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Synthesis and Applications of New Ionic Liquids

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Abstract

Ionic liquids (ILs) are promising new media constituted exclusively by ions which can be helpful in a variety of applications. The organic and ionic nature gives to these systems unique properties; a high solvent power towards organic, inorganic and polymeric compounds (including biopolymers) and a very low volatility (if any). This latter property determines the absence of solvent vapour in atmosphere thus avoiding explosive risk linked to that and the toxic effects for workers normally associated to the use of volatile organic solvents (VOC). Nevertheless, they have high polarity values, many have high conductivity values and low viscosity values as well. These properties are normally associated to an high thermal and electrochemical stability. It is to note that all the physico-chemical and biological properties of ionic liquids depend on the anion cation combination: the choice of the best combination of cation and anion is important to meet the requirements of any application.

Due to their low volatility, high solvent power, recyclability ionic liquids are generally considered promising alternative solvents with a low environmental impact (green solvents). However, nowadays to increase the sustainability of many important chemical processes it is necessary not only to use eco-friendly reagents and solvents but it is important also reduce wastes (*e.g.* through the use of catalyst and solvent recovery) and to take into account these principles also when solvents or reagents are produced.

During this PhD thesis we have tried to overcome some problems related to the synthesis and application of ionic liquids improving both preparation methods of ionic liquids and the system recyclability when these salts are used as solvents in some common organic reactions.

We have optimized the methylation procedures of tertiary amines with dimethylcarbonate (a nontoxic methylating agent) avoiding the use of high pressures and temperatures. We have methylated amines with different characteristics and reactivity, and optimized the reaction also for substrates where it is possible the competition between

nucleophile sites. This procedure has led to methylcarbonate-based salts, easily convertible to suitable ionic liquids by neutralization reaction with the appropriate acid. Using this procedure it is also possible to avoid halogen contamination of the final product.

Considering the widespread development of lithium-ion cells and the requirement to avoid the use of volatile compounds we have synthetized a new class of pyrazolium-based ionic liquids that have physico-chemical properties (density, viscosity, conductivity and so on) similar to the widely investigated and applied imidazolium salts but missing of the C(2) proton typical of imidazolium-based ionic liquids, are more resistant to oxidation processes and thus suitable for ion cells applications or, more in general as solvents for oxidative processes. To prepare this class of salts we have also applied new synthetic procedures. The physico-chemical properties of some 1-alkyl-2-methylpyrazolium and 1-alkyl-2,3,5-trimethyl-pyrazolium based ILs have been compared with the properties of analogous imidazolium salts.

CO_2 capture seems to have an exponential increase in interest. Actually, the adopted methods use amines but there are several drawbacks (*e.g.*, corrosion, evaporation loss, etc.). Since recent theoretical calculations evidence the possibility that halogen-functionalised ionic liquids may have an increased affinity to CO_2, we have thought to functionalise some ILs on the lateral alkyl chain with halogen to exploit this possibility.

At the same time, we have investigated the ability of some bis-imidazolium salts bearing a poli-hydroxylated-functionality to bind metals and act as ligand for metal catalyzed reactions which can be performed in water or ILs. In particular, imidazolium cations were connected by a C_1, C_2 or C_3 linear bridge bonded with one nitrogen atom of the imidazolium ring whereas on the other nitrogen bears an ethanolic or glyceryl function. These ILs have been characterized with IR and DSC techniques.

During the course of this thesis we have focused our attention also on oxidation reactions because of both their extensive application in industrial processes which generally are performed using toxic oxidants. Thus, the new ILs synthetized via methylcarbonates have been applied as reaction media in the Wacker oxidation of styrene by hydrogen peroxide using $PdCl_2$ as catalyst. The efficiency of these ILs was compared with hydrophilic and hydrophobic imidazolium systems (including those with nitrile functionalities). The nature of the ionic liquid strongly influences the product distribution.

In particular, in hydrophobic ILs, relevant amounts of 1,3-diphenyl-1-butene arising from styrene dimerization were detected, in addition to the expected phenylmethylketone. The formation of 1,3-diphenyl-1-butene may be attributed to the formation of Pd(0) species from “ClPdOH” (probably formed during the Wackerprocess) in a side-reaction. Consequently, the ability of the IL to favour or disfavour the reoxidation of “ClPdOH” to “ClPdOOH” by hydrogen peroxide, giving an homogeneousphase or a biphasic system, appears to be the main factor affecting selectivity.

Finally, tribromide-based ionic liquids have been synthesized and investigated as efficient solvents and bromination agents. The different physicochemical properties of the reaction media, which depend on the cation structure, have been used to improve the efficiency of the bromination process.

To all my family and friends

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1. Introduction

The term “cleaner production” encompasses goals and principles that fall nicely within the remit of waste minimisation. The United Nations Environmental Programme describes cleaner production as:

“*The continuous application of an integrated preventative environmental strategy to processes and products to reduce risks to humans and the environment. For production processes, cleaner production includes conserving raw materials, and reducing the quality and toxicity of all emissions and wastes before they leave a process.*” [1]

The term “green chemistry” is becoming the worldwide term used to describe the development of more eco-friendly, sustainable chemical products and processes. The term was coined almost ten years ago by the US Environmental Protection Agency and has been defined as:

“*The utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products*.”[2]

This is elaborated further in the form of the so-called Principles of Green Chemistry:[3]

- Waste prevention is better than treatment or clean-up;
- Chemical synthesis should maximize the incorporation of all starting materials;
- Chemical synthesis ideally should use and generate non-hazardous substances;
- Chemical products should be designed to be nontoxic;
- Catalysts are superior to reagents;
- The use of auxiliaries should be minimized;
- Energy demands in chemical syntheses should be minimized;

- Raw materials increasingly should be renewable;
- Derivations should be minimized;
- Chemical products should break down into innocuous products;
- Chemical processes require better control;
- Substances should have minimum potential for accidents.

The atom economy concept is one of the most useful tools available for minimum waste reaction design. The concept is that for economic and environmental reasons reactions should be designed to be atom efficient, *i.e.* as many of the reacting atoms as possible should end up in useful products.[4] The concept of atom economy has been expanded usefully by Sheldon, by the introduction of the term “E factor”, which is the ratio of the kilograms of by-product per kilogram of product.[5]

Obviously other factors also need to be taken into account in determining the most efficient, competitive and eco-friendly route. These factors include:

- Cost and availability of raw materials;
- Toxicity/hazardous nature of raw materials;
- Yield;
- Ease of product isolation and purification;
- Solvent requirements;
- Energy requirements;
- Equipment requirements, cost and availability;
- Process times;
- Nature of waste materials.

The wastes generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture adopts extensively these antiquated “stoichiometric” technologies.

Easy examples are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents ($LiAlH_4$, $NaBH_4$), oxidations with permanganate, MnO_2 and Cr(VI) reagents and a wide variety of reactions, *e.g.* sulfonations, nitrations, halogenations, diazotizations and Friedel-Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3). One solution may be the substitution of classical stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation are good examples of highly atom efficient, low-salt processes.

The generation of copious amounts of inorganic salts can similarly be large circumvented by replacing stoichiometric mineral acids, such as H_2SO_4, and Lewis acids and stoichiometric bases, such as NaOH, KOH, with recyclable solid acids and bases, preferably in catalytic amounts.

Frequently, many chemical reactions involve the use of reagents such as protecting groups and so-called catalysts that do not end up in the useful product. Organic solvents, often thought to be essential but sometimes not actually required at all, fall into this category. Some of these materials end up as waste and some are recovered, but in all cases valuable resources and energy are consumed that do not form part of the required product.[6]

1.1. Green solvents

A solvent is any substance that dissolves another substance so that the resulting mixture is a homogeneous solution. Solvents are some of the most ubiquitous classes of chemicals throughout society and the chemical industry.

When selecting a solvent for one of these widely varied applications, one needs to choose it based on the properties required for a particular application. These properties can be:

- Solubility;
- Polarity;
- Viscosity;

- Volatility.

However, just as one needs to select from these properties in order to meet certain performance criteria, Green Chemistry would suggest that reduced hazard is equally a performance criterion that needs to be met in the selection of a solvent. Some of the types of hazard that are common with a wide range of widely used solvents include the following:

- Inherent toxicity;
- Flammability;
- Explosively;
- Stratospheric ozone depletion;
- Atmospheric ozone production;
- Global warming potential.

Using the principles of Green Chemistry, researchers in industry and academia are developing new solvents or solvent systems which reduce the intrinsic hazards associated with traditional solvents. Of course, using no solvent at all in certain circumstances can be the ultimate solution to minimizing solvent associated hazards.[7]

1.1.1. Ionic liquids

Ionic liquids[8] have relatively low melting points, ideally below ambient temperature. The distinction is arbitrarily based on the salt exhibiting liquidity at or below a given temperature, often conveniently taken to be 100 °C.[9]

Room-temperature ionic liquids containing organic cations including quaternary ammonium, phosphonium, pyridinium, thiazolium, oxazolium and, in particular, asymmetric dialkylimidazolium-based salts are currently available in combination with a variety of anions (Figure 1.1) and have been studied for applications in both electrochemistry and synthesis.[10]

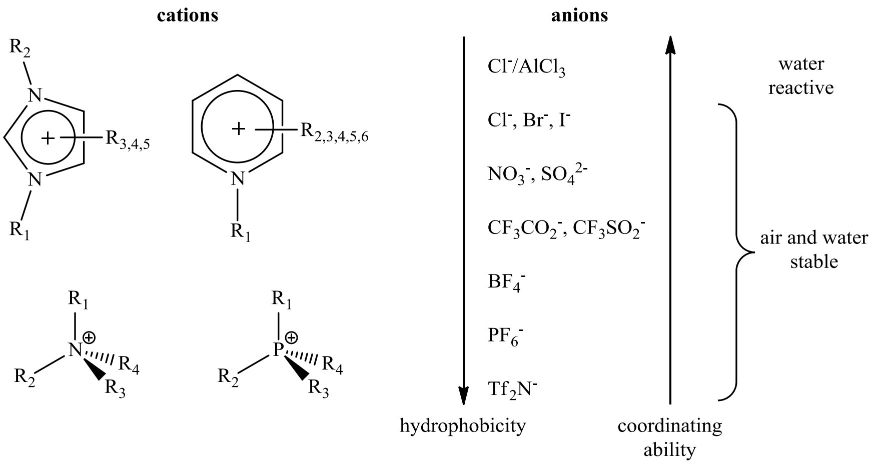


Figure 1.1. Examples of ionic liquids cation and anion pairs and general properties variations changing the anion.

The wide liquid ranges exhibited by ionic liquids, combined with their low melting points and potential for tailoring size, shape, and functionality, offer opportunities for control over reactivity unobtainable with molecular solvents. With the potential large matrix of both anions and cations, it becomes clear that it will be impossible to screen any particular reaction in all the ionic liquids.

Some simple physical properties of ionic liquids make them "greener" compared to other solvents (Table 1.1).[11]

Table 1. Properties and benefits in ionic liquids.

Physical Property		Benefit
Good solvents for a wide range of both inorganic and organic materials	→	Unusual combinations of reagents can be brought into the same phase
Often composed of poorly conducting ions	→	Highly polar non-coordinating solvents
Immiscible with several organic solvents	→	Provide a non-aqueous, polar alternative
Non volatile	→	Used in high vacuum systems

Synthesis

The synthesis of ionic liquids can generally be split into two sections: the formation of the desired cation, and anion exchange where necessary to form the desired product. In some cases only the first step is required, as with the formation of ethylammonium nitrate.[12]

Cations synthesis may be carried out either by protonation with a free acid as noted above, or by quaternization of an amine or a phosphine, most commonly with an alkyl halogenide. Alkylation reaction may be carried out with chloroalkanes, bromoalkanes, and iodoalkanes, with the required reaction conditions becoming steadily more gentle in the order Cl < Br < I, as expected for nucleophilic substitution reactions. The reactivity of the haloalkane also generally decreases with increasing alkyl chain length. The alkylation process possesses the advantages that a wide range of cheap haloalkanes are available, and the substitution reactions generally occur smoothly at even-handed temperatures. Furthermore, the halide salts formed can easily be converted into salts with other anions.

Quaternization reactions are extremely simple, mixing the nucleophile with the desired haloalkane, and the mixture is then stirred and heated.[13] Reaction temperature and time are very dependent on the haloalkane employed, chloroalkanes being the least reactive and iodoalkanes the most. Reaction mixture should be kept free of moisture, as the products are often extremely hygroscopic. The reaction may be carried out without the use of a solvent, as the reagents are generally liquids and mutually miscible, while the halide salt products are usually immiscible in the starting materials. Carrying out the reaction in organic solvent there is the advantage to easily separate the produced salt, insoluble in these solvents.[14] Furthermore, halide salts are generally more dense than the solvent, so solvent removal can be simply achieved by decantation. Haloalkanes and reaction solvents removal is generally not a problem, especially for the relatively volatile shorter chain haloalkanes. On the other hand, the presence even of small quantities of unreacted 1-methylimidazole (a coordinating base), could cause problems in many applications because of its high boiling point (198 °C).

Quaternization reactions with alkyl triflate and tosylates have also been used for the direct preparation of ionic liquids. The excellent leaving group abilities of the triflate and tosylate anions makes possible to carry out at ambient temperatures the reaction.[15] It is important to carry out these reactions under inert atmosphere, as the alkyl triflates and tosylates are extremely sensitive to hydrolysis. This approach has the major advantage of generating the desired ionic liquid with no side products, and in particular no halide ions.

Anion-exchange reactions of ionic liquids can really be divided into two distinct categories: direct treatment of halide salts with Lewis acids, and formation of ionic liquids by anion metathesis.[16]

Treatment of a quaternary halide salt Q^+X^- with a Lewis acid MX_n results in the formation of more than one anion species, depending on the relative proportions of Q^+X^- and MX_n. An example is the reaction between 1-ethyl-3-methylimidazolium chloride and $AlCl_3$ (Figure 1.2).

$$\text{[emim]Cl}^- + \text{AlCl}_3 \rightleftharpoons \text{[emim][AlCl}_4\text{]}$$

$$\text{[emim][AlCl}_4\text{]} + \text{AlCl}_3 \rightleftharpoons \text{[emim][Al}_2\text{Cl}_7\text{]}$$

$$\text{[emim][Al}_2\text{Cl}_7\text{]} + \text{AlCl}_3 \rightleftharpoons \text{[emim][Al}_3\text{Cl}_{10}\text{]}$$

Figure 1.2. Equilibrium equations for the reaction between $[emim]Cl^-$ and $AlCl_3$.

When $[emim]Cl^-$ is present in a molar excess over $AlCl_3$, only the first equilibrium need to be considered, and the ionic liquid is basic. On the other hand, when a molar excess of $AlCl_3$ over $[EMIM]Cl^-$ is present an acidic ionic liquid is formed, and the other two equilibria predominate.[17] The reaction is exothermic and most of the starting materials and the ionic liquids produced are water-sensitive.

The general metathesis reaction can be divided into two categories depending on the water solubility of the target ionic liquid: metathesis via free acids or group 1 metals/ammonium salts, or Ag salt metathesis.

The main goal of all anion exchange reactions is the formation of the desired ionic liquid uncontaminated with unwanted cations or anions, a task that is easier for water-immiscible ionic liquids. The synthesis of “second generation” ionic liquids, air- and water-stable ionic liquids, involved a metathesis reaction between imidazolium halide and a range of silver salts (*e.g.*, $AgNO_3$, $AgBF_4$, $AgCH_3CO_2$, Ag_2SO_4, $AgN(CN)_2$, etc.) in methanol or aqueous methanol solution.[18] The very low solubility of silver halide (iodide is the lowest soluble) in these solvents allowed it to be separate simply by filtration, and removal of the reaction solvent allowed isolation of the ionic liquids in high yields and purity. This method remains the most efficient for the synthesis of water-miscible ionic liquids, but is obviously limited by the relatively high cost of silver salts and the large quantities of solid by-product produced. Complete precipitation of silver halides from organic solvents can also be quite slow, leading to silver-contaminated products. The nature of the precipitate can also be troublesome; in some cases the silver halide forms as submicron particles which are difficult to filter.

The most common approach for the preparation of hydrophobic ionic liquids is firstly to prepare an aqueous solution of a halide salt of the desired cation. The cation exchange is then carried out either with the free acid of the appropriate anion, or else with a metal or ammonium salt. Where available, the free acid is probably to be favoured, as it leaves only HCl, HBr, or HI as the byproduct, easily removable from the final product by washing with water. One example is reaction between HPF_6 and the corresponding halide salt.[19] Washing should be continued until the aqueous residues are neutral, as traces of acid can cause decomposition of the ionic liquid over time. This can be a particular problem for salts based on the PF_6^- anion, which will slowly form HF, particularly on heating if not completely acid-free, but it may be preferable to avoid use of the free acid in systems where the presence of traces of acid may cause problems. The high viscosity of some ionic liquids makes efficient washing difficult, so their dissolution in either CH_2Cl_2 or $CHCl_3$ is recommended.

BF_4^- salts can be prepared by metathesis reaction of the corresponding chloride with ammonium tetrafluoroborate in acetone in high purity because reaction with the sodium salt leaves appreciable amounts of halide ions in the ionic liquid, as sodium halides are slightly soluble in acetone.[20] Depending water solubility on cation alkyl chain length, Seddon *et al*.[21] discussed metathesis reaction and subsequent purification procedure, through extraction with CH_2Cl_2, for tetrafluoroborate anion. For alkyl chains of 6-10 carbon atoms the ionic liquid separates as a dense liquid, whereas for chain length $n > 10$ a solid separates from the aqueous reaction mixture. Chains lengths $n = 4$-5 can be extracted and purified from aqueous solution by partitioning into an organic solvent. Metathesis *via* the alkyl halide with a silver salt is more useful for shorter chains for which the partition coefficient water:IL:organic solvent is too close to 1.

Performing anion metathesis the most common impurities are halide anions, or unwanted cations inefficiently separated from the final product. Both can be disadvantageous to the performance particularly in applications involving transition metal-based catalysts, which are often deactivated by halide ions. In general this is much more of a problem of water-soluble ionic liquids, as water-immiscible salts can usually be purified quite efficiently by washing with water. Also the physical properties such as density and viscosity can be radically altered by the presence of unwanted ions.[22]

Ion exchange materials are salts where one of the ions is fixed in a stationary (solid/gel) phase and the counter ion (in solution) is exchangeable. When a solution is passed through a column of ion exchange material, the counter ion A^- of the material will equilibrate with the corresponding ion B^- of the solution. Providing the column is of sufficient length and/or the equilibrium constant is sufficiently large, exchange will take place until complete exchange occurs and only species [cation]A^- is eluted as a pure solution.[23]

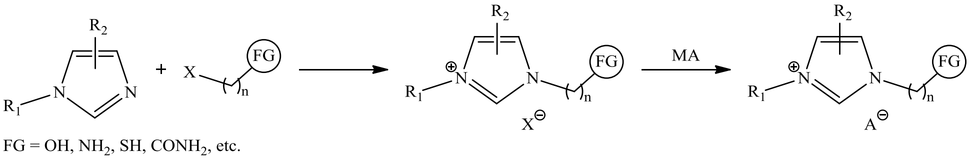
Ion exchange is almost always a reversible process and ion exchange materials usually show a preference for one ion over another. The most successful synthetic ion exchange occurs when the ion exchange material shows a strong preference for the counter ion of the starting material over the corresponding ion of the product. The factors which determine this preference are complex, but in crude, well known terms ion exchange materials tend to have a higher affinity for ions:[24]

- With higher valence;
- With smaller solvated volume;
- With greater polarizability;
- Which interact more strongly with the exchange material.

Commonly, target ILs cations and anions are available as either the alkali metal salt or the halide salt and the above principles suggest many ion exchange materials will show a preference for these counter ions and therefore IL synthesis from these starting materials will be successful. The preference principles are: to hinder the initial loading of an ion exchange material with an IL ion or, as long as the affinity difference is not too great, to pass several times high concentrated loading solution.[25]

By changing the nature of the ions present in an IL, it is possible to change the resulting properties of the IL. For example, the miscibility with water can be varied from complete miscibility to almost total immiscibility, by changing the anion from, for example, Cl^- to PF_6^-. Similarly, the lipophilicity of an IL is modified by the degree of cation substitution. Primary solvent features of ILs include the capability for H-bond donation from the cation to polar or dipolar solutes, H-bond accepting functionality in the anion (this is variable, *e.g.* Cl^- is a good H-bond acceptor whereas PF_6^- is poor), and π-π or C–H···π interactions (which enhance aromatic solubility).

Task-specific ionic liquids (Scheme 1.1), TSILs, may be defined as ionic liquids in which a functional group is covalently bonded to the cation or anion (or both).[26] The presence of a functional group may improve the catalytic reaction: (i) assisting in the activation of the catalyst; (ii) generating a novel catalytic species; (iii) improving the stability of the catalyst; (iv) optimising immobilisation and recyclability; (v) facilitating product isolation and (vi) influencing the selectivity of the reaction. In addition, the functionalised ionic liquid has to meet certain requirements to be of use in synthesis/catalysis as their inertness with respect to the reaction in question and their balance between catalyst stabilization and activation.[27]



Scheme 1.1. Functionalized imidazolium ionic liquids synthesis.

A wide variety of functional groups have been introduced directly onto the imidazolium moiety including alcohols (peptide synthesis),[28] carboxylic acids (polymer coordination),[29] amine and amide (catalyst stabilization),[30] phosphine (lubrication and catalyst stabilization),[31] thiols (nanoparticles stabilization),[32] multiple bonds (ionic polymers),[33] fluorous chains (lipophilic ionic liquids)[34] and chiral pendants (chiral induction).[35]

An area in which functionalised ionic liquids are already playing an important role in catalysis is heterogenisation on solid supports. The general concept involves the immobilisation of imidazolium and other cationic fragments onto solid supports using appropriate functional groups attached to the cation.

Melting Point

Ionic liquids are one class of molten salts and, inevitably, a substance that is composed solely of anions and cations must possess some kind of short-range organization so as to fulfil local electro-neutrality conditions and also to maximize the electrostatic interactions between ions of opposite sign. In ionic liquids the surprising feature is that the imposed short-range charge ordering does not lead to long-range ordered structures (crystalline forms) at room temperature. In fact, that is the defining characteristic of this novel and diverse class of compounds.

Significant randomness in organization is necessary to describe the structure of a liquid. However, a majority of materials exhibit only a 10-15% volume expansion on going from the crystalline to the liquid state. Since volume increases with the cube of distance the relatively small volume increase upon melting requires that atom-atom or ion-ion distances in the liquid state are not significantly different from those in the solid state.

The dominant force of attraction between ions that must be overcome upon melting a salt to an ionic liquid is the coulombic attraction between oppositely charged particles (Coulomb's law):

$$F = \frac{q_1 q_2}{\varepsilon r^2}$$

But the structure of an ionic liquid directly impacts upon its properties, in particular the melting point and liquid ranges. The charge, size and charge distribution on the respective ions are the main factors that influence the melting points of the salts. However, small changes in the shape of uncharged, covalent regions of the ions can have an important influence on their melting points.

The overall lattice energies of ionic solids depends on: (i) the product of the net ion charges, (ii) ion-ion separation, and (iii) packing efficiency of the ions. As the size of the anion increases, the melting point of the salt decreases, reflecting the weaker Coulombic interactions in the crystal lattice. Large anions are, in general, non-spherical and have significant associated covalency. A similar increase is observed with increasing cation size. In some large anions (*e.g.*, tetraphenylborate) additional attractive interactions such as aromatic π-π stacking can give rise to increased melting points. Anion and cation contributions cannot be taken in isolation; induced dipoles can increase melting points through hydrogen bonding interactions, seen in the crystal structures with halogen instead of PF_6^-.[36] Tf_2N^- anion provides a steric block allowing a greater charge delocalization.

The size of the respective cations not only decreases the Coulombic attraction by separating the centres of charge, but often the charge in a polyatomic ion will be delocalized over the surface (or volume) of the anion resulting in a dramatically reduced charge density. Because the ionic liquid must necessarily organize its high-charge density portions into local structures that obey electroneutrality and maximize Coulomb interactions, it follows that the low-charge density parts of the ions that do not participate in those interactions will tend to be segregated elsewhere. It is this interplay between the two types of interaction, Coulomb and van der Waals, that eventually leads to the formation of medium-range structures and the recognition of some ionic liquids as composed of a high-charge density, cohesive network permeated by low-charge density regions.[37] Comparing the melting points of some sodium salts it is possible to see that increasing the thermochemical anionic radius from $Cl^- < BF_4^- < PF_6^- < AlCl_4^-$ the melting point of the sodium salts is dramatically reduced from 801 °C to 185 °C. Tetraalkylammonium and phosphonium salts are examples of salts containing large cations with delocalized, or more correctly alkyl-shielded charge. Longer alkyl chains were required to obtain room temperature liquid tetraalkylammonium ionic liquids, *i.e.* at least two or three different alkyl groups are required to create crystal packing constraints; this usually requires several steps of alkylation. Additionally, the salts contain linear alkyl substituents, which have many rotational degrees of freedom, allowing the alkyl chains to "melt" at temperatures below the melting point and resulting in solid-solid polymorphic transitions. Melting points of organic salts have an important relationship to the symmetry of the ions: increasing symmetry in the ions increases melting points, by permitting more efficient ion-ion packing in the crystal cell. Conversely, a reduction of the cation symmetry causes a distortion from ideal close-packing of the ionic charges in the solid state lattice, a reduction in the lattice energy, and depression of melting points.

The acidity of the hydrogen bound to the C(2) of the imidazolium cation is commonly noted. Though less acidic, a partial positive charge, δ^+, also resides on the hydrogens bound to C(4) and C(5), as is common to all aromatic rings. In contrast to the normally observed δ^- charge on the face of an aromatic ring, some of the positive charge of the imidazolium cation is also distributed over the face of the ring, consistent with resonance structures that assign a positive formal charge to the nitrogens. Substitution at the C(2) of the imidazolium ring increases the melting points of the salts because of changes in the cation structure that can induce aromatic stacking or methyl-π interactions between cations.

Manipulation of the alkyl chain can produce major changes in the melting points, and also in the tendency to form glasses rather than crystalline solids on cooling, by changing the efficiency of ion packing. An increase in the substituent length initially reduces the melting point of the IL, with the major trend towards glass formation on cooling for n = 4-10. On extending the alkyl chain lengths beyond a certain point (around 8-10 carbons for alkyl-methylimidazolium salts), the melting points of the salts start to increase again with increasing chain length, as van der Waals interactions between the long hydrocarbon chains contribute to local structure by induction of microphase separation between the covalent, hydrophobic alkyl chains and charged ionic regions of the molecules. The crystalline phases of the ionic liquid are dominated by Coulombic ion-ion interactions, comparable to those in typical salt crystals, although since the ions are larger, the Coulombic interactions are weaker (decreasing with r^2).[38]

The upper limit of the liquid range is usually bounded by the thermal decomposition temperature of the ionic liquid, since most ionic liquids are non-volatile. Pyrolysis generally occurs between 350-450 °C through an E2 elimination degradation pathway of the *N*-substituent, essentially the reverse of the S_N2 substitution reaction to form the ionic liquid.[39]

Viscosity

In general a low viscosity is desired for solvent applications in order to minimize pumping costs and increase mass transfer rates while higher viscosities may be favourable for other applications such as lubrication or use in supported membrane separation processes.[40]

Looking at 1-alkyl-3-methylimidazolium ionic liquids, the most studied ILs class, viscosities increase, non-linearly, with increasing alkyl chain length.[41] Longer alkyl chain lengths in the l-alkyl-3-methylimidazolium cation not only lead to heavier and bulkier ions, but also give rise to increasing Van der Waals attractions between the aliphatic alkyl chains.

Van der Waals forces occur increasingly, for $n \geq 4$, since the ionic headgroup has little or no electron withdrawing effect on that part of the alkyl chain. In the extreme case, with $n > 12$, liquid crystal phases are formed with a microphase separation of the hydrophilic ionic headgroups and the hydrophobic alkyl chains. This scenario is consistent with the interdigitated layered structure observed in the solid state for long chain ionic liquid like $[C_{12}mim][PF_6]$.[42]

1.2. Ionic liquids in catalysis

Technology is called "green" if it uses raw materials efficiently, such that the use of toxic and hazardous reagents and solvents can be avoided while formation of waste or undesirable by-products is minimized. Catalytic routes often satisfy these criteria.[43]

Catalysts accelerate reactions and thus enable industrially important reactions to be carried out efficiently under practically attainable conditions. Very often, catalytic routes can be designed such that raw materials are used efficiently and waste production is minimized. Consequently, the chemical industry is largely based upon catalysis: roughly 85-90% of all products are made in catalytic processes, and the percentage is increasing steadily.

Another effective method to influence environmental safety is to reduce or remove volatile organic compounds, *i.e.* solvents. Solvents are among the most ubiquitous classes of chemicals throughout society and the chemical industry because their applications are so broad and varied. In particular, solvents are used on a huge scale in manufacturing as reaction medium for chemical transformations. An ideal system would not require any solvent at all. However, solvents are extremely helpful for a number of reasons. They allow reactants to come together in a homogeneous fashion improving selectivity and yields. They also have an important role as a heat transfer medium, dissipating heat liberated by an exothermic reaction or supplying the thermal energy required to initiate an endothermic one. As such, solvents elimination from many manufacturing processes is highly unlikely, especially for processes involving reactants and products that are solids under ambient conditions, and biphasic catalysis represents one of the best ways of improving the environmental efficiency of a chemical process.

Water is the solvent of choice as it is abundant, cheap, non-flammable, non-toxic and has many other desirable properties such as being polar, high thermal conductivity, heat capacity and heat of evaporation.[44] Nevertheless, alternative solvents to water for applications in biphasic catalysis[45] are needed for several reasons:[46]

- Many catalysts do not dissolve in water and thus their ligands must be modified with hydrophilic groups that can be expensive, especially for chiral ligands. Furthermore, some catalysts are unstable in water and decompose.
- The solubility of organic compounds in water is often poor. While this may be an advantage for product separation, lower reaction rates and yields are frequently observed. This problem may be overcome by increasing the stirrer rate or the temperature of the aqueous-organic biphasic system or adding phase transfer reagents, co-solvents, detergents and surfactants as well as the use of ultrasound and microwave dielectric heating.
- The high specific heat capacity of water means that distillation requires high energy, and reaction mixtures are difficult to heat or cool rapidly.
- Viscosity and pH effects.

Reaction media such as ionic liquids, fluorous solvents and supercritical fluids may offer a solution in avoiding some of the above mentioned problems.

1.2.1. Role of the ionic liquid

There are several features that make ionic liquids so attractive as solvents for conducting organic synthesis.[47]

Ionic liquids do not evaporate as they have no detectable vapour pressure. Since reducing the emissions of volatile organic compounds is viewed as one of the most important ways of reducing pollution from the chemical industry (and other industries) it is perhaps this property of ionic liquids that makes them so attractive as potentially benign replacements to organic solvents. Volatile organics (reaction products) can thus be easily removed from the ionic liquid under vacuum, by distillation or using a carrier gas such as CO_2.

Many metal catalysts (notably salts), organic compounds (especially polar compounds), gases and biocatalysts dissolve in ionic liquids, allowing homogeneously catalysed reactions to be performed.

Ionic liquids are immiscible with many organic solvents and compounds, which provides themselves to biphasic or multiphasic catalytic reactions. Most are also immiscible with fluorous phases and some are immiscible with water. In the ideal biphasic process involving ionic liquids, a soluble polar substrate is converted to a less polar, and thus insoluble, product, which will then form a separate phase. Attaching fluorous groups to the ionic liquid cation can reverse the solubility properties.

Ionic liquids have polarities comparable to lower alcohols, which are amongst the most widely used solvents in which to conduct homogeneously catalysed reactions. In contrast to lower alcohols, however, many ionic liquids are non-nucleophilic, which can have a pronounced effect on a catalysed reaction. For example, solvated catalytic intermediates are unlikely to form, and this feature could lead to different reaction mechanisms, and hence to different yields and selectivity. Ionic liquids with weakly coordinating, inert anions (such as Tf_2N^-, BF_4^-, or PF_6^- under anhydrous conditions) and inert cations (cations that do not coordinate to the catalyst themselves, nor form species that coordinate to the catalyst under the reaction conditions used) can be looked on as “innocent” solvents in transition metal catalysis.[48] Therefore, the use of an inert, weakly coordinating ionic liquid can result in a clear enhancement of catalytic activity, since some ionic liquids are known to combine high solvation power for polar catalyst complexes (polarity) with weak coordination (nucleophilicity).[49] The non-nucleophilic environment presented by many ionic liquids is also less likely to deactivate a catalyst and can lead to increased turnover numbers, which is essential in biphasic processes where catalyst recycling and reuse is required.

It is not always necessary to modify a catalyst for use in ionic liquids, and expensive ligands that modify the solubility properties of a catalyst are not necessarily required. For example, Wilkinson’s catalyst and the highly active C–C coupling catalyst $Pd(PPh_3)_4$ have been used in ionic liquids, although quantification of catalyst loss was not reported, and this might be high. Many catalysts are salts and in general these are very well retained in ionic liquids, and where necessary, ligands that anchor a catalyst in an ionic liquid phase are available.[50]

While very little toxicity data are available it would appear that many ionic liquids do not represent an immediate threat to health if handled properly. However, at present very little is known about their biodegradability and aquatic toxicity and it is envisaged that more data are needed prior to their use on a large scale. In addition, ionic liquids composed of fluoride containing anions such as BF_4^- or PF_6^- cannot be incinerated and therefore their use on a large scale might be problematic.

However the dissolution process of a solid, crystalline complex in an (often relatively viscous) ionic liquid can sometimes be slow. This is due to restricted mass transfer and can be speeded up either by increasing the exchange surface using ultrasonic bath or by reducing the ionic liquid's viscosity. Full immobilization of the transition metal catalyst, combined with the possibility of recycling it, is usually a crucial criterion for the large-scale use of homogeneous catalysis.

There are also drawbacks related to anion nature. Tetrafluoroborate and hexafluorophosphate are still relatively sensitive to hydrolysis forming gaseous HF and phosphoric acid. The hydrolytic formation of HF from the anion of the ionic liquid under the reaction conditions causes the following problems with regard to their use as solvents for transition metal catalysis: (i) loss or partial loss of the ionic liquid solvent, (ii) corrosion problems related to the HF formed, and (iii) deactivation of the transition metal catalyst through its irreversible complexation by F-ions.

Lewis acid ionic liquids

Ionic liquids formed by treatment of a halide salt with a Lewis acid (such as chloroaluminate or chlorostannate melts) generally act both as solvent and as co-catalyst in transition metal catalysis. The reason for this is that the Lewis acidity or basicity, which is always present, results in strong interactions with the catalyst complex.[51]

Acidic chloroaluminate(III) ionic liquids (where $X(AlCl_3) > 0.50$) catalyse reactions that are conventionally catalysed by aluminium(III) chloride, without suffering the disadvantage of its low solubility in many solvents. Indeed, they are also exceptionally powerful solvents.[52]

The major source of waste in the (fine) chemicals industry is derived from the widespread use of liquid mineral acids (HF, H_2SO_4) and a variety of Lewis acids. They cannot easily be recycled and generally end up, via a hydrolytic work-up, as waste streams containing large amounts of inorganic salts. Their widespread replacement by recyclable solid acids would afford a dramatic reduction in waste. Solid acids, such as zeolites, acidic clays and related materials, have many advantages in this respect.[53] They are often truly catalytic and can easily be separated from liquid reaction mixtures, obviating the need for hydrolytic work-up, and recycled. Moreover, solid acids are non-corrosive and easier (safer) to handle than mineral acids such as H_2SO_4 or HF.

A prominent example is Friedel-Crafts acylation, a widely applied reaction in the fine chemicals industry. In contrast to the corresponding alkylations, which are truly catalytic processes, Friedel-Crafts acylations generally require more than one equivalent of, *i.e.* $AlCl_3$ or BF_3.

Friedel-Crafts electrophilic alkylation and acylation reactions are normally run in an inert solvent and catalysed by suspended or dissolved $AlCl_3$. Acidic chloroaluminate ionic liquids have already been described as both solvents and catalysts for reactions conventionally catalysed by $AlCl_3$, such as catalytic Friedel-Crafts alkylation or stoichiometric Friedel-Crafts acylation.[54] In a very similar manner, Lewis-acidic transition metal complexes can form complex anions by reaction with organic halide salts.[55] The acylation of naphthalene, the ionic liquid gives the highest known selectivity for the 1-position.[56] Cracking and isomerisation reactions occur readily in acidic chloroaluminate(III) ionic liquids, *e.g.* polyethylene is converted to a mixture of gaseous alkanes with the formula (C_nH_{2n+2}, where n = 3-5) and cyclic alkanes with a hydrogen to carbon ratio less than two.[57] The distribution of the products obtained from this reaction depends upon the reaction temperature and differs from other polyethylene recycling reactions in that aromatics and alkenes are not formed in significant concentrations. Another significant difference is that this ionic liquid reaction occurs at temperatures as low as 90 °C, whereas conventional catalytic reactions require much higher temperatures, typically 300-1000 °C.[58]

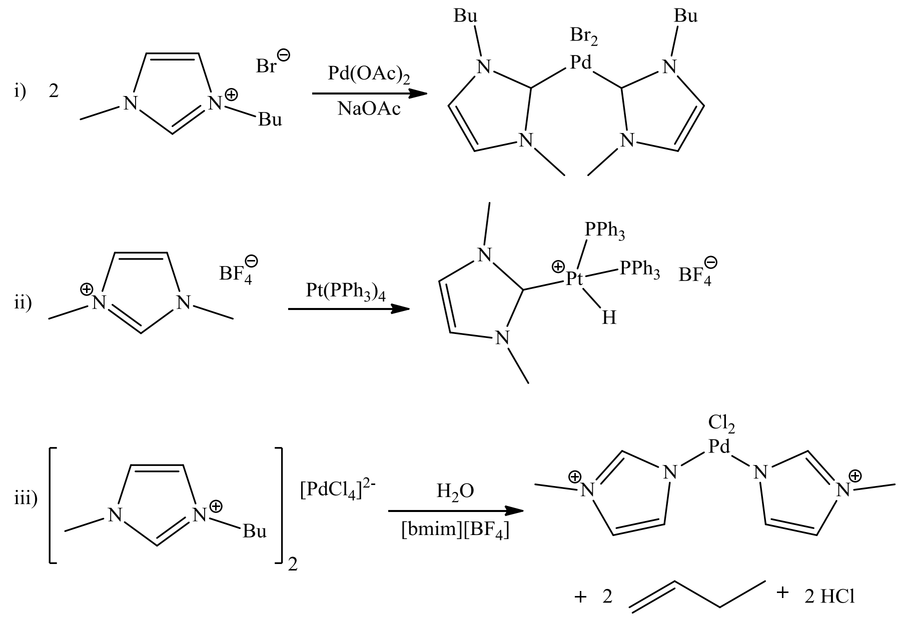
Protons in acidic ionic liquids have acidities greater than those of H_2SO_4 or liquid HF.[59] They are, for example, able to protonate benzene to the cyclohexadienyl cation. The acidic ionic liquid, [bmim][Al_2Cl_7], catalyses the alkylation of ethene with isobutane whereas neither HF nor H_2SO_4 are effective for this reaction.[60] The major product is 2,3-dimethylbutane (75-86%) which has a higher octane number than the products of alkylation of higher olefins. The product forms a separate upper phase and the ionic liquid is readily recycled. Olefin oligomerisation and polymerisation is also promoted by these strongly acidic ionic liquids, *e.g.* high molecular weight polyisobutene is readily obtained from isobutene.[61]

The catalytic activity and degree of polymerisation is determined by the chain length of the alkyl group in the 1-alkyl-3-methylimidazolium or *N*-alkylpyridinium cation which provides a convenient mechanism for controlling the product distribution. Polyisobutene is a commercially important lubricant and the ionic liquid process has several advantages compared with the conventional process which employs a supported or dissolved $AlCl_3$ catalyst. The polymer forms a separate phase and is readily separated and reused obviating the need for an aqueous wash and, hence, reducing waste and costs.[62]

Neutral ionic liquids

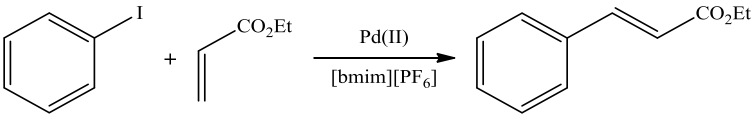
Chloroaluminate(III) ionic liquids are excellent catalysts and solvents in many processes, but suffer from several disadvantages, such as their moisture sensitivity and the difficulty of separation of products containing heteroatoms from the ionic liquid, whilst leaving the ionic liquid intact. Hence research is shifting to the investigation of ionic liquids that are stable to water. This allows for straightforward product separation and ease of handling.

Imidazolium moiety, as an ionic liquid cation, can act as ligand precursor for the dissolved transition metal. Its transformation into a ligand under the reaction conditions has been observed in three different ways (Scheme 1.2): (i) formation of metal carbene complexes by deprotonation of the imidazolium cation, (ii) formation of metal-carbene complexes by oxidative addition of the imidazolium cation to the metal centre, and (iii) dealkylation of the imidazolium cation and formation of a metal-imidazole complex.



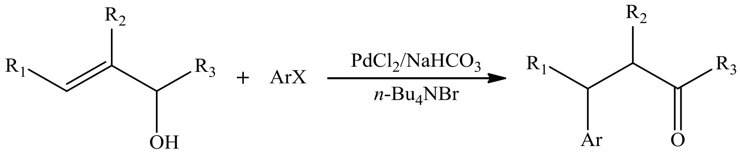
Scheme 1.2. Different potential routes for *in situ* ligand formation from an imidazolium cation.

The *in situ* formation of a metal-carbene complex with an imidazolium ionic liquid is based on the well-known, relatively high acidity of the C(2)'s H atom of the imidazolium ion.[63] This can be removed (*e.g.* by basic ligands of the metal complex) to form a metal-carbene complex. Pd-imidazolylidene complexes can be formed when $Pd(OAc)_2$ is heated in the presence of $[bmim]Br^-$ and the isolated Pd carbene complex is active and stable in Heck coupling reactions (Scheme 1.3, Figure 1.1).[64]



Scheme 1.3. Heck reaction in ionic liquid.

The homogeneous palladium-catalysed C–C coupling reactions of aromatic and vinylic systems[65] have received increasing attention due to their synthetic versatility.[66] The need for high amounts of palladium catalyst is one of the technical limitations for the applicability of this reaction. However, this limitation can be overcome by immobilizing the catalyst. Inasmuch as the Heck reaction is usually performed in polar solvents and that salt additives such as $[Bu_4N]Br^-$ can activate and stabilize the catalytically active palladium species, ionic liquids appear to be the ideal immobilizing agents (Scheme 1.4).[67] Indeed, Kaufmann has demonstrated that the vinylation of aryl halides can be performed by simple palladium catalyst precursors such as palladium chloride, palladium acetate, and $PdCl_2(PPh_3)_2$ dissolved in hexadecyltributylphosphonium bromide and tetrabutylammonium chloride ionic liquids, without the addition of phosphine ligands. Bromoarenes conversion and reaction yields up to 99%.

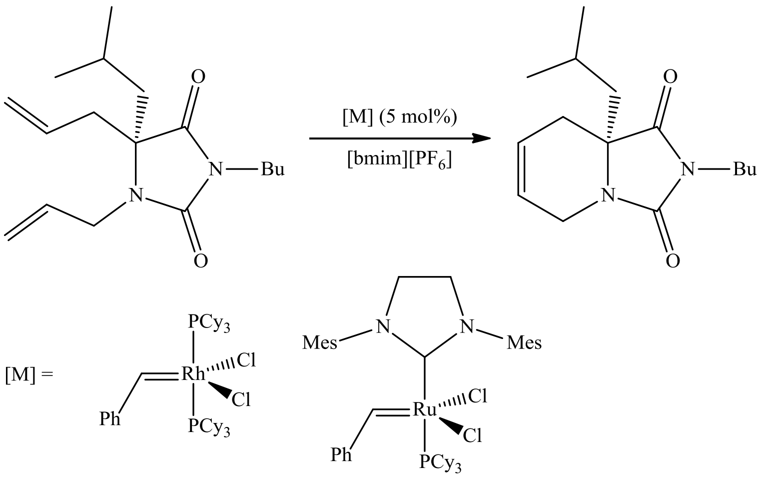


Scheme 1.4. $PdCl_2$ catalysed cross coupling in $[Bu_4N]Br^-$.

The reactions performed in ionic liquids have various advantages as compared to all previously described molecular solvents, such as catalytic efficiency for the vinylation of chloroarenes and improved thermal catalyst stability and lifetime during the reaction.[68]

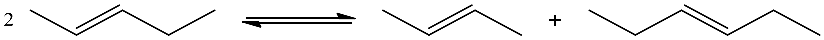
Homogeneous transition-metal-catalysed olefin metathesis (*i.e.*, ring-opening metathesis polymerization (ROMP), acyclic diene metathesis (ADMET), ring-closing metathesis (RCM), and metathesis of acyclic olefins) is a focal issue in both organic synthesis and polymer chemistry.[69]

Initial attempts to immobilize Ru-[70] and Mo-carbene[71] homogeneous catalyst precursors in [bmim][BF_4] and [bmim][PF_6] have failed. However, RCM of dienes such as 1,7-octadiene was achieved with the Grubbs Ru catalyst precursor initially dissolved in [bmim][PF_6]. The reaction in fact takes place in the organic phase where the Ru species are leached from the ionic liquid phase. However, it has been recently reported that the Grubbs Ru catalyst precursor in [bmim][PF_6] promoted the RCM of various dienes (Scheme 1.5) and the Ru catalyst were recycled (after extraction of the product with diethyl ether) for at least three cycles. The diene conversion drops from 97% on the first run to 61% on the second recycling.[72] The catalytic activity is strongly dependent on both anions, X = OTf being the anion of choice.



Scheme 1.5. RCM in ionic liquid.

Olefin disproportionation can also be performed by transition-metal metathesis catalysts based on W(VI) and Mo(V) compounds immobilized in [bmim][$AlCl_4$] ionic liquid (Scheme 1.6).[73] This is a practical method for the conversion of terminal or internal linear olefins into a thermodynamic mixture of olefins.



Scheme 1.6. Olefin disproportionation.

1.2.2. Multiphasic reactions

The separation of the products from the reaction mixture, the recovery of the catalysts, and the need for organic solvents are the major disadvantages in the homogeneous catalytic process. For these reasons, many homogeneous processes are not used on an industrial scale despite their benefits.

While the solubility of organometallic complexes in common organic solvents appears to be an advantage in terms of site availability and tunability, reaction selectivity, and activity, it is a major drawback in terms of catalyst separation and recycling. Most homogeneous metal catalysts are sensitive to heat, oxygen, moisture and so on. They easily loose catalytic activity forming metal clusters. These disadvantages made recycle use of the catalyst difficult, along with difficulty in catalyst separation from products and solvent. Efficient catalysts having high TON are not enough. The quest for new catalyst immobilization or recovery strategies to facilitate reuse is unceasing. Immobilization of the catalyst on a solid support has been widely studied. Except for Ziegler-Natta- and metallocene-type polymerization processes, in which the catalyst is not recycled due to its high activity, this technology has not yet been developed industrially, mainly because of problems of catalyst leaching and deactivation.

Catalyst decomposition can happen *via* a number of pathways. One intuitive and well-established example would involve oxygen sensitivity, or other oxidation modes. This is frequently observed with metal containing catalysts, and phosphine catalysts. Polymer-supported metathesis catalysts, as scavenging system to trap labile ligands, are becoming increasingly available.[74] Decomposed catalysts can (i) phase separate, such as *via* precipitation, (ii) co-leach with leached catalyst, (iii) be co-recovered with the catalyst or catalyst resting state, or (iv) be removed at other stages of the recycling process.

Catalyst leaching is usually associated with a phase boundary, and there are many types. For example, the active component of an insoluble or polymer-bound catalyst might slowly leach into solution by some mechanism, perhaps involving bond breaking. Alternatively, in liquid/liquid biphase catalysis, the catalyst might leach into the liquid phase that is not recycled, or that may contain the product. When the catalyst or catalyst resting state has leached into a product phase, the sample should exhibit some catalytic activity. Alternatively, an inactive decomposed catalyst might leach. There are many scenarios under which such species might cross a phase boundary more readily than the catalyst or catalyst resting state. Where a ligand must dissociate from a catalyst precursor before the catalytic cycle can be entered. The ligand might leach with little consequence for the recyclability of the catalyst.[75]

On the other hand, a heterogeneous catalyst has complementary character. They are stable, simple to separate, and thus easy to re-use. However, since structure is not always unambiguous, fine-tuning of the catalyst is not feasible.

One successful approach to close the advantage/disadvantage gap between homogeneous and heterogeneous catalysis is multiphasic catalysis.[76] In its simplest version, there are only two liquid phases (“biphasic” or “twophase” catalysis). The catalyst is dissolved in one generally polar phase while products and substrates are found in the other. Homogeneous catalysts are very often unstable at the high temperatures necessary for the distillation of high-boiling products. Multiphasic catalysis makes possible the products separation under mild conditions.

In the phase-transfer catalysis (PTC) approach, a catalytic amount of quaternary ammonium salt $[Q]^+[X]^-$ is present in an aqueous phase. The catalyst's lipophilic cation $[Q]^+$ transports the reactant's anion $[X]^-$ to the organic phase, as an ion-pair, and the chemical reaction occurs in the organic phase of the two-phase organic/aqueous mixture.[77]

Multiphasic catalysis relies on the transfer of organic substrates into the catalyst phase or on catalysis at the phase boundary but the current applications of this technique remain limited: firstly to catalysts that are stable in the presence of water, and secondly to substrates that have significant water solubility.

The major advantage of the use of two-phase catalysis is the easy separation of the catalyst and product phases. The tunable miscibility with organic products by variation of the temperature is the main advantage of perfluorinated solvents. Fluorous-phase catalysis makes possible the association of homogeneous phase catalysis and a biphasic separation of the catalyst and reaction mixture.[78] However, these solvents are still relatively expensive and require costly, specially designed ligands to keep the catalyst in the fluorous phase during the separation. In addition, a significant amount of perfluorinated solvent can remain dissolved in the organic phase, and contamination of the products can occur.[79]

scCO_2 in combination with homogeneous catalysis, its benefits could be the potential increase of reaction rates (absence of gas-liquid phase boundary, high diffusion rates) and selectivity, and also its lack of toxicity.[80] This approach still appears relatively expensive, especially for the bulk chemical industry.

Due to the high ionic liquids tunability, there are several achievable catalytic conditions. When the ionic liquid is able to dissolve the catalyst, and displays a partial solubility with the substrates and a poor solubility with the reaction products, the product upper phase, also containing the unconverted reactants, is removed by simple phase decantation, and the ionic liquid containing the catalyst is recycled.[81]

When the products are partially or totally miscible in the ionic phase, separation is much more complicated. In this case the reaction can be performed in one single phase, thus avoiding diffusional limitation, and the products separated in a further step by extraction.[82] In the separation step, a co-solvent that is poorly miscible with ionic liquids but highly miscible with the products can be added to facilitate product separation. When hydrophilic ionic liquids are used as solvents and the products are partly or totally soluble therein, the addition of polar solvents, such as water, in a separation step after the reaction can make the ionic liquid more hydrophilic and facilitate the separation of the products from the ionic liquid/water mixture.

Alternatively, some volatile products can be separated from the ionic liquid and catalyst by distillation. This is because the ionic liquid has effectively no vapour pressure and therefore cannot be lost. There also exists the possibility of extraction with supercritical solvents. A recent example is the use of supercritical carbon dioxide to extract naphthalene from [bmim][PF_6].[83]

Transition metal catalysts can also be immobilized in ionic liquids with melting points just above room temperature. The reaction occurs in a two-phase liquid-liquid system. By cooling the reaction mixture, the products can be separated by filtration from the “solid” catalyst medium, which can be recycled.[84] To achieve the development of such an approach in continuous process, the key point is to immobilize and stabilize the catalyst in the ionic liquid in the presence of an organic second phase with minimum loss of metal. If the active species is known to be ionic in conventional organic solvents one may expect that the catalyst should remain ionic and be retained without modification in the ionic liquid. Several examples are reported as olefin and aromatic hydrocarbon hydrogenation reactions catalysed by Rh[85] and Ru[86] complexes respectively and olefin dimerization Ni[87] catalysed. Otherwise, if the active species is assumed to be uncharged, leaching of the transition metal in the organic phase can be limited by the use of functionalized ligands. As the triumph of aqueous biphasic catalysis follow the laborious work involved in the development of water-soluble ligands, recent investigations have focused on the synthesis of new ligands with specific structures for highly active and selective two-phase catalysts, mainly phosphorus ligands with appropriate modifications, and for good solubility in the ionic liquid phase.

From a practical point of view, the concept of ionic liquid multiphasic catalysis can be applicable only if the resultant catalytic lifetimes and the elution losses of catalytic components into the organic or extracting layer containing products are within commercially acceptable ranges.

With homogeneous supported synthesis the goal is to combine the benefits of conventional homogeneous synthesis (good mass transfer and reaction rates, wide range of reaction types and conditions) with the benefits of heterogeneous solid supported synthesis (ease of separation).

The Heck reaction can also be performed in room-temperature ionic liquids such as [bmim][PF_6] and *N*-hexylpyridinium PF_6^-.[88] The vinylated products can be simply distilled off under reduced pressure or extracted with hexanes. The use of the hydrophobic [bmim][PF_6] allows the generation of a three-phase system ([bmim][PF_6]/H_2O/hexane). The palladium catalyst remains in the ionic liquid, the organic products remain in the hexane phase, and the salt by-products remain in the aqueous phase. The greater catalytic activity observed in the reactions performed in the imidazolium ionic liquids compared to those in the pyridinium analogues was attributed to the formation of Pd-carbene complexes (by base abstraction of the C(2) imidazolium proton) in the former melt.

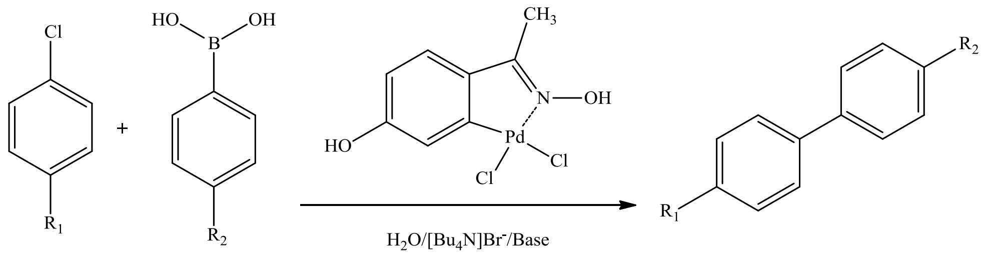
A homogeneous Pd catalyst usually precipitates from the solution and the recycling or the recovery of the active Pd catalyst is difficult. Heterogeneous catalysts would be much better from viewpoint of recycle use. Pd/C is a recoverable heterogeneous catalyst and is stable and relatively inexpensive, although its catalytic activity was under developed except in catalytic hydrogenations. Highly polar nature of an ionic liquid activates and stabilizes catalyst in Pd/C-catalysed Mizoroki-Heck reaction. Reaction is carried out heating a solution of aryl halide, olefin and base with 5-10% Pd/C dispersed in [bmim][PF_6]. The products are extracted by stirring with an apolar organic solvent.[89]

Transition metal-catalysed hydrogenation reactions in ionic liquids are particularly promising because on the one hand, a large number of known ionic hydrogenation catalysts are available and, on the other, the solubility of many alkenes and the availability of hydrogen in many ionic liquids appear to be sufficiently high for good reaction rates to be achieved.[90] Since the diffusion of hydrogen into ionic liquids has been found to be relatively fast, the latter contribution is of special importance.[91] Finally, the miscibility gap between the saturated reaction products and the ionic liquid is often large, so that a biphasic procedure is possible in the majority of cases.

In 1995 de Souza *et al.*[92] investigated the Rh-catalysed hydrogenation of cyclohexene in [bmim][BF_4]. Chauvin *et al.*[93] dissolved the cationic Rh “Osborn complex” in ionic liquids with weakly coordinating anions (*e.g.*, PF_6^-, BF_4^- and SbF_6^-) and used the obtained ionic catalyst solutions for the biphasic hydrogenation of 1-pentene.

A special example of transition metal-catalysed hydrogenation in which the ionic liquid used does not provide a permanent biphasic reaction system should be mentioned. Dyson *et al.*[94] reported the hydrogenation of 2-butyne-1,4-diol using an ionic liquid/water system that underwent a reversible two- phase/single-phase transformation upon a temperature switch. At room temperature, the ionic liquid [omim][BF_4] containing the cationic Rh catalyst formed a separate layer with water containing the substrate. At 80 °C however, a homogeneous single-phase reaction could be carried out.

García *et al.*[95] converted the highly active oxime carbapalladacyle complex into a reusable catalysts using ionic liquids because of the poor solubility of the original oxime carbapalladacycle complex in [bmim]-based ionic liquids (Figure 1.3) to use them in palladium-catalysed Suzuki-Miyaura (Scheme 1.7) and Heck cross-coupling reactions.



Scheme 1.7. Suzuki-Miyaura cross coupling catalysed by an oxime carbapalladacycle.

To increase the solubility and affinity of the complex they proceeded to the preparation of a derivative wherein a *N*-butylimidazolium tag was introduced to make the palladium complex more alike to [bmim][PF_6] as solvent. The main problem was, however, the gradual depletion in transition metal complex during reuse as consequence of some degree of complex extraction during product recovery. This depletion can be minimized by modifying the transition metal complex by adding an imidazolium pony tail, thus increasing the affinity of the catalyst for the ionic liquid.[96] This methodology requires further synthetic steps and leads normally to a decrease in the catalytic activity of the transition metal.

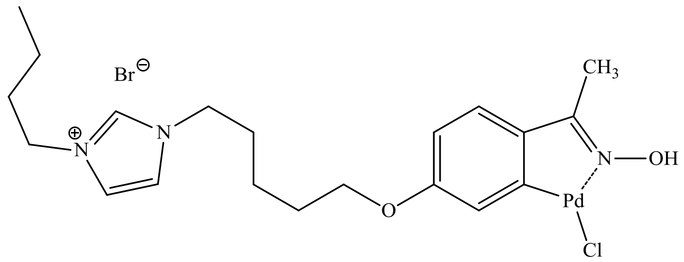
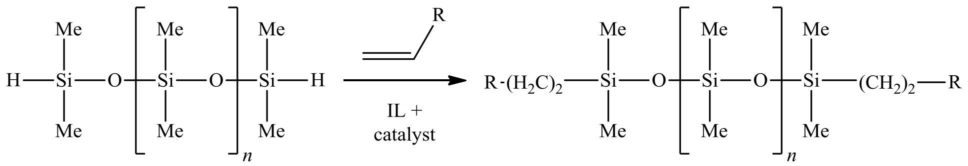


Figure 1.3. IL-coupled oxime carbapalladacycle complex.

The most obvious challenge with using RTILs as supports is the method of attachment of the compound to be supported to the RTIL, *i.e.*, fructose-derived RTIL,[97] that can be further functionalized in a variety of fashions.[98] Otherwise, basic conditions low stability represents a big limitation for these fructose-derived ionic liquids.

The other major area of supported synthesis is that of supported reagents and catalysts. In two literature examples (*i.e.*, a vanadyl salen complex for catalytic oxidations[99] and a ruthenium metathesis catalyst[100] tethered to ionic liquids) these species were not only catalytically active, but were also readily retained in ionic liquids layers and thereby recycled.

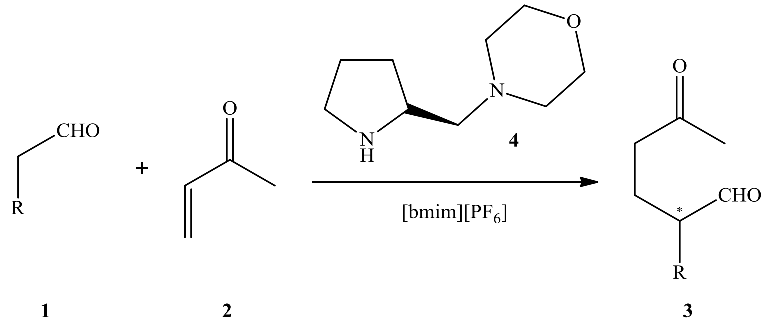
The hydrosilylation of C–C double bond containing compounds with SiH-functional polydimethylsiloxanes is a widely applied reaction in industrial synthesis for the production of organosilicon compounds (Scheme 1.8). Synthesis of organomodified polydimethylsiloxanes employing ionic liquids for the heterogenization and/or immobilization of the precious metal catalyst, *i.e.* platinum, produces standard hydrosilylation catalysts that can be used without the need of prior modification to prevent catalyst leaching. Typically, the reaction is performed in a liquid-liquid biphasic system where the substrates and products (upper phase) are not miscible with the catalyst/ionic liquid solution (lower phase).[101]



Scheme 1.8. Hydrosililation of olefins.

Additional current interests in this area are revisit of synthetic organic chemists to an organocatalyst. Since an organocatalyst does not involve any metal, there is no need to mind leaching out of metal. Design, tuning and reproduction of a catalyst might be easy without depending supply of metal from natural resource. However, compared to a metal catalyst, catalyst loading could not sufficiently be diminished. Low stability of an organocatalyst and recovery after the reaction is not suitable for recycle use.[102]

In spite of aldehydes versatility as electrophiles, a role as nucleophiles has been quite limited because of difficulty to generate their enolate or enol ether quantitatively, thus converting them into silyl-enol ethers or enamines. The asymmetric conjugate addition of unmodified aldehyde (**1**) to MVK (**2**) (Scheme 1.9) was effected in [bmim][PF_6] to afford (2*S*)-5-keto-aldehyde (**3**) in up to 59% *ee* in the presence of 20 mol% of optically active pyrrolidine derivative (**4**) derived from *L*-proline.[103]



Scheme 1.9. Asymmetric organocatalysed Michael addition in ionic liquid.

Since diethylamine is volatile and catalysts should be added freshly in each recycle experiment, immobilization of amine residues on solid surface was investigated. *N*-methylaminopropyl residue was grafted on amorphous and mesoporous silica gel by a post modification method.[104] Employing the aminopropylated silica gel, recyclable 1,4-conjugate addition reaction of citronellal was possible without any pre-treatment to re-activate the catalyst in Figure 1.4.[105]

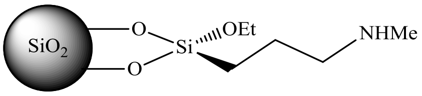


Figure 1.4. Amorphous *N*-mathylaminopropylated silica gel.

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Section 1

Synthesis and Characterization of New ILs

2. Synthesis of ionic liquids *via* DMC

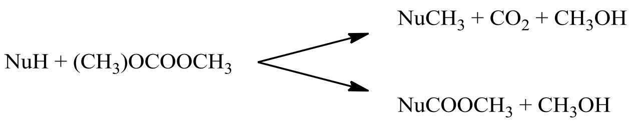
Methyl halides (CH_3X, X = I, Br, Cl), dimethylsulphate (DMS), and phosgene ($COCl_2$), represent the most widely applied methylating and carbonylating reagents (Scheme 2.1). Unfortunately, despite their efficiency in terms of reaction rate processes, dimethylcarbonate (DMC), Scheme 2.2, has been proposed in the last years as a valid green alternative to the above mentioned harmful and undesirable compounds.[1]

$$\mathrm{NuH + (CH_3)_2SO_4 + NaOH \longrightarrow NuCH_3 + NaCH_3SO_4 + H_2O}$$

$$\mathrm{NuH + CH_3I + NaOH \longrightarrow NuCH_3 + NaI + H_2O}$$

$$\mathrm{2\ NuH + COCl_2 + 2\ NaOH \longrightarrow ROCO_2R + 2\ NaCl + 2\ H_2O}$$

Scheme 2.1. Methoxylation and carbonylation of organic nucleophiles using DMS, MeI and $COCl_2$.



Scheme 2.2. Base catalysed methylation and carbonylation using DMC.

The low toxicity of this reagent is normally associated to favourable values of atom economy and mass index in the methylation process, factors that increase the greenness of DMC utilization. The atom economy generally follows the trend: MeOH >> DMC ≥ DMS > MeI. For methanol, 47% of its mass is incorporated in the final product, more than twice as much as the other reagents but on the reverse methanol and DMC require catalytic activation as opposed to DMS and MeI.[2]

Many of DMC properties make it a genuinely *green* reagent, particularly if compared to conventional alkylating agents such as methyl halides and DMS or to phosgene if used as a methoxycarbonylating reagent.[3]

2.1. Properties of DMC

DMC is a nontoxic compound which can be prepared following different approaches. Although the old phosgene route is still active in both SNPE and BASF plants, this process is highly undesirable from both safety and environmental standpoints: the toxicity/corrosiveness of phosgene, the generation of contaminated salts, and careful waste-water treatments are major drawbacks.[4] Consequently, today modern units for the synthesis of DMC operate with clean technologies which are based on three different reactions:

- Catalytic oxidative carbonylation of methanol with oxygen (Scheme 2.3).[5] Key advantages of this process, active from ‘80s, are the high safety improvement, the high selectivity (and therefore, purity in the final product), and the sole formation of water as a by-product;[6]

$$2\ CH_3OH + 1/2\ O_2 + CO \xrightarrow{\text{Cu salts}} CH_3OCO_2CH_3 + H_2O$$

Scheme 2.3. DMC synthesis by oxidative carbonylation.

- Carbonylation of methyl nitrite over a Pd-catalyst; in this case the former acts simultaneously as an efficient oxidant of the metallic catalyst;[7]
- The two-stage process of insertion of CO_2 into an epoxide, followed by a transesterification reaction with MeOH.[8] This strategy represents by far the most recent breakthrough in the production of DMC and the greenest and most promising solution stemming from a naturally abundant and cheap building block such as carbon dioxide.[9]

Although DMC is classified as a flammable liquid and smells like methanol, it does not have irritating or mutagenic effects, either by contact or inhalation and it is biodegradable. Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS, and extremely toxic phosgene (Table 2.1).

Reactions mediated by DMC also offer other relevant advantages from the synthetic/process standpoints: (i) they do not usually require additional solvents, since DMC may simultaneously act as a reagent and as a solvent for many organic substrates; (ii)

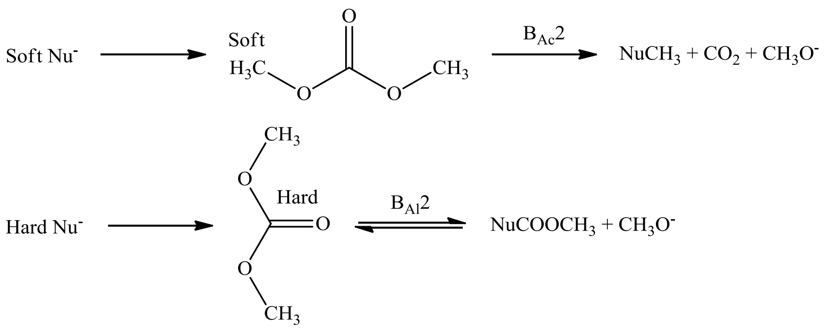
DMC does not produce inorganic salts because the leaving group, methyl carbonate, decomposes restoring the catalytic base and so waste-water treatment is not needed; (iii) they can be easily controlled because of their slight, if any, exothermic progress; (iv) also operating at 200-250 °C decomposition and polymerization side-reactions do not occur.[10]

Table 2.1. Some physical and thermodynamic properties of DMC.

Melting point (°C)	4.6
Boiling point (°C)	90.3
Density (d_4^{20})	1.07
Viscosity (μ^{20}, cps)	0.625
Flash point (°C)	21.7
Dielectric constant (ε^{25})	3.087
Dipole moment (μ, D)	0.91
ΔH_{vap} (kcal/kg)	88.2
Solubility H_2O (g/100 g)	13.9
Azeotropical mixtures	Water, alcohols, hydrocarbons

2.1.1. Mechanism

DMC possesses three electrophilic centres (the carbonyl and two methylic carbon atoms), which, in the presence of a generic nucleophile, may undergo two distinct reactions. Such centres can be classified according to HSAB principles: the carbonyl group is the hardest electrophile, as a result of its polarized positive charge and sp^2 hybridization; the two methyl groups represent softer electrophiles, thanks to their sp^3 orbitals and their saturated carbon atom, which has a weaker positive charge (Scheme 2.4).



Scheme 2.4. Soft and hard electrophile behaviour of DMC.

At a high temperature, it is known that the lack of solvation may favour a $B_{Al}2$ (bimolecular, base-catalysed, alkyl cleavage, nucleophilic substitution) mechanism with respect a $B_{Ac}2$ (bimolecular, base-catalysed, acyl cleavage, nucleophilic substitution) one.[11] In the case of DMC-mediated methylations, both reaction pathways occur in a definite sequence, which accounts for the high monomethyl selectivity observed in these reactions.

Various anions with different soft/hard character were compared with regard to nucleophilic substitutions on DMC, using different reaction conditions.[12] Results were in good agreement with the hard-soft acid-base (HSAB) theory.[13]

Accordingly, the high selectivity of monomethylation of CH_2 acidic compounds and primary aromatic amines with DMC can be explained by two different subsequent reactions, which are due to the double electrophilic character of DMC (Scheme 2.5). The first step consists of a hard-hard reaction, and selectively produces a soft anion, which, in the second phase, selectively transforms into the final monomethylated product, via a soft-soft nucleophilic displacement. Since hard-soft and soft-hard interactions are inhibited, double methylation and double carboxymethylation do not occur.

$$\begin{aligned}
\mathrm{ArCH_2X + B} &\rightleftharpoons \mathrm{ArCH^{-}X + BH^{+}}\\
\mathrm{ArCH^{-}X + CH_3OCOOCH_3} &\rightleftharpoons \mathrm{ArCH(COOCH_3)X + CH_3O^{-}}\\
\mathrm{BH^{+} + CH_3O^{-}} &\rightleftharpoons \mathrm{B + CH_3OH}\\
\mathrm{ArCH(COOCH_3)X + B} &\rightleftharpoons \mathrm{ArC^{-}(COOCH_3)X + BH^{+}}\\
\mathrm{ArC^{-}(COOCH_3)X + CH_3OCOOCH_3} &\longrightarrow \mathrm{ArC(CH_3)(COOCH_3)X + CO_2 + CH_3O^{-}}\\
\mathrm{ArC(CH_3)(COOCH_3)X + CH_3O^{-}} &\rightleftharpoons \mathrm{ArC^{-}(CH_3)X + CH_3OCOOCH_3}\\
\mathrm{ArC^{-}(CH_3)X + BH^{+}} &\rightleftharpoons \mathrm{ArCH(CH_3)X + B}
\end{aligned}$$

Scheme 2.5. Reaction pathway for the monomethylation of CH_2-acidic compounds with DMC.

Also primary amines, in presence of a base, which exalts the hard nature of the nucleophile, firstly react according to $B_{Ac}2$ mechanism, so producing a softer anion that reacts via a soft/soft interaction. Naked RNH^- is excluded from the mechanism; it looks like the role of the base is that of removing H^+ form protonated nitrogen increasing the negative charge on it.

2.1.2. Conditions

DMC exhibits a versatile and tunable chemical reactivity that depends on the experimental conditions. In the presence of a nucleophile (Y^-), DMC can react either as a methoxycarbonylating or as a methylating agent (Scheme 2.4).[14] Although there is not always a clear cut-off between the two pathways of Scheme 2.4, it is generally observed that:

- At the reflux temperature (T = 90 °C), DMC acts primarily as a methoxycarbonylating agent by a $B_{Ac}2$ mechanism where the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification product. Under these conditions, DMC can replace phosgene;
- At higher temperatures (usually $T \geq 160$ °C), DMC acts primarily as a methylating agent: a $B_{Al}2$ mechanism predominates where the nucleophile attacks the methyl group of DMC.

Of the two, only the methylation reaction is irreversible, because the CH_3OCO_2H that is formed decomposes to methanol and CO_2.

Since both methylation and methoxycarbonylation generate CH_3O^-, both reactions can be conducted in the presence of catalytic amounts of base. This avoids the formation of unwanted inorganic salts as by-products, and the related disposal problems. In principle, the methanol produced can be recycled for the production of DMC.[15] In contrast, methylation with methyl halides or DMS, and carbonylation with phosgene all generate stoichiometric amounts of inorganic salts.

The development of a new eco-friendly process is often associated with advanced reaction technologies. An aspect that sometimes imposes a careful balance between the environmentally benign character and the economic/safety feasibility of the process itself.

In the case of DMC, reaction conditions are not apparently green: the methylating ability of DMC can be exploited at a temperature > 160 °C (above the boiling point of DMC itself: 90 °C), which implies an autogenic pressure (> 3 bar) for batch-wise processes. Such conditions are not prohibitive, however, especially according to the industrial practice, where pressures up to 20-30 bar and temperatures up to 250 °C are not a concern.

Batch processes are carried out in pressure autoclaves where DMC is maintained as liquid by autogenous pressure.

Continuous flow reactions at atmospheric pressure require that both DMC and the reagent(s) in the vapour phase come into contact with a catalytic bed, because for which GL-PTC was developed.[16] Under these conditions, a gaseous stream of reagent and DMC flows over a catalytic bed usually composed of an inert porous inorganic material, usually corundum, which acts as a support for both an inorganic base (an alkaline carbonate) and a phase-transfer (PT) agent such as phosphonium salts,[17] crown ethers,[18] and polyethylene glycols (PEGs). The last systems, in particular, although less efficient than other PT agents, are desirable because thermally stable, nontoxic, and inexpensive.[19]

An alternative CF methodology for DMC methylations was developed as well, by using a CSTR.[20] In this configuration, the catalyst fills the reactor in the form of a liquid slurry of the PT agent and K_2CO_3, and it is kept under vigorous stirring at the desired temperature (160-200 °C). The mixture of DMC and the reagent is vaporized when it comes into contact with the catalytic bed and when a suitable feeding rate is reached, the apparatus works in gradientless conditions: the composition of the mixture collected at the outlet is equal to that present inside the reactor, and the reaction takes place instantaneously as far as reagents bubble through the bed.

In the presence of a weak base (*i.e.*, K_2CO_3), benzylic carbon with enhanced acidity (*e.g.*, bonded at EWG as CN, SO_2R, etc.) can be mono-C-methylated at complete conversions with a selectivity greater than 99%.[21] Under the same conditions, primary aromatic amines also react with DMC. In this case, although the reaction yields selectively the mono-*N*-methylated amines with no dimethylated by-products, sizable amounts of methyl carbamates ($ArNHCO_2Me$) are formed.[22]

These reactions are also efficiently catalysed by a number of inorganic and organic bases (*e.g.*, alkaline carbonates, metal alkoxides, DBU, DMAP, etc.) whose nature may affect the methylation rate, but they show no appreciable effect on the final selectivity.[23] Phenolic compounds are methylated in good yields with DMC in presence of catalytic amount of $BF_3{\cdot}Et_2O$ (~ 20 mol%) under microwave and solvent-free conditions. The same results are obtained when carboxylic acids or phenolic compounds in the presence of 10 mol% of DBU under microwave irradiation in about 1 minute.[24]

In some cases, to increase reaction rate, it is necessary the addition of catalyst. Much better results can be gathered in the presence of zeolites, particularly alkali metal exchanged Y-faujasites.[25] These aluminosilicates possess pseudospherical cavities (supercavities) of 11-8 Å in diameter, which can be accessed through channels whose size is 7.4 Å.[26] Less hindered substrates are all expected to be hosted by the catalytic supercavity of NaY.[27] On the contrary, if the “cage adsorption” is hindered by bulky substituents, a remarkable drop of selectivity is observed.[28]

Although zeolites are always less active than carbonate base, NaY is by far superior for chemoselectivity: at 150 °C, mercaptobenzoic acids, aminobenzoic acids and aminobenzyl alcohols undergo respectively S-methylation or mono-*N*-methylation reactions without affecting the acid groups, whereas the increase of the temperature (165 °C) allows the exclusive esterification of hydroxybenzoic acids (*ortho* and *para* isomers), mandelic acid, and phenyllactic acid, their aromatic and aliphatic OH substituents being fully preserved from methylation and/or methoxycarbonylation side reactions. Typical selectivities for such processes are in the range of 90-100%. On the contrary, in the presence of K_2CO_3, competitive reactions of *O*- and *S*-methylation, esterification, and *O*-

methoxycarbonylation take place simultaneously and anilines afford poor yields of mono-methylated product because of the competitive $B_{Ac}2$ process.[27]

The amphoteric nature of NaY suggests that two major points should account for such results: the electrophilic activation of DMC over NaY, that may be favoured increasing the amount of zeolite used, and a possible nucleophilic activation may take place through H-bonds with basic oxygen atoms of the framework of the aluminosilicate.

Although the zeolite must be used in a relatively high amount (weight ratios of NaY:substrate up to 3), to avoid disulphide formation, it can be easily separated by filtration, reactivated, and recycled without any loss of activity and/or selectivity.[29]

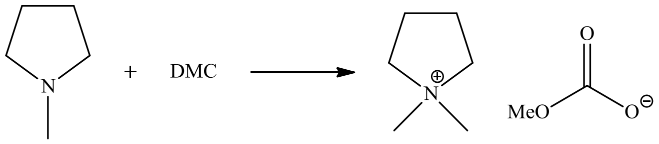
2.2. Synthesis of ionic liquids

Although ionic liquids are generally included in the list of alternative environmental friendly solvents some controversials still exist about the *green* character of these media and the possibility of large scale application. Surely, the ionic character determines the absence of solvent vapour in atmosphere thus avoiding explosive risk linked to that and the toxic effects for workers normally associated to the use of volatile organic solvents (VOC). Nevertheless, although the acute toxicity and eco-toxicity versus aquatic organisms as well as biodegradation can be an issue for some ILs, recent investigations show that it is possible to synthetize ionic compounds having a very low impact even on the aquatic environment: the careful design or selection of the IL to apply in a specific process should therefore be able to guarantee high performance and sustainability. About this point, it is noteworthy that the main feature of ILs is that all their properties (physical, chemical and biological) can be modified or modulated selecting the opportune anion-cation combination, or introducing on cation or anion specific functional groups. However, the limitless anion-cation pairs number can be seen not only as an opportunity but also as a limit until robust predictive methods are developed. However, probably the biggest limit to the green character of ionic liquids lies in their manufacturing process. Their synthesis, in fact, involves two potentially environmentally adverse steps: quaternization of a nitrogen or phosphorous atom, usually by methylation with hazardous alkyl halides followed by a halogen anion metathesis step that produces equimolar amounts of an inorganic salt.[30] In addition, the materials thus prepared inevitably contain residual undesirable halide ions.

In order to evaluate the possibility to prepare ionic liquid using DMC, we decided to investigate the behaviour of some aliphatic amines. It was already known that alkylimidazoles react with dimethyl carbonate to give the corresponding methylation product. This latter, immediately in the basic reaction conditions reacts with the formed CO_2, probably through a carbene structure, to produce zwitterionic species. In contrast with saturated amines, where only one reaction product is observed, two products, 1-butyl-3-methylimidazolium methylcarbonate and 1-butyl-3-methylimidazolium-2-carboxylate, are formed during the reaction.

Product distribution of the previous reaction differs from that of 1-methylimidazole in which the carboxylate zwitterion is isolated in up to 85% yield. This result may result from the greater steric hindrance of the butylated system or from the formation of solid 1,3-dimethylimidazolium-2-carboxylate displacing the product equilibrium.[31]

Among the investigated amines, pyrrolidine (Scheme 2.6) showed the best reactivity profile leading to almost quantitative conversions at the reflux temperature of the DMC after 72 h. Even though this substrate was not tested, we could expect this procedure needs longer time respect to Fabris' method. In 2009, Fabris *et al.*[32] reported the synthesis some ILs through a last methylation step with DMC. The proposed conditions were however quite strong: 7 equivalents of DMC respect to the nucleophile and an equivalent volume of methanol were combined (two phases) in a sealed steel autoclave and then heated for 20 hours at 140 °C under magnetic stirring. After cooling at room temperature, MeOH and residual DMC were removed from the mixture by rotary evaporation. However, the liquid nature of the precursor allowed the formation of a homogeneous phase also using lower volumes of DMC; reactions were therefore performed at higher concentrations that in the previously reported procedure. When the reaction was complete, a phase separation occurred, followed, after cooling down, by a fast solid precipitation.



Scheme 2.6. *N*-methylpyrrolidine methylation with DMC.

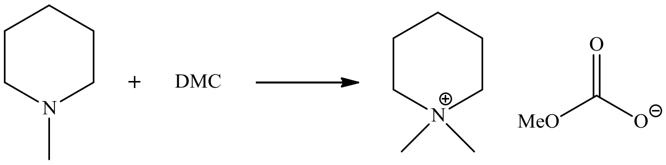
Rogers *et al.*[33] methylated *N*-methylpyrrolidine, an aliphatic amine, using 200% excess of DMC at 90 °C for 14 days in a pressurized system. Methylation of *N*-butylimidazole used harsher conditions (*i.e.*, T = 140-150 °C and microwaves) making the process less sustainable.

It has to be noted that, since almost stoichiometric amount of both reagents was used to prevent a viscosity increase during the reaction attempts were carried out to use the minimal amount of co-solvent to increase reaction rate favouring mass diffusion. However, when MeOH was used as co-solvent only poor conversions were obtained.

Table 2.2. *N*-methylpyrrolidine methylation with DMC.

	DMC		**Solvent**	**Time**	**Temperature**	**Yield**
	(mL)	**(eq)**		**(h)**	**(°C)**	**(%)**
***N*-methylpyrrolidine (5 mL)**	16	4	-	21	85	50
	4	1	MeOH (4 mL)	24	70	55
	”	”	MeOH (10 mL)	”	85	60
	30	7.5	-	72	90	94
	10	2.5	-	60	”	93

Growing up to a six membered cyclic amine, *N*-methylpyperidine (Scheme 2.7), reaction yields smoothly decreased. To reach conversions higher than 90% it was necessary to raise DMC:amine ratio up to 14.5, respect to the previous 2.5 (Table 2.3).

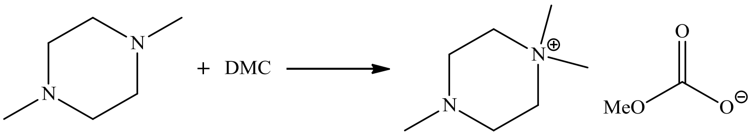


Scheme 2.7. *N*-methylpyperidine methylation with DMC.

Table 2.3. *N*-methylpyperidine methylation with refluxing DMC.

	DMC		**time**	**Yield**
	(mL)	**(eq)**	**(h)**	**(%)**
***N*-methylpyperidine (5 mL)**	45	13	60	53
	50	14.5	90	95

During the course of this PhD thesis simple alicyclic compounds bearing to equivalent tertiary nitrogen atoms were also tested in order to verify the possibility to use this nucleophiles to obtain selectively monoalkylation products. *N,N'*-dimethylpiperazine and diazabicyclo[2.2.2]octane, DABCO, were used as starting compounds, both bearing two equivalent sites (two tertiary nitrogen atoms) although the different steric requirements of the two systems determine a different basicity (nucleophilicity) of the related nitrogen atoms.



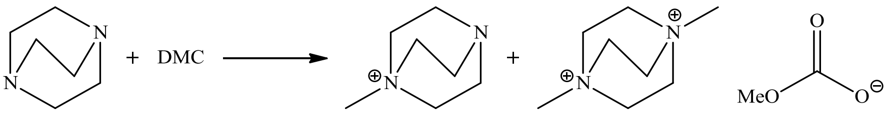
Scheme 2.8. *N,N'*-dimethypiperazine mono-methylation with DMC.

When the reactions were performed under comparable conditions (5-6 eq of DMC and 90 °C) the reaction of *N,N'*-dimethylpiperazine (Scheme 2.8) proceeded with a complete chemoselectivity, giving exclusively (> 99%) the monomethylation product, however only moderate conversions were obtained after 6 days (Table 2.4).

Table 2.4. *N,N'*-dimethylpiperazine mono-methylation with refluxing DMC.

	DMC		time	Yield
	(mL)	**(eq)**	**(h)**	**(%)**
***N,N'*-dimethylpiperazine**	20	6.5	90	30
(5 mL)	”	”	120	55

At variance, conversions higher than 90% were obtained in 60 h in the case of DABCO (Scheme 2.9), confirming that the system constraining makes nitrogens' lone pairs more available. As often observed, however, the higher reactivity is associated to a lower selectivity; mono and dialkylation products were formed in a 9:1 ratio (Table 2.5). It is however noteworthy that the addition of a co-solvent can increase reaction rate, at least in the case of DABCO, giving the possibility to use lower temperatures and a lower excess of DMC. When 10 mL of MeOH were used a smooth excess of the methylating agent, *i.e.* 1.1, was sufficient to obtain a conversion around 90% in ~ 6 h at 80 °C. Under these conditions only the monomethylation product was detected.



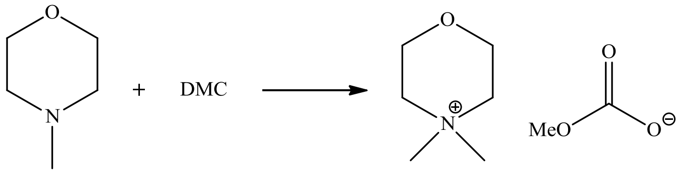
Scheme 2.9. DABCO mono- e di-methylation products with DMC.

Attempts to use acetone or acetonitrile as co-solvents showed that probably acetonitrile is more suitable for this application. The higher boiling point characterizing this solvent allows to carry out the reaction at 80 °C obtaining in 30 hours a high conversion (> 90%) and selectivity towards the expected product (monoalkylation product > 99%).

Table 2.5. DABCO mono- e di-methylation products with DMC.

	DMC		**Solvent**	**Time**	**Temperature**	**Monocation**	**Dication**
	(mL)	**(eq)**		**(h)**	**(°C)**	**(%)**	**(%)**
DABCO (5 g)	20	5.5	-	60	90	82	10
	16	4.4	MeOH (5 mL)	30	75	74	24
	4	1.1	MeOH (10 mL)	6.5	80	90	-
	12	3.3	MeOH (5 mL)	55	”	76	11
	8	2.2	Acetone (15 mL)	25	60	51	-
	12	3.3	MeCN (20 mL)	30	80	94	2
	8	2.2	”	”	”	92	1

Finally, when the same procedure was applied to a deactivated amine, *N*-methylmorpholine (Scheme 2.10) practically no conversion was obtained after days (Table 2.6).



Scheme 2.10. *N*-methylmorpholine methylation with DMC.

Several efforts were then performed to increase conversion enhancing DMC electrophilicity. Catalytic amounts of mineral acids brought to a 14% conversion after very long reaction times (more than six days). No better results have been reached using *o*-toluic acid.

Also $Sc(OTf)_3$, a Lewis acid widely used in catalysis as carbonyl activator, was tested.[34] According to a description of inductive effects on chemical bonds, both the coordination modes (A) and (B) are expected to strengthen the C=O bond (Figure 2.1).[35] Different effects can be anticipated for binding mode (C). This interaction should lengthen (weaken) the C=O and O–Me bonds and shorten (strengthen) the C–O ones.[36]

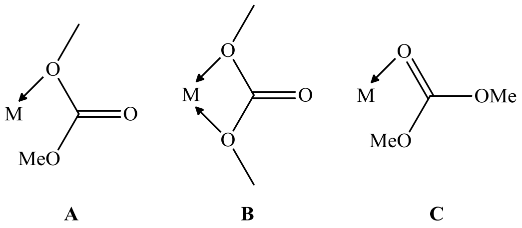


Figure 2.1. Coordination modes of DMC.

Table 2.6. *N*-methylmorpholine methylation with DMC.

	DMC		**Solvent**	**Catalyst**	**t**	**T**	**Yield**
	(mL)	**(eq)**			**(h)**	**(°C)**	**(%)**
***N*-methylmorpholine (5 mL)**	3.3	1.0	MeOH (10 mL)	-	70	75	-
	20.0	6.0	-	-	”	85	-
	6.5	2.0	MeOH (10 mL)	-	”	70	-
	25.0	7.8	-	HCl (0.05 mol%)	116	80	-
	”	”	-	HCl (0.1 mol%)	”	”	14
	50.0	15.6	-	$Sc(OTf)_3$ (0.5 mol%)	”	”	-
	”	”	-	$Sc(OTf)_3$ (1 mol%)	70	90	6
	”	”	-	$Sc(OTf)_3$ (2 mol%)	”	”	15
	”	”	-	$Sc(OTf)_3$ (5 mol%)	120	80	12
	12.5	3.9	-	$Sc(OTf)_3$ (2 mol%)	100	”	9
	50.0	15.6	-	”	”	”	5
	”	”	MeOH (5 mL)	”	”	”	-
	6.25	1.9	-	”	145	”	-
	50.0	15.6	-	*o*-toluic acid (5 mol%)	120	75	-

In principle, therefore, η^1–O(C=O) coordination of DMC to Sc(III) activates both the carbonyl group and the O–Me moieties and, consequently, must enhance not only the carbomethoxylating but also the methylating reactivity of the substrate (DMC), which is, notoriously, a typical example of ambident electrophile.[37]

The use of $Sc(OTf)_3$ (2 mol%) allowed to obtain the monoalkylation product in 15% yield, after 70 hours. Unfortunately, the conversion remained low though a high amount of DMC was employed or long reaction time were used.

N,N-Dimethylpyrrolidinium methylcarbonate and *N,N*-dimethylpiperidinium methylcarbonate are solid salts at room temperatures and solid compounds are also obtained after anion exchange. Since the more efficient approach to decrease ILs melting point is generally represented by the increase in cation asymmetry, to obtain ethyl-methyl-ammonium salts, the possibility to use DEC (diethylcarbonate) as ethylating agent was tested (Table 2.7).

Starting with neat conditions (without co-solvents), using a volume ratio DEC:amine of 3 at 90 °C, also after three days no reaction occurred using *N*-methylpyrroline as nucleophile; both reagents were recovered without no change (only a browning of the solution, probably due to amine oxidation, was observed). Analogously, no conversion was observed when the reaction was carried out at the same temperature and time conditions, but using a double amount of alkylating agent and nitric acid as catalyst (5 mol%).

Table 2.7. *N*-methylpyrrolidine ethylation with DEC.

	DEC		**Conditions**	**time**	**Temperature**	**Yield**
	(mL)	**(eq)**		**(h)**	**(°C)**	**(%)**
***N*-methylpyrrolidine (5 mL)**	15	3.8	-	72	90	-
	30	7.5	HNO_3 (5 mol%)	”	”	-
	15	3.8	MW	0.5	25-110	-

Since, it is well-known that microwave irradiation is able to enhance reactivity in the case of DMC methylation (Shieh *et al*.[38] have showed that microwave irradiations can increase reaction rate of both esterification of carboxylic acids and methylation of phenolic alcohol) we performed the ethylation reaction under microwave irradiation. No reaction was however observed.

So we decided to induct asymmetry using DMC methylation protocol also for butyl-alkylated amines. The reactions were conducted with an excess of DMC at its refluxing temperature and, to avoid oxidation side-product formation and anion decomposition (MeOH and CO_2) by atmospheric humidity, under Ar atmosphere. Although pyrrolidinium salt already crystallized in the reaction mixture, successive effort to recrystallize it brought to the best MeOH/AcOEt (2:49) mixture. Moreover, in spite to literature reported methods, cyclic amines quaternization was performed using common lab equipment avoiding the use of autoclave. It has to be noted that warming these salts under high *vacuum* led to decomposition product, probably through elimination mechanisms.

Virtually it is possible to form any salt from the $MeOCO_2^-/HCO_3^-$ precursor using acid with pK_a lower than that of H_2CO_3, but unexpected behaviour was observed by Aresta *et al.* in the reaction with HNO_3 leading to the formation of, depending on the reaction conditions, either [2-carboxy-1,3-dimethylimidazolium][NO_3] or [4-carboxy-1,3-dimethyl-imidazolium][NO_3], with no detectable decarboxylation.[39] Upon treatment only of the former with DMSO at room temperature, solvent promoted decarboxylation gives pure [mmim][NO_3] through a mechanism similar to Krapcho reaction.[40]

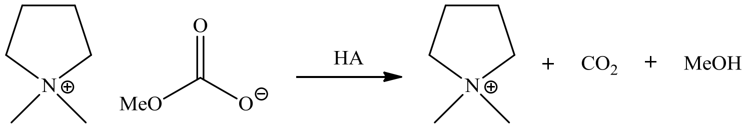
Rogers *et al.*,[33] using 1,2-dimethylimidazole instead of 1-methylimidazole, found that quenching the reaction with a EtOH/H_2O solution there was the HCO_3^- ionic liquid precursor formation. This method is more efficient than the previous one because the HCO_3^- formation does not require prior formation of a zwitterionic salt, thus eliminating the need for a two-step reaction, with the carboxylation step requiring elevated temperatures and extended times. The only limitation is the ability of the starting amine to undergo alkylation with dialkyl carbonate.

Although, the utilization of zwitterionic carboxylate precursors and their use in halide free synthesis of ILs show some limitations: (i) the necessity to use heterocyclic cation cores for zwitterionic carboxylate formation, (ii) synthesis of the zwitterionic imidazolium carbonate precursor is a two-step reaction, where the second step (carboxylation) is rate-limiting, and often low-yielding, (iii) possible formation of regioisomeric products during the zwitterionic synthesis having different reactivity in subsequent reactions, and (iv) need for use of low-volatile polar aprotic solvent such as

DMSO for decarboxylation, which is high hygroscopic and hard to remove from the reaction mixture.

Aresta *et al.*[41] reported simultaneous formation of both products with some selectivity for 1,3-dimethylimidazolium-2-carboxylate. They also noted that upon heating to 140 °C, a complete isomerization to 1,3-dimethylimidazolium-4-carboxylate occurred. These results are consistent with BASF's reported formation of the latter in the reaction of DMC with 1-methylimidazole at 140 °C.[42]

Pocker *et al.*[43] investigated the water- and acid-catalysed decarboxylation of monosubstituted derivatives of carbonic acid and concluded that alkyl carbonate anions behave similarly to the HCO_3^- anion in the presence of an acid and decompose to CO_2, gas and alcohol (Scheme 2.11).



Scheme 2.11. Anion exchange between *N*,*N*-dimethylpyrrolidinium methyl carbonate and a generic Brønsted acid HA.

Table 2.8. Anion exchange.

	[mmpyr]	[mmpip]	[mmpiz]	[mDABCO]
AcOH	√	√	√	√
HCO_2H	√	√	√	√
CF_3CO_2H	√	√	√	√
H_2SO_4	√	√	√	√
HNO_3	√	√	√	√
HBF_4	√	√	√	√
HPF_6	√	√	√	√
$HClO_4$	√	√	√	√
HBr				√
HCl		√		√

Thus, we decided to synthetized new ionic liquids halogen free starting from the previous methylcarbonate-based salts by titration with a Brønsted acid (Table 2.8). All exchanged compounds were hydroscopic but most of their high melting points did not permit to consider them as "ionic liquids". Salts with melting temperature that seem to be lower than 100 °C are formiate, acetate and trifluoroacetate salts, but differential scanning calorimeter measurements are necessary to confirm them.

2.3. Experimental section

***N*-butylpyrrolidine**

A mixture of 1-H-pyrrolidine (9.60 mL, 8.31 g, 107.8 mmol), 1-butylbromide (14.0 mL, 17.86 g, 129.0 mmol) and K_2CO_3 (119.25 g, 0.86 mol) in MeCN (250 mL) was stirred at 90 °C for 3 h. The reaction mixture was cooled at room temperature and filtered. The solid obtained was washed with Et_2O and so HCl 37% (8.93 mL, 129.4 mmol) was added dropwise maintaining the solution continuously under stirring. The yellowish solid obtained was dried at reduced pressure and then was dissolved in the *minimum* amount of water and a solution with 4.73 g (118.3 mmol) NaOH in 40 mL was added. The product was then extracted with Et_2O and the organic phase dried with Na_2SO_4 for 12 h and so evaporated using a Kugelrohr, obtaining the pure product (7.82 g, 57 %).

^{1}H NMR ($CDCl_3$): δ = 2.50 (m, 2H, NCH_2), 2.43 (m, 4H, NCH_2), 1.78 (m, 4H), 1.50 (m, 2H), 1.30 (m, 2H), 0.90 (m, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 53.3, 51.8, 32.2, 23.5, 20.8, 13.7.

***N*-butylpiperidine**

A mixture of 1-H-piperidine (9.86 mL, 8.49 g, 102.2 mmol), 1-butylbromide (13.2 mL, 16.84 g, 122.6 mmol) and K_2CO_3 (113.0 g, 817.6 mmol) in MeCN (250 mL) was stirred at 90 °C for 3 h. The reaction mixture was cooled at room temperature and filtered. The solid obtained was washed with Et_2O and so HCl 37% (10.15 mL, 129.2 mmol) was added dropwise maintaining the solution continuously under stirring for 45 minutes. The yellowish solid obtained was dried at reduced pressure and then was dissolved in the *minimum* amount of water and a solution with 4.29 g (107.3 mmol) NaOH in 40 mL was added. The product was then extracted with Et_2O and the organic phase dried with Na_2SO_4 for 12 h and so evaporated using a Kugelrohr, obtaining the pure product (7.26 g, 51%).

^1H NMR (DMSO-d_6): $\delta = 2.3$ (m, 6H, NCH_2), 1.44 (m, 10H), 0.91 (t, 3H, $J = 7.3$ Hz, NCH_3).

^{13}C NMR (DMSO-d_6): $\delta = 59.3$, 54.6, 29.1, 26.0, 24.5, 20.9, 14.0.

2.3.1. Methylcarbonate salts

***N,N*-dimethylpyrrolidinium methylcarbonate**

N-methylpyrrolidine (10.0 mL, 94 mmol) and DMC (60 mL) were mixed in a round bottomed flask and stirred, at room pressure, under reflux for 60 hours. Unreacted DMC was removed from the mixture by rotary evaporation, to give the expected product in almost quantitative yield.

^1H NMR (D_2O): $\delta = 3.47$ (m, 4H, CH_2N^+), 3.29 (s, 3H, CH_3O), 3.09 (s, 6H, CH_3N^+), 2.18 (m, 4H, CH_2).

^{13}C NMR (D_2O): $\delta = 161.27$, 66.72, 52.54, 49.74, 22.50.

***N,N*-dimethylpyperidinium methylcarbonate**

N-methylpyperidine (10.0 mL, 81 mmol) and DMC (100 mL) were mixed in a round bottomed flask and stirred, at room pressure, under reflux for 90 hours. Unreacted DMC was removed from the mixture by rotary evaporation, to give the expected product in a 95% yield.

^1H NMR (D_2O): $\delta = 3.49$ (s, 3H, CH_3O), 3.30 (m, 4H, CH_2N^+), 3.05 (s, 6H, CH_3N^+), 1.84 (m, 4H, CH_2), 1.61 (q, $J = 6.1$ Hz, 2H, CH_2).

^{13}C NMR (D_2O): $\delta = 161.24$, 63.76, 52.40, 49.84, 21.25, 20.72.

***N,N,N'*-trimethylpiperazinium methylcarbonate**

N,N'-dimethylpiperazine (5 mL, 4.14g, 36.2 mmol) and DMC (20 mL) were mixed in a round bottomed flask and stirred, at room pressure, under reflux for 120 hours. DMC unreacted was removed from the mixture by rotary evaporation, to give the expected mono-quaternized product in a 60% yield.

^{1}H NMR (D_2O): δ = 3.44 (t, *J* = 5.1 Hz, 4H, CH_2N^+), 3.32 (s, 3H, CH_3O), 3.16 (s, 6H), 2.83 (m, 4H), 2.35 (s, 3H).

^{13}C NMR (D_2O): δ = 161.22, 62.15, 48.51, 44.67.

***N*-methylDABCO methylcarbonate**

DABCO (5,00 g, 45.0 mmol), DMC (8 mL) and MeCN (20 mL) were mixed in a round bottomed flask and stirred, at room pressure, under a temperature of 80 °C for 30 hours. Unreacted MeOH/MeCN and DMC were removed from the mixture by rotary evaporation, to give the expected mono-quaternized product in a > 90% yield.

^{1}H NMR (D_2O): δ = 3.31 (m, 6H, CH_2N^+), 3.25 (s, 3H, CH_3O), 3.10 (m, 6H, CH_2N), 2.97 (s, 3H, CH_3N^+).

^{13}C NMR (D_2O): δ = 161.30, 54.81, 52.35, 49.70, 45.07.

***N*-butyl-*N*-methylpyrrolidinium methylcarbonate**

N-butylpyrrolidine (9.16 g, 72.0 mmol) and DMC (31 mL, 360 mmol) were mixed in a round bottomed flask and stirred, at room pressure, under reflux for 96 h. Unreacted DMC was removed from the mixture by rotary evaporation, to give the expected product (14.4 g, 92%) as a white solid.

^{1}H NMR (DMSO-d_6): δ = 3.43 (m, 6H), 3.17 (s, 3H), 2.98 (s, 3H), 2.08 (s, 4H), 1.68 (dt, *J* = 7.82 Hz, *J* = 12.03 Hz, 2H), 1.32 (m, 2H), 0.93 (t, *J* = 7.83 Hz, 3H).

^{13}C NMR (DMSO-d_6): δ = 156.2, 63.5, 53.9, 51.5, 47.3, 25.2, 21.2, 19.4, 12.5.

***N*-butyl-*N*-methylpiperidinium methylcarbonate**

N-butylpiperidine (5.61 g, 40.3 mmol) and DMC (17 mL, 201 mmol) were mixed in a round bottomed flask and stirred, at room pressure, under reflux for 96 h. Unreacted DMC was removed from the mixture by rotary evaporation, to give the expected product (4.43 g, 48%) as a white solid.

^{1}H NMR (DMSO-d_6): δ = 3.31 (m, 6H), 3.00 (s, 3H), 1.60 (m, 8H), 1.30 (m, 2H), 0.94 (t, *J* = 7.50 Hz, 3H).

^{13}C NMR (DMSO-d_6): δ = 157.83, 62.05, 61.36, 59.77, 50.61, 46.82, 22.88, 20.60, 19.20, 13.45.

2.3.2. Metathesis reactions

To 20 mL of a 0.5 M aqueous solution of methylcarbonate precursor an equivalent of the proper acid AH dissolved in water (water solution 1 M) was added dropwise at room temperature. The mixture was stirred for an additional 24 hours. The solvent and gaseous were removed on a rotary evaporator. All salts were checked for the presence of starting materials by NMR.

***N,N*-Dimethylpyrrolidinium nitrate**

^{1}H NMR (250 MHz, D_2O): δ = 3.43 (m, 4H, CH_2), 3.07 (s, 6H, CH_3N), 2.18 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 66.72, 52.48, 22.50.

***N,N*-Dimethylpyrrolidinium hydrogen sulfate**

^{1}H NMR (250 MHz, D_2O): δ = 3.35 (m, 4H, CH_2), 2.97 (s, 6H, CH_3N), 2.06 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 66.61, 52.54, 22.45.

***N,N*-Dimethylpyrrolidinium sulfate**

^{1}H NMR (250 MHz, D_2O): δ = 3.48 (m, 4H, CH_2N), 3.11 (s, 6H, CH_3N), 2.20 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 65.87, 51.73, 21.71.

***N,N*-Dimethylpyrrolidinium perchlorate**

^{1}H NMR (250 MHz, D_2O): δ = 3.47 (m, 4H, CH_2N), 3.09 (s, 6H, CH_3N), 2.18 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 66.72, 52.54, 22.50.

***N,N*-Dimethylpyrrolidinium formiate**

^{1}H NMR (250 MHz, D_2O): δ = 8.40 (s, 1H, HC), 3.49 (m, 4H, CH_2), 3.11 (s, 6H, CH_3N), 2.20 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 171. 37, 66.72, 52.54, 22.50.

N,N-Dimethylpyrrolidinium acetate

^{1}H NMR (250 MHz, D_2O): δ = 3.47 (t, *J* = 6.7 Hz, 4H, CH_2N), 3.10 (s, 6H, CH_3N), 2.20 (m, 4H, CH_2), 1.87 (s, 3H, CH_3C).

^{13}C NMR (62.9 MHz, D_2O): δ = 66.71, 52.55, 24.13, 22.54.

N,N-Dimethylpyrrolidinium trifluoroacetate

^{1}H NMR (250 MHz, D_2O): δ = 3.47 (m, 4H, CH_2), 3.09 (s, 6H, CH_3N), 2.18 (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ =117. 25 (q, *J* = 294.5 Hz), 66.72, 52.54, 22.50.

N,N-Dimethylpyrrolidinium hexafluorophosphate

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.47 (m, 4H, CH_2N), 3.10 (s, 6H, CH_3N), 2.12 (s, 4H, CH_2).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 66.17, 52.36, 22.77.

N,N-Dimethylpyrrolidinium tetrafluoroborate

^{1}H NMR (250 MHz, D_2O): δ = 3.48 (m, 4H, CH_2N), 3.10 (s, 3H, CH_3N), 2.20, (m, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 66.68, 52.49, 22.50.

N,N-Dimethylpyrrolidinium chloride

^{1}H NMR (250 MHz, D_2O): δ = 3.51 (m, 4H, CH_2N), 3.13 (s, 6H, CH_3N), 2.22 (s, 4H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 65.96, 51.77, 21.74.

N,N-Dimethylpiperidinium nitrate

^{1}H NMR (250 MHz, D_2O): δ = 3.30 (t, *J* = 5.8 Hz, 4H, CH_2), 3.05 (s, 6H, CH_3), 1.84 (m, 4H, CH_2), 1.61 (q, *J* = 6.0 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.76, 52.44, 21.28, 20.74.

N,N-Dimethylpiperidinium sulfate

^{1}H NMR (250 MHz, D_2O): δ = 3.33 (t, *J* = 5.8 Hz, 4H, CH_2), 3.09 (s, 6H, CH_3), 1.87 (m, 4H, CH_2), 1.64 (q, *J* = 6.2 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.82, 52.46, 21.29, 20.76.

N,N-Dimethylpiperidinium perchlorate

^{1}H NMR (250 MHz, D_2O): δ = 3.35 (t, *J* = 5.7 Hz, 4H, CH_2), 3.11 (s, 6H, CH_3), 1.90 (m, 4H, CH_2), 1.68 (q, *J* = 6.1 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.89, 52.55, 21.31, 20.78.

N,N-Dimethylpiperidinium formiate

^{1}H NMR (250 MHz, D_2O): δ = 8.37 (s, 1H, HC), 3.28 (t, *J* = 5.8 Hz, 4H, CH_2N), 3.03 (s, 6H, CH_3), 1.82 (m, 4H, CH_2), 1.58 (q, *J* = 6.2 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 171.23, 63.74, 52.39, 21.23, 20.69.

N,N-Dimethylpiperidinium acetate

^{1}H NMR (250 MHz, D_2O): δ = 3.28 (t, *J* = 5.8 Hz, 4H, CH_2), 3.05 (s, 6H, CH_3), 1.86 (s, 3H, CH_3), 1.84 (m, 4H, CH_2), 1.59 (q, *J* = 6.1 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.76, 52.44, 24.00, 21.25, 20.72.

N,N-Dimethylpiperidinium trifluoroacetate

^{1}H NMR (250 MHz, D_2O): δ = 3.28 (t, *J* = 5.7 Hz, 4H, CH_2), 3.04 (s, 6H, CH_3), 1.84 (m, 4H, CH_2), 1.61 (q, *J* = 6.1 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 117.25 (q, *J* = 294.5 Hz), 63.76, 52.40, 21.23, 20.70.

N,N-Dimethylpiperidinium hexafluorophosphate

^{1}H NMR (250 MHz, D_2O): δ = 3.22 (t, *J* = 6.8 Hz, 4H, CH_2N), 2.98 (s, 6H, CH_3N), 1.77 (m, 4H, CH_2), 1.53 (q, *J* = 6.1 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.74, 52.38, 21.21, 20.68.

_N,N_-Dimethylpiperidinium tetrafluoroborate

^{1}H NMR (250 MHz, D_2O): δ = 3.33 (t, *J* = 6.8 Hz, 4H, CH_2N), 3.09 (s, 6H, CH_3N), 1.87 (m, 4H, CH_2), 1.64 (q, *J* = 6.2 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.84, 52.50, 21.28, 20.74.

_N,N_-Dimethylpiperidinium chloride

^{1}H NMR (250 MHz, D_2O): δ = 3.34 (t, *J* = 6.7 Hz, 4H, CH_2N), 3.10 (s, 6H, CH_3N), 1.88 (m, 4H, CH_2), 1.64 (q, *J* = 6.1 Hz, 2H, CH_2).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.81, 52.47, 21.29, 20.76.

_N_-butyl-_N_-methylpiperidinium trifluoroacetate

^{1}H NMR (250 MHz, D_2O): δ = 4.27 (s, 1H), 3.45 (m, 4H), 3.32 (m, 2H), 2.99 (s, 3H), 2.07 (m, 4H), 1.67 (m, 2H), 1.30 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (62.9 MHz, D_2O): δ = 158.04 (q, *J* = 31.3 Hz), 117.27 (q, *J* = 299.9 Hz), 63.36, 62.87, 47.36, 25.00, 21.07, 19.36, 13.47.

_N_-methylDABCO nitrate

^{1}H NMR (250 MHz, D_2O): δ = 3.41 (m, 6H), 3.22 (m, 6H), 3.03 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.82, 52.49, 45.11.

_N_-methylDABCO sulfate

^{1}H NMR (250 MHz, D_2O): δ = 3.54 (m, 6H), 3.35 (m, 6H), 3.12 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.63, 52.72, 45.07.

_N_-methylDABCO perchlorate

^{1}H NMR (250 MHz, D_2O): δ = 3.42 (m, 6H), 3.22 (m, 6 H), 3.08 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.96, 52.52, 45.18.

_N_-methylDABCO formiate

^{1}H NMR (250 MHz, D_2O): δ = 8.61 (s, 1H, HC), 3.36 (m, 6H), 3.15 (m, 6H), 3.01 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 171.32, 54.83, 52.44, 45.08.

_N_-methylDABCO acetate

^{1}H NMR (250 MHz, D_2O): δ = 3.35 (m, 6H), 3.14 (m, 6H), 3.00 (s, 3H, CH_3N), 1.86 (s, 3H, CH_3C).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.85, 52.42, 45.09, 24.00.

_N_-methylDABCO trifluoroacetate

^{1}H NMR (250 MHz, D_2O): δ = 3.41 (m, 6H), 3.21 (m, 6H), 3.04 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 117,25 (q, *J* = 294.5 Hz), 54.81, 52.50, 45.09.

_N_-methylDABCO hexafluorophosphate

^{1}H NMR (250 MHz, D_2O): δ = 3.52 (m, 6H), 3.29 (m, 6H), 3.12 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.03, 52.65, 45.29

_N_-methylDABCO tetrafluoroborate

^{1}H NMR (250 MHz, D_2O): δ = 3.54 (m, 6H), 3.37 (m, 6H), 3.12 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.54, 52.72, 45.02.

_N_-methylDABCO chloride

^{1}H NMR (250 MHz, D_2O): δ = 3.45 (m, 6H), 3.24 (m, 6H), 3.08 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): δ = 54.84, 52.60, 45.15.

_N,N,N'_-trimethylpiperazinium nitrate

^{1}H NMR (250 MHz, D_2O): δ = 3.46 (s, 3H, CH_3N), 3.44 (t, *J* = 5.2 Hz, 4H, CH_2N^+), 3.16 (s, 6H, CH_3N^+), 2.84 (m, 4H, CH_2N).

^{13}C NMR (62.9 MHz, D_2O): δ = 62.08, 48.48, 44.61.

_N,N,N'_-trimethylpiperazinium sulfate

^{1}H NMR (250 MHz, D_2O): δ = 3.49 (s, 3H, CH_3N), 3.48 (t, *J* = 5.2 Hz, 4H, CH_2N^+), 3.19 (s, 6H, CH_3N^+), 2.87 (m, 4H, CH_2N).

^{13}C NMR (62.9 MHz, D_2O): δ = 63.15, 48.57, 44.63.

N,N,N’-**trimethylpiperazinium perchlorate**

^{1}H NMR (250 MHz, D_2O): $\delta = 3.52$ (t, $J = 5.0$ Hz, 4H, CH_2N^+), 3.24 (s, 6H, CH_3N^+), 2.91 (m, 4H, CH_2N), 2.40 (s, 3H, CH_3N)

^{13}C NMR (62.9 MHz, D_2O): $\delta = 62.21, 48.59, 44.64$

N,N,N’-**trimethylpiperazinium formiate**

^{1}H NMR (250 MHz, D_2O): $\delta = 8.42$ (s, 1H, HC), 3.45 (t, $J = 5.1$ Hz, 4H, CH_2N^+), 3.16 (s, 6H, CH_3N^+), 2.84 (m, 4H, CH_2N), 2.36 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): $\delta = 171.25, 62.06, 48.43, 44.56$

N,N,N’-**trimethylpiperazinium acetate**

^{1}H NMR (250 MHz, D_2O): $\delta = 3.43$ (t, $J = 5.2$ Hz, 4H, CH_2N^+), 3.14 (s, 6H, CH_3N^+), 2.85 (m, 4H, CH_2N), 2.36 (s, 3H, CH_3N), 1.87 (s, 3H, CH_3C).

^{13}C NMR (62.9 MHz, D_2O): $\delta = 61.96, 48.44, 44.56, 23.89$.

N,N,N’-**trimethylpiperazinium trifluoroacetate**

^{1}H NMR (250 MHz, D_2O): $\delta = 3.45$ (t, $J = 5.2$ Hz, 4H, CH_2N^+), 3.15 (s, 6H, CH_3N^+), 2.87 (m, 4H, CH_2N), 2.38 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, D_2O): $\delta = 117.26$ (q, $J = 294.5$ Hz), 61.92, 48.45, 44.55.

N,N,N’-**trimethylpiperazinium hexafluorophosphate**

^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.54$ (m, 4H, CH_2N^+), 3.20 (s, 6H, CH_3N^+), 3.03 (m, 4H, CH_2N), 2.54 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, DMSO-d_6): $\delta = 61.36, 48.79, 45.28$.

N,N,N’-**trimethylpiperazinium tetrafluoroborate**

^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 3.52$ (t, $J = 5.3$ Hz, 4H, CH_2N^+), 3.20 (s, 6H, CH_3N^+), 3.02 (m, 4H, CH_2N), 2.49 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, DMSO-d_6): $\delta = 62.08, 48.48, 44.61$.

N,N,N'-trimethylpiperazinium chloride

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.43 (t, J = 5.2 Hz, 4H, CH_2N^+), 3.22 (s, 6H, CH_3N^+), 3.02 (m, 4H, CH_2N), 2.50 (s, 3H, CH_3N).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 62.05, 48.45, 44.62.

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3. Pyrazolium-based ionic liquids

During the course of this PhD thesis, we developed a new series of pyrazolium based ionic liquids, a class of ionic compounds which has been scarcely investigated but often mentioned in the patent literature. Because of their structural similarity with imidazolium salts, the most studied organic cations in the ionic liquid contest, which moreover have the best physico-chemical properties (lower viscosity, higher conductivity and thermal stability, etc.), we thought high probable that also pyrazolium salts, analogously based on an five member aromatic system containing two nitrogen atoms, could maintain some of the peculiar features characterizing the imidazolium salts.

Otherwise, the presence of two directly bonded nitrogen atoms could not be neglected being able to modify charge distribution and probably some of the physico-chemical properties of the resulting salts. In particular, in the pyrazolium salts the C(2) proton, generally considered the more acidic proton in imidazolium system (C(2)–H), which is primarily implied in the hydrogen bond based networks among cations and anions, responsible of the three-dimensional structure of ILs and in the solute-solvent interactions, when ILs are used as reaction media, is missed.

Since the principal applications of pyrazolium based ILs are related to electrochemistry, inside of this chapter a brief overview will be given.

3.1. Ion-cells application

The concept of the lithium-ion or rocking chair batteries, where lithium ions intercalate between the cathode and the anode, was introduced in the early ‘80. In 1991, Sony Corporation introduced the first commercially viable lithium-ion secondary cell into the market. It contained coke as the anode and $LiCoO_2$ as the cathode. Electrolytes used in commercial lithium-ion cells contain organic solvents such as ethylene carbonate, dimethyl carbonate, 1,2-dimethoxy ethane together with a lithium salt (*e.g.*, $LiPF_6$).[1] In lithium-ion cells, intercalated carbon replaced lithium metal used in rechargeable lithium cells. During the first charge, solvent and the anion undergo reduction forming the solid electrolyte interphase (SEI); the lithium ion intercalation into the coke electrode occurs via the SEI. This passivating film prevents or minimizes further reactions of the electrolyte components and permits stable operation of the rechargeable cell. However, at high current densities the thickness of the SEI decreases, and direct reaction between lithium, cathode material and electrolyte occurs.[2] This leads to loss of capacity with cycling. While this cell includes good charge and discharge cycling at ambient temperature and below, its high temperature operation is limited to 40 to 50 °C because of the volatility of the solvents utilized in making the battery, as well as the dissolution of the SEI in the electrolyte which leads to a thermal runaway.

The higher temperature performance of lithium-ion cells can be improved incorporating anode materials which intercalate lithium ions at voltages higher than the reduction voltage of the electrolyte. Such cells show longer cycle life since solvent reduction at the electrode surface is eliminated, and do not suffer from a thermal runaway experienced by conventional lithium ion cells using coke or graphite as the anode. The higher voltage for lithium ion intercalation at the anode also eliminates the possibility of lithium metal deposition and dendrite formation, which shortens cell life. Possible anode materials for such cells include, $Li_4Ti_5O_{12}$, $LiWO_2$, and $LiMoO_2$. Despite the above described advantages, the use of traditional volatile solvents as electrolytes, still limits the higher operation temperature. Gel type solid polymer electrolytes can extend the higher temperature limit, but as the cell is heated, the liquid separates from the solid polymer, which is a limitation factor that affects high temperature operation. A solid (dry) polymer electrolyte has poor conductivity at ambient temperature; therefore, such an electrolyte permits cell operation only at higher temperatures. Lithium metal rechargeable cells are advantageous because of their potential for high energy densities. However, the use of organic solvents in the electrolyte limits high temperature operation due to solvent volatility. A lithium metal rechargeable cell developed by Tadiran Ltd. has a 125 °C upper operation temperature limit due to polymerization of its solvent, 1,3-dioxalane.[3]

3.1.1. Ionic liquids in lithium-ion cells

Most of the solvents used in lithium-ion cells have an electrochemical window in the range of 4.1-4.3 V. therefore in these high voltage cells, the oxidation of the electrolyte during charge (overcharge) can occur which leads to cathode degradation.[4] In addition, solvents generally used for these applications are volatile, some are flammable, thus introducing a safety hazard. Further, their operating range is rather narrow (*e.g.*, -99 °C to 32 °C for methyl formiate).[5]

Room temperature molten salts, due to their high thermal stability, non-volatility, electrochemical stability, non-flammability do not present a safety hazard. Therefore, they have been proposed as electrolytes in lithium-ion cells.[6] Lithium-ion cells based on ILs should neither catch fire nor burst under pressure, because the electrolyte is not flammable, and does not develop pressure even at high temperature.

However, although 1,3-dialkylsubstituted imidazolium salts are the most applied, their cathodic instability makes them unsuitable for second generation lithium batteries. Several essays have been done to verify the possibility to increase stability in reductive conditions, for example introducing electron-withdrawing groups in C(2) position, alkyl chains in C(3) position, delocalizing the positive charge of the imidazolium ring, or adding additives able to preserve lithium surface. Alternatively, ammonium (*i.e.*, pyrrolidinium and pyrazolium) and sulfonium salts have been also proposed.

However, preliminary results with lithium-ion cells constructed with carbon anodes and imidazolium based ionic liquids have shown that decomposition of the ionic liquid occurs when the cell is charged. This suggests that a passivating film does not form on carbon when those ionic liquids are used, resulting in continuous reduction of the electrolyte. However, non passivating anodes can be used instead of carbon to produce lithium-ion cells containing ionic liquids that operate at both low and high temperature.[7] The high temperature cells use does not affect significantly the cell performance except for the loss in capacity. The disadvantages of these solvents are however mainly related to their low conductivity and higher viscosity at low temperatures.[8]

Pyrazolium salts, failing C(2) proton, if suitably substituted, could probably represent an important alternative to imidazolium ones for lithium batteries. The absence of a proton between the two nitrogen atoms, characterizing the imidazolium salts, is expected to modify the chemical stability of the resulting liquids, also in oxidative conditions.[9] During last years, few pyrazolium salts have been studied from an electrochemical point of view, but in this sector salts “solid” at room temperature or with low melting points have attracted attention much more that simpler pyrazolium based ionic liquids. The increase of interest for this class of compounds can be associated to the suggestion that in current commercially available batteries, mixture of liquid electrolytes and polymers, defined gel-polymer electrolyte system, are used. Nevertheless, recently it has been proposed the use of solid compounds in a metastable state, defined as *plastic crystal*,[10] which are generally characterized by:

- Higher structural disorder, that determines bigger values of diffusivity and plasticity;
- Low melting entropy;
- Low dielectric constant, that makes this phase more similar a liquid state.

Plastic crystals are materials in which the molecules or ions possess some degree of rotational disorder in an otherwise well-ordered crystalline arrangement. Typically the material adopts a completely ordered, including rotationally ordered, state at low temperatures but at higher temperatures it passes into a rotationally disordered state *via* a first order change of phase. Such rotationally disordered phases are energetically much closer to the liquid state than the ordered phase and tend to also possess many lattice defects. A combination of the rotational mobility and the lattice defects produces measurable ion conductivity in these phases if the compound itself is ionic.

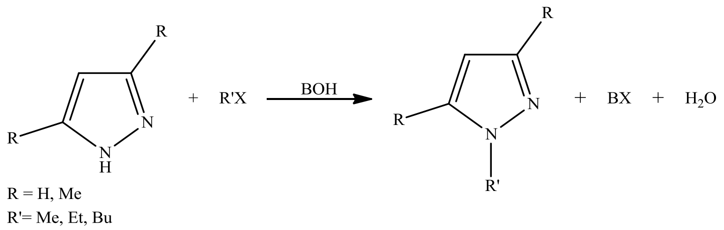
Plastic crystalline substances have also been known for many years and those based on ionic species can exhibit ion conduction.[11]

Solid materials with those properties are generally made of heterocyclic or aliphatic amines, and are not able to conductivities higher than 10^{-3} S cm^{-1} at room temperature in their plastic state. Amide salts in the pyrrolidinium family can exhibit ion conduction in the solid state due to the presence of plastic crystal phases. Doping these salts with lithium salts of the same anion leads to increases in conductivity of up to 2 orders of magnitude.[12]

Recently, it has been shown that some pyrazolium salts seem to have this property, and although their sector is just at the beginning, some have been tested in lithium batteries application. An ionic liquid with a plastic crystalline phase offers the advantage to maintain the properties of an electrolyte also at temperatures lower than the melting point and it is able to sustain, in these conditions, performances of a battery.[13] In particular, the ionic liquid 1,2-diethyl-3-methylpyrazolium bistriflimide, and its mixtures with $LiTf_2N$, have high conductivity values, both in solid and in liquid state. Applied in lithium batteries, this ionic liquid was able to give off the 83% and 67% of the theoretical capacity in liquid and plastic crystalline state respectively. Respect to other pyrazolium salts (*i.e.*, 1,2-diethylpyrazolium) without a plastic crystalline state it has also evidenced a rapid decrease in performances reducing the temperature, to disappear under melting point, although the latter is able to give off high performance at high temperature.

3.2. Synthetic methods

During the course of this PhD thesis, for the synthesis of pyrazolium salts we used two commercial starting materials: pyrazole and 3,5-dimethylpyrazole. Because of the lower reactivity of this heterocycle with respect imidazole, *N*-alkylation reactions (Scheme 3.1) were performed using alkyl iodide as electrophile instead of bromide or chloride ones.



Scheme 3.1. Pyrazoles alkylation.

In literature, *N*-methylation is generally carried out using iodomethane as methylating agent, K_2CO_3 as base and acetone as solvent. However, under these conditions the methylation process requires long reaction times and, in particular when halides bearing longer alkyl chains (*i.e.*, 1-iodoethane and 1-iodobutane) are used, conversions remain moderate also after reflux heating for several days.[14] In Table 3.1 are reported conditions and yields used for a preliminary screening.

Table 3.1. Alkylation with 2.2 eq K_2CO_3 in refluxing acetone.

	Alkylating agent (eq)	**t (days)**	**Yields (%)**
Pyrazole	BuI (1.6)	4	50
	MeI (1.6)	3	60
	EtI (1.6)	’’	50
3,5-dimethylpyrazole	BuI (1.6)	8	15
	EtI (1.1)	5	90
	MeI (1.1)	’’	80

In order to increase the rate of the alkylation process, nucleophilic substitution reactions have been carried out in acetonitrile, using KOH as base. Under these conditions, it has been possible to obtain the expected products in high yields and in a shorter time. Moreover, considering the highest reactivity of 3,5-dimethylpyrazole in comparison with the unsubstituted analogous, with this compound the alkylation reaction was also tested using 1-bromoethane and 1-bromobutane.

Optimized the reaction conditions for each substrate, the process was scaled up to the order of 10-50 grams and the products were isolated by extraction from the basic mixture with diethyl ether. After remotion of the low boiling compounds (*i.e.*, MeCN and alkylhalogenide) by evaporation at reduced pressure, the isolated *N*-alkyl-pyrazoles were characterized by nuclear magnetic resonance analysis (NMR) and used without any further purification as starting materials in the quaternization reaction. In Table 3.2 are reported conditions and yields for alkylation reactions using KOH as base.

Table 3.2. Alkylation with 1.9 eq KOH in acetonitrile.

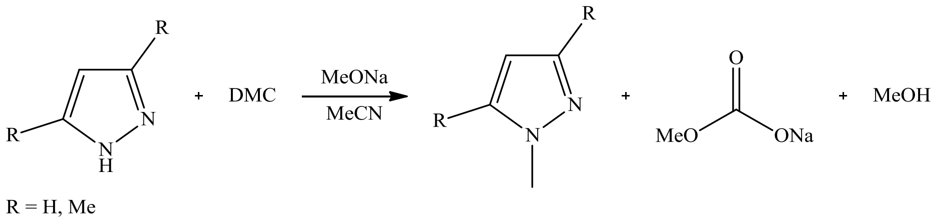
	Alkylating agent (eq)	**t (days)**	**T (°C)**	**Yields (%)**
Pyrazole	BuI (1.02)	2	60	87
	”	3	’’	89
	EtI (1.02)	”	’’	60
	MeI (1.02)	1	’’	67
3,5-dimethylpyrazole	”	”	50	90
	EtI (1.02)	2	’’	88
	EtBr (1.02)	2,5	’’	85
	BuBr (1.02)	’’	’’	99

Although methylation of the heterocyclic system (*e.g.*, pyrazolium, imidazolium, etc.) is generally the first step of the transformation process of these compounds in ionic liquids, the use of toxic reagents such as methyl iodide is often considered as a negative factor for the sustainability of the final product. A “green” solvent not only has to be eco-friendly but also nontoxic reagents have to be used in its synthesis, which moreover should be conducted under sustainable conditions. Therefore, we decided to test the possibility of using dimethylcarbonate (DMC) as methylating agent in the first alkylation step because of its low toxicity.

3.2.1. *N*-methylation of pyrazole with DMC

Heterocyclic systems containing NH groups in the presence of a base (*e.g.*, organic or inorganic) react following the first path in Scheme 2.1 to give exclusively the *N*-methylation product. Normally, methylation reactions are carried out at high temperature, > 100 °C, therefore, considering that DMC has a boiling point of 90 °C, methylation of pyrazole and imidazole have been conducted dropping DMC on the proper heterocycle under reflux conditions (bath temperature 140 °C) for 8 h and continuing the stirring for further 2 h. The side product formed during reaction, MeOH, was continuously distilled out during the process. Under these conditions, *N*-methylimidazole and *N*-methylpyrazole were obtained in 90% and 60% yield, respectively. Alternatively, the reaction have been conducted in autoclave at 160 °C.

Attempts to perform methylation reaction of pyrazole and 3,5-dimethylpyrazole under similar conditions to those described above, but dissolving directly pyrazole in DMC, gave the instantaneous formation of a solid, from which the expected product was isolated in low yield. Since the formation of a solid species could affect negatively the process, we tried to use acetonitrile as a co-solvent. Therefore, a series of experiments was carried out to find the optimal reaction conditions; in particular, the relative amounts of DMC, base and solvent were varied (Tables 3.3 and 3.4). In agreement with the higher reactivity of 3,5-dimethylpyrazole, its reaction with DMC could be performed at lower temperature and without the use of a co-solvent. In Scheme 3.2 is shown the general pattern of methylation with DMC.



Scheme 3.2. General DMC methylation mechanism.

Table 3.3. Pyrazole *N*-methylation with DMC at reflux (90 °C).

	DMC (eq)	**MeONa (eq)**	**MeCN (mL)**	**t (h)**	**Yield (%)**
pyrazole (0,5 g)	8.5	1.5	-	3	31
	”	2	-	”	53
	23	”	-	”	71
	17	1.5	-	6	77
	”	”	3	13	65
	8.5	”	5	6	75
	”	”	3	”	81
	6.4	”	5	”	78
	12.8	”	3	”	69
	”	2	”	”	80
	14.2	”	5	13	83
	”	1.5	”	”	68
	6.4	2	”	”	81

For both substrates, reactions were scaled up to the tens of grams and products were isolated from the basic mixtures by extraction with diethyl ether. After volatile products (*i.e.*, acetonitrile, ethanol and DMC) evaporation at reduced pressure, the isolated *N*-methylpyrazoles were characterized by NMR and then used as such in subsequent quaternization reactions.

Table 3.4. 3,5-dimethylpyrazole *N*-methylation with DMC at reflux (90 °C).

	DMC (eq)	**MeONa (eq)**	**MeCN (mL)**	**t (h)**	**Yield (%)**
3,5-dimethylpyrazole (0,5 g)	6.4	2	3	3	73
	4.3	”	4	”	56
	2.1	”	”	”	41
	”	”	3	”	60
	6.4	1.5	4	”	47
	”	”	3	”	86
	4.3	”	”	”	86
	2.1	”	”	”	76
	6.4	”	”	”	87
	4.3	”	”	”	76
	6.4	1.2	”	”	81
	4.3	”	”	”	81
	6.4	1.0	”	”	77
	”	1.2	2	”	78
	4.3	”	”	”	87
	”	”	3	1	67
	6.4	1.0	”	13	68
	8.5	1.2	-	3	83
	”	1.5	-	”	97

3.2.2. Quaternization reactions

Considering the low reactivity of the pyrazole system, quaternization reactions were conducted in acetonitrile at temperatures between 80-100 °C, using the most reactive alkyl iodides. As expected, *N*-methylpyrazole gave lower conversions than the corresponding 3,5-dimethylderivative and even after five days it was not possible to reach a conversion more than 20% with this substrate.

Quaternization reactions of both substrates were performed using both 1-iodobutane and 4-iodobutyronitrile in order to obtain side chain functionalized pyrazoles (Table 3.5).The functionalization of alkyl chain is a widely used procedure in ionic liquids chemistry as it allows to obtain reaction *media* with additional properties, that can work as solvents, ligands or as catalyst stabilizers. This class of ionic liquids, generally defined as *task specific ionic liquids*, has been widely developed in the case of imidazolium and pyridinium cations and it has been applied in organic synthesis, in materials separation and in nanonstructured materials preparation. Although functionalized ionic liquids can contain a covalently linked functionality both on cation or anion, generally the cation better sustain a reactive functional group and ionic liquids bearing the functionalized chain on the anion are few.

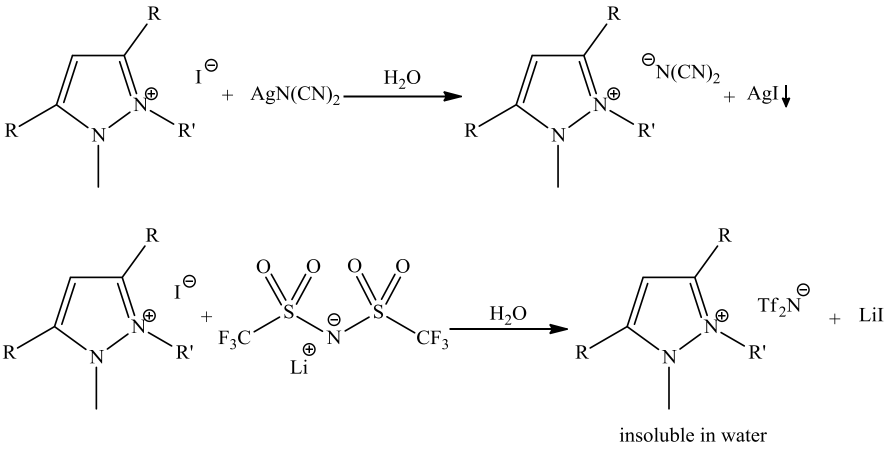
Table 3.5. Quaternization reactions.

	Alkylating agent (eq)	**t (days)**	**T (°C)**	**Yields (%)**
N-methylpyrazole	BuI (1.02)	5	80	20
	IPrCN (1.02)	4	100	26
1,3,5-trimethylpyrazole	BuI (1.5)	3	80	57
	BuI (1.02)	5	”	26
	BuOMs			-
	IPrCN (1.03)	4	90	75

Concerning the presence of a CN group on the side chain, it should be emphasized that imidazole, pyridine and pyrrolidine based ionic liquids containing a nitrile functionality have already been used successfully as solvent-ligands in organometallic chemistry. As 1-iodobutyronitrile is not a commercial compound, it was synthesized from 1-chlorobutyronitrile through nucleophilic substitution with sodium iodide.

Finally, it should pointed out that the attempt to functionalize 1,3,5-trimethylpirazole using butylmesylate did not lead to the isolation of any product even protracting the reaction for over a week.

However the expected reaction products, iodide salts, have been isolated from acetonitrile solution by solvent evaporation, after the addition of water and extraction of unreacted precursors. Then the iodide salts, solid at room temperature, were dissolved in water and subjected to anion metathesis reaction to obtain the desired salts based on dicyanamide and bis-(trifluoro-methylsulfonyl)imide (bistriflimide) (Scheme 3.3). These anions usually allow to obtain liquid salts at room temperature.



Scheme 3.3. Anion metathesis.

In dicyanamide metathesis reaction the corresponding silver salt, $AgN(CN)_2$, is used, exploiting the low solubility of silver iodide in water to isolate the water soluble liquid with the dicyanamide anion in pure form. In the synthesis of pyrazolium salts having bistriflimide, Tf_2N^-, as anion its idrofobicity is exploited to separate the product from the starting solution. The reaction is conducted in water using $LiTf_2N$ and after about one day of room temperature stirring the separation of two phases (*i.e.*, pure ionic liquid and aqueous phase containing LiI) can be observed.

In literature, it is reported that transition metals are typically not very soluble in ILs based on weak Lewis basic anions (*e.g.*, PF_6^-, BF_4^-, Tf_2N^-, etc.). Recently, ILs based on dicyanamide anion have been synthesized and characterized.[15] The DCA is a Lewis base having good ligand properties and it is expected that transition metal salts would dissolve well in the $N(CN)_2^-$-based ILs by forming complexed anions.[16] This feature makes it easier to prepare transition metal solutions for electrodeposition. Furthermore, the $N(CN)_2^-$-based ILs exhibit lower viscosity than their Tf_2N^- counterparts. Lower viscosity implies more efficient mass transport and higher conductivity for electrochemical applications.[17] Since dicyanamide-based ILs show a wider cathodic potential windows, important for electrodeposition of metals, they are chosen for electrodeposition of reactive metals (*e.g.*, Al and Mn).[18]

3.3. Characterization

Polarity is one of the most important solvent features that can provide both qualitative and quantitative information about the ability of a medium to interact with the species dissolved in it (*e.g.*, intermediates, transition states). Polarity, being a property sum of multiple effects, is usually difficult to express in a quantitative way using a single parameter.

However, dielectric constant is certainly the most used physico-chemical parameter to assess the ability of a solvent to interact with a specific solute and to evaluate the solvation ability of a specific chemical, normally based on “like dissolves like” principle. Nevertheless, even the most simple computational models, often used to describe electrostatic interactions in a solvation process, consider the solvent as an unstructured homogeneous *continuum* and use dielectric constant and other physical constants such as the permanent dipole moment and the refraction index, to quantitatively assess solvent effects.

Actually, solute-solvent interactions occur at molecular level within a *discontinuum* structured in single solvent molecules, each capable of interacting with the solute and other solvent molecules itself. A purely electrostatic approach, based on above described physical parameters, does not consider specific solute-solvent interactions and correlations between solvent's chemical effects (*e.g.* reaction rate, selectivity, etc.) and its polarity, expressed just as physico-chemical parameter, and have proved to be unable to describe the problem: the electrostatic approach was found to be a failure several times.

For a more satisfactory description of the solvent effect it is necessary to take into account both specific and nonspecific solute-solvent, solvent-solvent and, at high solute concentration, even solute-solute interactions. Otherwise, it is necessary to define solvent polarity on the basis of the overall capacity of solvation, which depends on all possible interactions (*e.g.*, nonspecific, specific intermolecular forces between or ions of solute and solvent molecules) excluding all those phenomena that can lead to irreversible chemical changes of solute molecules or ions (*e.g.*, protonation, oxidation, reduction and chemical complexes formation).

Therefore, the polarity of a solvent cannot be quantitatively described by a single physico-chemical parameter. However, the lack of a comprehensive theoretical equation to predict solvent effect on chemical reactivity and the inadequacy of polarity definition in terms of physical properties have led to introduction of several empirical parameters that quantify solvent polarity and to development of a large number of polarity scales. Among these, polarity scales based on measurement of UV-vis absorption of some chemicals, dyes usually referred to as "probes", are to be mentioned. Depending on the probe chemical structure is possible to obtain a quantitative assessment of a certain type of interaction and so the use of more probes can provide important data about different solute-solvent interactions that define the polarity of a medium.[19]

UV-vis absorption spectra of chemicals are influenced by the surrounding medium and solvents can lead to changes in position, intensity and shape of the absorption band. This phenomenon is called solvatochromism and is determined by the different solvation between the ground and the first excited states of the molecule. If increasing solvent polarity the ground state is better stabilized, this will lead to a negative solvatochromic effect which results in an ipsochromic shift (toward blue) of the considered absorption band; otherwise, the effect will be positive when the first excited state is more effectively stabilized getting a bathochromic shift (toward red). Usually, organic solvatochromic probes are relatively complex compounds able to give several kinds of solute-solvent interactions (*e.g.*, dipole-dipole, dipole-ion, hydrogen bond, π-π, etc.) so only a combined evaluation of the effects of the same solvent over several probes makes possible to define in a quali-quantitative manner its polarity by taking into account all possible interactions.

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3.3.1. Kamlet-Taft parameters

The definition of the polarity of a solvent according to Kamlet-Taft parameters is based on the use of more solvatochromic probes to recognize and evaluate, for the same solvent, different types of interaction that it can have with the solute and their relative relevance.[20] Especially, using three solvatochromic probes it is possible to evaluate three parameters that measure solvent polarizability (π^*), its hydrogen bond donor ability (HBD) α and its hydrogen bond acceptor ability (HBA) parameter β.[21]

In particular, π^* measures of solute-solvent interaction considered as dipole-dipole or dipole-induced dipole. So it measures the ability of a solvent to stabilize a net charge or induced dipole by nonspecific dielectric interaction. π^* value can therefore be regarded as a combination of polarizability-dipolarity of a solvent. Its scale takes the name from the $\pi - \pi^*$ transition of the probes initially used (nitroaromatic compounds) to determine this type of solvent effect.[22]

The scale ranges from $\pi^* = 0$ for cyclohexene to $\pi^* = 1.00$ for dimethyl sulfoxide. π^* value is generally evalued on the basis of the maximum of absorption of *N,N*-diethyl-4-nitroaniline:

$$\nu_{max} = \nu_0 + s\pi^*$$

with
ν_{max} = wavelenght at maximum absorbance;
$\nu_0 = 27.52\ 10^3\ cm^{-1}$;
$s = -3.128$.

α parameter is determined by comparing the shifts inducted by the solvent on $\pi - \pi^*$ absorption band of two similar probes (homomorphic), one of which cannot work as either hydrogen bond acceptor or donor (*N,N*-diethyl-4-nitroaniline), while the other works as hydrogen bond acceptor (Reichardt's dye, also known as betaine 30), Figure 3.1.

$$\alpha = \frac{E_T(30) - 14.6(\pi^* - 0.23\sigma) - 30.31}{16.5}$$

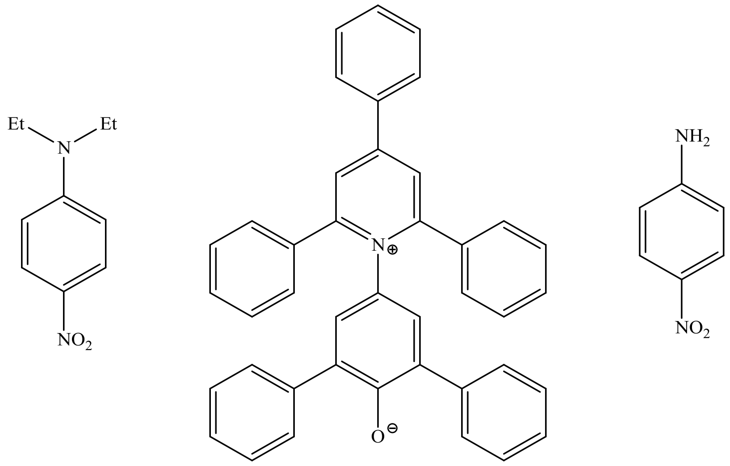


Figure 3.1. From the left, *N*,*N*-diethyl-4-nitroaniline, Reichardt's dye and 4-nitroaniline.

$E_T(30)$ is another parameter widely used to define solvent's polarity, determined on the basis of Reichardt's dye maximum absorption:

$$E_T(30)(kcal\ mol^{-1}) = \frac{28591.5}{\lambda_{max}(nm)}$$

where λ_{max} is the maximum absorption of the lower energy band, corresponding to intramolecular charge transfer (CT) $\pi - \pi^*$ of betaine 30 in its zwitterionic form. Because of its structure, solvatochromic properties of betaine 30 are strongly influenced by two solvent effects: dipolarity-polarizability and hydrogen bond formation ability, since both of them are able to stabilize the dipolar ground state respect to the less dipolar Frank-Condon excited state.

Ground and excited states of betaine 30 are shown in Figure 3.2 and it is clear how the different solvation between ground and excited states changing over from nonpolar or low polar solvents to polar ones determines a transition energy increase which is expressed in a absorption band shift to longer wavelength.

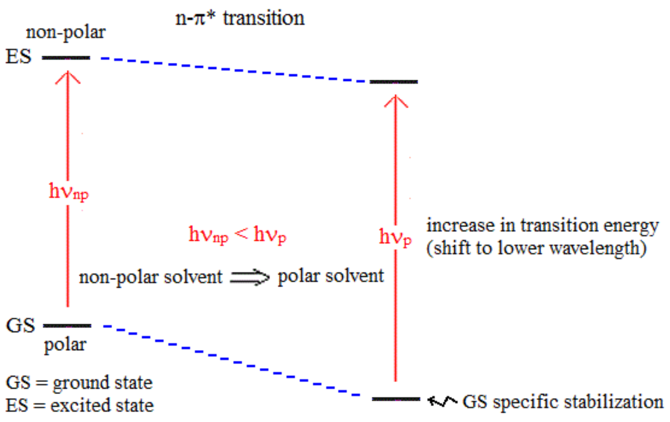


Figure 3.2. Ground and excited state of Reichardt's dye.

Finally, β parameter, which is an empirical measure of solvent ability to function as hydrogen bond acceptor (HBA), is evaluated by comparing the shift induced on the absorption $\pi - \pi^*$ band in two similar molecules; one acting as hydrogen bond donor (4-nitroaniline) and the other alkylated on nitrogen that cannot work as the former (*N*,*N*-diethyl-4-nitroaniline). For nor HBA or EPD solvents, as aliphatic hydrocarbons, $\beta = 0$ but for aromatic ones $\beta \sim 0.1$.

$$\beta = \frac{1.035\,\nu(2)_{max} - \nu(1)_{max} + 2.64\ 10^3 cm^{-1}}{2.8}$$

with

$\nu(1)_{max}$ = maximum absorbance of 4-nitroaniline;

$\nu(2)_{max}$ = maximum absorbance of *N*,*N*-diethyl-4-nitroaniline.

Table 3.6. Solvatochromic parameters of common organic solvents.

Solvent	π^*	Α	Β
Hexane	-0.08		
Chloroform	0.58	0.34	
Diethylether	0.27		0.47
Acetone	0.71	0.08	0.48
DMSO	1.00		0.76
MeCN	0.75	0.19	0.31
DMF	0.88		0.69
Ethanol	0.54	0.83	0.77
Water	1.09	1.17	0.18

Kamlet-Taft parameters, known for most popular molecular solvents (some values are reported in Table 3.6), have also been determined for some ionic liquids (Table 3.7).[23] With an examination of the values of the two tables, it is clear that ionic liquids are generally characterized by higher π^* values than most molecular solvents. From this it follows that they have higher ability to induce an electric dipole in compounds dissolved in them. π^* value varies a little between different ionic liquids,[24] but most low values are usually typical of bistriflimide anion bearing salts; probably, because of greater negative charge delocalization, which differentiates this from usually used tetrafluoroborate and hexafluorophospate anions, leads to a reduced capacity of corresponding ionic liquids to interact with betaine 30 by Coulombic forces.

Table 3.7. Solvatochromic parameters of some ILs.

Ionic liquid	π^*	**A**	**B**
[bmim][PF_6]	1.02	0.65	0.25
[bmim][BF_4]	0.98	0.67	0.45
[bm_2im][BF_4]	1.08	0.40	0.36
[emim][Tf_2N]	0.98	0.66	0.24
[hmim][Tf_2N]	0.97	0.65	0.26
[C_3(CN)mim][BF_4]	1.08	0.64	0.34
[bm_2im][Tf_2N]	1.00	0.41	0.24

α values vary in a wider context and, in the case of ionic liquids not bearing functional groups able to act as specific hydrogen bond donors (OH, NH_2), imidazole salts not substituted on heterocyclic C(2) have α values bigger than pyridinium and pyrrolidinium salts. Although this parameter is mainly determined by the cation nature, also anion exerts some influence. In particular, more basic anions, that give rise to stronger anion-cation interactions, reduce the cation ability to act as hydrogen bond donor. It should be noted that cation or anion ability to interact with a species dissolved in the ionic liquid should always be considered a process in competition with the cation or anion ability to interact with ion species of opposite charge adjacent thereto.[25]

Finally, β parameter is characterized by the anion nature and increase with its basicity.

In Table 3.8 are shown Kamlet-Taft parameters determined for the pyrazole based ionic liquids synthetized during this thesis. These parameters were determined at 25 °C using three solvatochromic probes (*i.e.*, Reichardt's dye, *N*,*N*-diethyl-4-nitroaniline and 4-nitroaniline) by recording the spectra of the solutions of these dyes in the ionic liquids investigated in the wavelengths between 250-600 nm.

Table 3.8. Solvatochromic parameters of pyrazolium salts.

Ionic liquid	π^*	α	Β
[bmpz][Tf_2N]	1.04	0.69	0.205
[bm_3pz][Tf_2N]	1.02	-	0.234
[bmpz][$N(CN)_2$]	1.13	0.46	0.554
[bm_3pz][$N(CN)_2$]	1.13	0.13	0.586
[$C_3(CN)m_3pz$][Tf_2N]	1.05	-	0.241
[bmim][Tf_2N]	0.97	0.64	0.248
[bmim][$N(CN)_2$]	1.12	0.46	0.708
[$C_3(CN)m_3pz$][Tf_2N]	1.03	0.65	0.219

To facilitate the comparison in the same table are also reported the values of some imidazolium based ionic liquids having structures closely related to the structures of the investigated pyrazolium salts. Unfortunately, for some bistriflimide based ionic liquids was not possible to determine α parameter because of immediate disappearance of the colour after betaine 30 addition. Absorption band at greater wavelengths of this probe, that determines the colour of the solution, is known to be particularly sensitive to acids or metal cations (*e.g.*, Ag^+) presence which can strongly interact with the phenolic proton. However, the ionic liquids considered should not show such acidy values to determine probe protonation and, of course, after the multiple washes to which were subjected during their synthesis, they did not contain metal cations capable to complex phenolate anion. The reason of this behaviour is thus currently unknown and still under study.

Considering data reported on Table 3.8, similarly to imidazolium based ionic liquids, pyrazolium ones have high polarizability/dipolarity. It is also noteworthy that 1,2-dialkylpyrazolium base ionic liquids show a significant ability to act as hydrogen bond donors; their α values are comparable to those of analogous imidazolium salts. In ionic liquids with five terms heterocyclic cation thus the acidity is not a peculiarity of the proton between the two nitrogen of the imidazolic system. This hypothesis was formulated on the basis of values measured for ionic liquids bearing as cation 1-methyl-3-butylimidazolium, bmim$^+$, and 1,2-dimethyl-3-butylimidazolium, bm$_2$im$^+$ (Table 3.7); the latter shows values significantly lower, because to the lack of C(2) proton. The introduction of other two methyl groups in position 3 and 5 of the pyrazole ring (adjacent to the two nitrogen atoms) drastically reduces the cation ability to act as hydrogen bond donor; the value calculated for [bm$_3$pz][N(CN)$_2$], with just one aromatic proton, is significantly lower than that of [bmpz][N(CN)$_2$]. Finally, the comparison between α values of bistriflimide based ionic liquids with dicyanamide based ones confirm that the cation ability to act as hydrogen bond donor is a property modulated by the anion basicity [bmpz][Tf$_2$N] is characterized by a value significantly greater than that measured for [bmpz][N(CN)$_2$].

3.3.2. Viscosity, density and conductivity

For all pyrazolium based ionic liquids, some fundamental properties such as viscosity (η) and conductivity (κ) were measured in the temperature range between 20 and 80 °C after thorough drying, avoiding as much as possible contact with air during the transfer and measures. The values of viscosity and conductivity at different temperatures are reported in Table 3.9 and Table 3.12.

Synthesized pyrazolium salts bearing the same anion and alkyl substituents of imidazolium salts were characterized by viscosity values comparable to the latter ones.

Table 3.9. Viscosities (cP) related to temperature (°C).

Ionic liquid	20	30	40	50	60	70	80
[bmpz][Tf$_2$N]	89.5	51.1	37	25.5	18.5	14.5	11.5
[bm$_3$pz][Tf$_2$N]	101.9	58.9	40.4	27.0	19.3	15.3	11.7
[bmpz][N(CN)$_2$]	37.2	24.4	17.5	12.9	9.9	8.1	6.4
[bm$_3$pz][N(CN)$_2$]	90.0	46.7	33.0	21.8	15.5	11.3	8.8
[C$_3$(CN)mpz][Tf$_2$N]	1488.0	650.9	304.6	171.6	99.2	65.3	47.4
[C$_3$(CN)m$_3$pz][Tf$_2$N]	722.2	303.8	165.8	92.2	57.8	38.4	27.7

Similarly to imidazolium salts, also in the case of 1-methyl-3-butylpyrazolium the viscosity increases changing from dicyanamide to anion bistriflimide anion. In the case of dicyanamide the viscosity is also sensitive to the presence or absence of the methyl in pyrazole ring. Viscosity of $[bm_3pz][N(CN)_2]$ is significantly higher than that of $[bmpz][N(CN)_2]$. On the other hand, the presence of two methyl groups in positions 3 and 5 on the pyrazole cation influences less the viscosity of analogous bistriflimide based ionic liquids. Finally, it should be noted that although the presence of a nitrile group in the side chain determines, as in the case of imidazolium based ionic liquids, a drastic increase in viscosity, however in this case the effect of methylation of the cation in positions 3 and 5 seems to play an opposite role: viscosity of $[bm_3pz][Tf_2N]$ is lower than that of $[bmpz][Tf_2N]$. In Figure 3.3 and Figure 3.4 trends graphs of viscosity as a function of temperature are shown.

Viscosity is a complex property and, at the current state of knowledge, although the imidazolium based ionic liquids have been definitely more widely studied of pyrazolium ones, even for these a correlation between structure and viscosity does not exist.

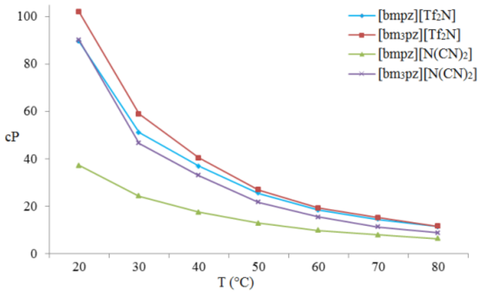


Figure 3.3. Viscosity of alkylic chain pyrazolium salts.

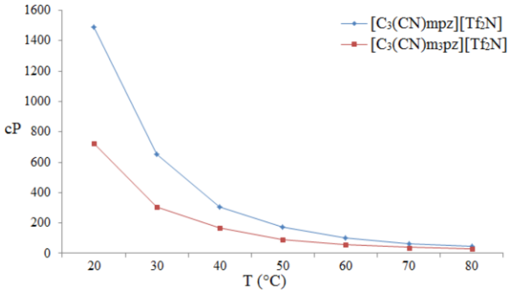


Figure 3.4. Nitrile-functionalised pyrazolium viscosities.

However, in an effort to get more information on the structure of ionic liquids from viscosity data we have analysed the development of this property as a function of temperature, using appropriate mathematical models. Initially, the viscosity data measured between 293 and 363 K were interpolated using the logarithmic form of Arrhenius equation, normally used to describe the dependence of viscosity on the temperature in the case of not dissociated liquid electrolytes:

$$\ln\eta = \ln\eta_\infty + \frac{E_\eta}{RT}$$

where E_η is the attivation energy for viscous flows, $\ln\eta_\infty$ is the viscosity at infinite temperature and R is the gas constant. All investigated ionic liquids approximately follow

Arrhenius equation (in Figure 3.5 the trend of studied ionic liquids is reported, whereas Figure 3.7 shows each trend). The biggest changes are observed in functionalized ionic liquid.

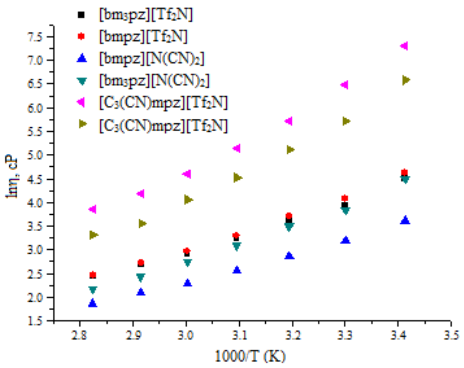


Figure 3.5. Comparison between viscosities of several pyrazolium salts considering Arrhenius equation.

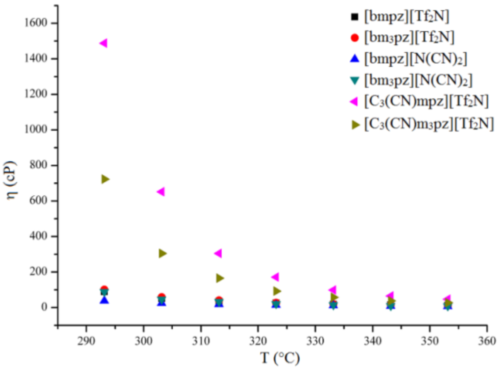


Figure 3.6. Comparison between viscosities of several pyrazolium salts considering VTF equation.

However, E_η, $\ln\eta_\infty$ and fitting parameter R values are reported in Table 3.10.

Table 3.10. Viscosity parameters depending on temperatures (K) following Arrhenius and VTF equations.

Ionic liquid	E_η kJ mol^{-1}	$\ln\eta_\infty$ cP	R	η_0 cP	B K	T_0 K	R^2
[bmpz][Tf_2N]	28.26	-7.3	0.995	0.91	356	215	0.998
[bm_3pz][Tf_2N]	29.93	-7.9	0.996	0.40	523	198	0.999
[bmpz][$N(CN)_2$]	24.60	-6.5	0.997	0.29	513	186	0.999
[bm_3pz][$N(CN)_2$]	32.34	-8.9	0.995	0.76	327	224	0.997
[C_3(CN)mpz][Tf_2N]	49.21	-13.0	0.994	0.046	1187	178	0.999
[C_3(CN)$m_3$pz][Tf_2N]	46.55	-12.7	0.994	0.45	569	215	0.998

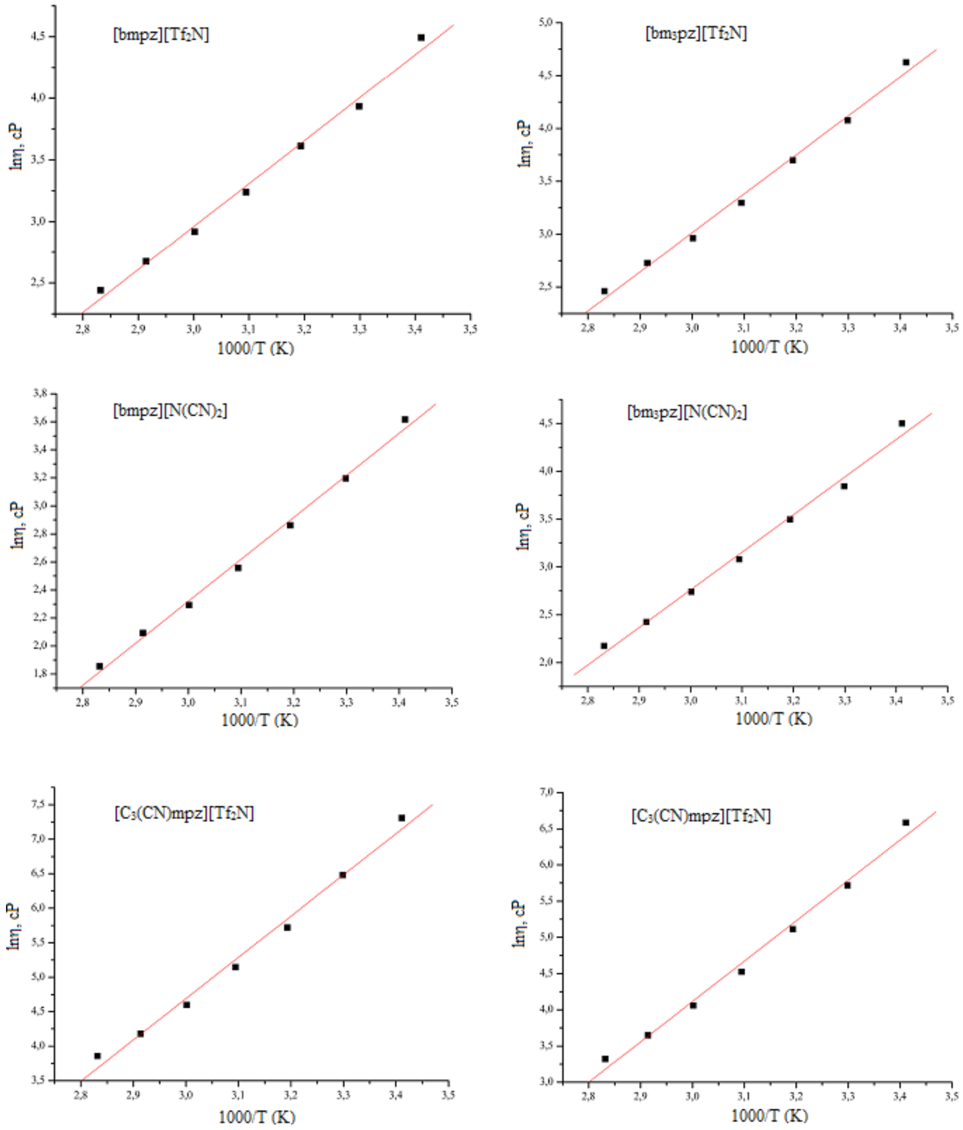


Figure 3.7. Single pyrazolium salts viscosities considering Arrhenius equation.

Viscosity values of these ionic liquids were also analysed using Vogel-Tamman-Fulcher (VTF) (Figure 3.8):

$$\eta = \eta_0 e^{\frac{B}{T-T_0}}$$

where η_0 (cP), B (K), and T_0 are fitting parameters. The best parameters and correlation coefficients are reported in Table 3.10.

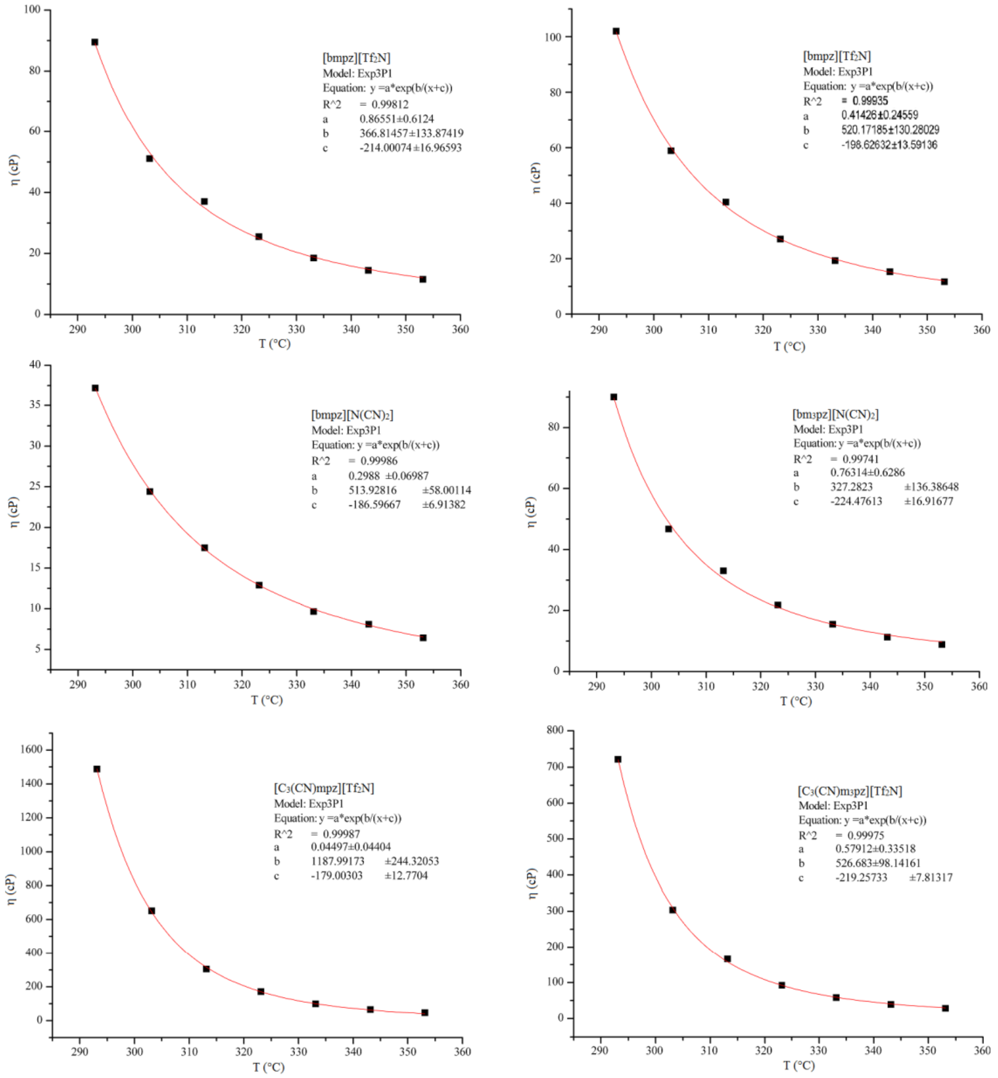


Figure 3.8. Single pyrazolium salts viscosities considering VTF equation.

For these compounds, considering the strong electrostatic interactions between anions and cations, the activation energies E_η can be seen as the energy barriers to be overcome to allow ions to move relative to one another and thus can give information on cation-anion interactions.

[bmpz][Tf_2N] E_η value is similar to the analogous imidazolium ($E_\eta = 25.40$). Moreover both E_η and B (B is actually an empirical parameter more similar to a free energy instead of an activation one) show a structure dependence. In particular, the association of

high E_η values with high and negative $\ln\eta_\infty$ for nitrile functionalized ionic liquids suggests an higher order and degree of association of these systems.

Table 3.11. Density values ρ (g/ml) of pyrazolium based ILs at 25 °C.

Ionic liquid	ρ
[bmpz][Tf_2N]	1.45
[bm_3pz][Tf_2N]	1.38
[bmpz][$N(CN)_2$]	1.07
[bm_3pz][$N(CN)_2$]	1.05
[C_3(CN)mpz][Tf_2N]	1.56
[C_3(CN)$m_3$pz][Tf_2N]	1.45

How expected, dycianamide pyrazolium salts have lower density values, alike to analogous imidazolium ones. Also Tf_2N^- have comparable values. The high viscosity increase associates with nitrile functionality in the side chain is not related to a similar behaviour of density. Moreover there are no differences due to the presence of the two methyls on the aromatic ring.

In Table 3.12 are reported the conductivity values of pyrazolium salts measured at different temperatures, between 20 and 80 °C.

Although the viscosity is not always able to account for the conductivity, there is usually an inverse correlation between these two parameters. According to viscosity data, the 1-methyl-3-butylpirazolium dicyanamide ionic liquid is characterized by higher conductivity, while the functionalized ionic liquids (*i.e.*, [C_3(CN)mpz][Tf_2N] and [C_3(CN)$m_3$pz][Tf_2N]) by the lowest conductivity values. The differences between conductivity values at a certain temperature depending on the structure, or for the same compound function of the temperature, are not always in accord with viscosity data.

As pointed out by Ohno *et al.*,[26] the conductivity is determined not only by the shape and radius of the ions but also by their anion-cation degree of association.

Table 3.12. Conductivities (mS/cm) correlated to temperature (°C).

Ionic liquid	20	30	40	50	60	70	80
[bmpz][Tf$_2$N]	2.90	3.70	4.41	5.15	5.91	6.69	7.36
[bm$_3$pz][Tf$_2$N]	2.36	2.94	3.68	4.56	5.22	5.98	6.80
[bmpz][N(CN)$_2$]	7.74	9.29	11.04	12.83	14.55	16.40	18.10
[bm$_3$pz][N(CN)$_2$]	2.60	3.80	5.24	6.61	8.16	9.74	11.48
[C$_3$(CN)mpz][Tf$_2$N]	0.24	0.42	0.64	0.95	1.28	1.75	2.17
[C$_3$(CN)m$_3$pz][Tf$_2$N]	0.36	0.62	0.93	1.31	1.76	2.40	2.93

Figure 3.9 shows the graph of conductivity of pyrazolium salts depending on the temperature. The trend of conductivity related to temperature depends on the ionic liquid nature.

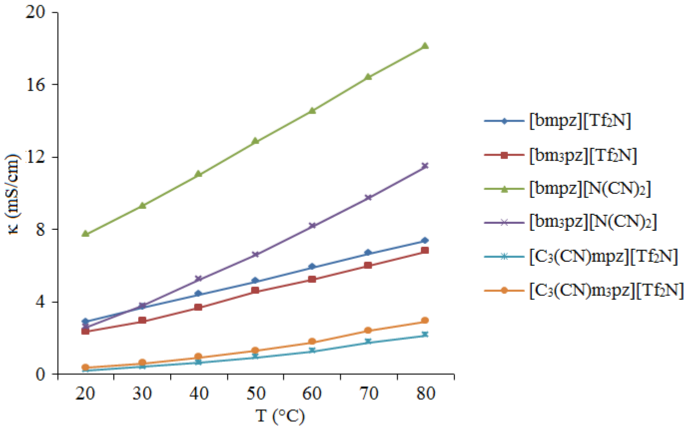


Figure 3.9. Conductivities (mS/cm) correlated to temperature (°C).

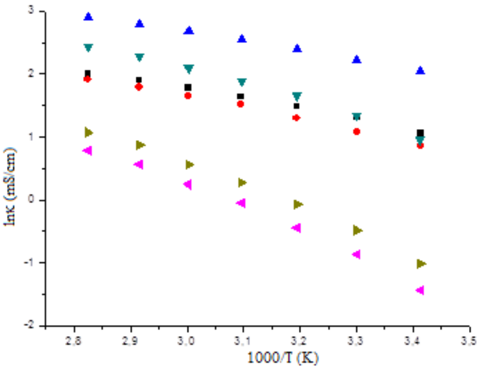


Figure 3.10. Plotted pyrazolium-based ionic liquids conductivities considering Arrhenius equation.

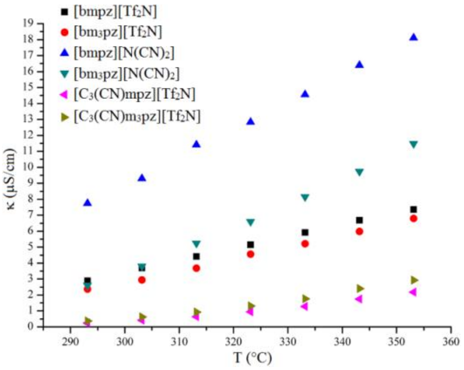


Figure 3.11. Plotted pyrazolium-based ionic liquids conductivities considering VTF equation.

As expected, on the basis of the trend of the viscosity on the temperature, the six ionic liquids pyrazolium based follow “approximately” the Arrhenius equation:

$$\ln\kappa = \ln \mathrm{A} + \frac{E_{\kappa}}{RT}$$

Figure 3.10 shows the Arrhenius plots of the six studied ILs studied and in Figure 3.12 are represented individual trends. The largest deviations were observed for functionalized ILs.

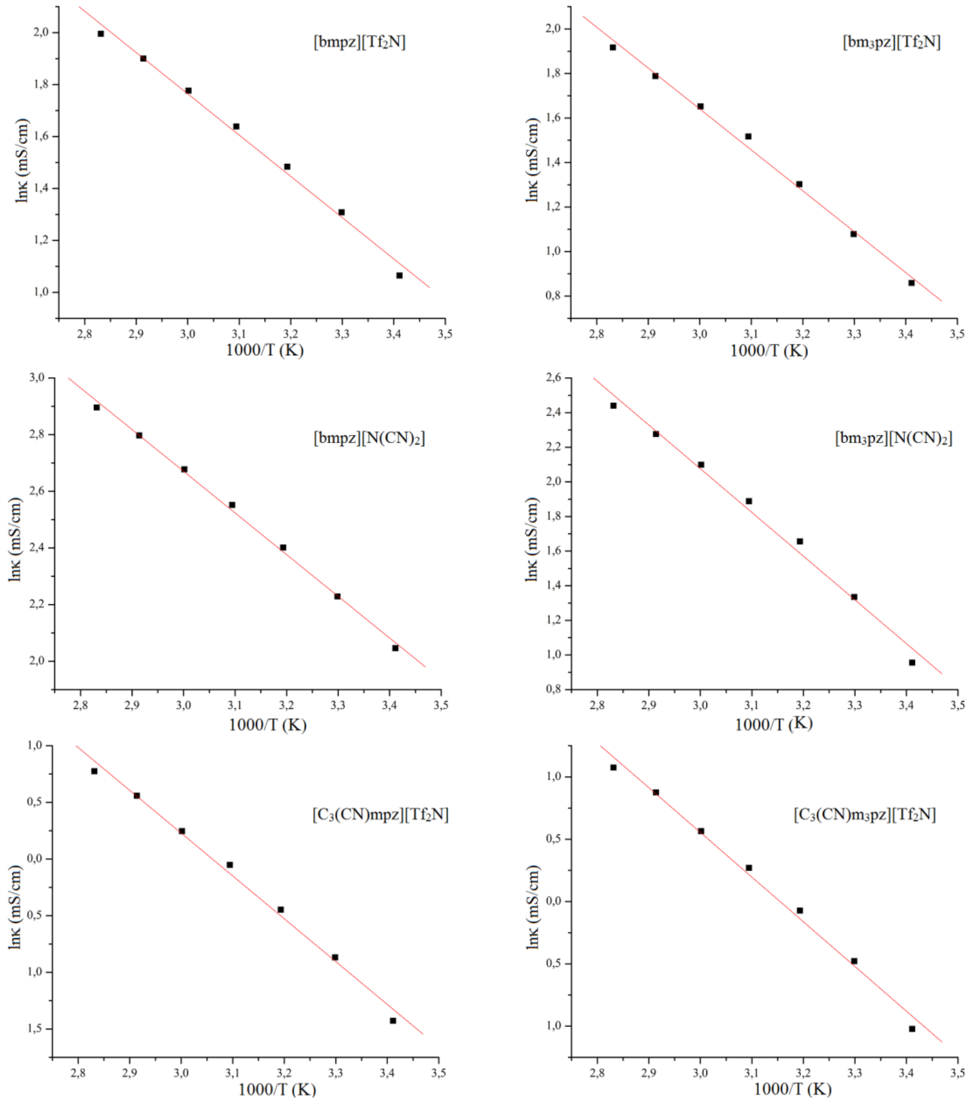


Figure 3.12. Arrhenius plot of pyrazolium-based ionic liquids conductivity.

Then, even the conductivity data were analysed on the basis of the Tamman-Vogel-Fulcher (VTF) equation:

$$\kappa = Ae^{-\frac{B}{T-T_0}}$$

where A (mS cm^{-1}), B (K) and T_0 (K) are fitting parameters. The best parameters and associated correlation coefficients are shown in Table 3.13, together with the Arrhenius parameters.

Table 3.13. Conductivity parameters depending on temperatures (K) following Arrhenius and VTF equations.

Ionic liquid	**E_κ kJ mol^{-1}**	**lnA cP**	**R**	**A cP**	**B K**	**T_0 K**	**R^2**
[bmpz][Tf_2N]	13.05	6.5	0.995	29.4	209	202	0.998
[bm_3pz][Tf_2N]	15.05	7.1	0.996	39.5	282	193	0.999
[bmpz][$N(CN)_2$]	12.06	7.0	0.998	96.0	298	174	0.999
[bm_3pz][$N(CN)_2$]	20.78	9.6	0.993	79.0	271	213	0.997
[C_3(CN)mpz][Tf_2N]	30.76	11.4	0.995	43.0	424	211	0.999
[C_3(CN)$m_3$pz][Tf_2N]	29.51	11.2	0.995	63.0	456	204	0.998

The fact that functionalized ILs present E_κ values higher than alkylic ones confirms the presence of a higher degree of aggregation in the former.

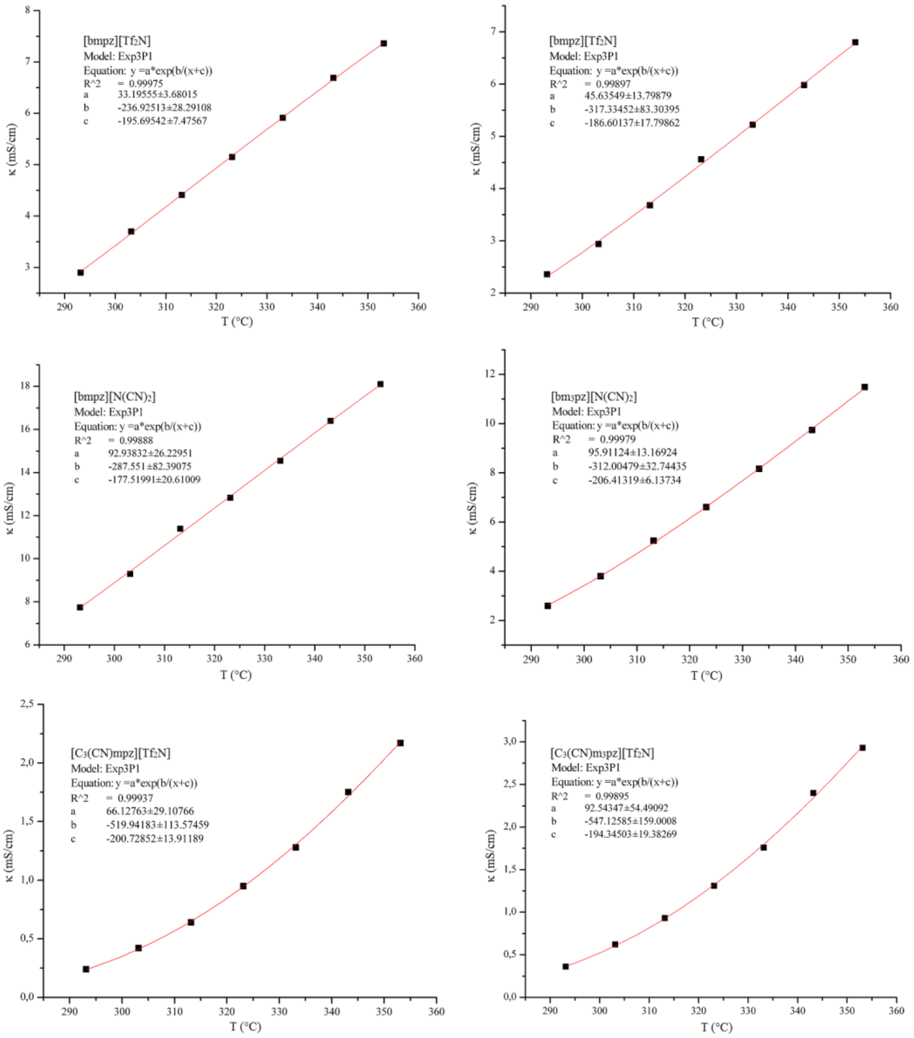


Figure 3.13. Single pyrazolium salts conductivities considering VTF equation.

3.3.3. Electrochemical window

The key criterion to select a solvent for electrochemical applications is the electrochemical stability of the solvent itself, which is determined by measuring the range within it is inert.

The size of this window depends on the oxidative and reductive stability of the compound used as solvent, and in the case of ionic liquids it is determined by the cation stability to reduction and anion stability to oxidation (chlorometallate ILs are not included in this class because their cathodic anion reduction is often the limiting step).

The mostly used method to determine the electrochemical windows is the cyclic voltammetry. In a three electrodes system the potential of an inert electrode is changed over time towards larger positive potential (anode) and negative (cathode) up to the current base value grows suddenly because of oxidation or reduction of the solvent. The oxidative and reductive potential limits are assigned when the base current reaches the threshold values. As the choice of limit value is subjective, the definition of the electrochemical window has a certain degree of uncertainty, typically around 0.2 V. It has also to be pointed out that in the case of ILs the presence of impurities (often water and halide) can have a big effect on the limit potentials that determine the electrochemical window. In particular, halides present as a result of an incomplete exchange reaction are more easily oxidizable than fluorinated anions (*e.g.*, bistriflimide), often used for electrochemical applications, and can cause an anodic potential reduction. With regard to the water, being able to be oxidized and reduced can substantially influence the electrochemical window. To prevent any problems arising from the presence of water, which may be present in significant amounts even in hydrophobic ionic liquids, the samples after being placed in the electrochemical cell, before performing their measures, underwent a process of re-drying, keeping them for 24 hours at 60-80 °C under vacuum.

Electrochemical windows of pyrazolium salts, determined using a platinum electrode as working electrode, are shown in Table 3.14.

Table 3.14. Electrochemical windows (V) of pyrazolium based ILs measured at 25 °C.

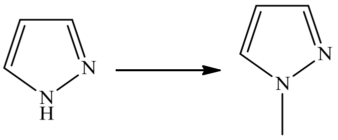
Ionic liquid	$E_{cathodic}$	E_{anodic}	E_{total}
[bmpz][Tf_2N]	-2.21	+2.53	4.74
[bm_3pz][Tf_2N]	-2.35	+1.95	4.30
[bmpz][$N(CN)_2$]	-2.40	+1.60	4.00
[bm_3pz][$N(CN)_2$]	-2.43	+1.27	3.70
[$C_3(CN)mpz$][Tf_2N]	-1.22	+2.98	4.20
[$C_3(CN)m_3pz$][Tf_2N]	-1.03	+2.47	3.50
[bmpz][Tf_2N]	-2.50	+2.12	4.62

Since the nature of the working electrode can influence the potential limit, for comparison purposes the electrochemical window of [bmim][Tf_2N] was measured, because its value is reported in literature. Values of Table 3.14 show that pyrazolium salts, as most of the ILs, have a wide electrochemical window. The electrochemical window of [bmpz][Tf_2N] does not present any substantial differences compared to the corresponding imidazolium salt, [bmim][Tf_2N]. The introduction of methyl groups on the pyrazolium ring, however, causes an anionic potential decrease with a narrowing of the window, which is more pronounced in [bm_3pz][$N(CN)_2$] and [$C_3(CN)m_3pz$][Tf_2N]. Dicyanamide ILs show the less broad electrochemical windows. Finally, the nitrile function introduction causes an increase in both cathodic and anodic potentials.

3.4. Experimental section

3.4.1. Synthesis of pyrazolium salts

***N*-methylpyrazole**



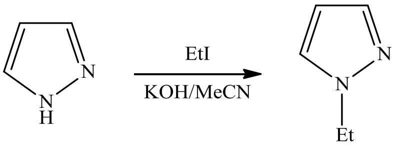
KOH (2.64 g, 40.01 mmol) was added to a 22 mL MeCN solution of pyrazole (1.5 g, 21.59 mmol) and methyliodide (5.2 mL, 23.93 mmol). The mixture was heated to 60 °C for 24 hours under magnetic stirring. After adding water the organic product was extracted with diethyl ether (4 × 25 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under vacuum. The isolated product (1.17 g, 66%) was characterized by NMR analysis.

To a solution of DMC (9.2 mL) and pyrazole (0.5g, 7.20 mmol) in 5 mL of MeCN, 0.79 g (14.39 mmol) of sodium methoxide were added heating the mixture to reflux for 13 hours, under magnetic stirring. After base neutralization with 1.2 mL of HCl 35% in 7.0 mL of water, the product was extracted with diethylether (5 × 6 mL). The organic phase was dried over $MgSO_4$ and after solvent removal, the isolated product (0.49 g, 83%) was identified by its NMR spectra.

^{1}H NMR ($CDCl_3$): δ = 7.48 (m, 1H), 7.34 (d, *J* = 2.2 Hz, 1H), 6.23 (t, *J* = 2.1 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 139.26, 130.08, 105.75, 38.79.

***N*-ethylpyrazole**

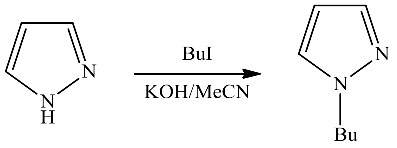


To a 40 mL MeCN solution with pyrazole (3.0 g, 43.17 mmol) and ethyliodide (3.56 mL, 44.51 mmol), 5.28 g (94.11 mmol) of KOH were added and the mixture was heated for 48 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 40 mL) and the organic phase dried over $MgSO_4$ obtaining, after solvent evaporation, the desired product (2.24 g, 54%), identified by NMR analysis.

^{1}H NMR ($CDCl_3$): δ = 7.47 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 6.21 (t, *J* = 2.0 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ = 139.32, 128.42, 105.56, 47.12, 15.89.

***N*-butylpyrazole**



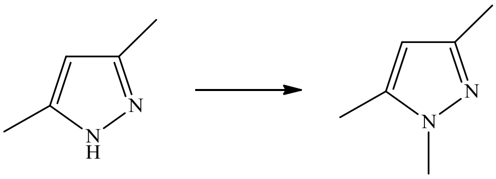
To a 40 mL MeCN solution with pyrazole (3.0 g, 43.17 mmol) and butyliodide (5.2 mL, 45.49 mmol), 5.33 g (95.00 mmol) of KOH were added and the mixture was heated for 48 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 50 mL) and the organic phase dried over $MgSO_4$

obtaining, after solvent evaporation, the desired product (4.77 g, 89%), identified by NMR analysis.

^{1}H NMR (CDCl$_3$): δ = 7.46 (s, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 6.20 (m, 1H), 4.11 (t, *J* = 7.11 Hz, 2H), 1.82 (m, 2H), 1.29 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (CDCl$_3$): δ = 139.28, 129.09, 105.40, 52.12, 32.77, 20.10, 13.88.

1,3,5-trimethylpyrazole



To a solution of 70 mL of acetone, 5.0 g (51.49 mmol) of 3,5-dimethylpyrazole and 3.50 mL (56.17 mmol) of methyliodide, 15.53 g (112.3 mmol) of K_2CO_3 were added. The reaction mixture was heated at 50 °C for 96 hours under magnetic stirring. After water addition, the organic layer was extracted with diethyl ether, dried over $MgSO_4$ and, after solvent removal, the obtained product (yield = 67%) was identified by NMR analysis.

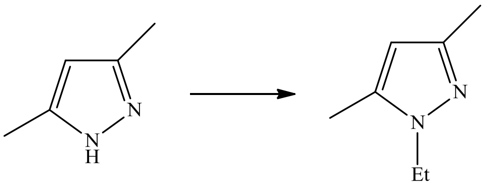
To a 20 mL MeCN solution with 3,5-dimetylpyrazole (1.5 g, 15.45 mmol) and methyliodide (1.07 mL, 17.19 mmol), 1.89 g (33.69 mmol) of KOH were added and the mixture was heated for 24 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 50 mL) and the organic phase dried over $MgSO_4$ obtaining, after solvent evaporation, the desired product (yield = 90%), identified by NMR analysis.

To a solution of DMC (37 mL) and 5.0 g (51.49 mmol) of 3,5-dimethylpyrazole 4.3 g (77.24 mmol) of sodium methoxide were added heating the mixture to reflux for 13 hours, under magnetic stirring. After base neutralization with 6.5 mL of HCl 35% in 50 mL of water, the product was extracted with diethylether (5 × 30 mL). The organic phase was dried over $MgSO_4$ and after solvent removal, the isolated product (yield = 90%) was identified by its NMR spectra.

^{1}H NMR (CDCl$_3$): δ = 5.77 (s, 1H), 3.68 (s, 3H), 2.19 (s, 6H).

^{13}C NMR (CDCl$_3$): δ = 147.36, 139.38, 105.08, 35.89, 13.67, 11.38.

1-ethyl-3,5-dimethylpyrazole



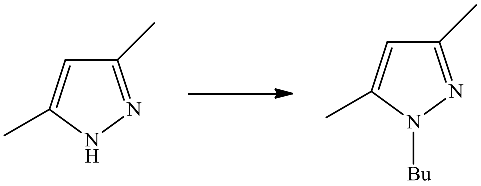
To a 40 mL MeCN solution with 3,5-dimetylpyrazole (3.0 g, 30.89 mmol) and ethyliodide (2.55 mL, 31.88 mmol), 3.78 g (67.37 mmol) of KOH were added and the mixture was heated for 48 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 40 mL) and the organic phase dried over $MgSO_4$ obtaining, after solvent evaporation, the desired product (yield = 89%), identified by NMR analysis.

To a 40 mL MeCN solution with 3,5-dimetylpyrazole (3.0 g, 30.89 mmol) and ethylbromide (2.59 mL, 34.70 mmol), 3.78 g (67.37 mmol) of KOH were added and the mixture was heated for 60 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 40 mL) and the organic phase dried over $MgSO_4$ obtaining, after solvent evaporation, the desired product (yield = 99%), identified by NMR analysis.

^{1}H NMR ($CDCl_3$): δ = 5.75 (s, 1H), 3.99 (q, J = 7.3 Hz, 2H), 2.19 (s, 6H), 1.36 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ = 147.35, 138.34, 105.12, 43.73, 13.75, 11.20.

1-butyl-3,5-dimethylpyrazole



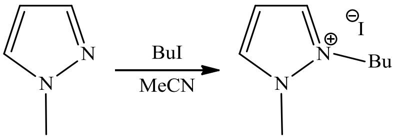
To a solution of 40 mL of acetone, 3.0 g (30.90 mmol) of 3,5-dimethylpyrazole and 5.4 mL (46.94 mmol) of butyliodide, 9.00 g (64.47 mmol) of K_2CO_3 were added. The reaction mixture was heated at 50 °C for 102 hours under magnetic stirring. After water addition, the organic layer was extracted with diethyl ether, dried over $MgSO_4$ and, after solvent removal, the obtained product (yield = 75%) was identified by NMR analysis.

To a 40 mL MeCN solution with 3,5-dimetylpyrazole (3.0 g, 30.89 mmol) and butylbromide (3.70 mL, 34.29 mmol), 3.78 g (67.37 mmol) of KOH were added and the mixture was heated for 60 hours at 60 °C under magnetic stirring. After water addition, the product was extracted with diethyl ether (5 × 40 mL) and the organic phase dried over $MgSO_4$ obtaining, after solvent evaporation, the desired product (yield = 89%), identified by NMR analysis.

^{1}H NMR ($CDCl_3$): δ = 5.74 (s, 1H), 3.91 (t, J = 7.4 Hz, 2H), 2.19 (s, 6H), 1.74 (m, 2H), 1.31 (dq, J = 14.6, 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ = 147.29, 138.68, 104.92, 48.75, 32.85, 20.28, 14.05, 13.77, 11.33.

1-butyl-2-methylpyrazolium iodide

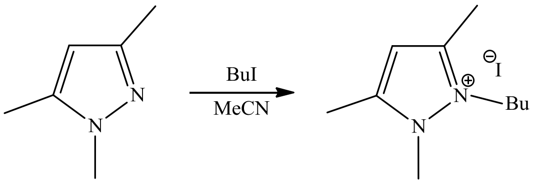


A solution with 4.12 g (25.55 mmol) of 1-methylpyrazole and butyliodide (3.04 mL, 26.60 mmol) in MeCN (20 mL) was heated to reflux for 120 hours under magnetic stirring. The product was washed with a water/diethyl ether mixture and the water phase dried under reduced pressure. The isolated product (yield = 20%) was identified by its NMR spectra.

^{1}H NMR (DMSO-d_6): δ = 8.55 (d, J = 2.8 Hz, 1H), 8.51 (d, J = 2.6 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 4.46 (t, J = 7.4 Hz, 2H), 4.15 (s, 3H), 1.80 (dt, J = 14.8, 7.5 Hz, 2H), 1.31 (dq, J = 14.6, 7.4 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H).

^{13}C NMR (DMSO-d_6): δ = 139.29, 129.14, 105.44, 52.14, 32.79, 20.11, 13.90.

1-butyl-2,3,5-trimethylpyrazolium iodide

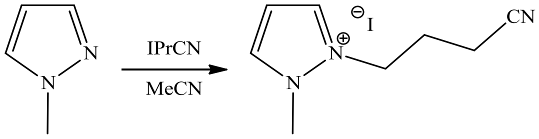


A solution with 6.59 g (35.46 mmol) of 1,3,5-trimethylpyrazole and butyliodide (4.22 mL, 36.92 mmol) in MeCN (25 mL) was heated to reflux for 120 hours under magnetic stirring. The product was washed with a water/diethyl ether mixture and the water phase dried under reduced pressure. The isolated product (yield = 57%) was identified by NMR analysis.

^{1}H NMR (D_2O): δ = 6.36 (s, 1H), 4.30 (t, *J* = 7.7 Hz, 2H), 3.87 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H), 1.72 (dt, *J* = 15.4, 7.5 Hz, 2H), 1.34 (dq, *J* = 14.8, 7.5 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (D_2O): δ = 146.78, 107.70, 46.76, 33.56, 30.54, 19.32, 13.09, 11.46.

1-butyronitril-2-methylpyrazolium iodide

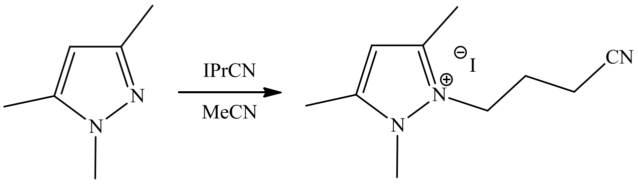


A solution with 11.86 g (144.44 mmol) of 1-methylpyrazole and 4-iodobutyronitrile (28.73 mL, 147.34 mmol) in MeCN (50 mL) was heated to reflux for 96 hours under magnetic stirring. The product was washed with a water/diethyl ether mixture and the water phase dried under reduced pressure. The isolated product (yield = 26%) was identified by its NMR spectra.

^{1}H NMR (D_2O): δ = 8.17 (d, *J* = 2.9 Hz, 1H), 8.11 (d, *J* = 2.6 Hz, 1H), 6.69 (t, *J* = 3.0 Hz, 1H), 4.52 (t, *J* = 7.2 Hz, 2H), 4.06 (s, 3H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.24 (p, *J* = 7.1 Hz, 2H).

^{13}C NMR (D_2O): δ = 138.32, 137.25, 119.60, 107.33, 48.07, 36.94, 24.11, 13.61.

1-butyronitril-2,3,5-trimethylpyrazolium iodide

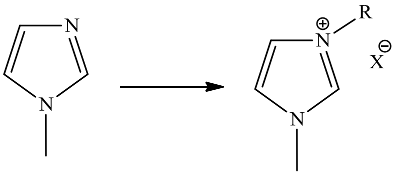


A solution with 10.74 g (97.48 mmol) of 1,3,5-trimethylpyrazole and 4-iodobutyronitrile (19.59 mL, 100.46 mmol) in MeCN (45 mL) was heated to reflux for 96 hours under magnetic stirring. The product was washed with a water/diethyl ether mixture and the water phase dried under reduced pressure. The isolated product (yield = 65%) was identified by its NMR spectra.

^{1}H NMR (D_2O): δ = 6.44 (s, 1H), 4.48 (t, *J* = 7.5 Hz, 2H), 3.94 (s, 3H), 2.66 (s, *J* = 7.0 Hz, 3H), 2.41 (s, 3H), 2.46 (s, 3H), 2.20 (dt, *J* = 14.5, 7.2 Hz, 2H).

^{13}C NMR (D_2O): δ = 146.87, 146.04, 119.54, 107.44, 44.45, 33.08, 23.58, 10.87, 10.72.

3.4.2. Synthesis of 1-alkyl-3-methylimidazolium salts



R = -Et, -Bu^n, -Pr^{n}CN
X = Br$^-$, Cl$^-$

1-butyl-3-methylimidazolium chloride

A solution with 10.0 mL (125 mmol) of *N*-methylimidazole and butylchloride (14.85 mL, 138 mmol) in water (40 mL) was heated to reflux for 5 days under magnetic stirring. The reaction mixture was then washed three timed with THF and kept decanting overnight. The water phase dried at reduced pressure obtaining the isolated product with a yield of 95%.

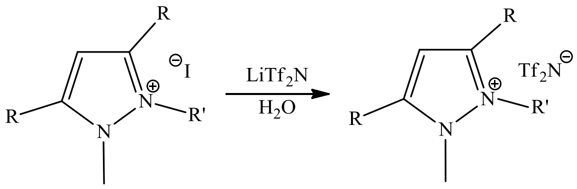
1-ethyl-3-methylimidazolium bromide

A solution with 10.0 mL (125 mmol) of *N*-methylimidazole and ethylbromide (9.6 mL, 156 mmol) in water (20 mL) was heated to reflux for 4 days under magnetic stirring. The reaction mixture was then washed three timed with THF and kept decanting overnight. The water phase dried at reduced pressure obtaining the isolated product with a yield of 92%.

1-butyronitril-3-methylimidazolium chloride

A solution with 4.0 mL (50.6 mmol) of *N*-methylimidazole and 4-chlorobutyronitrile (5.49 mL, 6.02 g, 58.1 mmol) in 70 mL of water was heated at 80 °C for 4 days under magnetic stirring. The reaction mixture was then washed three timed with THF and kept decanting overnight. The water phase was dried under reduced pressure obtaining 7.42 g of pure product (yield = 79%).

3.4.3. *N-N'*-dialkylpyrazolium bis(trifluoromethansulphonil)imide



R = -H, -Me
R' = -Me, -Bu^n, -Pr^{n}CN

To a solution of 1-butyl-2-methylpyrazolium iodide (12.0 g, 44.92 mmol) in 150 mL of water, 13.29 g (45.82 mmol) of $LiTf_2N$ were added. The reaction mixture was magnetically stirred for 7 hours at room temperature, until formation of a biphasic system. After taking out water phase, at the organic one dichloromethane was added and the whole system washed with water (3 × 50 mL). The organic phase was then dried by evaporation of the solvent at reduced pressure obtaining the pure product with a yield of 90%.

The same procedure has been used to prepare the below ionic liquids, reported with the respective yields and NMR spectra:

[bmpz][Tf$_2$N]: 89%

^{1}H NMR (coaxial DMSO-d_6): δ = 7.67 (d, *J* = 2.8 Hz, 1H), 7.61 (d, *J* = 2.7 Hz, 1H), 6.19 (t, *J* = 5.7 Hz, 1H), 3.93 (t, *J* = 7.5, 2H), 3.64 (s, 3H), 1.40 (dq, *J* = 15.2, 7.8 Hz, 2H), 0.91 (dq, *J* = 14.5, 7.2 Hz, 2H), 0.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (coaxial DMSO-d_6): δ = 136.89, 135.49, 118.78 (q, *J* = 321.9 Hz), 106.06, 48.72, 35.43, 29.08, 17.84, 11.46.

[bm$_3$pz][Tf$_2$N]: 98%

^{1}H NMR (coaxial DMSO-d_6): δ = 5.92 (s, 1H), 3.80 (t, *J* = 7.4 Hz, 2H), 3.40 (s, 3H), 1.91 (s, 3H), 1.89 (s, 3H), 1.26 (m, 2H), 0.90 (dd, *J* = 15.0, 7.4 Hz, 2H), 0.44 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (coaxial DMSO-d_6): δ = 145,60, 144.77, 118.85 (q, *J* = 321.9 Hz), 106.73, 45.61, 32.13, 29.37, 18.10, 11.64, 9.86.

[C$_3$(CN)mpz][Tf$_2$N]: 85%

^{1}H NMR (DMSO-d_6): δ = 8.56 (d, *J* = 2.8 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 6.88 (t, *J* = 6.2 Hz, 1H), 4.55 (t, *J* = 7.2 Hz, 3H), 4.15 (s, 3H), 2.65 (m, 2H), 2.19 (dt, *J* = 14.4, 7.2 Hz, 2H).

^{13}C NMR (DMSO-d_6): δ = 138.32, 137.25, 119.60 (q, *J* = 321.9 Hz), 107.32, 48.06, 36.93, 24.11, 13.60.

[C$_3$(CN)m$_3$pz][Tf$_2$N]: 80%

^{1}H NMR (coaxial DMSO-d_6): δ = 6.64 (s, 1H), 4.52 (t, *J* = 7.6 Hz, 2H), 4.02 (s, 3H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.53 (s, 3H), 2.48 (s, 3H), 2.14 (m, 2H).

^{13}C NMR (coaxial DMSO-d_6): δ = 146.34, 145.26, 120.01 (q, *J* = 321.9 Hz), 116.22, 107.02, 44.01, 32.31, 23.38, 12.50, 10.00.

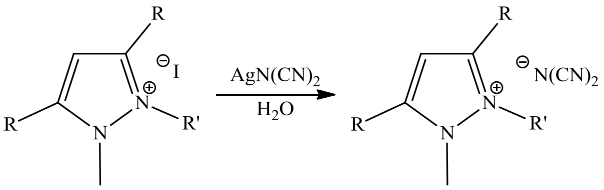
3.4.4. Dicyanamide-based ionic liquids

Silver dicyanamide

$$AgNO_3 + NaN(CN)_2 \longrightarrow AgN(CN)_2 + NaNO_3$$

30 mL of water were added to a mixed solution of silver nitrate (2.0g, 12 mmol, in 10 10 mL ow water) and sodium dicyanamide (1.0 g, 12 mmol, in 10 mL) and the resulting mixture was heated at 50 °C and stirred for 30 minutes. The obtained solid, $AgN(CN)_2$, was filtered in a sintered funnel and washed with water (40 mL) getting 100% of yield.

***N,N’*-dialkylpyrazolium dicyanamide**



R = -H, -Me
R' = -Me, -Bu^n, -Pr^{n}CN

To a solution of the appropriate alkylpyrazolium iodide in 100 mL of water 1.2 equivalents of silver dicyanamide, just prepared, in 150 mL of water, were added. After 2 hours, the solid obtained was filtered and the water solution was concentrated under reduced pressure for 6 hours.

The same procedure has been used to prepare the below ionic liquids, reported with the respective yields:

[bmpz][N(CN)$_2$]: 89%

^{1}H NMR (coaxial DMSO-d_6): δ = 8.00 (d, J = 2.5 Hz, 1H), 7.94 (m, 1H), 6.40 (t, J = 2.5 Hz, 1H), 4.09 (t, J = 7.4 Hz, 2H), 3.80 (s, 3H), 1.50 (m, 2H), 0.98 (dq, J = 14.7, 7.1 Hz, 2H), 0.53 (t, J = 7.3 Hz, 3H).

^{13}C NMR (coaxial DMSO-d_6): δ = 172.86, 137.19, 135.91, 118.37, 106.49, 48.96, 36.05, 29.53, 18.46, 12.47.

[bm$_3$pz][N(CN)$_2$]: 92%

^{1}H NMR (D$_2$O): δ = 6.38 (s, 1H), 4.31 (t, J = 7.7 Hz, 2H), 3.89 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 1.74 (dt, J = 15.5, 7.7 Hz, 2H), 1.36 (dq, J = 14.6, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (D$_2$O): δ = 146.84, 146.21, 120.17, 107.72, 46.70, 33.37, 30.54, 19.33, 13.07, 11.33.

3.4.5. Voltammetry

General data

HPLC grade CH$_3$CN (Carlo Erba) was stored under argon over 3-Å molecular sieves. [Bu_4^nN][PF$_6$] (Fluka, puriss. electrochemical grade), was used as purchased. Ferrocene (Fe(C$_5$H$_5$)$_2$, Fc) was prepared according to literature[27] and purified by sublimation

Cyclic voltammograms were performed with a Princeton Applied Research (PAR) 273A Potentiostat/Galvanostat, controlled by PAR M270 Electrochemical Software. All measurements were carried out under a purified argon atmosphere in a three-electrode home built cell at 303 K. Working and the counter electrodes were platinum (disk hemisphere sealed in Pyrex tubing). A quasi-reference electrode of platinum was employed as reference, and voltammograms were recorded at a scan rate of 100 mV s^{-1}. The working electrode area of 0.031 cm^2 was evaluated electrochemically using the peak current oxidation of a 2 mM ferrocene solution in CH$_3$CN (0.1 M [Bu_4^nN][PF$_6$]), through the Randles-Sevcik relationship:

$$i_p = (269.000)n^{3/2}AC\sqrt{Dv}$$

Where i_p is the peak current (A), n = 1 is the number of electrons in the charge transfer step, A is the electrode area (cm^2), D id the diffusion coefficient of Fc (taken to be 2.4×10^{-5} cm^2 s^{-1})[28], C is the concentration (mol cm^{-3}), v is the scan rate (V s^{-1}) and F is the Faraday constant (C mol^{-1}).

RTILs prior to measurement were dried stirring the samples in the electrochemical cell at the temperature of 353 K for 24 h under vacuum (10^{-2} torr). The Schlenk-type construction of the cell maintained anhydrous and anaerobic conditions. After several voltammograms were obtained on the RTIL samples, a small amounts of ferrocene was added, and the voltammogram was repeated. The anodic and cathodic limits of the electrochemical windows were then determined placing the $E_{1/2}$ of the ferrocene couple at 0.0 V.

3.5. References

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4. Bisimidazolium-based ionic liquids

Several examples of di- and polycationic liquids have been published in the last twenty years. At the beginning Engel *et al.*[1] have reported the synthesis of poly(tetralkylammonium) phosphate ionic liquids.

N-Heterocyclic carbenes (NHCs), first prepared independently by Wanzlick and Schönherr[2] and Öfele[3] in 1968, attracted little interest from the chemical community until 1991, when Arduengo *et al*.[4] revealed the first stable, crystalline NHC. The potential of this class of compounds to serve as spectator ligands in transition-metal complexes was recognized by Herrmann *et al*.[5] in 1995. Soon thereafter, the exploitation of the remarkable potential of NHC ligands in catalysis began. However, only NHCs derived from imidazolium or 4,5-dihydroimidazolium salts have found wide-spread use in homogeneous catalysis. The use of bulky carbenes as ligands in C–C and C–heteroatom cross-coupling and carbopalladation reactions has also resulted in significant improvements in catalyst performance compared to the more traditional phosphane ligands.[6]

There is a striking similarity of electron-rich organophosphanes PR_3 and *N*-heterocyclic carbenes (NHCs) in terms of their transition metal coordination chemistry, particularly the ligand properties and metal complex synthesis.[7] They are both pronounced σ-donor ligands with only little backbonding character.

4.1. Carbenes' general features

Carbenes are neutral compounds featuring a divalent carbon atom with only six electrons in its valence shell. Carbene's carbon atom can possess either a linear or a bent geometry. The linear implies an sp-hybridized centre with two nonbonding degenerate orbitals (p_x and p_y). Bending the molecule, p_y orbital remains almost unchanged (it is called p_π), while p_x orbital is stabilized since it acquires some s character (it is called σ), thus breaking molecule degeneracy and making carbon atom adopting an sp^2-type hybridization.

Carbene ground-state multiplicity is related to the relative energy of the σ and p_π orbitals, large σ-p_π separation favouring singlet ground state ($\Delta E_{st} = E_{triplet} - E_{singlet}$).[8]

ΔE_{st} is linearly correlated with the charge on the carbenic carbon. σ-EWGs withdraw electron density from the carbenic carbon, making it more positively charged. The increased charge, in turn, makes the carbon a better π-acceptor. As a result, π-donation from substituents is enhanced. Such "π-backbonding" is commonplace in transition metal chemistry, although the ligands are usually σ-donors and π-acceptors. In contrast σ-EDGs induce a small σ-p_π gap which favours the triplet state (Figure 4.1).[9]

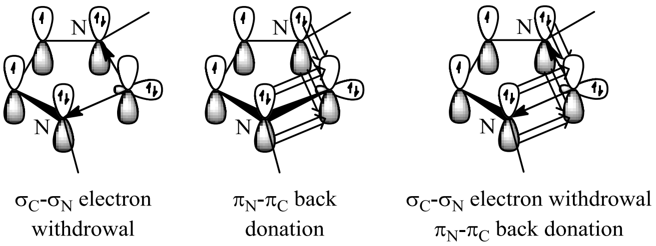


Figure 4.1. Electron stabilization of NHC.

Both phosphanes and NHCs can be tuned by incorporating substituents with predefined steric and electronic properties. In phosphanes these substituents are attached directly to the donor atom and therefore the steric and electronic effects cannot be separated. In contrast, NHCs allow, in principle, their steric and electronic properties to be tuned independently, because the contiguous N substituents, which determine the steric bulk of the ligand, are not directly connected to the carbene carbon atom and thus have only a limited effect on its electronic density.[10] The heterocyclic moiety is largely responsible for the electronic properties of the NHC ligand.[11] Direct incorporation of substituents at C(4) and C(5), has been of limited use because of the lack of versatile synthetic transformations to accomplish the task. Fusing an additional benzene ring expands the tunability of the electronic properties of the carbene ligands, as the substituents are not directly attached to the sensitive NHC heterocycle. Moreover, such distal substitution does not lead to perturbation of the steric environment that the ligands create around the metal centre. Both electron-rich and electron-poor salts show useful levels of activity, so even complexes of carbenes with EWGs are sufficiently electron rich to readily insert even into deactivated chloroarenes.[12]

Diaminocarbenes can be classified as highly bent carbenes because of their π-EDGs. Donation of the X substituent lone pairs results in a polarized four-electron three centre π-system. C–X bonds acquire some multiple bond character, which implies that these systems are best described by the superposition of two zwitterionic structure with a negative charge on the carbene centre.

4.2. NHC carbenes

From the comparison between imidazole-2-ylidene systems and imidazolin-2-ylidene, extra stabilization energy rules have been found. Planar amino substituents stabilize singlet carbenes significantly and the presence of the C=C double bond in the cyclic imidazol-2-ylidene brings about an additional stabilization ~ 25 kcal/mol. In contrast to the saturated C–C imidazolin-2-ylidene, the unsaturated heterocycle is characterized by large anisotropies of their magnetic susceptibilities, which derive from magnetically induced currents through the interatomic surfaces of the ring atoms, indication for cyclic electron delocalization in these species.[13] The higher stability of the unsaturated carbenes with imidazol-2-ylidene structure as compared to the C,C-saturated imidazolin-2-ylidene carbenes is caused by the enhanced p_π-p_π delocalization of the former, which leads to a significant electronic charge in the formally “empty” p_π orbital of the carbene carbon atom. However, both are strongly stabilized by electron donation from the nitrogen lone pairs into the formally “empty” p_π orbital.[14] Nevertheless, the aromatic character of these molecules is significantly smaller as compared to imidazolium cation or benzene.

In 1991, the crystal structure of the first stable, “bottle-able”, carbene (Figure 4.2) indeed revealed a small N–C–N bond angle (102.2°), characteristic of a singlet carbene, which was later confirmed by calculations.[15] The bulkiness of the adamantyl residues, however, played only a secondary role in stabilization of the carbene because the *N,N’*-dimethyl analogue was also stable.[16] In contrast, if electronic effects are negligible, bulky substituents on the nitrogen atoms can be crucial for the stabilization of thermodynamically less stable carbenes.[17] Since the electronic stabilization of the triplet relative to the singlet state is at a maximum when the carbene frontier orbitals are degenerate, a linear geometry will favour the triplet state.

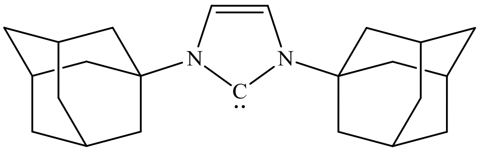
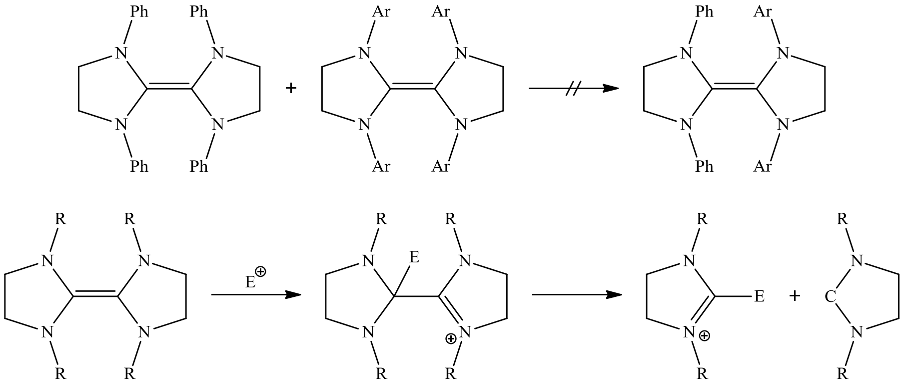


Figure 4.2. Bis-adamantyl-imidazolyl-2-ylidene.

Carbenes with less sterically demanding substituents were shown to dimerize readily and reversibly, but since the dimerization of diaminocarbenes and saturated NHCs is reversible, the tetraaminoethylene derivatives (carbene dimers) can be used as carbene sources upon heating.[18] Denk *et al.*[19] supported the existence of the Wanzlick equilibrium but with some reserves because in that study they also pointed out that metathesis product of two different enetetramines could also been explained by a [2+2] cycloaddition/cycloreversal, since high temperature NMR experiments did not show the presence of free carbenes, or electrophilic catalysed equilibration through unimolecular dissociation (uncatalysed dimerization mechanism have prohibitively high energy barrier).[20] In their study of equilibration of benzoimidazol-2-ylidenes with dimers, Hahn *et al.*[21] suggested that unimolecular dissociation was involved, but Lemal *et al.* were more cautious, suggesting that electrophilic catalysis of equilibration might be occurring (Scheme 4.1).



Scheme 4.1. Crossover experiments carried out by Lemal et al. and explanation for the reaction of electrophiles with dimers.

Alder *et al.*[22] pointed out that dimerization of singlet carbenes follows a not less important motion pathway that involves the attack of the occupied σ lone pair of one singlet carbene centre on the out of plane vacant p_π orbital of a second carbene. The high $\Delta G^{\ddagger}$

dimerization value (> 25 kcal/mol) is related to the carbene's vacant orbital high energy implication, due to electron donation by the nitrogen lone pair.[23]

4.3. Metal complexes

There are three different types of transition metal carbene complexes featuring three different types of carbene ligands: Fischer carbenes,[24] Schrock carbenes,[25] and Wanzlick-Arduengo carbenes (better known as NHC carbenes).[26]

Fischer type carbene complexes (Figure 4.3) are electrophilic heteroatom-stabilized carbenes coordinated to metals in low oxidation state. They can be prepared from $M(CO)_6$ (M = Cr, Mo, W). The reactivity of these carbene complexes can be understood as an electron-deficient carbene carbon atom due to the electron-attracting CO groups, while the alkoxy group stabilizes the carbene. They are therefore strongly electrophilic and can easily be attacked by nucleophiles. Carbene→metal donation is more than two times larger than the metal→carbene back-donation.

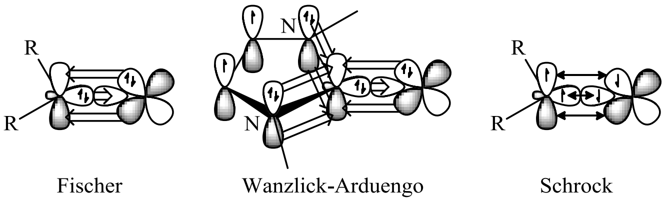


Figure 4.3. Bonding in Fischer, Wanzlick-Arduengo and Schrock carbene transition metal complexes.

Schrock-type carbene complexes (or transition metal alkylidenes) show nucleophilicity. They are formed by coordination of strong donor ligands such as alkyl or cyclopentadienyl with no π-acceptor ligand to metals in high oxidation states. The nucleophilic carbene complexes show Wittig's ylide-type reactivity. The different chemical behaviour was explained by a different bonding situation in Schrock-type complexes, where more covalent double bond character from the combination of a triplet carbene with a transition metal fragment in a triplet state was attributed.

The structures and reactivity of Fischer and Schrock carbenes can be explained by interactions of singlet and triplet carbenes with suitable metal d orbitals without any stabilisation from neighbouring nitrogen atoms at the carbene carbon atom.[27]

Fischer carbenes can be described as resulting from a σ-donor interaction of the singlet carbene lone pair into the empty d_{z^2} orbital of the metal. The metal than uses its full d_{xz} orbital for a π-backdonation into the empty p orbital of the carbene carbon atom. They are typically represented by 18-electron species and are found with low valent (late) transition metals and a carbene ligand where at least one of the two substituents carries a π-donor group (*e.g.*, a heteroatom or phenyl substituent).[28] In contrast, Schrock carbenes are electron deficient (10 to 16 valence electrons) early transition metal complexes with the metal atom in a high oxidation state and carbene substituents that are limited to alkyl groups and hydrogen. Their bonding situation can be described in terms of the interaction of a triplet carbene with a triplet metal fragment resulting in a covalent double bond.[29]

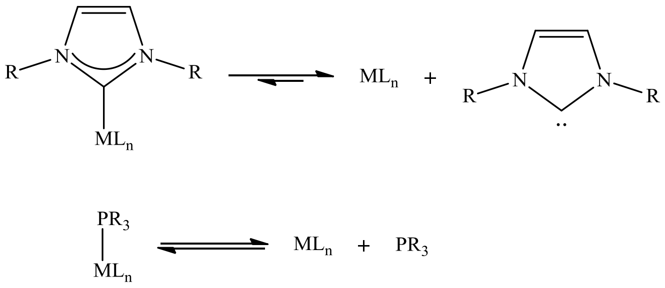
Since NHC carbenes are internally stabilized by $N\rightarrow C_{carbene}$ π-donations, which leads to a highly filled $p(\pi)$ orbital at the carbene carbon atom, the σ-donor contribution is the biggest but there is also a d_π-p_π M→C backdonation that is responsible for up to 20-30% of total M→C bond strength. The average $N–C_{carbene}$ and M–Ligand bond lengths elongate while the $M–C_{carbene}$ bond length contracts as the π-acidity of the NHC ligand increases. These results suggest that π-backbonding in NHC–M complexes is also tunable.[30] Corresponding to the low degree of M→C π-backbonding in transition metal NHC complexes, the M–C bond in these compounds is very long and has to be regarded as a single bond despite its π-backbonding degree.[31]

Ligands which contain significantly different chemical functionalities, such as hard and soft donors, are often called hybrid or hemilabile ligands and find increasing use in molecular chemistry. The s-block and early transition metals are only loosely bound to the carbene end and need to be anchored to the hard functional group, whereas late transition metals and many p-block elements bind strongly to the carbene end meaning that the functional group will have to be designed as the hemilabile part of the ligand. Typical anchor groups for hemilability at the carbene end are amides, alkoxides (arylalkoxides) and the Cp ligand family.[32]

There are two classical geometries or substitution patterns the ligand establishes in the coordination sphere of the metal complex: *meridional* (*mer*), generally realised by two carbenes substituted in the 2,6-position of a pyridine or in the 1,3-position of a benzene ring, and *facial* (*fac*), obtained by a tripod arrangement of three NHC moieties on a boron or an arene scaffold.

Herrmann *et al.*[33] have compared binding energies between NHC and phosphine-complexes. Phosphine dissociation process is more likely to take place than NHC dissociation. Substitution of N–H by N–Me in the NHC introduces only minor changes in the dissociation energies as long as steric effects are negligible and electronic factors dominate. Imidazolin-2-ylidene-based carbene ligands bind to both Pd(0) and Pd(II) centres substantially stronger than phosphine ligands, which have traditionally been successful in this type of catalytic processes. The dissociation energies increase in the order $PH_3 < PMe_3 < NHC(H) \sim NHC(Me)$, correlating with the electron deficiencies at the palladium centres in the various complexes. Thus imidazolin-2-ylidene-based carbene ligands result in strong bonds with both Pd(0) and Pd(II) dihalide systems relative to phosphine ligands. The strongly electron donating character of the NHC ligand may facilitate oxidative addition.

The equilibrium between the free carbene and its metal complex lies far more on the side of the complex than is the case for phosphines (Scheme 4.2). This minimizes the amount of free NHC in solution and thus increases the life time of the complex as well as its robustness against heat, air and moisture. It has to be kept in mind that *N*-heterocyclic carbenes, while they can be isolated and stored, are still very sensitive and reactive towards many electrophilic compounds.[34]

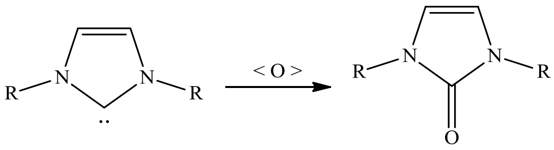


Scheme 4.2. Equilibrium of complexation.

For phosphine complexes, the R substituents on the phosphorus point away from the metal, resulting in the formation of a cone, that can be acceptably described using Tolman’s cone angle descriptors. The main practical problem, however, is that NHC ligands substantially present a local C_2 symmetry axis, whereas phosphines present a local

C_3 symmetry axis. Moreover, the rotation around the metal-carbene bond can substantially change the steric and electronic interactions. Substituents toward the metal wrap it to some extent forming a pocket.[35] Therefore, a "buried volume" parameter, $\%V_{Bur}$, fraction of the volume of the first coordination sphere around the metal occupied by a given ligand, has been used to compare the relative sizes of phosphine and NHC ligands. Based on this parameter, the largest NHCs, (bearing *e.g.* Bu^t, adamantyl, etc.) are significantly larger than even the largest tertiary phosphine, PBu^t_3, whereas other commonly used NHCs have steric properties similar to bulky phosphines.[10]

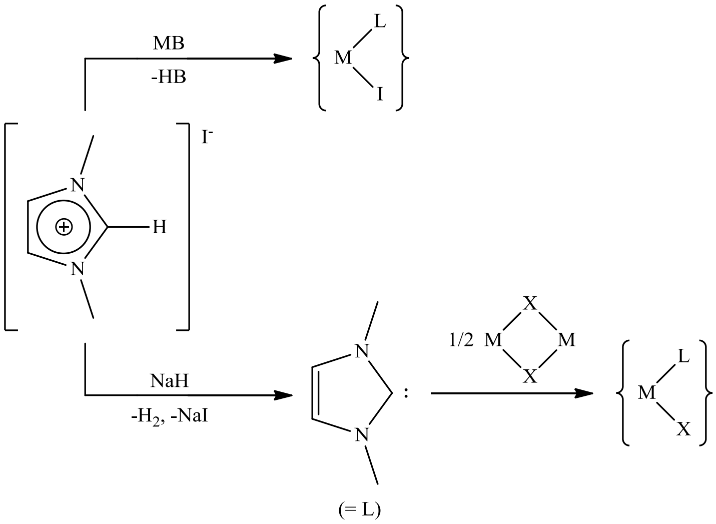
Despite the possibility to minimize air sensitivity of PBu^t_3 and related trialkylphosphines employing phosphonium salts as ligand precursors in catalytic reaction, ligand dissociation at any point of the reaction results in rapid ligand oxidation. Free NHCs are also susceptible to oxidative decomposition (Scheme 4.3), but unlike phosphines, that are seldom used as ancillary ligands in oxidation chemistry because of their intrinsic oxidative instability, when coordinated to a metal centre, NHCs are remarkably robust and hold significant promise for use in oxidation chemistry. NHCs possess key properties that enhance their potential utility: their strong σ-donating ability stabilizes metals in high oxidation states and their high M–L bond dissociation energies render them less susceptible to oxidative decomposition.



Scheme 4.3. Free carbene oxidation.

4.3.1. Synthesis

Metal complexes of NHC are available starting from azolium salts or the free carbenes. The former route depends on the metal-containing precursor compounds exhibiting sufficient basicity, either at the metal or at one of the ligands; the counterion of the azolium salt is normally attached to the metal in the course of the reaction (Scheme 4.4).[36] The second route, the free-carbene route, does not have these limitations.[37] The free carbene, as a highly nucleophilic molecule, can generate its own coordination site; this process works particularly well with halide- or acetate-bridged dinuclear complexes (Scheme 4.4).[38]

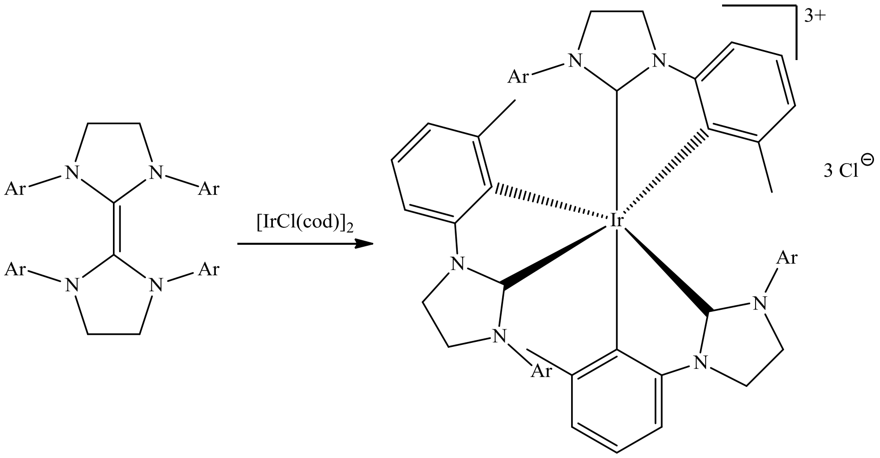


Scheme 4.4. MB = metal complex containing a Lewis base B; L = carbene ligand.

In the imidazolium route, the introduction of an iodide ion in the resulting metal complex may be a drawback of an otherwise straightforward and elegant method. Imidazolium BF_4^- or PF_6^- can certainly be generated from the iodides, but this requires a second step (salt metathesis), which does not always proceed cleanly. Another limitation of this route is the fact that imidazolium salts other than halides are normally poorly soluble in common organic solvents, including THF.

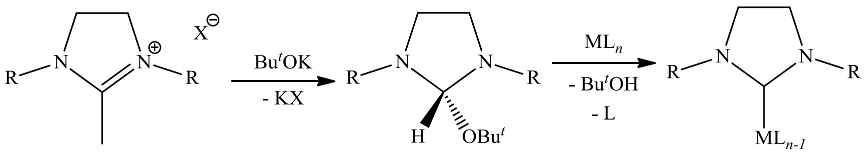
Another potentially severe drawback of the metallation procedure only became apparent with the discovery that imidazolium salts can sometimes metallate at C(4) or C(5), in the backbone part of the ring, a region normally considered inert.[39] This in turn means that catalysts that are made *in situ* by treatment of the imidazolium salt with $Pd_2(dba)_3$ may need to be considered as having uncertain structures until they can be isolated and characterized. The reactions that give abnormal C(4) or C(5) metallation prove to be very sensitive to conditions and even to counter ion.[40]

One of the methods more often used for the preparation of enetetramines is the dimerization of non-stable NHCs.[41] Electron-rich olefins as that in Scheme 4.1 are used as NHC precursors (carbenoids) in the synthesis of new carbene–transition metal adducts. All the NHC complexes obtained by this method contain saturated NHCs. Heating of enetetramines in refluxing toluene in the presence of metal precursors such as manganese, iron, ruthenium, chromium cobalt, and nickel carbonyls provides the corresponding NHC complexes. Triscarbene-chelate Ir(III) complexes can be obtained by the reaction of an aryl-enetetramine with $[IrCl(cod)]_2$. In the formation of the complex in Scheme 4.5, the reaction proceeds by the insertion of the metal into the C=C bond of the olefin followed by spontaneous orthometallation of the *N*-aryl substituent.[42]



Scheme 4.5. Aryl-enetetramine synthesis of Ir(III) carbene complex.

Due to difficulties with decomposition and the need to handle free NHCs under inert atmosphere conditions, the use of protected forms of free NHC carbenes has appeared as a useful alternative to the preparation of NHC complexes. *N*-heterocyclic rings containing alkoxide or trichloromethyl groups, such as shown in Scheme 4.6, can be considered as NHC-adducts in the sense that they can readily eliminate alcohol or chloroform to unmask the carbene, which would then coordinate to the metal. For these reactions it is not clear whether the released NHC reacts with the metal or the adduct first dimerizes to form the corresponding enetetramine. Notably, adduct formation does not occur for certain unsaturated imidazolium salts with a C=C backbone.[43]



Scheme 4.6. NHC complexes by carbene adducts.

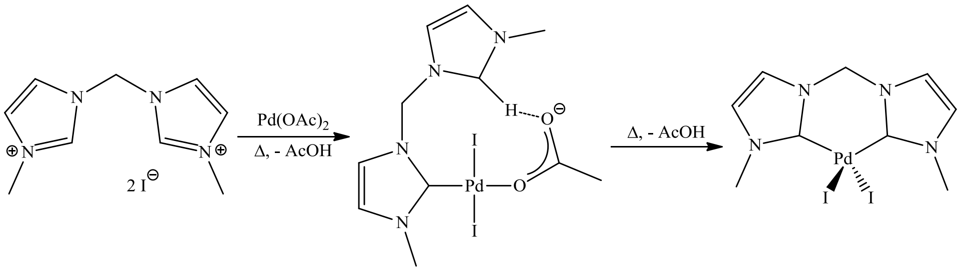
Free carbenes can be generated from the ionic imidazolium precursors by treatment with NaH, Bu^{t}OK or Bu^{n}Li at room temperature in THF.[44] This procedure is satisfactory only for relatively thermally robust carbenes that can survive rather prolonged reaction times.[45] An alternative access to 1,3-dialkylimidazoline-2-ylidenes needs the desulfurization of the corresponding cyclic thiourea derivatives, which are readily available. However, 24 hours in refluxing THF are required for the carbene to be formed in sufficient yields, excluding the preparation of heat-sensitive carbenes.[46]

The use of a strong base is very convenient in the sense that it warranties complete deprotonation of the azolium precursor, and can be used for a wide variety of azolium salts and metal precursors. However, for those metal or carbene precursors with acidic or electrophilic centres other than the C(2)–H position in the azolium ring (*e.g.*, methylene-bridged bis-imidazolium systems) undesired activations can be produced leading to decomposition products and weak bases have to be used (*e.g.*, NaOAc).

The "liquid-ammonia route" represents a milder conditions method: an azolium salt is dissolved or suspended in a mixture (~ 5:1) of liquid ammonia and a polar, aprotic solvent (typically THF) and is then treated with NaH. Depending on the solvent, the deprotonation reaction occurs between -80 and -30 °C. The deprotonating agent is sodium hydride or sodium amide (formed by solvolysis). The reaction goes to completion within minutes. The generated carbenes are completely soluble in ammonia/THF, whereas the solubility of the carbenes in pure THF is limited at very low temperatures. The free monomeric carbene of high purity is thus obtained as a colourless solution in ammonia/THF or in THF after removal of the ammonia by freeze-pump techniques. The sodium halide formed during the generation of the free carbene is removed by extracting the carbene with nonpolar solvents such as hexane and filtration, typically obtaining yields greater than 95%. The key advantage of the liquid-ammonia route is that the deprotonation proceeds rapidly and smoothly at low temperatures. Ammonia seems to have an activating effect on the acidic proton of the azolium salt. Furthermore, imidazolium salts are much more soluble in mixtures containing liquid ammonia than in pure aprotic organic solvents. This is of particular importance in the synthesis of carbenes derived from imidazolium salts.[47]

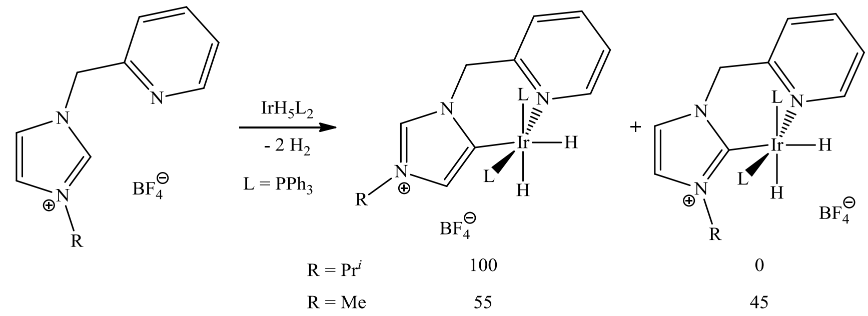
The use of metal(II) diacetates or acetilacetonate[48] is often used to prepare imidazolylidene, triazolylidene, and benzimidazlylidene complexes of Pd and Ni, providing monodentate, bidentate, and tridentate NHC complexes (Scheme 4.7). In these reactions the acetate is eliminated as acetic acid.[49]

In a common synthetic procedure of diimidazolium chelating systems, it is necessary to use mild reaction conditions of 50 °C in DMSO solution for a period of at least 4 hours to fully convert the diimidazolium dihalide salts into the intermediate palladium mono(carbene) complexes. After this time, the mixture can be heated to reflux in DMSO for at least 20 minutes in order to deprotonate the remaining imidazolium pendant arm in the 2' position to yield the chelating bis(carbene)palladium dihalide complexes.[50] When harsher initial temperature conditions are employed in this reaction using DMSO as solvent, very low yields are observed.[51]



Scheme 4.7. Deprotonation with a metal complex with a basic ligand.

Crabtree *et al.*[52] found that metallation of the NHC can occur *via* a metal bounding to the activated C(5) position, and not to the C(2) position. This "abnormal" NHC binding was first observed for the reaction of an *N*-Pr^i substituted methylene-linked pyridin-imidazolium salt and $IrH_5(PPh_3)_2$ (Scheme 4.8). The formation of the abnormal NHC is favoured by the lower steric strain at the metal centre. On moving to the smaller methyl group, a mixture of the normal and abnormal carbenes is obtained.



Scheme 4.8. “Abnormal” NHC bonding.

In unsaturated NHCs, both the nitrogen lone pairs and the C=C provide enough kinetic stability to allow the isolation of this type of carbenes. The use of preformed NHCs has the advantage that they can be directly used to replace labile ligands on a suitable complex precursor (*e.g.*, THF, carbonyl, phosphines, and pyridine). Imidazol-2-ylidenes and triazol-2-ylidenes react with a large variety of metal complexes to afford ligand replacement. In the case of the reaction with homoleptic metal carbonyls $M(CO)_n$ (M = Cr, Mo, W, Fe, Ni), one or two carbonyl ligands can be readily replaced. The reaction of free NHCs with dimeric complexes with bridging ligands such as halides, carbon monoxide, or acetonitrile can result in the cleavage of the dimetallic structure. Preformed NHCs can also be used for the preparation of complexes with metals unable to π-backdonate, like high oxidation state species of early transition metal complexes, before possible only for the Schrock type.[53]

Salt metathesis reactions represent the prevailing synthetic access to NHC and related metal complexes.[54]

They can be prepared from imidazolium salts through a silver base route, an *in-situ* reaction of imidazolium salts with a base in the presence of a silver salt, a transmetalation from tungsten NHCs to silver and halogen exchange reactions.[55] Halogen exchange reaction has to be demonstrate because it has been proposed that the source of chloride is the solvent (*i.e.*, 1,2-dichloroethane, dichloromethane) though halogen solvents are used for both the synthesis and the recrystallization.

NHC silver complexes are extensively used in pharmaceutical applications, catalysis, transmetalation reactions, etc.[56] In fact, their synthesis is mainly used to transfer to other metal systems because the silver carbene transmetalation method avoids harsh conditions and works efficiently. Xiao *et al.*[57] prepared the complex in Figure 4.4 by the reaction of 1,1'-dimethyl-3,3'-ethylenediimidazolium dibromide with Ag_2O in a solution mixture of dichloromethane and methanol. They also carried out the synthesis in methanol only and then recrystallized the product in chlorinated solvents obtaining no exchange of bromide for chloride, thus demonstrating that the halogen exchange occurs during synthesis.

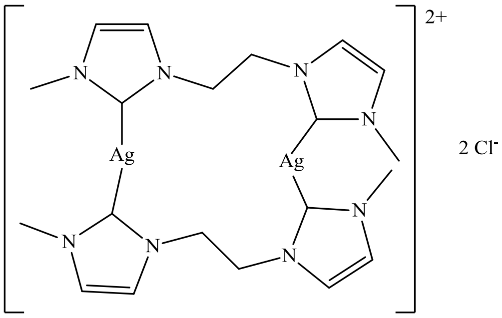
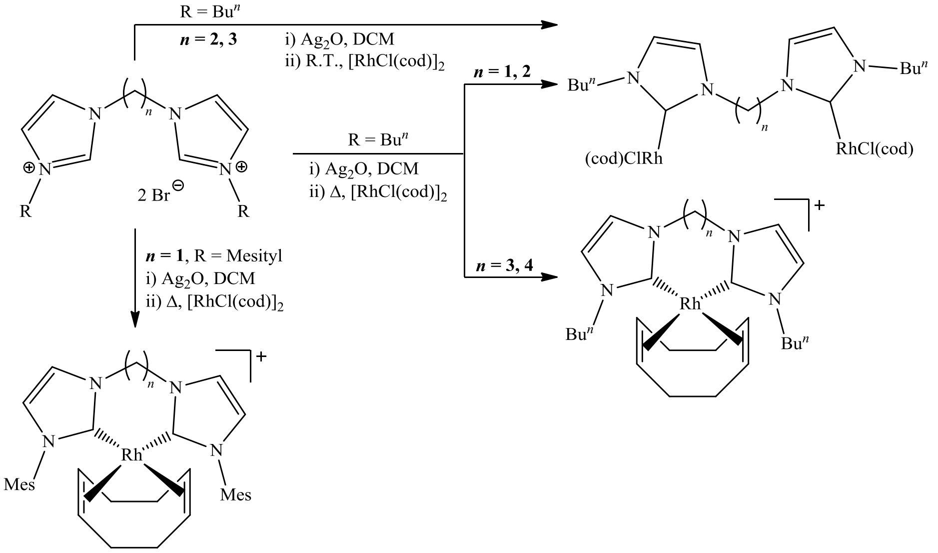


Figure 4.4. Synthesis of bis-Ag NHC complex.

In the generation of the silver-carbene, a variety of silver compounds can be employed, such as Ag_2O,[58] AgOAc,[59] and Ag_2CO_3.[60] Among them, silver oxide is the most commonly used.[61] Several reasons justify the choice of the Ag_2O technique. For instance, metalation reactions with silver oxide can be carried out in air and proceed at room temperature unless bulky imidazolium salts are employed. Moreover, no additional base is required, and the deprotonation usually takes place at the C(2)–H bond of the imidazolium salt.[62] Reaction times using Ag_2CO_3 were sometimes found to be longer than when using Ag_2O. Silver NHC carbenes can be made in water, thus deprotonation and subsequent metalation may be a concerted process.[63]

The reaction conditions used for the transmetallation can afford different types of compounds, *e.g.* the reaction of bisimidazolylidene complexes of silver with $[RhCl(cod)]_2$, yields dimetallic complexes of Rh(I) with a bridging bisimidazolylidene or monometallic Rh(I) complexes with a chelate bis-NHC ligand, depending on the length of the linker between the azole rings and the reaction temperature.[64] The size of the *N*-substituents also contribute to the final geometry of the complex, as shown by the introduction of bulky mesityl groups that force the chelating coordination (Scheme 4.9).[65]



Scheme 4.9. Transmetallation reactions changing temperature, *N*-linker moiety and linker length.

4.3.2. Catalytic applications

The primary role of the phosphine is to support Pd in its zero oxidation state, as PdL_4 or PdL_3 species. The search for new phosphine-free Pd catalysts is driven by both economic and academic reasons: phosphine ligands are expensive, toxic and unrecoverable. *N*-heterocyclic carbene complexes of palladium can also be formed in situ under the Heck reaction conditions using imidazolium melts as the immobilizing agents.[66] Palladium-carbene complexes were formed from the deprotonation of the imidazolium cation of $[bmim]Br^-$ in the presence of the catalyst precursor.[67]

Strassner *et al.*[68] performed the Heck coupling of bromoanisole or bromoacetophenone with styrene using NaOAc as base and dimethylacetamide as solvent, comparing the activity of several NHC. 1,1'-bis(4-bromophenyl)-3,3'-methylenediimidazoline-2,2'-diylidene-Pd(II)Br_2 showed lower activity because of both low solubility[69] and electronic properties of the substituents, whose influence is minimal but still important. Otherwise, in comparison with *N*-methyl substituted Pd-NHC complexes, aryl substituent stabilizes the catalytic active species. Mesomeric effect of methoxy- and butoxy-substituents stabilizes the catalytically active Pd^0 species. A great advantage of those catalysts is their high selectivity as can be seen from the selectivity towards *trans*-product especially when the *N*-phenyl groups have in *para* bromide or methoxide as substituents (complete selectivity is reached reducing the amount of catalyst to 0.01 mol%). The biggest advantage remains the full conversion at very low concentrations, which leads to very high TON (> 7 × 10^5) and TOF (> 25000 h^{-1}).

Most of the donor-functionalized NHC ligands have a N-donor, such as pyridine, imine or oxazoline as pendant groups. Phosphine-functionalized NHC ligands combine the stabilizing effect of the carbene with a labile Pd–P bond which can be broken reversibly to allow for a facile coordination of the olefin to the Pd centre. From theoretical calculations appears that the main features of the insertion are similar to those calculated for the dicarbene system, except for the absence of a second stable π-complex formed after rotation of the ethylene.[70] Zhou *et al.* used these phosphine-functionalized systems obtaining the coupling of aryl iodide and bromides with acrylates and styrene. Bulky groups to the *P*-phenyl rings of the phosphine-functionalized NHC ligands is also helpful to increase the activity of the catalyst (Figure 4.5).[71]

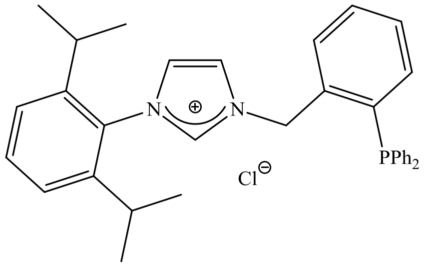
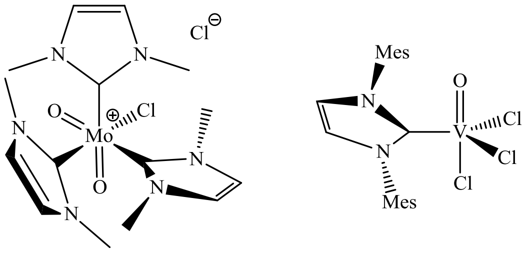


Figure 4.5. Zhou's bidentate catalyst.

Palladium-carbene complexes[72] are also formed when the reactions are performed in [bmim][BF_4] ionic liquid, clearly indicating the non-innocent nature of these media in palladium-catalysed coupling reactions (in particular in the presence of strong bases).[73] The Heck reaction of iodobenzene or bromoarenes substituted with electron-withdrawing groups with acrylates or styrene are markedly more efficient in [bmim]Br^- than in [bmim][BF_4] and this was attributable to the formation of more active palladium carbene catalytic active species in the imidazolium bromide salt.

As phosphine analogues, NHCs are frequently employed as ligands for low-valent transition-metal complexes but about their behaviour as ligands for high-oxidation-state metal complexes and for metals bearing oxidizing ligands such as oxides and peroxides there are just few examples in literature.

In contrast to CH_3ReO_3, that leads to ligand oxidation, complexes with other high-valent metal precursors are not especially strong oxidants. Consequently, the preparation of these complexes often can be achieved by simple addition of the NHC to an unsaturated metal centre or via displacement of a weakly coordinated solvent molecule such as THF (*e.g.*, cationic Mo(VI) complexes of the type $[MoO_2ClL_3]Cl^-$ (**a** in Figure 4.6),[74] trichloro-oxo-vanadium complexes (**b** in Figure 4.6),[75] with a Cl-$C_{carbene}$ interaction in which electrons from a chloride lone pair donate into the formally vacant p-orbital of the $C_{carbene}$ atom, etc.).

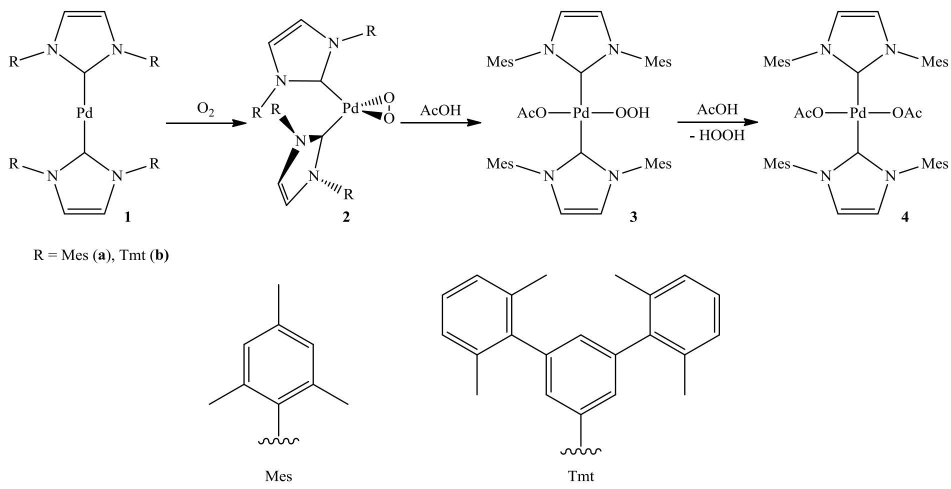


a **b**

Figure 4.6. NHC-coordinated high-valent metal complexes.

η^2-peroxopalladium(II) complexes were prepared via direct oxygenation of Pd(0) precursors bearing phosphines and isocyanides as ancillary ligands. Both of these ligand classes are susceptible to oxidation. Indeed, homogeneous Pd is a highly efficient catalyst for the aerobic oxidation of triphenylphosphine to triphenylphosphine oxide.[76]

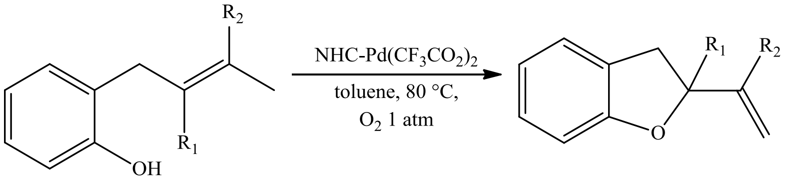
Complex **1a** (Scheme 4.10) is extremely air-sensitive and reacts with molecular O_2, even in the solid state, to produce the peroxo-complex, **2a**. Addition of AcOH to this complex yields the hydroperoxide complex, **3**. Prolonged reactions times are necessary before the second equivalent of AcOH reacts to produce H_2O_2 and **4**.[77] The Pd(0) complex **1b**, bearing the more hindered NHC ligand Tmt, also reacts with molecular O_2 to produce the η^2-peroxo complex.



Scheme 4.10. Reaction of Bis-NHC-Pd(0) complexes with molecular O_2.

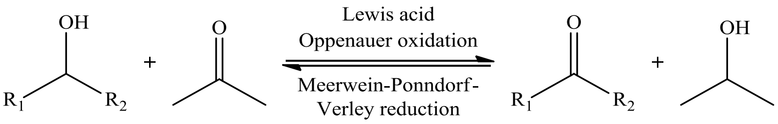
The industrial Wacker process, *i.e.* Pd-catalysed conversion of terminal alkenes to methyl ketones, typically employs $CuCl_2$ as co-catalyst or stoichiometric oxidant. Recently copper-free reaction conditions were identified for the Wacker-type oxidation of styrenes using Bu^{t}OOH as the oxidant. The in-situ-generated 1,3-diisopropyl-imidazol-2-yl-Pd(OTf)$_2$ complex is used as the catalyst minimizing polymerization and oxidative cleavage of the alkene, which represent common side reactions in the Wacker oxidation of styrene.[78]

Pd(II)-promoted oxidative cyclization of alkenes bearing tethered nucleophiles represents an intramolecular variant of the Wacker reaction (Scheme 4.11). The catalyst is prepared in situ by mixing 1.2 equivalents of the ligand imidazolium salt with $Pd(CF_3CO_2)_2$. $CF_3CO_2^-$ counterion is important because with acetate and chloride ions, the reaction is less efficient and produces mixtures of five- and six-membered heterocycles. Also the presence of base is necessary to avoid side reactions and maintain catalyst activity.[79] Nitrogen-containing heterocycles are prepared in a similar manner.



Scheme 4.11. Oxidative heterocyclization of oxygen nucleophyles.

Metal-catalysed oxidation of alcohols to aldehydes and ketones utilizing NHC ligands in an Oppenauer-type oxidation with an Ir or Ru catalyst has received significant recent attention.[80] These alcohol oxidation reactions consist of an equilibrium process involving hydrogen transfer from the alcohol substrate to a ketone, (*i.e.*, acetone, Scheme 4.12, or alkenes). Because these reactions avoid the use of a strong oxidant, the potential oxidative instability of NHC ligands is less problematic. Consequently, these reactions represent an important target for future research into the utility of NHCs. Despite the presence of an intermediate metal hydride, there is no indication that reductive elimination with the hydride, losing the ligand with formation of an imidazolium salt, is easy because the catalysts described in this section are capable of catalysing up to 5×10^4 turnovers before deactivation. The chelating character of the carbenes may help prevent decomposition by both chelation and holding the carbene ring in a conformation that disfavours reductive elimination, a reaction that is expected to require the empty p_z orbital on the carbene carbon to be collinear with the adjacent M–H bond.[81]



Scheme 4.12. Oppenauer oxidation.

The moderate effectiveness of Ir(III) catalyst NHC ligands might increase electron density at the metal centre enhancing the reactivity of the iridium-hydride–acetone intermediate.

4.3.3. Poli-hydroxylated bisimidazolium salts

The advent of water-soluble organometallic complexes, especially those based on sulfonated phosphorus- containing ligands, has enabled various biphasic catalytic reactions to be conducted on an industrial scale.[82] However, the use of water as a catalyst immobilizing phase has its limitations: (i) it is a highly polar and coordinating protic solvent; (ii) it is reactive toward many organometallic complexes and substrates; (iii) from an environmental perspective, trace amounts of organic compounds in water are notoriously difficult to remove. Moreover, the synthesis of specially designed water-soluble ligands/organometallic complexes is essential for its use. More recently, perfluorocarbons have been used as the nonaqueous phase for various catalytic liquid-liquid biphasic reactions such as the hydroformylation, oxidation, and oligomerization of olefins.[83] However, the synthesis of specially designed ligands/transition metal compounds to immobilize the catalyst precursors in the fluorinated phase and also in CO_2, have been investigated as an alternative green solvent for synthesis and catalysis but catalyst recycling apparently remains a problem.[84] One of the greatest challenges in this field is to develop an immobilizing agent that could act as a simple "solvent" for classical organometallic catalysts.[85]

Sulfonated triphenylphosphines are the most commonly used as water-soluble ligands, with which palladium goes into aqueous phase and catalytic reaction proceeds therefore in water. Casalnuovo and Calabrese synthetized and characterized water-soluble Pd(0) catalyst $Pd(PPh_2(m\text{-}C_6H_5SO_3M))_3$ ($M = Na^+, K^+$) that efficiently catalysed sp^2-sp^2 and sp-sp^2 C–C cross-coupling reactions in aqueous medium showing also tolerance towards a broad range of functional groups, including those present in unprotected nucleotides and aminoacids.[86]

Godoy *et al.*[87] prepared a series of sulfonate-functionalized-NHC complexes of Pd(II) (Figure 4.7), in which the ligands behave as monodentate, bis-chelating and, modifying the *n*-butyl-functionalized tridentate systems of Crabtree,[88] pincer coordinated and tested them in aqueous Suzuki-Miyaura coupling showing, with the mono- and the pincer-ligands, high TON values (~ 10×10^5) and quantitative yields with a poor catalyst loading (10^{-3} mol%).[89] The substitution in the pincer complex of the iodide with a pyridine to exploit the PEPPSI effect did not increase conversion percentages.[90]

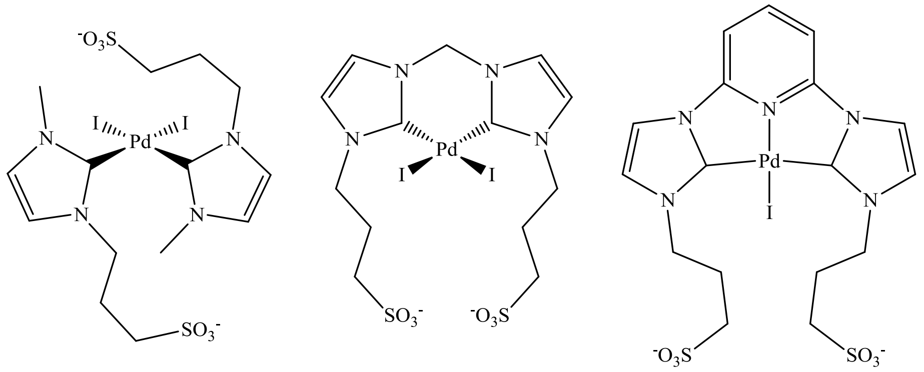


Figure 4.7. Sulfonate-functionalized NHC water soluble complexes.

TSILs have been widely used in catalysis because they can favour catalyst activation, generate new catalytic species and improve catalyst stability. Moreover, there is the possibility to use them as soluble support for organic synthesis (to support *i.e.*, catalyst, reagents or substrates) because of their solubility or insolubility in organic media.

"Liquid phase" synthesis retains many of the advantages of conventional solution chemistry, and still permits the fairly facile purification of the product. Thus *soluble* polymer supports has received considerable attention, so soluble polymers such as PEG have been used in synthesis. In particular, alcohol-functionalized molten salts have been extensively studied as replacements for solid polymer supports in heterogeneous catalysis.[91] Alcohol-functionalized-supported ionic liquid systems have been used in Suzuki-Miyaura cross-coupling reactions, demonstrating its advantage over conventional solution phase synthesis.[92] Moreover, hydroxylate lateral alkyl chains decrease ionic liquids toxicity towards aquatic species.[93] Nowadays, glycerol is generated as by-product from bio-diesel production and it is estimated that is this production increases as projected, glycerol will become widely available and inexpensive.[94]

Recently, poly-hydroxylated imidazolium systems have been prepared but with the aim to produce polydentate ligands by alcoholic function deprotonation. Arnold *et al.*[95] synthetized a series of alkoxide-*N*-heterocyclic carbene ligands providing new lithium alkoxycarbenes and a range of covalently bound organometallic Cu(II) carbene complexes, starting from an alkyl-imidazole, quaternized by reaction with an epoxide (Figure 4.8). These heterobidentate ligands combine the strong σ-donor *N*-heterocyclic carbene with an alkoxide. Yagyu *et al.*[96] prepared a tetradentate dicarbene ligand containing two aryloxy groups able to give air-stable Mn(III) *N*-heterocyclic carbene complex in moderate yield after reaction with $Mn(OAc)_2$.

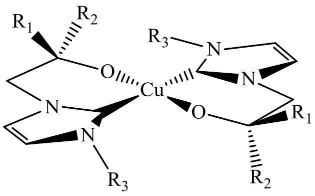


Figure 4.8. Alkoxy-functionalised NHC ligand.

Recently, Bellina *et al*.[97] tested glycerylimidazolium-based ionic liquids activity as both ligands and solvents for Pd(II) catalysed reactions. Despite a progressive loss in activity, especially with longer alkyl chains, that new class of ionic liquids appeared to be interesting because it did not require any metal ligand addition and for the imidazolium quaternized with an octyl chain the results were competitive with those using MW heating. Reaction yields increased on increasing cation alkyl chain, and so lypophilicity. The very low yields obtained using C(2)-methylated imidazolium salts suggested that Pd-carbene complexes, favoured by more basic counterion,[98] were involved.

Thus, we decided to synthetize alkyl-bridged bis-imidazolium ionic liquids bearing a (poli)hydroxylate alkyl chain as possible chelating systems. Ethylene- and propylene-bridged salts were prepared in toluene using an imidazole:dibrominated alkyl ratio of 1:0.5. A little excess of the alkyl was used with the formers to compensate the possible elimination reaction involving 1,2-dibromoethane. We have tried to extent this procedure to methylene bridged but with poor results, so looking at literature we found that Gardiner *et al*.[99] used to heat a toluene solution of 1-(mesityl)imidazole and 1 molar equivalent of CH_2Br_2 at 150°C for 2 days to yield a white powder of the product then washed with THF and dried *in vacuo*, obtaining yields near 70%.

We decided to use for both 1,1’-di(alkyl)-3,3’-methylenediimidazolium dihalide salts the same procedure adopted for longer bridged systems but with low yields, so we followed Bellina’s procedure that led to more than satisfactory yields. It concerned the use of dibromomethane as solvent, so in large excess, preventing the massive alkylating agent loss by evaporation, because of its low boiling point. Meyer *et al*.[100] started from the bridged system and then they used to quaternize both nitrogens in 3 and 3’ positions with two equivalents of 2-bromorthanol, employing acetonitrile as solvent. Despite the similar reaction conditions, *i.e.* 12 h at 90 °C, this procedure led only to poor yields (26%).

All synthetized samples were analysed with differential scanning calorimeter (DSC) to check whether transition occurred in the investigated temperature range (*i.e.*, -50-100 °C). At the beginning, for each sample, we followed a pre-heating procedure (starting from room temperature to a T_{max} lower than decomposition temperature at a rate of 10 °C min^{-1} and maintained at this temperature for 2 min), with the aim of destroying all traces of thermal history, if any. Samples were re-cooled at -10 °C min^{-1} down to T_{min} (generally 0

°C or lower) and kept at this temperature at least 5 min. Finally, the samples were reheated at 10 °C min^{-1} from T_{min} up to T_{max} (Table 4.1).

Table 4.1. T_{max} and T_{min}.

Sample	**T_{min} (°C)**	**T_{max} (°C)**
[GlyImC$_1$ImGly][2Br]	0	100
[GlyImC$_2$ImGly][2Br]	20	120
[GlyImC$_3$ImGly][2Br]	0	150
[EtOHImC$_1$ImEtOH][2Br]	-50	120
[EtOHImC$_2$ImEtOH][2Br]	0	150
[EtOHImC$_3$ImEtOH][2Br]	-50	150

Looking at the first preheating procedure, glyceryl-functionalised systems did not show the presence of any melting point (Figure 4.9). The methylene-bridged had a degradation temperature at 110 °C, so its scans were repeated lowering the applied T_{max} (100 °C). The propylene-bridged salt thermogram was semi-flat with a small endothermic pendency and a beginning of decomposition near 140 °C. Ethanol-functionalised salts showed a peculiar behaviour, especially methylene- and propylene-bridged systems. In both cases there was a transition phase with a very wide exothermic absorption centred at 67 °C that may correspond to a crystallization point. However, a peak extension in a so high range of temperature, *i.e.* from 40 to 100 °C for the methylene-bridged and from 30 to 80 °C for the propylene-bridged system, made these data tricky to be rationalized. One explanation could be the presence of a low organization level that led to a multiplicity crystalline forms, which crystallize in a broad temperature range.

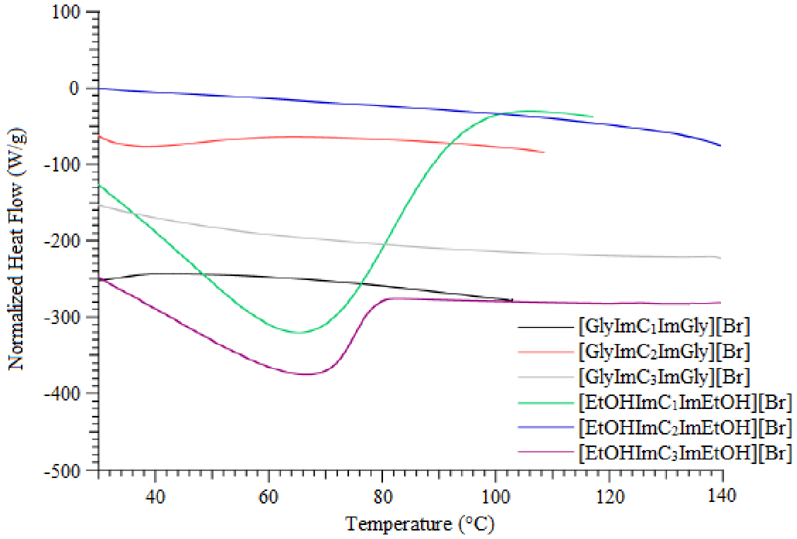


Figure 4.9. Preheating flow.

Traces of the second heat resulted flat likely because melting temperature was not achieved during the heating scan (Figure 4.10). A detailed analysis of the thermal stability of the investigated materials should be carried out, in order to set the DSC temperature range, to investigate the thermal transition avoiding thermal degradation.

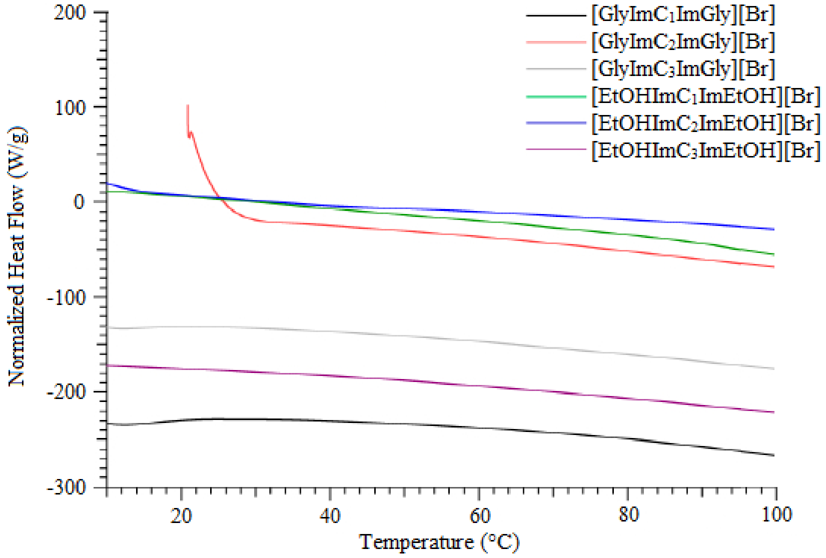


Figure 4.10. Second heating flow.

In literature, geminal imidazolium dicationic salts, in which two imidazolium units are connected by C_3-C_{12} alkylenes, had been considered more thermally stable than monoimidazolium analogues. Melting points and thermal stability of alkylene bis(alkylimidazolium) salts are affected by structural factors:

- Alkyl substituent;
- Length of the spacer between the two imidazolium dications;
- Anion nature.

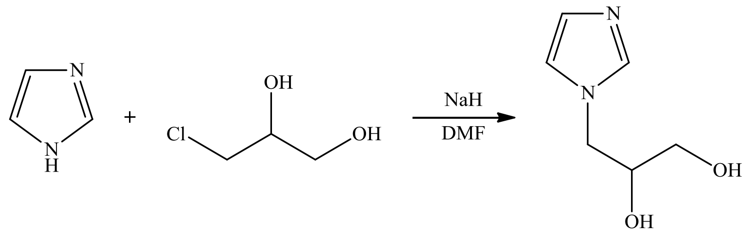
When longer linkage chains are used to separate the dications, a decrease in the melting point is observed for most ionic liquids. This may be related to an increase in the number of closely related configurational states and possibly crystalline polymorphs for these compounds. However, C_2 spacer salts show lower thermal stabilities than C_3 and C_4 spacer analogues and ILs density decreases with increasing linkage chain length. Also, the anion effect is significant. Better thermal stability are achieved with less nucleophilic anions: $TfO^- > BF_4^- > PF_6^- > Br^- > NO_3^- > TFA^-$.[101] A small variation in the surface tension is observed when different length linkage chains are used to connect the dications; however, the length of the substituted alkyl group on the imidazolium ring decreases the surface tension with increased length. For the Tf_2N^- dicationic salts, the viscosity generally increases when a longer alkyl chain is used to separate the dications. The addition of a longer alkyl group at the three position of the imidazolium ring also provides ionic liquids with higher viscosities.[102] Nevertheless, we should point out that those systems are functionalised with aliphatic alkyl chains without any functionality susceptible to oxidation or that can lead to degradation products and also more stable anion were also used, *i.e.* Tf_2N^-.

Spectroscopic data confirmed that the tridimensional structure of two isomers of geminal ILs is heavily affected by the shape of the involved cation, allowing a higher degree of structural order for 3,3'-di-Bu^n-1,1'-(1,4-phenilenedimethylene)diimidazolium Tf_2N^- than for the *ortho*-substituted. The presence of the thick network of π-π interactions in the latter represents a significant difference from the monocationic imidazolium IL. In the tridimensional structure of these germinal ILs, weak but cooperative interactions, such as π-π interactions play an important role.[103]

IR analysis of all synthetized salts and of their precursors. As expected, for both the biggest change can be seen in the O–H-stretching region. For glyceryl-functionalised salts there was the retaining of the peak at 3100 cm^{-1} and the precursor characteristic peak at 2733 cm^{-1} disappeared, replaced by a peak near 3150 cm^{-1}. For the methylene- and the propylene-bridged systems there is a large signal at 3307 cm^{-1} probably due to the formation of a H-bond framework. For ethylene-functionalised salts, unlike their precursor with a little but large absorption in the region of 3110 cm^{-1}, presented very tight bands, one of which (~ 3080 cm^{-1}) is maintained in all three products, and the other that shifted from 3300 cm^{-1} for ethylene-bridged system to 3330 cm^{-1} for the other ones.

4.4. Experimental section

3-(1*H*-imidazol-1-yl)propane-1,2-diol



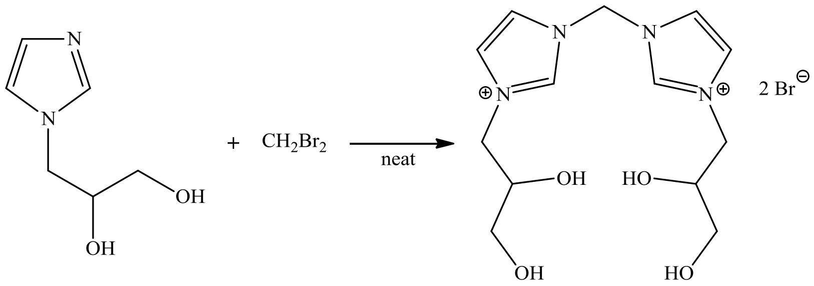
To a suspension of NaH (60% dispersion in mineral oil, 8.00 g, 200 mmol) in 25 mL of anhydrous DMF a solution of 1*H*-imidazole (12.54 g, 183 mmol) in 30 mL of anhydrous DMF was added dropwise. The resulting pale yellow mixture was stirred at room temperature for 4 hours, then a solution of 3-chloro-1,2-propanediol (14.1 mL, 18.61 g, 167 mmol) in 20 mL of anhydrous DMF was added dropwise and the resulting colourless suspension was stirred at 70 °C for 22 h. The reaction mixture was cooled at room temperature and filtered, and the solvent was removed by *vacuum*. The resulting viscous yellow oil was suspended in MeCN (160 mL), refluxed for 15 h and rapidly filtered. The clear solution obtained was cooled at room temperature and successively at 0 °C, affording the expected product (15.12 g, 64%) as a colourless solid.

^{1}H NMR (DMSO-d_6): δ = 7.56 (s, 1H), 7.12 (s, 1H), 6.86 (s, 1H), 5.12 (d, *J* = 5.1 Hz, 1H), 4.87 (t, *J* = 5.5 Hz, 1H), 4.08 (m, 1H), 3.84 (m, 1H), 3.68 (m, 1H), 3.28 (m, 2H).

^{13}C NMR (DMSO-d_6): δ = 136.9, 127.8, 120.1, 70.5, 63.1, 52.5.

^{1}H NMR (D_2O): δ = 7.61 (s, 1H), 7.11 (s, 1H), 6.96 (s, 1H), 4.02 (m, 4H), 3.50 (m, 3H).

1,1'-methylenebis(3-(2,3-dihydroxypropyl)-1*H*-imidazol-3-ium)



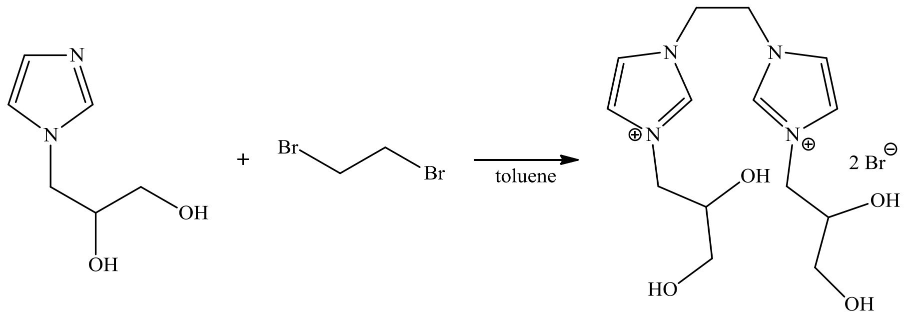
A mixture of 3-(1*H*-imidazol-1-yl)propane-1,2-diol (1.41 g, 9.91 mmol) and dibromomethane (0.35 mL, 0.87 g, 4.95 mmol) in 10 mL MeCN was stirred at refluxing acetonitrile temperature for 120 h. After stirring under *vacuum* the obtained oil was dissolved in hot MeOH and THF was added up to oil phase separation that, after decantation, was dried under reduced pressure obtaining the wanted product (1.86 g, 41%).

A mixture of 3-(1*H*-imidazol-1-yl)propane-1,2-diol (1.58 g, 11.12 mmol) and dibromomethane (4.0 mL, 9.91 g, 55.6 mmol) was stirred at 80 °C for 90 h. The top layer of the biphasic crude mixture, which contained unreacted starting material, was decanted and the bottom layer was washed with Et_2O (3 × 50 mL) heated at 85 °C and stirred under *vacuum* for 24 h. The desired product (2.39 g, 94%) was obtained as a pale yellow oil.

^{1}H NMR (D_2O): δ = 9.40 (s, 2H), 7.89 (s, 2H), 7.72 (s, 2H), 6.80 (s, 2H), 4.51 (dd, *J* = 14 Hz, *J* = 2.7 Hz, 2H), 4.31 (dd, *J* = 14 Hz, *J* = 8 Hz, 2H), 4.13 (m, 2H), 3.67 (d, *J* = 5.5 Hz, 4H).

^{13}C NMR (D_2O): δ = 137.6, 124.5, 122.1, 69.6, 62.5, 59.0, 52.0.

1,1'-(ethane-1,2-diyl)bis(3-(2,3-dihydroxypropyl)-1*H*-imidazol-3-ium)

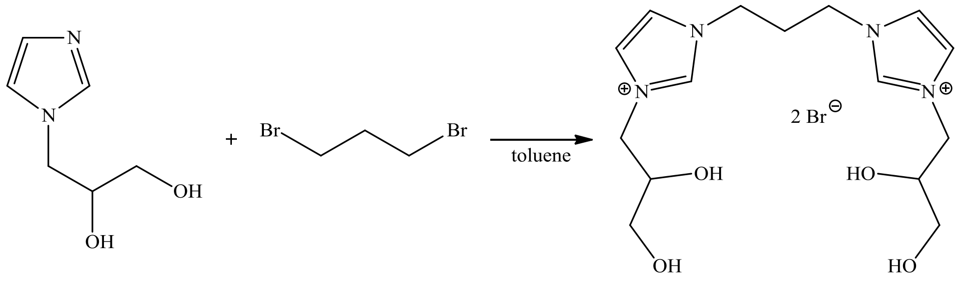


A mixture of 3-(1*H*-imidazol-1-yl)propane-1,2-diol (1.78 g, 12.6 mmol) and 1,2-dibromoethane (0.61 mL, 1.32 g, 7.1 mmol) in 12 mL toluene was stirred at 90 °C for 88 h. After cooling down to room temperature, the solution was washed with toluene (2 × 5 mL) and then with Et_2O (2 × 5 mL). Thus, the solution obtained was washed with MeOH (3 × 5 mL) and then kept decanting in MeOH up to product precipitation (0.91 g, 34%) as a white solid.

^{1}H NMR (DMSO-d_6): δ = 9.10 (s, 2H), 7.74 (s, 2H), 7.70 (s, 2H), 5.31 (d, J = 4.8Hz, 2H), 4.94 (m, 2H), 4.77 (m, 4H), 4.30 (m, 2H), 4.07 (m, 2H), 3.77 (m, 2H), 3.23 (m, 2H).

^{13}C NMR (DMSO-d_6): δ = 137.09, 123.70, 122.11, 69.40, 62.57, 52.35, 48.36.

1,1'-(propane-1,3-diyl)bis(3-(2,3-dihydroxypropyl)-1*H*-imidazol-3-ium)

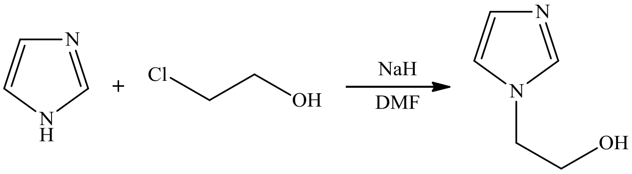


A mixture of 3-(1*H*-imidazol-1-yl)propane-1,2-diol (1.65 g, 11.6 mmol) and 1,3-dibromopropane (0.63 mL, 1.25 g, 6.1 mmol) in 13 mL toluene was stirred before at 90 °C for 23 h and then at refluxing toluene for 38 h. After cooling down to room temperature, the solution was washed with toluene (2 × 5 mL) and then with Et_2O (2 × 5 mL). The wax obtained was kept at reduced pressure to obtain the desired product (2.54 g, 85%).

^{1}H NMR (DMSO-*d*$_6$): δ = 9.24 (s, 2H),7.85 (s, 2H), 7.74 (s, 2H), 5.31 (s, 2H), 4.92 (s, 2H), 4.27 (m, 6H), 4.06 (dd, *J* = 13.6, 7.8 Hz, 2H), 3.78 (s, 2H), 3.31 (m, 4H), 2.43 (m, 2H).

^{13}C NMR (DMSO-*d*$_6$): δ = 136.70, 123.38, 121.83, 69.36, 62.52, 52.20, 45.65, 29.49.

2-(1*H*-imidazol-1-yl)ethan-1-ol

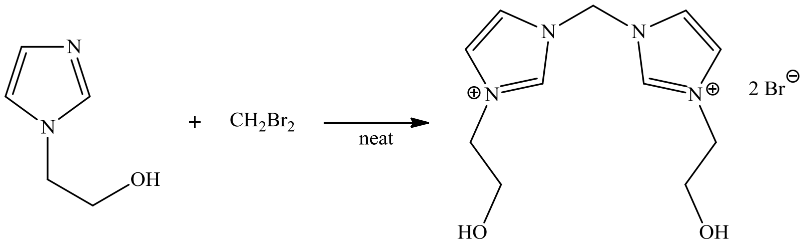


To a suspension of NaH (60% dispersion in mineral oil, 10.04 g, 251 mmol) in 300 mL of anhydrous DMF a solution of 1*H*-imidazole (14.32 g, 209 mmol) in 50 mL of anhydrous DMF was added dropwise. The resulting pale yellow mixture was stirred at room temperature for 3 hours, then a solution of 2-chloro-1-ethanol (14.2 mL, 17.10 g, 212 mmol) in 50 mL of anhydrous DMF was added dropwise and the resulting colorless suspension was stirred at 90 °C for 22 h. The reaction mixture was cooled at room temperature and filtered, and the solvent was removed by *vacuum*. The resulting white solid was dissolved in 45 mL of EtOH. The precipitated solid, NaCl, was filtered and the solution dried at reduced pressure obtaining the desired product (22.81 g, 98%) as a white solid.

^{1}H NMR ($CDCl_3$): δ = 7.35 (s, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 3.99 (t, *J* = 5.0 Hz, 2H), 3.80 (t, *J* = 5.0 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ = 137.22, 128.21, 119.55, 61.06, 49.94.

1,1'-methylenebis(3-(2-hydroxyethyl)-1*H*-imidazol-3-ium)

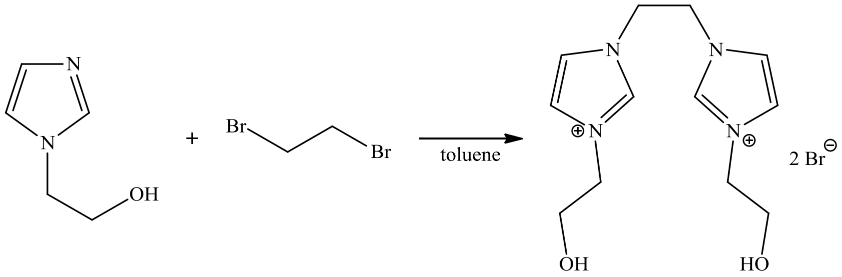


A mixture of 3-(1*H*-imidazol-1-yl)propane-2-ol (5.27 g, 47.0 mmol) and dibromomethane (17.0 mL, 42.1 g, 235.2 mmol) was stirred at 80 °C for 15 h. The reaction mixture results in a compact solid system, washed under stirring with CH_2Cl_2 and then dried at reduced pressure, obtaining the product (9.12 g, 68%) as a white powder.

^{1}H NMR (D_2O): δ = 7.82 (s, 2H), 7.68 (s, 2H), 6.73 (s, 2H), 4.38 (m, 4H), 3.95 (m, 4H).

^{13}C NMR (D_2O): δ = 123.97, 122.16, 59.36, 58.90, 52.28.

1,1'-(ethane-1,2-diyl)bis(3-(2-hydroxyethyl)-1*H*-imidazol-3-ium)

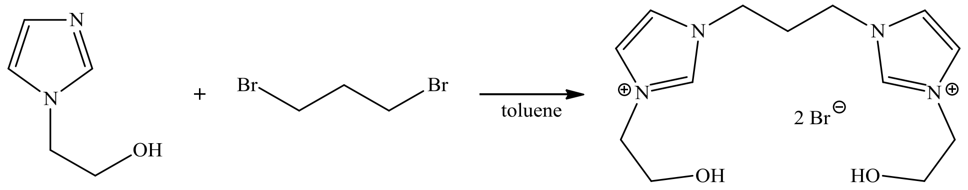


A mixture of 3-(1*H*-imidazol-1-yl)propane-2-ol (5.10 g, 45.5 mmol), 1,2-dibromoethane (2.3 mL, 5.01 g, 25.9 mmol) and toluene (25 mL) was stirred at 80 °C for 21 h. The solid obtained was washed before with CH_2Cl_2 and then dissolved in hot EtOH (15 mL). The solution was cooled down to room temperature and then kept at 0 °C overnight obtaining solid in needles that was filtered and so kept under reduced pressure to obtain the desired product (4.45 g, 33%).

^{1}H NMR (D_2O): δ = 8.85 (s, 2H), 7.84 (d, *J* = 2.0 Hz, 2H), 7.69 (d, *J* = 1.9 Hz, 2H), 6.75 (s, 4H), 4.40 (t, *J* = 4.8 Hz, 4H), 3.94 (t, *J* = 4.9 Hz, 4H).

^{13}C NMR (D_2O): δ = 136.50, 123.59, 122.37, 59.48, 51.88, 48.87.

1,1'-(propane-1,3-diyl)bis(3-(2-hydroxyethyl)-1*H*-imidazol-3-ium)



A mixture of 3-(1*H*-imidazol-1-yl)propane-2-ol (4.12 g, 36.8 mmol), 1,3-dibromopropane (3.8 mL, 7.50 g, 19.5 mmol) and toluene (20 mL) was stirred at 80 °C for 72 h. After evaporating the solvent, the wax obtained was washed under vigorous stirring with 35 mL CH_2Cl_2, obtaining a powder that was filtered and then kept under reduced pressure obtaining a white solid (6.97 g, 60%).

^{1}H NMR (D_2O): δ = 8.90 (s, 2H), 7.75 (s, 2H), 7.69 (s, 2H), 4.78 (m, 4H), 4.38 (m, 4H), 3.63 (m, 4H), 1.41 (m, 2H).

^{13}C NMR (D_2O): δ = 136.08, 123.08, 122.41, 59.73, 51.82, 50.23, 46.49, 29.72.

4.4.1. DSC

DSC measurements were performed with a EXSTAR7020 Differential Scanning Calorimeter. The instrument was calibrated at 10 °C min^{-1} in temperature and energy with high purity standards (indium, naphthalene, cyclohexane) according to the procedure for standard DSC. Dry nitrogen was used as purge gas at a rate of 30 mL min^{-1}. A fresh sample was employed for each analysis. Samples were heated to T_{max} at a rate of 10 °C min^{-1} and maintained at this temperature for 2 min and successively were cooled at -10 °C min^{-1} down to T_{min}. Consecutively the samples were reheated at 10 °C min^{-1} from T_{min} up to T_{max}.

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5. Dibromide-functionalised ILs

5.1. CO_2 capture

CO_2 capture technologies are categorized into chemical absorption, physical absorption, and membrane separation but currently, chemical absorption methods employing aqueous solutions of amines or ammonia are the technology of choice for CO_2 capture. These technologies display high CO_2 absorption capacities through forming chemical bonds by a single step termolecular mechanism (Figure 5.1).[1]

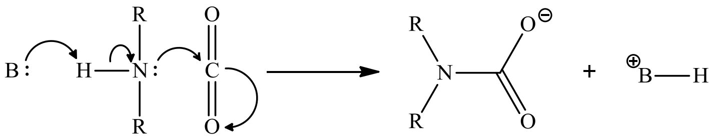


Figure 5.1. Reaction mechanism involved in the reaction between CO_2 and amines.

This method, however, presents several concerns:[2]

- Due to its energy cost related because of the high energy required to break the chemical bonds between the absorbents and the absorbed CO_2 in the regenerative desorption step;
- Limited amine adsorbent concentration in the solution, and thus reduced CO_2 absorption capacity, because of amines rapidly corrosion of alloy steel equipment;
- Amines and ammonia are prone to degrade either thermally or through chemical reactions, which causes the loss of active absorbents, produces extra waste streams, and therefore lead to additional operational cost;
- Owing to their volatility, amines and ammonia are to some extent lost into the gas stream-replenishment thereby adds to the cost of the process and environmental impact.

Compared with amine/ammonia solutions, ILs have several advantages:[3]

- Because of a physical absorption mechanism, less energy is required to remove the absorbed CO_2 from ILs in the regeneration step. The enthalpy of CO_2 absorption is typically ~ 10-20 kJ mol^{-1} for ILs (only a quarter of the energy, in comparison with standard amine solutions, is required to remove the same amount of CO_2 from ILs);
- Many ILs are both thermally (having a decomposition temperature normally above 300 °C) and chemically stable (they are less oxidizable, less reactive towards impurities and corrosive agents), minimizing both IL absorbents losses and waste streams production, making them recyclable;
- Many ILs are non-volatile solvents, non-flammable and thus are able to be used safely. Their low volatility also prevents their loss into the gas streams;
- High tunability.

Gases with large dipole moments (*e.g.*, water) or quadrupole moments (*e.g.*, CO_2 and N_2O), as well as those with the opportunity for specific interactions (*e.g.*, hydrogen bonding) have the highest solubility in the ionic liquids, whereas the solubility of the other nonpolar gases correlates well with their polarizability. However, carbon monoxide solubility does not follow this trend, indicating that dipole and quadrupole moments and polarizability cannot fully describe the behaviour of the gases in the ILs.[4]

5.1.1. Ionic liquids in CO_2 capture

Brennecke *et al.*[5] carried out a series of researches on separation processes for the system of CO_2-RTILs and found that ionic liquids have remarkable absorption capacities especially at relatively high pressure. CO_2 was reported to be more soluble in ILs than in organic solvents, being the maximum concentrations reported as high as 0.75 mol fraction. The phase diagram of CO_2-IL systems shows a two-phase region (the liquid phase of the IL-CO_2 mixture and the pure CO_2 phase) in the moderate-pressure range, and a single phase (the liquid phase of the IL-CO_2 mixture) in the high-pressure region. Another distinct difference is that, unlike organic solvents where dilation is generally observed on gas dissolution, ILs do not show a significant volume expansion even when a high mole fraction of CO_2 is dissolved.

Thermal expansion coefficients of ILs are smaller because, bearing either positive or negative charges, cations and anions all participate in coulombic interaction and form a more rigid packing than molecular solvents. Cations and anions are arranged to form a relatively rigid network, and that the ionic arrangement potentially contains a large amount of “free volumes” available to accommodate CO_2 molecules. The CO_2 molecules diffuse through the relatively rigid network and fill into these available free volumes without disturbing the arrangement of the ions and the anion seems to be the dominant factor related to thermal expansion.[6]

The nature of the anions appears to be one of the major factors dominating the dissolution of CO_2.[7] The interaction is suggested to be of a Lewis acid-base type where the anions act as Lewis bases and the CO_2 as Lewis acid. When interacting with hydrocarbon, CO_2 molecules act as a weak Lewis base since the oxygen atom on the CO_2 interacts with the C–H bond. CO_2 physical solubility in ionic liquids can be enhanced more or less, for instance, by fluorinating the cation or anion components or increasing alkyl chain length. When electronegative fluorine atoms are present, the C–F bond may interact with the Lewis acidic carbon atom on the CO_2 molecule. The enhanced CO_2 solubility in ILs with fluorinated anions originates from a different nature of intermolecular interactions involving the fluorine atoms of the anions.[8] Kazarian *et al.*[9] investigated the mixtures of CO_2 with [bmim][PF_6] and [bmim][BF_4] and they found evidence of a weak Lewis acid-base interaction between the CO_2 and the anions of the ILs. The Tf_2N^- anion increases all gas solubility relative to BF_4^- and PF_6^- ILs, whereas the BF_4^- anion has little effect on the solubility of these gases relative to PF_6^-. Changing the cation from imidazolium to quaternary ammonium or pyrrolidinium, all with the Tf_2N^- anion, made little difference in the CO_2 and solubility.

About cations, there are two factors that influences CO_2 solubility. The biggest effect is its alkyl chain length, *i.e.* for a given cation, the CO_2 solubility increases with increasing chain length. This may be due to entropic reasons, as the density of ILs decreases with increasing alkyl chain length; therefore, there may be more free volume within the longer chain ILs. For imidazolium cation based ILs, the effect of substitution at the C(2) position was also examined. It is known that the hydrogen in this position is acidic and can interact by hydrogen bond. The solubility differs only slightly at high pressures, with C(2)–H substituted rings having the marginally higher CO_2 solubility because for large amounts of CO_2 present in the liquid, some molecules may adopt a secondary position near the cation, in which the nitrogen is more polarized, with the primary position for CO_2 being near the anion.[10]

The use of non-fluorinated molecules have been explored due to the cost and potential environmental implications of their fluorinated counterparts. The addition of ether groups is believed to improve CO_2-philicity by increasing the flexibility of alkyl chains, leading to increased free volume.[11] The ether oxygen has also been shown to interact with the carbon of CO_2.[12] Ether functionality is also beneficial for ILs as the resultant flexibility allows preparation of ILs that are liquid at room temperature, where in some cases their alkyl analogues would be solids.

The nature of the TSIL system upon its reaction with CO_2 has significant implications for the design and implementation of CO_2 capture processes. Amine-functionalized TSILs have relatively high viscosities in the pure state, but upon contact with CO_2 the viscosity increases dramatically, forming a gel-like substance because the anions prefer to interact strongly with the -NH_2 tails of the cations via hydrogen bonding.[13] The high viscosity of amine-tethered TSILs before and after complexation with CO_2 is not entirely a hindrance. TSILs that have been deposited or supported on a porous matrix within a membrane, also known as supported ionic liquid membranes (SILMs), have been shown to exhibit high permeability and selectivity for CO_2.[14] High viscosity in this instance is desirable, and selectivity has been shown to increase with increasing temperature over a particular range. Significant opportunities exist to fine-tune membrane performance by altering the strength of the CO_2 complex.

5.1.2. Halogen-functionalised ionic liquids

Considering that CO_2 is an electron-rich molecule, halogenated compounds are able to form weak halogen bonds with it. This non-covalent interaction thus may improve CO_2 solubility when using halogenated ILs,[15] so we decided to design a family of new halogenated ionic liquids starting from allylated systems. We investigated mainly saturated systems and the imidazolium ring because the most studied to have a comparison with the literature.

The synthesis of the precursors was easily achieved by a dropwise addition of allylbromide to a solution of the amine in acetonitrile and subsequent purification by crystallization. All reactions were relatively fast and led to satisfactory yields of pure product. The subsequent bromination of the lateral double bond was obtained adding dropwise bromine to a solution of the former bromide salt and the precipitation of the product as a white solid was observed for all the prepared salts. Then the common anion metathesis with $LiTf_2N$ in water was the last step to obtain the wanted ionic liquids: 1-(2’,3’-dibromopropyl)-3-methylimidazolium bis(trifluoro-methylsulfonyl)imide ([C_3Br_2mim] [Tf_2N]); 1-(2’,3’-dibromopropyl)-tetrahydrothiophenium bis(trifluoro-methyl-sulfonyl)-imide ([C_3Br_2tht][Tf_2N]); 1-(2’,3’-dibromopropyl)-1-methylpyrrolidinium bis(trifluoro-methylsulfonyl)-imide ([C_3Br_2mpyr][Tf_2N]); 1-(2’,3’-dibromopropyl)-1-methylmorpholinium bis(trifluoro-methylsulfonyl)-imide ([C_3Br_2mmor][Tf_2N]); 1-(2’,3’-dibromopropyl)-1-methylpiperidinium bis(trifluoro-methylsulfonyl)-imide ([C_3Br_2mpip] [Tf_2N]).

Recently, Zhu *et al.*[16] investigated theoretically the interactions between 1-(2’,3’-dibromopropyl)-3-methyl-imidazolium bromide and CO_2 molecules. For all the possible binding regions of the bromide anion around the imidazolium ring, they obtained only few interaction patterns including halogen or hydrogen bonds of the ion pair under study. In the first structure the intermolecular $Br{\cdots}Br^-$ distance corresponded to a reduction > 20% of the sum of the van der Waals radii of the C(2’) bromide and the anion. In the second stable structure obtained by geometry optimization, the bromide anion was perpendicular to imidazolium ring interacting with protons on C(2), and on the lateral chains. In the last most stable structure the interactions are the same but with the bromide horizontal respect to imidazolium. Covalently bonded bromines can form linear halogen bonds with electron donors such as CO_2, indeed, considering only cation-CO_2 interactions, all calculated C–Br···O angles were close to 180° indicating the electrostatic nature of these interactions. Introducing bromide anion in the system, only the second and the third structures could interact with CO_2 molecules because the charge of both Br atoms in the first structure were negative, while the Br atoms on the alkyl chains of the formers carried positive charges, indicating that Br···O interactions in these systems are basically electrostatic in nature and belong to traditional weak halogen bond. These results displayed that some ILs are able to absorb CO_2 through weak halogen bonding interaction.

Viscosity (η) and conductivity (κ) were measured for all bromide-functionalised ionic liquids in the temperature range between 20 and 90 °C after thorough drying, although Tf_2N^- anion based ionic liquids show a very poor attitude towards absorbing atmosphere humidity, avoiding as much as possible contact with air during the transfer and measures. The values of viscosity and conductivity at different temperatures are reported in Table 5.1 and in Table 5.3.

Table 5.1. Viscosities (cP) related to temperatures (°C).

Ionic liquid	20	30	40	50	60	70	80	90
[C_3Br_2mim][Tf_2N]	1976	519.6	272.2	163.6	95.1	62.5	49.9	-
[C_3Br_2tht][Tf_2N]	1965	768.8	397.7	201.3	122.4	72.4	53.6	-
[C_3Br_2mpyr][Tf_2N]	4823	1232	387.5	210.9	123.9	65.2	29.4	-
[C_3Br_2mmorf][Tf_2N]	-	26012	6099	2030	846.7	391.9	225	122.8
[C_3Br_2mpip][Tf_2N]	12536	4485	1373	527.4	256.9	161.0	92.9	55.6

The imidazolium-based system showed the lowest conductivity values, but very close to those of tetrahydrothiophenium one. Otherwise, aliphatic ammonium salts were very viscous. The pyrazolium salt viscosity is comparable to less viscous systems at higher temperatures but at 20 °C it was almost 2.5 times more (Figure 5.2). Piperidinium and morfolinuim salts were the most viscous systems (Figure 5.3).

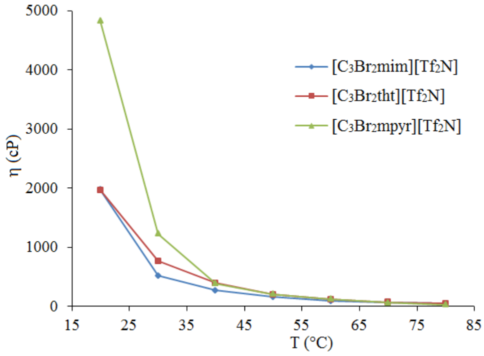


Figure 5.2. Viscosity values related to temperature of [C_3Br_2mim][Tf_2N], [C_3Br_2tht][Tf_2N] and [C_3Br_2mpyr][Tf_2N] salts.

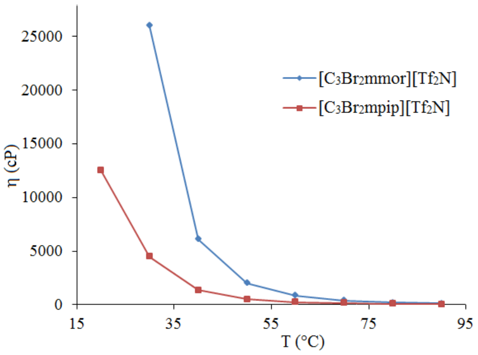


Figure 5.3. Viscosity values related to temperature of [C_3Br_2mmor][Tf_2N] and [C_3Br_2mpip][Tf_2N] salts.

Table 5.2. Viscosity parameters of depending on temperatures (K) following Arrhenius and VTF equations.

Ionic liquid	E_η kJ mol^{-1}	lnη_∞ cP	R	η_0 cP	B K	T_0 K	R^2
[C_3Br_2mim][Tf_2N]	46.94	-12.34	0.999	12.16	147	264	0.999
[C_3Br_2tht][Tf_2N]	51.53	-13.80	0.999	0.57	639	215	0.999
[C_3Br_2mpyr][Tf_2N]	69.43	-20.32	0.991	0.25	610	231	0.999
[C_3Br_2mmorf][Tf_2N]	84.06	-23.47	0.993	0.47	714	238	0.999
[C_3Br_2mpip][Tf_2N]	70.42	-19.68	0.994	0.10	1130	197	0.998

As for pyrazolium-based ionic liquids we have analysed the development of this property as a function of temperature, using appropriate mathematical models. Initially, the viscosity data measured between 293 and 363 K were interpolated using the logarithmic form of Arrhenius equation (Figure 5.4, Figure 5.7), normally used to describe the dependence of viscosity on the temperature in the case of not dissociated liquid electrolytes:

$$\ln\eta = \ln\eta_\infty + \frac{E_\eta}{RT}$$

where E_η is the attivation energy for viscous flows, lnη_∞ is the viscosity at infinite temperature and R is the gas constant (Table 5.2).

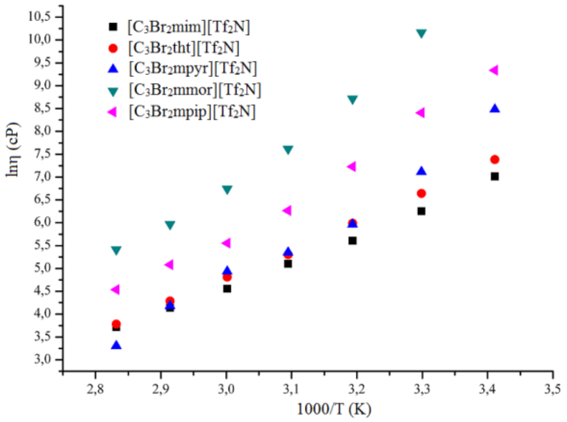


Figure 5.4. Comparison between viscosities of several dibromide-functionalised ionic liquids considering Arrhenius equation.

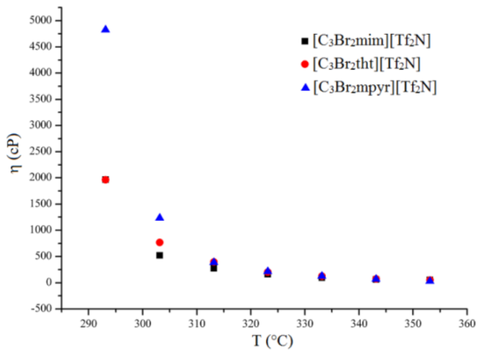


Figure 5.5. Comparison between viscosities of $[C_3Br_2mim][Tf_2N]$, $[C_3Br_2tht][Tf_2N]$ and $[C_3Br_2mpyr][Tf_2N]$ considering VTF equation.

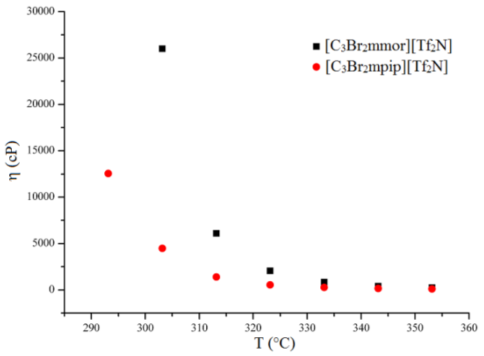


Figure 5.6. Comparison between viscosities of $[C_3Br_2mmor][Tf_2N]$ and $[C_3Br_2mpip][Tf_2N]$ considering VTF equation.

Looking at E_η values, energy barriers to be overcome to allow ions to move relative to one another, they are higher also of those of nitrile-functionalised pyrazolium salts (~ 49 kJ/mol). Moreover, the association of high E_η values with high and negative $\ln\eta_\infty$ suggests an higher order and degree of association of these systems. Morfolinium system highest values may be explained considering the possibility of dipole interactions of the oxygen lone pairs, indeed other systems miss heteroatoms in their rings.

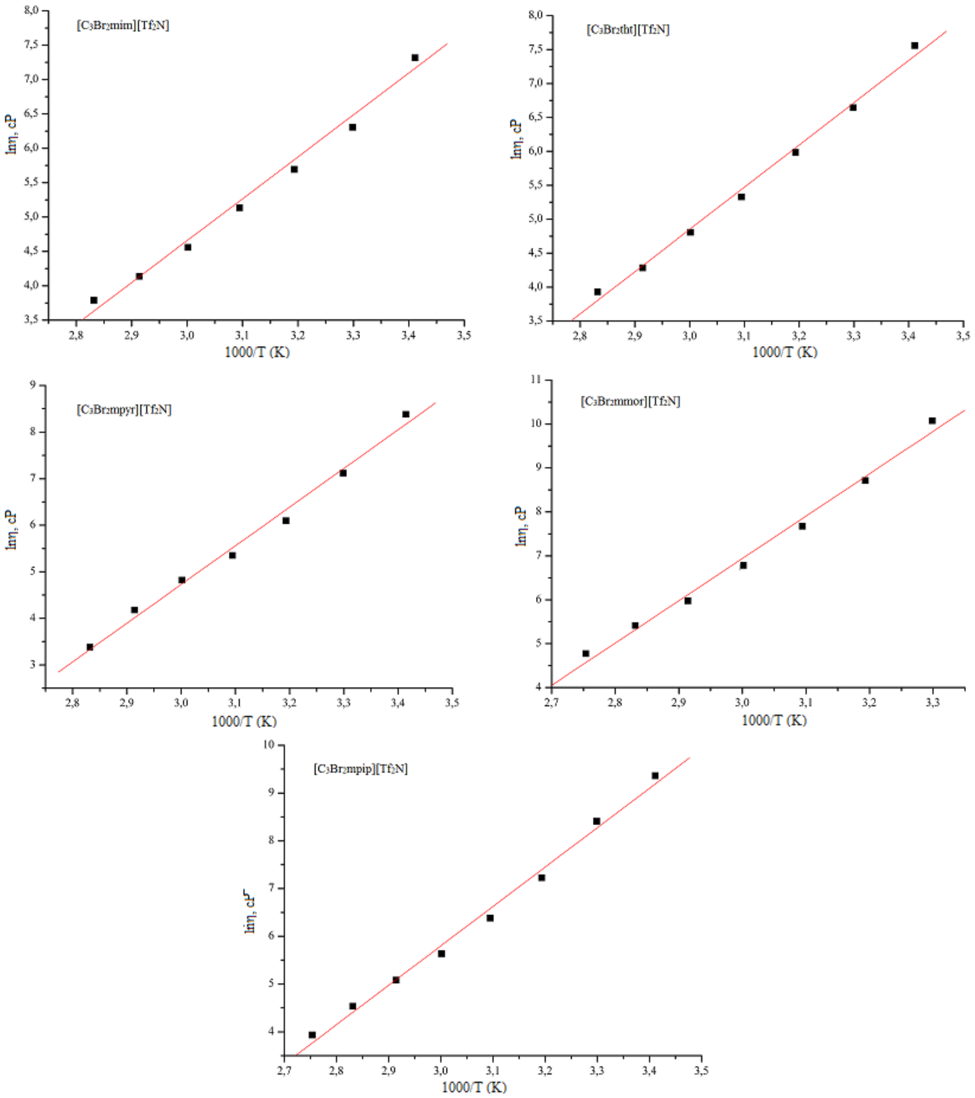


Figure 5.7. Single dibromide-functionalised ionic liquids viscosities considering Arrhenius equation.

Viscosity values of these ionic liquids were also analysed using Vogel-Tamman-Fulcher (VTF) (Figure 5.8, Figure 5.5 and Figure 5.6)

$$\eta = \eta_0 e^{\frac{B}{T-T_0}}$$

where η_0 (cP), B (K), and T_0 are fitting parameters. The best parameters and correlation coefficients are reported.

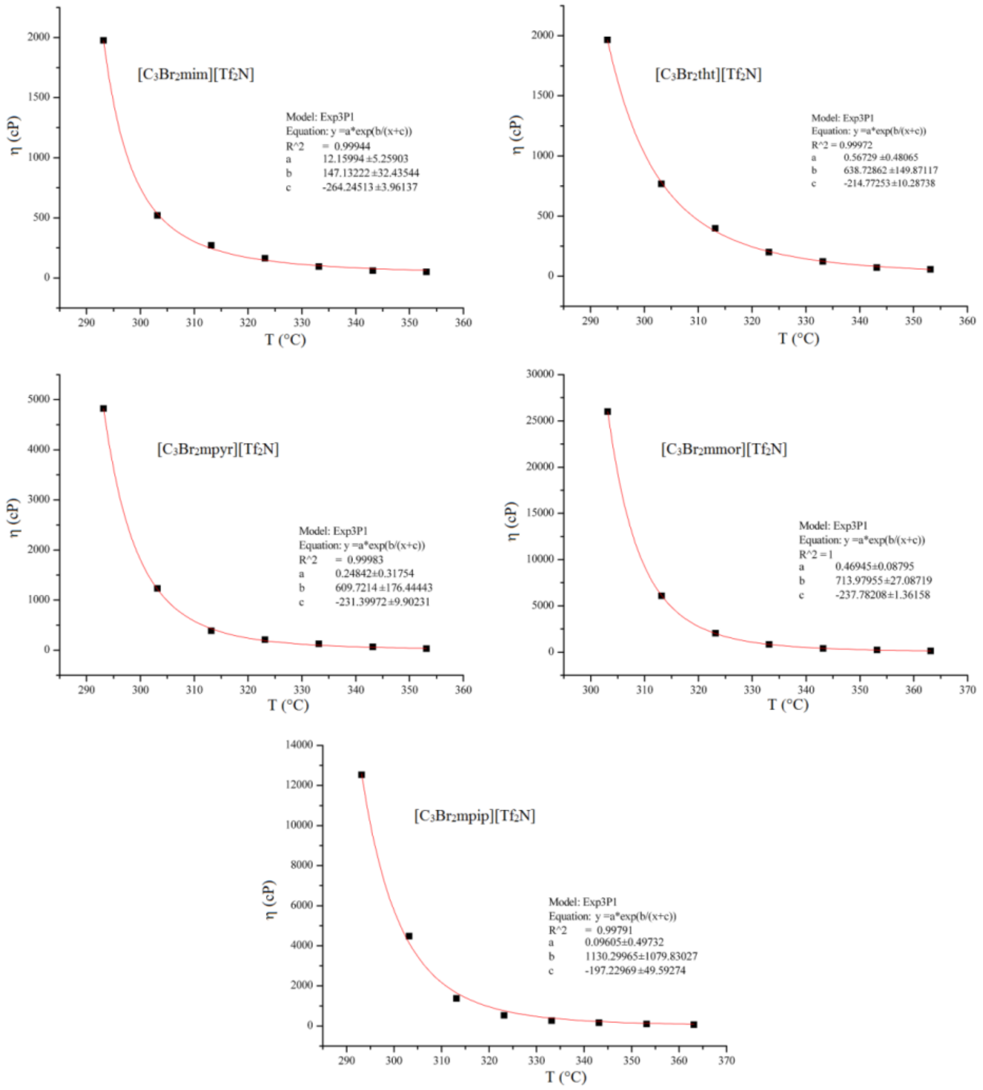


Figure 5.8. Single dibromide-functionalised ionic liquids viscosities considering VTF equation.

Table 5.3. Conductivities (μS/cm) correlated to temperature (°C).

Ionic liquid	20	30	40	50	60	70	80
[C_3Br_2mim][Tf_2N]	59	132	319	530	775	1326	1540
[C_3Br_2tht][Tf_2N]	118	182	361	553	754	973	1353
[C_3Br_2mpyr][Tf_2N]	152	271	424	759	1076	1376	1538
[C_3Br_2mmorf][Tf_2N]	4.15	10.84	29.5	46.9	104.7	182.2	276
[C_3Br_2mpip][Tf_2N]	45.1	101.2	156.5	329	510	726	870

Conductivity is strictly related to viscosity, being usually an inverse correlation between them (Table 5.3, Figure 5.9). According to viscosity data, conductivity values are so poor in comparison with pyrazolium-based ionic liquids. [C_3Br_2mmorf][Tf_2N] is characterized by the lowest conductivity, almost ten times lower than piperidinium salt. The most conductive liquids are also the less viscous ones, *i.e.* [C_3Br_2mim][Tf_2N], [C_3Br_2tht][Tf_2N] and [C_3Br_2mpyr][Tf_2N].

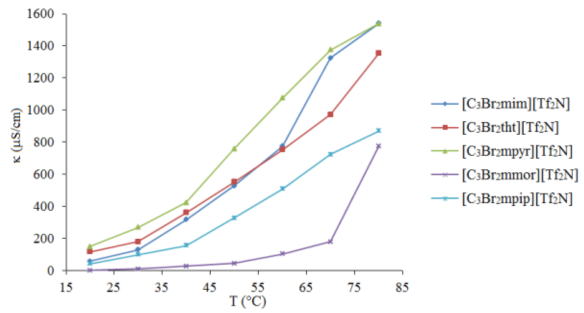


Figure 5.9. Conductivity values related to temperature of dibromide-functionalised ionic liquids.

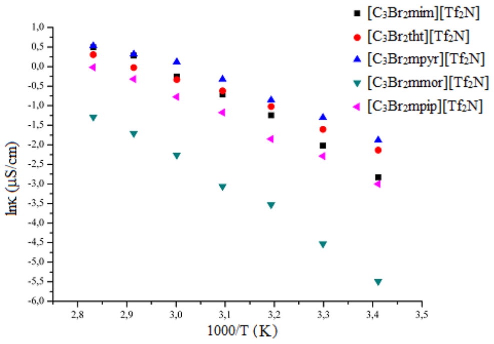


Figure 5.10. Plotted dibromide-functionalised ionic liquids conductivities considering Arrhenius equation.

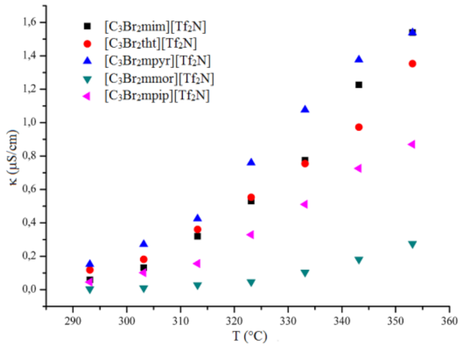


Figure 5.11. Plotted pyrazolium-based ionic liquids conductivities considering VTF equation.

On the basis of the trend of the conductivity respect to temperature, the five ionic liquids synthetized had some deviation respect to Arrhenius plot (Table 5.4). In Figure 5.10 and Figure 5.12 the Arrhenius trends of the five ionic liquids studied are represented plotted and singularly respectively.

Table 5.4. Conductivity parameters of depending on temperatures (K) following Arrhenius and VTF equations.

Ionic liquid	E_κ kJ mol^{-1}	lnA cP	R	A cP	B K	T_0 K	R^2
[C_3Br_2mim][Tf_2N]	-47.47	17.12	-0.994	19.3	257	251	0.998
[C_3Br_2tht][Tf_2N]	-35.34	12.41	-0.997	382	1157	148	0.998
[C_3Br_2mpyr][Tf_2N]	-34.50	12.39	-0.993	8.3	164	255	0.999
[C_3Br_2mmorf][Tf_2N]	-60.28	19.41	-0.996	1.5	147	265	0.999
[C_3Br_2mpip][Tf_2N]	-42.56	14.76	-0.997	6.5	192	257	0.998

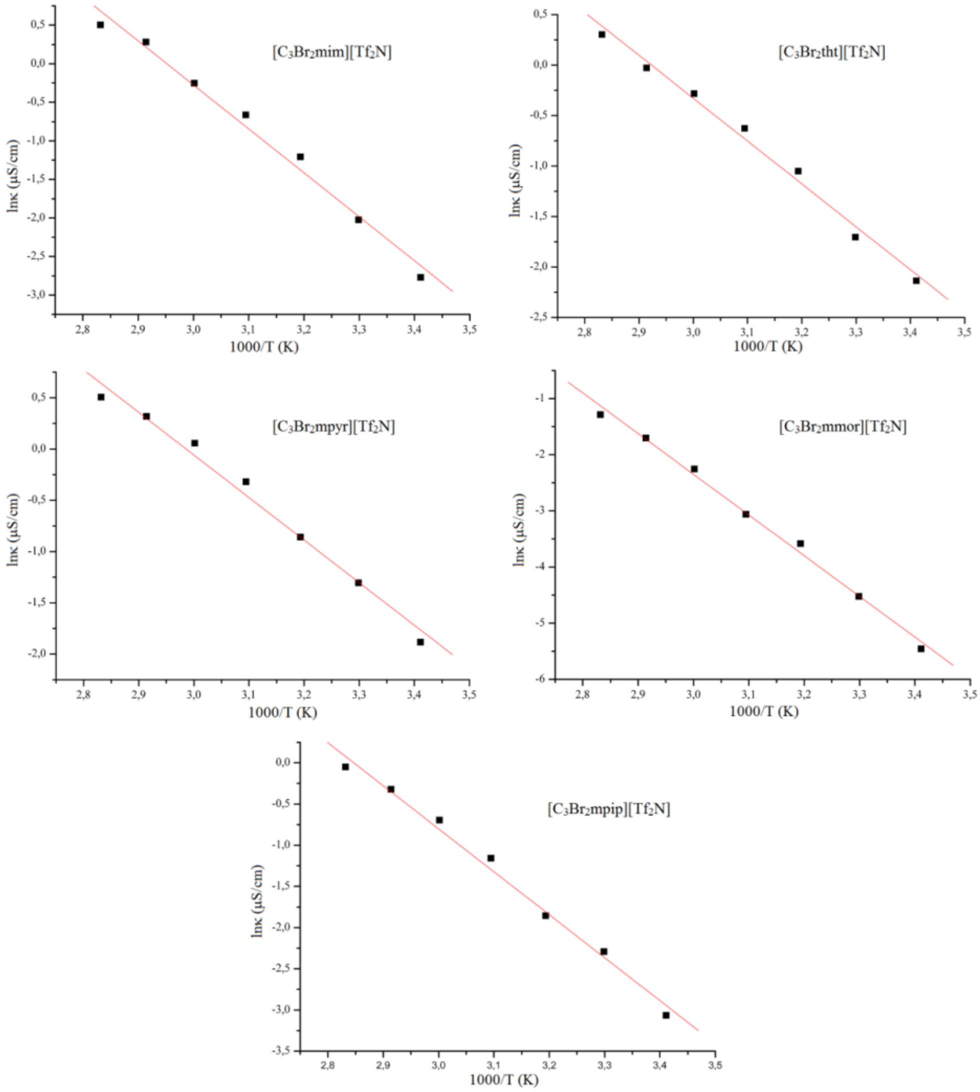


Figure 5.12. Arrhenius plot of dibromide-functionalised ionic liquids.

Conductivity data were also analysed on the basis of the VTF equation

$$\kappa = Ae^{-\frac{B}{T-T_0}}$$

In Figure 5.11 and Figure 5.13 are showed VTF trends plotted and singularly respectively. The high absolute values of E_κ demonstrate the presence of high aggregated structures. These values are even higher than those of nitrile-functionalised pyrazolium salts, whose highest value was ~ 30 kJ mol^{-1}. Thus, dibromide-functionalised salts may have aggregation energies two times higher than those of pyrazolium Tf_2N^-.

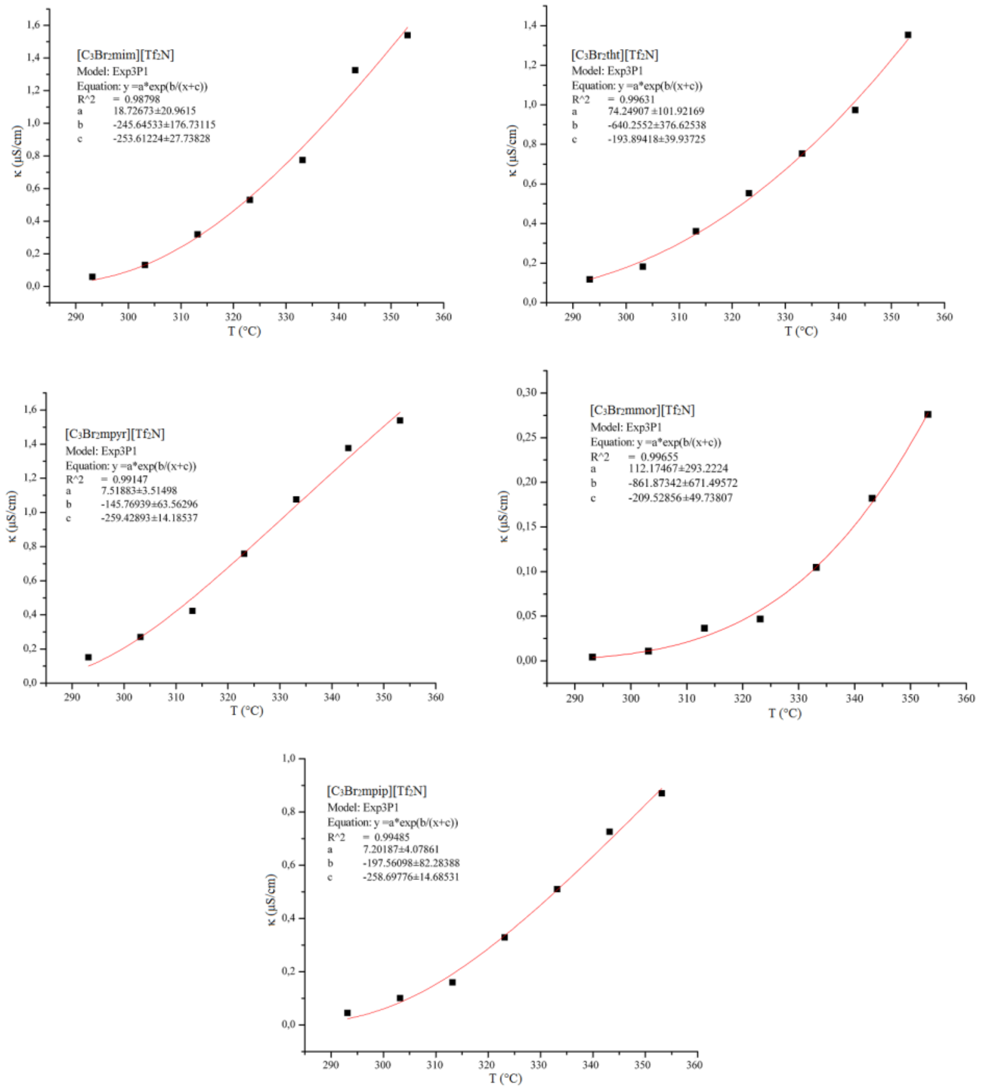


Figure 5.13. Single dibromide-functionalised ionic liquids conductivities considering VTF equation.

Also for these new salts we performed differential scanning calorimeter (DSC) tests to check whether transition occurred in the investigated temperature range (*i.e.*, -50-170 °C). At the beginning, for each sample, we followed a pre-heating procedure (starting from room temperature to a T_{max} lower than decomposition temperature at a rate of 10 °C min^{-1} and maintained at this temperature for 2 min). Samples were re-cooled at -10 °C min^{-1} down to T_{min}, *i.e.* -50 °C, and kept at this temperature at least 5 min. Finally, the samples were reheated at 10 °C min^{-1} from T_{min} up to T_{max} (150 °C).

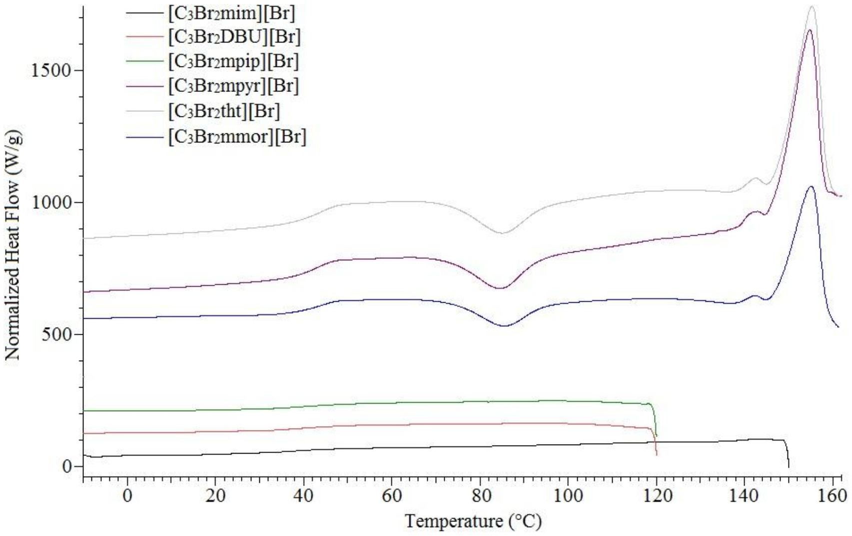


Figure 5.14. Second heating flow thermograms of dibromide-functionalised bromide salts.

Figure 5.14 shows thermograms of dibromide-functionalised bromide salts. DBU- and piperidinium-based salts did not present any melting point and degraded near 120 °C. The imidazolium-based salt was the only one liquid at room temperature. In its thermogram there was not any peak referred to a melt probably because of kinetic reasons. Indeed, the relatively fast temperature decrease did not permit the recrystallization of the substance that may be a very slow process. Also maintaining T_{min} for 5 minutes after preheating was not sufficient to obtain crystals. $C_3Br_2pyr^+$, $C_3Br_2tht^+$ and $C_3Br_2mor^+$ systems had very similar behaviours (Table 5.5) with an initial glass transition (~ 42 °C) followed by a re-crystallization (~ 142 °C) and then by a melting point (~ 155 °C).

Table 5.5. Thermograms of $C_3Br_2pyr^+$, $C_3Br_2tht^+$ and $C_3Br_2mor^+$ bromide salts.

Ionic liquid	T_g (°C)	T_{cc} (°C)	ΔH_{cc} (J/g)	T_{m1} (°C)	ΔH_{m1} (J/g)	T_{m2} (°C)	ΔH_{m2} (J/g)
[C_3Br_2mpyr][Br]	41.8	84.5	10.7	141.9	-0.52	154.8	-25.9
[C_3Br_2tht][Br]	42.5	85.0	10.1	142.2	-0.58	155.3	-32.0
[C_3Br_2mmorf][Br]	43.3	85.5	9.27	142.4	-0.23	155.2	-16.5

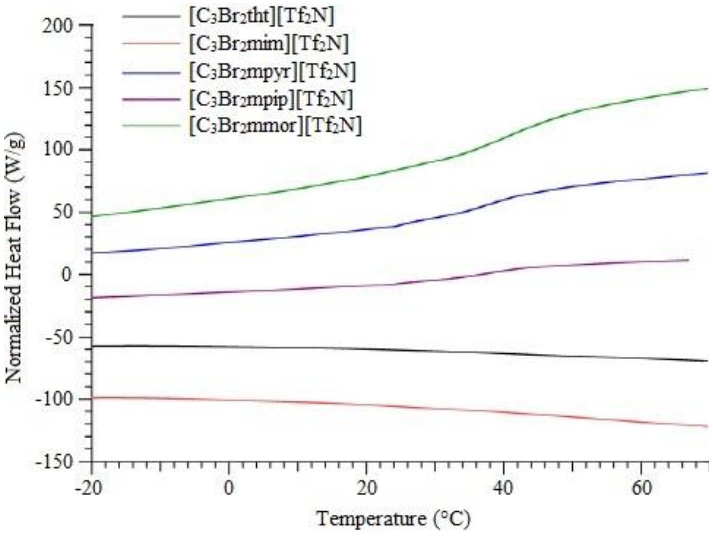


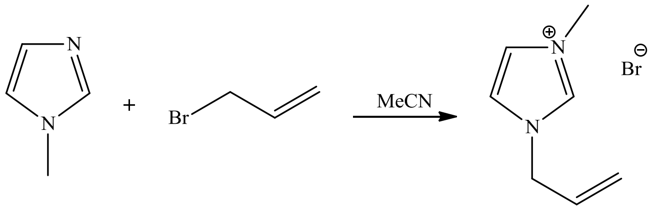
Figure 5.15. Second heating flow DSC analysis of dibromide-functionalised Tf_2N^- ionic liquids.

In Figure 5.15 thermograms of dibromide-functionalised Tf_2N^- ionic liquids are reported. The analysis was performed in a wider range but no melting peaks were detected thus, these ionic liquids could melt at a temperature less than -50 °C. For $C_3Br_2pyr^+$, $C_3Br_2pip^+$ and $C_3Br_2mor^+$ systems can be seen a signal at 37.5, 36.4 and 41.8 °C respectively, probably referred to a T_g (glass transition temperature).

5.2. Experimental section

5.2.1. Allyl-onium bromide salts

1-allyl-3-methylimidazolium bromide ([atht]Br$^-$)

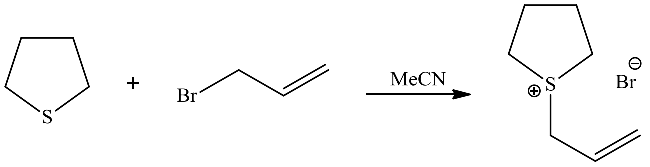


A solution of allylbromide (34.5 mL, 48.2 g, 395 mmol) and MeCN (15 mL) was added dropwise at 0 °C to a solution of *N*-methylimidazole (30.0 mL, 30.9 g, 376 mmol) and 60 mL of MeCN. Then the reaction mixture was heated and stirred at 50 °C for 29 hours. Solvents and unreacted reagents were removed by rotary evaporation, to give the expected product (75.14 g, 98%).

^{1}H NMR (D_2O): δ = 5.88 (m, 1H), 5.60 (m, 2H), 3.88 (d, J = 7.3 Hz, 2H), 3.44 (m, 4H), 2.26 (m, 4H).

^{13}C NMR (D_2O): δ = 126.44, 124.08, 43.76, 41.47, 27.91.

1-allyl-tetrahydrotiofenium bromide ([atht]Br$^-$)

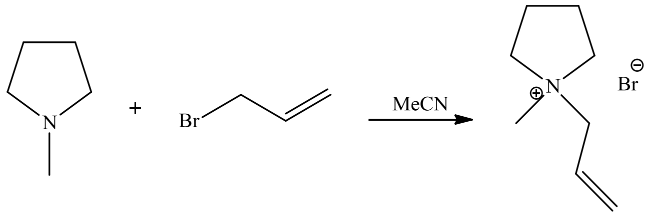


A solution of allylbromide (20.6 mL, 28.8 g, 236 mmol) and MeCN (25 mL) was added dropwise at 0 °C to a solution of tetrahydrotiofene (20.0 mL, 20.0 g, 225 mmol) and 35 mL of MeCN. Then the reaction mixture was heated and stirred at 60 °C for 24 hours. Solvents and unreacted reagents were removed by rotary evaporation, to give the expected product (45.32 g, 96%) as a white crystal solid.

^{1}H NMR (D_2O): δ = 5.88 (m, 1H), 5.60 (m, 2H), 3.88 (d, *J* = 7.3 Hz, 2H), 3.44 (m, 4H), 2.26 (m, 4H).

^{13}C NMR (D_2O): δ = 126.44, 124.08, 43.76, 41.47, 27.91.

1-allyl-1-methyl-pyrrolidinium bromide ([ampyr]Br$^-$)

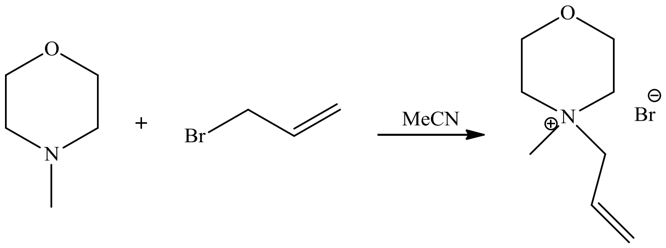


A solution of allylbromide (4.3 mL, 6.01 g, 49.26 mmol) and MeCN (5 mL) was added dropwise at 0 °C to a solution of *N*-methylpyrrolidine (5.0 mL, 4.01 g, 47.13 mmol) and 7 mL of MeCN. Then the reaction mixture was heated and stirred at 50 °C for 30 hours. Solvents and unreacted reagents were removed by rotary evaporation, to give the expected product (9.33 g, 96%) as a white solid.

^{1}H NMR (D_2O): δ = 6.05 (m, 1H), 5.66 (m, 2H), 3.94 (d, *J* = 7.3 Hz, 2H), 3.49 (m, 4H), 3.02 (s, 3H), 2.20 (m, 4H).

^{13}C NMR (D_2O): δ = 127.69, 124.86, 65.27, 63.10, 47.99, 47.93, 20.86.

1-allyl-1-methyl-morfolinium bromide ([ammorf]Br$^-$)

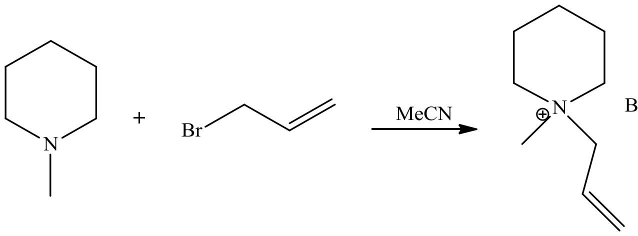


A solution of allylbromide (16.5 mL, 23.1 g, 189 mmol) and MeCN (20 mL) was added dropwise at 0 °C to a solution of *N*-methylmorpholine (20.0 mL, 18.22 g, 180 mmol) and 30 mL of MeCN, observing the precipitation of a white solid. Then the reaction mixture was heated and stirred at 50 °C for 24 hours. The reaction was cooled down to room temperature and then to 0 °C and the crystallized solid was filtered, washed with THF and dried, obtaining a white solid was obtained (35.59 g, 89%).

^{1}H NMR (DMSO-d_6): δ = 6.07 (m, 1H), 5.67 (m, 2H), 4.15 (d, *J* = 7.1 Hz, 2H), 3.93 (m, 4H), 3.39 (m, 6H), 3.11 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 128.19, 125.16, 59.77, 58.57.

1-allyl-1-methyl-piperidinium bromide ([ampip]Br$^-$)

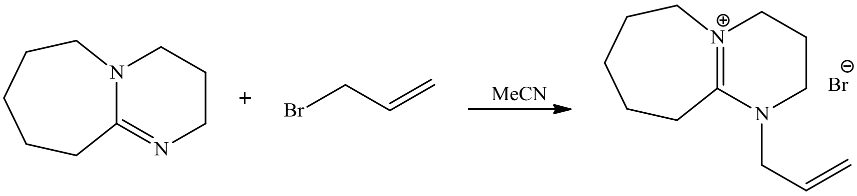


A solution of allylbromide (15.0 mL, 21.0 g, 172 mmol) and MeCN (20 mL) was added dropwise at 0 °C to a solution of *N*-methylpiperidine (20.0 mL, 16.16 g, 163 mmol) and 30 mL of MeCN, observing the precipitation of a white solid. Then the reaction mixture was heated and stirred at 50 °C for 16 hours. The reaction was cooled down to room temperature and then to 0 °C and the crystallized solid was filtered, washed with a 1:1 mixture of Et_2O/THF and then dried, obtaining a white solid was obtained (32.30 g, 90%).

^{1}H NMR (DMSO-d_6): δ = 6.05 (m, 1H), 5.64 (m, 2H), 4.00 (d, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 5.7 Hz, 4H), 2.97 (s, 3H), 1.80 (m, 4H), 1.50 (m, 2H).

^{13}C NMR (DMSO-d_6): δ = 127.52, 125.59, 59.73, 20.69, 19.21.

1-allyl-1,8-diazabicyclo[5.4.0]undecenium bromide ([aDBU]Br$^-$)

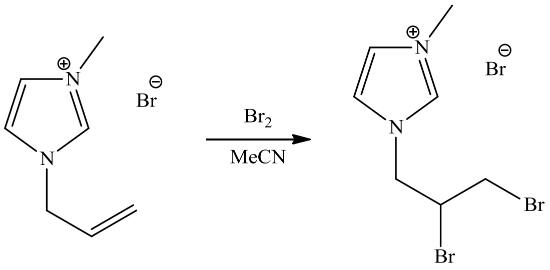


^{1}H NMR (D_2O): δ = 5.81 (m, 2H), 5.23 (t, *J* = 15.5 Hz, 1H), 4.20 (m, 2H), 3.65 (m, 6H), 2.82 (s, 2H), 2.15 (m, 2H), 1.76 (s, 6H).

^{13}C NMR (D_2O): δ = 167.08, 130.37, 118.21, 55.94, 55.74, 49.51, 47.27, 29.01, 28.45, 26.08, 22.88, 20.22.

5.2.2. 1-(2',3'-dibromopropyl)-derivatives

1-(2',3'-dibromopropyl)-3-methyl-imidazolium bromide

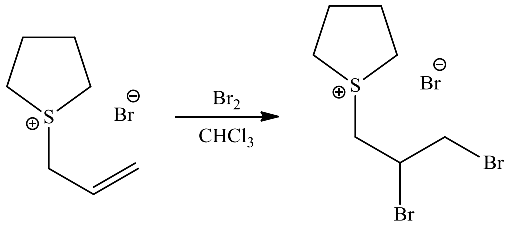


A solution of bromine (5.96 g, 37.29 mmol) and MeCN (4 mL) was added dropwise at 0 °C to a solution of 1-allyl-3-methylimidazolium bromide (7.57 g, 37.27 mmol) and 6 mL of MeCN, obtaining an orange solution. Then the reaction mixture was stirred at room temperature for 48 hours and then heated to 60 °C for other 6 hours. Solvents was removed by rotary evaporation, to give the expected product (13.43 g, 98%) as a white solid.

^{1}H NMR (D_2O): δ = 9.31 (s, 1H), 7.87 (s, 1H), 7.80 (s, 1H), 4.95 (m, 1H), 4.83 (dd, *J* = 14.6, 4.5 Hz, 1H), 4.61 (dd, *J* = 14.5, 9.0 Hz, 1H), 4.03 (d, *J* = 5.0 Hz, 2H), 3.46 (s, 3H).

^{13}C NMR (D_2O): δ = 136.51, 123.27, 122.44, 52.53, 47.38, 35.47, 32.06.

1-(2’,3’-dibromopropyl)-tetrahydrothiophenium bromide

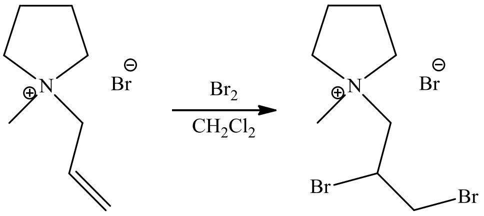


A solution of bromine (7.01 g, 43.86 mmol) and $CHCl_3$ (5 mL) was added dropwise at 0 °C to a solution of 1-allyl-tetrahydrotiophenium bromide (9.17 g, 43.85 mmol) and 15 mL of $CHCl_3$, obtaining an orange solution with the constant precipitation of a white solid. Then the reaction mixture was stirred at room temperature for 45 min and the solid filtered and washed with $CHCl_3$. Solvents was removed by rotary evaporation, to give the expected product (13.83 g, 85%) as a white solid.

^{1}H NMR (DMSO-d_6): δ = 4.94 (td, J = 9.9, 5.1 Hz, 1H), 4.06 (m, 2H), 3.89 (m, 2H), 3.58 (m, 4H), 2.19 (m, 4H).

^{13}C NMR (DMSO-d_6): δ = 47.95, 47.01, 45.41, 43.89, 37.34, 28.41, 28.30.

1-(2’,3’-dibromopropyl)-1-methyl-pyrrolidinium bromide



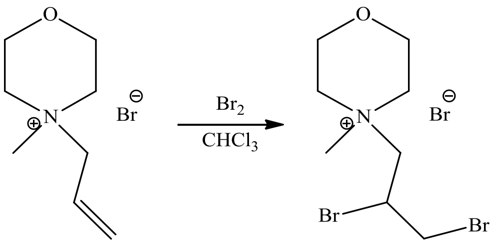
A solution of bromine (16.24 g, 101 mmol) and CH_2Cl_2 (10 mL) was added dropwise at 0 °C to a solution of 1-allyl-1-methylpyrrolidinium bromide (20.95 g, 102 mmol) and 20 mL of CH_2Cl_2, obtaining an orange solution with the constant precipitation of a white solid. Then the reaction mixture was stirred at room temperature for 24 h and then heated to reflux for 6 h. The obtained solid was filtered and washed with CH_2Cl_2.

Solvents was removed by rotary evaporation, to give the expected product (25.64 g, 70%) as a white solid.

^{1}H NMR (D_2O): δ = 4.18 (m, 1H), 4.01 (m, 2H), 3.80 (m, 2H), 3.65 (m, 4H), 3.19 (s, 3H), 2.24 (m, 4H).

^{13}C NMR (D_2O): δ = 67.76, 65.05, 64.77, 47.90, 40.52, 34.01, 20.70, 20.07.

1-(2’,3’-dibromopropyl)-1-methyl-morpholinium bromide

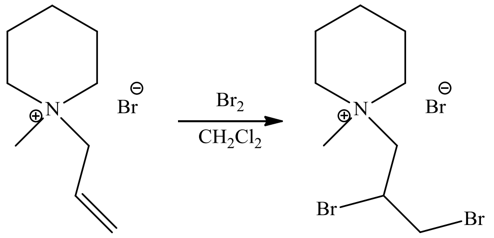


A solution of bromine (5.65 g, 35.14 mmol) and $CHCl_3$ (10 mL) was added dropwise at 0 °C to a solution of 1-allyl-1-methylpiperidinium bromide (7.86 g, 35.38 mmol) and 60 mL of $CHCl_3$, obtaining an orange solution with the constant precipitation of a white solid. Then the reaction mixture was stirred at room temperature for 1.5 h and then the obtained solid was filtered and washed with $CHCl_3$. Solvents was removed by rotary evaporation, to give the expected product (13.43 g, 99%) as a white solid.

^{1}H NMR (D_2O): δ = 4.20 (m, 2H), 4.04 (m, 5H), 3.73 (m, 6H), 3.35 (s, 3H).

^{13}C NMR (D_2O): δ = 69.20, 60.09, 59.80, 46.97, 38.37, 33.90.

1-(2’,3’-dibromopropyl)-1-methyl-piperidinium bromide

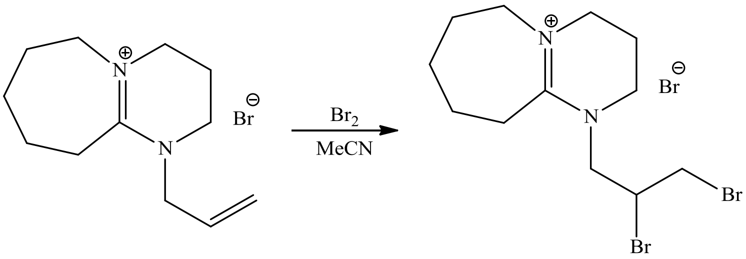


A solution of bromine (9.02 g, 56.10 mmol) and CH_2Cl_2 (10 mL) was added dropwise at 0 °C to a solution of 1-allyl-1-methylpiperidinium bromide (12.42 g, 56.42 mmol) and 25 mL of CH_2Cl_2, obtaining an orange solution with the constant precipitation of a white solid. Then the reaction mixture was stirred at room temperature for 32 h and then heated to reflux for 8 h. The obtained solid was filtered and washed with CH_2Cl_2. Solvents was removed by rotary evaporation, to give the expected product (19.23 g, 90%) as a white solid.

^{1}H NMR (D_2O): δ = 4.87 (m, 1H), 4.05 (m, 3H), 3.82 (t, *J* = 10.2 Hz, 1H), 3.55 (m, 4H), 3.21 (s, 3H), 1.92 (m, 4H), 1.65 (m, 2H).

^{13}C NMR (D_2O): δ = 68.20, 61.90, 61.65, 47.56, 39.08, 34.36, 19.87, 19.12.

1-(2’,3’-dibromopropyl)-1,8-diazabicyclo[5.4.0]undecenium bromide ([aDBU]Br$^-$)



^{1}H NMR (D_2O): δ = 4.59 (m, 1H), 4.16 (m, 1H), 3.96 (m, 2H), 3.80 (m, 1H), 3.55 (m, 5H), 2.91 (m, 1H), 2.06 (m, 5H), 1.71 (m, 4.83).

^{13}C NMR (D_2O): δ = 167.23, 56.68, 54.53, 48.58, 47.89, 47.04, 33.19, 27.78, 27.40, 24.63, 21.97, 18.86.

5.2.3. Bis(trifluoromethylsulfonyl)-imide metathesis

1-(2’,3’-dibromopropyl)-3-methyl-imidazolium bis(trifluoromethylsulfonyl)-imide

To a solution of 1-(2’,3’-dibromopropyl)-3-methyl-imidazolium bromide (7.11 g, 19.43 mmol) in 60 mL of water, 5.75 g (20.40 mmol) of $LiTf_2N$ were added. The reaction mixture was magnetically stirred for 7 hours at room temperature, until formation of a biphasic system. After taking out water phase, at the organic one dichloromethane was added and the whole system washed with water (3 × 15 mL). The organic phase was then dried by evaporation of the solvent at reduced pressure obtaining the pure product (10.27 g, 94%).

The same procedure has been used to prepare the below ionic liquids, reported with the respective yields and NMR spectra:

^{1}H NMR (DMSO-d_6): δ = 9.19 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 4.91 (td, *J* = 9.7, 5.5 Hz, 1H), 4.78 (dd, *J* = 14.6, 4.1 Hz, 1H), 4.60 (dd, *J* = 14.6, 8.8 Hz, 1H), 4.01 (dd, *J* = 5.6, 2.0 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 137.42, 123.82, 122.83, 119.53 (q, *J* = 321.8 Hz), 53.18, 50.49, 35.98, 35.06.

1-(2’,3’-dibromopropyl)-tetrahydrothiophenium bis(trifluoromethylsulfonyl)-imide: 95%

^{1}H NMR (DMSO-d_6): δ = 4.91 (m, 1H), 4.04 (m, 2H), 3.87 (m, 2H), 3.58 (m, 4H), 2.21 (m, 4H).

^{13}C NMR (DMSO-d_6): δ = 119.53 (q, *J* = 321.8 Hz), 48.06, 46.84, 45.40, 43.90, 37.19, 28.38, 28.28.

1-(2’,3’-dibromopropyl)-1-methyl-pyrrolidinium bis(trifluoromethylsulfonyl)-imide: 96%

^{1}H NMR (DMSO-d_6): δ = 5.15 M, 1H), 4.12 (dd, J = 10.9, 4.4 Hz, 1H), 4.00 (m, 3H), 3.58 (m, 4H), 3.12 (s, 3H), 2.11 (m, 4H).

^{13}C NMR (DMSO-d_6): δ = 119.52 (q, J = 321.9 Hz), 67.81, 64.30, 47.62, 43.61, 37.49, 20.91, 20.45.

1-(2’,3’-dibromopropyl)-1-methyl-morpholinium bis(trifluoromethyl-sulfonyl)imide: 88%

^{1}H NMR (DMSO-d_6): δ = 5.25 (m, 1H), 4.15 (m, 3H), 3.99 (m, 5H), 3.56 (m, 4H), 3.36 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 119.52 (q, J = 321.6 Hz), 69.47, 59.72, 59.58, 45.96, 41.83, 37.79.

1-(2’,3’-dibromopropyl)-1-methyl-piperidinium bis(trifluoromethylsulfonyl)-imide: 96%

^{1}H NMR ($CDCl_3$): δ = 4.55 (m, 1H), 3.98 (m, 3H), 3.72 (m, 1H), 3.55 (m, 4H), 3.25 (s, 3H), 1.97 (m, 4H), 1.76 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 119.52 (q, J = 321.9 Hz), 68.51, 63.12, 63.01, 49.29, 39.10, 34.70, 20.49, 20.14.

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Section 2

Applications of New ILs

6. Wacker-Tsuji reaction in ionic liquids

Oxidation is a core technology for converting petroleum-based materials to useful chemicals of a higher oxidation state and there is an increasing demand for selective and mild oxidation methods in modern organic synthesis. However, oxidation is among the most problematic process. During the last two decades there has been a spectacular development in this field and a large number of novel and useful oxidation reactions have been discovered. Significant progress has been achieved within the area of catalytic oxidation, of particularly interest in homogeneous catalysis, in fact it is the field where the largest contribution of homogeneous catalysis to industrial organic chemistry are found and has led to a range of selective and mild processes, also because they involve the use of soluble metal salts or complexes as the catalyst. For example, in the oxidation of alcohols and epoxidation of olefins enormous progress has been achieved over the last decade towards green methods, notably using homogeneous metal complexes. In this field, even for the production of bulk chemicals, homogeneous catalysis appear to compete effectively with heterogeneous one Table 6.1.[1]

Table 6.1. Bulk chemicals via catalytic oxidation processes.

Product	Reactant	Year	10^6 t/y	Oxidant	Process
Terephtalic acid	*p*-Xylene	1987	10.1	O_2	Homolytic
Ethylene oxide	Ethylene	1984	8.5	“	Heterolytic
Phenol	Toluene, cyclohexane, benzene/propilene	1987	4.2	“	Homolytic
Formaldehyde	Methanol	1984	3.9	“	Heterolytic
Acetaldehyde	Ethylene	1986	3.0	“	“
Vinyl acetate	Ethylene/AcOH	1986	2.6	“	“
Acetic acid	Acetaldehyde, light paraffins	1986	2.3	“	Homolytic
Propilene oxide	Propilene	1985	1.3	Bu^tOOH, PhEtOOH	Heterolytic

These reactions may be based on organocatalysis, metal catalysis or biocatalysis. In this regard enantioselective catalytic oxidation reactions are of particular interest.

The mechanisms of these reactions are very different and can be broadly classified into three categories. The first reactions (*e.g.*, conversion of ethylene to acetaldehyde) involve organometallic and redox chemistry of palladium. In the Wacker oxidation the nucleophilic attack by water on coordinated ethylene being a central reaction of the overall process. The second class (*e.g.*, oxidation of cyclohexane and *p*-xylene by air), on the other hand, involves chain reactions of organic radicals. In these reactions soluble cobalt and manganese ions catalyse the initiation steps. Reactions such as these, where the organic substrates are directly oxidized by air or dioxygen, are often called *autoxidation reactions*. The last reaction class (*e.g.*, conversion of propylene to propylene oxide) involves selective oxygen atom transfer chemistry, which has undergone a remarkable growth in the past two decades. The source of the oxygen atom in this type of reaction is not dioxygen but some other oxidizing agent, such as an organic hydroperoxide.[2]

6.1. Green oxidation processes

In contrast to reductions, traditionally, the production of many fine chemicals involved oxidations with stoichiometric quantities of, for example, permanganate, dichromate or periodate, resulting in the concomitant generation of copious amounts of inorganic salt-containing effluent. Nitric acid, the most conventional industrial oxidant, is cheap but unavoidably forms various nitrogen oxides.[3] The pressure of increasingly stringent environmental regulation is also providing a stimulus for the deployment of catalytic oxidations in the manufacture of fine chemicals.[4] In practice this implies an implementation of catalytic technologies which allow the use of oxygen and hydrogen peroxide (which produces water as the side product) as stoichiometric oxidants. Catalytic oxidation with O_2 is widely used in the manufacture of bulk petrochemicals.[5] In some cases, *e.g.* stereoselective conversion where a highly added benefit of the product prevails, the use of other oxidants will be considered as well.

6.2. Mechanisms of metal-catalysed oxidations

By contrast with many other simple diatomic omonuclear molecules, the oxygen molecule ground state (O_2, or dioxygen) is a triplet as it has two unpaired electrons with parallel spin (the highest occupied molecular orbitals (HOMO's) are a pair of π^* orbitals of identical energy), consequently, dioxygen may be regarded as a diradical, a formulation that is very useful in understanding its chemistry.

The direct reaction of $^3O_2$ with singlet organic molecules to give singlet products is a spin forbidden process with a very low rate. Fortunately, this precludes the spontaneous combustion of living matter, a thermodynamically very favourable process.[6]

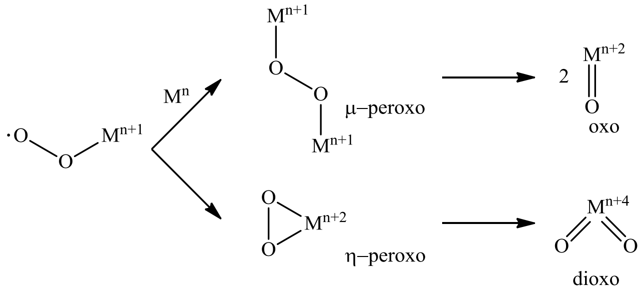
One way of circumventing this activation energy barrier involves a free radical pathway in which a singlet molecule reacts with $^3O_2$ to form two doublets (free radicals) in a spin-allowed process (first entry of Scheme 6.1).

$$\mathrm{RH} + {}^3\mathrm{O}_2 \longrightarrow \mathrm{R}^{\bullet} + \mathrm{HO}_2^{\bullet}$$

$$\mathrm{M}^n + \mathrm{O}_2 \longrightarrow \mathrm{M}^{n+1}\mathrm{OO}^{\bullet}$$

Scheme 6.1. Triplet oxygen reaction.

A second way to overcome this spin conservation obstacle is *via* reaction of $^3O_2$ with a paramagnetic (transition) metal ion, affording a superoxometal complex (second entry of Scheme 6.1). Subsequent inter- or intramolecular electron-transfer processes can lead to the formation of a variety of metal-oxygen species (Scheme 6.2) which may play a role in the oxidation of organic substrates.



Scheme 6.2. Metal–oxygen species.

In both one-electron steps processes: electrons added to the O_2 molecule populate antibonding (π^*) orbitals and weaken the O–O bond. This effect is evident in both the O–O bond length and its dissociation energy. This makes the resulting superoxo (O_2^{2-}) and peroxo ($O_2^{2\bullet}$) species much more reactive. This process is, however, highly endothermic (up to 50 kcal mol^{-1}) and is observed at moderate temperatures only with very reactive molecules that afford resonance stabilized radicals, *e.g.* reduced flavins.

As rationalized by Sheldon and Kochi,[7] basically all (metal catalysed) oxidations, with dioxygen or peroxide reagents, either under homogeneous or heterogeneous conditions, can be divided into two types on the basis of their mechanism: *homolytic* and *heterolytic*. The former involves free radicals as reactive intermediates. Such reactions can occur with most organic substrates and dioxygen, in the presence or absence of metal catalysts. This ubiquity of free radical processes in dioxygen chemistry renders mechanistic interpretation more difficult than in the case of hydrogenations or carbonylations where there is no reaction in the absence of the catalyst.

Heterolytic oxidations generally involve the (metal-mediated) oxidation of a substrate by an active oxygen compound, *e.g.* H_2O_2 or RO_2H. Alternatively, stoichiometric oxidation of a substrate by a metal ion or complex is coupled with the reoxidation of the reduced metal species by the primary oxidant (*e.g.* O_2 or H_2O_2).

Homolytic oxidations involve free radical intermediates, are catalysed by first row transition metals and characterized by one-electron redox steps. Some of these reactions are catalysed by metal as Co^{3+}, Mn^{3+} or Cu^{2+}. These metals vary considerably in their redox properties. However, the redox potentials change substantially with changes in solvent and changes in the ligand bound to the metal ion.

In homolytic reactions the hydrocarbon to be oxidized is not generally coordinated to the metal and is oxidized outside the coordination sphere via a radical chain. These processes are common and constitute the basis for several very important industrial applications. However radical chains are difficult to control, they do not often preserve the configuration of the substrate and typically lead to the formation of a wide variety of products. Consequently, reactions involving one-electron processes with dioxygen as the oxidant generally show only moderate to low selectivity towards the desired product.

By contrast heterolytic oxidations generally require activation of the substrate by coordination to the metal and are often highly selective and stereospecific. They do not involve free radical intermediates and use second- and third row transition metals which conserve their oxidation state or change it by a two electron redox step.

6.2.1. Homolytic mechanisms

Dioxygen reacts with organic molecules, *e.g.* hydrocarbons, via a free radical pathway. The corresponding hydroperoxide is formed in a free radical chain process as showed below.

Initiation:

$$In_2 \overset{k_i}{\rightarrow} 2In^{\bullet}$$

$$In^{\bullet} + RH \rightarrow InH + R^{\bullet}$$

Propagation:

$$R^{\bullet} + O_2 \xrightarrow{very\,fast} RO_2^{\bullet}$$

$$RO_2^{\bullet} + RH \overset{k_p}{\rightarrow} RO_2H + R^{\bullet}$$

Termination:

$$RO_2^{\bullet} + RO_2^{\bullet} \overset{k_f}{\rightarrow} RO_4R \rightarrow nonradical\,products$$

The reaction is autocatalytic, *i.e.* the alkyl hydroperoxide accelerates the reaction by undergoing homolysis to chain initiating radicals, and such processes are referred to as autoxidations.[8]

The susceptibility of any particular substrate to autoxidation is determined by the ratio $k_p/\sqrt{(2k_f)}$, which is usually referred to as its oxidizability.[9]

The reaction can be started by adding an initiator which undergoes homolytic thermolysis at the reaction temperature to produce chain-initiating radicals. The initiator could be the alkyl hydroperoxide product although relatively high temperatures (> 100 °C) are required for thermolysis of hydroperoxides. Alternatively, chain-initiating radicals can be generated by the reaction of trace amounts of hydroperoxides with variable valence metals, *e.g.* cobalt, manganese, iron, cerium etc. The corresponding alkoxy and alkylperoxy radicals are produced in one-electron transfer processes (Scheme 6.3).

$$\begin{array}{rcl} RO_2H + Co^{II} & \longrightarrow & RO^{\bullet} + Co^{III}OH \\ RO_2H + Co^{III} & \longrightarrow & RO_2^{\bullet} + Co^{II} + H^+ \\ \hline 2RO_2H & \xrightarrow{Co^{II}/Co^{III}} & RO^{\bullet} + RO_2^{\bullet} + H_2O \end{array}$$

Scheme 6.3. Metal initiated and mediated autoxidation.

In such processes the metal ion acts (in combination with ROOH) as an initiator rather than a catalyst. It is important to note that homolytic decomposition of alkyl hydroperoxides via one-electron transfer processes is generally a competing process even with metal ions that catalyse heterolytic processes with hydroperoxides. Since dioxygen can be regenerated via subsequent chain decomposition of the alkyl hydroperoxide this can lead to competing free radical autoxidation of the substrate.

Another class of metal catalysed autoxidations involves the direct one-electron oxidation of the substrate by the oxidized form of the metal catalyst. For example, the autoxidation of alkylaromatics in acetic acid in the presence of relatively high concentrations (~ 0.1 M) of Co(III) acetate involves rate-limiting one electron transfer oxidation of the alkylbenzene to the corresponding cation radical (Scheme 6.4).

$$\begin{array}{rcl} ArCH_3 + Co^{III} & \longrightarrow & [ArCH_3]^{+\bullet} + Co^{II} \\ [ArCH_3]^{+} & \longrightarrow & ArCH_2^{\bullet} + H^+ \\ ArCH_2^{\bullet} + O_2 & \longrightarrow & ArCH_2O_2^{\bullet} \\ ArCH_2O_2^{\bullet} + Co^{II} & \longrightarrow & ArCHO + HOCo^{II} \end{array}$$

Scheme 6.4. Direct homolytic oxidation of benzylic compounds.

This is followed by elimination of a proton to afford the corresponding benzylic radical, which subsequently forms a benzylperoxy radical by reaction with dioxygen. The primary products from substituted toluenes are the corresponding aldehydes, formed by reaction of benzylperoxy radicals with Co(II) (which simultaneously regenerates the Co(III) oxidant). The usual reaction of alkylperoxy radicals with the toluene substrate is largely circumvented by the efficient trapping of the benzylperoxy radical with the relatively high concentration of Co(II) present. The aldehyde product undergoes facile autoxidation to the corresponding carboxylic acid and metal-catalysed autoxidation of methylaromatics is a widely used method for the production of carboxylic acids. Since cobalt is usually added as

Co(II), reactive substrates such as aldehydes or ketones are often added as promoters to generate the high concentrations of Co(III) necessary for initiation of the reaction.

6.2.2. Heterolytic mechanisms

Catalytic oxidations with dioxygen can also proceed via heterolytic pathways which do not involve free radicals as intermediates. They generally involve a two-electron oxidation of a (coordinated) substrate by a metal ion. The oxidized form of the metal is subsequently regenerated by reaction of the reduced form with dioxygen. Typical examples are the Pd(II)-catalysed oxidation of alkenes (Wacker process) and oxidative dehydrogenation of alcohols (Scheme 6.5).

$$R_2CHOH + Pd^{II} \longrightarrow R_2C{=}O + Pd^0 + H_2O$$

Scheme 6.5. Oxidative alcohols dehydrogenation.

In a variation on this theme, which pertains mainly to gas phase oxidations, an oxometal species oxidizes the substrate and the reduced form is subsequently re-oxidized by dioxygen (Scheme 6.6). This is generally referred to as the Mars-van Krevelen mechanism.[10]

$$M{=}O + S \longrightarrow M + SO$$

$$M + 1/2\ O_2 \longrightarrow M{=}O$$

Scheme 6.6. Mars-van Krevelen mechanism.

A wide variety of oxidations mediated by monooxygenase enzymes are similarly thought to involve oxygen transfer from a high-valent oxoiron intermediate to the substrate (although the mechanistic details are still controversial).[11] However, in this case a stoichiometric cofactor is necessary to regenerate the reduced form of the enzyme resulting in the overall stoichiometry shown in Scheme 6.7.

$$RH + O_2 + DH_2 \xrightarrow{\text{monooxigenase}} ROH + D + H_2O$$

Scheme 6.7. Stoichiometry in monooxigenases mediated oxidations (D/DH = cofactors).

6.2.3. Catalytic oxygen transfer

Another way to avoid the need for a sacrificial reductant is to use a reduced form of dioxygen, *e.g.* H_2O_2 or RO_2H, as a single oxygen donor. Such a reaction is referred to as a catalytic oxygen transfer and can be described by the general equation shown in Scheme 6.8.

$$S + XOY \longrightarrow SO + XY$$

S = substrate; SO = oxidized substrate

XOY = H_2O_2, $R_{20}H$, R_3NO, NaOCl, $KHSO_5$, etc.

Scheme 6.8. Catalytic oxygen transfer.

Catalytic oxygen transfer processes are widely applicable in organic synthesis. Virtually all of the transition metals and several main group elements are known to catalyse oxygen transfer processes.[12] A variety of single oxygen donors can be used (Table 6.2) in addition to H_2O_2 or RO_2H.

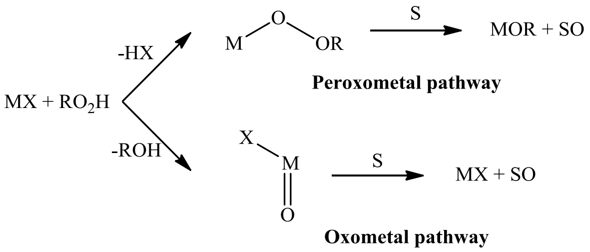
Table 6.2. Singlet oxygen atoms donors. ^{a}Calculated on 100% H_2O_2; ^{b}30% aq. H_2O_2; ^{c}Assuming only one oxygen atom is utilised.

Donor	% Active Oxygen	Product
H_2O_2	47.0^a $(14.1)^b$	H_2O
N_2O	36.4	N_2
NaO_2Cl	35.6	NaCl
O_3	33.3	O_2
HNO_3	25.4	NO_x
NaOCl	21.6	NaCl
CH_3CO_3H	21.1	CH_3CO_2H
Bu^tOOH	17.8	Bu^tOH
NaOBr	13.4	NaBr
$KHSO_5$	10.5	$KHSO_4$
$NaIO_4$	7.2^c	$NaIO_3$
PhIO	7.3	PhI

Next to price and ease of handling, two important considerations which influence the choice of oxygen donor are the nature of the co-product and the weight percentage of available oxygen. The former is important in the context of environmental sustainability and the latter bears directly on the volumetric productivity (kg product per unit reactor volume per unit time). With these criteria in mind it is readily apparent that hydrogen peroxide, which affords water as the co-product, is generally the preferred oxidant. The co-product from organic oxidants, such as RO_2H and amine oxides, can be recycled via reaction with H_2O_2. The overall process produces water as co-product but requires one extra step compared to the corresponding reaction with H_2O_2. With inorganic oxygen donors environmental considerations are relative. Sodium chloride and potassium bisulfate are obviously preferable to the heavy metal salts (*e.g.*, Cr, Mn, etc.) produced in classical stoichiometric oxidations. Generally speaking, inorganic oxidants are more difficult to recycle, in an economic manner, than organic ones. Indeed, the ease of recycling may govern the choice of oxidant, *e.g.* NaOBr may be preferred over NaOCl because NaBr can, in principle, be re-oxidized with H_2O_2. As noted earlier, a disadvantage of H_2O_2 and RO_2H as oxygen donors is the possible competition from metal-catalysed homolytic decomposition leading to free radical oxidation pathways and/or low selectivity based on the oxidant.[3]

Heterolytic oxygen transfer processes can be divided into two categories based on the nature of the active oxidant: an oxometal or a peroxometal species (Scheme 6.9). Catalysis by early transition metals (Mo, W, Re, V, Ti, Zr) generally involves high-valent peroxometal complexes whereas later transition metals (Ru, Os), particularly first row elements (Cr, Mn, Fe) mediate oxygen transfer via oxometal species. Some elements, *e.g.* vanadium, can operate via either mechanism, depending on the substrate. Although the pathways outlined in Scheme 6.9 pertain to peroxidic reagents analogous schemes involving M=O or MOX (X = ClO, IO_4, HSO_5, R_3NO etc.) as the active oxidant, can be envisaged for other oxygen donors.

Reactions that typically involve peroxometal pathways are alkene epoxidations, alcohol oxidations and heteroatom (N and S) oxidations. Oxometal species, on the other hand, are intermediates in the oxidation of alkane, benzylic and allylic C-H bonds and the dihydroxylation and oxidative cleavage of olefins, in addition to the above-mentioned transformations.[3]



Scheme 6.9. Peroxometal versus oxometal pathways.

For the sake of completeness oxygen transfer processes can be mediated by organic catalysts which can be categorized on the same basis as metal catalysts. For example, ketones catalyse a variety of oxidations with monoperoxysulphate ($KHSO_5$).[13] The active oxidant is the corresponding dioxirane and, hence, the reaction can be construed as involving a "peroxometal" pathway. Similarly, TEMPO-catalysed oxidations of alcohols with hypochlorite involve an oxoammonium salt as the active oxidant, *i.e.* an "oxometal" pathway.[14]

6.3. Hydrogen peroxide as oxidant[15]

Hydrogen peroxide has a number of advantages compared to other low cost oxidants. The first one is that some of these oxidants like for example sodium perborate, potassium hydroperoxysulfate or even many organic peroxy acids are prepared from hydrogen peroxide itself. This implies that their use while leading to the ultimate consumption of hydrogen peroxide, on the other hand it requires further chemical operations and plant facilities necessary to the recovery of the reduction products and their subsequent conversion into the active form.[16]

A second advantage comes from the active oxygen content (Table 6.2). This is calculated as the ratio between the weight of oxygen that can be transferred to a suitable substrate and the molecular weight of the oxidant. As is clear from Table 6.2, H_2O_2 largely exceeds all the others with the exception of ozone which suffers from being highly noxious and requiring costly equipment for its generation.[17]

A third advantage comes from another economic consideration: the lower amount of effluents that is a consequence of the higher oxygen content. As can be seen in Table 6.3, if a theoretical yield of 100% is assumed in all cases, H_2O_2 produces a far lower amount of effluent (H_2O) compared to all the others. Although in practice 100% yields are rarely obtained, the potential economic advantages intrinsic in the use of hydrogen peroxide are quite evident.

Table 6.3. Amounts of oxidant required and product formed to produce 1 kg of propylene in the reaction below.

Oxidant (kilos)	**Product (kilos)**
H_2O_2 (0.586)	H_2O (0.310)
Bu^tOOH (1.551)	Bu^tOH
NaClO (1.283)	NaCl (1.007)
$KHSO_5$ (2.622)	$KHSO_4$ (2.346)
$PhIO_4$ (3.790)	PhI (3.514)

$$C_3H_6 + \text{oxidant} \longrightarrow C_3H_6O + \text{side product}$$

Industrially, hydrogen peroxide is used mainly as a non-selective oxidant, *i.e.* for paper, textile and cellulose bleaching, water purification and, particularly in Europe, in the manufacture of perborate and percarbonate used in detergents. Just the 10% of the total world production is estimated to be employed in the manufacture of organic chemicals where the use of alkylhydroperoxide can be seen.

Like Bu^tOOH or PhEtOOH, H_2O_2 is relatively stable and requires to be converted in a more active form in order to be effective as oxidant. However, unlike Bu^tOOH or PhEtOOH two major drawbacks have reduced the use of hydrogen peroxide in reaction with organic chemicals.

The first one is related to the unavoidable presence of water that is both the reduction product and the solvent of commercial hydrogen peroxide. For example, several patents about conversion of propylene to propylene oxide use peracids (formed in situ from H_2O_2) as actual oxidants.[18] In these cases the peracid aqueous solution causes both problems in contact between the oxidant and the hydrophobic olefin and oxirane ring opening with subsequent lowering of yields. In all cases the problem was solved, for example, by producing the oxidant (perpropionic acid) from propionic acid and H_2O_2 in aqueous H_2SO_4 or removing water by continuous distillation during the reaction and using metaboric acid $(HBO)_n$ to adsorb the residual water.

The second major disadvantage with respect to the above hydroperoxides is the lower stability of aqueous hydrogen peroxide with respect to radical decomposition. For example, Ti(IV) species are excellent catalysts for the stereoselective epoxidation of olefins with Bu^tOOH, while on the other hand, species of Ti(IV) decompose catalytically H_2O_2.

More general, the basic hazardous properties and causes of incidents when working with hydrogen peroxide can be attributed to the followings:

- Decomposition to oxygen and water with the evolution of heat. The decomposition rate increases with temperature by a factor of approximately 2.2 times per 10 °C rise over the range of 20-100 °C.[19]
- Pressurization due to oxygen evolution. Hydrogen peroxide, in all forms, is thermodynamically unstable and continuously dismutates to water and oxygen. This decomposition is extremely important in handling it because of the generation of gas and heat (-98.3 kJ mol^{-1}). Typically, commercial material loses less than 1% m/m of its active oxygen per year, however, 20 metric tons of 70% m/m hydrogen peroxide losing only 0.3% m/m of its active oxygen per year will evolve 13 dm^3 of oxygen per day, enough to pressurize sealed equipment or give oxygen enrichment in the headspace of the container.
- Decomposition can be further accelerated by the presence of soluble impurities or by contact with active surfaces.[20] High and low pH will also destabilize hydrogen peroxide. pH affects the activity of the catalytic impurities and the stabilizers which are present.[21] Self-heating can rapidly accelerate the decomposition rate of destabilized hydrogen peroxide. Large amounts of oxygen and steam can be formed quickly (Table 6.4).

Table 6.4. Decomposition data for hydrogen peroxide.

H_2O_2 (%)	Isothermal volumes of H_2O_2	Adiabatic volumes of O_2 and steam	Adiabatic decomposition temperature (°C)
100	512	6643	996
60	263.3	1672	100
40	163.5	932	100
10	36.6	45	89

- The hazard of an explosion increases rapidly when hydrogen peroxide is mixed with organic materials. The most sensitive compositions are those that contain stoichiometric quantities of hydrogen peroxide, required to completely oxidize organic compound to water and carbon dioxide. This critical composition can also result from mixtures with organics if excess unreacted hydrogen peroxide is concentrated. It should be noted that reaction between hydrogen peroxide and organic compounds may take place yielding intermediates which have completely different explosive properties. Thus, mixtures with formic acid produce on standing performic acid and the resulting mixture is much more sensitive than the original one.[22] Hydrogen peroxide is a very reactive chemical, and an extremely powerful oxidizer under certain circumstances. Substitution reactions with organic reagents lead to a variety of peroxygen compounds, *e.g.* with carboxylic acids percarboxylic acids are formed. Furthermore, a number of compounds, such as sodium carbonate and urea, form peroxyhydrates with hydrogen peroxide. Hydrogen peroxide of strength higher than about 40% m/m can also form explosive mixtures with organic compounds. Such mixtures can equate to conventional high explosives in power, but may be much more sensitive in terms of detonation (Table 6.5).

Table 6.5. Explosive power and sensitivity of various substances.

Substance	Explosive power	Sensitivity (kg cm)
Nitroglycerine	52	2-5
85% m/m H_2O_2/glycerol	46	10-15
85% m/m H_2O_2/polyethylene	30	22
Picric acid	32	75
Trinitrotoluene	30	150
97% m/m H_2O_2	17	Insensitive

- Spontaneous reactions of hydrogen peroxide/sulphuric acid/water/organic mixtures. These reactions can accelerate rapidly and terminate violently, and can be outside the predicted explosive area.

- Vapour phase hydrogen peroxide explosions. Hydrogen peroxide vapour of concentration above 39% m/m at atmospheric pressure is explosive.

- Oxygen enrichment. Oxygen evolved by decomposition may give rise to atmospheres with a high oxygen content. Oxygen-rich flammable atmospheres have low ignition energies (Table 6.6). The rate of burning is also increased. Flame arrestors and other flame-proofing provisions may be ineffective. Explosive limits are broadened, but there are no significant changes to the lower explosive limit and flash point. Some vapors and gases which are not flammable in air are flammable in oxygen, for example, some chlorinated solvents.

Table 6.6. Minimum ignition energies (mJ) in air and oxygen.

Substance	In air	In oxygen
Methane	0.3	0.003
Acetone	1.15	0.0024
Diethyl ether	0.20	0.0013

Hydrogen peroxide and peroxycarboxylic acids (RCO_3H) are normally relatively stable, but as mentioned above they can be rendered unstable by a wide variety of contaminants, particularly at excessively high temperatures. Cleanliness, good housekeeping and proper storage are therefore essential. The major contaminants that cause decomposition are combustible organic materials (*e.g.*, cotton, wool, paper) or metals, particularly transition metals and their salts (Table 6.7).[23]

Table 6.7. Effect of added metal ions on the decomposition rate of hydrogen peroxide.

Metal ion	Amount added (ppm)	Active oxygen lost in 24 h at 100 °C (%)
None	-	2
Al(III)	10	2
Sn(IV)	10	2
Zn(II)	10	10
Fe(III)	1.0	15
Cu(II)	0.01	24
Cr(II)	0.1	96

When working with active oxygen compounds, steps should be taken to ensure that mixtures do not occur in the detonable area during the reaction or processing phases. It should be noted that when using 35% m/m or less hydrogen peroxide then it is unlikely that detonable compositions will be formed. Therefore, use of 35% m/m or less hydrogen peroxide should be employed wherever possible and higher strengths discouraged.

6.3.1. Physical properties of hydrogen peroxide

Hydrogen peroxide is a clear, colourless liquid which is completely miscible with water. Table 6.8 compares some of the important properties of hydrogen peroxide-water mixtures.

Table 6.8. Physical properties of hydrogen peroxide and water. Calculated for [a]100%, [b]35%, [c]50% and [d]75% H_2O_2 water solutions.

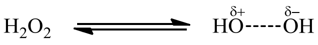
Property	$H_2O_2^a$	Water
Melting point (°C)	-0.43	0.0
Boiling point (°C)	150.2	100
	107.9[b]	
	113.8[c]	
	125.5[d]	
Freezing point (°C)	-33.0[b]	0
	-52.2[c]	
	-40.3[d]	
Heat of melting (J g^{-1})	368	334
Heat of vaporization (J g^{-1} K^{-1})		
25 °C	1519	2443
b.p.	1387	2258
Specific heat (J g^{-1} K^{-1})		
Liquid (25 °C)	2.629	4.182
Gas (25 °C)	1.352	1.865
Relative density (g cm^{-3})		
0 °C	1.4700	0.9998
20 °C	1.4500	0.9980
25 °C	1.4425	0.9971
Viscosity (mPa s)		
0 °C	1.819	1.792
20 °C	1.249	1.002
Critical temperature (°C)	257	374.2
Critical pressure (MPa)	20.99	21.44
Refractive index (η_D^{20})	1.4084	1.3330

Hydrogen peroxide and its highly concentrated aqueous solutions (> 65% m/m) are soluble in a range of organic solvents, such as carboxylic esters. Hydrogen peroxide and water do not form azeotropic mixtures and can be completely separated by distillation. Most workers, however, obtain 100% m/m hydrogen peroxide by fractional crystallization of highly concentrated solutions. Pure 100% m/m hydrogen peroxide is usually only of academic interest and is not produced on an industrial scale, although it may become important in the future.

The long liquid range of hydrogen peroxide indicates a degree of association, and the very high dielectric constant indicates the presence of linear chains. On the basis of the high dielectric constant, hydrogen peroxide is a good ionizing medium. Generally, strong acids in hydrogen peroxide remain strong. For example, plots of equivalence conductance versus the half-power of concentration yield straight lines which are characteristic of completely dissociated electrolytes.

6.3.2. Activation methods

For the half-reaction $H_2O_2 + 2H^+ + 2e^- \rightarrow 2H_2O$, hydrogen peroxide has a E^0 of 1.76 V. On the face of the E^0 value alone, one would expect the compound to be a relatively powerful oxidant (Table 6.9). However, hydrogen peroxide is, in fact, a relatively weak oxidizing agent. It can achieve some oxidations unaided, *e.g.* it reacts slowly with substrates such as olefins, aromatic hydrocarbons, alkanes, etc., but for the majority of applications, it requires activation in some way or other. In order to take advantage of its power, it may be required to “activate” the peroxide functionality, improving its reactivity toward a substrate through the formation of an intermediate peroxide, whose rate constant with the given substrate is significantly larger than that of hydrogen peroxide itself.[24]



$$H_2O_2 \rightleftharpoons H\overset{\delta+}{O}\text{-----}\overset{\delta-}{O}H$$

Scheme 6.10. Polarization of hydrogen peroxide.

The low intrinsic reactivity of hydrogen peroxide is actually an advantage, since it means that it can be selectively activated to perform a given oxidation. Although hydrogen peroxide is a weak oxidant, it does have both electrophilic and nucleophilic properties. The electrophilic character arises from the fact that the O–O bond is easily polarized (Scheme 6.10).

Table 6.9. Oxidation potentials of a range of oxidants.

Oxidant	**E^0 (V)**
F_2	3.00
$OH^{\bullet}$	2.80
$^1O_2$	2.42
O_3	2.01
H_2SO_5	1.81
H_2O_2	1.76
$KMnO_4$	1.70
HO_2^-	1.70
HOCl	1.49
Cl_2	1.27
ClO_2	1.27
O_2	1.20

Undissociated hydrogen peroxide behaves, to some extent, as a nucleophile, being about 104 times more nucleophilic than water. For example, hydrogen peroxide readily adds to carbonyl bonds giving rise to hydroxyhydroperoxides (peracetals and perketals). Such compounds are often used as polymerization initiators on account of their radical decomposition at moderate temperatures (O–O bond homolysis). Neutral hydrogen peroxide can also react with activated acyl compounds such as anhydrides to give peroxyacids. In alkaline solution, hydrogen peroxide dissociates (Scheme 6.11) showing a pK_a of 11.6.

$$H_2O_2 \rightleftharpoons H^+ + HO_2^-$$

Scheme 6.11. Dissociation of hydrogen peroxide under alkaline pH.

The perhydroxyl anion, HO_2^-, is a powerful nucleophile and will attack substrates such as electron-deficient olefins (*e.g.*, α,β-unsaturated ketones) and aldehydes. The perhydroxyl anion is also of value in bleaching and product purification, particularly of natural products. In addition, it can be used to generate more powerful oxidants by mixing with electron-deficient acyl compounds (giving peroxyacids) or with nitriles (Scheme

6.12). Under strongly acidic conditions (normally non-aqueous), hydrogen peroxide can be protonated or converted to the equivalent of the hydroxyl cation (Scheme 6.13).

$$RCOX + HO_2^- \rightleftharpoons RCO_3H + X^-$$

Scheme 6.12. Generation of more powerful oxidants via the use of perhydroxyl anion.

$$H_2O_2 + H^+ \rightleftharpoons H_3O_2^+$$

$$H_2O_2 + HA \rightleftharpoons H_3O_2 + A^+$$

Scheme 6.13. Action of strongly acidic conditions on hydrogen peroxide.

The resulting strong electrophile can be used in some oxidations, notably phenol hydroxylation, however the required extreme acidic conditions limit the applicability of this oxidant species; many products tend to react further by oxidation or acid catalysed condensation or rearrangement.

The O–O bond in hydrogen peroxide is relatively weak,[25] ~ 213 kJ mol^{-1}, and is susceptible to homolysis by a variety of methods including thermal, photolytic, radiolytic and metal-redox. The active species produced is the hydroxyl radical; when generated by UV irradiation at 254 nm, two hydroxyl radicals per mole of hydrogen peroxide are produced. In terms of oxidizing power, it is second only to fluorine. This high oxidizing power correlates to a relative lack of selectivity as an oxidant, and hence the hydroxyl radical has a limited role in synthesis. The use of hydrogen peroxide-UV systems is, however, known in water disinfection, and is growing in effluent treatment, where the power to degrade refractory organics to products treatable by biological processes is of value.

Due to the relative stability of aqueous solutions of hydrogen peroxide, the general aim is to increase its reactivity by converting H_2O_2 into a different, more active species. This is accomplished by three general methods:[26]

- By reacting H_2O_2 with metals capable to generate metal peroxy or hydroperoxy species, where the peroxo bond remains intact. These are formed for instance with Ti(IV), V(V), Mo(VI), W(VI) (d^0 metal centers) or with Pd(II) and Pt(II) (d^8 metal centers) and the result is an increase of either the electrophilic or nucleophilic character of the peroxygens with respect to the original oxidant.

- By using H_2O_2 as a monooxygen donor to produce highly reactive metal-oxo species. This behavior is typical of biomimetic systems based, for example, on Fe(II), Ru(II), Mn(II). The most widely successful monooxygen donors are iodosyl arenes or hypoclorite or even tert-butylhydroperoxide hydroperoxysulphate, hydrogen peroxide being employed in only a limited number of case. In the last 10 years a new class of metal-oxo oxidants, polyoxometallates which can be regenerated from H_2O_2, has rapidly emerged as one of the most promising sectors of this chemistry.
- Through radical decomposition of H_2O_2 with one-electron redox couples like Fe(II)/Fe(III) or Ti(III)/Ti(IV). These are the basis for the well-known Fenton and Udenfriend systems and a way of generating the highly reactive $HO^{\bullet}$ radical. Although these systems are not very selective they do have some interesting synthetic applications.

6.4. Oxidation reactions in ionic liquids

Considering the commercial importance of catalytic oxidations, and the fact that ionic liquids are expected to be relatively inert towards autoxidation with O_2 and oxidation in general from electrochemical studies,[27] surprisingly little attention has been devoted to performing such reactions in ionic liquids.[28] Moreover, for oxidation reactions with oxygen, the non-volatile nature of the ionic liquid is of real advantage for the safety of the reaction. While the application of volatile organic solvents may be restricted by the formation of explosive mixtures in the gas phase, this problem does not arise if a non-volatile ionic liquid is used as the solvent.

The first metal catalysed oxidation in an ionic liquid, in 2000, described the oxidation of aromatic aldehydes to their corresponding carboxylic acids.[29] During the last few years several dozen papers with transition metal catalysed oxidations have been published and of these epoxidation and dihydroxylation reactions have attracted most interest. In addition there are also numerous examples where ionic liquids act as catalyst or co-catalyst in oxidation reactions without serving as reaction medium. These include the oxidative carbonylation of amines with imidazolium and phosphonium alkylselenites,[30] nickel-catalysed oxidation of ethylbenzene with $[R_4N][BF_4]$ and $[bmim][PF_6]$ as co-catalyst,[31] direct oxidative carboxylation of styrene with $[Bu_4N]Br^-$ and the $PdCl_2$-catalysed oxidation of styrene with [bmim]-based ionic liquids.[32]

There are no differences between ionic liquids and molecular solvents with respect to the reagents used to oxidise a given substrate, but they may display different properties, especially in terms of their solubility.

In imidazolium-type ionic liquids the oxygen solubility is much lower. To overcome the intrinsic low solubility and to minimise mass transfer limitations, efficient mixing of the liquid and gaseous phases must be ensured. Addition of a suitable co-solvent may, however, be required nevertheless. Considering that perfluorinated solvents exhibit very high oxygen solubility, an ionic and perfluorinated solvents combination may help to increase the reaction rate.[33] Alternatively, ionic liquids bearing perfluorinated alkyl chains could probably be used, but little is yet known about their physical properties.

As aqueous oxidants, hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP) and sodium hypochloride are frequently used. Their main disadvantages are: not always reliable exact concentration and therefore over-oxidation of the substrate and/or catalyst may occur, and (ii) presence of relatively large quantities of water that may lead to further, unwanted reactions such as epoxides ring-opening. A valid alternative is the class of solid, and so easy to dose, oxidants comprises phenyliodide diacetate, urea hydrogenperoxide (UHP), and *N*-morpholine-*N'*-oxide (NMO), but they are significantly more expensive than aqueous oxidants. Moreover, one mole by-product per mole target molecule is produced with these organic oxidants, which may, *i.e.*, complicate the isolation of the desired product or interfere with the catalyst.

Methyltrioxorhenium (MTO) has proven to be an exceptionally versatile oxidation catalyst.[34] The ionic liquid $[emim][BF_4]$ was used with MTO and urea hydrogen peroxide to oxidize a series of olefins and allylic alcohols with high conversion and high epoxide yield.[35] This system offers the advantages of heterogeneous catalysis in a homogeneous solution: the products are easily removed by simple extraction with diethyl ether, and the reaction times are comparable to those using organic molecular solvents. One of the primary difference in the MTO/UHP chemistry in ionic liquids compared to that in molecular solvents is the solubility of urea hydrogen peroxide. The UHP adduct is sparingly soluble in molecular solvents (H_2O, $CHCl_3$, CH_2Cl_2), but UHP is readily soluble in [emim][BF_4]. This difference in solubility may account for the differences in reaction times between the two oxidation solutions.[36]

The MTO/peroxide system is very sensitive to halide contamination and especially to the presence of bromide and halides left over in the ionic liquids from the metathesis step that can compete with the olefinic substrate for oxidation in the catalytic cycle.[37] Bromide oxidation occurs with a much higher rate constant than the oxidation of styrene.[38] Moreover, depending on the [MTO] of the reaction, the amount of unreacted imidazole, coming from the ionic liquid synthesis, can lead to decomposition of the MTO catalyst to the inactive perrhenate.

It is of course essential that the ionic liquid is stable in the presence of the oxidant, which excludes ionic liquids with metallic anions such as chlorocuprates. In many oxidation reactions water is present as co-solvent, reagent or it is produced in the course of the reaction, which further eliminates the use of chloroaluminates. However, less care has to be taken with respect to drying the ionic liquid compared to other catalytic reactions when aqueous oxidants are used, but with a resulting wrong oxidant concentration.

Those catalysts that are employed in oxidation reactions are often relatively tolerant with respect to the presence of halide impurities. This is underlined from the fact that NaOCl or [bmim]Br^- are used as oxidant or solvent, respectively. However, some catalysts are able to oxidise halides to their corresponding hypohalous acids, which in turn catalyse the disproportionation of hydrogen peroxide to water and molecular oxygen.[39]

Conte *et al.*[40] carried epoxidations of electrophilic alkenes using a mixture of an ionic liquid containing the substrate and aqueous hydrogen peroxide in the presence of a simple base such as sodium hydroxide, so avoiding the use of transition metal catalyst. Complete consumption of the reactant is observed with small excesses of peroxide. An advantage over the epoxidation reactions carried out in aqueous systems is that no hydrolysis of the epoxides has been detected. Products are easily separated from the oxidation mixture by simple extraction with an immiscible solvent.

6.5. Wacker oxidation

The conversion of fossilized hydrocarbons to fuels and other chemical products, is a straightforward technology, mainly based on intensive oxidation processes.[41] Although it is important to consider a future switch to alternative material sources and technologies, such as the use of renewable feedstock, the development of low temperature, selective and direct hydrocarbon oxidation processes will continue to be an important topic. Transition metal based complexes are able to efficiently catalyse alkanes and alkenes oxidation.[42]

The synthesis of acetaldehyde by oxidation of ethylene, generally known as the Wacker process, was a major step in displacement of acetylene as a starting material in the manufacture of organic chemicals reducing the high costs due to the large energy input required to produce acetylene.[43] Although the Wacker process itself is now being displaced by CO-based technology, as the Monsanto acetic acid process, it is still a major application of homogeneous catalysis.[44]

Two electron oxidation is possible with Pd(II) compounds but there are many unique oxidation reactions (dehydrogenation) specific to Pd(II). After the oxidation is completed, Pd(II) is reduced to Pd(0). If a stoichiometric amount of palladium compounds is consumed the reaction cannot be a useful synthetic method. The Wacker process is the first example of oxidation of an organic compound with Pd(II). It is actually a combination of known reactions and thus not a catalytic reaction in the strictest sense. Its success rises from the invention of an ingenious catalytic cycle, in which the reduced catalyst is reoxidized *in situ* with $CuCl_2$, and in turn CuCl is easily reoxidized with oxygen, one of the fastest reaction in inorganic chemistry.[45] Consequently, ethylene is oxidized indirectly with oxygen without consuming $PdCl_2$ and $CuCl_2$ by the combination of these redox reactions. The catalytic oxidation of organic compounds with $PdCl_2$ and $CuCl_2$ can be summarized as shown.[46]

$$\begin{array}{rcl} H_2C{=}CH_2 + H_2O + PdCl_2 & \longrightarrow & HCOCH_3 + 2\ HCl + Pd(0) \\ Pd(0) + 2\ CuCl_2 & \longrightarrow & PdCl_2 + 2\ CuCl \\ 2\ CuCl + 2\ HCl + 1/2\ O_2 & \longrightarrow & 2\ CuCl_2 + H_2O \\ \hline H_2C{=}CH_2 + 1/2\ O_2 & \longrightarrow & HCOCH_3 \end{array}$$

Scheme 6.14. Wacker process oxidation.

In addition to $CuCl_2$, several inorganic compounds such as $Cu(OAc)_2$, HNO_3 and MnO_2 are used as oxidants of Pd(0).[47] Also benzoquinone (BQ), hydrogen peroxide and some organic peroxides are used. Alkyl nitrites are unique oxidants which are used in some industrial processes.[48]

It should be pointed out that the *in situ* reoxidation of Pd(0) is not always easy. The Pd(0) state is the more stable state than Pd(II). Palladium is called a noble metal because it is not easily oxidized, whereas Cu is a base metal, because it is easily oxidized. Therefore, the oxidation of Pd(0) with base metal salts such as $CuCl_2$ and $FeCl_3$ seems to be rather abnormal than unexpected.[49] The very small equilibrium constant calculated for the oxidation reaction of metallic Pd with free Cu(II) ion suggests the difficulty of oxidizing Pd(0) with Cu(II) salts. The reaction becomes easier in the presence of chloride ion, which stabilizes Pd(II) and Cu(I) states by the complex formation.[50]

In the Wacker process, the reaction is actually carried out in dilute HCl at a high concentration of chloride ion and an elevated temperature. The high concentration of $CuCl_2$ shifts the equilibrium further to the right.

The oxidation of Pd(0) should not be treated as an easy process, and the proper solvents, reaction conditions and reoxidants should be selected to carry out smooth catalytic reactions. In many cases, the catalytic cycle cannot be achieved and the reduced palladium must be recovered and then reused after oxidation with a suitable strong oxidizing agent such as HNO_3. The procedure for the recovery and reoxidation of Pd(0) is tedious and time consuming. Hence, the stoichiometric process is tolerable only for the synthesis of rather expensive organic compounds in limited quantities. This is a serious limitation in the application of oxidation reactions involving Pd(II). One important method for the oxidation reaction with Pd(II) is a gas-phase reaction using a solid Pd catalyst supported on active carbon or alumina. The supported catalyst behaves similarly to the Pd(II)-Cu(II) redox system in the oxidation reactions.[51] Actually industrial production of vinyl acetate is carried out in the gas-phase by using a supported Pd catalyst.[52]

6.5.1. Industrial process[53]

The process is operated in two versions, both in a homogeneous phase.[54]

In the *single-stage process* a mixture of ethylene and oxygen is passed through an aqueous solution of copper chloride and palladium chloride placed in a towerlike reactor at 120-130 °C and 3 bar. In order to avoid an explosive mixture of ethylene and oxygen, both are used in pure form and ethylene is used in stoichiometric excess over oxygen, so unreacted ethylene leaves the reactor together with acetaldehyde formed, cooled and separated by scrubbing with water. Ethylene is pumped back to the reactor after being supplied with fresh reagent. From the cycle-gas a small amount is withdrawn to avoid accumulation of inert gases and gaseous by-products. High purity feed gases have to be used. Crude acetaldehyde is collected in tank.

In the *two-stage process* ethylene and oxygen are reacted separately in separate reactors. First ethylene is reacted stoichiometrically with the catalyst solution, reducing cupric to cuprous chloride. In the second stage cuprous chloride is reoxidized by oxygen. As both gases are reacted separately, their purity does not need to be high, so air is usually used instead of pure oxygen. A procedure utilizing a feed-gas with low ethylene content has been developed, but the commercial plant has not been operated so far. The reaction is carried out at about 105-110 °C and 10 bar, a pressure higher than in the single-stage process. Acetaldehyde is separated from the catalyst solution by flashing the pressure to 1 bar while an acetaldehyde-water mixture is evaporated, then accumulated utilizing the reaction heat in the crude acetaldehyde column, and collected in tank. The catalyst is cycled by a pump and regenerated with air at 100 °C and 10 bar in the oxidation reactor and then returned back to the synthesis unit. Exhaust air and gases are scrubbed with water. Against many advantages, the use of non-pure olefin and of air instead of oxygen as oxidant, a greater capita investment must be put because of the double reactor system and the catalyst circulation that is more energy consuming than the gas recycling method.

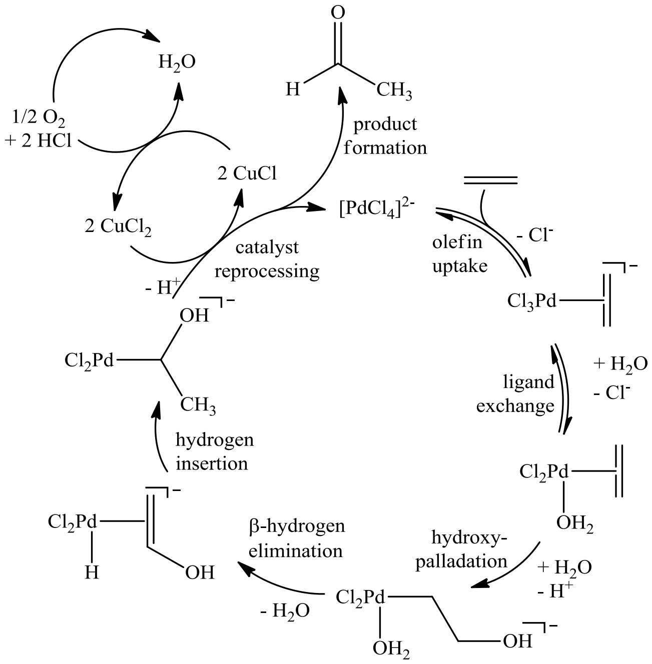
For both processes a purification section now follows involving several fractional distillation steps. The yield in both processes are quite similar, ~ 95%. Also, gaseous (*i.e.*, CO_2, methyl and ethyl chloride) and higher-boiling (*e.g.*, acetic acid, chlorinated acetaldehydes, oxalic acid, etc.) by-products are the same. Chlorination is a side reaction caused by cupric chloride. Environmental regulations require the removal of chlorinated by-products from the off-streams; this is efficiently carried out by catalytic burning, recovering hydrochloric acid.

In order to provide a high reaction rate, a chloride ion concentration is chosen which corresponds to a Cl/Cu ratio less than 2:1 as outlined above. If for a two-stage catalyst it lies between 1.6 and 1.7, the catalyst is reduced in one cycle to a degree of oxidation ($[Cu^{2+}]/[Cu^{2+}] + [Cu^{+}]$) of 0.6 to 0.7. Oxidation is carried out in one cycle up to a degree of oxidation of 1.9. In the single-stage process oxidation and reduction occur simultaneously. The catalyst solution is reduced to a stationary degree of oxidation where both reactions take place at an equal rate and this degree of oxidation is also dependent on the Cl/Cu ratio.

In both cases the catalyst cannot be reduced to a lower degree of oxidation since trouble will arise due to precipitation of cuprous chloride. Even the palladium salt concentration which can be kept in solution depends on catalyst oxidation degree. At lower degrees of oxidation the concentration decreases due to removal from the catalyst of metallic palladium. Due to the high corrosive ability of the catalyst solution, titanium is used as construction material for all catalyst-containing equipment. The reactor for the single-stage process is usually resin-lied.

Halide-free catalyst systems for ethylene oxidation have been developed.[55] Such systems typically comprise a palladium salt along with an heteropoly-acid salt such as a phosphomolibdovanadate. An obvious advantage is reduction in halide-promoted corrosion of process equipment.

6.5.2. Mechanism



Scheme 6.15. Overall catalytic cycle of the Wacker process.

An abbreviated scheme of the complete catalytic cycle of the process is shown in Scheme 6.15.[56]

The major features of the mechanism of ethylene oxidation are well established, but a lively controversy exists about the detailed mechanism. The resting state of $PdCl_2$ under the most relevant experimental conditions is tetrachloropalladate, $PdCl_4^{2-}$. The first step of the reaction should be the complexing of ethylene to give the palladium complex reported in Scheme 6.16 above.

$$Rate = \frac{-d[C_2H_4]}{dt} = \frac{k[PdCl_4^{2-}][C_2H_4]}{[H^+][Cl^-]^2}$$

$$\begin{aligned}
[PdCl_4]^- + C_2H_4 &\xrightleftharpoons{K_1} [PdCl_3(C_2H_4)]^- + Cl^- \\
[PdCl_3(C_2H_4)]^- + H_2O &\xrightleftharpoons{K_2} \underset{\textbf{A}}{[PdCl_2(C_2H_4)(H_2O)]} + Cl^- \\
[PdCl_2(C_2H_4)(H_2O)] &\xrightleftharpoons{} [PdCl_2(C_2H_4)(OH)]^- + H^+ \\
[PdCl_2(C_2H_4)(OH)]^- &\xrightleftharpoons{} [HOCH_2CH_2PdCl_2]^-
\end{aligned}$$

Scheme 6.16. Rate expression of the Wacker oxidation and origin of the chloride inhibition terms.

The next step is discussed contradictorily. The rate expression is first order in ethene but also exhibits a second-order chloride inhibition and a first order proton inhibition. Henry established that the second-order chloride inhibition results from two rapid equilibriums in the palladium coordination sphere, through the replacement of a chloride ligand by the olefin followed by the replacement of another chloride ligand by a water molecule. There is no controversy for the mechanism leading to intermediate **A**, $[PdCl_2(C_2H_4)(H_2O)]$.[57] Dissociation of acidic hydrogen ion explains the inhibiting influence of acids. The major point of disagreement is the insertion reaction of OH^+ to the coordinated alkene to give σ-bonded β-hydroxyethylpalladium intermediate. This intermediate has never been observed but is commonly assumed to be present in the reaction mixture.

In one view, this addition is considered to be the result of migration of a coordinated OH ligand from palladium to carbon. This migration, or ethylene insertion into a Pd–OH bond, is consistent with the observed kinetic.[58] The alternative view is that coordinated olefin is attacked by water (or OH^-). This view is supported by stereochemical studies of addition to coordinated *cis*- or *trans*-1,2-dideuteroethene which indicate attack by an external nucleophile.[59] Both mechanisms operate and reaction conditions determine which predominates.

Because in ethene oxidation no H/D exchange with solvent occurs, the hydrogen migrations involved in transformation of the $HOCH_2CH_2Pd$ intermediate to CH_3CHO occur entirely within the coordination sphere of palladium.

The Wacker chemistry can also be used to oxidise higher olefins, in particular terminal olefins are converted to methylketones. In general rates and yields of ketone formation decrease with alkyl chain length. For example, one commercial syntheses of acetone is the palladium-catalysed oxidation of propylene.[60] This particular reaction is rapid and clean under like those used in the Wacker process. Propylene is oxidised to acetone in 90% yields in 5’ at 20 °C in aqueous palladium chloride solution.[61] Higher olefins require a polar organic solvent, but also give good yields of the corresponding methylketone.

6.5.3. Alternatives in Wacker oxidation

While most of the reported Wacker oxidations utilize Cu/O_2, advances using peroxides as the terminal oxidant have been made. But, concerning the use of copper chloride, it was found that $CuCl_2$ acting as a Lewis acid, can promote the undesirable skeletal rearrangement of some substrates (*e.g.*, terpenes)[62] accompanied by chloride nucleophilic addition. It was then tried to develop a $CuCl_2$-free catalytic system. Mimoun *et al.*[63] have described a highly selective procedure using rhodium catalysts and involving molecular oxygen activation, but deactivation of the catalytic system was observed.[64] Advances have been made also using more handily peroxides instead of oxygen as terminal oxidants.

Mimoun synthetized a palladium alkyl peroxidic complex consisting of tetrameric molecules $[ROC_2PdOOBu^t]_4$ that undergo an oxygen transfer to terminal olefins through a pseudocyclic peroxypalladation mechanism. The nature of the products resulting from the decomposition of the peroxometallacycle depends on the electrophilicity of the metal. Strong d^0 electrophilic metals such as Mo(VI) and V(V)[65] direct the electron transfer toward the alkyl carbon atom, producing epoxides, while less electrophilic group 8 metals such as Pd or Rh direct the electron transfer toward the β-carbon atom, from which β-hydride migration produces methyl ketones.[66] The palladium hydroperoxidic species analogous to the alkylhydroperoxidic complexes, obtained by the addition of H_2O_2 to palladium compounds, showed a reactivity towards olefin very close to the latter.

The use of *sc*CO_2 was investigated by Jiang *et al.*[67] as *medium* for 1-octene oxidation. The selectivity for terminal ketone (66.7%) was increased, relative to methanol solution, although the conversion (33.8%) in scCO_2 was decreased. Since inorganic salts such as $PdCl_2$ and $CuCl_2$ are insoluble in *sc*CO_2, the reaction system is heterogeneous, which slows the reaction. Using alcohols as co-solvent increases the solubility of the catalytic system and improves the selectivity (> 80%) but shows an invariant conversion percentage respect to alcohol alone and leads to the increased formation of acetal as the main by-product.

TS-1 zeolite systems have been used for styrene oxidation but they have shown several drawbacks. Low reaction temperatures increase the proportion of the products adsorbed within the zeolite pores, whereas high reaction temperatures increase the formation of oligomeric compounds in the reaction medium and rapid H_2O_2 decomposition. Likewise, higher reaction times favour both types of phenomena. There is also a high decline of the TS-1 activity during the first hours of reaction that can be assigned to the chemisorption of different aromatic species on the Ti sites, as well to the presence of diffusion limitations arising from the high degree of occupancy of the zeolite pores and intersections.[68]

6.5.4. Ionic liquids

Considering that ILs have attracted a lot of interest in the last decade as novel reaction media, and since they have shown to be especially useful in metal catalysed processes, it is surprising that there are only a few papers on ILs concerned with the Wacker reaction. They both study the oxidation of styrene to acetophenone, an important feedstock for a variety of pharmaceuticals and it is industrially prepared by the acetylation of benzene using acetyl chloride/acetic anhydride.

In the first one there was an implementation of the *sc*CO_2 method by the addition of ~ 2.5 mol% of ionic liquid to a mixture of styrene, palladium chloride and H_2O_2. The tested ionic liquids are [bmim][PF_6] and [bmim][BF_4], with the latter showing the best conversion percentages. The improvement is discrete due to a conversion and selectivity increase respectively from 83, without ionic liquid, to 96% and from 49 to 56%. A plausible mechanistic pathway delineating the synergistic participation of ionic liquids in the enhancement of oxidation may include the formation of an oxaziridinium ion type intermediate involving the imidazolium cation.[69] Although the reaction development, problems related to *sc*CO_2 high costs remain.[51]

The first work applying an ionic liquid, [bmim][BF_4], as the sole solvent used the classical Wacker catalytic system (*i.e.*, $PdCl_2$-$CuCl_2$ in O_2 atmosphere). Water was necessary probably in order to obtain a lower viscous system. Although both high conversion and selectivity were obtained with the possibility to recycle the catalytic system with only low loose in conversion, the use of copper chloride remains the biggest drawback.[52]

We conducted styrene oxidation with H_2O_2 (35%) in the presence of palladium chloride in 16 different ILs (Figure 6.1): hydrophobic ILs, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), 1-ethyl-3-methylimidazolium bistriflimide ([emim] [Tf_2N]), 1-butyl-2,3-dimethylimidazolium bistriflimide ([bm_2im][Tf_2N]), 1-hexyl-3-methyl-imidazolium bistriflimide ([hmim][Tf_2N]), 1-butyronitrile-3-methylimidazolium bis-triflimide ([C_3(CN)mim][Tf_2N]) and 1-butyronitrile-pyridinium bistriflimide ([C_3(CN)py] [Tf_2N]), and hydrophilic ILs, including both the widely applied imidazolium salts, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-ethyl-3-methylimidazolium dicyanamide ([emim][N(CN_2)], and the less investigated cyclic onium salts, *N*,*N*-dimethylpiperidinium and *N*,*N*-dimethylpirrolidinium, with nitrate, hydrogensulfate, formiate, and trifluoroacetate anions, were used. These new ILs were obtained following the DMC halogen free procedure starting from *N*-methylpyrrolidine and *N*-methylpiperidine.[70]

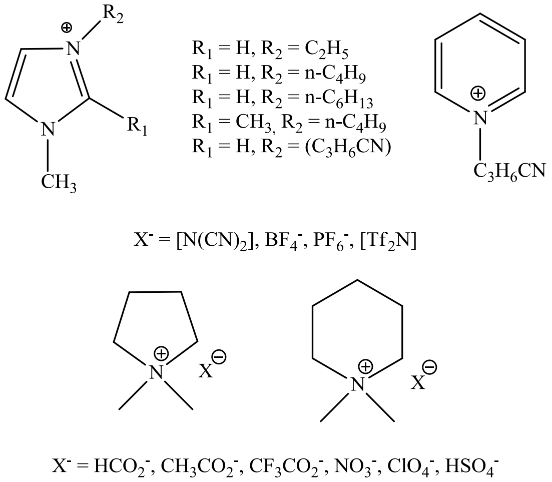
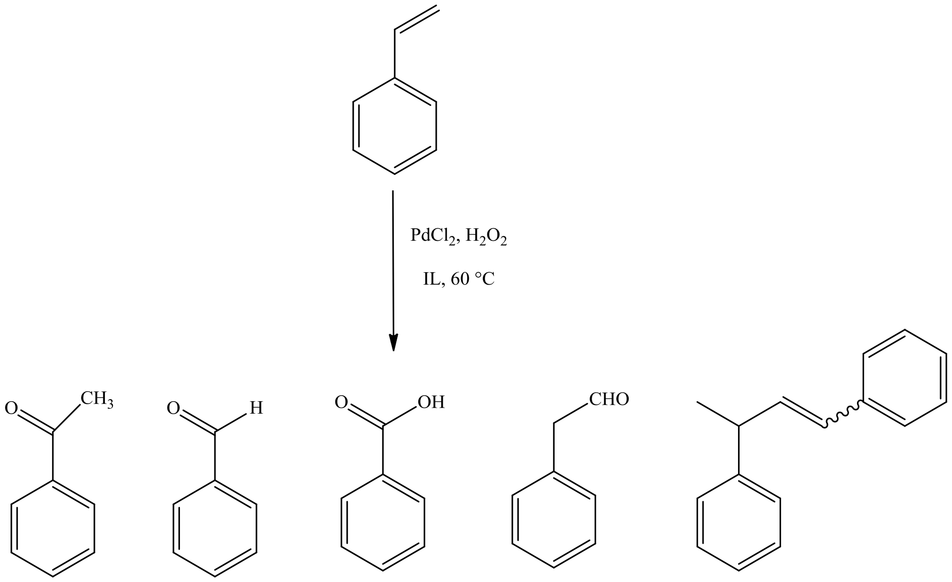


Figure 6.1. ILs evaluated as solvents in the Wacker reaction.

Oxidation of styrene (10 mmol) in the selected ILs (1 mL) were carried at 60 °C using a mole ratio of H_2O_2 to styrene of 1.15 and 0.1 mmol $PdCl_2$. To evaluate the efficiency of the ILs, reactions were stopped after three hours prior to complete conversion, and the products (Scheme 6.17) were extracted with ethyl ether and analysed by NMR and GC-MS. The results are summarized in Table 6.10.



1 **2** **3** **4** **5**

Scheme 6.17. Isolated reaction products.

In hydrophilic ILs, phenylmethylketone (**1**) is the main oxidation product accompanied by lower amounts of benzaldehyde (**2**) and benzoic acid (**3**). Only traces of the aldehyde (**4**), the anti-Markovnikov Wacker product, were found in some reactions. In contrast, the product distribution is significantly different in hydrophobic ILs, where in addition to the oxidation products the formation of relevant amounts of 1,3-dipheyl-1-butene (**5**) was always observed, sometimes accompanied by small amounts of (poly)styrenes.

1,3-Dipheyl-1-butene probably arose from the selective dimerization of styrene through a process which may be catalyzed by palladium species and generally requires the presence of a Lewis acid. The formation of 1,3-dipheyl-1-butene has been recently reported in [bmim][PF_6] using, however, $Pd(OAc)_2$-$Cu(OTf)_2$ and $Pd(OAc)_2$-$In(OTf)_3$ as catalytic systems.

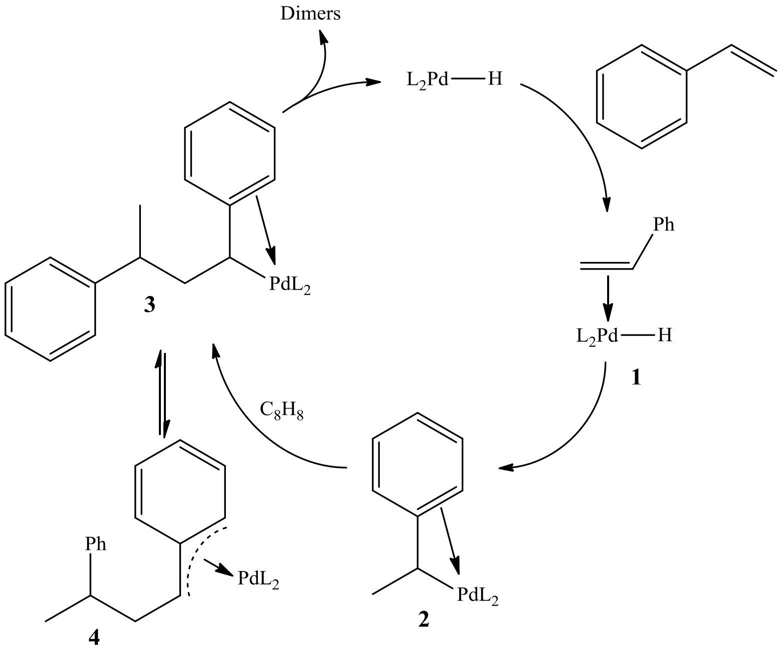
On the basis of the proposed mechanism, dimerization of styrene should occur through nucleophilic attack of Pd(0)-styrene complexes, generated by reduction of

$Pd(OAc)_2$ with 1,3-dialkylimidazolium salt, on the styrene double bond activated by complexation with copper triflate.[71]

Table 6.10. Conversion and product distribution in the Wacker styrene oxidation in ILs. [a]All products were characterized by GC-MS and NMR.

	IL	**Conv (%)**	**Selectivity[a]**			
			1	**2**	**3**	**5**
1	[bmim][BF_4]	45	90	10		
2	[emim][$N(CN)_2$]	< 3				
3	[mmpip][AcO]	< 3				
4	[mmpip][CF_3CO_2]	85	92	8	-	-
5	[mmpip][NO_3]	42	90	8	2	-
6	[mmpyrr][NO_3]	80	90	5	-	-
7	[mmpyrr][HSO_4]	14	85	7	-	-
8	[mmpyrr][HCO_2]	13	100	-	-	-
9	[mmpyrr][ClO_4]	28	90	10	-	-
10	[mmpyrr][CF_3CO_2]	80	93	7	-	-
11	[bmim][PF_6]	78	60	3	2	35
12	[emim[Tf_2N]	90	30	3	-	67
13	[bm_2im][Tf_2N]	60	30	4	-	66
14	[hmim][Tf_2N]	44	20	3	-	77
15	[$C_3(CN)py$][Tf_2N]	100	75	7	3	15
16	[$C_3(CN)mim$][Tf_2N]	100	62	3	5	30
17	[$C_3(CN)mim$][BF_4]	60	80	10	10	-

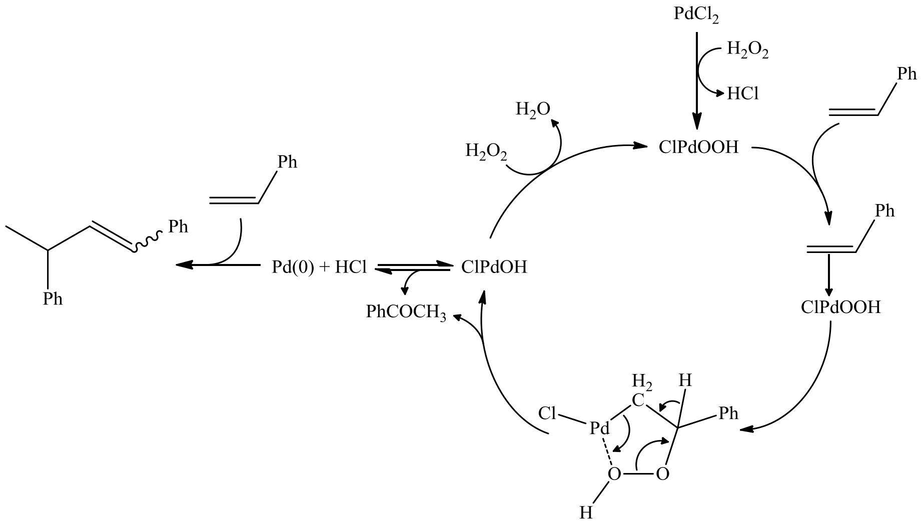
The mechanism that involves a palladium hydride species (Scheme 6.18) is the commonly accepted hypothesis concerning olefin oligomerization by transition-metal catalysts. Activation of the precatalyst in the presence of styrene leads to a coordinately unsaturated Pd–H species, which is able to add styrene.[72]



Scheme 6.18. Catalytic cycle based on the β-hydrogen transfer route.

The addition of the styrene molecule to the palladium hydride provides **3**. Pd→C_2 insertion of the monomer into the Pd–H bond leads to **4**. Further Pd→C_2 insertion of the second styrene molecule into the Pd–C bond regenerates **3**. The palladium intermediate **3** retains its 16-electron configuration owing to the edge coordination of the phenyl ring of the last inserted styrene. This dimer chain might be stabilized in a secondary way by the η^3-benzyl-palladium bond affording **4**, which cannot undergo β-elimination process. The high selectivity toward a head-to-tail dimerization product might be explained by the formation of intermediates **3** and **4** with the stabilization of the active species.[73] Finally, β-elimination through a $\eta^3\leftrightarrow\eta^1$ isomerization terminates the chain, giving 1,3-diphenyl-1-butene and regenerating the palladium hydride active species.

Despite using different a palladium salt and the absence of copper or indium salts it is likely that an analogous mechanism is in operation in Tf_2N-based ILs. Nevertheless, the possibility that the IL cations with acidic protons can polarize the styrene double bond, combined with the fact that Pd(0) may be formed under the reaction conditions, cannot be excluded. In molecular solvents it has been reported that the palladium catalysed olefin oxidations using hydrogen peroxide and PdX_2 salts occurs through a palladium hydroperoxidic species (“XPdOOH”), probably formed by the addition of H_2O_2 to the palladium salt (Scheme 6.19, X = Cl).[63] “XPdOOH” species may undergo oxygen transfer to the olefin through a pseudocyclic hydroperoxypalladation mechanism of the coordinated olefin giving the corresponding ketone and “XPdOH”.



Scheme 6.19. Proposed mechanism for competitive palladium catalysed styrene oxidation and dimerization.

In the presence of an excess of H_2O_2, hydroxyl species “XPdOH” is able to regenerate “XPdOOH”. However, at low H_2O_2 concentrations, hydroxypalladation of the olefin can take place, affording the corresponding ketone and Pd(0), the later usually precipitating as black-palladium in molecular solvents, but is stabilized in ILs.

If the formation of Pd(0) in ILs competes with the regeneration of “XPdOOH” species, as in molecular solvents, one can hypothesize that oxidation and dimerization are two competitive processes having Pd(0) as key intermediate (Scheme 6.19) and conditions that disfavor the regeneration of “XPdOOH” from “XPdOH” will result in increased levels of **5**.

In agreement with this hypothesis, the formation of **5** is only observed in hydrophobic ILs that afford a biphasic system with the aqueous solution of H_2O_2. The biphasic nature of the system and the relatively high viscosity of these ILs probably reduce the re-oxidation rate of “ClPdOH” (due to mass transfer limitations). It is noteworthy that attempts to perform the dimerization process in the same ILs using exclusively $PdCl_2$ as catalyst gave significantly lower amounts of **5**, suggesting that a more efficient mechanism for Pd(0) formation is present during the oxidation process.

Formation of **5** in hydrophobic ILs makes these media unsuitable for the Wacker reaction. However, data reported in Table 6.10 show that hydrophilicity alone is not sufficient to ensure high yields and selectivity, and the IL structure significantly affects product distribution and reaction rate. Low conversions (if any) are observed in ILs composed of basic anions or amphoteric anions (Table 6.10, entries 2, 3, 7 and 8), whereas high conversions and selectivity are obtained under comparable conditions in [mmpip][CF_3CO_2], [mmpyrr][CF_3CO_2] and [mmpyrr][NO_3].

Since recent toxicity data indicates that ammonium salts bearing short alkyl chains (including pyrrolidinium and piperidinium salts) are less toxicity than most commonly used ILs (mainly based imidazolium salts), and given that the procedure to prepare this class of IL with methylcarbonate is more environmentally benign and results in contaminant-free media, these ILs might have an important role as “green” media for oxidation reactions.[74] However, since recycling of the solvent and the catalyst is another vital parameter the potential of these media to be reused was explored (Table 6.11).

In the recycling experiments reactions were also stopped after three hours. Generally, a progressive decreases in conversion was observed, which may be attributed to the progressive formation of palladium black, Pd(0), that was observed in most reactions performed in the hydrophilic ILs. However, at least in the case of [mmpip][CF_3CO_2], it was possible to repeat the process four times maintaining a satisfactory conversion and selectivity. Related to the problem of the formation of black palladium, it is noteworthy that this behaviour was not observed in nitrile containing ILs. In agreement with the previously observed ability of these ILs to stabilize Pd(0) species (nanoparticles) high conversions were obtained using [C_3(CN)mim][Tf_2N] also after four recycles.[75] Unfortunately, the relevant amounts of 5 formed also in the recycling experiments reduced the possibility to use this IL as solvents for the Wacker oxidation. It is noteworthy that the use of the hydrophilic 1-butylnitrile-3-methylimidazolium tetrafluoroborate ([C_3(CN)mim] [BF_4]) gave the expected ketone 2 with high selectivity (dimer 5 was not detected) and satisfactory conversion in the first cycle (Table 6.10, run 17), supporting the hypothesis that in [C_3(CN)mim][Tf_2N] the biphasic system favours the formation of dimer 5.

Table 6.11. Recycling experiments.

IL	Re-cycle	Conv (%)	Selectivity			
			1	**2**	**3**	**5**
[mmpip][CF_3CO_2]		85	92	8	-	-
	R1	80	91	6	3	
	R2	70	88	7	5	
	R3	75	85	7	8	
	R4	12	80	15	5	
[mmpyrr][NO_3]		80	90	5	-	-
	R1	75	90	5		
	R2	55	60	27	13	
	R3	33	36	33	31	
	R4	< 2				
[mmpyrr][CF_3CO_2]		80	93	7	-	-
	R1	65	91	9		
	R2	30	70	20	10	
	R3	18	70	30		
	R4	-				
[bmim][PF_6]		78	60	3	2	35
	R1	70	73	11	2	14
	R2	20	95	5	-	-
	R3	10	95	5	-	-
[bm_2im][Tf_2N]		60	30	4		66
	R1	50	52	11		37
	R2	18	62	8		30
[C_3(CN)mim][Tf_2N]		100	62	3	5	30
	R1	95	62	-	8	30
	R2	90	60	3	18	19
	R3	90	60	10	10	20
	R4	85	60	15	5	20
[C_3(CN)mim][BF_4]	R1	60	80	10	10	-
	R2	22	90	10	-	-

However, the low conversion obtained at the second cycle, probably due to the relevant amounts of black palladium formed during the first cycle, shows that [C_3(CN)mim][BF_4] is not able to stabilize sufficiently Pd(0) species, at least under the reaction conditions.

In summary, the selectivity of the Wacker reaction of styrene towards the oxidation product has been shown to be high in hydrophilic ILs. In particular, high conversions and selectivity were obtained in [mmpip][CF_3CO_2], [mmpyrr][CF_3CO_2] and [mmpyrr][NO_3]; three halogen-free ILs obtained through a relatively benign protocol (via methylcarbonate). In contrast, in hydrophobic ILs significant amounts of 1,3-dipheyl-1-butene, arising from styrene dimerization, are formed in addition to the expected phenylmethylketone product. A plausible mechanistic explanation for the formation of this by-product involves the formation of Pd(0) via a side-process during the oxidation cycle. Therefore, the ability of the IL to favor or disfavor the re-oxidation of “ClPdOH” to “ClPdOOH” by reaction with hydrogen peroxide may be considered as the main factor affecting the possibility to obtain the expected ketone as the main (or practically only) product. In turn, re-oxidation of “ClPdOH” or reduction of the metal center to Pd(0) is strongly influenced by the “accessibility” of H_2O_2. In hydrophilic ILs the reaction mixture forms a single homogeneous phase and oxidation is favored whereas in hydrophobic ILs the aqueous solution of H_2O_2 is immiscible, with the formation of a biphasic system, and reduction of Pd(II) to Pd(0) becomes relevant.

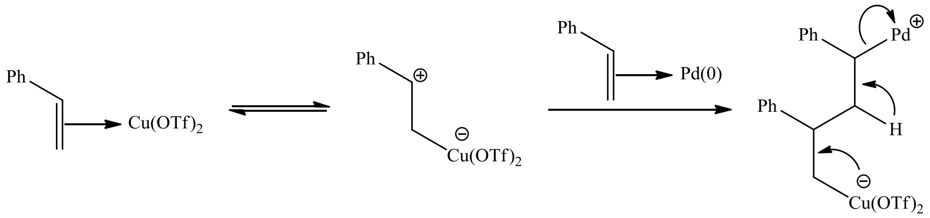
6.6. Appendix

Dimerization of olefins in ionic liquids

The selective dimerization of styrene is a great practical method for the production of 1,3-diphenyl-1-butene, and the initiators for this reaction are generally strong Brönsted acids, Lewis acids or zeolite catalysts. However, some byproducts such as indan derivative or higher oligomers are formed.[76] Among all the electrophilic transition metal catalysts for the dimerization of vinylic monomers, palladium complexes, known as powerful and widely used catalysts for C–C bond formation, have been particularly studied because of their high selectivity in the dimerization of vinylbenzene, and the carbocationic mechanism has been demonstrated.[77] Moreover, asymmetric styrene dimerization using chiral palladium catalyst in the presence of indium(III) triflate in 1,4-dioxane was reported.[78]

Peng *et al.*[79] performed the reactions at room temperature and pressure and using 1-4 mol% $Pd(OAc)_2$, 1 mol% Lewis acid (*i.e.*, $Cu(OTf)_2$, $Cu(CF_3CO_2)_2$, $Zn(OTf)_2$, $In(OTf)_3$), for 2.5-4.5 hours. Complete substrate conversion, and of 80 and 76% for the second and third catalyst reuse respectively, was observed with reaction times as short as 2.5 hours using $Cu(OTf)_2$ as Lewis acid, with a selectivity usually greater than 98%. No reaction was observed when either the Pd complex, the Lewis acid or the ionic liquid was absent. Weakly coordinating ligands seem to favour this reaction as using $PdCl_2$ and $Pd(PPh_3)_3Cl_2$ catalyst only very low yields and no reaction respectively were observed.

A supposed mechanism sees the reduction of Pd(II) by the ionic liquid, followed by formation of a σ-complex between the olefin and the copper triflate. This polarized complex then reacts with the Pd(0)-π-complex with the substrate to form the final product as shown in Scheme 6.20.[80]



Scheme 6.20. Lewis acid catalysed styrene homocoupling.

The biphasic oligomerisation of olefins using chloroaluminate ionic liquids as catalyst solvent for Ni-complexes has been first described by Chauvin *et al.*[81] These authors used a slightly acidic ionic liquid of the type $Cl/AlCl_3/AlEtCl_2$ as solvent for a Ni(II)-catalyst precursor. Wasserscheid *et al.*[82] have investigated 1-butene dimerization in chloroaluminate ionic liquids using a nickel catalyst. This biphasic system had several advantages over running the reaction in toluene as the solvent, such as high activity even at low temperatures, high TOF and no detachable leaching of the catalyst.

6.7. Experimental section

Reagents were ACS grade and used as received. ^1H and ^{13}C NMR spectra of all the ILs were obtained on a Bruker 250 MHz spectrometer. Chemical shifts are reported downfield from TMS. GC-MS were performed with a gas-chromatograph equipped with a DB-5 capillary column (30 m 6 0.25 mm; coating thickness 0.25mm) and an ion trap mass detector. Analytical conditions: injector and transfer line temperatures 220 and 240 °C, respectively; oven temperature programmed from 60 °C to 240 °C at 3 °C min; carrier gas helium at 1 ml min; injection of 0.2 ml (10% hexane solution); split ratio 1:30. Identification of the constituents was based on comparison of the retention times with those of authentic samples, and matching against commercial (NIST 98 and ADAMS) and home-made mass spectra library built up from pure substances and MS literature data.

General procedure for the Wacker oxidation

Reactions were carried out in glass vials equipped with Teflon screw caps under magnetic stirring using a parallel synthesizer. $PdCl_2$ (0.1 mmol) was added to the selected IL (1.0 ml) followed by H_2O_2 (35%, 11.5 mmol) and styrene (10 mmol). The reaction mixtures were heated at 60 °C and stirred vigorously for 3 h. Subsequently, the mixtures were cooled to room temperature and the products extracted with diethyl ether (3 x 5 ml). The combined extracts were washed with water and dried with $MgSO_4$, and analyzed by GC-MS and NMR spectroscopy.

6.8. References

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7. Halogenation reactions in ionic liquids

The addition of chlorine or bromine to alkenes is a very general reaction. Brominated organic compounds are important building blocks in organic synthesis and play an important role in transition-metal-mediated coupling reactions, being intermediates in the preparation of organometallic species. They often exert enhanced biological activity. Considering arene bromination reversibility,[1] there could be two applications: selective protodebromination in presence of a bromine scavenger (*e.g.*, sodium sulphite) and utilization of bromine as a protecting group in reaction of aromatic compounds.[2] For these reasons bromination reactions have received more attentions as compared to other halotrasformation.

7.1. Mechanism

Considerable insight has been gained into the mechanism of halogen addition by studies on the stereochemistry of the reaction. There is much evidence that when the attack is on Br^+ (or a carrier of it), the bromonium ion is often an intermediate and the addition is *anti*.[3]

Theoretical calculations indicate that little charge is transferred from the olefin to the halogen and that dispersion energy is the main driving force for complexation. Interactions different from dispersion ones (*e.g.*, steric interactions, molecular motions, charge transfer, inductive effects) vary little from one system to another. It is noteworthy that for crowded alkenes the ionization potential does not vary significantly but there is a big change in polarizability, the aptitude of the electronic cloud to undergo deformation under the action of an electric field. The opposite behaviour is observed with no hindered olefins. The first species formed by the interaction of bromine with a double or triple bond in is a charge transfer complex, π-complexes, whose stability at least in the case of alkenes is affected by both the donor ionization potential and the polarizability of the double bond:

the magnitude of the charge transfer depends significantly on the polarizability of the olefin.[4]

Calculations show that first iteration intermolecular energies are of the same nature for both bromine and chlorine complexes: they are only more repulsive with the former at intermediate distances, the curve becoming attractive for a slightly larger intermolecular distance. As with chlorine, the charge transfer and induction energy, though important, hardly compensates the repulsive energy, and dispersion energy must be added to correctly describe the system stability. The contribution of both atoms to the π ethylene orbital is larger for bromine and iodine respect to chlorine but with no possibility to form a three-centres covalent bond. At the total energy minimum position, the π ethylene orbital is more perturbed by the presence of the halogen molecule but there is no qualitative change definitively excluding the possibility of a three-centre covalent bond. Thus binding has to be intend in terms of intermolecular interactions.[5] This is compatible with experimental data which conclude the existence of a “charge transfer complex” (CTC).[6] consisting in the ionization of olefin-Br_2 bond.[7]

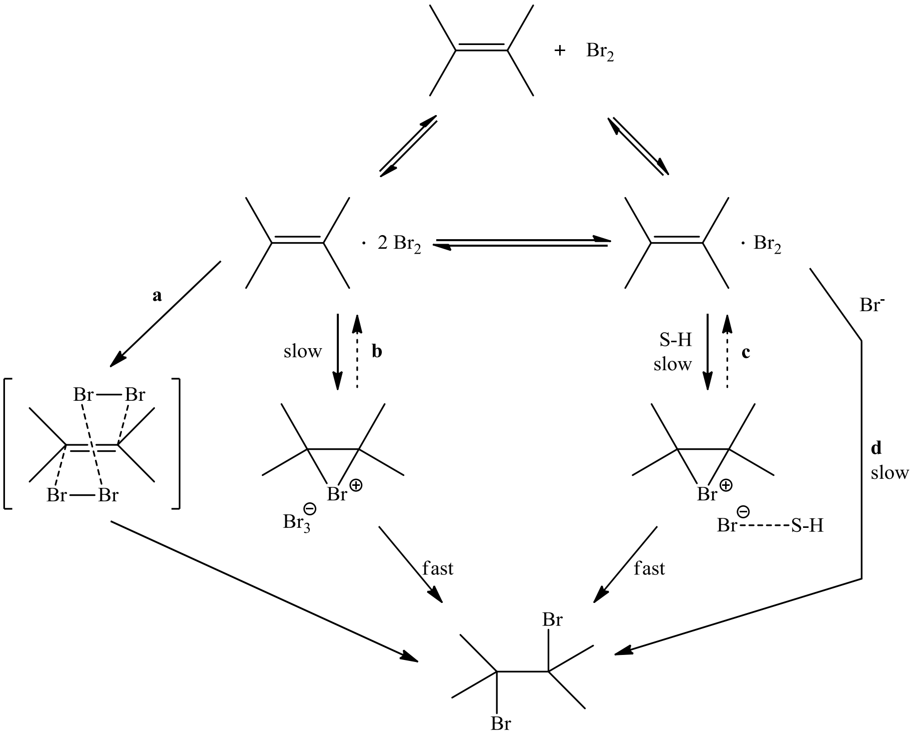
It has been shown[8] that in protic media the subsequent ionization of the Br_2-olefin π-complexes is assisted by solvent hydrogen bonding to the developing bromide ion, whereas in aprotic media the assistance is provided by a second Br_2 molecule, stabilizing the anion as tribromide ion.[9]

Larger bromine aggregates can well take part in the product-determining step if the ion pair intermediates, once formed, are subjected to fast bromide-polybromide equilibration in the presence of Br_2. A pentabromide species is formed, besides the tribromide, when bromide and excess bromine are dissolved in an aprotic solvent of moderate polarity (*i.e.*, 1,2-dicloroethane). Its formation from Br_3^- and Br_2 is exothermic and involve an entropy decrease. In a solvent incapable of electrophilic solvation the larger Br_5^- ion is expected to be more stabilized than the Br_3^- one by internal charge delocalization.[10]

Different intermediates are therefore likely to be involved in the product-determining step of olefin bromination depending on the Br_2 concentration during the course of the addition. Depending on the dropwise addition of Br_2 or of the olefin respectively a low or high halogen concentration should be produced favouring the tribromide or pentabromide type ion intermediate.

The first pathway (**a** in Scheme 7.1)[11] has been proposed for the slow brominations in apolar solvents like CCl_4 and consists of a direct rearrangement of a 1:2 olefin-Br_2 complex through a nonpolar six-membered transition state. This mechanism requires a second-order dependence on Br_2 of the bromination rate. Kinetic investigations under these conditions are however conflicting.

In solvents of even very modest polarity, the 1:2 complex can instead undergo a rate-determining cleavage of a bromine-bromine bond to give a bromonium-tribromide ion pair intermediate, which then collapses rapidly to dibromide and molecular Br_2 (**b**). Br_3^- formation is not affected by the nature of the cation.[12] Also pathway **b** involves a second-order dependence on Br_2 of the rate that has been clearly demonstrated for brominations in several chlorinated hydrocarbon solvents.[7]



Scheme 7.1. Bromination pathways in increasing polarity solvent.

A similar ionic mechanism, where a solvent-assisted bromine-bromine bond breaking occurs in a 1:1 olefin-Br_2 CTC and the reaction is first-order in Br_2 (**c**), has been definitely established for bromination at low Br_2 concentration in hydroxylic solvent, which provide specific electrophilic solvation by hydrogen bonding to the leaving bromide ion. At higher Br_2 concentration, a third-order process of type **b** has been reported also in acetic acid.

In the presence of added bromide salts,[13] which in low polarity aprotic solvents bind Br_2 as a highly stable Br_3^- ion, or when preformed Br_3^- salts are used as the brominating reagent, the bromination has been shown to proceed through rate- and product-determining nucleophilic attack by Br^- on 1:1 olefin-Br_2 CTCs (**d**). A mechanism of the latter type is probably involved also in brominations carried out in the presence of basic compounds (heteroaromatic amines or ethers) able to complex bromine, as suggested by product distribution studies.

Stereoselectivity is 100% *anti* for a bromonium ion and less for carbocations. For the latters, bromination must be 100% regioselective, but for the formers, the charge distribution is less straightforward. The orientation of nucleophile addition is qualitatively expected to follow Markovnikov’s rule. Chemoselectivity between two nucleophiles (*e.g.*, bromide ion, solvent) depends on their relative nucleophilicities and also on the electrophilicity of the ionic intermediate. More solvent-incorporated product is formed from carbocations than from bromonium ions. This picture is too simple because steric effects must be taken into account.[14]

The dissociation of the olefin-bromide charge transfer complex is assisted by the solvent in protic media and by a second bromine in nonprotic ones but, after the first fast CTC formation step, this preequilibrium reduces the information content of the experimental rate constant regarding the intermediate structure, since its equilibrium rate constant is related to the formation of the ionic intermediate and to that of the CTC.[15] The rate-determining step leads to the ionic intermediate by unimolecular dissociation of the CTC. Since bromonium ions are not formed from bromine and olefins in the gas phase,[16] the solvent must strongly assist CTC ionization. Most of the assistance comes from the electrophilic solvation of the living bromide,[8] but nucleophilic solvent participation has also been detected.

Reversible formation of bromonium ions postulates that nucleophilic attack in the last product-forming step is slow. In protic solvents where nucleophiles are always present, this is generally not the case. However, crowding of the double bond can slow the last step by sterically inhibiting the reaction of the nucleophile with the intermediates, as in the bromination of adamatylideneadamantane. In non-nucleophilic aprotic solvents, the nucleophilic bromide ion is supplied by the dissociation of the tribromide counterion, which is not necessary fast.[17]

Intermediate structures and product selectivity are mainly governed by the double-bond substituents. The two-fold nature of the intermediate can be viewed as a result of the competition between the entering bromine atom and the substituents in stabilizing the positive charge developed during the reaction. When none of the substituents is able to stabilize the charge better than the bromine atom (*e.g.*, alkyl groups, strongly electron-attracting groups), the bromination intermediates are bromonium exclusively. The products are, then, formed 100% stereoselectively whatever the solvent and even when crowded substituents inhibit nucleophile attack.[18]

Dubois *et al.*[19] correlated methyl-substituted ethylene bromonium ions and region- or chemoselectivity. The choice of methyl as substituent made this correlation hindrance independent. In electrophilic attack, the free enthalpy of activation $\Delta G^{\ddagger}$ decreases directly with increasing π net charge on olefin’s double bond.

$$\delta\Delta G^{\ddagger}_{(Br^{-})-(MeOH)} = \delta\Delta G^{\ddagger}_{(Br^{-}-C_{\alpha})} - \delta\Delta G^{\ddagger}_{(MeOH-C_{\alpha})}$$

The “nucleophilic” transition state, carbon-pentacoordinated TS, is more crowded than the electrophilic one (the solvent stabilizes bromine during CTC formation) which is a carbon-tetracoordinated TS. Therefore, steric effects could easily be more important for the nucleophilic TS.

Regioselectivity corresponds to the difference in the probably of the MeOH to attack at C_{α} or C_{β} and this competition is expressed by the difference of free enthalpies of activation and it is zero for symmetrical intermediates:

$$\delta\Delta G^{\ddagger}_{\alpha-\beta} = \delta\Delta G^{\ddagger}_{(MeOH-C_{\alpha})} - \delta\Delta G^{\ddagger}_{(MeOH-C_{\beta})}$$

Any increase in hardness of carbenium centre would favour its attack by methanol molecules which are relative harder than bromide ions.[20] Following the HSAB principle, methanol, a nucleophile harder than bromide, adds preferentially to the carbocation, harder than bromonium (where the charge is delocalized on three atoms). When the degree of substitution on site C_α goes from 0 to 2 with no change on site C_β, a strong C_α positive charge increase is observed and a positive charge decrease on C_β but relatively small in comparison to the vacation on C_α, because the increase in positive charge on site C_α occurs mainly at the expense of the charge carried by bromine. Indeed, for ethylene bromonium ion the attack is not regioselective and only 38% of monobromurated product (MB) is formed; when a methyl is introduced on C_α, both regio- and chemoselectivity (MB = 61%) increase; for a methyl-disubstituted C_α the reaction becomes regiospecific and MB reaches 85%. In contrast, when the degree of substitution changes on C_β and C_α is already disubstituted the positive charge increase on site C_β occurs at the expense of the positive charge carried by site C_α and so chemoselectivity decreases. But if C_β is only monosubstituted, the disubstitution of site C_α gives it a relatively strong carbenium character and hardness, because the charge increase in both carbon atoms occurs at the expense of the positive charge carried by the bromine, so reaction is still regiospecific and maintains its chemoselectivity.

When very stable carbocations can be formed (*e.g.*, from aryl olefins with electron-donating substituents or enol ether), open intermediates predominate. The products are, then, formed highly regio- and chemoselectively but nonstereoselectively.[21]

Competition between bromonium ion and carbocation intermediates occurs with moderately electron-releasing or -attracting groups. In this situation, the multipathway scheme must be considered in its whole. Predictions of the product selectivity could be made from the relative importance of the three pathways. These three examples establish the multipathway scheme for electrophilic bromination of aryl olefins.

Several examples have been found where addition of bromine is not stereospecifically *anti*. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.[22] Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent.

Whether the involved intermediate ions are symmetrically or asymmetrically bridged or are open β-bromo-carbocations depends upon the ability of the remote substituents to stabilize a positively charged benzylic carbon. Starting with a couple of *E* and *Z para*-substituted stilbenes, the *erythro*:*threo* ratio of dibromurated product, arising from a *cis*-*trans* isomerization, increases decreasing reagents concentrations. This behaviour points to equilibration of the reaction intermediates formed from either isomer of the *cis*-*trans* couple to a symmetrically bridged *trans*-bromonium ion, which, at low concentrations, appears to be the most stable intermediate form and can be opened only in a *trans* fashion to give the *erythro* or *meso*-dibromide. The highest stability of symmetrically bridged forms, when produced under high-dilution conditions, is likely related to the tendency of the intermediates to dissociate from ion pairs to separated ions when the concentration is lowered enough. More bridging is probably required to stabilize the separated carbocation than a tight ion pair, because the positive charge on the benzylic carbon is no longer stabilized electrostatically by the close counterion. On the other hand, in non-nucleophilic solvents, the lifetimes of the intermediates are expected to be longer for separated species than for tight ion pairs, so that the former have more opportunity to equilibrate to the most stable *trans*-bromonium ion form, free of steric strain, before reacting.[23]

In styrene bromination, a bromonium ion and a benzylic carbocation are implicated. For stilbene bromination, depending on the substituents, all three pathways leading to bromonium ion and both carbocations may be followed. Bromination of α-methylstilbenes is a dual-pathway addition where the two carbocations, tertiary and secondary, can be formed competitively in the rate-determining step. This multipathway scheme is generally applicable because by these means the stereo and the regiochemistry of electrophilic additions can be accurately predicted, but only in subordination to the knowledge of the free energy. Kinetic study of X,Y-disubstituted stilbenes with one EDG shows that the effect of two substituents on each of the two aromatic rings are not additive, which suggest a highly dissymmetric charge distribution, consequently, as a preliminary to the prediction of the stereo- and regiochemistry in electrophilic additions, it is necessary to develop interactive free energy relationships which take into account the nonadditivity of multiple substituents effects.[24]

In contrast, additivity is observed when the two substituents are both electron-attracting.[25] These results can be interpreted in terms of the three-pathway mechanism: EDGs favour the carbocationic intermediates and EWGs the bromonium ions.

On the other hand, in styrene bromination only the C_α and Br paths are involved. Stereochemical data on the β-methylstyrene reaction indicate bromine bridged dependency on the ring substituent.[26] Intermolecular Br^+ transfer from ion to olefin must be considered to be competitive with the various product-forming steps during the electrophilic bromination of olefins. The extent of reversibility during the bromination of stilbenes appears to be affected by remote substituents that can modify the extent of bridging and the charge distribution between the bromine and carbons of the intermediate and was based on the dependence of the α- and β-methyl effects of the X substituent, the trend of which differs markedly from that observed in hydration, an electrophilic addition unequivocally going through carbocations[27] (*e.g.*, *p*-CF_3 groups interfere with the development of a carbocation at either benzylic carbon favouring the formation of symmetrically bridged ions).[14]

The intermediate from the *p*-methoxy-substituted stilbene is long-lived in MeOH and also in AcOH since full rotation is achieved before its trapping by these solvents; accordingly, the enforced path is the free ion route. For the *p*-methyl-substituted stilbene, the lifetime of its intermediate is very short in MeOH (no rotation) but very long in tetrafluoroethene, in agreement with preassociation and free ion paths, respectively, and also in agreement with the relative rates of carbocation trapping by these solvents.[28] Thus, conformational barriers can be used as clocks for measuring carbocation lifetimes.

In methanol, the methoxy adduct, the major product, is formed 100% stereospecifically and regioselectively, whatever the substituents. Similar results are observed for acetoxy bromides in acetic acid. A plausible interpretation considers the relative rates of conformational equilibration of the carbocation and of the nucleophile attack on more or less dissociated ion pairs.[29] The exclusive formation of dibromides in methylene chloride and methoxy bromides in methanol is nonstereoselective and substituent independent. This support the conclusion that there are no bromonium ion intermediates in the bromination of α-methylstilbenes in agreement with HSAB principle.

Kinetic solvent effects on 1-pentene and on several olefins are large and almost independent of the olefin structure.[30] These results, taken with those described above, are consistent with a high polar effect and strong electrophilic assistance but little or no nucleophilic involvement of the solvent in the rate-determining step. The bromination transition states are, therefore, strongly electrophilically but weakly nucleophilically assisted. This must mean that the solvent mainly influences the anionic but not the cationic part of the activated complex. It can be reasonably inferred that the charge distribution (*i.e.*, the relative contribution of the bromonium and carbocation pathways) does not vary significantly with the solvent.[31] Several stereochemical data agree with this conclusion: (i) the bromination of alkenes going solely through bromonium ions is always 100% stereoselective, whatever the solvent;[32] (ii) the reaction of α-methylstilbenes via carbocations is nonstereoselective in methylene chloride for dibromide formation and also in methanol for methoxy bromides.[33] In contrast, the stereochemistry is observed to be solvent-dependent in the styrene[34] and stilbene series where kinetic data indicate competition between bromonium and carbocation intermediates.

Most of the systems in which reversibility is implicated involve special features, such as benzylic carbons or isomerization of a double bond (*e.g.*, stilbenes), or severe hindrance so that the product-forming steps are retarded by steric congestion.[35]

In solvents of low dielectric constant, the addition is 90-100% *anti*, but with an increase in dielectric constant, the reaction becomes less stereospecific, until, at a dielectric constant of ~ 35, the addition is completely nonstereospecific.[36] Both *cis* and *trans* products are obtained in bromination of phenylacetylene because bromonium ion is not formed where the open cation can be stabilized in other ways (*e.g.*, addition of Br^+ to 1-phenylpropene gives the ion $PhC^+HCHBrCH_3$, which is a relatively stable benzylic cation).[37]

Reversibility appears most easily demonstrable in solvents of low polarity and with special olefins in which: i) steric bulk impedes the product-forming step or; ii) a less stable *cis* olefin can revert to a more stable trans isomer.[14] This would imply that the product-determining step can also be partially rate-determining. For *cis*-stilbene this reversibility was shown by the occurrence of *cis-trans* isomerization accompanying the bromination of the olefin. This isomerization was rationalized by a release of molecular Br_2

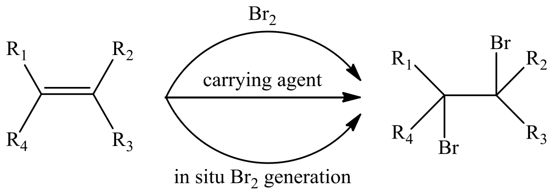
from the *trans*-bromonium-tribromide ion pair resulting from the rearrangement of the first-formed, strained *cis*-bromonium species through an open β-bromocarbonium ion.[38]

Bromine bridging is not the only stereochemistry-determining factor. The large solvent dependence of the stereochemistry does not arise from bridging variations with solvent, since this latter is substituent- but not solvent-dependent, as shown by the comparison of kinetic substituent effects in the several solvents studied. The stereochemical outcome of bromination is controlled not only by the bridged or unbridged structure of the cationic intermediate but also by its association with its nucleophilic partners and its lifetime. In this context, an important result is the substituent-independent stereospecificity of the reaction of *cis*-stilbenes and of *trans*-β-methylstyrenes in MeOH, but not in nonnucleophilic solvents, which is the consequence of their pre-association with the nucleophile, well before the product-forming step itself.[39]

Return is significant in protic and halogenated solvents when the intermediates are bridged but not when they are open.[13] Moreover, the severe energetic requirements of *syn* vs *anti* addition, which involve strong bromine-bromine repulsions and Br^- *trans* location, respectively, are fairly well exhibited by the absence of Br^- collapse of the nucleophile-bromocation-bromide sandwiches, in contrast with the diffusion-controlled Br^- reactions with analogous non-brominated carbocations.[40]

7.2. Methods

The standard method for the generation of vicinal dibromides (Scheme 7.2) is the conversion of unsaturated compounds with molecular bromine but during the last ten years, several new bromination methods have been developed, to avoid the its wide use, although it produces a reduced amount of wasting by-products. An appropriate measure to circumvent the hazardous potential of neat bromine is the use of supported bromine as an easy to handle carrying agent. A third approach is the generation of bromine in situ by using bromide compounds and oxidants.[41]



Scheme 7.2. Methods for electrophilic bromination of alkenes.

Employing carrying agents as a transport medium for bromine reduces the hazardous potential of molecular bromine. An ideal carrying agent to be applicable should be:

- Nontoxic or created no emissions during the work-up procedure;
- Recyclable to a degree much higher than 95%;
- Prepared and worked-up in an agreeable manner.

It is more resource demanding because even if 95% (ideally this amount should be even higher, ionic liquids, for examples, should be recyclable to an extent of 99% or more) of the carrying agent is assumed to be recyclable, and this is the reason to use such reagents, a large amount of solvent is necessary for reaction and extraction purposes. However in industry solvents are often recycled to a high degree, although this environmental performance is offset by the significant energy demand of recovery. Even with a 95% of recyclability, the amount of waste produced is high.

The use of a carrying agent merely causes a forward displacement of the problem into an earlier reaction step. The overall hazard potential remains because the inherent safety risk is connected to the specific properties of a problematic substance. Though, during the bromination step, a range of technological equipment is required to handle especially chlorinated solvents.

Generation of bromine *in situ* is strictly linked to a high production volume of coupled products. Instead of bromine, other substances such as acetic acid. Hydrobromic acid and hydrogen peroxide, though not as volatile as bromine, are also dangerous substances, the safety aspect is less of a motivation than the sensible utilization of the coupled product hydrogen bromide resulting from the bromination of hydrocarbons.

Polymeric reagents offer the advantages of both solution-phase chemistry and solid phase organic synthesis. Otherwise they are insoluble in the reaction medium and consequently the separation of products from the reaction mixtures is easier.[42] The reaction can be often driven to completion by using excess of polymeric reagent without the need for additional purification steps. A number of polymer-supported reagents have been reported for the bromination reactions of organic substrates.[43] Steric interactions between organic molecules and polymer supported reagents are usually very important factors and in the case where greater steric hindrance appeared, the reaction failed.[44]

Yaroslavsky *et al.*[45] reported the synthesis of *N*-bromopolymaleimide but its preparation does not assure a definite and reproducible bromination percentage. Poly(*N*-bromoacrylamide)[46] and PVP-bromine[47] complexes also react with olefinic compounds to give the corresponding dibromo-derivatives. In the first case the bromination procedure determines a limited conversion rate and for all three methods were carried on unsafely conditions (*e.g.*, carbon tetrachloride as solvent and relatively high temperatures).

Organic ammonium tribromide, such as pyridinium tribromide,[48] tetramethyl-ammonium tribromide[49] and tetrabutylammonium tribromide[50] have been used as mild and selective brominating agents but their solid nature implied to use them just like reagents and a solvent (*e.g.*, CH_2Cl_2/MeOH system)[51] must be used.

In 1992 Muathen[52] synthetized DBU Hydrobromide Perbromide ($DBUHBr_3$), more stable than the most widely used pyridine analogous, and employed it for aromatic bromination using four different hazardous procedures. For reactive systems $HgCl_2$ was used as catalyst, for polycyclic compounds reaction underwent in refluxing AcOH, deactivated rings were treated with Ag_2SO_4/H_2SO_4 and for heteroaromatics the CH_2Cl_2/MeOH system was chosen.

Ionic liquids avoid the use of chlorinated solvents and seem to be the best variants of this method, because nontoxic ones can be chosen and the recyclability is claimed to be efficient, reducing waste production. Although, scale-up of the work-up procedure does not seem to be possible without significant changes, including the introduction of a solvent for extraction and washing procedures. Therefore, the potential ecotoxicological effects and biodegradability of the carrier have to be taken into account.[53]

However, bromine is used regardless in this production line and as it appears very early in the synthesis sequence, the technology should be already properly adjusted. These protocols suffer from a high coupled-product formation and indirect processes cause pollution (*i.e.*, propylene oxide investigate as an example of a chlorine-free product, is produced using chlorine).[54]

Oxidation of HBr with H_2O_2 is faster than the oxidation of HCl because of the lower oxidation potential of HBr, which enables the oxidative bromination of organic molecules under milder conditions and with a smaller excess of reagents.[55] A solution of HBr and H_2O_2 in a biphasic H_2O/CCl_4 system was used for the dibromination of various alkenes and alkynes.[56] 1,5-cyclooctadiene was transformed mainly to the 1,2-dibrominated derivative, while in an one-phase reaction in MeOH an intermediate bromohydrin was formed, which transformed into a bicyclic system.[57] V_2O_5 catalytic system can increase Br^- to Br_2 conversion speed.[58] The use of HBr can be circumvented starting from a bromide salt and a mineral acid avoiding HCl because of its anion nucleofilicity. Furthermore, this method has the advantages of low transportation and storage risks and employs the relatively safe 35% H_2O_2. The drawbacks are high prices and low productivity, not effective for deactivated aromatic substrates and the fact that concurrent unwanted decomposition of the peroxide occurs determined mostly by bromide than by both acids or vanadium catalyst.[59]

Sodium periodate ($NaIO_4$) oxidatively halogenates a variety of olefins and aromatics with alkali metal halides as halogen source under mild conditions. Dibromides formation is facilitated in the presence of acetic acid as solvent requiring no strong acidic conditions also with electron-deficient substrates such as α,β-unsatured amides.[60]

Mixtures of oxone (2 $KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) and NaBr afford a convenient laboratory preparation of bromine. In CCl_4/H_2O two phase solvent system cleaner reactions and higher yields are obtained. Still the problem of side-product formation, especially using NaCl as chlorinating agent (*i.e.*, polychlorinated compounds), and the use of hazardous solvents remain.[61]

When Na_2CO_3 is added to the reaction system KBr/H_2O followed by Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)), the sole product is *trans*-1,2-dibromostyrene, while using acetic acid led to the formation of *cis*-1,2-dibromostyrene as the major product.[62]

7.3. Bromination reaction in ionic liquids

Ionic liquids in bromination reaction can be seen as both solvents or reagents, in the former case using a brominating agent or generating bromine *in situ* and in the latter one as bromine reservoir. In analogy with the behaviour of the bromine addition reaction in molecular solvents the stereochemistry of bromination in ILs is strongly affected by substrate structure, ionic liquid nature and presence of bromide ions. Probably, also in ILs, the lifetime of the ionic intermediate is the main factor affecting the stereochemistry of aryl substituted olefins.[63]

In the last ten years, dihaloalkenes and dihaloalkanes have been obtained in high yield and high stereoselectivity by addition of halogens (Br_2, BrCl, ICl and IBr) to alkenes and alkynes in ILs.[64] In these media the reaction generally give exclusively or preferentially the *anti* addition products, and the stereospecificity of the addition process is generally higher than that characterizing the same reactions in chlorinated solvents, also when carbenium ions are involved (*e.g.*, bromine addition to *cis*-stilbene and derivatives bearing EDGs). Since, open β-bromocarbenium ions give the *syn*-addition products mainly through an *anti* attack of the counter anion, after rotation around the C–C bond, the stereochemistry of the products obtained in ILs suggests that in these media the intermediates have a reduced lifetime; rotation around the C–C bond is not able to compete with the faster nucleophilic trapping.

But, ILs have been used also as solvent in bromination procedure using *N*-bromosuccinimide (NBS). Traditionally, using this reagent it is possible to perform the radical bromination at benzylic positions in boiling CCl_4, which is favoured by the addition of a radical initiator (Wohl-Ziegler bromination),[65] while the nuclear brominations of activated aromatic systems are favoured in polar aprotic solvents. Regioselectivity of the reaction in ILs indicates that the electrophilic aromatic substitution process is favoured over a radical one; the behaviour of ILs is similar to polar aprotic solvents, although ILs are able to significantly enhance the reaction rates.[66] In this process, ILs can play a dual role as solvent and activator of the *N*-halosuccinimides increasing the polarization of N–Br bond, thereby avoiding the use of environmental VOCs.[67] In this field, recently Yadav *et al.*[68] have developed a product isolation procedure and ionic liquid recovery using the hydrophobic [bmim][PF_6]. Nevertheless, they have also extended the use of *N*-halosuccinimides (*i.e.*, NBS and NIS) to haloydrins synthesis using hydrophilic ionic liquid/water systems.[69]

But, ILs have been also used for bromination procedure under oxidative conditions. Vanadium(V)-catalysed oxy-bromination of styrene in water/CH_2Cl_2 lead to two parallel process involving vanadium-bound hypobromite ion, responsible of bromohydrin formation, and bromine leading to the dibrominated compound. If with hydrophilic ionic liquids there is no improvement, in hydrophobic ones/water systems a significant enhancement in yields and selectivity towards bromohydrins formation has been observed.[70] Otherwise, Mo(VI) is used as catalyst for acetylene bromination with KBr/H_2O_2 system, obtaining good selectivity values.[71]

Nevertheless, aromatic chlorination in 1-methylimidazolium nitrate-HCl, [Hmim][NO_3]-HCl, can be performed using an approach characterized by a very high atom economy. This Bronsted acidic IL is able to oxidize halogenidric acids, being at the same time re-oxidized by oxygen. The NO_3^- anion is indeed fundamental for the oxidation of chloride, but being reformed during the course the reaction it can be considered a stoichiometric catalyst.[72]

7.3.1 Trihalide salts

Recently, it has been shown that it is possible to use ionic liquids as alternative solvents in electrophilic halogenation using trihalide salts (*i.e.*, Br_3^-, $BrCl_2^-$, $BrCl_2^-$ or $BrCl_2^-$).[73]

The chemical shift of aromatic protons in dialkylimidazolium ionic liquids is anion dependent: in particular the C(2)–H signal moves downfield with increasing anion basicity, and thus hydrogen-bonding capability,[74] which can be a useful tool for determining whether Br_3^- formation accompanies bromine dissolution in these solvents. The chemical shift values of [bmim]Br^- showed an appreciable dependence on the Br_2 concentration. Bromine amount corresponding to the molarity of the solvent gives the greatest variation in chemical shifts. Addition of higher concentrations of Br_2 did not produce further significant modification in the ^{1}HNMR spectra. Since in general the chemical shifts of the ring protons move downfield with increasing anion basicity, and thus hydrogen-bonding capability, counter-anion change from Br^- to Br_3^- is supported by the anion basicity decrease after the addition of Br_2 to [bmim]Br^-.

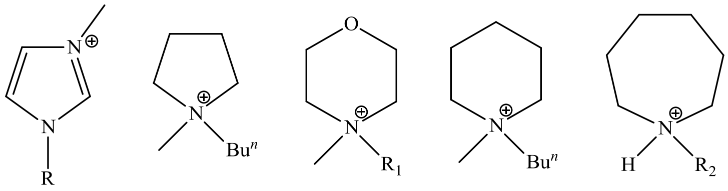
Electrophilic solvation of Br_3^- by the ionic liquid is relatively unimportant, while the Br^- ion is hydrogen-bonded to the solvent, reducing its nucleophilicity and so nucleophile attack speed. On the other hand, hydrogen bonding to the leaving bromide ion formed by breaking of the Br–Br bond may well balance or overbalance this retarding effect. Therefore, anion is always coordinated to the cation, and consequently both bond formation and bond breaking are affected by electrophilic solvation. In ILs, hydrogen bonding may therefore be less important, in particular if bond formation and bond breaking in the TS are synchronous.[75]

IBr_2^- appears to be the best H-bond acceptor among the trihalide ions with [bmim] as cation. In solvents having low or high H-bond strength the cation is hydrogen-bonded (via the H(2) site) to the counteranion or to the solvent. The very high polarizability and low charge density of this anion involve a relatively weak cation-anion interaction that is easily broken down also by a very weak H-bond acceptor solvent as dichloromethane is.[76]

We decided to explore a wide group of tribromide salts looking for a rationalization of the interactions involved, especially with cation variations. Their preparations were quite simple and in the general procedure to an appropriate amount of the starting bromide salt an equimolar amount of Br_2 was added slowly under stirring at room temperature. The eventually excess of Br_2 could be easily removed under vacuum. This procedure gave rise to the best results when the expected product was liquid, otherwise an increase in temperature was needed.

Trihalide salts exhibited chains of closely spaced anions (within the sum of the van der Waals distance) along with asymmetric X–X bond lengths, which suggest that these materials may be able to transfer halide anions through dissociation to X_2 and X^- and thus are good candidates for halide ion conductivity.[77] The fact that trihalide bonds are much longer than the typical covalent bond lengths is the indication of hypervalent bonding, which is considerably weaker than covalent.

The degree of interaction between the anion and cation of each salt also influences the melting point, with a shorter anion···cation contact, indicative of stronger electrostatic interaction, contributing to a higher melting point. At least in the case of imidazolium salts, tribromide salts display greater N···X distances than the monobromides, which is consistent with the lower melting points and is likely to be a result of the more diffuse charge on the tribromide anion. In contrast, triiodide salts display slightly shorter anion···cation interactions, suggesting that other factors are more dominant in determining the melting point.



R = H, C_2, C_4, C_8
R_1 = C_2, C_8
R_2 = C_4, C_7

Figure 7.1. Tribromide of alkyl-functionalised onium salts.

At the beginning we concentrated our attention on some simple alkyl-functionalised onium salts (Figure 7.1). Moreover, we synthetized tribromide salts of dibromide-functionalised onium salts (Figure 7.4). We would have seen also how small variations (*i.e.*, chain length) could have influenced melting point. Commonly, conversion to tribromide salt reduced the melting point respect to the precursor but it was not possible to rationalize, as found in literature, to a general behaviour because there were some exceptions.

We performed DSC tests to check the presence of the occurrence any phase transition in the investigated temperature range (*i.e.*, -40-200 °C). For these samples we did not performed the pre-heating procedure because they showed low thermal stability. The followed procedure started cooling the sample from room temperature to -40 °C, with a rate of 10 °C min^{-1}, and then maintaining this temperature for 5 minutes. The samples were heated at 10 °C min^{-1} up to 200 °C.

The first group gathers methyl-imidazolium salts bearing chain with different lengths on the other nitrogen.

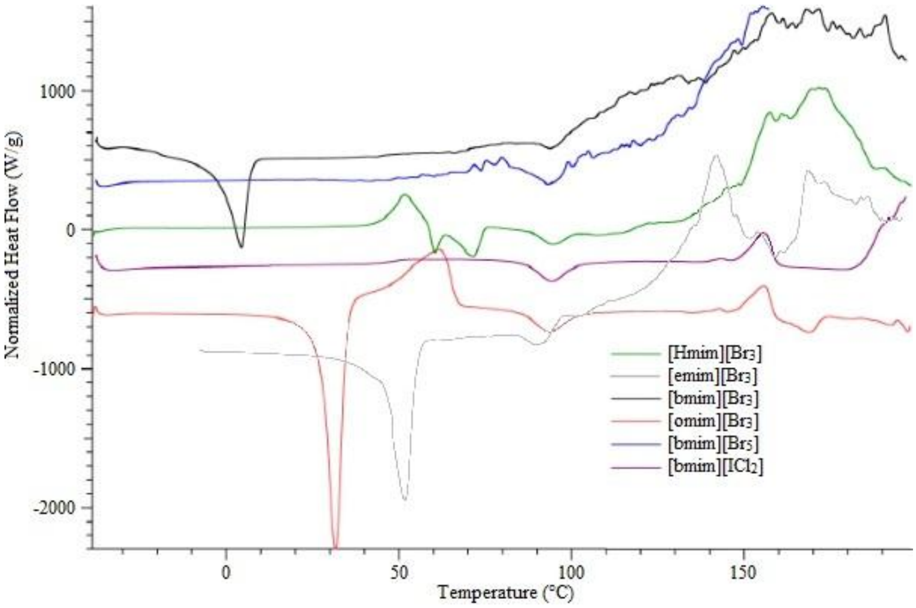


Figure 7.2. Heating flow thermograms of alkyl-methylimidazolium tribromide salts.

[Hmim], [emim], [bmim] tribromide showed evident degradation signals (Figure 7.2) from 100 °C. [bmim][Br_5] had a very early degradation (starting from ~ 50 °C). [omim][Br_3] and [bmim][ICl_2] seemed to be the most stable salts with high degradation temperatures. Butyl-methylimidazolium tribromide had a melting temperature decrease since it melted at 8.2 °C (rather than 50 °C of the precursor). However, as opposed to literature results, [emim] and [omim] tribromide salts had a melting point increase in relation to the bromide precursors. The former with an increase of about 70 °C (depending on which melting point of the starting bromide salt is considered, *i.e.* 65 or 75 °C). The octyl-methylimidazolium tribromide had the biggest positive shift, going from -61.9 to 155.7 °C. Also [Hmim]Br_3^- had an increase of melting point temperature, going from 33 (or 44) to 51.7 °C. Therefore, the generalization found in literature that tribromide have lower melting points than bromide precursors is not so obvious because other factors, in addition to polar interaction, contribute to the T_m (Table 7.1).

Table 7.1. Melting points (°C) of some bromide and tribromide salts. ${}^{a}T_g$.

Cation	Br^-	Br_3^-
Hmim	33-41	51.7
emim	65-75	140
bmim	43-50	8.2
omim	-61.9	155.7
ommorf	155.5	68.7
bmpip	241	-10.7[a]
bmpyr	215	40.8[a]

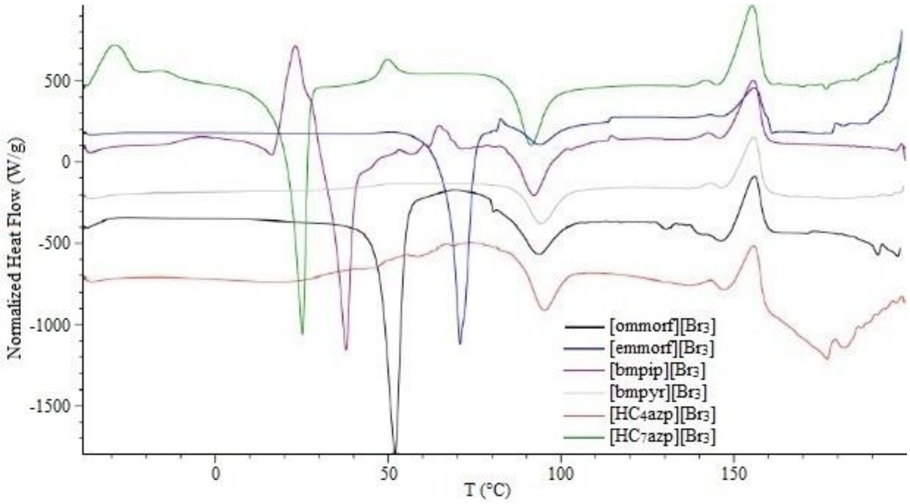


Figure 7.3. Heating flow thermograms of unsaturated tribromide salts.

The samples in the thermograms above (Figure 7.3) showed an extremely heterogeneous behaviour with a crystallization near 93 °C and a melting (bimodal pattern) between 140 and 160 °C. However, piperidinium, heptylazepanium and both morfolinium salts exhibited intense exothermic peaks between 20 and 80 °C probably because of rearrangement or degradation processes. For what concern the lateral chain enlarging, no effects can be seen in terms of crystallization and melting temperatures. There is just a shift of the rearrangement peak toward lower temperature for the [ommorf] (T_m = 68.7 °C, lower compared to that of the bromide precursor, *i.e.* 155.5 °C) compared to [emmorf]. Butyl-methyl-piperidinium and -pyrrolidinium tribromide exhibited a T_g at -10.7 and 40.8 °C respectively.

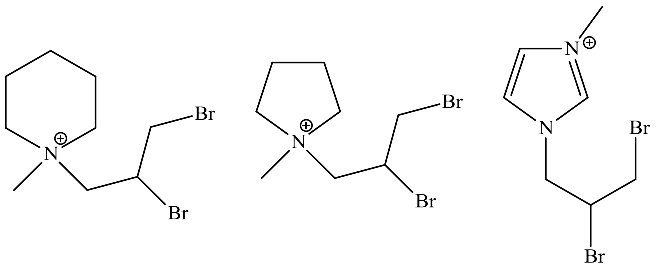


Figure 7.4. Tribromide of dibromide-functionalised onium salts.

We have also measured the thermograms of some dibromide-functionalized tribromide salts (Figure 7.4).

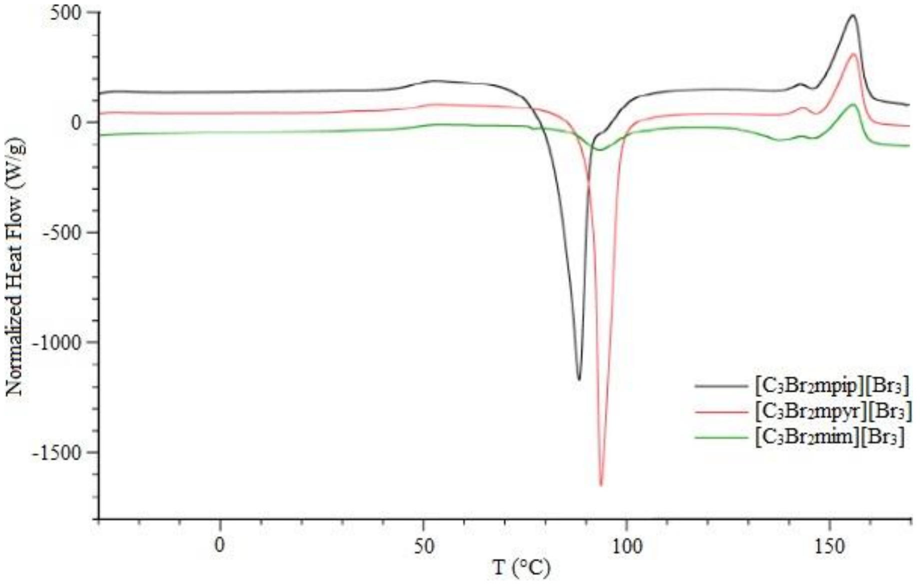


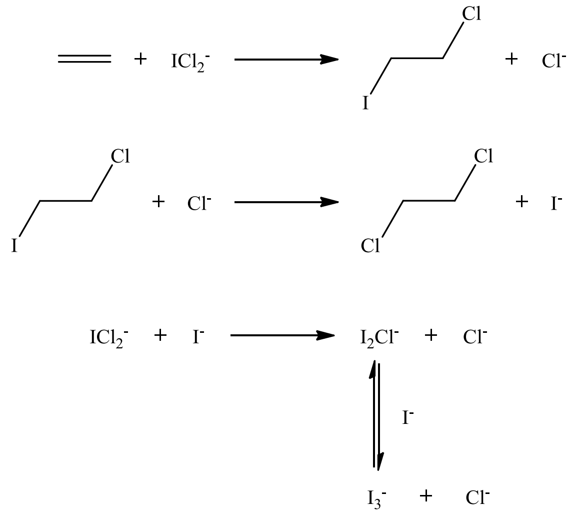
Figure 7.5. Heating flow thermograms of dibromide-functionalized tribromide salts.

For all three salts there was a glass transition near 50 °C and a bimodal melting pattern between 140 and 160 °C (as for the previous systems). For the unsaturated pyrrolidinium and piperidinium salts there was also a deep exothermic crystallization peak (Figure 7.5). All three systems displayed T_g ~ 47 °C.

The electrophile Br_3^- arises by the diffusion controlled binding of the Br_2 by the solvent, when the reaction is carried out in an ionic liquid having a bromine as anion. In presence of Br^- ions Cl_2 should give the $BrCl_2^-$ species. *Ab initio* calculations have shown that the X–Y–X anions, where Y is heavier than X, are more stable than the isomers Y–X–

X both in gas phase and solution. As a result, the Y–X–X anions, if formed from X_2 and Y_2, are expected to easily isomerize to the X–Y–X anions *via* cleavage of the X–X bond.[78] In agreement with reactivity data and spectroscopic measurements the various trimeric anions showed two distinct levels of stability: derivatives like Br_3^-, I_3^-, IBr_2^- and ICl_2^- may be classified as quite stable species, whereas Br_2Cl^-, I_2Br^- and I_2Cl^- are rather unstable.[79]

The ILs ability to repress the formation of unwanted by-products is of fundamental important in halogenation reactions. For example, the electrophilic addition of ICl_2^- to olefins in chlorinated solvents is an apparently very slow reaction, which generally gives the expected *anti* addition products in low yields. Progressive darkening of the reaction mixtures, observed when the reactions are carried out in molecular solvents (1,2-dichloroethane or dichloromethane), may be attributed to the formation of I_3^-, arising from the reaction of formed chloride anion with the addition products, according to Scheme 7.3.[80] Fortunately, this unwanted substitution reaction, which leads to reactant decomposition and simultaneously to the formation of dichloro-derivatives besides the expected iodochloroadducts, in ionic liquids does not compete significantly with the addition process. More in particular, this reaction is practically suppressed when the addition of ICl_2^- is performed in ILs having a considerable hydrogen bonding donor ability as [emim] and [bmim][Tf_2N].



Scheme 7.3. I_3^- formation during ICl_2^- electrophilic addition.

On the other hand, the regiochemistry of the addition product to styrene is in agreement with the presence in solution of $BrCl_2^-$ anion able to react with the double bonds giving an electrophilic bromine and a nucleophilic chloride.[81]

Consequently, ICl_2^- and IBr_2^- based ILs can be considered interesting "green" alternative media for the synthesis of iodochloro- and iodobromo-derivatives, in particular when the olefin structure favours the formation of rearrangement and elimination products but higher yield and stereoselectivity may be achieved also using [bmim][PF_6] as solvent and ICl or IBr as reagents. Furthermore, in this case shorter reaction times are necessary, there is no formation of dibromo adducts, attributed to IBr disproportionation,[82] and the IL solvent can be more easily recycled and reused.[83]

While the rates of the electrophilic addition of ICl_2^- to double and triple bonds increase on going from DCE to ILs,[84] the substitution reactions are generally slower in these latter media.[85] [Bu_4N][ICl_2] as reagent in chlorinating solvent leads to very low reaction rates because of the partial transformation of the ICl_2^- species in I_3^-, confirmed by UV experiments. This decomposition may be completely repressed performing the reaction in ILs having higher H-bond donor ability. In these ILs is generally possible to isolate the corresponding iodochloro derivatives in high yield, without observation of reactant decomposition and formation of the corresponding dichloro adducts because ILs not only increase the rate of the addition process but also reduce the nucleophilicity of Cl^- anion, reducing the rate of the substitution process.[86] In the case of ICl_2^- addition, the bond breaking precedes bond making, the transition state has greater iodiranium character and the attack by chloride is not in itself the rate determining step, although it might be part of a concerted process. In this situation, the ability of the IL to form hydrogen bonds with the leaving Cl^- plays the main role.

Assuming that alkynes bromination[87] reaction in [bmim]Br^- occurs through the mechanism generally accepted for the reaction in molecular solvents,[88] the process should involve as the first step an equilibrium between two complexes of Br_2:Br_3^- and 1:1 alkyne–Br_2 π complex. This step is followed by the rate-determining nucleophilic attack by the bromide, either detached from Br_2 after the formation of alkyne–Br_2 π complex or present in solution, while the Br–Br bond is being broken and a new bromide ion is formed. Bromination with Br_3^- occurs through a TS characterised by a nonsynchronous C–Br bond formation and Br–Br bond breaking. If bond formation is advanced with respect to bond breaking, viscosity may have an accelerating effect while hydrogen bonding should have an inverse role. If, on the other hand, bond breaking prevails, opposite effects may be observed. Kinetic and stereochemical data recently obtained for bromination of alkynes in [bmim][Br_3] suggests that solvent viscosity is more important than hydrogen bonding in determining the reactivity of alkynes in Br_3^- addition reaction.

Otherwise, using [bmim][PF_6] the competition of two pathways has been proposed for Br_2 addition to alkynes. The first pathway involves a second-order dependence of the rate on bromide. The ionisation of the π complex, catalysed by a second molecule of Br_2, gives a bromirenium tribromide intermediate, depending on the ability of the substituents on the triple bond to stabilise the positive charge. This then collapses to give the dibromo adduct. In the second pathway an imidazolium-assisted bromine–bromine bond breaking occurs in the 1:1 π complex to give a bromirenium bromide intermediate and the reaction is of first order in Br_2.[87]

Tribromide ILs have also been used as reactants, mixed with [bmim][BF_4], using Br_3^- as bromine source to synthetize 2-benzothiazoles,[89] or [bmim]Br^-, to obtain β-bromostyrenes from α,β-unsaturated carboxylic acids.[90]

However, the replacement of a molecular solvent with an ionic liquid, despite the improved physicochemical and solvent properties of these media (low vapour pressure, not flammable, high solvent power, high chemical stability), is not necessary able to increase the process sustainability or to give significant improvements to the procedure.

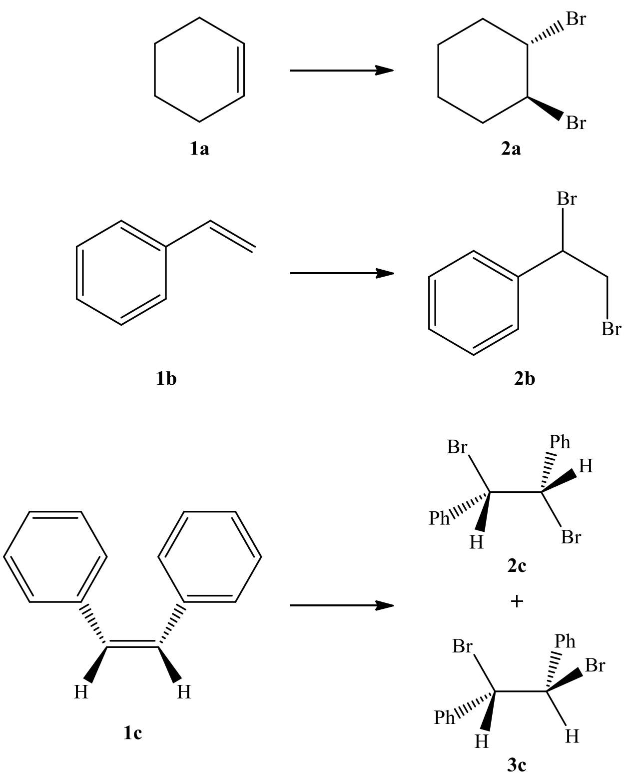
A possibility to increase the sustainability of the electrophilic bromination of unsaturated compounds might arise from the use of proper tribromide-based ionic liquids as carrying agents and media.

Aromatic monobromination reaction in [bmim][Br_3] is general applicable to several substituted phenols[91] and anilines[92] containing different groups. When the *para* is occupied the reaction leads to selective monobromination in the *ortho* position. The same regioselectivity was found by Borikar *et al.* using [bbim][Br_3],[93] whereas Chiappe *et al.*[94]

made a comparison between [Hmim][Br_3] and [bmim][Br_3].[95] Reactions carried out in the former exhibit significantly higher conversions, although they are characterized by a product distribution very similar to that found in the latter.[96]

Recently, other cations have been associated to tribromide ion; Kavala *et al*. synthetized 1,2-dipyridiniumdibromide-ethane (DPDBE), re-generable adding 2 equiv of KBr and of Oxone;[97] 1-butyl-3-methylpyridinium,[98] N-octylquinolinium,[99] cetylpyridinium, have been used as both brominating or acetylating agent[100] whereas the chiral L-prolinolium (leading however to very poor *ee*), represents the first example of protic secondary ammonium salt used in bromuration reaction.[101]

About the work done in our laboratory,[102] we considered that the choice of ionic liquid cation, being able to strongly affect the physicochemical properties of the system, may be able to increase the sustainability of the products recovery step. The optimal conditions for three representative compounds, *i.e.*, cyclohexene (**1a**), styrene (**1b**), and *cis*-stylbene (**1c**) giving, respectively, a liquid product, a solid compound soluble in common molecular solvents and a solid compound insoluble in most of the widely used organic solvents, have been examined taking into account waste production as well as environmental, health and safety aspects (Scheme 7.4).



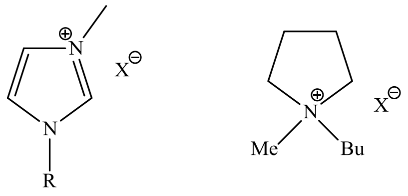
Scheme 7.4. Bromination of various alkenes.

Cis-Stilbene (**1c**) was selected since it allows evaluation of the stereoselectivity of the process. Mixtures of *anti* and *syn* adducts (dibromides **2c** and **3c**) are generally obtained starting from this olefin in the absence of strong nucleophiles (halide anions or nucleophilic solvents).

In previous works carried out in our laboratory, as mentioned above, although it was possible to recycle the reaction system, relevant amounts of waste products were generated for each kilogram of dibromo adduct.

Considering that immobilization of bromine in a halide based ionic liquid can give a halogen carrier with different physicochemical properties depending on the cation, we have prepared a series of tribromide-based ionic liquids by bromine addition to selected bromide salts, 1-methylimidazolium bromide [Hmim]Br$^-$, 1-ethyl-3-methylimidazolium bromide ([emim]Br$^-$), 1-butyl-3-methylimidazolium bromide ([bmim]Br$^-$), 1-octyl-3-

methylimidazolium bromide ([omim]Br$^-$) and *N*-butyl-*N*-methylpyrrolidinium bromide ([bmpyr]Br$^-$) (Figure 7.6).



R = H
X = Br; [Hmim]Br$^-$
X = Br$_3$; [Hmim][Br$_3$]
R = Et
X = Br; [emim]Br$^-$
X = Br$_3$; [emim][Br$_3$]
R = Bu^n
X = Br; [bmim]Br$^-$
X = Br$_3$; [bmim][Br$_3$]
R = C$_8$H$_{17}$
X = Br; [omim]Br$^-$
X = Br$_3$; [omim][Br$_3$]

X = Br; [bmpyr]Br$^-$
X = Br$_3$; [bmpyr][Br$_3$]

Figure 7.6. Investigated ionic liquids in bromination reaction.

With the exception of [omim]Br$^-$ all the other bromides were solid at room temperature. The transformation of the Br$^-$ anion into the more charge-diffused Br$_3^-$ anion resulted in a decrease in water affinity (all five tribromide salts can be included in the class of water immiscible ionic liquids) whereas a significant reduction of the melting point was observed only in some cases. More in particular, [bmim][Br$_3$] and [bmpyr][Br$_3$] appeared as low viscous liquids at room temperature and below it, [omim][Br$_3$] as a liquid-low melting solid (mp ~ 28-30 °C) and [emim][Br$_3$] and [Hmim][Br$_3$] as crystalline compounds (mp 49 and 70 °C, respectively).

However, it should be noted that cation structure affects not only physicochemical properties of these salts but also their environmental impact. In the case of bromide salts, it has been shown that toxicity towards the aquatic environment increases on going from pyrrolidinium to imidazolium salts and, in the case of these latter compounds, toxicity increases on alkyl chain length increasing. Environmental impact of [bmpyr]Br$^-$ and [Hmim]Br$^-$ is therefore lower than that of all the other salts here investigated.[103]

To test the efficiency of the selected tribromide-based ionic liquids, the reactions were carried out at room temperature or at the lowest temperature at which the systems were liquid (ranging from 40 to 70 °C) by addition of the three target alkenes to an equimolar amount of the ionic liquid with stirring (Table 7.2).

Table 7.2. Bromination of alkenes **1a-c** with tribromide-based ILs. [a]Work up procedure A. [b]Work up procedure B. [c]Work up procedure C.

Alkene	Ionic liquid	Product	Yield (%)	Selectivity (%)
1a	[Hmim][Br$_3$]	**2a**	98[a]	98
	[emim][Br$_3$]		93[a]	99
	[bmim][Br$_3$]		92[a]	99
	[omim][Br$_3$]		93[a]	99
	[bmpyr][Br$_3$]		97[a]	99
1b	[Hmim][Br$_3$]	**2b**	92[b], 95[b]	98
	[emim][Br$_3$]		93[b]	99
	[bmim][Br$_3$]		95[b]	99
	[omim][Br$_3$]		94[b]	99
	[bmpyr][Br$_3$]		98[b]	99
1c	[Hmim][Br$_3$]	**2c**	90[c]	98
	[emim][Br$_3$]		92[c]	99
	[bmim][Br$_3$]		90[c]	99
	[omim][Br$_3$]		90[c]	99
	[bmpyr][Br$_3$]		98[c]	99

The alkene addition always resulted in the rapid disappearance of the colour and the formation of a solid phase due to the transformation of the tribromide salt into the corresponding bromide or to the formation of a solid dibromo adduct or to both phenomena. When the product was a liquid, *i.e.* cyclohexene, the formation of a byphasic system at room temperature allowed an easy and efficient separation of the reaction product from the formed bromide salts. Perhaps, the latters could be washed with the minimal amount of a nonpolar solvent (*e.g.*, toluene, hexane) and recycled after transformation into the corresponding tribromides. Workup procedure for alkenes giving a solid product was more complicated and more medium-dependent. In the case of the most effective ionic liquid, [bmpyr][Br$_3$], it gave a semisolid mixture that allowed efficient stirring until the end of the process, until at room temperature. Then the solid dibromides could be isolated from the reaction mixture by extraction with diethyl ether or by filtration after dissolution of the thus formed [bmpyr]Br$^-$ in a minimal amount of water or alcohol (*i.e.*, MeOH or EtOH). This latter procedure is particularly suitable for dibromides, such as those arising from stilbenes, which have very low solubility in organic solvents or water. The solid dibromides, recovered in quantitative yield, were pure by NMR analysis. On the other hand, after solvent removal the bromide salts could be converted into the corresponding tribromides and reused over and over again.

NMR and GC-MS analysis of the reaction products confirmed that the reaction occurs in all investigated ionic liquids in a stereospecific way, giving exclusively the *anti*-addition products. Nevertheless, should be noted that the expected dibromo adducts were practically the sole reaction products also when the protic [Hmim][Br_3] was used as brominating agent, in which only traces (< 2%) of HBr addition were detected in the GC-MS chromatogram of the reaction product arising from bromination of styrene in this medium.

In conclusion, considering that tribromide salts are one of the most efficient systems to obtain dibromo derivatives with high stereo- and chemoselectivity, these data show that it is possible to use the “chemical tunability” of ionic liquids to modulate the properties of the system and to increase the sustainability of the process. Using tribromide-based ionic liquids, it is possible to carry out these reactions practically under solvent-free conditions and products can be recovered by simple phase separation or by filtration after addition of a very small amount of ethanol or water. The exhausted ionic liquids can be easily recycled reducing the low atom economy problems related to the application of bromine carriers. Among the investigated ionic liquids, which cannot be considered exhaustive, the best systems appeared to be [Hmim][Br_3] and [bmpyr][Br_3]. The first is associated with relatively low toxicity towards aquatic environment and extremely easily to synthetize (its precursor is obtained by neutralization of *N*-methylimidazole by HBr in aqueous medium), while the second is associated with relatively low environmental impact and it has the properties of a liquid reagent at room temperature (*i.e.*, a more efficient stirring of the reaction mixture even at room temperature, a higher solvent power). Finally, it is to note that these ionic liquids can be used for several other organic transformations previously investigated as aromatic bromination and carbonyl functionalization.

7.4. Experimental section

7.4.1 Synthesis of tribromide-based ionic liquids

To an appropriate amount of the starting ionic liquid (bromide or chloride) an equimolar amount of Br_2 was added slowly under stirring. Attention was paid to avoid an excess of halogen which, at least in the case of Br_2, could be eventually removed under vacuum.

1-methylimidazolium tribromide [Hmim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 3.87 (s, 3 H, CH_3), 7.66 (s, 1 H, CH), 7.68 (s, 1 H, CH), 9.04 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 35.6 (CH_3), 119.8 (CH), 123.2 (CH), 135.9 (CH).

1-ethyl-3-methylimidazolium tribromide [emim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 1.41 (t, J = 7.5 Hz, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 4.17 (q, J = 7.5 Hz, 2 H, CH_2), 7.66 (s, 1 H, CH), 7.75 (s, 1 H, CH), 9.07 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 15.2 (CH_3), 35.8 (CH_3), 44.3 (CH_2), 112.0 (CH), 123.6 (CH), 136.3 (CH).

1-butyl-3-methylimidazolium tribromide [bmim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.89 (t, J = 7.5 Hz, 3 H, CH_3), 1.25 (sext, J = 7.5 Hz, 2 H, CH_2), 1.76 (quint, J = 7.5 Hz, 2 H, CH_2), 3.84 (s, 3 H, CH_3), 4.15 (t, J = 7.5 Hz, s H, CH_2), 7.67 (s, 1 H, CH), 7.74 (s, 1 H, CH), 9.08 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 13.4 (CH_3), 15.9 (CH_2), 31.4 (CH_2), 35.9 (CH_3), 48.6 (CH_2), 112.4 (CH), 123.7 (CH), 136.5 (CH).

1-octyl-3-methylimidazolium tribromide [omim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.84 (t, J = 7.2 Hz, 3 H, CH_3), 1.24 (m, 8 H, CH_2), 1.76 (m, 2 H, CH_2), 3.84 (s, 3 H, CH_3), 4.13 (t, J = 7.3 Hz, 2 H, CH_2), 7.67 (s, 1 H, CH), 7.74 (s, 1 H, CH), 9.07 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 14.1 (CH_3), 22.2 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 35.9 (CH_3), 48.9 (CH_2), 112.4 (CH), 123.7 (CH), 136.5 (CH).

N-butyl-N-methyl-pyrrolidinium tribromide [bmpyr][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.92 (t, J = 7.2 Hz, 3 H, CH_3), 1.31 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 2.08 (m, 4 H, 2 CH_2), 2.97 (s, 3 H, CH_3), 3.30 (m, 2 H, CH_2), 3.45 (m, 4 H, 2 CH_2).

^{13}C NMR (DMSO-d_6): δ = 13.7 (CH_3), 19.4 (CH_2), 21.2 (CH_2), 25.9 (CH_2), 47.6 (CH_3), 63.1 (CH_3), 63.6 (CH_2).

N-ethyl-N-methyl-morpholinium tribromide [emmor][Br_3]

^{1}H NMR (DMSO-d_6): δ = 1.25 (t, J = 7.3 Hz, 3H), 3.09 (s, 3H), 3.38 (m, 4H), 3.50 (q, J = 7.3 Hz, 2H), 3.90 (m, 4H).

^{13}C NMR (DMSO-d_6): δ = 6.96, 45.40, 58.51, 59.48, 59.87.

N-octyl-N-methyl-morpholinium tribromide [ommor][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.86 (m, 3H), 1.29 (m, 10H), 1.67 (m, 2H), 3.10 (s, 3H), 3.40 (m, 6H), 3.90 (m, 4H).

^{13}C NMR (DMSO-d_6): δ = 14.12, 20.87, 22.20, 25.89, 28.61, 31.31, 46.17, 59.09, 59.96, 64.01.

N-butyl-N-methyl-piperidinium tribromide [bmpip][Br_3]

^{1}H NMR (DMSO-d_6): δ = .

^{13}C NMR (DMSO-d_6): δ =

1-butylazepanium tribromide [HC_4azp][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.31 (m, 2 H), 1.62 (m, 6 H), 1.78 (m, 4 H), 3.09 (m, 4 H), 3.36 (m, 2 H), 9.08 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.67, 19.54, 23.14, 25.81, 25.87, 53.88, 56.35.

1-heptylazepanium tribromide [HC$_7$azp][Br$_3$]

^{1}H NMR (DMSO-d_6): δ = 0.85 (t, *J* = 0.65 Hz, 3 H), 1.27 (m 8 H), 1.60 (m, 6 H), 1.78 (m, 4 H), 3.07 (m, 4 H), 3.33 (m, 2 H), 9.09 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.97, 22.02, 23.02, 23.67, 25.88, 26.00, 28.20, 31.04, 53.73, 56.44.

1-(2’,3’-dibromopropyl)-3-methyl-imidazolium tribromide

^{1}H NMR (D$_2$O): δ = 9.31 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 4.93 (m, 1H), 4.80 (dd, *J* = 14.6, 4.5 Hz, 1H), 4.60 (dd, *J* = 14.5, 9.0 Hz, 1H), 4.02 (d, *J* = 5.0 Hz, 2H), 3.45 (s, 3H).

^{13}C NMR (D$_2$O): δ = 136.50, 123.26, 122.43, 52.52, 47.38, 35.47, 32.06.

1-(2’,3’-dibromopropyl)-1-methyl-pyrrolidinium bromide

^{1}H NMR (D$_2$O): δ = 4.15 (m, 1H), 3.98 (m, 2H), 3.78 (m, 2H), 3.62 (m, 4H), 3.19 (s, 3H), 2.22 (m, 4H).

^{13}C NMR (D$_2$O): δ = 67.75, 65.03, 64.75, 47.89, 40.52, 34.00, 20.70, 20.07.

1-(2’,3’-dibromopropyl)-1-methyl-morpholinium bromide

^{1}H NMR (D$_2$O): δ = 4.17 (m, 2H), 4.00 (m, 5H), 3.72 (m, 6H), 3.34 (s, 3H).

^{13}C NMR (D$_2$O): δ = 69.17, 60.07, 59.78, 46.96, 38.37, 33.90.

1-(2’,3’-dibromopropyl)-1-methyl-piperidinium bromide

^{1}H NMR (D$_2$O): δ = 4.84 (m, 1H), 4.02 (m, 3H), 3.80 (t, *J* = 10.2 Hz, 1H), 3.54 (m, 4H), 3.21 (s, 3H), 1.91 (m, 4H), 1.65 (m, 2H).

^{13}C NMR (D$_2$O): δ = 68.18, 61.77, 61.63, 47.54, 39.07, 34.35, 19.87, 19.12.

7.4.2. Bromination procedure and products analysis

To a round-bottomed flask equipped with a magnetic stirrer and containing the halogenating ionic liquid (3-4 g, ca. 10 mmol), eventually warmed to the minimal temperature to obtain a liquid system, was added 1 equivalent of the unsaturated compound. The mixture was stirred at the same temperature until disappearance of the colour and subjected to the most suitable workup procedure.

Workup A: formation of a liquid product

After cooling to r.t., the liquid product was separated by decantation and the residue was washed with a small amount of toluene (1 mL). The collected product was analysed by GC-MS.

Workup B: formation of a solid product

After cooling to r.t., the reaction product was extracted with Et_2O (3 × 3 mL). The combined extracts were analysed by GC-MS and by NMR.

Workup C: formation of a solid product

After cooling to r.t., 0.5 mL of a protic solvent (EtOH or H_2O) were added and the insoluble reaction product was separated by filtration through a sintered funnel. The product was then analysed by NMR.

GC-MS and NMR spectra of compounds **2a-c** were identical to those reported in literature.

Recycling procedure

After product recovery, traces of organic solvents or water were eliminated from the collected ionic liquids at reduced pressure and the salts were reused after transformation into the corresponding tribromide-based ionic liquids.

7.5. References

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