the ionic liquid anion which is mostly responsible for determining the solvent $\beta$ values, changing the anion and therefore the $\beta$ value was found not affect the nucleophilicity of chloride or bromide ions.

As with their previous studies, Crowhurst and co-workers carried out Eyring activation parameter analyses for the reactions. As the results for chloride, cyanide, thiocyanide, acetate and trifluoroacetate were consistent with their previous work, the activation energies are not extensively discussed in terms of reaction mechanism. Rather, the LSER correlations between $\Delta G^\#_{298}$ for the reactions and the Kamlet-Taft parameters for the solvents are given in order to understand more about how changing the solvent affects the reaction. A statistically reliable LSER was not possible for the activation entropies and enthalpies. The Gibbs energy of activation is directly proportional to $\ln k_2$ so the authors reasonably assumed that the LSER correlations for $\Delta G^\#_{298}$ would be identical to those with $\ln k_2$. Superficially this was found to be the case, but on more detailed inspection, many differences become apparent. The outcomes of the LSER correlations with $\Delta G^\#_{298}$ are listed in Table 17.
Table 17 - The results of the LSER analysis

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>R²</th>
<th>S value</th>
<th>F value</th>
<th>LSER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl⁻</td>
<td>0.98</td>
<td>1.38</td>
<td>164</td>
<td>ΔG₂³⁹₈K≠ = 72.3 + 19.2α</td>
</tr>
<tr>
<td>Ac⁻</td>
<td>0.95</td>
<td>1.86</td>
<td>70</td>
<td>ΔG₂³⁹₈K≠ = 71.4025 + 19.9α</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.44</td>
<td>767</td>
<td>ΔG₂³⁹₈K≠ = 90.0 + 21.6α - 3.2β - 18.5π*</td>
</tr>
<tr>
<td>TFA⁻</td>
<td>0.97</td>
<td>1.29</td>
<td>47</td>
<td>ΔG₂³⁹₈K≠ = 94.2 + 12.4α - 12.8π*</td>
</tr>
<tr>
<td>SCN⁻</td>
<td>0.91</td>
<td>0.85</td>
<td>40</td>
<td>ΔG₂³⁹₈K≠ = 82.5 + 6.19α</td>
</tr>
<tr>
<td>CN⁻</td>
<td>0.95</td>
<td>1.437</td>
<td>72.91</td>
<td>ΔG₂³⁹₈K≠ = 66.8 + 15.7α</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>0.99</td>
<td>80</td>
<td>ΔG₂³⁹₈K≠ = 79.9 + 12.3α - 12.8π*</td>
</tr>
</tbody>
</table>

From this data it can be seen that α, or hydrogen bond donating ability of the solvent, accounts for changes in ΔG₂³⁹₈ with changing solvent. The results support the authors’ previously proposed reaction mechanism that on formation of the activated complex, the nucleophile loses some hydrogen bond accepting ability.

Landini et al. conducted a study into the reactivity of anionic nucleophiles in two ionic liquids, [C₆C₁im][ClO₄] and [C₆C₁im][PF₆], and also in various molecular solvents with a range of dielectric constants for comparison.

![Reaction Scheme](image)

Reaction Scheme 15 - Nucleophilic substitution reactions of methanesulfonate derivatives studied by Landini and co-workers

The kinetic analysis of these reactions is listed in Table 18.
Table 18 - $k_2$s for the reactions by Landini and co-workers

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>$10^4k_2 / \text{M}^{-1} \text{s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[C$_6$C$_1$im][PF$_6$]</td>
</tr>
<tr>
<td>N$_3^-$</td>
<td>31.7</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>3.3</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>3.7</td>
</tr>
<tr>
<td>I$^-$</td>
<td>3.7</td>
</tr>
<tr>
<td>SCN$^-$</td>
<td>0.8</td>
</tr>
<tr>
<td>$p$-NO$_2$PhO$^-$</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Landini and Maia found that the anion reactivity increases going from [C$_6$C$_1$im][PF$_6$] to [C$_6$C$_1$im][ClO$_4$] which is in agreement with the results reported by Lancaster and Welton. The nucleophiles follow the trend N$_3^-$ $\gg$ I$^-$ $\approx$ Br$^-$ $\approx$ Cl$^-$ $\approx$ [4-NO$_2$PhO]$^-$ in [C$_6$C$_1$im][PF$_6$]. In [C$_6$C$_1$im][ClO$_4$] the trend changes to N$_3^-$ $\gg$ I$^-$ $\gg$ [4-NO$_2$PhO]$^-$ $\approx$ Br$^-$ $\approx$ SCN$^-$. Anion nucleophilicity was found to increase considerably in dimethyl sulfoxide compared with the ionic liquids and methanol as mostly free ions are present in dimethyl sulfoxide. The second order rate constants recorded in chlorobenzene are dramatically higher than in any other solvent. The authors explain that the rate enhancement is caused by destabilisation of the anionic nucleophile in the non-polar medium.

Of particular interest to this project, Landini notes that changing the nucleophilic source from an imidazolium salt to a bulky tetroctylammonium salt where the cation is less prone to hydrogen bond formation, the reactivity of all of the ions increased by around five fold. On use of the tetroctylammonium salts, the trend in nucleophilicities also follows the trend expected in polar aprotic media and in the gas phase: N$_3^-$ $\gg$ Cl$^-$ $\gg$ Br$^-$ $\gg$ [4-NO$_2$PhO]$^-$. Landini proposes that the relative nucleophilicities of the anions and the rate enhancement upon the use of tetroctylammonium salts reflects the increasing interaction (hydrogen bonding) of the anion with the ion paired imidazolium cation on increasing the charge density of the anionic nucleophile.

Betti followed up Landini’s work with a study including additional nucleophiles, [C$_6$H$_5$COO]$^-$ and [C$_6$H$_5$CH$_2$COO]$^-$. 
Table 19 summarises the results of all kinetic analyses obtained.

Table 19 - The second order rate constants measured by Betti and co-workers

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>$10^4k_2$ / M$^{-1}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[C$_6$C$_1$im][PF$_6$]</td>
</tr>
<tr>
<td>N$_3^-$</td>
<td>31.7</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>3.3</td>
</tr>
<tr>
<td>Br$^-$</td>
<td>3.7</td>
</tr>
<tr>
<td>I$^-$</td>
<td>3.7</td>
</tr>
<tr>
<td>SCN$^-$</td>
<td>0.8</td>
</tr>
<tr>
<td>[p-$\text{NO}_2\text{PhO}$]$^-$</td>
<td>3.2</td>
</tr>
<tr>
<td>[PhCOO]$^-$</td>
<td>5.3</td>
</tr>
<tr>
<td>[PhCH$_2$COO]$^-$</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Once again the authors found very high reaction rates in chlorobenzene due to destabilisation of the anionic nucleophiles and consequent high reactivity. On order to assess the effect of cation-anion interaction, the reaction in chlorobenzene was also run using [C$_8$C$_1$C$_1$im]$^+$ salts as the sources of the nucleophiles.
The results are listed in Table 20.

**Table 20 - Kinetic analysis in chlorobenzene**

<table>
<thead>
<tr>
<th>Anion</th>
<th>10^3 k_2 / M^-1 s^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl^-</td>
<td>13.3</td>
</tr>
<tr>
<td>Br^-</td>
<td>8.3</td>
</tr>
<tr>
<td>I^-</td>
<td>4.6</td>
</tr>
<tr>
<td>p-NO_2PhO^-</td>
<td>5.2</td>
</tr>
</tbody>
</table>

**Q^+**

<table>
<thead>
<tr>
<th>Anion</th>
<th>10^3 k_2 / M^-1 s^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C_8C_1im]^+</td>
<td>28</td>
</tr>
<tr>
<td>[C_8C_1im]^+</td>
<td>19.6</td>
</tr>
<tr>
<td>[C_8H_17N]^+</td>
<td>37</td>
</tr>
</tbody>
</table>

All anionic nucleophiles were found to increase in reactivity on use of the [C_8C_1im]^+ salts which agrees with the result Landini had previously found on use of another poor hydrogen bond donating cation, tetraoctylammonium. According to the authors, this result proves that anion-cation interactions can play an important role in the reaction rates of nucleophilic substitution reactions.

Having published several investigations into ionic liquid solvent effects on substitution reactions between anionic nucleophiles and charge neutral electrophile and between neutral nucleophile and neutral electrophile, Welton and co-workers expanded the study further by examining the reaction between neutral nucleophiles and a charged electrophile. The authors studied the reaction of three charge neutral amine nucleophiles, BuNH_2, Bu_2NH and Bu_3N, with cationic electrophiles, dimethyl-p-nitrophenylsulfonylum salts. Solvents studied include dichloromethane, tetrahydrofuran, acetonitrile, methanol and ionic liquids [C_4C_1py][OTf], [C_4C_1py][NTf_2], [C_4C_1im][OTf] and [C_4C_1im][NTf_2]. Reaction Scheme 17 represents the reaction studied by Welton and co-workers.

Reaction Scheme 17 - The substitution reaction studied by Welton et al.

The authors measured the rate constants for each of the reactions and, as with their previous works, related the results to the Kamlet-Taft parameters for each solvent to gain an
understanding of the solvent dependency of the reaction. The results of the kinetic study and the Kamlet-Taft parameters used for the solvents are shown in Table 21.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$k_2 / M^{-1} s^{-1}$</th>
<th>Kamlet-Taft Parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^\text{a} \text{BuNH}_2$</td>
<td>$^\text{a} \text{Bu}_2\text{NH}$</td>
<td>$^\text{a} \text{Bu}_3\text{N}$</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>0.154</td>
<td>0.25</td>
<td>0.068</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>0.016</td>
<td>0.030</td>
<td>0.0092</td>
</tr>
<tr>
<td>THF</td>
<td>0.0385</td>
<td>0.028</td>
<td>0.0016</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>0.00064</td>
<td>0.00097</td>
<td>0.000421</td>
</tr>
<tr>
<td>C$_7$H$_8$</td>
<td>0.239</td>
<td>0.14</td>
<td>0.0067</td>
</tr>
<tr>
<td>[C$_4$C$_1$py][NTf$_2$]</td>
<td>0.060</td>
<td>0.133</td>
<td>0.060</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>0.026</td>
<td>0.068</td>
<td>0.00186</td>
</tr>
<tr>
<td>[C$_4$C$_1$py][OTf]</td>
<td>0.030</td>
<td>0.0380</td>
<td>0.0023</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][OTf]</td>
<td>0.0134</td>
<td>0.016</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Using Hughes-Ingold theory to predict solvent behaviour, high polarity solvents should decelerate the reaction studied due to dispersal of charge density going from reactants to activated complex. It can be seen from Table 21 that the kinetic results do not reflect the Hughes-Ingold predictions. The dielectric constants$^{59}$ are of the order C$_7$H$_8$ (2.38)$^{60}$ < THF (7.61)$^{70}$ < CH$_2$Cl$_2$ (9.08)$^{61}$ < ionic liquids (ca. 11-15) < CH$_3$OH (32.7)$^{62}$ < CH$_3$CN (37.5)$^{63}$ and whilst methanol supports the slowest reaction rates recorded, the fastest reaction rates were found for n-butylamine only in toluene and in dichloromethane and [C$_4$C$_1$im][NTf$_2$] for the other nucleophiles.

Welton and co-workers note the poor correlation of the rate constants with solvent dielectric constant. The failure of the Hughes-Ingold rules to predict the solvent effects indicates that some specific effects which are overlooked in the Hughes-Ingold theory play a role in the reaction rate and so the authors carried out an in-depth examination of the rates constants in relation to the Kamlet-Taft parameters, $\alpha$, $\beta$ and $\pi^*$. The authors found that the relative nucleophilicities and ordering of the nucleophilicities of different amines changed on changing solvent. For example, the reaction of $^\text{a} \text{BuNH}_2$ is fastest in toluene whereas the fastest reaction with $^\text{a} \text{Bu}_2\text{NH}$ is found in dichloromethane. The authors therefore conducted an LSER analysis. The study was sure to include ionic liquids of systematically chosen
cations and anions of to investigate the effect of changing the physiochemical properties of the ionic liquid. The results of the LSER are listed in Table 22.

Table 22 – Kamlet-Taft LSER fits for the reaction of amines with a cationic electrophile carried out by Welton and co-workers

<table>
<thead>
<tr>
<th>Amine</th>
<th>Parameters</th>
<th>LSER</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBuNH$_2$</td>
<td>$\alpha$, $\beta$ and $\pi^*$</td>
<td>$\ln k_2 = -2.38 - 3.59\alpha - 4.16\beta + 2.10\pi^*$</td>
</tr>
<tr>
<td>nBu$_2$NH</td>
<td>$\alpha$, $\beta$ and $\pi^*$</td>
<td>$\ln k_2 = -2.66 - 2.79\alpha - 5.01\beta + 2.89\pi^*$</td>
</tr>
<tr>
<td>nBu$_3$N</td>
<td>$\beta$ and $\pi^*$</td>
<td>$\ln k_2 = -5.62 - 6.46\beta + 4.26\pi^*$</td>
</tr>
</tbody>
</table>

The authors reported excellent correlations using the Kamlet-Taft approach to describe solvent polarity. It was found that in all cases, $\beta$, the hydrogen bond accepting property of the solvent, directed the rate constants. The $\beta$ coefficients are all large and negative which suggests that higher values of $\beta$ will lead to a decrease in $k_2$. This result contradicts the authors’ previous results for the reactions between amines and charge neutral electrophiles. Welton and co-workers explain that solvents with high $\beta$ values will hydrogen bond with the relatively acidic protons on the cationic electrophiles and therefore increase charge density at the reaction centres. These interactions will deactivate the substrates and decrease the reaction rates.

The authors propose that during the activation process, the acidity of the sulfide protons reduces and so to the strength of the hydrogen bonds from these protons to the solvent. Therefore the hydrogen bonds are weaker in the activated complex than in the reactant sulfonium electrophile. The activated complex is less stabilised relative to the reactants and the activation energy increases. Hence, the reaction rate is decreased by strong hydrogen bond accepting solvents.
In Figure 11, the authors depict the hydrogen bonding opportunities for the activated complex. The hydrogen bonds between the amine and the solvent (H\textsuperscript{a}) get stronger during the activation process producing a stabilising effect. Those between the solvent and the sulfonium species (H\textsuperscript{c}) decrease during the activation process and destabilise the activated complex relative to the reactants.

Both the primary and secondary amines were found to correlate with the solvent hydrogen bond donating properties. The negative coefficient demonstrates that hydrogen bond donating solvents decrease k\textsubscript{2} for these nucleophiles. This is due to deactivation of the nucleophile by hydrogen bond donation depicted in Figure 12.

In all experiments, \(\pi^*\) has a positive correlation. The Hughes-Ingold rules predict a negative correlation leading the authors to conclude that \(\pi^*\) is a poor gauge of Hughes-Ingold polarity. Significantly, Welton and co-workers report a clear cation/anion effect observed in ionic liquids with the ionic liquids of low \(\beta\) providing the fastest reactions and those with high \(\alpha\) and \(\beta\) giving the slowest.
The Welton group followed up this study with an investigation into the solvent effects on nucleophilic substitution reactions between charged nucleophiles and charged electrophiles, thereby covering all bases in terms of possible charge density evolution throughout the S$_{N}$2 process. The authors report the S$_{N}$2 reaction of the trifluoromethanesulfonate and bis(trifluoromethanesulfonfonyl)imide salts of dimethyl-4-nitrophenylsulfonium ([p-NO$_2$PhS(CH$_3$)$_2$]$^+$/[X$^-$]; [X$^-$] = OTf, NTf$_2$) with chloride ion in ionic liquids and molecular solvents. The reaction under investigation is shown below in Reaction Scheme 18.

![Reaction Scheme 18 - The reaction between cationic electrophile and anionic nucleophile](image_url)

Welton et al. studied many different molecular solvents: acetonitrile, dimethyl sulfoxide, propylene carbonate, 1-butanol, acetone, tetrahydrofuran, dichloromethane and also numerous ionic liquids: [C$_4$C$_1$p][NTf$_2$], [C$_4$C$_1$im][NTf$_2$], [C$_4$C$_1$C$_1$im][NTf$_2$], [C$_4$C$_1$im][OTf], [C$_4$C$_1$p][OTf], [HC$_4$im][OTf]. As for their previous investigations, the authors carried out the reactions at various concentrations of chloride ion under pseudo-first order conditions to obtain second order rate constants. However, only for the reactions carried out in ionic liquids were linear dependencies on chloride concentrations observed. The reactions recorded in the molecular solvents showed partial order kinetics with some of the reactions seeming to show a negative dependence on chloride concentration. Therefore, rate constants could be obtained for the ionic liquid reactions only. The authors do not report or discuss the reaction rates in this work but do demonstrate the kinetics observed in each solvent from which it is clear that there is some change in mechanism for the reaction on changing from ionic liquids to molecular solvents.

Welton and co-workers describe the ion metathesis step which forms a reactive quaternary ion pair. This step must take place in molecular solvents before the reaction can proceed. The ion metathesis reaction occurs to give dimethyl-4-nitrophenylsulfonium chloride as shown in Reaction Scheme 19.
The authors report the apparent negative order of the reaction rate with chloride concentration in fairly low polarity solvents such as acetone, dichloromethane and tetrahydrofuran. The salt formed on the right hand-side of the equilibrium in Reaction Scheme 19 is insoluble in these solvents and precipitates from solution. As the chloride concentration increases, the equilibrium constant for this metathesis moves further to the right and leads to greater formation of dimethyl-4-nitrophenylsulfonium chloride. The amount of electrophile in solution therefore decreases and the rate of reaction is seen to slow down.

Welton and co-workers report that in polar conventional solvents such as acetonitrile and dimethyl sulfoxide, the same ion metathesis takes place to form dimethyl-4-nitrophenylsulfonium chloride, but that this salt exists as ion pairs in solution. The kinetic experiments in these solvents show the reaction between these ion pairs and therefore increasing concentration of the nucleophile increases the rate of reaction but not linearly as prescribed by the pseudo-first order reaction conditions. The reactions of these ion pairs are of importance to this project and are therefore discussed in detail in Chapter 2.

Given that the ionic liquids clearly exhibited different solvent behaviour to the conventional solvents, Welton and co-workers surmised that the reaction must proceed through a different mechanism in the different media. The kinetic behaviour seen in the ionic liquids suggests that the reaction does not progress through ion pairs but through freely solvated ions. The authors suggest that there are two possible scenarios: either the ionic liquids fully dissociate the solute salts so that no ion pairs form or the ion pairs do form in ionic liquids but do not react the same way as they do in molecular solvents. In the dissociating solvents studied (dimethyl sulfoxide and acetonitrile) the solutes will form both ion pairs and free ions and both species will be involved in the reaction. However, recalling that in reaction kinetics we only observe the slowest step of the fastest, Welton et al. propose that the ion pairs are more reactive in molecular solvents than the free ions and so dominate the kinetic behaviour. The authors explain that the same kinetic behaviour is not seen in ionic liquids because the ion
pairs do not form. The authors suggest that the very slow reaction rates observed in the ionic liquids supports the theory that ion pairs do not form. Alternatively, the ion pairs could exist but perhaps they are the less reactive species compared with free ions in ionic liquids.

Welton and co-workers further investigated ion pairing in ionic liquids by measuring the UV spectrum of the salt 1-ethyl-4-(methoxycarbonyl) pyridinium iodide in the same ionic liquids and molecular solvents as used in the kinetic experiments. In conventional solvents the salts show a well-defined peak attributed to a charge transfer absorbance from an iodide to pyridinium that has been used to define the Kosower Z scale of solvent polarity. None of the ionic liquids tested showed the absorbance at concentrations similar to the chloride salt concentration used to study the nucleophilic substitution. The authors take this result as strong evidence that the solute ions do not associate with each other but rather with the ionic liquid ions of opposite charge. Therefore, whilst ionic liquid ions are strongly associated with one another, they have the ability to completely dissociate solute ions. Welton and co-workers suggest that ionic liquids are exceptionally dissociating solvents with the ability to form ionic mélanges.

Figure 13 - The ionic liquid mélange

Ionic liquids have been found to have dielectric constants in the range of 10-15 which are lower than a number of the molecular solvents the authors tested. By conventional theory which states that the association of ions in solutions is driven by Coulombic forces and is inversely proportional to the dielectric constant of the solvent, it would be expected that ion pairs would be dissociated to a lesser extent in ionic liquids when compared with dimethyl sulfoxide or acetonitrile for example. The work by Welton and co-workers shows that this is
clearly not the case and the authors suggest that in an ionic liquid, solute ion Coulombic interactions are no longer the driving force for ion pairing as the solute ions can ion pair with any ion of opposite charge that is in the vicinity, the majority of which will be solvent ions. The authors propose that the ionic liquid ions screen the charges of the solute ions from one another and term the ionic liquids as “super-dissociating” to describe their ability to stabilise solute ions individually. The consequence of this super dissociation is that solute ions react as freely solvated species in ionic liquids whereas the strong Coulombic interactions of the solute ions in a molecular solution ensures that the species react as ion pairs. For a molecular solvent to be able to overcome the Coulombic interactions that bind the solute ions, very strong specific interactions such a hydrogen bonding are required. This greatly reduces the reactivity of the reactants and hence Welton et al. found no reaction in methanol.

Conclusions

Kinetic and mechanistic studies of nucleophilic substitution reactions in ionic liquids have so far stemmed from the desire to compare the efficacy of ionic liquids compared with molecular solvents and to assess how ionic liquids affect well-known reactions. Many works have found that dielectric constants are poor descriptors of ionic liquid solvent polarity and that the Hughes-Ingold rules are generally insufficient to predict or explain reaction rates in ionic liquids. Kamlet-Taft parameters have been found to better describe ionic liquid solvent polarity and their specific effects, particularly when combined with LSER analysis. Specifically, the Kamlet-Taft parameters α and β often show good correlations with reaction rates implying hydrogen bonding effects may be of great importance in ionic liquids. The parameter π* was generally found to be less useful and show poorer correlations with reaction rates.

The most comprehensive work on nucleophilic substitutions in ionic liquids to date has been carried out by the Welton group. Welton and co-workers have studied the nucleophilic substitution reactions where the electrophilic species is either neutral methyl-p-nitrobenzenesulfonate or a charged dimethyl-4-nitrophenylsulphonium salt, and the nucleophilic species is either neutral (amine) or charged (halide anion). These works have demonstrated that where either or both the nucleophilic or electrophilic species is neutral, the kinetic data vs. empirical solvent polarity measurements can be understood by careful application of the classical Hughes-Ingold predictions of solvent polarity (where ionic liquids
are considered polar) on reaction rates combined with analysis of hydrogen bonding effects provided by the Kamlet-Taft parameters.

In the case of the reaction between the charged nucleophilic and charged electrophilic species Welton et al. have found an “ionic liquid effect”.\(^{83}\)

Where the reactants are charged species, the inherent Coulombic attraction between solute ions is screened by the ions of the ionic liquid. This screening makes the formation of ion pairs through which the S\(_{\text{N}}\)\(_{2}\) reaction may occur very unlikely and instead we see the mechanism proceeds \textit{via} freely solvated ions. Ionic liquids can therefore be termed “super-dissociating” solvents: there is no need for ions to associate in ionic liquids to preserve charge neutrality. In this hypothesis the solute salts do not ion pair in ionic liquids was subsequently supported by a theoretical investigation carried out by Lynden-Bell.\(^{72}\)

This project will delve deeper into the idea of the “ionic liquid effect” by investigating the use of nucleophilic species of varying size, shape and chemical properties. The Eyring activation parameters for these S\(_{\text{N}}\)\(_{2}\) reactions between charged nucleophiles and charged electrophiles will be calculated and analysed to establish the extent to which the reactants/transition states are stabilised in ionic liquids.
Ion Pairing

To begin exploring how solute ions (salts) interact with an ionic liquid, it is necessary to understand both how salts behave in conventional solvents and also how the ions from which the ionic liquid is composed behave in the neat liquid. Whilst significant research has been reported on salts and their ion pairing tendencies in molecular solvents, the same cannot be said for salts dissolved in ionic liquids/ionic liquid mixtures. Indeed the question arises as to whether the standard concept of ion pairing applies in the ionic liquid medium.

Ion Pairing in Molecular Solvents

Perhaps the simplest example of the ion pairing phenomenon is found in an electrolyte solution. The electrolyte dissociates to form cations and anions and enables the solution to conduct electricity. It is well understood that when dissolved an electrolyte will behave as one of two species: ionophore or ionogen.\textsuperscript{73} Ionophores (e.g. alkali halides) are ionic in dilute solutions, in the fused state and in the crystalline state whereas ionogens (e.g. hydrogen halides) will only form ions in solution if an appropriate reaction takes place with the solvent. Dissolved electrolytes may form an equilibrium mixture of ion pairs and free ions depending on the ionizing power and dissociating ability of the solvent.\textsuperscript{11} This behaviour is shown pictorially in Figure 14.\textsuperscript{11}

![Figure 14 - Various ionic species of varying ion interaction](image)

IUPAC defines an ion pair as being a pair of oppositely charged ions held together by Coulomb attraction without formation of a covalent bond.\textsuperscript{74} Experimentally, an ion pair behaves as one unit in determining conductivity, kinetic behaviour, osmotic properties and they will orient themselves as an electric dipole when an external field is applied. The oppositely charged ions share a common solvation shell and ion pairs have a life time long
enough to be recognizable as a kinetic entity.\textsuperscript{75} Electrostatic binding forces are the only interactions assumed\textsuperscript{76} and can be defined by the Coulombic Interaction Energy, $E$:

\[ E = \frac{q_1 q_2}{4\pi \epsilon r^2} \]

\textbf{Equation 4 - The Coulombic interaction energy}

$E$ is inversely proportional to the permittivity of the medium and the separation of charge where $\epsilon_o$ is the permittivity of a vacuum, $q$ is the charge of the ion, $r$ is the separation of ions and $\epsilon$ is the relative permittivity of the medium.\textsuperscript{77}

The question arises as to how close together ions must be to constitute an ion pair rather than free ions. An arbitrary specified “distance of closest approach” $R$ is chosen to minimize subjectivity and species are generally described as ion pairs if two oppositely charged ions in solution stay together at a separation, $r$, which is smaller than $R$. Bjerrum became the first person to suggest imposing this limitation reasoning that, although this cut-off distance $R$ is arbitrary, it is reasonable, since the work required to separate such ion pairs is at least twice the thermal energy.\textsuperscript{78} The electrostatic work required to separate the two ions (i and j) with charges $z_i$ and $z_j$ is $W_{ij}(r) = -z_i z_j e^2 / \epsilon_r r$, where $e$ is the unit charge, $\epsilon_r$ is the dielectric constant of medium and $r$ is the distance between the two ions.\textsuperscript{79} Bjerrum then calculated the likelihood of ion i to be at distance $r$ from the ion j. For ions of opposite charges, the probability would have a minimum at a certain distance:

\[ R = \frac{z_i z_j e^2}{\epsilon_r k_B T} \]

\textbf{Equation 5 - The distance of closest approach}

where $k_B$ is the Boltzmann constant and $T$ is the temperature in Kelvin. The “Bjerrum ion pair” is therefore defined as oppositely charged ions whose centres are separated by a distance no greater than $R$.

Depending on ion charges and the relative permittivity of the solvent, ion pairs can be treated as a real species in solution where the properties of the ion pair are easily separated from the long range non-specific interactions that exist in all solutions. It follows then that there are varying degrees of ion association which constitute an ion pair: a contact ion pair has no solvent/neutral molecules between the charged species; solvent shared ion pairs have one solvent molecule between charges; and solvent separated ion pairs with a greater degree of
separation are known as “loose” ion pairs. Ultrasonic and dielectric relaxation techniques are amongst the very few experimental methods with the ability to distinguish between contact ion pairs, solvent shared ion pairs and solvent separated ion pairs.\(^{80}\)

![Diagram of ion pair types](image)

**Figure 15 - Schematic representation of ion pair types: (a) solvent separated, (b) solvent shared and (c) contact ion pair**

Members of a loose ion pair can readily interchange with other free or loosely paired ions in solution. This interchange is occasionally detected experimentally via isotopic labelling. Free ions will only exhibit long-range, non-specific ion-ion interactions (characterised by activity coefficients) but these can be very difficult to differentiate from ion pair interactions (characterised by association constants) when ion association is weak as activity coefficients and association constants start to correlate strongly.\(^{79}\)

Experimental methods available to distinguish between ion pairs and free ions include conductivity measurements (as only free ions are responsible for electrical conductivity in solution), potentiometry and, somewhat less directly, by measuring the thermodynamic properties of electrolyte solutions. The consequences of ion pairing for thermodynamic properties, such as density (partial molar volumes) and enthalpy changes are also considered. Whilst spectroscopic measurements (UV-vis, IR, Raman, and NMR) distinguish between free ions and ion pairs on the one hand, and covalent molecules on the other, as the spectroscopic properties of ions are generally independent of the degree of association with the counter ion, these methods have nonetheless contributed greatly to illuminating ion pairing phenomena when united with kinetic analyses.

Grunwald can be credited as the first to envisage the existence of two distinct ion pair species in solution (contact ion pair vs. solvent-separated ion pair)\(^{81}\) with Weinstein and Robinson adopting this concept to account for their observations when studying the solvolysis of arene sulfonates.\(^{82}\) Hogen-Esch and Smid reported the first compelling evidence for the existence
of contact and solvent-separated ion pairs when measuring the absorption spectra of sodium fluorenide salt in THF at various temperatures (i.e. 25 °C and below -50 °C). A sharp absorption peak at 355 nm was observed at room temperature which decreased on cooling, with a new peak developing at 373 nm at lower temperatures. Below -50 °C, only the peak at 373 nm was observed. The reversibility of this process and the existence of two separate bands at lower temperatures indicate the presence of a new species. At lower temperatures, the sodium cation loses its influence on the π-system of the carbanion as THF molecules infiltrate the solvation shells of the ion pairs. Conductivity studies of the system showed that only a few per cent of the total ions were free ions under the conditions of the electronic spectroscopy experiments, suggesting that there must in fact be three types of ionic species present – free ions, contact ion pairs and something in between the two. The authors classified the species formed at low temperatures as a solvent-separated ion pair, which was spectroscopically indistinguishable from free ions.

Solvation and Ion Pairing

For many subsequent years since Bjerrum first developed a theoretical treatment of ion pairing in strong electrolytes, the study of solvent effects on ion pairing determined that the association of ions in electrolyte solutions is governed entirely by the bulk permittivity of the solvent, \( \varepsilon_r \). This is hardly surprising given that the Bjerrum approach credits ion association in solution to the electrostatic attraction between oppositely charged ions.

The Bjerrum approach generally applies to solvent solutions with either very weak or very strong relative permittivities. Many salt solutions of solvents with \( \varepsilon_r \) greater than 40 such as water, formic acid and formamide, contain almost no ion associates whereas hydrocarbons and other solvents with \( \varepsilon_r \) less than 15 produce solutions where nearly none of the ions will be dissociated. However, when \( \varepsilon_r \) is neither particularly high nor low, e.g. alcohols, acetonitrile and acetone, the degree of ion association depends on both the properties of the solvent and the identity of the electrolyte. Ion size, hydrogen bond forming ability and charge distribution all contribute to ion association in these solvents and the Bjerrum approach is no longer suitable. There are even some cases in water in which the usual ion pairing inferred from electrostatic considerations is not observed, including the phenomenon of hydrophobic association. For salts composed of large ions, such as quaternary ammonium iodides, ion association increases with the size of poorly hydrated ions which will break down the usual structure of water and form hydrophobic solvent cages around them. The
ordinary structure of water can be maintained to some extent by forcing the large, poorly hydrated cations and anions to ion pair.

The current understanding of electrolytes in molecular solvents describes an assortment of ionic species with varying degrees of association: ion aggregates, contact ion pairs, solvent-separated ion pairs, solvent-shared ion pairs and fully dissociated free ions. In each case the cation and anion require one another’s proximity to preserve charge neutrality. In an ionic liquid solvent composed entirely of ionic species, there is no such requirement.

Intermolecular/Interionic Interactions in Ionic Liquids

Ionic liquids comprise various interactions: non-polar side chains exhibit London forces, Coulombic interactions exist between the separated charges and hydrogen bonds may contribute to the overall structure of the ionic liquid if the relevant functional groups are present on the ions. Long range ordering observed in molten salts has also been found in ionic liquids by neutron scattering techniques. In ionic liquids, alternating distinct solvation shells of cations and anions have been observed up to 20 Å, which extends over a much longer range than in molecular solvents, in good agreement with the point charge model that befits molten salts. The cation-anion distribution suggests a strongly ordered structure, but the truth is somewhat more complex for the large, asymmetric, charge diffuse ionic liquid ions which have some directional interaction capability.

It has been shown via ab initio calculations that there are seven stable positions for the anion to sit around the cation and butyl side chain in the \{[C₄mim]Cl\} ion pair giving rise to several conformers and potential geometries. It was determined from these calculations that the chloride ion is most stable when positioned close to the N-C-N region of the imidazolium ring as positions near the C²-H part of the ring were found to be notably higher in energy.

![Figure 16 - The 1-butyl-3-methylimidazolium cation. [C4C1im]^+](image)
The size of the anion affects whether it sits in-plane, above or below the N-C-N regions with smaller anions such as chloride likely to be found in-plane and larger anions likely to be found either above or below. Where the anion is found to sit above or below the plane, the thermodynamic preference comes largely from a stronger dispersion component (by ∼14-17 kJ mol⁻¹) when compared with the in-plane interactions. The anion must be located closer to the imidazolium ring in order to achieve this larger dispersion interaction. Whilst this type of local ion data is difficult to extract from neutron scattering experiments, Hardacre et al. have shown that the position of highest probability for the chloride ion is in a band around the C2-H in good agreement with the computational studies. Combined x-ray and neutron scattering techniques of the crystalline solids have shown that the bulk structural features of some ionic liquids are similar in both the solid and liquid phases but though tempting, it is inadvisable to draw strong conclusions about ionic liquid structures from this data. These techniques give only a snapshot of conformations and geometries which will be in constant flux by the very definition of the liquid state.

Computational simulation and experimental results of local structures have been widely debated in connection with the existence and strength of hydrogen bonds between the positively and negatively charged moieties. The concept of hydrogen bonding in ionic liquids gives rise to much controversy given the ambiguous nature of these bonds. The IUPAC definition of a hydrogen bond as “an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation” is open to various interpretations in terms of bond angles, bond lengths and frequency shifts in spectra. From these guidelines we can assume that in ionic liquids capable of hydrogen bond formation, electrostatic-type hydrogen bonds will always exist between cation and anion but the effects of which can easily be buried under the stronger Coulombic interactions of the charged species.

The issue of hydrogen bonding between anions and cations contributes to a fundamental question for this project where we seek to understand the solvent environment for dissolved species and the transition states in chemical reactions. We have been able to probe the competition between solvent-solute interactions and the solvent-solvent interactions by varying the counterions of both solute and solvent. Lancaster and Welton have previously demonstrated the ability to control the solvation capability of ions by varying counterions through studying the nucleophilicity of halides in various ionic liquids.
**Ion Pairing in Ionic Liquids**

As previously discussed, it is common for salt solutions in molecular solvents to form discrete ion pairs. In ionic liquids, ion pairs have been detected by IR spectroscopy but neither NMR spectroscopy nor dielectric relaxation spectroscopy techniques have supported the presence of these species. As the precision of these measurements with time decreases from IR to dielectric relaxation to NMR, it can be inferred that the formation and decomposition of solute ion pairs is in equilibrium with the solvent ion associations. In an ionic liquid a “discrete” ion pair may very well prove impossible as the ions under investigation are inherently associated with the bulk network of charges and all the related intermolecular interactions described previously.

The molar conductivity of ionic liquids can be estimated from the self-diffusion coefficients, $\Lambda_{NMR}$, for ionic liquids where the ions are fully dissociated (free ions), using the Nernst–Einstein equation. This equation relates the bulk molar conductivity to the ion self-diffusion coefficients:

$$\Lambda_{NMR} = \frac{N_A e^2}{k_B T} (D^+ + D^-)$$

*Equation 6 - The Nernst-Einstein equation*

Where $D^+$ and $D^-$ represent the diffusion coefficients of the cation and anion (determined by pulsed field gradient NMR), $N_A$ is Avogadro’s number, $e$ the electric charge on each ionic carrier, $k_B$ the Boltzmann constant and $T$ is temperature.

Conductivity measurements only take into account the mobility of the ionic species while diffusion coefficients determined by NMR relate to all the species present in the electrolyte: free ions, ion pairs and larger aggregates. Therefore the Nernst–Einstein equation can be used to calculate the dissociation ratio. Generally, due to ionic association, the calculation of molar conductivities from NMR diffusion coefficients overestimates the conductivity values with respect to the experimental ones.

The ratio between the conductivity calculated from the diffusion coefficients and the measured conductivity is known as the “Haven Ratio” ($R_H$).
\[ R_H = \frac{\Lambda_m}{\Lambda_{m,NMR}} \]

**Equation 7 - The "Haven Ratio"**

\( R_H \) should equal 1 when a system is comprised solely of fully dissociated ions and decreases with increasing association. It would be reasonable to expect that for ionic liquids, \( R_H \) would increase with temperature as the additional thermal energy provided would breakdown intermolecular interactions. Remarkably, as temperature increases, \( R_H \) decreases, suggesting that at higher temperatures the bulk ionic network breaks down but the number of distinct ion pairs rises.\(^{99}\) These findings are consistent with the fact that during the distillation of imidazolium-based ionic liquids, the vapour phase consists exclusively of ion pairs. This fact is not so counterintuitive after all when we consider how much energy would be required to separate opposing charges in the gas phase— it is only by pairing together to form a net-neutral species that ionic liquids are able to exist as a vapour at all.

In a study of the haven ratios of various ionic liquids, Tokuda *et al.* found \( R_H \) to decrease\(^{100}\) and detected stronger interionic interactions as measured by solvatochromic probes\(^ {101}\) as the alkyl side chains grew in length. This would suggest that with increasing chain length, intermolecular interactions increase and therefore the ionic species also exhibit a stronger correlation of movement. The lifetime of these interactions is, however, not long enough to identify discrete ion pairs.

The Stokes-Einstein equation which correlates the self-diffusion coefficients with viscosity:

\[ D_i = \frac{k_B T}{6\pi \eta r_i} \]

**Equation 8 - The Stokes-Einstein equation**

as an additional means to determining the extent of dissociation following the Walden rule:

\[ \Lambda \eta = k \]

**Equation 9 - The Walden rule**

where \( \Lambda \) is the molar conductivity and \( \eta \) is the viscosity; \( k \) is a temperature dependent constant. Though formally constructed on observations of the properties of dilute aqueous solutions, the Walden rule has been found to apply equally to molten salts.\(^ {102}\) On a plot of log \( \Lambda \) vs. log \( \eta \), this rule predicts a straight line that passes through the origin; this has become known as a "Walden plot".\(^ {103}\) A solution of KCl in water is commonly used to provide the
reference line from which the relative ionicities of ionic liquids can be assessed. Ionic liquids tend to fall below the reference line, to a greater or lesser extent according to their structure. Whilst this suggests that there is generally some degree of ion association, there are some notable examples, e.g. \([\text{C}_{3}\text{mPyr}][\text{dca}]\), where the ions appear to be almost completely independent of one another. This result could easily be seen as improbable as one would anticipate strong ion correlations during conductive motions in response to an electric field, to an extent that would not be present in the dilute electrolyte represented by the KCl solution.

Indeed, given that the Nernst-Einstein equation, upon which these measures of ionicity were conceived, was initially devised for infinitely dilute solutions of ions in a uniform and non-structured dielectric medium, the applicability in ionic liquids is called into question. In addition, according to Abbott’s Hole Theory which states that the movement of an ion requires a hole of sufficient size to move into, the diffusion rate of ions inside the ionic liquids is very slow due to their large sizes. In his work, Abbott argues that the movement of ions in ionic liquids can be considered uncorrelated as the concentration of available holes of sufficient size is very small.

A conclusive interpretation of the Nernst-Einstein or Stokes-Einstein equations which is wholly appropriate for determining the extent of ion dissociation in neat ionic liquids is yet to be found. Furthermore, the bulk of research into ion association/dissociation reported in the literature is concerned with ionic liquid solvent ions rather than solute ions. This work will elucidate association or dissociation behaviour of salts dissolved in salts.
**Preferential Solvation of Ions in Ionic Liquids**

It is a known phenomenon that solvent molecules and counterions compete for space in the vicinity of a given ion in an electrolyte solution. At increased electrolyte concentrations and declining solvent activities, solvent molecules are sequentially released from the ion solvation shells as solvent separated ion pairs come together to form a contact ion pair. On the whole, the association constant is found to depend on the relative permittivity of the solvent with deviations from the smooth dependence of \( \log K_A \) on \( 1/\varepsilon_r \) being attributed to preferential solvation.

In this project, the kinetics and thermodynamics of an SN2 type reaction were studied in the ionic liquid \[\text{[C}_4\text{C}_1\text{im}][\text{NTf}_2]\]. The reacting ionic species remained the same throughout the investigation, but the counterion was varied in terms of size, shape and chemical properties in an effort to observe non-ideal behaviour indicative of preferential solvation. The term “preferential solvation” is used to define the observation that the solvation shell has a composition of solvent molecules which is different in ratio to that of the bulk solvent.\(^{105}\) The solvation environment of a solute is determined both by the solvent composition (and therefore net value of \( \varepsilon_r \)) and by the chemical properties of the solute. Preferential solvation causes large deviations from ideal solvent behaviour where each component of the solvent has an equal influence on the solute.

Preferential solvation occurs if the solute is able to make Gibbs energy of solvation more negative by neighbouring itself with a component of the solvent in particular. Solutes tend to be preferentially solvated in most binary solutions – the solute will inevitably have a greater affinity to one component or another. The question arises as to whether the same can be said when we dissolve a salt in a neat ionic liquid – will the solute ions have a greater affinity for each other, for the solvent ions, or neither? It seems unlikely that a solute would dissolve in an ionic liquid, if it were the case that the cations and anions would seek each other out and therefore ion pair or precipitate. This work aims to test the limits of the ionic liquid’s ability to dissociate solute ions by actively encouraging preferential ion pairing.

Methods used to study preferential solvation include thermodynamics, kinetics and spectroscopy. There have been several investigations into preferential solvation of ions in aqueous solvent mixtures\(^{106}\) but very few reported in organic solvents due to the limited solubility of electrolytes in such media. The work of Chatterjee and Bagchi on the
preferential solvation of N-alkylpyridinium iodides in various molecular solvent mixtures used UV-vis spectroscopy to monitor the solvatochromic charge transfer band of the solute as the solvent environment changed.\textsuperscript{107} The study concluded that both solvent-solute interactions and discrepancies in size have a role to play in preferential solvation.

Another useful technique to probe preferential solvation of ions in solvents is NMR spectroscopy which enables measurements of the chemical shift of metal ions in various solvents to be monitored.\textsuperscript{11} Measurements are based on the assumption that the chemical shift of the solute ion is determined in an additive fashion by the solvent molecules comprising the solvation shell.

Hunter et al. have demonstrated that the ability of a solute to hydrogen bond can have significant effects on the immediate solvent environment through studying the complex which forms between tri-\textit{n}-butylphosphineoxide and perfluoro-\textit{tert}-butanol (Reaction Scheme 21) in various solvents.\textsuperscript{108}

\begin{equation*}
\text{Bu}_3P=O^- + \text{F}_3\text{C}-\text{CF}_3 \overset{\text{H}}{\rightleftharpoons} \text{Bu}_3P=O^-\text{H}^+\text{F}_3\text{C}-\text{CF}_3
\end{equation*}

\textbf{Reaction Scheme 21 - Tri-\textit{n}-butylphosphine oxide (a) is one of the strongest known hydrogen bond acceptors (\(\beta=10.2\)) and (b) perfluoro-\textit{tert}-butanol is a strong hydrogen bond donor (\(\alpha=4.9\))}

This complex contains a single hydrogen bond between an extremely strong hydrogen bond acceptor and an extremely strong hydrogen bond donor, so that complexation can be detected in even the most competitive solvent environments. Hunter used \textsuperscript{31}P NMR to monitor this complexation in a solvent mixture of tetrahydrofuran and chloroform which is known to exhibit strong deviations from ideal behaviour and does not obey regular solution theory.\textsuperscript{109} Chloroform has good H-bond-donor but relatively weak H-bond-acceptor properties (\(\alpha=2.2, \beta=0.8\)). In contrast, tetrahydrofuran is a good H-bond acceptor but a very weak H-bond donor (\(\alpha=0.9, \beta=5.3\)).\textsuperscript{108} Therefore in pure chloroform, the H-bond donor perfluoro-\textit{tert}-butanol is poorly solvated, and in pure tetrahydrofuran, the H-bond acceptor tri-\textit{n}-butylphosphine oxide is poorly solvated and in both cases complexation will be preferred. In the mixed solvent, however, the solutes interact strongly with their preferred solvent and the association constant will remain low.
Chemical kinetics is an additional, if somewhat less direct, method of determining preferential solvation effects. By measuring the rates of reactions in several solvents and at various temperatures, it is possible to glean information about the most probable solvation shell composition. This method requires a well-defined reaction to follow in order to detect any deviations from the known mechanism and a good understanding of the solvent and reactants’ chemical properties to deduce the likely factors contributing to a rate change. Humeres et al., researched the SN2 reaction of sodium 4-nitrophenoxide and iodomethane in acetone/water mixtures.\textsuperscript{110} The reaction proceeded fastest in neat acetone, whilst the addition of water to the solution caused the reaction rate to decrease significantly. The authors determined that the decrease in reaction rate was caused by preferential solvation of the phenoxide ion by water, thus greatly reducing the reactivity of the phenoxide.

The old adage “like dissolves like” is mostly applicable at the molecular level – highly polar ions will generally be preferentially solvated by the more polar solvent in a solvent mixture. However, solvent polarity alone does not determine the extent of preferential solvation of ions: size, shape and specific interactions area also significant.\textsuperscript{111}

*Solvent-Solute Interactions*

The physiochemical properties that depend on the solvent-solute interactions of ionic liquids can be investigated by means of solvatochromic probes of various functionalities. Solvatochromic probes provide a simple and convenient means to study microenvironments dependent on solvent properties such as polarity, viscosity, polarizability and hydrogen bond donating/accepting capabilities\textsuperscript{112} as previously discussed in this chapter. They can also detect preferential solvation as the response of the spectroscopic probe depends on the composition of the solvation microsphere. Many spectroscopic probe techniques assume an ideal solvent behaviour where solvent–solvent interactions can be neglected and the measured spectral response describes the solvent-solute interactions.\textsuperscript{113} Deviations from ideal behaviour and ionic liquid specific solvent-solute interactions can therefore be detected by these spectroscopic probes that would otherwise be overlooked by the bulk measurements of typical physical treatments.

There is the possibility that the introduction of a probe itself can cause deviations from ideal behaviour *via* preferential solvation and observations of non-ideal behaviour which, in this case, would not be representative of the bulk liquid. Equally there is the possibility, and a great deal of supporting evidence,\textsuperscript{114} that ionic liquids tend to self-aggregate and probe
molecules can be used to detect these microheterogeneities without actually causing them. For example, environment sensitive probes were used to detect microheterogeneities in ionic liquids by studying the translational diffusion of the probes. \(^\text{115}\) Samanta et al. attributed the observed biphasic diffusion dynamics for the probes to the microheterogeneous nature of the ionic liquids caused by segregation of the alkyl chain of the constituents. The presence of polar and nonpolar regions in these ionic liquids has been detected by various methods and reported by several groups.\(^\text{116},\text{117},\text{118}\)

Imidazolium-based ionic liquids in particular show significant heterogeneity attributed to the hydrophobic alkyl side chains which form separate polar and nonpolar domains when the chain length is propyl or greater.\(^\text{119}\) Maschmeyer et al. examined the effect of these domains on reactivity by kinetic studies of the bimolecular nucleophilic substitution of \(N-(p\)-fluorophenyl-diphenylmethyl)-4- picolinium chloride ([Ar\(_3\)Pic][Cl]).

As [Ar\(_3\)Pic]Cl is ionic in both initial and transition states, Maschmeyer postulated that the constituents of this salt would reside preferentially within the polar domains of the ionic liquid. The experiments sought to identify any effects caused by interactions between the polar and non-polar domains with the alcohol, ROH, by varying the length of the alkyl side chains and the R group on the nucleophile. It was observed that increasing the alkyl chain length increased the rate of the reaction. It was explained that as the chain length increases, the hydrogen bond acidity of the ionic liquid solvent is reduced, and so the salt’s interaction with the polar domain is therefore also reduced and its reactivity increases.\(^\text{120}\) The rate increase was attributed to a phenomenon called “pseudo-encapsulation” whereby the reactants concentrate in the polar domains which become relatively smaller in volume as the
alkyl side chain of the ionic liquid increases. This type of nanostructural heterogeneity changes the relative concentrations of the reactants and therefore affects the observed reaction rate and has been detected in micellar systems.
Methods
Chemical reactions are often carried out in solution and it is well known that different types of solvents can substantially affect reaction rates and mechanisms. These effects are most measurable in cases where a polar intermediate is formed as the solvent molecules form a sphere around it and can either serve to stabilise or destabilise the intermediate depending on the solvent polarity as described by the Hughes-Ingold principles discussed previously. Given that the reaction rate can be impeded or enhanced according to choice of solvent, it is clear that the solvent must be selected carefully to suit the process. Solvent selection is a particularly crucial step when determining the viability of large scale industrial processes. The following section provides an introduction to the methods (and their limitations) used herein to investigate the solvent effects of ionic liquids.

Kinetics
Kinetics comprises of the rate of reaction and all of the factors which can affect it discussed in terms of a reaction mechanism. Time is the fundamental variable in any kinetic measurement and we record the time taken for a system to change from one state to another. The principal factors which can influence reaction rate include concentration, pressure, temperature and nature of reactants. Chemical kinetic theory is difficult to apply with precision when we consider possible complexities in kinetic modelling arising from a large number of variables and the high degree of accuracy required to determine experimental rate coefficients. Consequently, details of the extent of the reaction derived from chemical thermodynamics are combined with the rate of reaction measured via chemical kinetics to give insight into the reaction mechanism and its energetic parameters. The activation energy for a reaction can be measured experimentally using the Arrhenius and Eyring equations. Both denote an energy barrier to reaction by relating the rate of reaction to temperature.

This work uses concentration and temperature changes to probe reaction mechanisms and energetics. In accordance with collision theory of chemical reactions, concentration contributes significantly to reactions. An increase in concentration causes the frequency of collisions to increase and the likelihood of a successful collision increases. Temperature can influence reaction rates on two levels. Firstly, at high temperatures the collision frequency is increased (as with high concentrations) and, more importantly, molecules have more thermal energy. The number of molecules with sufficient energy to react (the activation energy) is considerably higher at elevated temperatures.
Limitations of Kinetics

Investigating the rates of chemical reactions over the range of conditions described above can give us information about the reaction mechanism namely by showing whether a reaction proceeds by one or more steps. If a reaction is indeed stepwise, kinetic measurements provide evidence for the mechanism of the discrete steps. Evidence for reaction mechanisms can also be gathered by non-kinetic studies, but little can be known about a mechanism until its kinetics has been investigated. Ultimately, however, there will always be some doubt regarding the details of a reaction mechanism. All scientific investigations, kinetic or otherwise, are subject to the confinements of falsificationism, i.e. can disprove a theory but can never verify it with absolute certainty.

Transition State Theory

Transition state theory is a method that can be used to explain differences between the solvation of reactants and the solvation of the activated complex as changing the solvent can lead to an alteration in the Gibbs energy of activation. This theory was initially developed to understand static effects.

Also known as activated-complex theory, transition state theory is a treatment of chemical processes that assumes they progress via continuous change in the relative positions and potential energies of the constituent atoms and molecules. On the reaction pathway going from the initial to final state of the atoms or molecules, there exists an intermediate configuration of chemical species at which the potential energy has a maximum value known as the “activated complex”. The IUPAC definition for activated complex is “that assembly of atoms which corresponds to an arbitrary infinitesimally small region at or near the col (saddle point) of a potential energy surface.” The configuration corresponding to this maximum is known as the activated complex, and its state is referred to as the transition state. The term “transition state” is often incorrectly used interchangeably with the term “activated complex”. However, the transition state represents only the maximum potential energy configuration of the chemical species during the reaction whereas the activated complex refers to all the configurations that the atoms pass through in the transformation from products to reactants. In terms of free energies, the activated complex represents all the energetic states in between the free energies of the reactants, the transition state, and the products. This can be visualized in terms of a reaction coordinate, where the transition state is the molecular configuration at
the peak of the diagram while the activated complex can refer to any point along the continuum.\textsuperscript{123}

![Figure 17 - The transition state](image)

The rate at which the final state is attained is determined by the number of activated complexes formed and the frequency with which they go over to the final state. These quantities may be calculated for simple systems by using statistical-mechanical principles. In this way the rate constant of a chemical or physical process may be expressed in terms of atomic and molecular dimensions, atomic masses, and interatomic or intermolecular forces.

It is important to note that because transition state theory applies in the gas phase, solvent molecules can be studied in the gas phase and then extrapolated to bulk solution. Given that solvents can affect the species present and therefore the energies and therefore reaction rates, deviations from ideal behaviour determined experimentally can then be attributed to these solvent effects.

There are two ways in which solvents affect reaction rates of homogeneous chemical reactions: (i) through static, or equilibrium, effects and (ii) through dynamic, or frictional, solvent effects. The static influence of solvents can be understood by transition state theory in the quasi thermodynamic form. Activation energies, entropies and volumes depend on the solvent. The well-known Hughes-Ingold approach to solvent polarity effects on reaction rates discussed previously are based on equilibrium solvation of the activated complex and transition state theory ideas. Solvent dynamics have been determined to be significant by the Langevin equation which has shown a dependence of reaction rates on the short time solvent friction experienced by the reacting system and not the friction constant.\textsuperscript{124}
Taking the example of species A and B reacting to form products C and D:

\[ A + B \rightarrow [A - B]^\# \rightarrow C + D \]

\textbf{Reaction Scheme 23}

The solvating power of the solvent determines how the species A, B and A-B are solvated and accelerates or decelerates the process.

\[ \Delta G^\#_I \neq \Delta G^\#_II \neq \Delta G^\#_III \]

\textbf{Figure 18} - Gibbs energy diagram for a reaction in three solvents with different solvating power

\( \Delta G_I^\# \) in Figure 18 is the Gibbs energy of activation for a reaction in which there is no solvation of the reactants or the activated complex. If the same reaction is carried out in a solvent in which only the activated complex is solvated then the Gibbs energy of activation becomes \( \Delta G_{II}^\# \) and the rate increases. If another solvent is used where only the reactants are solvated then the Gibbs energy of activation becomes \( \Delta G_{III}^\# \) and the rate decreases. Given that in reality every species participating in the reaction is solvated, the rate is determined by the difference in the degree of solvation of the reactants and the activated complex.

It is worth considering here that solvent-solute interactions tend to be rather complex, as discussed previously, and so attempting to predict solvent effects via measurement of reaction rates may be a gross over-simplification. In spite of this, much work has been done in order to correlate Gibbs energies of activation or rate constants with solvent properties.
such as the relative permittivity, the dipole moment, the refractive index and empirical solvent polarity parameters.\textsuperscript{125}

Transition state theory implies that the required reorientational relaxation of the solvent molecules during activation is sufficiently fast that the activated complex is in thermal equilibrium with the solvent due to the high frequency of collisions of the reacting species with the solvent molecules. Transition state theory is based on a number of assumptions:

1. The reactants are in quasi-equilibrium with the activated complex;
2. Reactant internal states are in equilibrium but products do no feature in the theory;
3. The activated complex has all the properties of a standard molecule except that one vibrational degree of freedom is transformed into a translational degree of freedom which leads to the decomposition of the activated complex;
4. The activated complex exists at the top of the energy where the likelihood of reforming the reactants is as likely as forming products. The transition state is a configuration space surface in the region of this maximum; and
5. The one way equilibrium flux coefficient equals the rate constant. The probability of the forward reaction through the activated complex is given by the transmission coefficient which is assumed to approach unity.

*Transition State Theory Limitations*

As discussed in the classic Kramers’ papers,\textsuperscript{126} when a system is coupled strongly to its surroundings, progress along the reaction pathway becomes diffusive in nature. Systems crossing the barrier by diffusion have no memory of their velocity and are therefore more likely to reverse their motion near the barrier top.\textsuperscript{127} The validity of transition state theory for reactions in solution is called into question for reactions where the diffusion description is valid such as the motion of large molecular units, broad barrier reactions, dense viscous solvents and strongly dipolar, slowly relaxing solvents. Non-equilibrium solvation of the activated complex can occur in these solvents and the solvent reorientation may contribute to the reaction rate. Significant frictional effects which are not described by transition state theory can contribute to the experimentally determined activation parameters. In such cases, the rate constant will vary with friction which can be defined as some measure of the coupling of the solvent such as density, viscosity and internal pressure. Despite high collision frequency in a dense solvent, the assumed vibrational energy equilibrium need not hold at the transition state.\textsuperscript{128}
In reactions with sharp barriers and weakly dipolar rapidly relaxing solvents, transition state theory generally holds well. On the other hand, frequent solvent collisions could severely interfere with the unimpeded barrier passage assumed by transition state theory. Therefore we find that transition state theory both under and over estimates solvent effects.\textsuperscript{129} At low friction, the rate lies below the transition state theory prediction. At intermediate friction, the theory is reasonable and at high friction, it begins to overestimate the rate, which will decrease with friction, eventually reaching the diffusion controlled regime where it is inversely proportional to the friction coefficient. When frictional effects are large enough, the primary reaction step becomes diffusional on a vibrational length scale. The rate constant predicted by transition state theory will generally depend on solvent dynamics and will vary non-monotonically with friction (i.e. with some measure of coupling to the solvent such as density pressure on viscosity). Quasi thermodynamic activation parameters such as the volume of activation will be affected. If the rate is tied inappropriately in a transition state format, these parameters will contain non-thermodynamic, solvent dynamic contributions that can be very significant.

Ionic liquids may have strong coupling effects on the reaction system given that they are generally much more viscous than conventional solvents. The short time friction effects between a solute and an ionic liquid may be much longer than in molecular solvents and the standard transition state theory may no longer apply.

Charge transfer reactions such as S\textsubscript{N}2 displacements assume in the standard approach that the transition state has an equilibrium solvation and that the solvent plays no role in the reaction coordinate. However, it is unclear if the required reorientation of solvent dipoles is always sufficiently fast for equilibrium solvation to apply. If solvent reorientation – dielectric relaxation – plays a role in the reaction, we should think of it in terms of non-equilibrium solvation. The rate will depend on solvent reorientation rates and transition state theory will break down. If solvent reorientation becomes rate limiting then the rate is inversely proportional to solvent reorientation.

Viscosity describes the resistance which an ordinary fluid offers to its own flow on the movement of a solid through it. The rate of motion of an object can easily be calculated from viscosity using the Stokes-Einstein equation. Stokes-Einstein equation gives the dependence of the diffusion coefficient (D) of a sphere on viscosity (η):
Equation 10 – The Stokes-Einstein Equation

\[ D = \frac{k_B T}{6\pi \eta r} \]

D is the diffusion constant, \( k_B \) is Boltzmann's constant, \( T \) is the absolute temperature, \( \eta \) is the viscosity and \( r \) is the radius of the spherical particle.

Viscosity is expressed as poise (P) with units of \( \text{gm}^{-1} \text{s}^{-1} \) or as cP where 1cP = 0.01P. This equation was derived to explain the motion of non-interacting spheres in a continuous medium; it has been shown to describe the motion of small molecules comparable to the solvent molecules in size. However, it will not necessarily describe the effect of viscosity on the rates of rotations about bonds in a molecule, or indeed the rates of conformational changes in a molecule. Rates of conformational changes are described in terms of transition state theory, but conventional transition state theory must be modified to include the effects of viscosity.

Transition state theory shows how the energy of the system changes as the initial state A turns into final state B. Figure 19 depicts a conformational change from A to B or a chemical reaction from A to B.

![Figure 19 - Potential energy diagram](image)

As A distorts, the energy rises to a maximum value (the transition state) and then falls as B is produced. The X axis shows reaction progress termed the reaction coordinate.

\[ \Delta H_{\text{AB}}^{\ddagger} = \Delta H_{\text{BA}}^{\ddagger} - \Delta H_{\text{AB}}^{\dagger} \]

Equation 11
In Transition state theory, a molecule going from A to B crosses the barrier only once before being trapped as product B. Later, B may revert from state B to A, but this event would be unconnected.

A rate constant can be calculated from the equilibrium concentration of the transition state as a function of the activation energy $\Delta H_{AB}^\dagger$ with $k_{AB}$ being the forward reaction rate constant:

$$k_{AB} = A_{AB} \exp\left(\frac{\Delta H_{AB}^\dagger}{RT}\right)$$

Equation 12

$A_{AB}$ and $\Delta H_{AB}^\dagger$ are pre-exponential factors and enthalpies of activation in the forwards direction.

The pre-exponential factors are given by:

$$A_{AB} = \tau kT/h \exp(\Delta S_{AB}^\dagger)$$

Equation 13

$\tau$ is the transmission coefficient, $\Delta S_{AB}^\dagger$, is the entropy of activation

In transition state theory, $\tau$ is made equal to 1.

Possible solvent effects discussed previously include both static and dynamic effects. Static effects occur on rates when the solvent interacts preferentially with either state A, B or the activated complex. The solvent could interact less well with state A than state B, thus raising the energy of state A relative to state B. The result would be a change of the equilibrium constant and an increase of the rate of $k_{AB}$. Static effects will have no effect on the equilibrium constant if the interaction change is with the transition state. Transition state theory takes no account of solvent viscosity (fluidity). This follows on from the postulate that $A \rightarrow B$ crosses the barrier only once.

Kramers was the first to introduce frictional effects into kinetic theory by having a transmission coefficient approximately less than 1. Physically this means that even when the system is poised at the transition state and going from A to B, it will not necessarily get there because directional motion may go back to A. Even when the molecule has sufficient energy, it will not do so in one attempt. The frictional forces caused by the solvent environment will cause the molecule to undergo Brownian motion to and fro over the barrier.
In the limit of high friction, Kramers showed that the transmission factor ($\tau$) will be inversely related to friction so that:

$$k_{AB} = A_{AB}/\zeta \exp\left(-\Delta H_{AB}^f/RT\right)$$

Equation 14

where $\zeta$ is the friction coefficient. It is usually assumed $\zeta$ is linearly related to solvent viscosity so the rate becomes inversely related to solvent viscosity $\eta$.

$$k_{AB} = \frac{A_{AB}}{\eta \exp\left(-\frac{\Delta H_{AB}^f}{RT}\right)}$$

Equation 15

However, equivalence between frictional effects on movement over a molecular barrier and bulk viscosity is not obvious since movement over the energy barrier will correspond to very small molecular changes, whereas viscosity is a measure of resistance to molecular motion through a solvent involving long-time collective motion of solvent molecules.

This is clear if we consider the timescale of motion over the barrier: for chemical reactions the barrier is very sharp and the timescale for motion of an individual molecule in the region of the barrier top is of the order $10^{-12}$ to $10^{-13}$ s. The rate constant will be many orders of magnitude slower because the reaction is rare. Over very short timescales, it is the short time solvent response that is important, not long time overall response by viscosity. What matters is what the solvent can do on a short timescale. For very sharp barriers there is insufficient time for completed collisions with solvent molecules so hardly any friction. So friction independent theory holds well.

For broad energy barriers (isomerizations) the timescale for barrier crossing will be longer – frictional effects will be felt and rates will become proportional to bulk viscosity.

Rates could be expressed as:

$$k \propto \eta^{-x}$$

Equation 16

where $x$ can be between 1 and 0. For $x = 1$ the full effect of solvent viscosity will be seen whereas $x = 0$ will be friction independent.
Viscosity is temperature dependent described by the Andrado equation:

\[ \eta = \eta_0 \exp\left(-\frac{E_\eta}{RT}\right) \]

Equation 17

where \( E_\eta \) is the activation energy for viscous flow and \( \eta_0 \) is a constant over a wide range of temperatures. If rate depends on viscosity, the activation energy will then include a term for the viscous flow of the medium.

**Thermodynamics - Eyring Activation Parameters**

When analysing transition state theory, we place an emphasis on the temperature dependence of the rate constant. Making the assumption that \( \Delta H^\neq \) and \( \Delta S^\neq \) do not vary with temperature we can use the Eyring equation to solve for these parameters.

The Eyring equation, which is based on transition state theory, provides a theoretical construct to describe the dependence of the reaction rate on temperature:

\[
\ln\left(\frac{k_z h}{k_B T}\right) = \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{R \cdot T}
\]

Equation 18 - The Eyring Equation

In this equation \( h \) represents Planck’s constant \((6.626 \times 10^{-34}\text{J.s})\), \( k_B \) is the Boltzmann constant \((1.381 \times 10^{-23}\text{J/K})\), \( T \) is the reaction temperature in Kelvin and \( R \) is the universal gas constant \((8.31447 \text{ J/mol/K})\). The thermodynamic parameters \( \Delta H^\neq \) (activation enthalpy) and \( \Delta S^\neq \) (activation entropy) can be calculated with kinetic data using the Eyring equation by plotting \( 1/T \) against \( \ln k_2/T \) – see Figure 20.
As we can see from the general expression $\Delta G^\neq = \Delta H^\neq - T\Delta S^\neq$, the entropy contribution to the energy of activation is temperature dependent. At higher temperatures the energy associated with entropy changes affects rate more than at lower temperatures. It is therefore possible for a reaction to switch from being enthalpy controlled at lower temperatures to being entropy controlled at higher temperatures.

Curvature in an Eyring plot, though uncommon, can mean that $\Delta H^\neq$ is temperature dependent. In cases such as these heat capacity effects become important. A clear break in an Eyring plot most often indicates a change in the rate-determining step or reaction mechanism.

Magnitudes of $\Delta H^\neq$ and $\Delta S^\neq$ provide information about how the enthalpy and entropy of the transition state differ from those of the reactants.

In the activated complex, some bonds will be partially broken, meaning bond strengths in the activated complex are lower than the starting materials. Achieving transition state is almost always endothermic.

$\Delta H^\neq$ can be affected by factors other than the bond strengths such as solvent effects. Favourable interaction with the transition state will lower $\Delta H^\neq$ even though it may not significantly influence the extent of the bond breaking or bond forming. Rarely is $\Delta H^\neq$ near zero or negative such as the combination of radicals.

$\Delta S^\neq$ is more complex. It measures the degree of order lost or produced when comparing transition state to reactant. If translational, vibrational or rotational degrees of freedom are lost or gained on going to the transition state, $\Delta S^\neq$ can become negative or positive. $\Delta S^\neq$ can also be affected by solvation. If a significant amount of ordering is required in the solvent to
make favourable enthalpy interactions with the transition state, the $\Delta S^\neq$ value can become more negative than expected.

A further complication arises because the Eyring equation is really only applicable to elementary reactions. When applied to a complex reaction (as is commonly the case) the resulting $\Delta S^\neq$ term depends upon the implied standard state and the interpretation of absolute values of $\Delta S^\neq$ is incorrect. Positive $\Delta S^\neq$ implies an increase in translational and rotational degrees of freedom often indicating the creation of two molecules. Negative $\Delta S^\neq$ implies decreasing rotational and translational degrees of freedom and usually suggests the combination of two molecules. Large negative $\Delta S^\neq$ suggests molecules combining and positive $\Delta S^\neq$ suggests an activated complex with a significant amount of bond cleavage to form two molecules.

Rate constants depend exponentially on $\Delta G^\neq$ - every change of 1.36 kcal/mol in $\Delta H^\neq$ or $T\Delta S^\neq$ is worth a factor of ten.
Research Objectives

Salts Dissolved in Salts

This study aims to explore the solvent effects of ionic liquids in nucleophilic substitution reactions involving ionic reactant species. The project hopes to provide greater understanding of ionic liquids at a molecular level in order to be able to predict their effects on other chemical processes.

Continuing the research of Ranieri\textsuperscript{130} and Lui\textsuperscript{131} into the ion association/dissociation behaviour of solute ions in molecular solvents, ionic liquids and binary mixtures, this work aims to carry out for the first time calculations of the thermodynamic parameters, $\Delta H^\ddagger$ (activation enthalpy), $\Delta S^\ddagger$ (activation entropy) and $\Delta G^\ddagger$ (Gibbs energy of activation), for the nucleophilic substitution reaction between dimethyl-4-nitrophenylsulfonium bis(trifluoromethanesulfonyl)imide and 1-butyl-3-methylimidazolium chloride in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide by following the reaction at various temperatures using UV-vis spectroscopy.

As described in earlier in this chapter, it is not only the nature of the solvent which affects the relative nucleophilicity of the nucleophile but also the nature of the solute cation. If the free ion is inherently more nucleophilic than any ion paired species then perhaps some change in kinetic and thermodynamic behaviour will be observable if the extent of solute ion association is manipulated. This research investigates the role of the solute cation and its effects on nucleophilicity in S\textsubscript{N}2 reactions in ionic liquids. This concept could also be understood in terms of the extent of ion association in ionic liquids as the nature of the cation is altered.

Ionic liquids are known to exhibit special behaviour when solvating S\textsubscript{N}2 reactions between charged species and this work will test the limits of this behaviour. The Welton group have posed the theory that there is no preferential ion pairing in ionic liquids as a result of studying these reactions. It is the intention of this project to look for instances that would disprove this theory according to the principles of negative empiricism. Observing that there are no ion pairs does not confirm the nonexistence of ion pairs. By carrying out nucleophilic substitutions between dimethyl-4-nitrophenylsulfonium bis(trifluoromethanesulfonyl)imide and a vast array of nucleophilic sources (including alkaline earth metal halides, phosphonium halides and ammonium halide salts) in an attempt to falsify the theory that ion pairs do not
exist in ionic liquids, we will glean a greater understanding of the extent to which the statement holds correct.

This work will also determine the Eyring activation parameters for the substitution reaction with each selected nucleophilic salt for comparison and in order to understand how the reaction energetics change as the solute properties change. This will allow for a more comprehensive analysis of the reaction mechanism and the role of the ionic liquid solvent in the reaction. Stabilisation/destabilisation effects will become apparent through determination of rate constants and their probable causes can be hypothesised from the corresponding activation energies and transition state theory.

Ultimately this project aims to inform solvent choice for future projects and processes and also to expand our knowledge of the fundamental properties of ionic liquids.
Chapter 2: Ionic Liquid Effect - Reactions of anionic nucleophiles with cationic centres in Ionic Liquids and Molecular Solvents

Objectives

- Determine the rate constant, \( k_2 \), of the \( S_N^2 \) reaction of the \( \text{bis}({\text{trifluoromethanesulfonyl}})\text{imide salt of dimethyl-4-nitrophenylsulfonyl} \ ([p-NO_2\text{PhS(CH}_3_2][\text{N(CF}_3\text{SO}_2}_2]) \) with 1-butyl,3-methylimidazolium chloride in various molecular solvents and ionic liquids under \textit{pseudo}-first order conditions.
- Determine the activation free energy (\( \Delta G^\ddagger \)), enthalpy (\( \Delta H^\ddagger \)) and entropy (\( \Delta S^\ddagger \)) for each reaction.
- Infer mechanistic details and solvent behaviour for each reaction through contrast and comparison of results.

Outcomes

- Partial order kinetics observed for the reaction in molecular solvents.
- \textit{Pseudo}-first order kinetics observed for the reaction in ionic liquids.
- Activation energies calculated for ionic liquid reactions only as \( k_2 \)s not possible to obtain from molecular solvent data.
- Different reaction pathway when solvent changes from molecular to ionic liquids.
- Theoretical modelling of the reaction involving a quaternary ion pair has excellent correlation with the experimental results for molecular solvents.
- Rate depends on the concentration of solvent shared ion pairs in molecular solvents.
- Rate depends on the concentration of the nucleophile in ionic liquids.

Key Figures
Introduction

The main purpose of this project is to elucidate the solvent effects on reactive processes in ionic liquids with a view of optimizing the ability to “design” the solvent for expressed applications. This section will be investigating further into the effects that ionic liquids have on the $S_{N2}$ reaction between charged nucleophilic and electrophilic species previously found by our group to exhibit an “ionic liquid effect”. By accruing such information we will be better placed to predict the effects, advantageous or not, that an ionic liquid will have on a given chemical transformation.

The term “ionic liquid effect” has been coined to describe the difference in mechanism observed for $S_{N2}$ reactions between charged species when the solvent is changed from molecular to ionic liquid. Forming the basis of this project, the work of Welton and co-workers was repeated, verified and expanded to include salts with different physical and chemical characteristics. This chapter continues to elucidate the ionic liquid effect observed for $S_{N2}$ reactions between a charged electrophile and charged nucleophiles via kinetic investigations. Kamlet-Taft parameters are used to describe the polarity of the ionic liquid and molecular solvents to measure the extent of any solvent effects and will provide information about the ability of the Kamlet-Taft parameters to predict solvent behaviour. The results are also of fundamental interest in catalysis, where the (electrophilic) catalytic centre often carries a positive charge.

Results and Discussion

The process under examination was the $S_{N2}$ reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium ([p-NO$_2$PhS(CH$_3$)$_2$][N(CF$_3$SO$_2$)$_2$]) with chloride ion, as shown in Reaction Scheme 24. Initially, reactions using the bromide ion in the ionic liquids were also considered but studies with this halide were not extended due to the similarity to the results obtained with the chloride species.

![Reaction Scheme 24 - The $S_{N2}$ reaction of a chloride ion with a sulfonium centre](image)

The reactions were assayed using UV spectroscopy, with each substrate having $\lambda_{max}$ at 252 nm and the demethylated products having a $\lambda_{max}$ at 342 nm. The imidazolium-based ionic
liquid which was used as the solvent has a cut-off at 240 nm and therefore caused no problems in interpreting the UV spectroscopy results. UV spectroscopy allows for continuous and rapid measurement of the electronic transitions of reactants and products as a function of time. According to the Beer-Lambert Law, the concentration and absorbance are directly proportional and therefore appropriate for measuring reaction rates. The sulfonium salt was synthesised as described in the experimental section in Chapter 8 directly before use and kept under anaerobic conditions.

The nucleophilic displacement by the chloride ion was studied in various molecular solvents and one ionic liquid of very high purity. The molecular solvents chosen were dichloromethane, acetonitrile and butoxyethanol and the ionic liquid was \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) due to its relatively low viscosity, 44 cP,\(^{132}\) and its well-known synthetic and purification procedures. A chloride salt of a quaternary ammonium cation was also used to study the effect of the counter cation on the nucleophilicity of the chloride. Tetrabutylammonium chloride was used in acetonitrile and \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\). Reactions using tetrabutylammonium thiocyanate and bromide salts were also studied in acetonitrile to verify that the non-linear kinetics observed in molecular solvents were not limited to the chloride nucleophile.

![Chemical structures of chloride salts](image)

**Figure 21 - The chloride salts used in the substitution reaction**

The electrophile was found to be stable in all solvents as no change in UV/vis absorbance was detected in the absence of the nucleophile after 24 hours.

Highly polar molecular solvents such as methanol and water were not used to study the process as no reaction occurs between the sulfonium and chloride ions. Nitromethane could not be studied as the reaction could not be followed using UV spectroscopy due to this solvent’s high extinction coefficient. Chloroform could not be used as the sulfonium salts (tested with various anions) were not soluble.

This reaction is bimolecular and the rate therefore depends upon the concentrations of both the nucleophile and the electrophile. Integrated rate equations and therefore the treatment of kinetic data becomes more complex as the reaction order increases. It is common in this type
of process to create pseudo-first order kinetic behaviour by using a large excess (>100 times) of one reagent which shows a linear dependence of \( k_{\text{obs}} \) upon nucleophile concentration. For this bimolecular reaction, the chloride ion or other nucleophilic reagent was used in excess so that the concentration remains effectively constant. Therefore we only consider the change in absorption of the electrophile \([p-\text{NO}_2\text{PhS(CH}_3)]\text{][NTf}_2\) or the demethylated product \(p-\text{NO}_2\text{PhSCH}_3\) with respect to time.

This linear relationship was observed when the reaction was carried out in the ionic liquid solvent but was not the case when the reaction took place in any of the molecular solvents.

![Reaction in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)](image)

**Figure 22 - Dependence of \(k_{\text{obs}}\) on chloride concentration in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)**
Accordingly, it was only possible to calculate the second order rate constant, $k_2$, for the reactions carried out in the ionic liquids. Data for ionic liquids other than $[C_4C_{1}im][NTf_2]$ were provided by a colleague, Giuseppe Ranieri, for comparison:

![Diagram showing dependence of $k_{obs}$ on chloride concentration in molecular solvents](image)

**Figure 23** - Dependence of $k_{obs}$ on chloride concentration in molecular solvents

![Diagram showing dependence of $k_{obs}$ on chloride concentration in ionic liquids](image)

**Figure 24** - Dependence of $k_{obs}$ on the chloride concentration in ionic liquids\(^{130}\)
Table 23 - Second order rate constants for an S_N2 reaction in ionic liquids

<table>
<thead>
<tr>
<th>Ionic Liquid</th>
<th>( k_2 ) / M(^{-1}) s(^{-1})</th>
<th>Kamlet-Taft Parameters</th>
<th>( \alpha )</th>
<th>( \beta )</th>
<th>( \pi^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C(_4)C(_1)im][NTf(_2)]</td>
<td>0.0012</td>
<td>( \alpha )</td>
<td>0.62</td>
<td>0.24</td>
<td>0.98</td>
</tr>
<tr>
<td>[C(_4)C(_1)im][NTf(_2)](^{156})</td>
<td>0.0036 ± 0.0008</td>
<td>( \beta )</td>
<td>0.38</td>
<td>0.24</td>
<td>1.01</td>
</tr>
<tr>
<td>[C(_4)C(_1)Py][OTf](^{156})</td>
<td>0.00527 ± 0.0006</td>
<td>( \pi^* )</td>
<td>0.40</td>
<td>0.46</td>
<td>1.02</td>
</tr>
<tr>
<td>[C(_4)C(_1)Im][OTf](^{156})</td>
<td>0.00116 ± 0.00009</td>
<td></td>
<td>0.62</td>
<td>0.46</td>
<td>1.01</td>
</tr>
<tr>
<td>[C(_4)C(_1)Py][NTf(_2)](^{156})</td>
<td>0.0048 ± 0.0004</td>
<td></td>
<td>0.43</td>
<td>0.25</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Taking a cursory glance at Table 23, it would seem that the reaction rate is slowest for the ionic liquids with the highest \( \alpha \) values, \([C\(_4\)C\(_1\)im][NTf\(_2\)]\) and \([C\(_4\)C\(_1\)im][OTf]\), and faster for those ionic liquids with lower values of \( \alpha \) in agreement with the Welton group’s previous studies. Additionally, the solvents which share a common cation have similar \( \alpha \) and \( k_2 \) values.

That the rate constant is governed by the hydrogen bond donating property of the solvent (\( \alpha \)) would suggest that the nature of the cation plays a dominant role in determining the effects that the solvent will have upon the nucleophilic substitution reaction when the nucleophile is anionic. This theory has been supported by a theoretical study into the interaction between the ionic liquid cation, \([C\(_4\)C\(_1\)im]\(^+\)), and the chloride anion.\(^{133}\) This work has shown that the hydrogen bonding between the ions is stronger than the conventional hydrogen bond due to a Coulombic contribution. It is therefore reasonable to propose that the slower reaction rate seen in ionic liquids with higher \( \alpha \) values (and consequently a stronger cation/chloride interaction) is observable because the initial activation of the nucleophile entails the cleavage of one or more of these cation/chloride hydrogen bonds. If the cation/chloride hydrogen bond cleavage is indeed the activation step, a stronger cation/chloride interaction caused by higher \( \alpha \) values means the energy of activation would be greater and the reaction rate would decrease.

In the case of polar molecular solvents, acetonitrile and butoxyethanol, non-linear partial-order kinetics were observed. For the same experiments in similarly polar solvents, the Welton group have proposed that the reaction proceeds via ion pairs and that it is the reaction between these ion pairs that is observed in the kinetic experiments.\(^{58}\)
When the solvent used was a relatively non-polar molecular liquid (dichloromethane), a white precipitate was observed and $k_{\text{obs}}$ had a negative-order dependence on nucleophile concentration (as the nucleophile concentration was increased, the observed rate of reaction decreased). This precipitate was isolated and identified as dimethyl-4-nitrophenylsulfonium chloride. This type of reaction is well described and it is understood that the chloride ion which is present in large excess will instigate an ion metathesis reaction to give dimethyl-4-nitrophenylsulfonium chloride.

![Reaction Scheme 25](image)

**Reaction Scheme 25 - The ion exchange (Q+ refers to the quaternary cation originally associated with the chloride ion)**

This salt is insoluble in the relatively low polarity solvent dichloromethane and precipitates out of solution. When the quaternary ammonium chloride (Q+Cl-) concentration is increased the equilibrium constant for this metathesis leads to formation of more (insoluble) dimethyl-4-nitrophenylsulfonium chloride and the concentration of electrophile remaining in solution is therefore decreased. This results in an apparent reduction in reaction rate and can even level out the observed rate if sufficient quaternary ammonium chloride salt is added to complete formation of dimethyl-4-nitrophenylsulfonium chloride.
Although not carried out in this work, it would be possible to predict the observed decrease in reaction rate if the precise decrease in concentration of dimethyl-4-nitrophenylsulfonium ion could be estimated by calculating the solubility constant $K_s$.

Empirical observations indicate a different mechanism in more polar molecular solvents such as butylythanol and acetonitrile. The initial metathesis step would lead to the formation of dimethyl-4-nitrophenylsulfonium chloride as for the less polar solvents, but this salt mixture can also exist as quaternary ion pairs in polar solvents. (Reaction Scheme 27).

It is the reaction of these quaternary ion pairs that are observed in the kinetic experiments (Reaction Scheme 28). Therefore, as expected, increasing the concentration of nucleophile would increase the rate of reaction, although not linearly as prescribed by pseudo-first order conditions.
Reaction Scheme 28 - The formation of products from ion pair

Alternatively, the quaternary ion pair formed could redistribute between a sulfonium-ammonium pair and a di-ammonium quadrupolar ion pair (Reaction Scheme 29).

Reaction Scheme 29 - The redistribution of ion pair

The di-quaternary ammonium quadrupolar ion pair can undergo a monomer-dimer equilibrium shift to complete the reaction cycle (Reaction Scheme 30).

Reaction Scheme 30 - The monomer-dimer equilibrium

An overall kinetic scheme can be worked out following the previous assumptions (Reaction Scheme 31):
The simplified kinetic scheme (E+ = electrophile)

\[ \text{E}^+\text{Cl}^- + \text{Q}^+\text{Cl}^- \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} \left( \text{E}^+\text{Cl}^- \; \text{Q}^+\text{Cl}^- \right) \]  \hspace{1cm} (1)

\[ \left( \text{E}^+\text{Cl}^- \; \text{Q}^+\text{Cl}^- \right) \overset{k_2}{\rightarrow} \text{products} \]  \hspace{1cm} (2)

\[ \left( \text{E}^+\text{Cl}^- \; \text{Q}^+\text{Cl}^- \right) + \text{Q}^+\text{Cl}^- \overset{k_3}{\rightarrow} \text{E}^+\text{Cl}^- + \left( \text{Q}^+\text{Cl}^- \right)_2 \]  \hspace{1cm} (3)

\[ \left( \text{Q}^+\text{Cl}^- \right)_2 \overset{\text{rapid}}{\rightleftharpoons} \text{2Q}^+\text{Cl}^- \]  \hspace{1cm} (4)

**Reaction Scheme 31 - The simplified kinetic scheme (E+ = electrophile)**

The corresponding rate law can be written:

\[ \frac{d[\text{products}]}{dt} = k_2(\text{E}^+\text{Cl}^-\text{Q}^+\text{Cl}^-) \]

Equation 19

From the proposed kinetic scheme (Reaction Scheme 31) the following expression can be derived:

\[ \frac{d[(\text{E}^+\text{Cl}^-\text{Q}^+\text{Cl}^-)]}{dt} = k_1(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) - k_{-1}(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) \]

\[ - k_2(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) - k_3(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) \]

Equation 20

Applying the steady state approximation to \([(\text{E}^+\text{Cl}^- \; \text{Q}^+\text{Cl}^-)]\) gives:

\[ \frac{d[(\text{E}^+\text{Cl}^-\text{Q}^+\text{Cl}^-)]}{dt} \approx 0 \approx k_1(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) - k_{-1}(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) \]

\[ - k_2(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) - k_3(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-) \]

\[ \rightarrow [(\text{E}^+\text{Cl}^-\text{Q}^+\text{Cl}^-)] = \frac{k_1(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-)}{k_1 + k_2 + k_3(\text{Q}^+\text{Cl}^-)} \]

Equation 21

Substituting Equation 21 into Equation 19 gives:

\[ \frac{d[\text{products}]}{dt} = \frac{k_1 k_2(\text{E}^+\text{Cl}^-)(\text{Q}^+\text{Cl}^-)}{k_1 + k_2 + k_3(\text{Q}^+\text{Cl}^-)} \]
Given that *pseudo*-first order conditions were used and therefore the chloride salt (Q+Cl-) was in excess in all reactions, the Equation 22 can be simplified:

\[
\frac{d[products]}{dt} = k_{obs}[E^+Cl^-]
\]

**Equation 23**

Where \(k_{obs}\) is a constant defined by:

\[
k_{obs} = \frac{k_1k_2[Q^+Cl^-]}{k_1 + k_2 + k_3[Q^+Cl^-]}
\]

**Equation 24**

The experimental evidence supporting Equations 23 and 24 is as follows:

1. The reactions are found to be 1st order in \([E^+Cl^-]\) in ionic liquids, i.e. in each case plotting \(-\ln([E^+Cl^-])\) vs. time gives a straight line, so we can say that Equation 23 is valid.

2. Equation 24 can be rewritten as Equation 25 which means that linearity and a positive intercept have to be observed when \(1/k_{obs}\) is plotted versus \(1/[Q^+Cl^-]\). This was observed in each of the experiments.

\[
\frac{1}{k_{obs}} = \frac{k_{-1} + k_2}{k_1k_2} \cdot \frac{1}{[Q^+Cl^-]} \cdot \frac{k_3}{k_1k_2}
\]

**Equation 25**

The process was also attempted in polar protic solvents water and methanol but the nucleophilic substitution reaction did not take place. The sulfonium chloride salt was isolated from solution as a stable species and characterized via NMR after one week and no decomposition products were detected. UV-vis spectroscopy also confirmed the absorbance of the sulfonium salt to have remained constant after the same period of time. This can likely be attributed to the solvents forming strong hydrogen bonds with both the nucleophile and the electrophile and greatly reducing their reactivities.58 We can therefore conclude that it is only in ionic liquids that *pseudo*-first order kinetic behaviour for this nucleophilic substitution reaction is observed.

The linear kinetic behaviour seen in the ionic liquid solutions clearly indicates that the reaction does not take place in the same way in molecular solvents as in ionic liquids. As it is
well understood that the reaction occurs via ion pairs in molecular solvents, it seems reasonable to suggest that the reacting species in ionic liquids are free ions.\textsuperscript{134} Given that we have tested molecular solvents which are known to be dissociating\textsuperscript{68} (DMSO, acetonitrile), there will exist both ion pair and free ion species in the reaction mixture. Kinetic theory states that we observe the slowest step of the fastest reaction, so we can infer that ion pairs are considerably more reactive than freely solvated ions. This suggests that the linear kinetic behavior observed in ionic liquids can be attributed to the fact that there is only one reacting species and furthermore explains why the observed reaction rate in ionic liquids is very slow compared to molecular solvents.

![Reaction Scheme](image)

In this reaction, increasing the concentration of the nucleophile would increase the rate of reaction as expected, but not in the linear pseudo-first order fashion predicted as the rate would depend also on the ion pair formation. Theoretical modelling of this reaction involving a quaternary ion pair has excellent correlation with the experimental results as described above.

**Conclusions**

The linear kinetic behaviour observed in ionic liquids suggests that the reaction is not proceeding via ion pairs but through free solvated ions.\textsuperscript{134} Ion pairing in solution is driven by the mutual attraction of oppositely charged ions. This attraction is mainly in the form of Coulombic forces and is inversely proportional to the dielectric constant. But when the
solvent itself is composed entirely of ions and the solute and solvent cations are of similar dimensions then there will be no preferential Coulombic attraction for any given anion and vice versa. Indeed the question arises as to whether is is wholly appropriate to denominate the ions as solute or solvent once a homogeneous mixture is formed; this work will continue to do so however, to facilitate discussion of the results given that more correct terms have yet to be developed. The role of Coulombic interactions in determining ion pair formation is diminished and there is no longer a relationship between the degree of solute dissociation and the dielectric constant of the solvent. It is only through a chance meeting that solute ions will be able to form ion pairs and even then the pairing will be short lived. The “super-dissociating” property of ionic liquids screens solute charges so well that the S_N2 reaction between two charged species in ionic liquids follows a fundamentally different pathway to the same reactions in molecular solvents. This phenomenon has been termed the “ionic liquid effect”.

Experimental

*The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2]\) with \([C_4C_1im]Cl\) in \([C_4C_1im][NTf_2]\)*

The reaction of \([C_4C_1im]Cl\) with dimethyl-4-nitrophenylsulfonyl bis(trifluoromethylsulfonyl)imide was studied in \([C_4C_1im][NTf_2]\) at 25°C.

<table>
<thead>
<tr>
<th>([S^-]) / mM</th>
<th>([Cl^-]) species / M</th>
<th>(k_{obs}/s^{-1})</th>
<th>(k_2/M^{-1}s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.368</td>
<td>0.0223464</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0446928</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0074488</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0148976</td>
<td>0.025</td>
<td>0.0012 ± 0.0007</td>
</tr>
<tr>
<td>0.368</td>
<td>0.037244</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.019553073</td>
<td>0.032</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{obs}\) against the initial chloride concentration as shown in Figure 25.
The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2]\) with \([C_4C_1im]Cl\) in acetonitrile

The reaction of \([C_4C_1im]Cl\) with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in acetonitrile at 25°C.

Table 25 - The reactions in acetonitrile

<table>
<thead>
<tr>
<th>[Cl(^-)] / M</th>
<th>[S(^+)] species / mM</th>
<th>(k_{obs} \times 10^3/s)</th>
<th>(\sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00942</td>
<td>0.121</td>
<td>2.51</td>
<td>7.69E-05</td>
</tr>
<tr>
<td>0.00942</td>
<td>0.121</td>
<td>0.777</td>
<td>2.35E-04</td>
</tr>
<tr>
<td>0.00377</td>
<td>0.121</td>
<td>1.79</td>
<td>9.09E-05</td>
</tr>
<tr>
<td>0.0151</td>
<td>0.121</td>
<td>2.89</td>
<td>2.55E-03</td>
</tr>
<tr>
<td>0.0113</td>
<td>0.121</td>
<td>2.71</td>
<td>3.44E-03</td>
</tr>
<tr>
<td>0.00188</td>
<td>0.121</td>
<td>1.28</td>
<td>2.41E-03</td>
</tr>
<tr>
<td>0.0423</td>
<td>0.121</td>
<td>3.35</td>
<td>1.77E-03</td>
</tr>
<tr>
<td>0.0847</td>
<td>0.121</td>
<td>3.33</td>
<td>2.65E-02</td>
</tr>
</tbody>
</table>
Figure 26 shows graphically the dependence of $k_{\text{obs}}$ on the chloride concentration:

![Graph showing dependence of $k_{\text{obs}}$ on chloride concentration](image)

It is easy to see the non-linear nature of the reaction rate against chloride concentration in acetonitrile though the dependence of $k_{\text{obs}}$ on chloride concentration is positive-order as expected.

**The reaction of $[p\text{-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]$ with $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ in Butoxyethanol**

The reaction of $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ with dimethyl-4-nitrophenylsulphonium $\text{bis}(\text{trifluoromethylsulfonyl})\text{imide}$ was studied in butoxyethanol at 25°C.

**Table 26 - The reactions in butoxyethanol**

<table>
<thead>
<tr>
<th>$[\text{Cl}^-]$ / M</th>
<th>$[\text{S}^+]$ species / mM</th>
<th>$k_{\text{obs}} \times 10^3$ / s$^{-1}$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0946</td>
<td>0.229</td>
<td>7.8</td>
<td>7.48E-03</td>
</tr>
<tr>
<td>0.01892</td>
<td>0.229</td>
<td>6.5</td>
<td>1.59E-02</td>
</tr>
<tr>
<td>0.00946</td>
<td>0.229</td>
<td>6</td>
<td>9.27E-02</td>
</tr>
<tr>
<td>0.07568</td>
<td>0.229</td>
<td>7.6</td>
<td>1.02E-02</td>
</tr>
<tr>
<td>0.03784</td>
<td>0.229</td>
<td>6.6</td>
<td>8.16E-03</td>
</tr>
<tr>
<td>0.05676</td>
<td>0.229</td>
<td>7</td>
<td>2.94E-02</td>
</tr>
<tr>
<td>0.000946</td>
<td>0.229</td>
<td>3</td>
<td>4.55E-02</td>
</tr>
</tbody>
</table>
Figure 27 shows graphically the dependence of $k_{obs}$ on the chloride concentration, which shows non-linear positive-order reaction kinetics as for the reaction in acetonitrile.

**Butoxyethanol**

![Butoxyethanol graph]

**Figure 27 - Dependence of $k_{obs}$ on chloride concentration in butoxyethanol**

*The reaction of $[p$-NO$_2$PhS(CH$_3$)$_2$][NTf$_2$] with $[C_4C_1im]Cl$ in dichloromethane*

The reaction of $[C_4C_1im]Cl$ with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in dichloromethane at 25°C.

**Table 27 - The reactions in dichloromethane**

<table>
<thead>
<tr>
<th>[Cl$^-$] / M</th>
<th>[S$^-$] species / mM</th>
<th>$k_{obs} \times 10^3$/s$^{-1}$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00332</td>
<td>0.14</td>
<td>15.7</td>
<td>3.46E-04</td>
</tr>
<tr>
<td>0.00996</td>
<td>0.14</td>
<td>10.2</td>
<td>8.16E-05</td>
</tr>
<tr>
<td>0.0166</td>
<td>0.14</td>
<td>8.42</td>
<td>1.41E-05</td>
</tr>
<tr>
<td>0.0232</td>
<td>0.14</td>
<td>6.72</td>
<td>2.50E-04</td>
</tr>
<tr>
<td>0.0332</td>
<td>0.14</td>
<td>5.86</td>
<td>1.41E-05</td>
</tr>
<tr>
<td>0.0498</td>
<td>0.14</td>
<td>5.44</td>
<td>1.41E-05</td>
</tr>
<tr>
<td>0.000664</td>
<td>0.14</td>
<td>20.2</td>
<td>2.16E-04</td>
</tr>
<tr>
<td>0.00133</td>
<td>0.14</td>
<td>19.3</td>
<td>1.63E-04</td>
</tr>
<tr>
<td>0.00199</td>
<td>0.14</td>
<td>18.3</td>
<td>1.41E-04</td>
</tr>
</tbody>
</table>

Figure 28 shows the apparent negative-order dependence of $k_{obs}$ on nucleophile concentration.
Qualitative isolation of dimethyl-4-nitrophenylsulfonium chloride

Dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was added to a saturated solution of tetrabutylammonium chloride in dichloromethane. A white precipitate separated from the dichloromethane phase. The precipitate was quickly washed with diethyl ether in order to remove unreacted dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide and dichloromethane, which would otherwise favour the reaction between the sulfonium and chloride ions. The obtained product was dried and analysed by NMR in D2O. A silver nitrate test confirmed the presence of chloride.

δH (ppm) (D2O): 8.56 (2H, d, 3J = 9.6 Hz, CH-3,5), 8.24 (2H, d, 3J = 9.6 Hz, CH-2,6), 3.36 (6H, s, -S-CH3).

The reaction of \( [p-\text{NO}_2\text{PhS(CH}_3)_2] \) with \([\text{Hex}_4\text{N}]\text{Cl}\) in \([\text{C}_4\text{C}_1\text{im}]\) at 25 °C. The results are shown below in Table 28.
Table 28 - The reactions with tetrachexylammonium chloride in [C₄C₅im][NTf₂]

<table>
<thead>
<tr>
<th>[Cl⁻] / M</th>
<th>[sulfonium] / mM</th>
<th>k_{obs} / s⁻¹</th>
<th>k₂ / M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(mean value)</td>
<td></td>
</tr>
<tr>
<td>0.0545</td>
<td>0.121</td>
<td>0.000617</td>
<td></td>
</tr>
<tr>
<td>0.0109</td>
<td>0.121</td>
<td>0.000576</td>
<td></td>
</tr>
<tr>
<td>0.0436</td>
<td>0.121</td>
<td>0.000611</td>
<td>0.0007± 0.0001</td>
</tr>
<tr>
<td>0.0164</td>
<td>0.121</td>
<td>0.000585</td>
<td></td>
</tr>
<tr>
<td>0.0055</td>
<td>0.121</td>
<td>0.00057</td>
<td></td>
</tr>
<tr>
<td>0.0273</td>
<td>0.121</td>
<td>0.000592</td>
<td></td>
</tr>
</tbody>
</table>

The values of k₂ were determined by plotting k_{obs} against the initial chloride concentration as shown below in Figure 29.

![Figure 29 - The extrapolation of k₂ for the reactions in [C₄C₅im][NTf₂]](image-url)
Chapter 3: Energetic Considerations of Solvent Effects

Objectives

- Determine the activation free energy ($\Delta G^\neq$), enthalpy ($\Delta H^\neq$) and entropy ($\Delta S^\neq$) for the $S_N2$ reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium by $[C_4C_1im]Cl$ in $[C_4C_1im][NTf_2]$ under pseudo-first order conditions and infer mechanistic details and solvent behaviour for the reaction.
- Compare and contrast the results with the Eyring activation parameters calculated by Welton and co-workers for the $S_N2$ reaction of the charge neutral species, methyl-4-nitrobenzenesulfonate, by $[C_4C_1im]Cl$ in $[C_4C_1im][NTf_2]$

Outcomes

- Activation energies $\Delta G^\neq$, $\Delta H^\neq$ and $\Delta S^\neq$ were calculated for the reaction.
- The Eyring activation parameters calculated were found to have similar characteristic to the reaction between chloride and the charge neutral electrophile methyl-$p$-nitrobenzenesulfonate in the ionic liquids $[C_4C_1im][NTf_2]$
- The Gibbs energy of activation appears to be enthalpy dominated

Key Figure

![Eyring Plot for $[C_4C_1im]Cl$](image)

\[ y = -9105.4x + 18.542 \]

\[ R^2 = 0.9889 \]
**Introduction**

This work so far has reported the quantitative kinetic studies of nucleophilic substitutions by the chloride ion in ionic liquids. By comparing these results with work previously performed in our group, it is possible to see the effect that changing the cation, and therefore hydrogen bond donating ability of the ionic liquid solvent, has on the reaction. Chiappe and co-workers have also made kinetic and mechanistic studies of nucleophilic substitutions\(^{135}\) as well as other reactions.\(^ {136}\) This body of work shows that from a distance, the classical Hughes-Ingold rules can be applied to ionic liquids if they are considered as polar solvents. However, a closer examination of the results reveals the specific ionic liquid ion-solute interactions to be of great importance in determining reaction rates.

In Chapter 2, a novel mechanism involving free solvated ions for the S\(_{N2}\) reaction between charged nucleophilic and electrophilic species that is specific to ionic liquids has been proposed. It has also been suggested that this reaction takes place more slowly in ionic liquids with high \(\alpha\) values as the initial step of activation involves the breaking of a particularly strong hydrogen bond which forms between the ionic liquid cation and the chloride nucleophile. Higher values of \(\alpha\) would mean a stronger hydrogen bond and therefore more energy would be required to break it and thus the reaction rate would decrease.

To gain greater insight into the reaction process, the activation enthalpy (\(\Delta H^\ddagger\)) and entropy (\(\Delta S^\ddagger\)) were determined using the Eyring Equation.

**Results and Discussion**

The Eyring Equation, which is based on transition state theory, provides a theoretical construct to describe the dependence of the reaction rate on temperature:

\[
\ln \left( \frac{k_2 \cdot h}{k_B \cdot T} \right) = \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{R \cdot T}
\]

*Equation 26 – The Eyring Equation*

In this equation \(h\) represents Planck’s constant \((6.626 \times 10^{-34}\text{ J.s})\), \(k_B\) is the Boltzmann constant \((1.381 \times 10^{-23}\text{ J/K})\), \(T\) is the reaction temperature in Kelvin and \(R\) is the universal gas constant \((8.31447\text{ J/mol/K})\). For each temperature, a second order rate constant \((k_2)\) must be derived according to the procedure set out in Chapter 2.
The thermodynamic parameters $\Delta H^\ddagger$ (activation enthalpy) and $\Delta S^\ddagger$ (activation entropy) can be calculated with kinetic data using the Eyring equation by plotting $1/T$ against $\ln k_2$. Figure 30 shows the Eyring plot for the reaction of dimethyl-4-nitrophenylsulphonium bis(trifluoromethylsulfonyl)imide with [C$_4$C$_1$im]Cl in the ionic liquid [C$_4$C$_1$im][NTf$_2$] at $T = 18, 25, 35, 50$ and $80^\circ$C.

According to the Eyring plot, Figure 30, and the Eyring equation, the activation enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) can be determined:

$$\Delta H^\ddagger = -(\text{slope} \times R)$$

$$\Delta H^\ddagger = \frac{(-9105.4 \times R)}{10^3} = 75.703 \text{ kJ/mol}$$

$$\Delta S^\ddagger = \left(\text{intercept} - \ln\left(\frac{k_B}{\hbar}\right)\right) \times R$$

$$\Delta S^\ddagger = \left(18.542 - \ln\left(\frac{k_B}{\hbar}\right)\right) \times R = -43.38 \frac{1}{R} \text{ mol}$$

Having estimated the activation enthalpy and entropy, the Gibbs free energy for the activation process can be calculated easily:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$
The enthalpy of activation in ionic liquid [C₄C₁im][NTf₂] is similar to that of the ion paired chloride nucleophile in the SₐN₂ reaction between methyl-p-nitrobenzenesulphonate and chloride ion observed in dichloromethane at 79.5 kJ/mol.⁵⁴ Seemingly in contradiction to this evidence, this report has previously suggested that ion pairing does not occur in ionic liquid solvents and any ion pairs which do form have no observable influence on the reaction rate. This hypothesis holds if we consider that the chloride will be interacting strongly with the solvent by way of a hydrogen bond to the ionic liquid cation. The solute ion will always be associated with another solvent ion of opposite charge until it comes into contact with the reactive species when it will become available to react as a free ion. Conceivably all of the nucleophilic anion species will be held in longer range structures throughout the ordered bulk of the ionic liquid in some electrostatic association with the solvent cations. So although there is a great deal of ion association, it cannot be termed ion pairing as it is not specific to one particular pair of ions; it is every anion and every cation all connected with each other until such a time when the electrophile and nucleophile happen to be close enough to react. One of the great challenges currently facing ionic liquid research is how to describe the concept of ion pairing in ionic liquids and whether or not this phenomenon is even possible in such media.

SₐN₂ reactions are associative and negative activation entropies are expected. This is what we see for the above reaction in [C₄C₁im][NTf₂] where \( \Delta S^\# = -43 \text{ kJ/mol} \). This value is in the same region as the \( \Delta S^\# \) for the SₐN₂ reaction between methyl-p-nitrobenzenesulphonate and chloride ion observed in dichloromethane: -58 kJ/mol.⁵ Three That the entropy of activation is actually slightly less negative for reactions in ionic liquids compared to the free ion reaction in dichloromethane, suggests that the extent to which the reaction occurs via free ions is smaller in ionic liquids. Again this can be explained by the stronger than “classical” hydrogen bonding between the nucleophile and the ionic liquid cation. Association of oppositely charged ions to form a complex or ion pair is generally accompanied by a decrease in net charge. Therefore the resulting species will be less well solvated and solvent molecules, or in this case solvent ions, will be released into the bulk from the solvation shells of the reacting ions and increases in both volumes and entropy are expected. This increase in entropy is
compensated by the association of the reactants and typically the overall increase in entropy is small.

As a result of the Coulombic force enhanced hydrogen bonding and the long range order of ionic liquids, the unreacted mixture starts off as being more ordered in the ionic liquid than in dichloromethane. Therefore, on association of the reacting species, the overall entropy loss between the initial and final state will be smaller for the ionic liquid and this is what we observe.

Of course, when ions associate there are effects other than solvent release to be taken into consideration. Translational freedom will be contracted for associating ions, the newly formed complex or ion pair will produce new rotational freedom and the overall long range electrostatic effects of the ions and products will be different. The extent to which these processes contribute to the activation entropy and therefore the overall Gibbs energy of activation can be thought of relative to the enthalpy of activation, i.e. the overall reaction rate can be attributed to either activation enthalpy or entropy depending on their relative contributions to the Gibbs energy of activation.

The $\Delta G^\ddagger$ for the reaction has been calculated to be 88.63 kJ/mol from $\Delta H^\ddagger$ and $\Delta S^\ddagger$ as described earlier. Previous work by the Welton group has determined 84.4 kJ/mol to be the $\Delta G^\ddagger$ for the reaction of chloride with methyl-$p$-nitrobenzenesulfonate in the same ionic liquid, $[\text{C}_4\text{C}_{1\text{im}}][\text{NTf}_2]$. Although the electrophilic species are different for each experiment, pseudo-first order reaction conditions were achieved in both by using a high concentration of chloride. It is perhaps unsurprising that the Gibbs energy of activation values are analogous as it is the effect of the nucleophile that is profiled and this species is the same in each case. It should be noted that all Eyring parameters calculated in this work for the reaction between chloride and dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide in $[\text{C}_4\text{C}_{1\text{im}}][\text{NTf}_2]$ are comparable to those calculated for the reaction of chloride with methyl-$p$-nitrobenzenesulfonate in the same ionic liquid solvent. We can see in Table 29 that in both cases, as expected, the Gibbs energy of activation is enthalpy dominated.
Table 29 - Eyring parameters for nucleophilic substitutions by chloride ion in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ 

<table>
<thead>
<tr>
<th>Ionic Liquid</th>
<th>Nucleophile</th>
<th>Electrophile</th>
<th>$\Delta H^\ddagger$ / kJ mol$^{-1}$</th>
<th>$T\Delta S^\ddagger$ / kJ mol$^{-1}$</th>
<th>$\Delta G^\ddagger$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>$\text{Cl}^-$</td>
<td>methyl-$p$-nitrobenzenesulfonate</td>
<td>71.8</td>
<td>-42.4</td>
<td>84.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>$\text{Cl}^-$</td>
<td>dimethyl-4-nitrophenylsulfonium $[\text{NTf}_2]$</td>
<td>75.70</td>
<td>-43.9</td>
<td>88.63</td>
</tr>
</tbody>
</table>

Conclusions

It was found that using the Eyring activation parameter approach to kinetic data from nucleophilic substitution reactions of dimethyl-4-nitrophenylsulfonium $\text{bis}(\text{trifluoromethylsulfonyl})$imide with the chloride ion in ionic liquids yielded results consistent with similar substitution reactions performed by the Welton group. From thermodynamic parameter analysis alone, it is not immediately evident that there is an “ionic liquid effect” on this reaction. However, it has already been shown in Chapter 2 that such an effect does indeed exist; if we compare the reaction mechanism to that of the reaction carried out in molecular solvents. This leads to the conclusion that the pathway followed for nucleophilic substitutions in ionic liquids, whether between charged/charged, charged/neutral nucleophilic and electrophilic species, are likely to take place via very similar mechanisms. Perhaps this is unsurprising given the excellent ability of ionic liquid ions to screen reactive species: the consequent reaction occurs via freely solvated electrophiles and nucleophiles regardless of their nature. The consistency displayed by ionic liquids in this particular type of substitution cannot be found for molecular solvents, where ion pairing causes an alteration in the reaction mechanism when changing the reactants from charged/neutral to charged/charged species.

When investigating a new class of solvents, it is easy to think one is testing for irregular solvent behaviour when compared with the well understood laboratory solvents. Perhaps what we are really discovering are the idiosyncrasies of the molecular solvents which, up until the present day, have shaped the paradigm of solution chemistry. If the mechanism for all nucleophilic substitutions, despite the form of the reactants, can be confirmed unvarying
in ionic liquids, then this “novel” behaviour – the “ionic liquid effect”, may prove to be the new standard.

**Experimental**

All reactants, ionic liquids and molecular solvents were prepared as described in the experimental section of Chapter 8.

All UV/vis measurements were taken and analysed according to the method described in the experimental part of Chapter 8. Temperatures were achieved and maintained using a thermostatic circulator.
Chapter 4: Cation Effect - Reactions with quaternary ammonium chlorides of various sizes and shapes

Objectives

- Determine the rate constant, $k_2$, of the $S_N2$ reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium by various $R_4N$ chloride salts in $[C_4C_{1}im][NTf_2]$ under pseudo-first order conditions
- Determine the activation free energy ($\Delta G^\ddagger$), enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) for each reaction and infer mechanistic details and solvent behaviour for each reaction through contrast and comparison of results

Outcomes

- Pseudo-first order kinetics observed for all reactions in $[C_4C_{1}im][NTf_2]$ and rate constants determined
- Neither quaternary ammonium cation size nor shape were seen to affect reaction mechanism
- Reaction rates were found to increase with increasing length of alkyl chains on the quaternary ammonium chlorides
- Activation energies calculated for each reaction were found to vary with length of the alkyl substituents on the quaternary ammonium chlorides
- Reaction appears to switch from being enthalpy controlled when the counterion is small and be entropy controlled when the cation is large

Key Figure

![Quaternary Ammonium Salt Activation Energies](image-url)

**Quaternary Ammonium Salt Activation Energies**

- $\Delta G$
- $\Delta H$
- $\Delta S$

**Energy (kJ mol$^{-1}$)**

**Molecular weight**
**Introduction**

Gajewski proposed an effective correlation between rate constants of four different reactions and cohesive energy densities of solvents and solvation parameters\(^{137}\) and several recent studies have demonstrated that ionic liquids can influence the kinetics of these reactions.\(^{138,139,140}\) Continuing our work on the solvent effects of ionic liquids, we now examine the issue of whether newly created solvent media comprising ionic liquids and non-reacting solute ions can influence the rates and mechanism of a popular bimolecular organic reaction, i.e., S\(_N\)2 type nucleophilic substitution.

The term “ionic liquid effect” has been used to describe the difference in mechanism observed for S\(_N\)2 reactions between charged species when the solvent is changed from molecular to ionic liquid. This chapter continues to elucidate the ionic liquid effect observed for S\(_N\)2 reactions between a charged electrophile and charged nucleophiles via kinetic investigations by changing the nature of the nucleophilic source. In an effort to increase ion association between the solute ions, small cations such as tetraethylammonium chloride are studied. The chain length on the tetraalkylammonium chloride is also increased to eight carbons in a bid to observe any difference in behaviour when compared with the more tightly bound ammonium chloride salts. Finally, asymmetric tetraalkylammonium chloride salts are investigated. The Eyring activation parameters are calculated for each process to provide some insight into the energetics of each reaction.

**Results and Discussion**

The process under examination was the S\(_N\)2 reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium ([\(p\)-\(NO_2\)PhS(CH\(_3\)_2][N(CF\(_3\)_2SO\(_2\)_2]) by tetraalkylammonium chloride salts of varying alkyl chain lengths, as shown in Reaction Scheme 33 and Figure 31. Initially, due to their inherently strong interionic interactions, alkali metal halides such as potassium chloride were tested. It was proposed that the great affinity of the charge dense metal cations for the small, hard chloride anion would provide the greatest chance of observing ion pairing behaviour in ionic liquids. Unfortunately these salts (LiCl, NaCl, KCl and CsCl) could not be used for this reaction due to low solubility in [C\(_4\)C\(_1\)im][NTf\(_2\)] – please refer to the experimental section at the end of this chapter for further information.
The reactions were assayed using UV spectroscopy, with each substrate having $\lambda_{\text{max}}$ at 252 nm and the demethylated products having a $\lambda_{\text{max}}$ at 342 nm. The imidazolium-based ionic liquid which was used as the solvent has a cut-off at 240 nm and therefore caused no problems in interpreting the UV spectroscopy results. The sulfonium salt was synthesised as described in the experimental section of Chapter 8 directly before use and kept under anaerobic conditions.

The nucleophilic displacement by the chloride ion was studied in the ionic liquid [C$_4$C$_1$im][NTf$_2$] due to its relatively low viscosity, 44 cP, and its well-known synthetic and purification procedures. Chloride salts of various quaternary ammonium cations were also used to study the effect of the counter cation on the nucleophilicity of the chloride ion in an effort to detect preferential ion pairing. Tetraethylammonium, tetrahexylammonium, tetraoctylammonium and trioctylmethylammonium chloride salts were used in [C$_4$C$_1$im][NTf$_2$]. Reactions were carried out at various temperatures to generate the activation energies for each reaction.

The electrophile was found to be stable in all solvents as no change in UV/vis absorbance was detected in the absence of the nucleophile after 24 hours.

This reaction is bimolecular and the rate therefore depends upon the concentrations of both the nucleophile and the electrophile. It is common in this type of process to create pseudo-first order kinetic behaviour by using a large excess of one reagent which shows a linear dependence of $k_{\text{obs}}$ upon nucleophile concentration. In this case the nucleophile (chloride) was used in excess and the second order rate constants for each reaction calculated.
The linear relationship expected was observed for each reaction in the ionic liquid solvent but the rate of the reaction was found to increase with increasing molecular weight of the counter cation. Summarised in Table 30 are the second order rate constants recorded for various nucleophilic tetraalkylammonium chloride salts.

Table 30 - Kinetic results for various [R₄N]Cl salts

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>T / °C</th>
<th>k₂ / M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Et₄N]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0002 ± 0.00002</td>
</tr>
<tr>
<td>[Hex₄N]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.001 ± 0.0001</td>
</tr>
<tr>
<td>1:1 mix [Et₄N]Cl:[Oct₄N]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0023 ± 0.0011</td>
</tr>
<tr>
<td>[Oct₄MeN]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0048 ± 0.0007</td>
</tr>
<tr>
<td>[Oct₄N]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0609 ± 0.0003</td>
</tr>
<tr>
<td>[C₄C₁im]Cl</td>
<td>[C₄C₁im][NTf₂]</td>
<td>25</td>
<td>0.0012 ± 0.0007</td>
</tr>
</tbody>
</table>

The slowest rate observed (0.0002 M⁻¹ s⁻¹) was for the reaction involving tetrahexylammonium chloride. Interestingly this rate constant, along with that recorded for tetraethylammonium chloride, was even lower than for the base case reaction using [C₄C₁im]Cl (0.0012 M⁻¹ s⁻¹) where there would be no other effect on the chloride than solvent effects due to the counter ion being the same as the solvent cation. This could be seen as an indication of preferential ion association but the fact that the reaction kinetics remained linear suggests that the extent of ion pairing was not significant and/or that the reacting species observed in ionic liquids are always fully dissociated free ions.

It is especially clear that a cation effect exists for this reaction in light of the much higher rate constant observed for the largest cation studied – tetraoctylammonium. At 0.0609 M⁻¹ s⁻¹, the reaction between tetraoctylammonium chloride and the sulfonium electrophile in [C₁C₄im][NTf₂] is 300 times faster than the same reaction with tetraethylammonium chloride and 50 times faster than the reference case using [C₄C₁im]Cl. Indeed, taking a glance at the Figure 32 where the molecular weight of the cations is compared with the resulting rate constant, tetraoctylammonium chloride produces a markedly faster reaction than any of the other salts tested.
This rate increase could be attributed to size of the tetraoctylammonium cation and the inherent inaccessibility of the nitrogen atom at the cation centre. The effect of the cation on the chloride would therefore be greatly reduced to the extent that the chloride may not be associated with the cation at all and exist as a free ion. This “naked anion” effect has been described by Liotta et al.\textsuperscript{141} as meaning that anions that are poorly solvated and therefore very reactive. Their work investigated Pedersen’s discovery that crown ethers could be used to solubilize inorganic salts into aprotic organic solvents.\textsuperscript{142} In non-polar solvents such as benzene, these naked ions would exist almost exclusively as ion pairs or even higher aggregates when the cation is very large. The high nucleophilicity of these “naked anions” in non-polar solvents may also be due the high reactivity of these ion pairs.

In ionic liquids, given that linear 
\textit{pseudo-}\n
first order reaction kinetics are observed, there is no evidence of ion pairing. However, the resulting rate increase on introduction of the large, greasy tetraoctylammonium cation may promote dissociation of the anion and enhance its nucleophilicity. By making the nucleophile more available to react, the larger cations reduce the ion exchange energy required to deliver the nucleophile to the electrophile and therefore increase the likelihood of a successful reaction. This concept is summarised in Figure 33.
Figure 33 - Large quaternary ammonium cations decrease the ion exchange energy

In an earlier study into the reaction between a selection of halides and methyl-p-nitrobenzene sulfonate in ionic liquids, we have proposed the reaction mechanism where initially the chloride ion is fully coordinated by a number of ionic liquid cations as shown in reaction Reaction Scheme 34.\textsuperscript{143}

In the study, the Welon Group described the equilibrium through which one face of the chloride becomes uncoordinated and therefore able to perform as a nucleophile and resulting in the observed reaction. Throughout the activation process the remaining cations bound to the halide become less associated as the negative charge distributes between several atoms. This dissociation of the ionic liquid cations from the chloride to a greater or lesser degree compensates for the loss of entropy arising from the associative nature of the S\textsubscript{N}2 reaction being an associative process. In this study we propose that the initial state has more entropy when large cations are present. Additionally, the chloride ion would be poorly coordinated in the presence of large cations and the energy cost of breaking the association between ionic liquid cation and chloride would be lower and the enthalpy of activation therefore reduced.

The same logic can be applied to the reaction between the tetraalkylammonium chloride salts and the sulfonium based electrophile. In this case, however, there is an additional solute
cation effect. This work proposes that there exists in the ionic liquid solution two distinct reactive species:

1. The chloride ion coordinated solely by ionic liquid cations.
2. The chloride ion coordinated by both ionic liquid cations and solute cations.

![Diagram of reactive species](image)

**Figure 34 – The reactive species present. Please note that the chloride in reactive species (2) may be coordinated by 2-7 cations (see Table 31)**

Figure 34 shows a reduction in the chloride coordination number on incorporating a solute cation into the coordination sphere. It should be noted that the coordination number can increase or decrease on incorporation of a solute cation and this will be determined by the size of the solute cation. It is expected that the greatest coordination number would be achieved by using smaller cations and would produce the least reactive chloride ions. Therefore it is also expected that reducing the coordination number by increasing the size of the coordinating cations would increase the chloride reactivity. The larger solute cations such as tetraoctylammonium would disrupt the coordination sphere of the chloride and cause an increase in reactivity. It could be argued that these more reactive chlorides become dominant in the reaction kinetics and this is why we observe an increase in reaction rate on the addition of larger solute cations to the reaction mixture.

It has previously been reported that six chlorides reside around any given [C₄C₁im]⁺ (as described by Hardacre et al.¹⁷⁷). In order to verify this figure, Richard P. Matthews, a colleague specialising in theoretical chemistry of ionic liquids, conducted the inverse analysis of several molecular dynamics simulations of [C₄C₁im]Cl at various temperatures. The simulation runs were performed for the [C₄C₁im]Cl at constant temperature and volume using the DL_POLY simulation code.¹⁴⁴ The simulations were carried out using 128 pairs of cations and anions in a central simulation box. Simulations were run at four temperatures (353K, 365K, 385K and 400K) for a total simulation time of 10 ns each. The generation of starting structures and further simulation details are as reported by the Hunt group.¹⁴⁵ The number of [C₄C₁im]⁺ cations around any given chloride was determined by analysis of a
nearest neighbour list for each chloride at 20 ps intervals. At any given time each chloride is surrounded by ~ 5-7 [C₄C₁im]⁺ cations (if specific hydrogen bonding interactions are ignored) with six cations occurring ~45% of the time. 5 and 7 cations occur 26% and 27% respectively. This result was found to be independent of temperature.

We propose that the reactive species present may be of a higher or lower coordination number given that the 6 cation coordinated chloride ion is an average of a range of coordination numbers present. We have calculated for this range to be 5-7 cations per chloride ion for [C₄C₁im]Cl. Introducing solute cations which are smaller or larger than [C₄C₁im]⁺ is likely to broaden the range of possible coordination numbers. In Table 31 we suggest coordination numbers of 2-7 cations per chloride may be possible. We propose the possibility that the most reactive species present may not be 6 coordinated species, but could well be the chloride species which are coordinated by only 2 cations or even 7. It is impossible to determine experimentally which species is responsible for the reaction kinetics but we can imagine that the reaction rates we observe are an average of the reactions of all of the chloride ions with varying coordination numbers and therefore varying reactivities. In which case, when a solute cation is of similar size to the ionic liquids solvent cation, it may to a small extent enhance or impede the average reaction rate.
In Reaction Scheme 35 we show the possible reactions taking place which contribute to the overall reaction rate. On the left-hand side, R1 depicts vertically the chain of events which lead to a reaction when there are no contributions from the solute cations and only ionic liquid cations are present. On the right-hand side, R2 depicts the same reaction but where a solute cation is found within the coordination sphere of the chloride ion. The total contributions of R2 will be much smaller than R1 due to the relative concentration of solute cations but can marginally increase or decrease the overall reaction rate by looser or tighter coordination of the solute cation to the chloride compared with $[\text{C}_4\text{C}_1\text{im}]^+$. Recalling Figure 32, we observe that when the solute cation size is comparable to that of the ionic liquid cation, there is little change in the overall reaction rate.
On addition of a solute cation which is much larger compared to the ionic liquid cation (e.g. [Oct$_4$N]$^+$), the coordination sphere of a chloride ion which is adjacent to a solute cation could be expected to change dramatically. We propose that the subsequent reduction in coordination number significantly enhances the reactivity of this species and causes an observable and significant enhancement of the reaction rate.

**Reaction Scheme 36** - Summary of possible reactions when solute cation is large

Reaction Scheme 36 depicts the activation steps dependent on whether the reacting chloride is initially surrounded by exclusively ionic liquid cations (R1) or whether a large solute cation is in the coordination sphere (R2*). Clearly, all of the chloride species are reactive and we propose are so to a greater extent on inclusion of a large solute cation in the immediate solvation sphere. The rate constant we extract is an average of the rates generated by the individual chloride ions. It is therefore possible that the overall rate constant is enhanced relative to the base case reaction (R1) by reducing the coordination sphere of some of the ions.
via incorporation of larger solute cations (R2*). Recalling Figure 32, we observe a significant increase in $k_2$ when a large solute cation such as tetraoctylammonium is added to the reaction mixture.

The likelihood that a solute cation will be in the coordination sphere of the nucleophile can be calculated using the liquid pseudo-lattice model.

**Liquid Pseudo-Lattice Model**

The Welton Group have previously published the pseudo-lattice treatment of solute ions whilst studying ion association/dissociation behaviour of 1-ethyl-4-(methoxycarbonyl)pyridinium iodide and determined the lattice site model to be consistent with their results.\(^{146}\) In this study we use the anion coordination number determined by Hardacre and co-workers using neutron diffraction data for the 1,3-dimethylimidazolium cation in ionic liquid 1,3-dimethylimidazolium chloride, which indicated a first solvation shell of six anions.\(^{50}\) The zero or near zero energy prescribed by the pseudo-lattice model suggests that the interionic interactions, whether solvent-solute, solvent-solvent or solute-solvent, have similar energies. It is therefore impossible to separate out the interionic interactions as is found for intermolecular interactions in near ideal mixture of toluene and benzene. When salts are dissolved in ionic liquid solvents, the solute ions neither preferentially pair up to form a discrete species nor are the infinitely separated. The mixture behaves ideally and solute ions will only meet by random chance, the probability of which is determined by solute concentration and solvent molar volume.

The experimentally observed linear relationship between the second order rate constant and the concentration of the chloride ion implies that the probability of a direct contact between the electrophile and nucleophile is only dependent on the concentration of these ions. As we have discussed earlier, this behaviour suggests that there are neither attractive nor repulsive interactions between the solute ions which lead to ion pairing which therefore indicates that ion contacts are statistically random.
Figure 35 - Schematic of solute ions (red and blue) solvated as a contact ion pair (left) or freely solvated ions (right)

Assuming that the ion contacts are statistically random allows use of a lattice site model with the site exchange energy equal to zero depicted in Figure 35. This model can be used to calculate the likelihood that the solute ions are located on adjacent lattice sites. We assume that each nearest neighbour pair have opposite charges. Also that $r = \text{number of cations in the solvation shell of a chloride anion}$, that $m_{\text{cat}}$ is the number of solute cations in the solution and $m_T$ is the total number of cations in the solution (calculated from the pure ionic liquid molar volume). Therefore the probability that any given cation in the solvation shell of a chloride anion is not a solute cation would be:

$$\frac{(m_T - m_{\text{cat}})}{m_T}$$

Equation 28

The probability that none of the $r$ cations in the solvation shell of a chloride anion are a solute cation would be:

$$[(\frac{m_T - m_{\text{cat}}}{m_T})^r]$$

Equation 29

The probability, therefore, of having at least one solute cation in the solvent shell, $P_{[\text{cat}]\text{Cl}}$, is:

$$P_{[\text{cat}]\text{Cl}} = 1 - \left[\frac{(m_T - m_{\text{cat}})}{m_T}\right]^r$$

Equation 30

The derivation of Equation 30 can be found elsewhere. Table 31 shows the probability that a given chloride ion is surrounded by at least one solute cation for a 50 mmol solution of [cat]Cl in [C4C1im][NTf2] and for a range of coordination numbers ($r$) with the molar volume of the ionic liquid estimated to be 3.3 mol/L. We can see form Table 31 that as the number of
cations in the coordination sphere \((r)\) increases, the probability that a solute cation is present also increases.

Table 31 - the probability that at least one solute cation is in the chloride coordination sphere

<table>
<thead>
<tr>
<th>(m_T) (mol/L)</th>
<th>(m_{cat}) (mmol)</th>
<th>(r)</th>
<th>(P_{[cat][Cl]})</th>
<th>(P_{[cat][Cl]}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.0300</td>
<td>0.03</td>
<td>0.0300</td>
<td>3.01</td>
</tr>
<tr>
<td>3</td>
<td>0.0447</td>
<td>0.04</td>
<td>0.0447</td>
<td>4.48</td>
</tr>
<tr>
<td>4</td>
<td>0.0592</td>
<td>0.06</td>
<td>0.0592</td>
<td>5.92</td>
</tr>
<tr>
<td>5</td>
<td>0.0735</td>
<td>0.07</td>
<td>0.0735</td>
<td>7.34</td>
</tr>
<tr>
<td>6</td>
<td>0.0875</td>
<td>0.09</td>
<td>0.0875</td>
<td>8.75</td>
</tr>
<tr>
<td>7</td>
<td>0.1013</td>
<td>0.10</td>
<td>0.1013</td>
<td>10.14</td>
</tr>
</tbody>
</table>

We can conclude from the kinetic results and the pseudo-lattice model coordination argument that no preferential ion pairing effect is observed. It is well established that more interacting cations reduce nucleophilicity. However, this is always limited by the solvent cation \([\text{C}_4\text{C}_1\text{im}]^+\) – if ion pairing effects dominate, then there is no driving force to displace a stronger cation \([\text{C}_4\text{C}_1\text{im}]^+\) with a weaker one (e.g. [Oct₄N]⁺) when the weaker one is outnumbered by a factor of 1000. Therefore the fact that we observe faster rates when using larger, weaker solute cations and slower rates using smaller, harder solute cations compared with the base case scenario \([\text{C}_4\text{C}_1\text{im}]\text{Cl}\) is good evidence that this is not preferential ion pairing, but rather random ion pairing coupled with some mechanistic quirk caused by the competing reactivities of the chlorides with different solvation spheres which we have yet been unable to identify.

We propose the possibility that the overall reaction rate is the sum of many ion exchanges and equilibria each experiencing their own solvent effects and that it would be a gross oversimplification to attribute the rate to any one solvent effect.

Further work is needed to determine a range of concentrations of solute cation to chloride ion, from which one could assume two competing mechanisms for the two possible chloride coordination spheres – one for \{Cl[\text{C}_4\text{C}_1\text{im}]6\} and one for \{Cl[\text{C}_4\text{C}_1\text{im}]5(cat)\}. We would then be able to calculate two constants which, if consistent across multiple ratios, would provide strong evidence to support this theory.
An additional explanation for the observed rate enhancement upon using large ammonium cations could be a favourable interaction of these cations with the activated complex. In this nucleophilic substitution reaction, two charged species come together to form a single, more charge diffuse activated complex species depicted in Figure 36.

![Figure 36 - Representation of the transition state](image)

A bond is partially formed between the chloride ion and the substitution site whilst simultaneously a bond is partially broken between the substitution site and the leaving group. It is possible that the large single entity, low charge density activated complex formed on combining two ions is stabilised by the presence of larger, charge diffuse cations. To gain insight into the reaction energetics, the Eyring equation was used to calculate the activation parameters for the reactions.

**Eyring Activation Parameters**

If a reaction takes place in a solvent then the activated complex and reactants will be solvated to varying degrees according to the solvating power of the solvent used. This differential solvation, as we have already discussed in Chapter 1, can accelerate or retard the reaction. The difference of both Gibbs transfer energies determines the reaction rate in solution and can give us further information on the relative stabilities of the reactants and activated complex. A dissection therefore of the reaction rate solvent effects into initial and transition state contributions leads to more direct information about the likely local solvent environment for each species.

**Results and discussion**

The thermodynamic parameters $\Delta H^\dagger$ (activation enthalpy) and $\Delta S^\dagger$ (activation entropy) can be calculated with kinetic data using the Eyring equation by plotting $1/T$ against $\ln k_2$ as described in Chapter 3. Figure 37 shows the Eyring plot for the reaction of dimethyl-4-nitrophenylsulphonium bis(trifluoromethylsulfonyl)imide with [Et$_4$N]Cl in the ionic liquid [C$_4$C$_1$iim][NTf$_2$] at $T = 25, 35, 50, 60$ and $80^\circ$C. The Eyring plots for the reactions listed in Table 32 can be found in the experimental section at the end of this chapter.
A summary of the activation energies recorded for each of the reactions between the tetraalkylammonium chlorides and of dimethyl-4-nitrophensulphonium bis(trifluoromethylsulfonyl)imide can be found in Table 32.

Table 32 - The Eyring activation parameters for various tetraalkylammonium salts

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>$\Delta H^\ddagger$ / kJ mol$^{-1}$</th>
<th>$\Delta S^\ddagger$ / kJ mol$^{-1}$</th>
<th>$\Delta G_{298}^\ddagger$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Et$_4$N]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>55.64</td>
<td>-34.75</td>
<td>90.37</td>
</tr>
<tr>
<td>[Hex$_4$N]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>50.01</td>
<td>-40.46</td>
<td>90.82</td>
</tr>
<tr>
<td>1:1 mix [Et$_4$N]Cl:[Oct$_4$N]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>58.25</td>
<td>-30.07</td>
<td>88.33</td>
</tr>
<tr>
<td>[Oct$_3$MeN]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>55.22</td>
<td>-30.59</td>
<td>85.79</td>
</tr>
<tr>
<td>[Oct$_4$N]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>34.80</td>
<td>-45.45</td>
<td>80.26</td>
</tr>
<tr>
<td>[C$_4$C$_1$im]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>71.8</td>
<td>-42.4</td>
<td>84.4</td>
</tr>
</tbody>
</table>

A change from [Et$_4$N]Cl to [Oct$_4$N]Cl causes the reaction rate to accelerate which corresponds to a decrease in $\Delta G^\ddagger$ of 10.11 kJ mol$^{-1}$. Although one would expect that the solvation energies of the chloride ion in [C$_1$C$_4$im][NTf$_2$] would be identical to each other, the Gibbs energy of activation arises from the difference between the initial and transition states. Therefore we could assume that $\Delta G^\ddagger$ changes for each reaction due to the changing solute cation affecting the stability of either the initial or transition state (or both) relative to the reaction where the solute cation is the same as the ionic liquid solvent cation i.e. [C$_1$C$_4$im]$^+$. 

Figure 37 - Eyring plot for the reaction with tetraethylammonium chloride

The repertoire of the activation parameters for various tetraalkylammonium salts: $\Delta H^\ddagger$, $\Delta S^\ddagger$, $\Delta G_{298}^\ddagger$.
Bimolecular reactions such as the nucleophilic substitution of \([p-NO_2PhS(CH_3)_2][N(CF_3SO_2)_2]\) with chloride ion which reduce or diffuse charge in the activation process usually show small negative entropies of activation due to an increase in solvation during the activation process. However, in ionic liquids, we can postulate the reverse to be true – ionic reactants may be stabilised by solvent ions whereas the activated complex may be relatively destabilised by the large discrepancy in polarity with the solvent. A negative entropy of activation indicates a greater degree of ordering in the transition state and a less negative or positive \(\Delta S^\ne\) indicates a greater degree of order in the initial state due to a decrease in solvation around the transition state.

In this case, the smaller nucleophilic salt cations may be expected to contribute to greater stabilisation of the reactant ions and a decrease in solvation (and decrease of ordering) around the activated complex characterised by less negative entropies of activation. At the other end of the scale, the larger cations might destabilise the reactant ions and help stabilise the transition state characterised by large negative entropies of activation. This theory is supported by the results summarised in Table 32.

The \(\Delta S^\ne\) values in Table 32 show that the largest decrease of activation entropy is obtained when using the largest counter cations (tetraoctylammonium). This observation can be rationalised because large, greasy ions are likely to show some structure breaking effects due to the large diffusion of charge and inaccessibility of the central atom which causes disruption to the local solvent organisation in the initial state. With smaller cations, however, much smaller entropy losses could be expected as a result of decreased solvation during the activation process – small ions will solvate well the charges on the reactants but poorly solvate the large charge diffuse activated complex. Large cations may do exactly the reverse and be relatively more stabilising to the activated complex.

In a recent study by Maschmeyer, ionic liquids were found to enhance the rate of a nucleophilic substitution reaction through variation of the alkyl chain length on the ionic liquid imidazolium cation. The rate enhancement was attributed to the *pseudo* encapsulation of reactants in the polar domains of the ionic liquid which changed the effective concentrations of the reagents. In a similar vein, perhaps rather than preferential association of any ionic species, in this project what we are witnessing is the *pseudo* encapsulation, or stabilisation, of the activated complex by the large non-polar domains of the solute cations.
It is expected that reactions proceeding via relatively neutral activated complexes should have smaller negative entropies of activation in more polar environments than in less polar, less structured environments. The data in Table 32 supports this concept. What can also be observed in Table 32 is a change in the more weighted contributor to the overall $\Delta G^\ddagger$. For more tightly bound solute salts, the reaction is enthalpy dominated whilst for the less tightly bound salts the reaction becomes entropy dominated. In fact, of all of the salts tested, it was only the reaction involving purely tetraoctylammonium chloride which exhibited entropy controlled energetics. Tetradecylammonium chloride was synthesised to further probe this result but could not be purified adequately for the results to meaningful.

Tetradodecylammonium chloride (purchased from Sigma) was not soluble in the ionic liquid solvent $[C_1C_4im][NTf_2]$. 

As can be seen in Table 32, an open-faced tetraalkylammonium salt was also studied in order to detect any asymmetric cation effects. Most of this investigation has concerned symmetrical, bulky, anion activating cations such as tetrahexylammonium and whilst asymmetric cations such as trioctylmethylammonium are generally considered to exhibit similar anion activating properties, it was proposed that the more accessible nature of the cationic centre could lead to a stronger association with the anion and therefore deactivate the nucleophile.

![Figure 38 - Open and closed faced tetraalkylammonium cations](image)
The symmetrical tetrahexylammonium cation has a molecular weight almost identical to the open-faced trioctylmethylammonium cation and the activation enthalpy of the trioctylmethylammonium was found to be almost 5 kJ mol\(^{-1}\) lower than for the tetrahexylammonium. Moreover, the activation entropy was found to become less negative by 9.87 kJ mol\(^{-1}\) and these energies combined account for the reduction in \(\Delta G^\ddagger\) and also the rate increase observed on going from tetrahexylammonium to trioctylmethylammonium. We can surmise therefore that the chloride ion is not preferentially associated with an accessible cation compared with a bulkier, symmetric cation.

The results for trioctylmethylammonium chloride are, however, by no means conclusive. Regarding the proposal that the non-polar domains of the solute cation may be stabilising the activated complex, it may be expected that the trioctylmethylammonium cation would behave more similarly to the tetraoctylammonium cation. In fact, what we observe from the activation energies is that whilst trioctylmethylamnonium has \(\Delta G^\ddagger\) and \(T\Delta S^\ddagger\) values that are more similar to those of tetraoctylammonium than any of the other cations tested, the \(\Delta H^\ddagger\) value is recorded at around 50 kJ mol\(^{-1}\) and the reaction remains enthalpy dominated as for the smaller cations. What can be taken from this evidence is that trioctylmethylammonium provides the long alkyl substituent, non-polar domain stabilisation of the activated complex to some degree but extension of the methyl chain to octyl is required to change the energetics of the reaction. Why all four alkyl chains need to be long is unclear from these results. Perhaps the accessibility of the charged central atom on the open-faced trioctylmethylammonium is great enough to distort the stabilisation of the activated complex provided by the three octyl chains.

A 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride was employed as the nucleophile for this reaction to test whether the cation effect observed for tetraoctylammonium chloride would be observable at smaller concentrations. The result would also give a good indication of whether the reactant stabilising effect of the smaller tetraethylammonium cation or the activated complex stabilising effect of the larger tetraoctylammonium cation was more important for this substitution reaction. The \(T\Delta S^\ddagger\) for the mixture is -30.03 kJ mol\(^{-1}\) which is the least negative recorded in Table 32 closely followed by the purely tetraethylammonium chloride reaction at 34.75 kJ mol\(^{-1}\). The \(T\Delta S^\ddagger\) for the mixture is also 15.38 kJ mol\(^{-1}\) less negative than the \(T\Delta S^\ddagger\) recorded for the tetraoctylammonium chloride reaction. The small \(T\Delta S^\ddagger\) value for the mixture of chlorides supports the idea that the smaller tetraethylammonium cation stabilises the reactants whilst
the tetraoctylammonium cation stabilises the activated complex. The $\Delta H^\neq$ value is 2.61 kJ mol$^{-1}$ higher for the mixture than for the tetraethylammonium chloride and 23.45 kJ mol$^{-1}$ higher than for the tetraoctylammonium chloride reaction. This would suggest that the reactant stabilising effect of the tetraethylammonium is more pronounced that the activated complex stabilising effect of the tetraoctylammonium.

Referring back to Table 30, the rate of reaction is ten times faster for the reaction with the mixture of cations than for the tetraethylammonium chloride reaction and 30 times slower than for the purely tetraoctylammonium chloride reaction. Taking into consideration both the comparison of the Eyring activation parameters and the derived rate constants, we can surmise that although a rate enhancement caused by the stabilising effect of the larger solute cation is observed, the deactivation of the nucleophile through stabilisation by the smaller solute cation is of greater significance. Overall, the 1:1 mixture produces results more similar to those of the reaction using only the tightly bound tetraethylammonium chloride salt.

As can be seen in Figure 39, plotting the activation energies $\Delta G^\neq$, $\Delta H^\neq$ and $T\Delta S^\neq$ against molecular weight of the cation (in the case of the 1:1 mixture taking an average) reveals a general trend of decreasing $\Delta H^\neq$ and $T\Delta S^\neq$ with increasing molecular weight with $\Delta G^\neq$ also decreasing but at a much slower rate.

These results are consistent with decreasing stabilisation of the reactants and increasing stabilisation of the activated complex as the cation size increases. The decrease in activation
enthalpy that is observed can be attributed to both a reduction in reactant stability and also a reduction in anion exchange energy. This idea was proposed earlier in this chapter in the discussion of the “naked anion” effect. The large cations are far less associated with small halide ions such as chlorides than the smaller cations studied and this discounted ion association serves to increase the reactivity of the anion by making it more available to react thereby reducing the enthalpy of activation. Where solute cations are similar in size and charge to those of the ionic liquid, there will be less disruption to the ionic liquid Coulombic interactions than when small high charge density cations or large charge diffuse cations are introduced.

Since the activated complex is large and charge separated it is less capable of favourable interactions with ionic liquid ions than the reactant ions. This disrupts the interionic interactions and the local structure of the ionic liquid breaks down. This leads to an increase in entropy and a less negative $\Delta S^\neq$.

**Conclusions**

We have previously demonstrated that ionic liquids can be termed “super-dissociating” solvents for solute salts. This work has aimed to probe the “ionic liquid effect” where ionic liquids ions provide a high level of charge screening so that the solute ion Coulombic attractions are met by any oppositely charged ions that happen to be in the vicinity and not necessarily those of the solute. In an effort to encourage the solute ions to seek each other specifically in ionic liquids solvents, we have dissolved tightly bound, short chain quaternary ammonium salts where the cation and anion are more similar in size to each other than the solvent ion. We have then increased the size and changed the shape of the quaternary ammonium salts to determine whether a cation effect exists. Through kinetic studies of the $S_N2$ substitution reaction of dimethyl-4-nitrophenylsulfonium and quaternary ammonium chloride salts we have sought to find evidence of ion pairing but have observed only the reaction of freely solvated ions rather than the ion pair mechanism seen in molecular solvents.

We have observed a distinct solute cation effect on the rate of bimolecular displacement reaction. A clear rate increase is observed when longer chain ($R \geq 6$) quaternary ammonium chlorides are studied and a distinct rate decrease for the smallest cation studied, tetraethylammonium. This is surely not a preferential ion pairing effect, as displayed by the fact that large, non-interacting cations yield faster kinetics. If it were an ion pairing effect, we
would observe the opposite result. The fundamental inconsistency in these results is that the less ion pairing potential exists, the more prominent the cation effect which leads to the conclusion that the observed results do not arise from ion pairing effects.

It is possible that the observed rate changes can be attributed to the contributions of chloride ions whose reactivities differ from the bulk through differential coordination. Chloride ions may be coordinated by solute cation and solvent cations, thereby increasing or reducing the number of cations in the coordination sphere relative to those chlorides solvated by solvent cations only. Further work is required to determine the extent of these contributions to the overall rate constant.

The Eyring activation parameters for each reaction were also obtained and revealed changing enthalpy and entropy contributions to the overall Gibbs energy of activation as the size of the solute cation increased. We were able to switch the reaction from being enthalpy dominated to entropy dominated on variation from tetraethylammonium to tetraoctylammonium. The rate increase and change in energetics has been ascribed to reactant destabilisation and activated complex stabilisation by large, charge diffuse cations with the reverse being true for small, charge dense cations. It has been proposed also that the reactivity of the nucleophile is increased when paired with larger cations by way of the “naked anion” effect reducing the ion exchange energy required to deliver the nucleophile to the electrophile. On the other hand, smaller cations have a greater affinity for the small anion and inhibit its relative availability for reaction and reactivity.

Finally, let us be clear that the results described herein pertain to a solute specific effect in ionic liquid solvents. Via investigation of the reaction of anionic nucleophiles and cationic centres we have observed no evidence of conventional ion pairing, but perhaps we have witnessed a form of preferential solvation. Upon dissolving salts into liquid salts it could be argued that all ions not participating in a reaction have the ability to act as the solvent and the reaction polarity requirements dictate which ions solvate the reactants and activated complex. It is well known that ionic liquids have the ability to solubilise a wide range of organic reactions and this could be due to an ability to adapt local polarity via preferential interaction with either the ionic liquid’s polar or non-polar domains.

As discussed in Chapter 1: “preferential solvation” is used to define the observation that the solvation shell has a composition of solvent molecules which is different in ratio to that of the bulk solvent. Preferential solvation occurs if the solute is able to make the Gibbs energy of
solvation more negative by neighbouring itself with a component of the solvent in particular and this work has recorded a reduction in the Gibbs energy on the introduction of large quaternary ammonium salts.

Ion pairing, as it is currently understood, may not apply in the ionic liquid environment. Dissolving ions into a sea of ions, where preservation of charge neutrality is provided by the ionic liquid, may be akin to dissolving non-polar molecules into non-polar solvents. Ions and polar molecules will ion pair and aggregate in low polarity solvents the same way that low polarity molecules aggregate in ionic liquids and it is in these circumstances that we find preferential solvation effects. Large, relatively low polarity ions introduced into ionic liquids have been seen to preferentially interact with the large, low polarity activated complex formed on the combination of two reacting ions.

**Experimental section**

*The reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\)[NTf\(_2\)] with alkali metal chlorides in [C\(_4\)C\(_1\)im][NTf\(_2\)]*

The reactions of LiCl, KCl, NaCl and CsCl with dimethyl-4-nitrophenylsulfonium bis(trifluoromethanesulfonyl)imide were studied in [C\(_4\)C\(_1\)im][NTf\(_2\)]. In each case, the alkali metal chloride was stirred in the ionic liquid for two weeks after which the solid white salts had not dissolved. Both the potassium and caesium chloride salt mixtures were filtered before using in a test reaction with the sulfonium electrophile. UV-vis spectroscopy revealed no loss in concentration of the electrophile or appearance of the demethylated product and it was therefore determined that no chloride had exchanged into the ionic liquid.

*The reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\)[NTf\(_2\)] with tetraethylammonium chloride in [C\(_4\)C\(_1\)im][NTf\(_2\)]*

The reaction of tetraethylammonium chloride with dimethyl-4-nitrophenylsulfonium bis(trifluoromethanesulfonyl)imide was studied in [C\(_4\)C\(_1\)im][NTf\(_2\)] at 25 °C. The results are shown below in Table 33.
Table 33 - The Reactions with tetraethylammonium chloride in [C₄C₁im][NTf₂]

<table>
<thead>
<tr>
<th>[Cl⁻] / M</th>
<th>[sulfonium] / mM</th>
<th>( k_{\text{obs}} / \text{s}^{-1} ) (mean value)</th>
<th>( k_2 / \text{M}^{-1} \text{s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0818</td>
<td>0.368</td>
<td>0.000593</td>
<td></td>
</tr>
<tr>
<td>0.1309</td>
<td>0.368</td>
<td>0.000602</td>
<td></td>
</tr>
<tr>
<td>0.0491</td>
<td>0.368</td>
<td>0.000584</td>
<td>0.0002 ± 0.00002</td>
</tr>
<tr>
<td>0.0164</td>
<td>0.368</td>
<td>0.000576</td>
<td></td>
</tr>
<tr>
<td>0.1636</td>
<td>0.368</td>
<td>0.000611</td>
<td></td>
</tr>
<tr>
<td>0.0655</td>
<td>0.368</td>
<td>0.000592</td>
<td></td>
</tr>
</tbody>
</table>

The values of \( k_2 \) were determined by plotting \( k_{\text{obs}} \) against the initial chloride concentration as shown below in Figure 40.

Tetraethylammonium chloride at 25°C

\[
y = 0.0002x + 0.0006
\]
\[
R^2 = 0.9806
\]

Figure 40 - The extrapolation of \( k_2 \) for the reactions in [C₄C₁im][NTf₂]

The reaction of \( [p -NO_2PhS(CH_3)_2][NTf_2] \) with tetrahexylammonium chloride in

\[ [C_4C_1im][NTf_2] \]

The reaction of tetrahexylammonium chloride with dimethyl-4-nitrophenylsulphonium bis(trifluoromethanesulphonyl)imide was studied in [C₄C₁im][NTf₂] at 25 °C. The results are shown below in Table 34.
Table 34 - The reactions with tetrachexylammonium chloride in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\)

<table>
<thead>
<tr>
<th>[Cl(^-)] / M</th>
<th>[sulfonium] / mM</th>
<th>(k_{\text{obs}} / \text{s}^{-1}) (mean value)</th>
<th>(k_2 / \text{M}^{-1} \text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0545</td>
<td>0.121</td>
<td>0.000617</td>
<td></td>
</tr>
<tr>
<td>0.0109</td>
<td>0.121</td>
<td>0.000576</td>
<td></td>
</tr>
<tr>
<td>0.0436</td>
<td>0.121</td>
<td>0.000611</td>
<td>0.001 ± 0.00011</td>
</tr>
<tr>
<td>0.0164</td>
<td>0.121</td>
<td>0.000585</td>
<td></td>
</tr>
<tr>
<td>0.0055</td>
<td>0.121</td>
<td>0.00057</td>
<td></td>
</tr>
<tr>
<td>0.0273</td>
<td>0.121</td>
<td>0.000592</td>
<td></td>
</tr>
</tbody>
</table>

The values of \(k_2\) were determined by plotting \(k_{\text{obs}}\) against the initial chloride concentration as shown below in Figure 41.

The reaction of \([p -\text{NO}_2\text{PhS(CH}_3)_2)]\text{NTf}_2\] with tetraoctylammonium chloride in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\] was studied at 25 °C. The results are shown below in Table 35.

The reaction of tetraoctylammonium chloride with dimethyl-4-nitrophenylsulfonium \(\text{bis(trifluoromethanesulfonyl)}\)imide was studied in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\] at 25 °C. The results are shown below in Table 35.
The values of \( k_2 \) were determined by plotting \( k_{\text{obs}} \) against the initial chloride concentration as shown below in Figure 42.

![Graph showing the extrapolation of \( k_2 \) for the reactions in \([C_4C_1im][NTf_2]\)](image)

\[ y = 0.0609x + 0.0005 \]
\[ R^2 = 0.9552 \]

**Tetraoctylammonium chloride 25°**

The reaction of \([p -NO_2PhS(CH_3)_2][NTf_2]\) with 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride in \([C_4C_1im][NTf_2]\) was studied in \([C_4C_1im][NTf_2]\) at 25 °C. The results are shown below in Table 36.

<table>
<thead>
<tr>
<th>[Cl(-)] / M</th>
<th>[sulfonium] / mM</th>
<th>( k_{\text{obs}} / \text{s}^{-1}) (mean value)</th>
<th>( k_2 / \text{M}^{-1} \text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0067</td>
<td>0.169</td>
<td>0.000954</td>
<td></td>
</tr>
<tr>
<td>0.0133</td>
<td>0.169</td>
<td>0.001137</td>
<td></td>
</tr>
<tr>
<td>0.0267</td>
<td>0.169</td>
<td>0.001864</td>
<td>0.0609 ± 0.0003</td>
</tr>
<tr>
<td>0.0333</td>
<td>0.169</td>
<td>0.002596</td>
<td></td>
</tr>
<tr>
<td>0.0166</td>
<td>0.169</td>
<td>0.001555</td>
<td></td>
</tr>
<tr>
<td>0.0300</td>
<td>0.169</td>
<td>0.002347</td>
<td></td>
</tr>
</tbody>
</table>

151
Table 36 - The reactions with 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride in [C₄C₁im][NTf₂]

<table>
<thead>
<tr>
<th>[Cl⁻] / M</th>
<th>[sulfonium] / mM</th>
<th>k_{obs} / s⁻¹</th>
<th>k₂ / M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0067</td>
<td>0.169</td>
<td>0.00058</td>
<td></td>
</tr>
<tr>
<td>0.0200</td>
<td>0.169</td>
<td>0.000612</td>
<td></td>
</tr>
<tr>
<td>0.0267</td>
<td>0.169</td>
<td>0.00063</td>
<td>0.0023 ± 0.001</td>
</tr>
<tr>
<td>0.0333</td>
<td>0.169</td>
<td>0.000644</td>
<td></td>
</tr>
<tr>
<td>0.0133</td>
<td>0.169</td>
<td>0.000601</td>
<td></td>
</tr>
</tbody>
</table>

The values of k₂ were determined by plotting k_{obs} against the initial chloride concentration as shown below in Figure 43.

1:1 tetraethylammonium and tetraoctylammonium chlorides 25°C

Figure 43 - The extrapolation of k₂ for the reactions in [C₄C₁im][NTf₂]

The reaction of [p -NO₂PhS(CH₃)₂][NTf₂] with trioctylmethylammonium chloride in [C₄C₁im][NTf₂]

The reaction of trioctylmethylammonium chloride with dimethyl-4-nitrophenylsulfonium bis(trifluoromethanesulfonil)imide was studied in [C₄C₁im][NTf₂] at 25 °C. The results are shown below in Table 37.
Table 37 - The reactions with trioctylmethylammonium chloride in \([C_4C_1im][NTf_2]\)

<table>
<thead>
<tr>
<th>[Cl] / M</th>
<th>[sulfonium] / mM</th>
<th>(k_{obs} , / , s^{-1}) (mean value)</th>
<th>(k_2 / , M^{1} , s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0067</td>
<td>0.121</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>0.0167</td>
<td>0.121</td>
<td>0.000142</td>
<td></td>
</tr>
<tr>
<td>0.0267</td>
<td>0.121</td>
<td>0.000187</td>
<td>0.0048 ± 0.0007</td>
</tr>
<tr>
<td>0.0333</td>
<td>0.121</td>
<td>0.000229</td>
<td></td>
</tr>
<tr>
<td>0.0200</td>
<td>0.121</td>
<td>0.000152</td>
<td></td>
</tr>
</tbody>
</table>

The values of \(k_2\) were determined by plotting \(k_{obs}\) against the initial chloride concentration as shown below in Figure 44.

**Trioclymethylammonium chloride 25°C**

![Graph showing the extrapolation of \(k_2\) for the reactions in \([C_4C_1im][NTf_2]\)](image)

The Eyring plot for the reaction of \([p\,-NO_2PhS(CH_3)_2][NTf_2]\) with tetraethylammonium chloride in \([C_4C_1im][NTf_2]\)

**The Eyring plot for the reaction of \([p\,-NO_2PhS(CH_3)_2][NTf_2]\) with tetraethylammonium chloride in \([C_4C_1im][NTf_2]\)**

The Eyring activation energies for the reaction of \([p\,-NO_2PhS(CH_3)_2][NTf_2]\) with tetraethylammonium chloride in \([C_4C_1im][NTf_2]\) listed in Table 32 were calculated from the Eyring plot in Figure 46 having studied the reaction in \([C_4C_1im][NTf_2]\) at 25, 35, 50, 60 and 80 °C.
Table 38 - The reactions with tetrachloroammonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>$k_2$ / M$^{-1}$ s$^{-1}$</th>
<th>1/T</th>
<th>ln $k_2$/T (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298.15</td>
<td>0.0002</td>
<td>0.003354016</td>
<td>-14.2148</td>
</tr>
<tr>
<td>323.15</td>
<td>0.0008</td>
<td>0.003094538</td>
<td>-12.909</td>
</tr>
<tr>
<td>353.15</td>
<td>0.0079</td>
<td>0.002831658</td>
<td>-10.7078</td>
</tr>
<tr>
<td>333.15</td>
<td>0.0034</td>
<td>0.003001651</td>
<td>-11.4926</td>
</tr>
<tr>
<td>308.15</td>
<td>0.0003</td>
<td>0.003245173</td>
<td>-13.8423</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting ln$k_2$/T against against 1/T as shown below in Figure 45.

![Eyring plot](image-url)

Figure 45 - The Eyring plot for the reactions in [C$_4$C$_1$][NTf$_2$]

Table 39 - Extraction of the activation energies

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>$\Delta H^\ne$ / J mol$^{-1}$</th>
<th>$\Delta S^\ne$ / J K$^{-1}$ mol$^{-1}$</th>
<th>$T\Delta S^\ne$ / J mol$^{-1}$</th>
<th>$\Delta G^\ne_{298}$ / J mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7206.3</td>
<td>9.75</td>
<td>59913.18</td>
<td>-116.52</td>
<td>-34739.2</td>
<td>94634.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\kappa$</th>
<th>$k_B$</th>
<th>$h$</th>
<th>$k_B\kappa/h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>
The Eyring plot for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\)[\(\text{NTf}_2\)] with tetrahexylammonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The Eyring activation energies for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\)[\(\text{NTf}_2\)] with tetrahexylammonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) listed in Table 32 were calculated from the Eyring plot in Figure 46 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25, 45, 65 and 80 °C.

Table 40 - The reactions with tetrahexylammonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2 / \text{M}^{-1} \text{s}^{-1})</th>
<th>(1/T)</th>
<th>(\ln k_2/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean value)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>298</td>
<td>0.0007</td>
<td>0.003354</td>
<td>-12.962</td>
</tr>
<tr>
<td>318</td>
<td>0.0035</td>
<td>0.003143</td>
<td>-11.4175</td>
</tr>
<tr>
<td>353</td>
<td>0.0223</td>
<td>0.002832</td>
<td>-9.67006</td>
</tr>
<tr>
<td>338</td>
<td>0.0075</td>
<td>0.002957</td>
<td>-10.7163</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting \(\ln k_2/T\) against \(1/T\) as shown below in Figure 46.

Figure 46 - The Eyring plot for the reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)
Table 41- Extraction of the activation energies

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>ΔH(^\circ)</th>
<th>ΔS(^\circ)</th>
<th>TΔS(^\circ)</th>
<th>ΔG(^\circ)(_{298})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>/ J mol(^{-1})</td>
<td>/ J K(^{-1}) mol(^{-1})</td>
<td>/ J mol(^{-1})</td>
<td>/ J mol(^{-1})</td>
</tr>
<tr>
<td>-6015.6</td>
<td>7.2857</td>
<td>50013.7</td>
<td>-136.96</td>
<td>-40815.1</td>
<td>90828.76</td>
</tr>
</tbody>
</table>

κ \(k_B\) \(h\) \(k_Bk/h\)

1 \(1.38E-16\) \(6.63E-27\) \(2.08E+10\)

The Eyring plot for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) with 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride in \([\text{C}_4\text{C}_1\text{im}]\,[\text{NTf}_2]\)

The Eyring activation energies for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) with 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride in \([\text{C}_4\text{C}_1\text{im}]\,[\text{NTf}_2]\) listed in Table 32 were calculated from the Eyring plot in Figure 47 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}]\,[\text{NTf}_2]\) at 25, 40, 50, 65 and 70 °C.

Table 42 - The reactions with 1:1 mixture of tetraethylammonium chloride and tetraoctylammonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2) / M(^{-1}) s(^{-1})</th>
<th>1/T</th>
<th>ln (k_2/T) (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.0028</td>
<td>0.003356</td>
<td>-11.5752</td>
</tr>
<tr>
<td>313</td>
<td>0.005</td>
<td>0.003195</td>
<td>-11.0445</td>
</tr>
<tr>
<td>323</td>
<td>0.0098</td>
<td>0.003096</td>
<td>-10.403</td>
</tr>
<tr>
<td>338</td>
<td>0.037</td>
<td>0.002959</td>
<td>-9.11988</td>
</tr>
<tr>
<td>343</td>
<td>0.07</td>
<td>0.002915</td>
<td>-8.49699</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting ln\(k_2/T\) against 1/T as shown below in Figure 47.
The Eyring plot for the reaction of $[p$-NO$_2$PhS(CH$_3$)$_2$][NTf$_2$] tetraoctylammonium chloride in [C$_4$C$_1$im][NTf$_2$]

The Eyring activation energies for the reaction of $[p$-NO$_2$PhS(CH$_3$)$_2$][NTf$_2$] with tetraoctylammonium chloride in [C$_4$C$_1$im][NTf$_2$] listed in Table 32 were calculated from the Eyring plot in Figure 48 having studied the reaction in [C$_4$C$_1$im][NTf$_2$] at 25, 50, 80, and 85 °C.
Table 44 - The reactions with tetraoctylammonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>( k_2 / \text{M}^{-1} \text{s}^{-1} )</th>
<th>1/T</th>
<th>ln ( k_2/T ) (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.0587</td>
<td>0.003355705</td>
<td>-8.53241</td>
</tr>
<tr>
<td>323</td>
<td>0.14</td>
<td>0.003095975</td>
<td>-7.74377</td>
</tr>
<tr>
<td>353</td>
<td>0.6001</td>
<td>0.002832861</td>
<td>-6.37713</td>
</tr>
<tr>
<td>358</td>
<td>0.68999</td>
<td>0.002793296</td>
<td>-6.25161</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting ln\( k_2/T \) against \( 1/T \) as shown below in Figure 48.

![Figure 48 - The Eyring plot for the reactions in [C_4C_1im][NTf_2]](image)

Table 45 - Extraction of the activation energies.

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>( \Delta H^\circ )</th>
<th>( \Delta S^\circ )</th>
<th>TAS^\circ</th>
<th>( \Delta G^\circ_{298} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4186.6</td>
<td>5.4134</td>
<td>34807.3924</td>
<td>-152.53</td>
<td>45445.0</td>
<td>80261.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( \kappa )</th>
<th>( k_B )</th>
<th>( h )</th>
<th>( k_B \kappa /h )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>
The Eyring plot for the reaction of \([p\text{-}NO_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) triocetylmethylammonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The Eyring activation energies for the reaction of \([p\text{-}NO_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) with triocetylmethylammonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) listed in Table 32 were calculated from the Eyring plot in Figure 49 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25, 35, 50 and 70 °C.

Table 46 - The reactions with triocetylmethylammonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2 / \text{M}^{-1} \text{ s}^{-1}) (mean value)</th>
<th>1/T</th>
<th>(\ln k_2/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>308</td>
<td>0.0138</td>
<td>0.003247</td>
<td>-10.0132</td>
</tr>
<tr>
<td>343</td>
<td>0.1067</td>
<td>0.002915</td>
<td>-8.07546</td>
</tr>
<tr>
<td>323</td>
<td>0.0408</td>
<td>0.003096</td>
<td>-8.97673</td>
</tr>
<tr>
<td>298</td>
<td>0.0048</td>
<td>0.003356</td>
<td>-11.0362</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting \(\ln k_2/T\) against 1/T as shown below in Figure 49.

\[
y = -6642.1x + 11.42 \\
R^2 = 0.9816
\]

**Figure 49 - The Eyring plot for the reactions in [C\(_4\)C\(_1\)im][NTf\(_2\)]**
<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>$\Delta H^\ne$</th>
<th>$\Delta S^\ne$</th>
<th>$T\Delta S^\ne$</th>
<th>$\Delta G^\ne_{298}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6642.1</td>
<td>11.42</td>
<td>55222.42</td>
<td>-102.59</td>
<td>-30587.4</td>
<td>85794.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\kappa$</th>
<th>$k_B$</th>
<th>$h$</th>
<th>$k_B\kappa/h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>
Chapter 5: Specific interaction effect - Reactions with hydrogen bond donating cations

Objectives

- Determine the rate constant, $k_2$, of the $S_N^2$ reaction of the $\text{bis}(\text{trifluoromethanesulfonyl})$imide salt of dimethyl-4-nitrophenylsulfonium ($[p$-$\text{NO}_2\text{PhS(CH}_3_2)]\text{[N(CF}_3\text{SO}_2)_2]$) by chloride salts with hydrogen bond donating abilities in $[\text{C}_4\text{C}_1\text{im}]\text{[NTf}_2]$ under pseudo-first order conditions
- Determine the activation free energy ($\Delta G^\neq$), enthalpy ($\Delta H^\neq$) and entropy ($\Delta S^\neq$) for each reaction
- Infer mechanistic details and solvent behaviour for each reaction through contrast and comparison of results

Outcomes

- Cations with very strong hydrogen bond donating abilities did not react at all
- For hydrogen bond donating salts where the reaction proceeded, pseudo-first order kinetics were observed in $[\text{C}_4\text{C}_1\text{im}]\text{[NTf}_2]$ and $k_2$s determined
- Hydrogen bond donating cations were not seen to affect reaction mechanism but reaction rates were found to decrease with a decrease in total molecular weight of the chloride salt
- Activation energies calculated for each reaction (no discernible trend)

Key Figure

<table>
<thead>
<tr>
<th>Cation</th>
<th>Mw</th>
<th>$\Delta H$</th>
<th>$\Delta S$</th>
<th>$\Delta G$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJ/mol</td>
<td>kJ/mol</td>
<td>kJ/mol</td>
<td></td>
</tr>
<tr>
<td>Choline</td>
<td>139</td>
<td>59</td>
<td>-34</td>
<td>93</td>
</tr>
<tr>
<td>$\text{C}_2\text{C}_1\text{imOH}$</td>
<td>162</td>
<td>74</td>
<td>-1.3</td>
<td>87</td>
</tr>
</tbody>
</table>
Introduction
Studies on solvent effects are generally carried out by means of relationships between reactivity properties that are reaction rate or several types of selectivity and empirical parameters representing different kinds of solute solvent interactions. As we have seen in Chapter 1, specific intermolecular interactions such as hydrogen bonds have the capacity to greatly increase or reduce the activity of a nucleophile. Specific interactions also comprise one of the limitations of the Hughes-Ingold principles and therefore must be examined separately to determine whether or not these interactions contribute significantly to the reaction rate or mechanism. In terms of creating a situation whereby preferential ion pairing could be induced between solute ions in ionic liquids, introducing cations with the ability to form hydrogen bonds seems a reasonable progression given that charge dense cations capable of strong Coulombic interactions had given no definitive answer.

Results and discussion
The process under examination was the $S_N2$ reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulphonium $[\rho$-NO$_2$PhS(CH$_3$)$_2$][N(CF$_3$SO$_2$)$_2$] with chloride ion, as shown in Reaction Scheme 37.

![Reaction Scheme 37 - The S$_N2$ reaction](image)

The chloride salts studied in this section were those capable of forming hydrogen bonds between solute ions. Successful reactions occurred between the sulfonium electrophile and both choline chloride and ionic liquid precursor $[C_1C_2OIm]$ Cl.

![Figure 50 - Hydrogen bond donating cations investigated](image)

In attempt to increase the strength of the hydrogen bonds, triethanolammonium chloride and diethanolammonium chloride were also investigated. In both cases no reaction took place, possibly due to the fact that these salts can exist as hydrochloride salts and whereby the hydrogen from the central atom and the chloride ion form an HCl adduct. Adduct formation
would significantly reduce the reactivity of the nucleophile. Additionally there is the possibility that extremely strong hydrogen bonds between the cation and anion form an unreactive ion pair. However, due to the fact that no reaction takes place, we were unable to measure the extent of deactivation relative to the other reactants regardless of whether the species formed is an ion pair or an HCl adduct. From this study all we can say with certainty is that the chloride ion nucleophilicity is reduced to zero when di- and tri-ethanolammonium cations are present.

![Image](image_url)

**Figure 51 - Triethanolammonium and diethanolammonium cations**

The reactions were assayed using UV spectroscopy, with each substrate having $\lambda_{\text{max}}$ at 252 nm and the demethylated products having a $\lambda_{\text{max}}$ at 342 nm. The imidazolium-based ionic liquid which was used as the solvent has a cut-off at 240 nm and therefore caused no problems in interpreting the UV spectroscopy results. The sulfonium salt was synthesised as described in the experimental section in Chapter 8 directly before use and kept under anaerobic conditions.

The nucleophilic displacement by the chloride ion was studied in one ionic liquid of very high purity. The ionic liquid was $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ due to its relatively low viscosity, 44 cP, and its well-known synthetic and purification procedures.

The electrophile was found to be stable in all solvents as no change in UV/vis absorbance was detected in the absence of the nucleophile after 24 hours.

This reaction is bimolecular and the rate therefore depends upon the concentrations of both the nucleophile and the electrophile. It is common in this type of process to create pseudo-first order kinetic behaviour by using a large excess of one reagent which shows a linear dependence of $k_{\text{obs}}$ upon nucleophile concentration.

The expected linear relationship was observed when the reaction was carried out when choline chloride and $[\text{C}_2\text{C}_1\text{imOH}]$ chloride were used as the source of the nucleophile in the ionic liquid solvent. In the case of di and tri ethanolammonium chloride nucleophiles, no reaction was seen to take place.
Table 48 - Kinetic results for various hydrogen bonding chloride salts

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>T / °C</th>
<th>k&lt;sub&gt;2&lt;/sub&gt; / M&lt;sup&gt;-1&lt;/sup&gt; s&lt;sup&gt;-1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Me&lt;sub&gt;3&lt;/sub&gt;EtOHN]Cl</td>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im][NTf&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>25</td>
<td>0.0004 ± 0.0001</td>
</tr>
<tr>
<td>[C&lt;sub&gt;1&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;OHim]Cl</td>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im][NTf&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>25</td>
<td>0.0054 ± 0.0015</td>
</tr>
<tr>
<td>[di-EtOHOHMeNH]Cl</td>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im][NTf&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>[tri-EtOHNH]Cl</td>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im][NTf&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im]Cl</td>
<td>[C&lt;sub&gt;4&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;im][NTf&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>25</td>
<td>0.0012 ± 0.0007</td>
</tr>
</tbody>
</table>

The slowest rate observed (0.0004 M<sup>-1</sup> s<sup>-1</sup>) is for the reaction involving choline chloride. Interestingly this rate constant is, within error, very similar to that recorded for the reaction using tetraethylammonium chloride (0.0002 M<sup>-1</sup> s<sup>-1</sup>) where there would be no hydrogen bonding effects on the chloride. This could be seen as an indication that hydrogen bonding with cation does not, in this case, affect the reactivity of the nucleophile or rather that the electrostatic interaction with the short chain tetraalkylammonium cations is the dominant factor driving ion association. The rate observed for the reaction involving 1-methyl-3-ethanolimidazolium chloride (0.0054 M<sup>-1</sup> s<sup>-1</sup>) is approximately ten times faster than that of choline chloride suggesting that there is some deactivation of the chloride by the choline cation, perhaps through stronger ion association, compared with the hydroxyl-functionalised imidazolium cation. Interestingly, the reaction involving 1-methyl-3-ethanolimidazolium chloride is also marginally faster than the base case reaction for [C<sub>4</sub>C<sub>1</sub>im]Cl. Given the fact that the reaction kinetics remained linear for the reactions involving choline chloride and 1-methyl-3-ethanolimidazolium chloride suggests that in both cases the reaction proceeds through free ions and that the extent of any solute ion association is not significant enough to change the reaction mechanism.

Recalling Figure 32 from Chapter 4, we can see that despite the hydrogen bond donating functionality, the results for choline and 1-methyl-3-ethanolimidazolium cations sit fairly well amongst results for the tetraalkylammonium cations when we compare reaction rate with cation molecular weight. Choline and 1-methyl-3-ethanolimidazolium results are shown in black on Figure 52.
We can conclude therefore, that even when cations possess a hydrogen bonding functionality it is the size of the cation and therefore the number of cations in the coordination sphere of the chloride ion which determine the overall reaction rate. See Reaction Scheme 35, Chapter 4.

On the other hand, both di- and tri-ethanolammonium chloride were found not to have reacted with the electrophile after two days in solution. It has been proposed that this is due to complete deactivation of the nucleophile, either through formation of a strongly hydrogen bonded ion pair or through formation of the HCl adduct which could be seen as an extreme example of hydrogen bonding! It seems unlikely however that every single chloride ion in solution would abstract the hydrogen from every single choline cation. For no reaction to have taken place there must be some additional interaction causing the chloride ions to lose any semblance of nucleophilicity. Given that the reaction does not proceed in the hydrogen bond donating solvents water and methanol, it seems reasonable to suggest that where hydrogen bonding potential is significant, the chloride nucleophilicity is reduced to the point that no reaction takes place.

The di- and tri-ethanolammonium cations each possess multiple hydrogen bond donating functional groups which may cause ion pairing to the extent that all chloride ions are held close to the solute cations and therefore more likely to form a very strongly hydrogen bonded ion pair which does not react. Additionally, the proximity of the chloride to the triethanolammonium cation would increase the likelihood of HCl adduct formation. We
propose that some equilibrium between the adduct form and ionic form exists in the ionic liquid where both forms totally deactivate the nucleophile. Whilst not clear from this study, it would seem reasonable to suggest that the ionic side of the equilibrium would be favoured in an ionic liquid solvent.

![Reaction Scheme](image)

**Reaction Scheme 38 - HCl adduct and dissociated ionic forms of triethanolammonium chloride**

The kinetic results for the hydrogen bond donating cations also seem to adhere to the theory posed in chapter four regarding coordination number of the chloride ion. Choline is the smallest and hardest cation tested and is approximately the same size as tetraethylammonium. These cations produced the slowest rate constants measured and it is conceivable that these cations are able to increase the coordination number of the chloride solvation sphere.

It is clear that a cation effect exists for these reactions in light of the much higher rate constant observed for the largest cation studied: 1-methyl-3-ethanolimidazolium chloride, despite the hydrogen bonding properties of these cations seeming to have no special effect.

**Eyring Activation Parameters**

As we have seen from the kinetic analysis of this reaction, there appears at first glance to be little to no effect upon addition of a hydrogen bonding functionality to the solute cation. To gain greater insight into the reaction process and to enable comparison with previous studies, the activation energies were determined using the Eyring equation. As described elsewhere in this work, examination of the reaction rate solvent effects into initial and transition state contributions leads to more direct information about the likely local solvent environment for each species.

**Results and discussion**

The thermodynamic parameters $\Delta H^\ddagger$ (activation enthalpy) and $\Delta S^\ddagger$ (activation entropy) can be calculated with kinetic data using the Eyring equation by plotting $1/T$ against $\ln k_2$ as described in Chapter 3. Figure 53 depicts the Eyring plot for the reaction of dimethyl-4-
nitrophenylsulfonium \( \text{bis(trifluoromethylsulfonyl)imide} \) with choline chloride in the ionic liquid \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at \( T = 25, 40, 60, \) and \( 80^\circ \text{C} \). The Eyring plots for the reactions listed in Table 49 can be found in the experimental section at the end of this chapter.

![Eyring plot for the reaction with choline chloride](image)

\( y = -7075.6x + 9.8707 \)
\( R^2 = 0.9298 \)

A summary of the activation energies recorded for each of the reactions between the hydrogen bonding functionalized chloride salts and of dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide can be found in Table 49.

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>( \Delta H^\neq ) / kJ mol(^{-1})</th>
<th>( T\Delta S^\neq ) / kJ mol(^{-1})</th>
<th>( \Delta G_{298}^\neq ) / kJ mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline Cl</td>
<td>([\text{C}_1\text{C}_4\text{im}][\text{NTf}_2])</td>
<td>59</td>
<td>-34</td>
<td>93</td>
</tr>
<tr>
<td>([\text{C}_2\text{C}_1\text{imOH}][\text{Cl}])</td>
<td>([\text{C}_1\text{C}_4\text{im}][\text{NTf}_2])</td>
<td>77</td>
<td>-1.2</td>
<td>81</td>
</tr>
<tr>
<td>([\text{C}_4\text{C}_1\text{im}][\text{Cl}])</td>
<td>([\text{C}_1\text{C}_4\text{im}][\text{NTf}_2])</td>
<td>71.8</td>
<td>-42.4</td>
<td>84.4</td>
</tr>
</tbody>
</table>

Associative substitutions generally have large negative entropies of activation. In both cases listed in Table 49, whilst still negative, we observe less negative entropies of activation that we might expect. The \( T\Delta S^\neq \) for the reaction involving the ionic liquid precursor \([\text{C}_2\text{C}_1\text{imOH}][\text{Cl}]\) is particularly low, and at \(-1.2 \) kJ mol\(^{-1}\), was the lowest recorded in this entire study. Losses in entropy for associative processes can be compensated for to a greater or lesser extent by reorganisation of the solvent around the reacting species. From Table 49 we could suggest that activation entropy becomes less negative as the solute cation becomes...
more similar to the ionic liquid cation and therefore more attractive to the ionic liquid anion. This suggests that the loss in entropy on the electrophile and nucleophile coming together is being partly compensated by a simultaneous disruption of the bulk ionic liquid structure. The ionic liquid structure is disturbed as ionic starting materials come together to form a charge-separated activated complex.

The enthalpic barrier to reaction is in both cases fairly large, as would be expected for a reaction which involves charged reactants forming a charge separated activated complex. What we also observe is a fairly dramatic increase of 18 kJ mol\(^{-1}\) in \(\Delta H^\neq\) going from choline chloride to \([C_2C_1imOH]Cl\) combined with a substantial decrease in \(T\Delta S^\neq\). These results could suggest that the solute cations are indeed hydrogen bonding to the nucleophile as intended but that the reason we see no change in reaction mechanism is because the reaction still takes place via free ions. Instead of reacting as an ion paired species, the hydrogen bond between the solute cation and the chloride must be broken in order for the chloride to act as a nucleophile. This would provide a dissociative contribution to the process and so increasing the enthalpy of activation and decreasing the entropy of activation as we observe.

![Figure 54 - A schematic representation of the solvent release on ion association](image)

Figure 54 depicts (a) a solvent separated ion pair with each ion retaining its solvent shell of translationally immobilised solvent. (b) a solvent shared ion pair which has lost some of the solvent. (c) a contact ion pair which has lost all solvent molecules from between the ions.

**Conclusions**

It is clear in light of the kinetic analysis and thermodynamic treatment that a cation effect exists for these reactions. The rate constant observed for the largest cation studied, 1-methyl-3-ethanolimidazolium chloride, is much higher compared with choline. Indeed it was shown that when comparing the reactions rates with the cation size, the both choline and 1-methyl-3-ethanolimidazolium salts fit with the trend observed for the tetraalkylammonium salts –
smaller cations produce slower reaction rates. However, the hydrogen bonding properties of each cation seem to have no discernible effect. It could be considered unsurprising that we do not see a hydrogen bonding effect given that hydrogen bond donors deactivate the nucleophile. Kinetics perceives the fastest reaction of the slowest step, so even if there are strong hydrogen bonds, their effects on the reaction kinetics will not be observed given that the bulk of the chloride ions are coordinated by ionic liquid cations only. If the attachments were long-lived and gave rise to ion pairing, a change in reaction kinetics would be expected and this is not observed.

**Experimental Section**

*The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2]\) with choline chloride in \([C_4C_1im][NTf_2]\)*

The reaction of choline chloride with dimethyl-4-nitrophenylsulphonium bis(trifluoromethylsulfonyl)imide was studied in \([C_4C_1im][NTf_2]\) at 25°C.

<table>
<thead>
<tr>
<th>([\text{S}^+]/\text{mM})</th>
<th>([\text{Cl}^-]/\text{species}/\text{M})</th>
<th>(k_{\text{obs}}/\text{s}^{-1})</th>
<th>(k_2/\text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.121</td>
<td>0.0108</td>
<td>0.000578</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0217</td>
<td>0.000582</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0270</td>
<td>0.000583</td>
<td>0.0004 ± 0.0001</td>
</tr>
<tr>
<td>0.121</td>
<td>0.0325</td>
<td>0.000587</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0379</td>
<td>0.000589</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0542</td>
<td>0.000597</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{\text{obs}}\) against the initial chloride concentration as shown in Figure 55.
The reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\)[\text{NTf}_2]\) with \([\text{C}_1\text{C}_2\text{OHim}]\text{Cl}\) in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([\text{C}_1\text{C}_2\text{OHim}]\text{Cl}\) with dimethyl-4-nitrophenylsulfonium \(\text{bis}(\text{trifluoromethylsulfonyl})\text{imide}\) was studied in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25°C.

Table 51 - The reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

<table>
<thead>
<tr>
<th>([S^+] / \text{mM})</th>
<th>([\text{Cl}^-] \text{ species / M})</th>
<th>(k_{\text{obs}} / \text{s}^{-1})</th>
<th>(k_2 / \text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.121</td>
<td>0.0217</td>
<td>0.000582</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0650</td>
<td>0.000869</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0867</td>
<td>0.000979</td>
<td>0.0054 ± 0.0015</td>
</tr>
<tr>
<td>0.121</td>
<td>0.1083</td>
<td>0.00104</td>
<td></td>
</tr>
<tr>
<td>0.121</td>
<td>0.0541</td>
<td>0.000798</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{\text{obs}}\) against the initial chloride concentration as shown in Figure 56.
Figure 56 - Extrapolation of $k_2$ for the reactions in $[C_4C_1im][NTf_2]$.

The Eyring plot for the reaction of $[p$-NO$_2$PhS(CH$_3$)$_2]$[NTf$_2$] with choline chloride in $[C_4C_1im][NTf_2]$.

The Eyring activation energies for the reaction of $[p$-NO$_2$PhS(CH$_3$)$_2]$[NTf$_2$] with choline chloride in $[C_4C_1im][NTf_2]$ listed in Table 49 were calculated from the Eyring plot in Figure 57 having studied the reaction in $[C_4C_1im][NTf_2]$ at 25, 40, 60 and 80 °C.

Table 52 - The reactions with choline chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>$k_2$ / M$^{-1}$ s$^{-1}$ (mean value)</th>
<th>1/T</th>
<th>ln $k_2$/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.0004</td>
<td>0.003354</td>
<td>-13.5211</td>
</tr>
<tr>
<td>313</td>
<td>0.0005</td>
<td>0.003193</td>
<td>-13.3471</td>
</tr>
<tr>
<td>333</td>
<td>0.0051</td>
<td>0.003002</td>
<td>-11.0867</td>
</tr>
<tr>
<td>353</td>
<td>0.0135</td>
<td>0.002833</td>
<td>-10.1715</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting ln$k_2$/T against 1/T as shown below in Figure 57.
The Eyring plot for the reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\)[NTf_2] with \([\text{C}_1\text{C}_2\text{OHim}]\text{Cl}\) in \([\text{C}_4\text{C}_1\text{im}]\)[NTf_2]

The Eyring activation energies for the reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\)[NTf_2] with \([\text{C}_1\text{C}_2\text{OHim}]\text{Cl}\) in \([\text{C}_4\text{C}_1\text{im}]\)[NTf_2] listed in Table 49 were calculated from the Eyring plot in Figure 58 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}]\)[NTf_2] at 25, 50, 65 and 85 °C.

Table 54 - The reactions with \([\text{C}_1\text{C}_2\text{OHim}]\text{Cl}\) at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2 / \text{M}^{-1} \text{s}^{-1})</th>
<th>1/T</th>
<th>(\ln k_2/T) (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.0054</td>
<td>0.003355705</td>
<td>-10.91844981</td>
</tr>
<tr>
<td>323</td>
<td>0.0323</td>
<td>0.003095975</td>
<td>-9.210340372</td>
</tr>
</tbody>
</table>
The Eyring activation parameters can be calculated by plotting $\ln k_2/T$ against $1/T$ as shown below in Figure 58.

![Graph showing the Eyring plot for the reactions in $[C_4C_1im][NTf_2]$](image)

Figure 58 - The Eyring plot for the reactions in $[C_4C_1im][NTf_2]$

**Table 55 - Extraction of the activation energies**

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>$\Delta H^#$</th>
<th>$\Delta S^#$</th>
<th>$T \Delta S^#$</th>
<th>$\Delta G^#_{298}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>/ J mol$^{-1}$</td>
<td>/ J K$^{-1}$ mol$^{-1}$</td>
<td>/ J mol$^{-1}$</td>
<td>/ J mol$^{-1}$</td>
</tr>
<tr>
<td>-8885</td>
<td>18.642</td>
<td>73869.89</td>
<td>-4.25</td>
<td>-1266.5</td>
<td>86548.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\kappa$</th>
<th>$k_B$</th>
<th>$h$</th>
<th>$k_Bk/h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>
Chapter 6: Cation Effect - Reactions with quaternary phosphonium chlorides

Objectives

- Determine the rate constant, \( k_2 \), of the \( S_N^2 \) reaction of the \( bis(\text{trifluoromethanesulfonyl})\text{imide salt of dimethyl-4-nitrophenylsulfonium ([} p- \text{NO}_2\text{PhS(CH}_3\text{)}_2][\text{N(CF}_3\text{SO}_2)_2]) \) by various quaternary phosphonium chloride salts in \([C_4C_{1\text{im}}][\text{NTf}_2] \) under pseudo-first order conditions
- Determine the activation free energy (\( \Delta G^{\ddagger} \)), enthalpy (\( \Delta H^{\ddagger} \)) and entropy (\( \Delta S^{\ddagger} \)) for each reaction
- Infer mechanistic details and solvent behaviour for each reaction through contrast and comparison of results

Outcomes

- Significantly faster reaction rates observed when using tetraalkylphosphonium salts
- Eyring activation parameters reveal significant shift in reaction energetics
- Tetraalkylphosphonium chloride reaction to be elucidated: electronegativity, structure breaking ability, thermal dependency

Key Figure

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>T / °C</th>
<th>( k_2 / \text{M}^{-1} \text{ s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>([P_{4444}]\text{Cl})</td>
<td>([C_1C_{4\text{im}}][\text{NTf}_2])</td>
<td>25</td>
<td>0.0236</td>
</tr>
<tr>
<td>([P_{2228}]\text{Cl})</td>
<td>([C_1C_{4\text{im}}][\text{NTf}_2])</td>
<td>25</td>
<td>0.1243</td>
</tr>
<tr>
<td>1:9 mix ([P_{4444}]\text{Cl}:[C_1C_{4\text{im}}]\text{Cl})</td>
<td>([C_1C_{4\text{im}}][\text{NTf}_2])</td>
<td>25</td>
<td>0.0303</td>
</tr>
<tr>
<td>([C_4C_{1\text{im}}]\text{Cl})</td>
<td>([C_4C_{1\text{im}}][\text{NTf}_2])</td>
<td>25</td>
<td>0.0012</td>
</tr>
</tbody>
</table>
Introduction

Having studied the nucleophilic substitution of \([p\text{-NO}_2\text{PhS(CH}_3\text{)}_2]\)[N(CF\(_3\)SO\(_2\))\(_2\)] with the chloride ion in ionic liquids using various ammonium based chloride salts, this project progressed to a preliminary investigation of phosphonium chlorides as the source of the nucleophile. As for ammonium salts, the traditional use for phosphonium salts is phase transfer catalysis. Despite the fact that they are usually more expensive than the corresponding ammonium salts, phosphonium salts are used because they have the advantage of being more thermally and chemically stable at elevated reaction temperatures.

Of interest to this work is whether or not the decrease in electronegativity of the cation central atom on changing from nitrogen to phosphorous will have any effect on the cation interactions with the nucleophile and therefore on the reaction rate and/or mechanism. Additionally, a phosphonium ion possesses vacant 3d orbitals over which it can spread the positive charge making the ion softer in nature compared with the more charge dense ammonium ion. This chapter will investigate whether there is a solute cation effect on a nucleophilic substitution reaction between charged species when pairing soft cations such as tetraalkylphosphoniums with hard anions such as chloride.

Results and Discussion

The process under examination was the S\(_{N2}\) reaction of the \(\text{bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium ([p-NO}_2\text{PhS(CH}_3\text{)}_2][N(CF}_3\text{SO}_2\text{]}\_2\)}\) with tetraalkylphosphonium chloride salts of varying alkyl chain lengths. The reaction is shown in Reaction Scheme 39 and the phosphonium salts are depicted in Figure 59.

![Reaction Scheme 39 - The reaction investigated](image)

The reactions were assayed using UV spectroscopy, with each substrate having \(\lambda_{\text{max}}\) at 252 nm and the demethylated products having a \(\lambda_{\text{max}}\) at 342 nm. The imidazolium-based ionic liquid which was used as the solvent has a cut-off at 240 nm and therefore caused no problems in interpreting the UV spectroscopy results. The sulfonium salt was synthesised as described in the experimental section in Chapter 8 directly before use and kept under anaerobic conditions.
The nucleophilic displacement by the chloride ion was studied in the ionic liquid [C₄C₁im][NTf₂] due to its relatively low viscosity, 44 cP, and its well-known synthetic and purification procedures. Chloride salts of various quaternary phosphonium cations were used to study the effect of the counter cation on the nucleophilicity of the chloride ion in an effort to detect preferential ion pairing. Tetrabutylphosphonium and triethyloctylphosphonium chloride salts were used in [C₄C₁im][NTf₂]. Additionally, a mixture including both tetrabutylphosphonium chloride and 1-butyl-3-methylimidazolium chloride was studied. Reactions were carried out at various temperatures to generate the activation energies for each reaction.

![Figure 59 - Tetraalkylphosphonium cations studied](image)

The electrophile was found to be stable in all solvents as no change in UV/vis absorbance was detected in the absence of the nucleophile after 24 hours.

This reaction is bimolecular and the rate therefore depends upon the concentrations of both the nucleophile and the electrophile. It is common in this type of process to create pseudo-first order kinetic behaviour by using a large excess of one reagent which shows a linear dependence of $k_{obs}$ upon nucleophile concentration. In this case the nucleophile (chloride) was used in excess and the second order rate constants for each reaction calculated.

The linear relationship expected was observed for each reaction in the ionic liquid solvent and the rate of the reaction was found to increase compared with similar reactions involving tetraalkylammonium chlorides described in Chapter 4. Summarised in Table 56 are the second order rate constants recorded for various nucleophilic tetraalkylphosphonium chloride salts.
The slowest rate observed (0.0236 M⁻¹ s⁻¹) was for the reaction involving tetrabutylphosphonium chloride. Interestingly this rate constant is two orders of magnitude larger than that recorded for tetraethylammonium chloride (0.0002 M⁻¹ s⁻¹) which can be found in Chapter 4. It is also significantly faster than for the base-case reaction using [C₄C₁im]Cl (0.0012 M⁻¹ s⁻¹) where there could be no solute cation effect on the chloride due to the counter ion being the same as the solvent cation. The large increase in reaction rate could signify a change in reaction mechanism but the fact that the reaction kinetics remained linear suggests that what we are seeing is an increase in the reactivity of the nucleophile. It appears that in all cases the reacting species observed in ionic liquids are the fully dissociated free ions.

It is especially clear that a cation effect exists for this reaction in light of the much higher rate constant observed for triethyloctylphosphonium chloride. At 0.1243 M⁻¹ s⁻¹, the reaction between triethyloctylphosphonium chloride and the sulfonium electrophile in [C₁C₄im][NTf₂] is 600 times faster than the slowest reaction recorded in this work with tetraethylammonium chloride. Additionally, triethyloctylphosphonium chloride produces a markedly faster reaction than tetrabutylphosphonium chloride. Given that the four symmetrical alkyl chains will better screen the central positive charge for the tetrabutylphosphonium cation compared with the relatively accessible triethyloctylphosphonium, it could be argued that interaction with the large, soft positive charge enhances the reactivity of the nucleophile. It is also possible that the solute cations can interact with and stabilise the activated complex and increase the reaction rate in this way.

Given the very large size of the phosphonium cations relative to the nucleophile, it is also possible that a chloride ion in the vicinity would be coordinated by just one or two cations. Such a low coordination number would greatly enhance the nucleophilicity of the chloride.

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>T / °C</th>
<th>k₂ / M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>[P₄₄₄₄]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0236</td>
</tr>
<tr>
<td>[P₂₂₂₈]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.1243</td>
</tr>
<tr>
<td>1:9 mix [P₄₄₄₄]Cl:[C₁C₄im]Cl</td>
<td>[C₁C₄im][NTf₂]</td>
<td>25</td>
<td>0.0303</td>
</tr>
<tr>
<td>[C₄C₁im]Cl</td>
<td>[C₄C₁im][NTf₂]</td>
<td>25</td>
<td>0.0012</td>
</tr>
</tbody>
</table>
relative to higher coordination number of four or five cations. Please refer to Chapter 4 for further explanation.

![Figure 60 - Chloride ion coordinated by two cations](image)

It is also possible that the solute cations can interact with and stabilise the activated complex and increase the reaction rate in this way. To gain greater insight into the reaction energetics, an Eyring activation parameter analysis was carried out for each phosphonium salt.

**Eyring Activation Parameters**

To understand the unexpectedly high $k_2$ for the reaction of triethylcetylphosphonium chloride with the electrophile in $[C_4C_1im][NTf_2]$, we needed to gain further information on the reactions in the ionic liquid. Therefore, the effect of temperature on reaction rate was also studied in order to determine the Eyring activation parameters for each solute cation studied. As in previous chapters, given that there was a linear dependence of $k_{obs}$ on $[Cl]$ at 25 °C, the values of $k_2$ were determined at various temperatures. From these data, the activation enthalpy and entropy of each reaction was calculated by use of the Eyring equation.

**Results and discussion**

The thermodynamic parameters $\Delta H^\ddagger$ (activation enthalpy) and $\Delta S^\ddagger$ (activation entropy) can be calculated with kinetic data using the Eyring equation by plotting $1/T$ against $\ln k_2$ as described in Chapter 3. Figure 61 shows the Eyring plot for the reaction of dimethyl-4-nitrophenylsulfonium bist(trifluoromethylsulfonyl)imide with $[P_{4444}]Cl$ in the ionic liquid $[C_4C_1im][NTf_2]$ at $T = 25, 30, 40$ and $50^\circ$C. The Eyring plots for the reactions listed in Table 57 can be found in the experimental section at the end of this chapter.
A summary of the activation energies recorded for each of the reactions between the tetraalkylphosphonium chlorides and of dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide can be found in Table 57.

Table 57 - Eyring Activation parameters

<table>
<thead>
<tr>
<th>Nucleophilic Salt</th>
<th>Solvent</th>
<th>$\Delta H^\circ$ / kJ mol$^{-1}$</th>
<th>$\Delta S^\circ$ / kJ mol$^{-1}$</th>
<th>$\Delta G^\circ_{298}$ / kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[P$_{4444}$]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>80.06</td>
<td>-0.9</td>
<td>80.96</td>
</tr>
<tr>
<td>[P$_{2228}$]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>76.01</td>
<td>-1.5</td>
<td>77.55</td>
</tr>
<tr>
<td>1:9 mix [P$_{4444}$]Cl:[C$_1$C$_4$im]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>119.35</td>
<td>+37.4</td>
<td>81.94</td>
</tr>
<tr>
<td>[C$_4$C$_1$im]Cl</td>
<td>[C$_1$C$_4$im][NTf$_2$]</td>
<td>71.8</td>
<td>-42.4</td>
<td>84.4</td>
</tr>
</tbody>
</table>

The Gibbs activation energy decreases with increasing rate of reaction as expected though remains similar to values observed for several other solutes tested. Associative substitutions generally have large negative entropies of activation. In two cases listed in Table 57, whilst still negative, we observe very much smaller negative entropies of activation than we might expect. Indeed in the case of the 1:9 mix [P$_{4444}$]Cl:[C$_1$C$_4$im]Cl, we find a fairly large positive activation entropy. Losses in entropy for associative processes can be compensated for to a greater or lesser extent by reorganisation of the solvent around the reacting species. From Table 57 we could suggest that activation entropy becomes less negative as the solute cation charge centre becomes more accessible. Compared with the tetraalkylammonium cation
studied in Chapter 4, the tetraalkylphosphonium cations have a much larger and softer positive charge with a better ability to interact with surrounding anions whether they are solute or ionic liquid anions. It is possible that soft cations solvate the activated complex relative to the chloride ions and hard cations stabilise the chloride ions relative to activated complex and therefore soft cations increase the reaction rate whereas hard cations impede the reaction’s progress. The loss in entropy on the electrophile and nucleophile coming together is being partly compensated by a simultaneous disruption of the bulk ionic liquid structure. The ionic liquid structure is disturbed as ionic starting materials come together to form a charge-separated activated complex.

The enthalpic barrier to reaction is in all cases fairly large, as would be expected for a reaction which involves charged reactants forming a charge separated activated complex. What we also observe is a small decrease of 4 kJ mol$^{-1}$ in $\Delta H^\circ$ going from tetrabutylphosphonium chloride to triethyloctylphosphonium chloride. This could suggest that the more accessible cation is either better destabilising the reactants or stabilising the activated complex relative to the symmetrical cation. Given that the activation entropies are roughly the same for each cation, we can conclude that the reduction in activation enthalpy is the main factor contributing to the increased rate of reaction observed going from $[P_{4444}]^+$ to $[P_{2228}]^+$.

Conclusions

Having investigated two tetraalkylphosphonium chloride salts, it is clear that relative to the other ammonium based cations tested there is an even more pronounced cation effect on the nucleophilic substitution reaction between charged electrophile and charge nucleophile. The fastest rates recorded for the reaction between chloride and dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide in $[C_4C_1im][NTf_2]$ were for those involving phosphonium salts. It is proposed that the addition of large tetraalkylphosphonium solutes to the reaction mixture disrupts the long range structure of the ionic liquid causing destabilisation of the reactants and promoting the reaction. It has also been suggested that there is a significant enhancement in reactivity for those chlorides coordinated by a phosphonium solute cation contributing to the overall enhancement of the rate constant. We have found no evidence of ion pairing effects on the use of large, soft phosphonium cations and conclude that addition of these solutes improves the energetic favourability of the substitution reaction without altering the reaction mechanism via increasing the entropy of activation to near zero. Further work is
required to elucidate the extent of the phosphonium cation effect including varying the lengths of the alkyl substituents, introducing hydrogen bonding functionalities to the cation.

**Experimental**

_The reaction of [p-NO₂PhS(CH₃)₂][NTf₂] with [P₄444][Cl] in [C₄C₁im][NTf₂]_

The reaction of [P₄444][Cl] with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in [C₄C₁im][NTf₂] at 25°C.

**Table 58 - The reactions in [C₄C₁im][NTf₂]**

<table>
<thead>
<tr>
<th>[S⁺] / mM</th>
<th>[Cl⁻] species / M</th>
<th>kₐₚₛ / s⁻¹</th>
<th>k₂/M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>0.0322</td>
<td>0.0251</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.0481</td>
<td>0.0257</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.0642</td>
<td>0.0266</td>
<td>0.0236 ± 0.00025</td>
</tr>
<tr>
<td>0.12</td>
<td>0.0160</td>
<td>0.0243</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.0401</td>
<td>0.025435</td>
<td></td>
</tr>
</tbody>
</table>

k₂ values were determined by plotting kₐₚₛ against the initial chloride concentration as shown in Figure 62.

**[P₄444]Cl 25 °C**

\[ y = 0.0469x + 0.0236 \]

R² = 0.9907

Figure 62 - Extrapolation of k₂ for the reactions in [C₄C₁im][NTf₂]
The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2]\) with \([P_{2228}]Cl\) in \([C_4C_1im][NTf_2]\)

The reaction of \([P_{2228}]Cl\) with dimethyl-4-nitrophenylsulfonyl \(bis\)(trifluromethylsulfonyl)imide was studied in \([C_4C_1im][NTf_2]\) at 25°C.

Table 59 - The reactions in \([C_4C_1im][NTf_2]\)

<table>
<thead>
<tr>
<th>([S^+] / \text{mM})</th>
<th>([\text{Cl}^-] \text{ species} / \text{M})</th>
<th>(k_{obs}/\text{s}^{-1})</th>
<th>(k_2/\text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>0.02</td>
<td>0.002567</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.04</td>
<td>0.005177</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.06</td>
<td>0.007234</td>
<td>0.1243 ± 0.0021</td>
</tr>
<tr>
<td>0.12</td>
<td>0.08</td>
<td>0.01052</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>0.1</td>
<td>0.012325</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{obs}\) against the initial chloride concentration as shown in Figure 63.

![Figure 63 - Extrapolation of \(k_2\) for the reactions in \([C_4C_1im][NTf_2]\)](image-url)
The reaction of \([p-NO_2PhS(CH_3)_2][\text{NTf}_2]\) with \([\text{P}_{4444}\text{Cl}] (10\%) : [\text{C}_1\text{C}_4\text{im}]\text{Cl} (90\%)\) mixture in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([\text{P}_{4444}\text{Cl}] (10\%) : [\text{C}_1\text{C}_4\text{im}]\text{Cl} (90\%)\) mixture with dimethyl-4-nitrophenylsulfonium \(\text{bis(trifluoromethylsulfonyl)imide}\) was studied in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25°C.

Table 60 - The reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

<table>
<thead>
<tr>
<th>([\text{S}^+] / \text{mM})</th>
<th>([\text{Cl}^-] \text{ species} / \text{M})</th>
<th>(k_{\text{obs}} / \text{s}^{-1})</th>
<th>(k_2 / \text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.112</td>
<td>0.009</td>
<td>0.002567</td>
<td></td>
</tr>
<tr>
<td>0.112</td>
<td>0.018</td>
<td>0.005177</td>
<td></td>
</tr>
<tr>
<td>0.112</td>
<td>0.027</td>
<td>0.007234</td>
<td>0.0303 ± 0.0051</td>
</tr>
<tr>
<td>0.112</td>
<td>0.045</td>
<td>0.01052</td>
<td></td>
</tr>
<tr>
<td>0.112</td>
<td>0.036</td>
<td>0.012325</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{\text{obs}}\) against the initial chloride concentration as shown in Figure 64.

**Figure 64 - Extrapolation of \(k_2\) for the reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)**
The Eyring plot for the reaction of \([p - \text{NO}_2\text{PhS}(\text{CH}_3)_2][\text{NTf}_2]\) with tetrabutylphosphonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The Eyring activation energies for the reaction of \([p - \text{NO}_2\text{PhS}(\text{CH}_3)_2][\text{NTf}_2]\) with tetrabutylphosphonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) listed in Table 57 were calculated from the Eyring plot in Figure 65 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25, 30, 40, and 50 °C.

**Table 61 - The reactions with tetrabutylphosphonium chloride at various T**

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2 / \text{M}^{-1} \text{s}^{-1})</th>
<th>1/T</th>
<th>(\ln k_2/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298.15</td>
<td>0.046</td>
<td>0.003354</td>
<td>-8.77671</td>
</tr>
<tr>
<td>323.15</td>
<td>0.5521</td>
<td>0.003095</td>
<td>-6.37214</td>
</tr>
<tr>
<td>303.15</td>
<td>0.0598</td>
<td>0.003299</td>
<td>-8.53098</td>
</tr>
<tr>
<td>313.15</td>
<td>0.2013</td>
<td>0.003193</td>
<td>-7.34964</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting \(\ln k_2/T\) against against 1/T as shown below in Figure 65.

![Figure 65 - The Eyring plot for the reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)](image-url)
Table 62 - Extraction of the activation energies

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>ΔH(^{≠}) / J mol(^{-1})</th>
<th>ΔS(^{≠}) / J K(^{-1}) mol(^{-1})</th>
<th>TΔS(^{≠}) / kJ mol(^{-1})</th>
<th>ΔG(^{≠})_298 / J mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9629.3</td>
<td>23.395</td>
<td>80058.00</td>
<td>-3.031</td>
<td>-0.90</td>
<td>80961.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>K</th>
<th>(k_B)</th>
<th>h</th>
<th>(k_B\epsilon/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>

The Eyring plot for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) with triethyloctylphosphonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The Eyring activation energies for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]\) with triethyloctylphosphonium chloride in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) listed in Table 57 were calculated from the Eyring plot in Figure 66 having studied the reaction in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25, 30, 40 and 50 °C.

Table 63 - The reactions with triethyloctylphosphonium chloride at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>(k_2 / \text{M}^{-1} \text{s}^{-1})</th>
<th>1/T (mean value)</th>
<th>(\ln k_2/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.1296</td>
<td>0.003356</td>
<td>-7.740396</td>
</tr>
<tr>
<td>303</td>
<td>0.6954</td>
<td>0.0033</td>
<td>-6.777001</td>
</tr>
<tr>
<td>313</td>
<td>0.722</td>
<td>0.003195</td>
<td>-6.071933</td>
</tr>
<tr>
<td>323</td>
<td>1.75</td>
<td>0.003096</td>
<td>-5.218037</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting \(\ln k_2/T\) against 1/T as shown below in Figure 66.
The Eyring plot for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\)[NTf_2] with \([P_{4444}]\text{Cl (10\%)} : [C_1C_4\text{im}]\text{Cl (90\%)}\) mixture in \([C_4C_1\text{im}][\text{NTf}_2]\]

The Eyring activation energies for the reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\)[NTf_2] with \([P_{4444}]\text{Cl (10\%)} : [C_1C_4\text{im}]\text{Cl (90\%)}\) mixture in \([C_4C_1\text{im}][\text{NTf}_2]\) listed in Table 57 were calculated from the Eyring plot in Figure 67 having studied the reaction in \([C_4C_1\text{im}][\text{NTf}_2]\) at 25, 30, 40, and 50 °C.
Table 65 - The reactions with [P₄₄₄₄]Cl (10%) : [C₇C₄im]Cl (90%) mixture at various T

<table>
<thead>
<tr>
<th>T / K</th>
<th>k₂ / M⁻¹ s⁻¹</th>
<th>1/T</th>
<th>ln k₂/T (mean value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.03</td>
<td>0.003356</td>
<td>-9.20365</td>
</tr>
<tr>
<td>303</td>
<td>0.0491</td>
<td>0.0033</td>
<td>-8.72763</td>
</tr>
<tr>
<td>313</td>
<td>0.3237</td>
<td>0.003195</td>
<td>-6.87414</td>
</tr>
<tr>
<td>323</td>
<td>1.1647</td>
<td>0.003096</td>
<td>-5.62519</td>
</tr>
</tbody>
</table>

The Eyring activation parameters can be calculated by plotting lnk₂/T against against 1/T as shown below in Figure 67.

![Eyring plot](image)

\[ y = -14356x + 38.86 \]
\[ R^2 = 0.991 \]

Figure 67 - The Eyring plot for the reactions in [C₇C₄im][NTf₂]

Table 66 - Extraction of the activation energies.

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>ΔH⁻ / J mol⁻¹</th>
<th>ΔS⁻ / J K⁻¹ mol⁻¹</th>
<th>TΔS⁻ / kJ mol⁻¹</th>
<th>ΔG⁻ / J mol⁻¹</th>
<th>k</th>
<th>k_B</th>
<th>h</th>
<th>k_Bk/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14356</td>
<td>38.86</td>
<td>119355.8</td>
<td>125.54</td>
<td>37.41</td>
<td>81943.25</td>
<td>1</td>
<td>1.38E-16</td>
<td>6.63E-27</td>
<td>2.08E+10</td>
</tr>
</tbody>
</table>
Chapter 7: Anion Effect – reactions with various nucleophilic tetrabutylammonium salts

Objectives

- Determine the rate constant, $k_2$, of the $S_n2$ reaction of the bis(trifluoromethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulfonium ([p-NO$_2$PhS(CH$_3$)$_2$][N(CF$_3$SO$_2$)$_2$]) with various nucleophilic tetrabutylammonium salts in [C$_4$C$_1$im][NTf$_2$] and in acetonitrile under pseudo-first order conditions
- Determine relative nucleophilicities and any deviations from expected behaviour
- Compare and contrast observations in acetonitrile with reactions in [C$_4$C$_1$im][NTf$_2$]

Outcomes

- Reaction rates decreased with decreasing nucleophilicity in [C$_4$C$_1$im][NTf$_2$]: SCN$^-$ > Br$^-$ ≈ Ac$^-$ > Cl$^-$
- Ionic liquid did not affect the inherent nucleophilicity of each salt
- No effect on reaction mechanism was observed in the ionic liquid
- Partial order kinetics indicative of an ion pairing reaction mechanism were observed for the reactions in acetonitrile
- Reaction rates did not correlate with the nucleophilicity scale
- Aprotic polar acetonitrile acts as a poor solvent for nucleophiles and the order is reversed Cl$^-$ > Br$^-$ > SCN$^-$

Key Figure

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Cation</th>
<th>Nucleophile</th>
<th>$k_2$ (M$^{-1}$s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>[C$_4$C$_1$im]$^+$</td>
<td>Cl$^-$</td>
<td>0.0012</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>[Bu$_4$N]$^+$</td>
<td>Ac$^-$</td>
<td>0.0967</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>[Bu$_4$N]$^+$</td>
<td>Br$^-$</td>
<td>0.0971</td>
</tr>
<tr>
<td>[C$_4$C$_1$im][NTf$_2$]</td>
<td>[Bu$_4$N]$^+$</td>
<td>SCN$^-$</td>
<td>0.1771</td>
</tr>
</tbody>
</table>
Introduction
The use of alternative solvents for chemical processes has become an important area of research as concern about the impact of the chemical industry on the environment has increased. Ionic liquids, which have been shown to be useful for numerous chemical reactions, form a large part of this research and have been applied to a wide range of chemical syntheses. Understanding how ionic liquids affect the reactivity of solutes within them is an ever expanding area of investigation to which this work aims to contribute.

In order for this work to understand how ionic liquids might affect reactivity and to gain some insight into their usefulness in stoichiometric chemical reactions, it is necessary to draw quantitative comparisons of reactivity in molecular solvent systems and ionic liquid systems. To date there have been some quantitative investigations of reactions in ionic liquid systems including several by the Welton group yet many questions remain unanswered. Specifically in this chapter we will investigate the effect of a solute cation on anion nucleophilicities. Previous studies have investigated the nucleophilicities of various anions where the parent cation is the same as the ionic liquid cation. We report a quantitative analysis of anion nucleophilicity using tetrabutylammonium salts in a 1-butyl-3-methylimidazolium bis(trifluormethanesulfonyl)imide {[C$_4$C$_1$im][NTf$_2$]}.

Results and Discussion
The process under examination was the S$_{N}$2 reaction of the bis(trifluormethanesulfonyl)imide salt of dimethyl-4-nitrophenylsulphonium ([$p$-NO$_2$PhS(CH$_3$)$_2$][N(CF$_3$SO$_2$)$_2$]) by various anionic nucleophiles, as shown in Reaction Scheme 40 with the anion represented by [X$^-$]. The use of methyl $p$-toluene sulphonate and its analogues as probes of anion nucleophilicity is well established.

\[
\text{O}_2\text{N} - \text{S} \quad + \text{[X$^-$]} \quad \rightarrow \quad \text{O}_2\text{N} - \text{S} + \text{CH}_3\text{Cl}
\]

*Reaction Scheme 40 - The S$_{N}$2 reaction with various anionic nucleophiles*

The rates of the reactions of tetrabutylammonium salts of the polyatomic anions acetate ([Ac$^-$]), trifluoroacetate and thiocyanate ([SCN$^-$]) and also monoatomic bromide ([Br$^-$]) and chloride ([Cl$^-$]) with dimethyl-$p$-nitrobenzenesulphonium imide were measured in the ionic liquid [C$_4$C$_1$im][NTf$_2$]. In addition, the reaction was performed in the molecular solvent...
acetonitrile (MeCN) in order to draw comparisons. The reactions were assayed using UV spectroscopy, with each substrate having $\lambda_{\text{max}}$ at 252 nm and the demethylated products having a $\lambda_{\text{max}}$ at 342 nm. The imidazolium-based ionic liquid which was used as the solvent has a cut-off at 240 nm and therefore caused no problems in interpreting the UV spectroscopy results. The sulfonium salt was synthesised as described in the experimental section in Chapter 8 directly before use and kept under anaerobic conditions. The electrophile was found to be stable in all solvents as no change in UV/vis absorbance was detected in the absence of the nucleophile after 24 hours.

This reaction is bimolecular and the rate therefore depends upon the concentrations of both the nucleophile and the electrophile. It is common in this type of process to create pseudo-first order kinetic behaviour by using a large excess of one reagent which shows a linear dependence of $k_{\text{obs}}$ upon nucleophile concentration.

All runs were performed using an excess of the nucleophile. Pseudo-first order rate constants ($k_{\text{obs}}/s^{-1}$) were calculated for the reaction of the sulfonium electrophile with chloride, bromide, acetate and thiocyanide anions in $[C_4C_{1}im][\text{NTf}_2]$. From these the bimolecular rate constants, $k_2$, have been determined for the reactions in the ionic liquid as can be seen in Table 67. Additionally, a run in which no nucleophile was added showed a that a no reaction occurred in the $[C_4C_{1}im][\text{NTf}_2]$ ionic liquid. From Table 67, it can be seen that the lowest $k_2$ value for all of the nucleophiles was found to be for the chloride ion. Consequently, all $k_2$ values are shown relative to chloride.

**Table 67 - Second-order rate constants $k_2/M^{-1}s^{-1}$ for the reaction of anions with dimethyl-p-nitrobenzenesulfonate in $[C_4C_{1}im][\text{NTf}_2]$ at 25 °C and relative to those with the chloride ion $k_2/k_2(\text{Cl}^-)$**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Cation</th>
<th>Nucleophile</th>
<th>$k_2 / M^{-1}s^{-1}$</th>
<th>$k_2/k_2(\text{Cl}^-)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[C_4C_{1}im][\text{NTf}_2]$</td>
<td>$[C_4C_{1}im]^+$</td>
<td>Cl$^-$</td>
<td>0.0012</td>
<td>1</td>
</tr>
<tr>
<td>$[C_4C_{1}im][\text{NTf}_2]$</td>
<td>$[\text{Bu}_4N]^+$</td>
<td>Ac$^-$</td>
<td>0.0967</td>
<td>80.6</td>
</tr>
<tr>
<td>$[C_4C_{1}im][\text{NTf}_2]$</td>
<td>$[\text{Bu}_4N]^+$</td>
<td>Br$^-$</td>
<td>0.0972</td>
<td>80.9</td>
</tr>
<tr>
<td>$[C_4C_{1}im][\text{NTf}_2]$</td>
<td>$[\text{Bu}_4N]^+$</td>
<td>SCN$^-$</td>
<td>0.1771</td>
<td>147.6</td>
</tr>
</tbody>
</table>
It is known that in molecular solvents, the nucleophilic substitution reaction between a charged electrophile and charged nucleophile takes place via an ion pairing mechanism and therefore exhibits partial order reaction kinetics. The reactions in the ionic liquid however, are known to follow linear pseudo-first order kinetics due to the reaction mechanism depending on the concentration of the nucleophile free ions. As expected, second order rate constants could not be measured for the reactions in MeCN due to the partial order kinetics observed in this solvent and the reactions in the ionic liquid also behaved as expected, confirming that in this solvent this reaction is pseudo-first order in anion concentration.

By evaluating the slope of the plots of $k_{\text{obs}}$ against [nucleophile], it is possible to compare the relative rates of reaction of the anions with electrophile. The values of $k_2$ recorded suggest that the relative reactivity is of the order thiocyanide (147.6): bromide (80.9): acetate (80.6): chloride (1). It would appear that bromide and acetate are of approximately equal nucleophilicity in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ with thiocyanide being the most nucleophilic of the anions in this system.

The results recorded in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$ are compared to anion nucleophilicity for a similar substitution reaction between the anions and methyl-p-nitrobenzenesulfonate in ionic liquid $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]^{54}$ in Table 68.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>nucleophile</th>
<th>$k_2$(Me-p-NBS)$^{54}$</th>
<th>$k_2$(diMe-p-NBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>Cl$^-$</td>
<td>0.012</td>
<td>0.0012</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>Ac$^-$</td>
<td>0.0093</td>
<td>0.0967</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>Br$^-$</td>
<td>0.019</td>
<td>0.0972</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</td>
<td>SCN$^-$</td>
<td>0.00397</td>
<td>0.1771</td>
</tr>
</tbody>
</table>

The normal order of nucleophilicities in protic solvents (e.g. water or methanol) is SCN$^- >$ Ac$^-$ > Br$^-$ > Cl$^-$. The observed relative nucleophilicity the anions depends on several other factors including the extent to which the anion is solvated$^{153}$ (including ion-dipole, dipole-dipole and H-bonding interactions) and the polarizability of the anion. It is not clear from this study which of these factors is most important given that we have investigated just one ionic liquid. It is notable that 1,3-dialkylimidazolium cations form strong hydrogen bonds to halide ions,$^{154}$ whereas this interaction is not so pronounced for the polyatomic anions. We would
therefore expect, and indeed observe, that the trend in relative nucleophilicity for the reaction between the charged electrophile and charged nucleophile is similar for this ionic liquid to what we would expect to see in a protic solvent.

The literature comparison available to anion nucleophilicity in ionic liquids detailed in Table 68 shows that the relative order of nucleophilicities is Br\(^{-}\) > Cl\(^{-}\) > Ac\(^{-}\) > SCN\(^{-}\) as found by Welton et al. for the reaction between anionic nucleophile and methyl-p-nitrobenzenesulfonate in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\). Clearly, different types of S\(_{N}\)2 reactions (i.e. charged electrophile with charged nucleophile vs. neutral electrophile with charged nucleophile) do not show the same behaviours and cannot be treated the same. Although it is not possible at this stage of investigation to be certain of the reason for this difference, we can assume that the Coulombic attraction between the solvent and the nucleophile and the solvent and electrophile will be stronger when both species are ionic. In this case, the Hughes-Ingold principles suggest that destruction of charge on formation of the activated complex will cause reactions to be slower for more polar solvents and therefore nucleophiles with higher ionicities. So for the reaction between a charged nucleophile and a neutral electrophile, the Hughes-Ingold principles suggest that the relative decrease in reaction rate on increasing solvent polarity due to charge dispersal on forming the activated complex is less significant and specific effects may gain importance in determining nucleophilicities. When both nucleophile and electrophile are ionic it seems that hard anions show slower reaction rates when compared with soft anions which is likely to be a result of ionic liquids better stabilising hard anionic nucleophiles.

**Conclusions**

This work has used in situ techniques to carry out kinetic measurements in ionic liquids. The relative reactivities of chloride, bromide, acetate and thiocyanide ion towards dimethyl p-nitrobenzenesulfonium bis-imide in ionic liquid \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) and have been determined and show a trend different to that observed for a similar reaction in the same ionic liquid. This work has supported the investigations into the effect of the imidazolium cation; the effect of the solute cation and the use of charged reactive species. This investigation will be continued by the studying the effect of changing the solute cation (both coordinating and non-coordinating) and by studying the reactions over a range of temperatures. The data obtained will then be analysed through calculation of the Eyring activation parameters using Eyring plots.
Experimental

The reaction of \([p-\text{NO}_2\text{PhS}(\text{CH}_3)_2]\)[NTf\(_2\)] with \([\text{Bu}_4\text{N}][\text{Ac}]\) in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([\text{Bu}_4\text{N}][\text{Ac}]\) with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25°C.

Table 69 - The reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

<table>
<thead>
<tr>
<th>([\text{S}^+]/\text{mM})</th>
<th>([\text{Ac}^-]/\text{species}/\text{M})</th>
<th>(k_{\text{obs}}/\text{s}^{-1})</th>
<th>(k_2/\text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.289</td>
<td>0.032</td>
<td>0.0028</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.048</td>
<td>0.0043</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.064</td>
<td>0.0061</td>
<td>0.0967 ± 0.0031</td>
</tr>
<tr>
<td>0.289</td>
<td>0.016</td>
<td>0.0015</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.024</td>
<td>0.0020</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{\text{obs}}\) against the initial acetate concentration as shown in Figure 68.

\[\text{[Bu}_4\text{N]}[\text{Ac}]\]

\[y = 0.0967x - 0.0002\]
\[R^2 = 0.9913\]

Figure 68 - Extrapolation of \(k_2\) for the reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)
The reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\text{NTf}_2\) with \([\text{Bu}_4\text{N}][\text{SCN}]\) in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([\text{Bu}_4\text{N}][\text{SCN}]\) with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25°C.

Table 70 - The reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

<table>
<thead>
<tr>
<th>([\text{S}^+]) / mM</th>
<th>([\text{SCN}^-]) species / M</th>
<th>(k_{\text{obs}} / \text{s}^{-1})</th>
<th>(k_2/\text{M}^{-1}\text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.289</td>
<td>0.016</td>
<td>0.0017237</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.032</td>
<td>0.003982</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.048</td>
<td>0.006825</td>
<td>0.1799 ± 0.0087</td>
</tr>
<tr>
<td>0.289</td>
<td>0.064</td>
<td>0.010355</td>
<td></td>
</tr>
<tr>
<td>0.289</td>
<td>0.024</td>
<td>0.002815</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{\text{obs}}\) against the initial thiocyanide concentration as shown in Figure 69.

\[y = 0.1799x - 0.0015\]
\[R^2 = 0.9916\]

Figure 69 - Extrapolation of \(k_2\) for the reactions in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([p\text{-NO}_2\text{PhS(CH}_3)_2]\text{NTf}_2\) with \([\text{C}_4\text{C}_1\text{im}]\text{Cl}\) in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\)

The reaction of \([\text{C}_4\text{C}_1\text{im}]\text{Cl}\) with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in \([\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]\) at 25°C.
Table 71 - The reactions in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\)

<table>
<thead>
<tr>
<th>[S(^{-})] / mM</th>
<th>[Cl(^{-})] species / M</th>
<th>(k_{obs}/s^{-1})</th>
<th>(k_2/M^{-1}s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.368</td>
<td>0.0223</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0447</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0074</td>
<td>0.015</td>
<td>0.0012 ± 0.0007</td>
</tr>
<tr>
<td>0.368</td>
<td>0.0149</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.0372</td>
<td>0.055</td>
<td></td>
</tr>
</tbody>
</table>

\(k_2\) values were determined by plotting \(k_{obs}\) against the initial chloride concentration as shown in Figure 70.

\[
y = 0.0012x + 7E-06 \\
R^2 = 0.9913
\]

Figure 70 - The reaction in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\)

The reaction of \([p-\text{NO}_2\text{PhS(CH}_3)_2]\text{NTf}_2\) with \([\text{Bu}_4\text{N}]\text{Br}\) in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\)

The reaction of \([\text{Bu}_4\text{N}]\text{Br}\) with dimethyl-4-nitrophenylsulfonium \(\text{bis}(\text{trifluoromethylsulfonyl})\text{imide}\) was studied in \([\text{C}_4\text{C}_1\text{im}]\text{NTf}_2\) at 25°C.
Table 72 - The reactions in [C₄C₁im][NTf₂]  

<table>
<thead>
<tr>
<th>[S⁻] / mM</th>
<th>[Br⁻] species / M</th>
<th>kobs /s⁻¹</th>
<th>k₂/M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.368</td>
<td>0.032</td>
<td>0.002472</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.048</td>
<td>0.004324</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.064</td>
<td>0.006153</td>
<td>0.0972 ± 0.0022</td>
</tr>
<tr>
<td>0.368</td>
<td>0.016</td>
<td>0.001584</td>
<td></td>
</tr>
<tr>
<td>0.368</td>
<td>0.024</td>
<td>0.001986</td>
<td></td>
</tr>
</tbody>
</table>

k₂ values were determined by plotting \( k_{\text{obs}} \) against the initial bromide concentration as shown in Figure 71.

![Figure 71 - Extrapolation of \( k_2 \) for the reactions in \([C_4C_1im][NTf_2]\)](image)

The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2] \) with \([Bu_4N][SCN] \) in acetonitrile

The reaction of \([Bu_4N][SCN] \) with dimethyl-4-nitrophenylsulfonium \( bis(\text{trifluoromethylsulfonyl}) \)imide was studied in acetonitrile at 25°C.
Table 73 - The reactions in acetonitrile

<table>
<thead>
<tr>
<th>[SCN(^-)] / M</th>
<th>[S(^+)] species / mM</th>
<th>(k_{obs} \times 10^3/\text{s}^{-1})</th>
<th>(\sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0061</td>
<td>0.327</td>
<td>0.0554</td>
<td>1.42E-03</td>
</tr>
<tr>
<td>0.0122</td>
<td>0.327</td>
<td>0.0594</td>
<td>2.55E-04</td>
</tr>
<tr>
<td>0.0183</td>
<td>0.327</td>
<td>0.0628</td>
<td>4.21E-05</td>
</tr>
<tr>
<td>0.0244</td>
<td>0.327</td>
<td>0.0654</td>
<td>9.19E-04</td>
</tr>
<tr>
<td>0.0305</td>
<td>0.327</td>
<td>0.0659</td>
<td>2.08E-03</td>
</tr>
</tbody>
</table>

Figure 72 shows graphically the dependence of \(k_{obs}\) on the thiocyanide concentration:

![Graph of \(k_{obs}\) vs. [SCN\(^-\)] in MeCN at 25 °C](image)

The reaction of \([p-NO_2PhS(CH_3)_2][NTf_2]\) with \([Bu_4N]Cl\) in acetonitrile

The reaction of \([Bu_4N]Cl\) with dimethyl-4-nitrophenylsulfonium \(\text{bis}\) (trifluromethylsulfonyl)imide was studied in acetonitrile at 25°C.

Table 74 - The reactions in acetonitrile

<table>
<thead>
<tr>
<th>[Cl(^-)] / M</th>
<th>[S(^+)] species / mM</th>
<th>(k_{obs} \times 10^3/\text{s}^{-1})</th>
<th>(\sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0072</td>
<td>0.327</td>
<td>0.0975</td>
<td>4.51E-04</td>
</tr>
<tr>
<td>0.0144</td>
<td>0.327</td>
<td>0.1373</td>
<td>1.12E-03</td>
</tr>
<tr>
<td>0.0216</td>
<td>0.327</td>
<td>0.1352</td>
<td>4.66E-07</td>
</tr>
<tr>
<td>0.0288</td>
<td>0.327</td>
<td>0.1500</td>
<td>5.47E-04</td>
</tr>
<tr>
<td>0.0359</td>
<td>0.327</td>
<td>0.1652</td>
<td>1.50E-03</td>
</tr>
</tbody>
</table>

Figure 73 shows graphically the dependence of \(k_{obs}\) on the chloride concentration:
Figure 73 - Dependence of $k_{obs}$ on chloride concentration in acetonitrile

The reaction of $[\text{p-NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]$ with $[\text{Bu}_4\text{N}]\text{Br}$ in acetonitrile

The reaction of $[\text{Bu}_4\text{N}]\text{Br}$ with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in acetonitrile at 25°C.

Table 75 - The reactions in acetonitrile

<table>
<thead>
<tr>
<th>$[\text{Br}^-]$ / M</th>
<th>$[\text{S}^+]$ species / mM</th>
<th>$k_{obs} \times 10^3$/s$^{-1}$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0072</td>
<td>0.327</td>
<td>0.1066</td>
<td>1.80E-03</td>
</tr>
<tr>
<td>0.0145</td>
<td>0.327</td>
<td>0.1193</td>
<td>5.00E-04</td>
</tr>
<tr>
<td>0.0289</td>
<td>0.327</td>
<td>0.1260</td>
<td>1.00E-03</td>
</tr>
<tr>
<td>0.0362</td>
<td>0.327</td>
<td>0.1417</td>
<td>1.30E-03</td>
</tr>
</tbody>
</table>
Figure 74 shows graphically the dependence of $k_{\text{obs}}$ on the bromide concentration:

![Graph showing the dependence of $k_{\text{obs}}$ on bromide concentration in acetonitrile](image)

**Figure 74 - Dependence of $k_{\text{obs}}$ on bromide concentration in acetonitrile**

The reaction of $[p$-$\text{NO}_2\text{PhS(CH}_3)_2][\text{NTf}_2]$ with $[\text{Bu}_4\text{N}]$[Ac] in acetonitrile

The reaction of $[\text{Bu}_4\text{N}]$[Ac] with dimethyl-4-nitrophenylsulfonium bis(trifluoromethylsulfonyl)imide was studied in acetonitrile at 25°C. At similar concentrations to the previous reactions, the reaction progressed too quickly to be followed using the UV/vis method. It was qualitatively concluded therefore that acetate is the strongest nucleophile for this reaction in acetonitrile.
Chapter 8: Experimental Section

All reagents used were obtained from VWR or fisher scientific at highest purity and dried using suitable drying agents.

**Ionic Liquids Syntheses**

Air and moisture sensitive materials have been handled using standard Schlenk techniques and in a nitrogen atmosphere dry box when required. $^1$H and $^{13}$C NMR liquid state data were collected at room temperature on a Bruker 400 MHz spectrometer. Coupling constants are recorded in Hz and chemical shifts measured in ppm (versus tetramethylsilane). Melting points were determined using a Gallenkamp Sanyo MPD 350 heater. 1-methylimidazole (>99%, Aldrich) and 1-methylpyrrolidine (Acros Organics) were freshly distilled from potassium hydroxide prior to use. Anhydrous 1-chlorobutane (>99.5%, Aldrich) was distilled over phosphorous pentoxide. Lithium bis(trifluoromethylsulfonyl)imide was purchased from Solvent Innovation GmBH. All standard solvents were purified by distillation from standard drying agents. The simple AgNO$_3$ test was used to establish the chloride content of the ionic liquids. This test has found all ionic liquids synthesised to have a chloride content of less than 1.4 mg/L given that this value is the solubility of AgCl in water. The water content of all ionic liquids synthesised was measured using Karl Fischer titration analysis.

*Synthesis of 1-butyl-3-methylimidazolium chloride [C$_4$C$_1$im]Cl*

1-chlorobutane (106 mL, 1.01 mol) was added slowly to 1-methylimidazolide (50 mL, 0.63 mol) in ethylacetate (100 mL) at room temperature in a 1L round bottomed flask for 4 hours. The temperature was then increased to 45°C and stirring continued for 14 days in order for the C1C4ImCl salt to crystallise out. The white precipitate formed and after cooling the solvent was removed *via* canula. The remaining white crystals were washed with ethylacetate (2 x 150 mL) with the washing being removed *via* canula. Before use the crystals were dried overnight under vacuum, giving white powder (95.6, 87%).

$\delta$H: (400 MHz, DMSO-$d_6$) / ppm 9.54 (1H, s, N2CH), 7.89 (1H, s, NCH), 7.81 (1H, s, NCH), 7.49 (2H, t, 3J = 6.0 Hz, NCH2CH2CH2CH3), 3.87 (3H, s, NCH3), 1.75 (2H, quintet, 3J = 6.0 Hz, NCH2CH2CH2CH3), 1.23 (2H, sextet, 3J = 8.0 Hz, NCH2CH2CH2CH3), 0.91(3H, t, 3J = 6 Hz, NCH2CH2CH2CH3)
δC: (100 MHz, DMSO-d6) / ppm 136.73 (s, N2C), 123.55 (s, NCH), 122.26 (s, NCH), 48.35 (s, NCH2CH2CH2CH3), 35.67 (s, NCH3), 31.37 (s, NCH2CH2CH2CH3), 18.74 (s, NCH2CH2CH2CH3) and 13.27 (s, NCH2CH2CH2CH3).

m/z (ESI+): 313, [(C4C1im)2Cl]+ and 139, [(C4C1im)−, 100%]

m/z (FAB-): 209, [(C4C1im)Cl2]− and 35, [(Cl)-, 100%]

Elemental Analysis (predicted): %C = 55.23 (55.01), %H = 8.74 (8.66), %N = 16.12 (16.04)

m.p. 73°C

Synthesis of 1-butyl-1-methylpyrrolidinium chloride [C4C1Py]Cl

1-chlorobutane (65 mL, 0.62 mol) was added to N-methylpyrrolidine (50 mL, 0.48 mol) freshly distilled in ethylacetate (200 mL). The mixture was gently stirred at 40°C in a 1L round bottomed flask for 1 day and then 1 day at 50°C, followed by 4 days at 65°C in order for the C1C4PyCl salt to crystallize out. After cooling, the solvent was removed via canula and then under vacuum. The solid formed was re-crystallised with a mixture of acetonitrile/ethyl acetate, yielding white crystals. (47.5g, 56%)

δH: (400 MHz, DMSO-d6) / ppm 3.60-3.38 (6H, m, N(CH2)2 and NCH2(CH2)2CH3), 3.02 (3H, s, NCH3), 2.05 (4H, s, NCH2(CH2)2), 1.65 (2H, m, J = 6.0 Hz, NCH2CH2CH2CH3), 1.27 (2H, sextet, 3J = 8 Hz, NCH2CH2CH2CH3), 0.89 (3H, t, 3J = 8 Hz, NCH2CH2CH2CH3).

δC: (100 MHz, DMSO-d6) / ppm 63.14 (s, N(CH2)2), 62.51 (s, NCH2(CH2)2CH3), 47.25 (s, NCH3), 24.95 (s, N(CH2)2(CH2)2), 20.97 (s, NCH2CH2CH2CH3), 19.29 (s, N(CH2)2CH2CH3), 13.51 (s, N(CH2)3CH3)

m/z (ESI+): 319, [(C4C1py)2Cl]+ and 142, [(C4C1py)−, 100%]

Elemental Analysis (predicted): %C = 60.70 (60.83), %H = 11.20 (11.34), %N = 7.94 (7.88)

m.p. 106°C

Synthesis of 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [C4C1im][NTf2]

A solution of lithium bis(trifluoromethylsulfonyl)imide [LiNTf2] (50g, 0.17mol) in water (50mL) was added to a solution of [C4C1im]Cl (30.4g, 0.17mol) in dichloromethane (100mL) and stirred vigorously at room temperature for 8 hours. From the two phase mixture the lower
phase was collected and washed repeatedly with water (10 x 100 mL) until no chloride traces remained in the washings (test with silver nitrate solution). The ionic liquid in dichloromethane was purified through a short alumina column topped with a thin layer of activated charcoal (ca < 5 mm). The solvent was then removed in vacuo (24 hours) giving a colourless, viscous liquid.

δH: (400 MHz, DMSO-d6) / ppm 9.06 (1H, s, N2CH), 7.68 (1H, s, NCH), 7.62 (1H, s, NCH), 4.17 (2H, t, 3J = 8.0 Hz, NCH2CH2CH2CH3), 3.86 (3H, s, NCH3), 1.79 (2H, quintet, 3J = 8.0 Hz, NCH2CH2CH2CH3), 1.29 (2H, sextet, 3J = 8.0 Hz, NCH2CH2CH2CH3), 0.91 (3H, t, 3J = 6 Hz, NCH2CH2CH2CH3)

δC: (100 MHz, DMSO-d6) / ppm 136.61 (s, N2C), 123.61 (s, NCH), 122.27 (s, NCH), 119.68 (q, 1JC-F = 320 Hz, [N(SO2CF3)2]-), 48.80 (s, NCH2CH2CH2CH3), 35.63 (s, NCH3), 31.48 (s, NCH2CH2CH2CH3), 18.83 (s, NCH2CH2CH2CH3) and 12.92 (s, NCH2CH2CH2CH3).

m/z (ESI+): 558, [(C4C1im)2N(Tf)2]+ and 139, ([C4C1im]+, 100% )
m/z (ESI-): 699, [(C4C1im)(N(Tf)2)2]- and 280, ([N(Tf)2]-, 100%

Elemental Analysis (predicted) : %C = 28.75 (28.64), %H = 3.68 (3.61), %N = 10.02 (10.02) (10.02%).

Synthesis of 1-butyl-3-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide [C1C4py][NTf2]

A solution of [C1C4py]Cl (35.8g, 0.202 mol) in dichloromethane (50 mL) was added to lithium bis-(trifluoromethylsulfonyl)imide (57.4g, 0.2 mol). This mixture was stirred for 72 hours at room temperature then filtered. The resulting salt was washed with dichloromethane (3 x 50 mL) and the combined organic extracts were washed with water until the silver nitrate tests determined the aqueous phase to be halide free. The solvent was then removed under vacuum and the ionic liquid passed through a short acidic alumina column topped with a layer of activated charcoal (5 mm) to give a colourless liquid.

δH: (400 MHz, DMSO-d6) / ppm 3.55-3.25 (6H, m, N(CH2)2 and NCH2(CH2)2CH3), 2.98 (3H, s, NCH3), 2.09 (4H, s, NCH2(CH2)2), 1.69 (2H, m, J = 8 Hz, NCH2CH2CH2CH3), 1.32 (2H, sextet, 3J = 8 Hz, NCH2CH2CH2CH3), 0.94 (3H, t, 3J = 8 Hz, NCH2CH2CH2CH3).
δC: (100 MHz, DMSO-d6) / ppm 119.64 (q, 1JC-F = 320 Hz, [N(SO2CF3)2]+), 63.61 (s, N(CH2)2), 63.30 (s, NCH2(CH2)2CH3), 47.56 (s, NCH3), 25.00 (s, N(CH2)2(CH2)2), 21.05 (s, NCH2CH2CH2CH3), 19.23 (s, N(CH2)2CH2CH3), 13.06 (s, N(CH2)3CH3)

m/z (ESI+): 564, [(C4C1py)2N(Tf)2]+ and 142, ([C4C1py]+, 100%)

m/z (ESI+): 702, [(C4C1py)(N(Tf)2)2]+ and 280, ([N(Tf)2]+, 100%)

Elemental Analysis (predicted): %C = 31.15 (31.26), %H = 4.82 (4.77), %N = 6.62 (6.63)

Synthesis of S_N2 reagents

Preparative Part

Dimethylsulfate was purchased from Aldrich and distilled from CaO before use. Lithium bis(trifluoromethylsulfonyl)imide was purchased from Solvent Innovation GmbH and used as received. 4-nitrothioanisole was purchased from Avocado and used as received. All molecular solvents were purified by distillation from standard drying agents. All syntheses were performed in anaerobic conditions using standard Schlenk techniques. The preparations and spectral data for the ionic liquids are described in the experimental section at the end of this work (chapter 4).

¹H and ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm (vs. trimethylsilane) and coupling constants are recorded in Hz. FAB mass spectra were recorded on a VG AutoSpec Q mass spectrometer. UV/vis spectra were recorded on a Perkin Elmer UV-visible Lambda 2 spectrophotometer. The temperatures were kept constant using a thermostatic circulator. Melting points were obtained on a Gallenkamp Sanyo MPD 350 heater.

Synthesis of dimethyl-4-nitrophenylsulfonium methylsulfate

Dimethylsulfate (2.52 cm³, 26.7 mmol) was added drop-wise at room temperature to p-nitrothioanisole (3.0 g, 17.7 mmol). The resulting creamy solution was heated at 95°C and stirred for two hours. The yellow/cream solid which precipitated was recrystallised twice from isopropanol. The resulting crystals were soft and cream coloured.

δH (ppm) (DMSO-d6): 8.51 (2H, d, ³J = 9.2 Hz, CH-3,5), 8.34 (2H, d, ³J = 9.2 Hz, CH-2,6), 3.37 (3H, s, CH₃-so₃) and 3.33 (6H, s, -S-CH₃).
\( \delta_C \) (ppm) (DMSO-d6): 150.18 (CS(CH$_3$)$_2$), 134.10, (CNO$_2$), 131.46 (CH-2,6), 124.86 (CH-3,5), 61.15 (CH$_3$OSO$_3$) and 30.11 (S(CH$_3$)$_2$).

m.p. : 152°C

UV/vis: \( \lambda_{\text{max}} \) (CH$_2$Cl$_2$) = 252 nm

**Synthesis of dimethyl-4-nitrosulfonium bis(trifluoromethylsulfonylimide)**

Dimethyl-4-nitrophenylsulfonium methylsulfate (3.02 g, 10 mmol) and lithium bis(trifluoromethylsulfonylimide) (2.94 g, 10 mmol) were stirred in water at room temperature for eight hours. A heavier liquid separated from the solution which was isolated and was washed with dichloromethane then water. The liquid was dried under vacuum to give a highly viscous yellow/orange liquid.

\( \delta_H \) (ppm) (acetone-d$_6$): 8.58 (2H, d, \( ^3J = 8.8\) Hz, CH-3,5), 8.51 (2H, d \( ^3J = 9.2\) Hz, CH-2,6), 3.65 (6H, s, -S-CH$_3$).

\( \delta_C \) (ppm) (acetone-d$_6$): 153.09 (CS(CH$_3$)$_2$), 134.92, (CNO$_2$), 133.46 (CH-2,6), 127.25 (CH-3,5), 121.98 (q, \( ^1\)J$_{13C}$-$^{19F}$ = 319.9 Hz, [N(SO$_2$CF$_3$)$_2$]) and 30.11 (S(CH$_3$)$_2$).

UV/vis: : \( \lambda_{\text{max}} \) (acetonitrile) = 249 nm

m/z (FAB$^+$) MS: 648, [(pNO$_2$PhS(CH$_3$)$_2$(NTf)$_2$]$^+$, 0.65%; 184, [pNO$_2$PhS(CH$_3$)$_2$]$^+$, 100%.

**Purification of tetraalkylammonium salts**

All tetraalkylammonium salts were purchased from Sigma Alrich at minimum 97% purity. The salts were then further purified by recrystallisation from ethanol using diethyl ether. The salts were then dried over P2O5 under reduced pressure for three days before use.

**Purification of tetraalkylphosphonium chlorides**

All tetraalkylphosphonium salts were purchased Cytec and and recrystallised from ethanol and dried under vacuo for 3 days before use.
Methodology and Data Handling of Kinetic Measurements

The ionic liquid used was imidazolium-based and could therefore be back corrected to zero to around 240 nm. It should be noted that the more pure the ionic liquid was, the better the back correction.

The reaction chosen for study was that of bis(trifluoromethanesulfonyl)imide salts of dimethyl-4-nitrophenylsulfonium ([p-NO₂PhS(CH₃)]⁺[X]⁻; [X]⁻ = [N(CF₃SO₂)₂ = NTf₂]⁻ with chloride ion. This particular substrate was chosen to react with the chloride ion because it has a \( \lambda_{\text{max}} \) at 252 nm and the demethylated product as a clearly visible \( \lambda_{\text{max}} \) at 342 nm.

Determining Rate Constants: \( k_{\text{obs}} \) and \( k_2 \)

All reactions were carried out under pseudo-first order conditions, meaning an excess of the nucleophile is used to produce first-order kinetics in the experimental observations. Only in the ionic liquids were such reaction kinetics observed and so first-order kinetic analysis was employed.

The chromophore of the electrophilic species and its demethylated product form allow the substitution reaction to be followed by UV/vis spectroscopy. As the absorbance is a physical property which varies linearly with the extent of the reaction, the techniques does not require absolute concentrations of reactants and products to be known but rather dilution factors relative to an initial stock concentration.

For for an “A to B” process, where both A and B are UV-active species (with A and B denoting their concentration and \( \alpha \) and \( \beta \) their absorbance), absorbance, \( \alpha \), will decrease as the reaction proceeds whilst absorbance, \( \beta \) will increase during this time. The changes in absorbance over time are illustrated schematically in Figure 75 and Figure 76.
On account of the reactions in ionic liquids being comparatively slow, the method used in this work was such that the final concentration/absorbance was not included. For first-order reactions such as those described here in ionic liquids, Guggenheim described a method for finding the rate constant where the end/Infinity value is unknown. If one considers the integrated first-order rate law for a process $A \rightarrow B$, where both $A$ and $B$ are UV-active species and the reactions follows a decrease in absorbance $\alpha$ and an increase in absorbance $\beta$, then we find:

$$ A = A_0 e^{-kt} $$

Equation 31

$$ B = B_\infty (1 - e^{-kt}) $$

Equation 32
If times \( t_1, t_2, t_3, \ldots \), concentrations \( B_1, B_2, B_3, \ldots \), and times \( t_1 + \Delta, t_2 + \Delta, t_3 + \Delta, \ldots \), concentrations \( B_1 + \Delta, B_2 + \Delta, B_3 + \Delta, \ldots \) are selected, where \( \Delta \) is a constant time interval, then:

\[
B_\infty - B_t = (B_\infty - B_0)e^{-kt}
\]

**Equation 33**

\[
B_\infty - B_{t+\Delta} = (B_\infty - B_0)e^{-kt(t+\Delta)}
\]

**Equation 34**

Subtracting Equation 33 from Equation 34 gives:

\[
B_{t+\Delta} - B_t = (B_\infty - B_0)e^{-kt}(1 - e^{-k\Delta})
\]

**Equation 35**

\[
\ln(B_{t+\Delta} - B_t) = -kt + \ln(B_\infty - B_0)(1 - e^{-k\Delta})
\]

**Equation 36**

\[
\ln(B_{t+\Delta} - B_t) = -kt + C
\]

**Equation 37**

Thus a plot of \( \ln(B_{t+\Delta} - B_t) \) against \( t \) should be linear with a slope equal to \(-k_{obs}\).

This method was followed to calculate pseudo-first order rate constants, \( k_{obs} \), but the absorbance values measured in the UV experiments were used instead of concentrations. Thus \( \ln(\beta_{t+\Delta} - \beta_t) \) was plotted against \( t \). For good accuracy, the time interval between the two series of readings was chosen to be at least twice the half-life. Reactions were studied at various initial concentrations of the nucleophile, chloride, and second order rate constants, \( k_2 \), were extrapolated from a plot of \( k_{obs} \) against chloride concentration by linear regression analysis (\( k_{obs} = k_2 \times [\text{Cl}]_0 \)).

**UV measurements procedure**

A stock solution containing the nucleophile (chloride) dissolved in the solvent under investigation was added to a 0.5 cm path length UV/vis quartz cuvette under anaerobic conditions, after which neat solvent would be added to total the volume at 1.1 cm³. After thermostatting for five minutes, the reaction was initiated with an injection of 0.1 cm³ of the
electrophile dissolved in the solvent of interest. All values plotted are the average of at least three different experiments at each concentration of nucleophile.

Error calculations

Errors for the second order rate constants obtained in the kinetic studies were determined by calculating the standard deviations for each $k_{obs}$ (averaged from three separate experiments), dividing by the corresponding nucleophile concentration and taking the mean value to achieve the absolute error.

Where partial order kinetics was observed, the standard deviation for each mean $k_{obs}$ value is provided.

For example:

Table 76 - Example error calculation

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<th>Reaction using $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ in $[\text{C}_4\text{C}_1\text{im}][\text{NTf}_2]$</th>
<th>$k_{obs1}$</th>
<th>$k_{obs2}$</th>
<th>$k_{obs3}$</th>
<th>$k_{obs}$ (mean)</th>
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<th>Absolute Error</th>
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Analytical techniques

Nuclear Magnetic Resonance Spectroscopy

$^1$H NMR and $^{13}$C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm (versus tetramethylsilane) and coupling constants in Hz.

Mass Spectrometry

FAB mass spectra were recorded on a VG AutoSpec-Q2 mass spectrometer. ESI mass spectra were recorded on a Micromass LCT Premier spectrometer.
**Elemental Analysis**

All elemental analyses were carried out by the London Metropolitan University service.

**UV-vis Spectroscopy**

UV/vis spectra were recorded on a Perkin Elmer UV-visible Lambda 2 spectrophotometer calibrated to ± 0.2 nm using a holmium oxide standard. A thermostatic circulator controlled the sample holder temperature and all spectra were obtained with an accuracy of ≥ 0.5 nm using 0.5 cm quartz cells. Dry solvents were used unless otherwise stated.

**Melting Points**

Melting points were determined on a Gallenkamp Sanyo MPD 350 heater.
Chapter 9: Overall Conclusions and Future work

To date, the Welton Group’s kinetic studies into ionic liquid solvent behaviour have shown that during the nucleophilic substitution reaction between a charged nucleophile and charged electrophile ionic liquids are “super-dissociating” towards solute ions. The term “super-dissociating” in this instance refers to the ability of the ionic liquid ions to screen the charges of solute ions so that ion pairs do not form. The group have also demonstrated that solute ions neither associate nor dissociate in ionic liquids and that they may in fact form an non-discriminating ideal mixture via investigation of Kosower’s charge transfer complex 1-ethyl-4-(methoxycarbonyl)pyridinium iodide in several ionic liquids. In molecular solvents, solute salts are known to form ion pairs, aggregates and free ions as the solute ions of opposite charges must be in close proximity to preserve charge neutrality. In both the study of a nucleophilic substitution reaction and the study of a charge transfer reaction, the Welton group concluded that ionic liquids can solvate individual ions completely due to the solvent’s ability to preserve charge neutrality.

This work has taken the question of ion pairing in ionic liquids a step further by investigating the role of the solute cation and anion in the nucleophilic substitution reaction between charged electrophile and charged nucleophile. By changing the chemical make-up of the solute cation whilst keeping the nucleophile constant, we have shown that it is possible to increase the reactivity of the nucleophile for the reaction in ionic liquids. We propose that on increasing the size of the solute cation we reduce the number of cations in the coordination sphere of the nucleophile and therefore increase its reactivity. Nonetheless, it appears that the reaction in ionic liquids takes place via free ions regardless of the nature of the solute cation.

This work has also shown that the solute anion (nucleophile) reactivity for the reaction in ionic liquids follows the same trend for the selection of anions as found in the gas phase. This information is important because in the gas phase there are no solvent effects to consider. Therefore we find more evidence supporting the idea that ionic liquids are non-discriminating towards solute anions and that the relative solute anion reactivity is unaffected by the ionic liquid investigated (1-butyl-3-methylimidazolium bisimide).

Whilst this work concludes qualitatively that the reactivity of the chloride ion can be manipulated for a nucleophilic substitution reaction with a charged electrophile in ionic liquids by changing the solute cation, the question of how to quantify this phenomenon in
order to predict absolute reaction rates based on concentrations remains. This project proposes that there exists in the ionic liquid solution two distinct reactive species:

3. The chloride ion coordinated solely by ionic liquid cations.
4. The chloride ion coordinated by both ionic liquid cations and solute cations.

![Figure 77 - The reactive species present](image)

Figure 77 shows a reduction in the chloride coordination number on incorporating a solute cation into the coordination sphere.

It should be noted that the coordination number can increase or decrease on incorporation of a solute cation and this will be determined by the size of the solute cation. The greatest coordination number is achieved by using smaller cations and produces the least reactive chloride ion and reducing the coordination number by increasing the size of the coordinating cations increases the chloride reactivity. We propose that an equilibrium of ion exchange exists between the more and less reactive species in solution and that by carrying out a chloride ion concentration profile (maintaining chloride concentration but changing solute cation concentration) it would be possible to determine this equilibrium constant.

$$k_{eq}$$

$$[\text{Nu}^-]$$   \[\text{fast}\]  \[\text{slow}\]  $$[\text{Nu}^-]$$

![Figure 78 - Ion exchange equilibrium](image)

Figure 78 depicts the ion exchange equilibrium between the more reactive nucleophile (lower coordination number), and the less reactive species (higher coordination number). Further work is needed to determine a range of concentrations of solute cation to chloride ion, from which one could assume two competing mechanisms for the two possible chloride coordination spheres – one for \{Cl[C_4C_1im]6\} (slow) and one for \{Cl[C_4C_1im]5(cat)\} (fast).
We would then be able to calculate two constants which, if consistent across multiple ratios, would provide strong evidence to support this theory.

It is also clear that it would be beneficial to carry out this project in an assortment of ionic liquids with different properties. This investigation has focused on changing the nature of the solute and has involved only one commonly used and easily purified ionic liquid solvent and a selection of molecular solvents. Given that we can be certain nucleophilic substitution reactions between charged electrophiles and charged nucleophiles follow different reaction mechanisms on changing from molecular solvent to ionic liquid, a study of some of the reactions presented in this work in different ionic liquid solvents would allow for inter-ionic liquid comparison and further elucidation of ionic liquid solvent effects.


Definition of the hydrogen bond (IUPAC Recommendations 2011).
126 H. A. Kramers, Physica (The Hague), 1940, 7, 284.


